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REVISTA DE MEDICINĂ MILITARĂ

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- *article removed at the request of the authors*
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The article was received on November 26, 2020, and accepted for publishing on March 05, 2021.

REVIEW

Leadership skills in surgeons: a review of the literature

Alexandra Sopu[1], Juergen Apel[1]

Abstract: *Clinicians, professors of medicine in general, students, and professionals from the health sciences tend to focus their efforts on technical training related to their discipline in practice as well as activities that produce some benefit direct or personal satisfaction. It is unusual to devote time and effort to training in areas such as teaching or expand their skills in sociological and organizational aspects. Would you like to take a course on strategic planning if not a director or officer of the hospital? Manage time in your schedule for a workshop on communication and conflict management? Have room in your schedule for educational activities on leadership, organizational change, and diffusion of innovations, science or science complexity of implementation? Generally, doctors and teachers do not spend much time on these activities (at least voluntarily) because we feel that what we have learned from these topics on personal experience is enough [1].*

Effective teamwork, not only in the operating room but also throughout the perioperative route is considered an important and critical component of the safety and effectiveness of surgical care and leads to good results and quick recovery of surgical patients. Therefore, considerable efforts have been made to understand how teams work within the route of surgical care and to improve teamwork [2].

The simple act of bringing together some experts does not guarantee that turned out an expert team. Given the evidence suggests that teamwork in the operating room sometimes is far from harmonious and effective, the importance of training the surgical team to work effectively is receiving international acceptance as a key strategy to maximize safety in surgery.

This systematic literature review aims to present a review of literature that focuses on the importance and role of leadership skills in the surgeon and how these skills can play a significant role in increasing the quality of care and patients' safety in operating room (OR) settings.

Keywords: *leadership, surgeons, operating room, qualities, leader, surgical team, conflict*

INTRODUCTION

Clinicians, professors of medicine in general, students, and professionals from the health sciences tend to focus their efforts on technical training related to their discipline in practice as well as activities that produce some benefit direct or personal satisfaction. It is unusual to devote time and effort to training in areas such as teaching or expand their skills in sociological and organizational aspects. Would you like to take a course on strategic planning if not a director or officer of the hospital? Manage time in your schedule for a workshop on communication and conflict management? Have room in your schedule for educational activities on leadership, organizational change, and diffusion of innovations, science or science complexity of implementation? Generally, doctors and teachers do not spend much time on these activities (at least voluntarily) because we feel that what we have learned from these topics on personal experience is enough [1].

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The way to see the errors and patient safety has changed radically over the last 15 years. Effective teamwork, not only in the operating room but also throughout the perioperative route is considered an important and critical component of the safety and effectiveness of surgical care and leads to good results and quick recovery of surgical patients. Therefore, considerable efforts have been made to understand how teams work within the route of surgical care and to improve teamwork [2].

During the past 15 years, the conceptualization of security in surgery has changed substantially. There is a growing awareness that the skills required to consistently achieve security in surgery go far beyond the knowledge and technical skills of the surgeon [3]. Teamwork, defined in terms of "a set of behaviors, actions, cognitions, and attitudes that facilitate the work to be done" [4], is increasingly seen as an essential component of safe surgery. Work crews are essential when "errors can result in serious consequences; when the complexity of the activity exceeds the capacity of one person; when the working environment is ill-defined or ambiguous or stressful; when you need to make many decisions quickly, and when the lives of others depend on the collective view of the members'. The importance of teamwork to the safety and efficiency of operations has been recognized for some time and, therefore, is an integral part of the education, training, and evaluation of workers in many industries. It seems that, finally, the health community begins to embrace the concept of "work teams are a source of security" [5].

The simple act of bringing together some experts does not guarantee that turned out an expert team. Given the evidence suggests that teamwork in the operating room sometimes is far from harmonious and effective, the importance of training the surgical team to work effectively is receiving international acceptance as a key strategy to maximize safety in surgery. The development of training interventions to provide surgical team knowledge, skills, and attitudes that serve as a foundation for effective performance has become a dominant theme in the literature of surgery, anesthesia, and nursing.

OBJECTIVE

This systematic literature review aims to present a review of literature that focuses on the importance and role of leadership skills in the surgeon and how these skills can play a significant role in increasing the quality of care and patients' safety in operating room (OR) settings.

METHODS

A systematic review of the available literature was performed on leadership skills in the operating room. The search was made on the PubMed, JSTOR, and Cochrane library databases on June 10th, 2020 using the following formula: (Leadership skills AND Surgeons AND Operating Room). First, the articles were screened by title and abstract. The following inclusion criteria for relevant articles were used during the initial screening of titles and abstracts: must focus on leadership skills of surgeons, must focus on models of leadership for surgeons, and must focus on skills required by surgeons to be good leaders for the OR team. Other exclusion criteria were: studies published before 2010, studies other than the English language, studies conducted in under-developed countries, studies focusing on non-technical skills other than leadership skills.

In the second step, the full texts of the selected articles were screened, with further exclusions according to the previously described criteria. Moreover, articles not reporting clinical results were excluded. Relevant data were then extracted and collected in a single database with a consensus of the two observers to be analyzed for the present manuscript.

Table 1 provides the list of articles that are included in the review.

Table 1: List of articles included in the review.

Author (year)	Title
Yue-Yung Hu, Sarah Henrickson Parker, Stuart R Lipsitz, Alexander F Arriaga, Sarah E Peyre, Katherine A Corso, Emilie M Roth, Steven J Yule, Caprice C Greenberg (2016).	Surgeons' Leadership Styles and Team Behavior in the Operating Room
Arora, S., Hull, L., Fitzpatrick, M., Sevdalis, N. and Birnbach, D. (2015).	Crisis Management on Surgical Wards.
Balch, C., Shanafelt, T., Sloan, J., Satele, D. and Freischlag, J. (2019).	Distress and Career Satisfaction Among 14 Surgical Specialties, Comparing Academic and Private Practice Settings.
Culley, D., Fahy, B., Xie, Z., Lekowski, R., Buetler, S., Liu, X., Cohen, N. and Crosby, G. (2014).	Academic Productivity of Directors of ACGME-Accredited Residency Programs in Surgery and Anesthesiology.
Danis, D., Klinkner, G., Malec, A. and Rees, S. (2007).	Improving Patient Safety by Standardizing Handoff Communications.

Author (year)	Title
Dominguez, D., Garcia, C. and LaFrance, K. (2013).	Developing A New Graduate Program In Healthcare Management: Embracing The Transformation Of Healthcare Management Education On A Pathway To Success.
Doumouras, A., Keshet, I., Nathens, A., Ahmed, N., and Hicks, C. (2012).	A Crisis of Faith? A Review of Simulation in Teaching Team-Based, Crisis Management Skills to Surgical Trainees.
Graafland, M., Schraagen, J. and Schijven, M. (2012).	Systematic review of serious games for medical education and surgical skills training.
Hudspeth, R. (2008).	Complex Healthcare Regulation.
Khatrouch, I., Kaddes, M., Kermad, L., Boujelbene, Y. and ElMhamedi, A. (2013).	New approach for building multidisciplinary teams: case of surgical teams.
Kothari, S., Brethauer, S., Rosenthal, R., Nguyen, N. and Morton, J. (2015).	Response to "Ensuring Excellence in Centers of Excellence Programs".
McKean, S. (2012).	Principles and practice of hospital medicine.
Mitchell, L., Flin, R., Yule, S., Mitchell, J., Coutts, K. and Youngson, G. (2011).	Thinking ahead of the surgeon. An interview study to identify scrub nurses' non-technical skills.
Mumghamba, E. (2013).	Integrating a Primary Oral Health Care Approach in the Dental Curriculum: A Tanzanian Experience.
Parker, S., Flin, R., McKinley, A. and Yule, S. (2019).	The Surgeons' Leadership Inventory (SLI): a taxonomy and rating system for surgeons' intraoperative leadership skills.
Parker, S., Yule, S., Flin, R. and McKinley, A. (2012).	Surgeons' leadership in the operating room: an observational study.
Patel, V., Warren, O., Humphris, P., Ahmed, K., Ashrafian, H., Rao, C., Athanasiou, T. and Darzi, A. (2010).	What does leadership in surgery entail?
Siassakos, D., Fox, R., Bristowe, K., Angouri, J., Hambly, H., Robson, L. and Draycott, T. (2020).	What Makes Maternity Teams Effective and Safe? Lessons From a Series of Research on Teamwork, Leadership, and Team Training.
Sittig, D. (2011).	Defining Health Information Technology–Related Errors.
Stevens, L., Cooper, J., Raemer, D., Schneider, R., Frankel, A., Berry, W. and Agnihotri, A. (2017).	Educational program in crisis management for cardiac surgery teams including high realism simulation.
Thomas, E., Sexton, J. and Helmreich, R. (2003).	Discrepant attitudes about teamwork among critical care nurses and physicians*.
Valentine, M., Nembhard, I. and Edmondson, A. (2014).	Measuring Teamwork in Health Care Settings.
Winlaw, D., Large, M., Jacobs, J. and Barach, P. (2011).	Leadership, surgeon well-being and non-technical competencies of pediatric cardiac surgery.
Yeung, J., Ong, G., Davies, R., Gao, F. and Perkins, G. (2012).	Factors affecting team leadership skills and their relationship with quality of cardiopulmonary resuscitation
Yule, S. and Paterson-Brown, S. (2012).	Surgeons' Non-technical Skills.

RESULTS

Importance of Leadership and Teamworking for Surgeons

From the technological point of view, surgery is highly complex and is a practice that faces a constantly changing scenario. The surgeon works in the Department of Surgery, often in a specialized unit, and participates with interdisciplinary teams, and develops their daily clinical practice with other specialists and technicians working in different settings (such as operating room, ward) [6]. The primary objective of a surgeon is to provide the best patient care, with greater safety. When required today in most prestigious forums, safe surgery for the patient, it must be remembered that the complications that arise during treatment (about 45% in surgical patients) are rarely the result of the failure of a single individual, but in over 80% of cases they are related to poor planning of patient care systems, or with failures in teamwork [7].

A significant number of studies draw attention to the importance of effective teamwork, which by nature must be interdisciplinary, to get quality treatment over the surgical patient stays. Among them are two: the one entitled "To Err is Human: Building a Safer Health System" [8] published by the Institute of Medicine in 2000, in which the high percentage of errors detected was evaluated in the Health System of the USA and the well-known Kennedy Report in May, which analyzed the very high mortality of pediatric cardiovascular surgery service in Bristol, UK. As a result of the Surgery Quality Improvement Project with which has reduced mortality by a third and two-fifths in morbidity in all the services of surgery [9]. They participated in June. The overall analysis has led to a clear conclusion: the causes of

human errors and their adverse consequences for the patient are deficiencies related to teamwork, as well as the communication between its members.

While the topical figure of an individualist and arrogant surgeon, and even violent with his surgical environment, has already been exceeded, it is not uncommon that surgeons think they work together, when in fact, most do in the group [10]. Team working requires leadership essentially, to ensure that decisions making is done by consensus, analyze the reasons for the disagreements and try to fix them, ensure that the objectives are understood and accepted by the team, encourage all members to contribute their ideas, require the operation of the equipment is periodically reviewed [11]. It can only be made possible by the work of each of its members to appreciate, and finally, that leadership is shared, as necessary. Teamwork is not easy, but with good leadership and proper training of its members in cognitive abilities, and personal relationships, it can be achieved.

The results of recent research, advise that surgical services training programs to develop teamwork in specific tasks (operating room, emergency department, hospital ward), as has already been done, and successfully in other high-risk professions, such as aviation, by applying the methodology called crew resource management (CRM). The key elements of this methodology that can be applied to the work of the surgeons are: the "briefing" (a previous discussion of the action plan), the question between senior member and juniors team of decisions, and take "de-briefing" sessions (understood as the discussion of what happened afterward). Compliance with these requirements can only be achieved in an atmosphere of work and communication between members of a team in which everyone is always willing to learn [12].

The "Non-technical skills for surgeons' project, designed by the University of Aberdeen, has identified several cognitive skills and personal relationships, which must be the essential complement to the expertise of the surgeon, to keep the OR, high levels of quality and safety [13]. These skills include the surgeon's ability to exercise leadership, the state of permanent alert, the ability to take the right decision at all times, and the ability to stimulate communication and teamwork. It is currently available instruments to assess, on stage at the theatre, the teamwork, and skills that are not just technical.

Several studies have shown a relationship between teamwork (surgeons, anesthetists, and instrumentalists) [14], the "performance" and safety in the operating room. It is estimated that up to 1/3 of the duration of the activity in an operating room, communication failures occur in the team. 33% of these failures originate delays, workarounds an unsolved problem ("workaround"), increased environmental stress, unnecessary expense, and disturbance to the patient. A recent study assessed for the first time, the impact that a training course in non-technical skills (CRM methodology) had on the results of two types of surgery, showing that the improvement observed in the teamwork produced the best technical results. These data confirm, albeit in a different field, the results of the multicenter project MedTeams [15], in the US, where the application of CRM in the emergency services model was evaluated and found to a reduction in clinical errors (30.9 to 4.4%) and improved teamwork and attitudes of its members [16]. This is the clearest example of how improved teamwork can avoid complications. It is possible that system-based training, as well as patient simulators that allow the practice of specific behaviors, can avoid the need for real instructors.

However, since efficient teamwork does not arise spontaneously, should be encouraged as soon as possible the development of new hospital culture, for the hospital administration and the Department of Surgery must provide the training tools to help its implementation. But above all, it is essential to have well-trained surgical leaders, able to motivate and change, for the good behavior of team members, with the ultimate goal, to always be the best possible result for the patient. It would be desirable that scientific societies and the NHS itself develop programs similar to the Royal College of Surgeons of England, aimed at the specific training of leaders, and their corresponding surgical equipment, improving, no doubt, patient safety [17].

Leadership in Surgeons

Leadership is one of the most important qualities for a successful surgeon. Surgical outcomes depend critically on a surgical team rather than on an individual; therefore, the role of surgeons is essential for optimal management of patients in a surgical service [18]. There are different kinds of leadership: one who asks the group to follow him, the group encouraged to follow you, or those who are forced to follow. It is important to remember that the most effective leader is using different styles at different times. One should be aware of the strengths and weaknesses in him/her as a leader and recognize what kind of leadership is most often used, as must implement leadership strategies in line with the situation [19].

Several points should be present in every surgeon in assuming the leadership role within a surgical team and in OR [20]:

- One must learn the art of conflict resolution: it is important

to remember that there is a conflict over a point of view and always more of a perception of truth. The surgeon should try to understand each different point and perspective, but it has not always solved them, has to determine the ideal to maintain the cohesion of the group and its mission.

• Role model: is defined as a guide; they are people showing the right path to be followed, through their actions and behaviors. It is a huge responsibility and a great opportunity to demonstrate their attitudes and skills. They can demonstrate such using a suitable treatment with the patient, excellent academic foundation, and good relationships.

• Counsellor: young interns and residents come daily to the surgeon with conflicts, patient care questions, personal problems, etc. In these situations, the surgeon should be a director and confidant. He/she should be affable, confident ear, who can provide advice on mental and physical health for the residents. Also, he/she helps monitor the stress level of the residents.

• It is the right program director to indicate the stress level of the residents; remember the old phrase of "praise in public and criticize in private". Feedback should attentively, timely, and honest, but critical. Compliments are an effective way to encourage positive behavior, academic, interpersonal, and professional effort among residents.

CONCLUSIONS

In conclusion here are some final tips for excellent leadership development for surgeons:

1. Be seen as someone approachable and trustworthy; residents gain a better understanding as people.

2. Time Management: schedule daily activities; new things appear daily, so the surgeon should learn to prioritize the moment they happen.

3. Surgeons must take time for personal growth and professional development.

4. Surgeons must create a relationship with their boss, additional close work with the program director.

Limitations of this Study

Since this is a systematic literature review, therefore, the main limitation of this study is that it lacks primary research. This is a purely secondary research study although the research reviewed in this review does contain primary research evidence.

Also, the author of this review could only conduct searches in only three databases. Another limitation of this review is that it includes studies in English only and therefore studies published in another language have been excluded.

The scope of the review is also limited because it focuses on the leadership skills of surgeons only and does not focus on the leadership skills of other staff in the operating room. Although there are several limitations in this review yet as explained in previous sections the search strategy is comprehensive and systematic which ensures reliability and validity of the results and findings.

Implications of this review

The main implication of this review is for surgeons and students. They can understand the importance of leadership skills and include the development of leadership skills in their development plans.

Besides, the management and administration of hospitals can also benefit from this review and motivate surgeons and other staff to develop leadership skills and ultimately maximize the quality of care and patients' safety in their hospitals.

The review stresses the importance of leadership skills and therefore it recommends that administrations should plan and implement training courses for surgeons and OR staff to enhance their leadership skills.

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ORIGINAL ARTICLES

The effect of Dexmedetomidine on sedation of patients undergoing open-heart surgery in a military hospital

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Abstract: *Background: Dexmedetomidine facilitates patient communication with the ICU nurses, and is a valuable drug for use in patients undergoing mechanical ventilation due to a reduction in the duration of mechanical ventilation and prevalence of delirium.*

Objectives: In this study, investigators aimed to compare the effect of Dexmedetomidine with placebo on sedation in patients undergoing open-heart surgery.

Methods: In this double-blind clinical trial, 69 patients with open-heart surgery who underwent a cardiopulmonary bypass pump, were randomly assigned into two groups of Dexmedetomidine (group D) and placebo (group P). At the end of the operation, patients in groups D and P respectively received 1 µ / kg infusion of Dexmedetomidine and normal saline in 10 minutes. In case of a lack of proper sedation, midazolam with the doses of 1 mg titration was used up to reaching the goal of sedation. Also, for pain relief, morphine titrated at a dose of 1 mg was Injected, and dosage was recorded in both groups. In each shift, patients were examined for delusions by the nurse involved in their care, using the "Confusion Assessment Method for the ICU (CAM-ICU)". For patients with delirium, 1 to 5 mg of Haloperidol was used. Also, the length of stay in the ICU was recorded.

Results: There was no significant difference between the two groups in systolic blood pressure, diastolic blood pressure, and heart rate at different stages of treatment ($p<0.05$). comparison of the two groups in terms of the length of stay in ICU, duration of mechanical ventilation, staff satisfaction, and occurrence of Delirium after surgery indicated that there were significant differences between the two groups ($p<0.05$). There was a significant difference between the two groups in the dose of morphine and midazolam ($p<0.05$).

Conclusion: This study showed that sedation with Dexmedetomidine significantly reduced the incidence of postoperative delirium, the length of stay in ICU, the duration of mechanical ventilation, the satisfaction rate of ICU staff, and the dose of analgesic and sedative medication. As there were no reported hemodynamic complications as well, it seems that it can be indicated as a safe and appropriate drug for sedation of patients in the ICU.

Keywords: *Dexmedetomidine, Intensive care unit, Open heart surgery, sedation*

BACKGROUND

Propofol and Dexmedetomidine are preferred drugs for sedation and short-term sleep in ICU [1]. The use of Dexmedetomidine in ICU has a similar cost and prognosis to Propofol [2]. Dexmedetomidine is a potent and selective agonist of alpha-2 receptors, which has sedative, anxiolytic, and analgesic effects. The effects of sleepy sleep are similar to normal sleep, so patients taking Dexmedetomidine easily

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wake up and cooperate [3]. The rate of respiratory depression is at least [3, 4]; and can be safely used in patients who are not mechanically ventilated [4]. In 2003, the use of Dexmedetomidine was approved by the FDA [3]. Dexmedetomidine is preferable to routine drugs for up to 24 hours for mild to moderate sedation [5] and is easy to use in patients undergoing mechanical ventilation in ICU. It reduces the duration of mechanical ventilation compared to midazolam [6, 7], and the time of extubation compared to midazolam and propofol [5, 6]. The use of Dexmedetomidine alone has led to less anxiety after extubation [7]. Among sedative and analgesic drugs, Dexmedetomidine is a unique drug due to brain protection. Its properties make it possible for ICU patients to be used and reduce the complications of ICU admission, such as cognitive impairment [8]. Sedation by Dexmedetomidine reduces the risk of developing delirium [4, 6, 7, 9], and can even treat delirium [4]. Compared to Propofol, Dexmedetomidine decreases the prevalence and duration of delirium after cardiac surgery in the elderly [10].

Dexmedetomidine facilitates patient communication with ICU nurses [6]. It is a valuable drug for use in patients undergoing mechanical ventilation due to a reduction in the duration of mechanical ventilation, length of stay in the ICU, and prevalence of delirium [11]. However, it is reported that using guidelines to limit the use of Dexmedetomidine is cost-effective [12]. The previous study recommended limiting the dose of Dexmedetomidine to 0.7 µg/kg/hour, the use of bolus fentanyl doses before the onset of infusion of Dexmedetomidine, and the use of certain criteria for non-intubated patients [13].

In this study, the authors aimed to compare the effect of Dexmedetomidine with placebo on sedation in patients undergoing open-heart surgery.

MATERIALS AND METHODS

In this double-blind clinical trial study, 69 patients with open-heart surgery who underwent a cardiopulmonary bypass pump, who were referred to Baqiyatallah Hospital, were randomly assigned into two groups of Dexmedetomidine (group D) and placebo (group P). Emergency patients, patients with liver failure, renal failure, grade 2 or 3 heart block, systolic blood pressure below 90 mmHg, history of neurological and psychiatric illnesses, use of psychiatric drugs, opiate addicts, redo surgery, and patients requiring re-surgery Were excluded.

To induce anesthesia, investigators used fentanyl at a dose of 500-700 µg and diazepam at a dose of 10 mg. To facilitate endotracheal intubation, cisatracurium was used at a dose of 0.15 mg/kg. To maintain anesthesia, infusion of fentanyl, midazolam, and cisatracurium was used and propofol infusion was considered if needed. With the help of TNG and inotropic drugs, systolic blood pressure was maintained in the range of 95 to 115 mmHg. During CPB, blood pressure was maintained at 60 to 80 mmHg and hematocrit between 20 to 22%. When patients found appropriate conditions for acid and base, electrolytes and hematocrit (22% or more), they were separated from the pump.

In group D, at the end of the operation in the operating room, when the patient was completely monitored and mechanically ventilated, patients received 1 µ/kg infusion of Dexmedetomidine in 10 minutes and were transferred to ICU. In ICU, the dose of 0.2 µg/kg/h was used for the initiation, and depending on the patient's need, to achieve Richmond agitation-sedation scale (which was scored from −5 [unresponsive] to +4 [combative], −2 to +1 (lightly sedated to restless)), the dosage was increased up to 0.7 µg/kg/h, Increased. After reaching the extubation condition, the patient was extubated and the dose of Dexmedetomidine was continued to achieve RASS= 0 (calm and alert).

In group P, after the completion of the surgery, a placebo (normal saline) was infused over 10 minutes and the patients were transferred to the ICU. In ICU, placebo infusion continued and the purpose of sedation was reaching to mechanical ventilation, RASS= -2 to + 1, and after extubation, RASS = 0.

For the lack of proper sedation, midazolam with a dose of 1 mg titration was used up to reaching the goal of sedation, and the dosage was recorded. Also, for pain relief, morphine titrated at a dose of 1 mg was Injected, and dosage was recorded in both groups.

The patient was extubated under acceptable conditions in terms of hemodynamics, acid and base, and alertness. The mechanical ventilation period was indicated from the end of the surgery to the extubation of the patient. During the period of mechanical ventilation, continuous monitoring of the vital signs was considered for both groups; and in case of hypotension (systolic blood pressure less than 90 mmHg or 30% reduction in blood pressure relative to the initial pressure) and also in case of bradycardia (heart rate Under 40/min), infusion of the drugs was discontinued, and in the absence of improvement, they were treated with ephedrine at a dose of 10 mg and atropine at a dose of 0.1 mg/kg, respectively.

In each shift, patients were examined for delusions by the nurse involved in their care, using the "Confusion Assessment Method for the ICU (CAM-ICU)". For patients with delirium, 1 to 5 mg of Haloperidol was used. From the

arrival of the patient to the ICU until the discharge from the ICU, it was recorded as the length of stay. At the time of the patient's discharge from the ICU, the satisfaction rate of three of the personnel involved in patient care was assessed using the Visual Analogue Scale (VAS) scoring method. Patients were monitored for ECG, and any new-onset arrhythmia was recorded. Data were gathered by a form including age, sex, type of surgery, CPB time, Cross Clamp time, systolic blood pressure, diastolic blood pressure, and heart rate. Investigators examined the effect of Dexmedetomidine on patients' hemodynamics, delirium, the length of stay in ICU, the duration of mechanical ventilation, and the dose of sedative medications. P-value < 0.05 was considered statistically significant.

Ethical Considerations: This research project was approved by the Ethics Committee of Baqiyatallah University of Medical Sciences (number: IR.BMSU.REC.1398.090 date: 2019-06-25) and it was registered in the Iranian registry of clinical trials (IRCT20161022030421N4). Consent letters were obtained from participants.

RESULTS

In this study, 69 patients in two groups were evaluated consisting of 34 patients in the group D and 35 patients in group P. There was no significant difference between the two groups based on age, sex, and type of surgery (Table 1) (p=0.514, p=0.555, p=0.143 respectively).

Table 1: Demographic and type of surgery base on groups

		Case (N=34)		Control (N=35)		P-Value
		Mean±SD	Min-Max	Mean±SD	Min-Max	
Age		59.8±12.04	21-78	61.6±11.15	38-79	0.514[1]
		N (%)		N (%)		
Gender	Female	15 (44.1)		13 (37.1)		0.555[2]
	Male	19 (55.9)		22 (62.9)		
Type of Surgery	CABG	23 (67.6)		29 (82.9)		0.143[2]
	Valvular	11 (32.4)		6 (17.1)		

1: Independent Sample T-Test; 2: Pearson Chi-Square Test

According to preoperative factors, there was no significant difference between the two groups (Table 2) (p<0.05). CPB time was 59.7±18.87 minutes in group D and 61.6±18.69 minutes in group P and no significant difference was noted (p=610).

Table 2: Comparison of the two groups based on pre-operative factors

		Case (N=34)		Control (N=35)		P-Value
		Mean±SD	Min-Max	Mean±SD	Min-Max	
Clinical factors	Ejection fraction	46.6±8.5	30-60	47.3±8.26	20-55	0.797[1]
		N (%)		N (%)		
	Hypertension	26 (76.5)		25 (71.4)		0.633[3]
	Diabetes mellitus	17 (50)		22 (62.9)		0.281[3]
	Kidney disease	5 (14.7)		3 (8.6)		0.477[4]
	Lung disease	5 (14.7)		9 (25.7)		0.256[3]
	Smoker and Opioid addiction	9 (47.4)		10 (52.6)		0.845[3]

1: Mann-Whitney Test; 2: Independent Sample T-Test; 3: Pearson Chi-Square Test; 4: Fisher Exact Test

Also, Cross Clamp time was 46.8±17.15 minutes in group D and 50.4±19.6 minutes in group P, and no significant difference was shown between groups (p=501). There was no significant difference between the two groups in systolic blood pressure, diastolic blood pressure, and heart rate at different stages of treatment (Tables 3-5) (p<0.05).

Table 3: Comparison of the two groups based on systolic blood pressure (mmHg) in different stages

	Case (N=34)		Control (N=35)		P-Value
	Mean±SD	Min-Max	Mean±SD	Min-Max	
Primary (Before drug)	110.3±18.93	80-161	113.9±21.07	74-175	0.47[1]
During bolus dose infusion	116.2±14.49	80-143	117.8±15.65	92-150	0.669[1]
During mechanical ventilation	118.3±12.9	99-145	116.5±14.41	91-149	0.577[1]
After mechanical ventilation in ICU	118.2±12.01	94-148	120.3±12.6	100-146	0.485[1]

1: Independent Sample T-Test

Table 4: Comparison of the two groups based on diastolic blood pressure (mmHg) in different stages

	Case (N=34)		Control (N=35)		P-Value
	Mean±SD	Min-Max	Mean±SD	Min-Max	
Primary (Before drug)	65.8±13.65	45-99	66.2±15.37	33-101	0.893[1]
During bolus dose infusion	68.5±10.53	51-95	67.8±11.19	50-100	0.789[1]
During mechanical ventilation	67.7±8.78	51-90	66.9±10.23	51-99	0.529[1]
After mechanical ventilation in ICU	66±7.58	53-87	68.5±9.29	51-96	0.198[2]

1: Independent Sample T-Test; 2: Mann-Whitney Test

Table 5: Comparison of the two groups based on heart rate (N) in different stages

	Case (N=34)		Control (N=35)		P-Value
	Mean±SD	Min-Max	Mean±SD	Min-Max	
Primary (Before drug)	83.8±14.43	60-110	88.2±13.83	59-113	0.206[1]
During bolus dose infusion	82.4±14.89	55-108	89.7±17.78	53-138	0.073[1]
During mechanical ventilation	83±16.2	55-118	90.3±15.54	51-126	0.067[1]
After mechanical ventilation in ICU	83±14.04	53-115	90.7±15.49	50-122	0.037[1]

1: Independent Sample T-Test

In terms of the prevalence of delirium after surgery; in group D, 5 patients (14.7%) and group P, 16 patients (45.7%) were delirious and the comparison between the two groups showed a significant difference (p=005).

The duration of mechanical ventilation in group D was 8.2±4.32 hours, and in the group, P was 12.7±3.94 hours. There was a significant difference between groups (p<0.001). Comparison of the two groups regarding the length of stay in ICU showed that in group D, length of stay in the ICU was 3.2±0.48 hours and in the group, P was 3.8±0.65 hours, and the difference was significant (p<0.001).

The satisfaction rate of three nurses involved in patient care showed that the VAS score was 9.2±1.2 in group D and 6.9±1.77 in group P and a significant difference was noted (p<0.001).

Regarding the opioid dose in the two groups: The mean dose of morphine in the D group was 1.18±2.7 mg (Min-Max 0-13) and in the P group 8.5±4.12 mg (Min-Max 0-15), with a significant difference between the two groups (p=0.001). Comparison of the dose of the sedative drug in the two groups: The mean dose of midazolam in the D group was 1.5±2.75 mg (Min-Max 0-13) and in the P group 3.7±3.88 mg

(Min-Max 0-13), the difference between the two groups being significant (p=0.004). New-onset atrial fibrillation occurred in one patient in group D, and four patients in group P.

DISCUSSIONS

In this study, investigators evaluated patients undergoing open-heart surgery and transferred to intensive care units with mechanical ventilation, in two groups of Dexmedetomidine and placebo. There was no significant difference in systolic and diastolic blood pressure and heart rate between the two groups at different stages. Mechanical ventilation time and length of stay in ICU in the Dexmedetomidine group were significantly reduced. The prevalence of delirium in group D was also significantly decreased. The satisfaction of ICU nurses was significantly higher in group D. Patients in group D required significantly lower doses of morphine and midazolam. New-onset atrial fibrillation occurred in one patient in group D and four patients in group P.

Fish and colleagues implemented an updated sedation and analgesia guideline, which was provided by the community of critical care medicines (SCCM) on their patients. They compared the prognosis of the patients, one to five years after the implementation of the protocol, with one year before proceeding with the protocol. Their protocols included 1 - Using a bolus dose of analgesic and sedative medicine before starting the continuous infusion; 2 - Using concomitant sedatives and analgesics; 3 - Using Propofol and Dexmedetomidine instead of midazolam, when needing the continuous infusion of sedative, and 4 - measuring pain in patients in the intensive care unit. They concluded that with this guideline, the duration of mechanical ventilation, the length of stay in the ICU, and the duration of admission to the hospital were decreased, without any increase in mortality. It was also economically feasible [14].

Diaz and colleagues at Northwest Hospital assessed patients taking Dexmedetomidine. The evaluation data included the primary diagnosis of the disease, the indication of the use of Dexmedetomidine, the duration of treatment, the number of consumed needs, the infusion rate, the recorded CAM-ICU score, the amount of Propofol, opiate and the benzodiazepine supplement, the length of stay in the ICU and the duration of staying in the hospital. They appropriately prescribed Dexmedetomidine for all patients admitted to ICU and had CAM-ICU and RASS in over 92% of patients. Their goal was to achieve light sedation; the dose was not higher than 1.2 µg/kg/hour, and the inappropriate use of the drug was longer than 48 hours when the Propofol was used simultaneously [15].

Furthermore, Elzohry and colleagues used Dexmedetomidine alone to induce anesthesia in the endoscopy of the gastro-intestinal tract with bolus dosage of one microgram per kilogram and then 0.8 micrograms per kilogram per hour, concluding that, this drug can provide adequate analgesia and sedation, with rapid onset and rapid recovery in these patients, and the occurrence of complications such as bradycardia and hypotension was not serious and could be controlled [16].

Previous studies [1, 14, 15] were the confidence point for the current study to use this drug with a dose of 1 µg/kg for patients transferred to the ICU, and the results of the study showed that using Dexmedetomidine at this dose was not associated with hemodynamic disorders and had no adverse effects.

Morelli and colleagues in a cross-over study in patients with septic shock treated patients with Propofol, switched Propofol to Dexmedetomidine for 4 hours and re-set Propofel for 8 hours, and evaluated the degree of sedation and the dose of Norepinephrine at the end of these hours. They concluded that changing the drug from Propofol to Dexmedetomidine would reduce the dose of norepinephrine in patients with septic shock [17].

The same with the current study, Morelli, and colleagues addressed anxiety in using this drug. However, when it was used in patients with septic shock without complications, it seems that it can be used with less concern in ICU patients.

Guo and his colleagues assessed the patients undergoing mechanical ventilation randomly in two groups. In the control group, the sedation score was, 3 to -4 (RASS, 3 to -4), and in the intervention group, the sedation score was, 0 to -1 (RASS, 0 to -1) (that is, the condition that the patient was awake, be comfortable and collaborative). They concluded that in the intervention group, the duration of mechanical ventilation and the length of stay in the ICU was shorter, the prevalence of pneumonia due to mechanical ventilation, and delirium was lower, and the dose of sedative medication decreased [18].

In the current study, investigators attempted to put the patient's sedation around, -2 to +1 RASS and did not have any complications at this level. In a study on 498 non-surgical and surgical patients admitted to the ICU, Schrader and colleagues examined two Propofol and Dexmedetomidine drugs for hemodynamic disorders. For the first time, hemodynamic instability and frequency of hemodynamic instability were the benchmarks for comparing two drugs. They concluded that hemodynamic instability did not differ significantly between the two groups of Propofol and Dexmedetomidine in terms of duration and frequency [19].

This study, consistent with all of the studies mentioned, demonstrated the safety and the appropriateness of the use of Dexmedetomidine for the sedation of patients in the intensive care unit. In confirming Baylon's study, Dexmedetomidine should probably be a counterpart to sedative medications, especially in patients admitted to ICU [20].

In a retrospective study, Brianna Thompson and colleagues compared the effects of Propofol and Dexmedetomidine on the incidence of atrial fibrillation after cardiac surgery. They noted no significant difference in the prevalence of atrial fibrillation between the two groups because of the significant difference in prophylactic use of amiodarone [21]. In the current study, new atrial fibrillation occurred in one patient in the sample group and four patients in the control group in the ICU. Therefore, more research is needed to assess the effect of Dexmedetomidine in the prevention of new-onset arrhythmia.

CONCLUSION

This study showed that sedation with Dexmedetomidine significantly reduced the incidence of postoperative delirium, length of stay in ICU, duration of mechanical ventilation, the satisfaction rate of ICU staff, and the dose of sedative medication. As there were no reported hemodynamic complications as well, it seems that it can be indicated as a safe and appropriate drug for sedation of patients in the ICU.

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ORIGINAL ARTICLES

The assessment of the vitamin D deficiency between the patients with acute coronary syndrome and those with stable coronary artery disease in a military hospital

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Abstract: *Background: A few studies compared the vitamin D deficiency condition between the patients with the acute coronary syndrome (ACS) and those with stable coronary artery disease. The present comparative study aimed to assess the vitamin D deficiency status between the patients with ACS and those with stable coronary artery disease.*

Methods: This cross-sectional study was performed on 200 consecutive patients with the diagnosis of ACS or stable coronary artery disease. Serum Vitamin D level was measured by immunoassay and its serum level was categorized as normal (> 30 ng/ml), insufficient (20 to 30 ng/ml), and deficient (< 20 ng/ml).

Results: Overall, 103 patients were categorized as stable angina group, 74 had unstable angina, 10 had STEMI, and 13 had NSTEMI. There was no difference in serum vitamin D3 level across the four groups including stable angina group (13.81 ± 15.13 ng/ml), unstable angina group (15.13 ± 11.11 ng/ml), STEMI group (21.58 ± 19.87 ng/ml), and NSTEMI group (18.67 ± 13.07 ng/ml) (p = 0.276). No difference was also found in the mean vitamin D3 level between the groups with new MI (15.98 ± 12.44 ng/ml versus 14.01 ± 15.31 ng/ml, p = 0.318). In total, 8.5% had normal vitamin D levels and 9.0% had vitamin D insufficiency, while the majority of patients (82.5%) were vitamin D deficient. The vitamin D deficiency was comparable in the patients with stable angina compared to those in ACS groups. According to ROC curve analysis, measuring serum vitamin D3 had a moderate value to discriminate stable angina from ACS (AUC = 0.651). In this regard, the best cutoff point for serum vitamin D3 level to discriminate stable angina from ACS was 9.0 ng/ml yielding a sensitivity of 70.1% and a specificity of 57.3%.

Conclusion: The measurement of vitamin D and thus the presence of vitamin D deficiency have no sufficient power to discriminate ACS from stable coronary artery disease.

Keywords: *vitamin D deficiency, coronary syndrome, artery disease*

INTRODUCTION

Acute coronary syndrome (ACS) has been now known as the major cause of death whole of the world, especially in industrial countries. Potentially, the presence of various genetic, metabolic, and environmental risk factors can increase the risk for mortality and disability in affected patients [1]. In this regard, some metabolic and endocrinological factors have been identified to link the progression and severity of coronary artery disease (CAD). Within the last few years, a significant association between deficiency of some vitamins and minerals and CAD has been found [2-4]. In this regard, an association of vitamin D deficiency and different cardiovascular risk factors and

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diseases has been extensively evaluated. Some prospective and observational studies have addressed the possible linkage of vitamin D deficiency and the development of CAD and its risk factors [5, 6]. Thus, vitamin D deficiency not only has a major role in bone metabolism, homeostasis regulation, and immune pathways, but also the presence of vitamin D receptors on cardiomyocytes, endothelial cells, and vascular smooth muscle cells suggests the role of vitamin D in vitamin D-mediated cardiovascular system [7-9]. It has been shown that cardiac muscle functioning depends on the circulating blood concentration of calcitriol [10]. Calcitriol affects the growth, proliferation, and morphology of murine cardiomyocytes. In detail, treatment with calcitriol increased the expression of the cardiac muscle protein myotrophin. The link between vitamin D deficiency and cardiovascular risk factors has been also shown [11]. According to the Framingham Offspring Study [5], individuals with low activated vitamin D faced more with incident cardiovascular disease such as myocardial infarction, coronary insufficiency, and heart failure compared to those with a normal level of vitamin D. Thus, treatment with vitamin D supplementation could reduce cardiovascular death and length of hospitalization in ACS patients; however, a few studies compared the vitamin D deficiency condition between the patients with ACS and those with stable coronary artery disease. The present comparative study aimed to assess the vitamin D deficiency status between the patients with ACS and those with stable coronary artery disease.

METHODS

This cross-sectional study was performed on 200 consecutive patients with the diagnosis of ACS or stable coronary artery disease. The ACS was diagnosed according to the ACS criteria defined based on clinical symptoms, ECG changes, and cardiac enzyme rising. Stable coronary artery disease was defined as typical exertional chest pain relieved by rest or nitroglycerin administration and a positive exertional ECG test. The exclusion criteria were history of surgery within 6 months ago or having a hematologic disease or any hemoglobinopathy or coagulopathy, history of chronic clinical conditions such as liver or kidney disease or malignancies, or history of cerebrovascular disease or other simultaneous cardiovascular disorders.

Baseline characteristics and clinical data of participants including demographics, anthropometric parameters (weight, height, and body mass index), cardiovascular risk factors (current smoking, hypertension, hyperlipidemia, and opium addiction) as well as laboratory parameters (fasting blood sugar, hemoglobin A1c, lipid profile, thyroid functional hormones, and serum creatinine) were collected from the hospital recorded files. Serum Vitamin D level was measured by immunoassay and its serum level was categorized as normal (> 30 ng/ml), insufficient (20 to 30 ng/ml), and deficient (< 20 ng/ml). The primary endpoint was to assess the relation between the type of ACS and the severity of vitamin D deficiency. The secondary endpoint was to determine the best cutoff point for vitamin D to differentiate ACS from stable coronary artery conditions. The ethical committee of Kerman University of Medical Sciences approved the study research proposal all procedures were in accord with the standards of the World Medical Association Declaration of Helsinki for research involving human subjects. Informed consent was obtained from all study participants.

Results were presented as mean ± standard deviation (SD) for quantitative variables and were summarized by absolute frequencies and percentages for categorical variables. Continuous variables were compared using t, and one-way ANOVA tests, or non-parametric Mann-Whitney U, or Kruskal-Wallis tests whenever the data did not appear to have normal distribution or when the assumption of equal variances was violated across the groups. The ROC curve analysis was also used to determine the value of vitamin D measurement to predict the presence of ACS and also to determine the best cutoff value of this vitamin to discriminate ACS from stable angina. For the statistical analysis, the statistical software SPSS version 16.0 for windows (SPSS Inc., Chicago, IL) was used. P values of 0.05 or less were considered statistically significant.

RESULTS

Overall, 103 patients were categorized as stable angina group, 74 had unstable angina, 10 had STEMI, and 13 had NSTEMI. Comparing baseline characteristics and clinical data (Table 1) across the groups showed that the patients with stable angina were older than the patients in other groups.

Also, hypertension was more frequent in those with STEMI, while hyperlipidemia was more prevalent in those with stable angina. Family history of CAD was found less and opium addiction was revealed more in the NSTEMI group when compared to other groups. Statin use, aspirin use as well as the history of prior PCI was all more in a group with stable angina than in other groups, while prior CABG was scheduled more in the NSTEMI group.

Meanwhile, there was no difference across the four groups in terms of gender, mean BMI, history of diabetes, smoking, alcohol use, thyroid dysfunction, prior SK use, and left ventricular dysfunction.

Table 1: Baseline characteristics and clinical data of study population

	Stable angina (N = 103)	Unstable angina (N = 74)	STEMI (N = 10)	NSTEMI (N = 13)	P-value
Male gender	60 (58.3)	46 (62.2)	7 (70.0)	10 (76.9)	0.555
Age, year	64.29 ± 8.85	59.92 ± 11.25	60.70 ± 12.09	61.92 ± 8.78	0.058
BMI, kg/m^2	27.92 ± 3.82	27.54 ± 2.93	26.43 ± 2.31	26.45 ± 3.94	0.333
Hypertension	87 (84.5)	46 (62.2)	10 (100)	9 (69.2)	0.002
Diabetes	34 (33.0)	33 (45.6)	5 (50.0)	6 (46.2)	0.480
Hyperlipidemia	96 (93.2)	17 (23.0)	0 (0.0)	3 (23.1)	< 0.001
Family history	44 (42.7)	31 (41.9)	4 (40.0)	3 (23.1)	0.035
Smoking	29 (28.2)	12 (16.2)	2 (20.0)	2 (15.4)	0.260
Opium use	7 (6.8)	5 (6.8)	1 (10.0)	2 (15.4)	0.033
Alcohol use	9 (8.7)	2 (2.7)	0 (0.0)	0 (0.0)	0.210
Hyperthyroidism	3 (2.9)	1 (1.4)	0 (0.0)	0 (0.0)	0.963
Hypothyroidism	7 (6.8)	1 (1.4)	0 (0.0)	0 (0.0)	0.611
CCU admission	69 (67.0)	29 (39.2)	5 (50.0)	5 (38.5)	0.011
Statin use	99 (96.1)	56 (75.7)	7 (70.0)	9 (69.2)	< 0.001
Aspirin use	90 (87.4)	53 (71.6)	8 (80.0)	9 (69.2)	0.023
NSAIDS use	2 (1.9)	2 (2.7)	0 (0.0)	0 (0.0)	0.883
Prior PCI	96 (93.2)	15 (20.3)	1 (10.0)	3 (23.1)	< 0.001
Prior SK receive	11 (10.7)	3 (4.1)	1 (10.0)	0 (0.0)	0.475
Prior CABG	3 (2.9)	13 (17.6)	3 (30.0)	2 (15.4)	0.013
LVEF	48.99 ± 8.18	47.58 ± 10.46	44.80 ± 10.29	43.85 ± 5.67	0.152

Regarding laboratory parameters (Table 2), mean serum FBS was significantly lower in the group with stable angina, while serum HDL level was higher among those with stable angina than other patients. The highest liver enzymes were revealed in those with STEMI. The patients with stable angina had a significantly higher level of T3 than other ones.

Table 2: Baseline laboratory indices in the study population

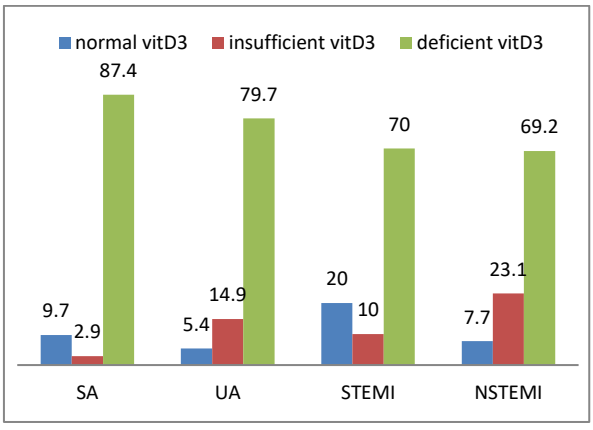
	Stable angina	Unstable angina	STEMI	NSTEMI	P-value
Hemoglobin	14.77 ± 2.89	13.89 ± 1.60	14.73 ± 1.12	14.16 ± 2.20	0.106
Hematocrit	48.61 ± 36.91	40.85 ± 4.46	41.78 ± 3.46	41.09 ± 6.48	0.258
Platelet	226.21 ± 65.72	218.84 ± 58.57	195.70 ± 48.04	223.54 ± 73.51	0.495
ESR	15.17 ± 6.46	16.14 ± 15.67	13.10 ± 7.56	14.69 ± 15.00	0.848
CRP	0.97 ± 8.36	0.32 ± 0.47	0.50 ± 0.52	0.62 ± 0.51	0.918
FBS	115.27 ± 36.98	143.47 ± 61.22	170.70 ± 68.86	166.85 ± 71.98	< 0.001
Creatinine	3.25 ± 14.27	1.33 ± 0.97	1.14 ± 0.21	1.19 ± 0.20	0.613
Uric acid	7.83 ± 11.78	5.59 ± 1.93	4.74 ± 1.44	6.45 ± 2.09	0.317
Triglyceride	157.69 ± 71.86	148.07 ± 86.70	137.50 ± 68.42	105.87 ± 93.43	0.153
Cholesterol	183.37 ± 50.72	171.80 ± 52.83	170.10 ± 40.04	170.23 ± 50.33	0.433
LDL	98.46 ± 30.33	105.40 ± 42.09	100.34 ± 25.09	105.91 ± 42.84	0.609
HDL	46.43 ± 30.16	36.38 ± 8.52	36.90 ± 7.91	34.54 ± 10.22	0.018
AST	21.36 ± 7.96	24.38 ± 19.29	65.40 ± 42.45	34.38 ± 26.31	< 0.001

	Stable angina	Unstable angina	STEMI	NSTEMI	P-value
ALT	26.89 ± 17.69	28.46 ± 24.30	52.00 ± 33.04	34.46 ± 22.99	0.005
ALKP	181.25 ± 73.84	185.70 ± 60.70	170.40 ± 30.67	225.92 ± 79.55	0.144
Calcium	13.56 ± 19.05	8.98 ±0.61	8.86 ± 0.33	9.16 ± 0.47	0.141
Phosphorus	4.16 ± 1.25	3.99 ± 0.58	3.38 ± 0.71	3.83 ± 0.72	0.091
PTH	30.48 ± 30.51	47.81 ± 21.74	43.29 ± 11.42	49.96 ± 15.40	0.227
T3	2.99 ± 3.86	0.89 ± 0.97	0.70 ± 0.14	0.68 ± 0.17	< 0.001
T4	45.44 ± 47.98	62.71 ± 19.19	65.74 ± 11.80	61.28 ± 11.44	0.102
TSH	4.19 ± 14.30	2.64 ± 4.32	2.14 ± 1.59	1.62 ± 1.18	0.698
HbA1C	6.33 ± 1.36	14.88 ± 70.03	7.99 ± 2.01	7.61 ± 2.63	0.622

There was no difference in serum vitamin D3 level across the four groups including stable angina group (13.81 ± 15.13 ng/ml), unstable angina group (15.13 ± 11.11 ng/ml), STEMI group (21.58 ± 19.87 ng/ml), and NSTEMI group (18.67 ± 13.07 ng/ml) (p = 0.276). No difference was also found in the mean vitamin D3 level between the groups with new MI (15.98 ± 12.44 ng/ml versus 14.01 ± 15.31 ng/ml, p = 0.318).

In total, 8.5% had normal vitamin D levels and 9.0% had vitamin D insufficiency, while the majority of patients (82.5%) were vitamin D deficient. As shown in Figure 1, the vitamin D deficiency was comparable in the patients with stable angina compared to those in other ACS groups (p = 0.338). However, vitamin D deficiency was more prevalent in the old MI group compared to the new MI group (87.0% versus 78.0%, p = 0.011).

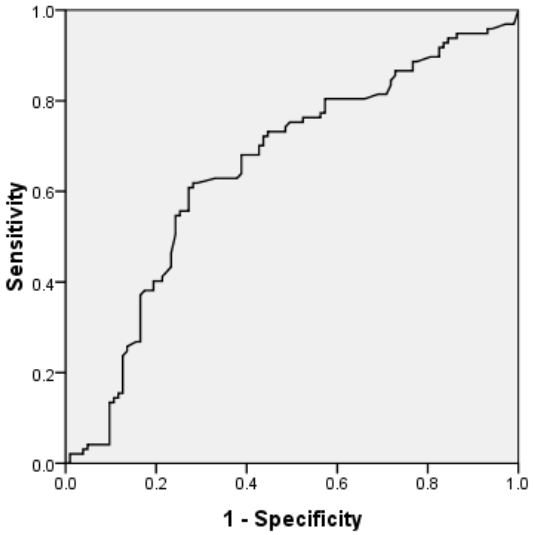
Figure 1: Vitamin D deficiency in ACS subgroups



The level of vitamin D was similar in the patients with and without hypertension (15.04 ± 14.56 ng/ml versus 14.88 ± 11.93 ng/ml, p = 0.9450), the groups with and without diabetes mellitus (13.46 ± 4.17 ng/ml versus 15.35 ± 15.08 ng/ml, p = 0.760), and those with and without hypertriglyceridemia (13.29 ± 4.02 ng/ml versus 15.03 ± 12.49 ng/ml, p = 0.714).

According to ROC curve analysis, measuring serum vitamin D3 had a moderate value to discriminate stable angina from ACS (AUC = 0.651, 95% CI: 0.573 – 0.728, P < 0.001) (Figure 2). In this regard, the best cutoff point for serum vitamin D3 level to discriminate stable angina from ACS was 9.0 ng/ml yielding a sensitivity of 70.1% and a specificity of 57.3%.

Figure 2: ROC curve analysis to determine the value of vitamin D level to discriminate stable angina from ACS



Diagonal segments are produced by ties.

DISCUSSIONS

There is modest evidence that lower vitamin D levels are associated with an increased risk of CAD. However, few studies have researched CAD as a separate disease entity from cardiovascular disease. It has been now suggested that people with low vitamin D levels had twice the risk of developing a heart attack compared to those with adequate vitamin D levels, but it has remained uncertain the effect of vitamin D levels on CAD risk particularly in variant angina.

Hence, we attempted to compare the value of vitamin D measurement and thus vitamin D deficiency in differentiating stable coronary conditions from ACS variants. In this regard, we could demonstrate a similar incidence of vitamin D deficiency in stable coronary arteries and those without this condition. Even, using ROC curve analysis, it was shown that the measuring vitamin D level could discriminate stable coronary involvement and ACS variants with moderate power. However, a higher incidence of vitamin D3 might be predicted in those with old MI than in patients that newly suffered MI. In a study by Raina et al [12] in India, it was suggested a significant correlation between vitamin D deficiency and chronic stable angina. In India, results similar to the pointed were seen by Sanjeev Kumar et al. [13] who studied 100 patients undergoing CAG. They found that the mean 25(OH) D level was 14.8 ng/mL; vitamin D deficiency was present in 80% and only 7% had an optimal 25(OH) D level that was near to our result. More interestingly, another study that divided 2910 patients with coronary artery disease history (acute myocardial infarction – unstable angina – stable angina) into three groups based on their angiography results showed that although vitamin D deficiency is prevalent in all groups, it is more prevalent in patients with stable angina and also it is indicative of a worse prognosis [14] that was numerically near to our results.

The similarity in incidence of vitamin D deficiency in our study subgroups may be due to this fact that the majority of patients included into the study had vitamin D deficiency so 82.5% were vitamin D deficient that is a considerable finding. Another reason for the insignificant association between vitamin D level and the ACS variants could be related to no significant association between the level of vitamin D and various cardiovascular risk subgroups. As we assessed this association, the level of vitamin D was similar in cardiovascular risk subgroups. In fact, because of a probable causative relation between cardiovascular risk factors and vitamin D deficiency, our finding can be explained. Another reason for paradoxical results across the studies may be due to the different cutoff points for defining vitamin D deficiency. During a Framingham–Off spring study on 1739 participants who were followed up within 5.4 years Wang and colleagues [15] revealed that vitamin D deficiency is associated with cardiovascular disease. However in the mentioned study levels < 15 ng/ml were considered as vitamin D deficiency. Also, in Siadat et al study [16], it was considered levels lower than 30 ng/ml as vitamin D deficiency, while in our study, vitamin D deficiency was defined as the levels of lower than 20 30 ng/ml.

It seems that the effect of vitamin D on cardiovascular risk can be mediated by some mechanisms including reduction of the risk for underlying metabolic disorders such as diabetes and high blood pressure, lowering the thickening of the arterial walls, reduces the risk of respiratory infections, suppression of inflammatory pathways, and reduction the risk of arterial calcification or hardening [17-21]. Furthermore, some studies are indicative of a relation between vitamin D deficiency and cardiovascular disease, increased blood pressure, increased insulin resistance, heart failure, and fatal strokes [22-26] that can explain the association between CAD risk and vitamin D deficiency; however, this association was not proved in our study population.

As a new result, the best cutoff value for differentiating stable angina from ACS conditions was 9.0 that considerably lower than the cutoff values defined for vitamin D deficiency. We could not find a similar study on determining the best cutoff values for vitamin D to predict stable angina and thus the obtained result on this subject should be more assessed in further studies.

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ORIGINAL ARTICLES

An organizational chart of an Emergency Health Operation Center

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Abstract: *Nowadays, a wide range of natural and man-made disasters, disease outbreaks and pandemics give rise to health emergencies at a global level. Thus, a health security strategy is urgently required through central planning. At the national level, that vision can be implemented with a properly organized and fully functional Emergency Health Operation Center (EHOC). The main executive sections of an EHOC are Command, Planning, Operations, Logistics, Administration, Communications/Intelligence, and Reporting/Briefing. Each of the above sections has several functions and sub-functions, all operating according to a concrete legal basis and detailed operating procedures.*

Keywords: *emergency planning, public health, operation center, health crisis*

INTRODUCTION

In our epoch, due to the extreme complexity of the modern age, natural and man-made threats the management of health crises should imply an effective and integrated action plan, qualified with characteristics that define the effectiveness and success of such a system. An EHOC is such a system that can lead and coordinate the overall national medical response in every emergency incident, especially when involving mass casualties that either exceeds the management capabilities of the nation's health mechanism or disorganize the existing procedures planned for routine conditions. A successful EHOC should be based on two pillars: Legal authority and organizational structure; both will be herein briefly discussed.

DISCUSSION

Legal authority

The legal authority of an EHOC refers to the development of a concrete legislation directive for the public health authorities as regards roles, responsibilities, and coordination with national disaster management resources for legal health operations. That legislation should establish policy guidance, officials of the government and involved organizations, and other executive officers and professionals tasked to provide leadership at a strategic level. The legal authority of an EHOC varies among countries, while the key governmental agencies usually involved are unfortunately often scattered in various Ministries. The long list of those national agencies includes, but is not limited to the following: Fire Brigade; Police; Ministry of National Defence; Coast Guard; Ministry of Transport and Communications; Civil Airlines; Medical School Laboratories; National Public Health Organization; National Center for Emergency Assistance (NCEA); Hospital units (public and private); National Atomic Energy Committee; Forensic Services; Ministry of Foreign Affairs; Non-governmental healthcare and humanitarian responders [1]. The concomitant spread of leadership centers combined with defective multi-ministerial coordination has been proved devastatingly ineffective in the last decades in many environmental or man-made disasters throughout the world. Hence, an EHOC

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must be set under a unified command, a sort of an all-hazard ministry or deputy ministry "of Interior Threats", or "of Civil Protection"; that Ministry can substitute roles, authorities, personnel, and infrastructure of other Ministries and also replace at the highest level both the GSCP and all sorts of emergency committees, mechanisms and operation centers of other Ministries.

Organizational structure

An EHOC should operate within the framework of a thoroughly planned national incident management system, with dedicated personnel and a consolidated operational terminology. Organizational prerequisites for such a system are described in detail in relative handbooks [2-4] and involve at minimum the following executive sections:

1. Command
2. Planning
3. Operations
4. Logistics
5. Administration
6. Communications/Intelligence
7. Reporting/Briefing

The function of an EHOC should be based on competent personnel and equipment installed in a capacious building, consisting of at least an operation-command room, a communication room, and a multipurpose meeting room. The operational doctrine of an EHOC is based on the C4-I principle, i.e. Command – Control – Communication – Coordination – Intelligence. These procedures are prioritized for the planning and response to potential public health risks, albeit they do not replace the daily operational control of resources and services. The goal of C4-I is operational cross-disciplinary coordination at the regional, national and international level and is an integral part of the Concept of Health Operations [5]. Each of the above sections has several functions and sub-functions, (data illustrated in Figure 1), operating according to relevant response actions, called Standard Operating Procedures (SOPs), as described below:

1. Command Section: The EHOC director exerts ex officio the vertical, unified command. He/she is a senior medical officer, with documented expertise in the field of Health Crises and with vast experience in managing complex health operations. The EHOC director will be subordinated to the GSCP and will be supported at his command by a deputy director. Two branches are straight subordinated to the EHOC director:

a) A *Legal Operations Unit* (LOU), staffed by dedicated legal advisers, supports the EHOC leader in taking complicated decisions without unacceptably high legal risks (mainly in emergencies, when some regulations of normal life might need to be temporarily revised or suspended for EHOC operations to be carried out).

b) The *Ancillary Services Unit* (ASU), a supportive bundle of services. Apart from full secretarial support, that unit covers personnel's health, safety and security, cleaning, and janitorial affairs of buildings.

Apart from managing, coordinating, and collaborating skills, the EHOC director must be able to set and follow priorities and optimize results based on available resources. A thorough presentation of the required qualifications of an EHOC director is described by Efstathiou et al [6]. The EHOC director is responsible for the following specific functions:

- The overall operational function and legal responsibility of the EHOC.

- The application of effective command systems, which clearly define roles and responsibilities for all EHOC staff.

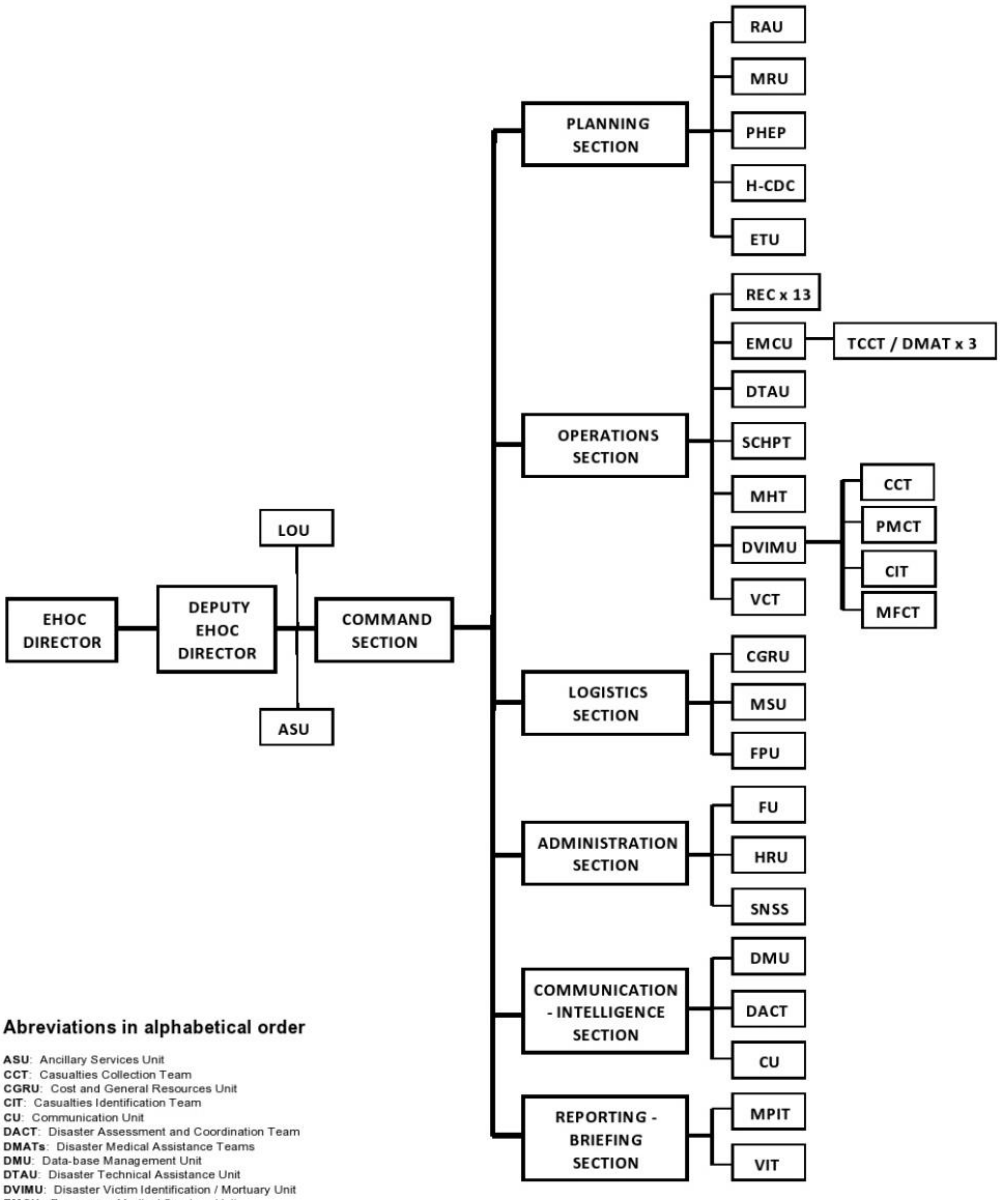
- The final responsibility for verification of any possible health event, mobilization of the national mechanism, and information of government. That highly demanding decision is accomplished through the systematic gathering of relevant information from various sources, such as operational contacts, expert networks, printed reports, and media information.

- The coordination (called "interoperability") among EHOC's sections and also between EHOC as a concrete system and any participant organization, including local and private agencies, when a major health incident/operation takes place. As major participants, apart from the national agencies are considered the following international stakeholders:

- Center for Disease Control and Prevention (CDC), with worldwide action; a European-CDC, as well as national CDCs also exist (Planning Section, bellow).
- Monitoring and Information Center (MIC): The operational heart of the United Nations Health Security Committee; mobilizes international aid for mass disaster incidents.
- World Health Organization (WHO): Provides the ultimate health assistance worldwide.
- North Atlantic Treaty Organization (NATO): An intergovernmental military alliance, also providing some specific health standardization agreements (STANAGs).

2. Planning Section: It emphasizes coordination, interoperability, and cooperative team working through relevant SOPs, with the following branches and sub-functions:

Figure 1: Organizational structure of an EHOC



Abreviations in alphabetical order

ASU: Ancillary Services Unit
CCT: Casualties Collection Team
CGRU: Cost and General Resources Unit
CIT: Casualties Identification Team
CU: Communication Unit
DACT: Disaster Assessment and Coordination Team
DMATs: Disaster Medical Assistance Teams
DMU: Data-base Management Unit
DTAU: Disaster Technical Assistance Unit
DVIMU: Disaster Victim Identification / Mortuary Unit
EMCU: Emergency Medical Services Unit
ETU: Exercises and Training Unit
FPU: Food Provisions Unit
FU: Facility Unit
H-CDC: Hellenic Disease Control and Prevention Unit
HRU: Human Resources Unit
LOU: Legal Operations Unit
MFCT: Mass Fatality Care Team
MHT: Mental Health Team
MPIT: Media and Public Information Team
MRU: Medical Resource Unit
MSU: Medical Supplies Unit
PHEP: Public Health Emergency Response Planning Unit
PMCT: Post-mortem data Collection Team
RAU: Risk Assessment Unit
RECs: Regional Emergency Coordinators
SCHPT: Shelter Care and Humanitarian Priorities Team
SNSS: Strategic National Sanitary Stockpile
TCCTs: Trauma and Critical Care Teams
VCT: Veterinary Care Team
VIT: Victim Information Team

a) *Risk Assessment Unit* (RAU); as a component of a comprehensive risk management program, RAU conducts hazard-specific vulnerability analyses according to the following flow-chart: Information gathering – data analysis – assessment – prioritization of actions – follow up of resultant outcome.

b) *Medical Resource Unit* (MRU); it predicts the local needs

in medical resources, supervises hospital operation in emergency status, and registers medical devices, pharmaceutical stock, beds and bedding, laboratory capabilities, supplies and reserves, personal safety equipment, bio-safety facilities, etc.

c) *Public Health Emergency Planning Unit* (PHEP); it devises hazard generated procedures, priorities and risks, preparedness programs, and all relevant SOPs, both hazard- and response-specific, in a form of an operation manual or handbook. Expected activities are described in flow-chart diagrams and regard all actions to take place from the first hour up to several weeks after the incident. Such SOPs exist for all levels of response and describe, among others, personnel, equipment, supplies and also define operational time points. In their standard form, SOPs include a basic plan describing current legislation, operational phases, and appendices describing incident functions, response specific and deactivation plans, checklists, templates, job cards, resources, and relevant literature [7].

d) *Disease Control and Prevention Unit* (CDC); the national link to the European-CDC.

e) *Exercises and Training Unit* (ETU) for continuous and efficient training of the EHOC staff according to international standards [8]; ETU also conducts preparatory planning for future emergency response scenarios, reviews existing national and international regulations, frameworks, and planning guidelines, and organizes periodically full-scale exercises on a realistic base. A final goal for ETU is an overall improvement of awareness, competence, operational readiness, and continuous updating of plans and procedures.

3. Operations Section: The cardinal EHOC branch comprises preparedness and response activities provided by trained personnel capable of responding within two hours after identification of a major health incident. Specific SOPs are:

- Gathering and analyzing all relevant pieces of information.
- Stepwise analysis and evaluation of all factors affecting the mission; in these are included not only medical factors but also general ones (environment, weather conditions, available time, humanitarian implications, cooperation reluctance or conflict of interest among various public and private participants, staff security, etc).
- Consideration of all alternative case-based actions; that is called mitigation, i.e. threat/hazard/disease-specific, on occasion, actions to minimize health-related impact after hazard occurrence.
- Activation of preparedness levels, from Level 3 (lowest) up to Level 1 (highest), according to the existing situation after interaction with bio-surveillance laboratories network and with the national response framework given by GSCP. The preparedness SOPs include a detailed and continuously updated catalog of involved personnel, methods of fast recall on a 24h/7d basis, key-persons, and all other necessary details of an early warning protocol.
- Flexibility, surge capacity, i.e. ability to respond in multiple emergency health incidents, surge capability, i.e. ability to cope with unusual/special medical needs, and adequate durability, i.e. long-lasting response [9].
- Close collaboration and engagement with scientific entities in strategic preparedness and tactical operations, such as associates from the academic world, seismologists, meteorologists, building engineers, forensic scientists, laboratory experts, anthropologists, epidemiologists, etc.
- Linkage and integration of healthcare volunteers, non-governmental organizations, and major humanitarian responders, e.g. Red Cross.
- Recovery actions at multiple levels, which restore the stricken environment to as close to former “normal” status after a major health incident.
- Promotion of environmental health, social engagement, mobilization, and solidarity of the community.

Hence, according to the above functions the Health Operations Section acts in the following response stages: Incident recognition – Notification – Activation – Mobilization – Operations – Demobilization - Transition to recovery. The Operations Section is divided into several branches [9], as follows:

a) *Regional Emergency Coordinators* (RECs), acting as operational liaisons between central EHOC and the corresponding regional departments of Civil Protection for each of the administrative districts of the nation’s territory; for each REC there should be established a mobile (in a vehicle) operation center with satellite intercommunication with the regional Civil Protection liaison.

b) An *Emergency Medical Services Unit* (EMCU); which is a field-level rapid deployment medical force subdivided into three (3) Trauma and Critical Care Teams (TCCTs). Depending on the incident, these teams can be reorganized in equipment and staffing to Disaster Medical Assistance Teams (DMATs) [10]. DMATs provide primary and acute care, triage of mass casualties, initial resuscitation and stabilization, advanced life support, and preparation of sick or injured for evacuation. All victims are managed by use of the internationally standardized procedure of colored cards which illustrate a brief medical history and mainly the medical priority for each victim (by the respective color). After prompt evacuation from the disaster area (when it is such), a rapid pre-hospital triage, followed by emergency initial stabilization and then by urgent transport of casualties

constitutes the operational "holy trinity" for these teams. At the disaster point the TCCT/DMAT leader should be the first official responder who will undertake the following SOPs:

- Rapid estimation of hazard situation on the operation field along with an estimation of a probable number of casualties.
- Prompt notification to his/her superiors about urgent requirements in staff and equipment (ambulances, bedding, paramedics, body bags for fatalities, cold storage facilities, drinking water supply, etc.).
- Together with the (non-medical) on-site delegate of Civil Protection, they immediately delineate operational disaster zones around the disaster point.
- Outside the "hot zone" the above two operational delegates minister to the needs of less injured victims; the TCCT/DMAT leader, in particular, activates the operational teams of sub-paragraphs (c-g) of the EHOC Operation Section (described below).
- Remains in the "hot zone" and coordinates the rescue teams until he/she receives a replacement order.

c) A *Disaster Technical Assistance Unit* (DTAU), consisting of non-medical technical specialists who will provide, support, and repair mechanical and electrical equipment of operation.

d) A *Shelter Care and Humanitarian Priorities Team* (SCHPT); it coordinates humanitarian affairs, especially of the more vulnerable population groups, and prioritizes on-site non-medical, but still life-threatening needs that can heavily affect a disaster area, such as shelter, covers, safety, nutrition, drinkable water, etc. This unit cooperates with the Construction/Engineering Branch of the Civil Protection for shelters and sanitation systems construction.

e) A *Mental Health Team* (MHT), consisting of psychiatrists, psychologists, and social workers. They assess early post-disaster stress within the affected population and responders and support their mental health status by interventional and/or pharmaceutical practices and by cooperation with corresponding church/religion representatives.

f) A *Disaster Victim Identification/Mortuary Unit* (DVIMU); provides expertise, technical assistance, and support for casualties and human remains documentation, in collaboration with the Reporting/Briefing Section of the EHOC (described below). The unit further develops four operational branches; the Casualties Collection Team (employs laborers), the Post-mortem data Collection Team (collects and evaluates fingerprints, DNA/dental samples, etc, for forensic medicine purposes), the Casualties Identification Team, and the Mass Fatality Care Team (offers disaster mortuary services).

g) A *Veterinary Care Team* (VCT); offers care to animal casualties and to operating animals (e.g. rescue dogs), using veterinary medical support, equipment, supplies, and pharmaceuticals.

4. Logistics Section: It determines and supervises the provision of emergency resource needs for the unceasing operational function of the EHOC on a 24h/7d basis. It is divided into the following branches:

a) *Cost and General Resources Unit* (CGRU); it monitors cash flow and expenses and coordinates all sources of funding. Additionally, it can provide direct cash from a special account for immediate access in urgent needs of high priority, thus avoiding time-consuming bureaucracy.

b) *Medical Supplies Unit* (MSU); it monitors needs and provides required quantities of medical and pharmaceutical supplies as well as personal protective equipment for frontline health care workers.

c) *Food Provisions Unit* (FPU); it provides all services, resources, and supplies regarding nutrition to operation needs and also ensures that operating EHOC personnel have sufficient supplies of food and drinkable water.

5. Administration Section: It provides facility systems and supports the overall physical infrastructure (premises, furniture, equipment, etc.) of the EHOC; The section is divided into the following branches:

a) *Facility Unit* (FU); it organizes building and sectional layout of EHOC units in dedicated, purpose-built facilities, with adequate space for its staff, physically and environmentally secure, accessible, and survivable in the event of a threat or disaster.

b) *Human Resources Unit* (HRU); it formulates job descriptions and classifies staff requirements based on the knowledge, skills, and abilities required for the role and function of each person in the EHOC.

c) *Strategic National Sanitary Stockpile* (SNSS); it develops and deals with the national repository of basic life-support medications (antibiotics, antidotes, etc) and surgical supplies for any nation-wide event of a mass health emergency.

6. Communications/Intelligence Section: The equipment of that sector includes high technology infrastructure (computers, servers, internet stations, software, etc.) and all tools available to support an effective, all-weather-resistant continuous communication and data management according to high-level privacy and security standards. Of utmost importance is the timely, efficient, and accurate information flow on a 24 hour/7 day basis, between the Command section and each of the corresponding field-units

from the Operations sector. For that to be accomplished a sophisticated web-based digital tool allowing fast, real-time information sharing to multiple recipients is constantly in function. Some specific sub-functions of that section are:

- A continuous surveillance system, for gathering and exchanging information about sensitive civil national territories (e.g. cities and forest areas), by use of a broad camera-surveillance network and by electronic processing of the data-flow from an advanced, interactive mapping application. The relevant SOPs address all kinds of environmental and man-made threats, monitoring procedures, and actions according to certain hazard thresholds.
- An internet monitoring and medical intelligence/analysis system that verifies information to prevent duplication/ contradictory data collection.
- A rapid early warning/alert system triggering the coordinated rapid recall of staff back to their positions.
- A classified and secure web-based priority system for high-level communication and providing of information among national and transnational decision-makers.

The Communications/Intelligence sector is divided into the following branches:

a) *Data-base Management Unit* (DMU); it controls and centralizes information distribution to appropriate stakeholders for coordinated resource mobilization and correct decision-making to a wide range of emergencies.

b) *Disaster Assessment and Coordination Team* (DACT); it links the abovementioned data with relevant colleagues and experts from both country-level contacts and from the European Monitoring and Information Centre (MIC), as well as from UN/WHO.

c) *Communication Unit* (CU), equipped with telecommunication infrastructure and emergency communication services for sharing urgent relevant information among operational delegates from national and European governmental and private health agencies.

7. Reporting/Briefing Section: Chief is a senior Public Information Officer with pronounced communication skills to prevent inaccurate information spreading and panic diffusion, thus public composure and confidence to be preserved. The chief of the section applies uniform medical reporting SOPs according to the basic requirements: Who – when – where - what and how to report. The Reporting / Briefing section is divided into two branches:

a) *Media and Public Information Team* (MPIT), for regular management of the media and consequently of public expectations for the incident, by the timely transmission of valid information, carefully filtrated for any confidential or higher classified evidence.

b) *Victim Information Team* (VIT); it acts as the liaison between the afflicted population (victims or their families) and state authorities to serve their needs, to manage the list of missing persons, and to provide discreet information, in cooperation with DVIMU and MFCT of the Operations Section. The VIT also formulates antemortem medical records for the deceased and provides forensic support by coordination with local and national law enforcement agencies.

CONCLUSIONS

Albeit the proper function of an EHOC depends on numerous factors, qualifications, and principles, only two ones can be regarded as primary; first, the political will to radically reform the national and trans-national administrative "status quo" at the highest level, so that various authorities to be centralized under the same command through an appropriate legislative framework and second, a properly structured and fully functional organizational plan of an exemplary EHOC.

Disclosure statement
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ORIGINAL ARTICLES

Correlation between FibroScan and AST/ALT ratio and splenic size in NASH patients in a tertiary care center

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Abstract: *Background: Non-Alcoholic Steatohepatitis (NASH) is an aggressive form of Non-Alcoholic Fatty Liver disease (NAFLD), with liver inflammation and scarring. Due to a lack of clinical biomarkers and asymptomatic nature, NASH is often under-diagnosed. It is the most common cause of chronic liver disease in the USA. Liver biopsy is the gold standard to diagnose NASH, but it is invasive and life-threatening and histologic evaluation of a liver biopsy sample is imperfect as a reference because of sampling variability due to the irregular distribution of fibrosis. Aim: Validating AST/ALT ratio as a stand-alone scoring system in NASH is scarce and so this study aims to establish a correlation between FibroScan values and AST/ALT ratio. Methodology: All NASH patients, who underwent FibroScan were included. Their demographics, FibroScan, AST, ALT values were recorded in M S Excel and Pearson correlation between FibroScan values and AST/ALT ratios of 150 NASH patients was calculated using SPSS. Results: Out of 150 NASH patients, 72% were males and 57.33% belonged to 40-50 years age group. FibroScan values and AST/ALT ratio showed positive Pearson correlation of 0.245, (p value=0.003). FibroScan values and splenic size also showed a positive Pearson correlation of 0.289 (p value<0.001). Conclusion: Males of 40-50 years age group had higher distribution of NASH, so middle aged males should be screened routinely as they are at a higher risk. FibroScan value with AST/ALT ratio and splenic size showed a positive correlation, thus showing that AST/ALT ratio and splenic size increases with increase in liver stiffness.*

Keywords: *NAFLD, NASH, FibroScan, Elastography, AST/ALT*

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is a broad term used for a range of liver conditions affecting people who drink little to no alcohol, and is the most common cause of chronic liver disease in the United States of America [1], affecting approximately 90% of the obese population and 15-40% of the general population [2]. As the name implies, the main characteristic of NAFLD is excessive fat stored in the hepatic cells of the liver [1]. It consists of a spectrum of conditions: benign steatosis or non-alcoholic fatty liver (NAFL), steatosis accompanied by inflammation and fibrosis or nonalcoholic steatohepatitis (NASH), and finally cirrhosis [3].

The rising prevalence of NAFLD globally may be accounted for by changes in dietary habits and an increase in sedentary lifestyle [4]. Insulin resistance and oxidative stress play an important role in NAFLD development and progression [5]. Due to the lack of clinical biomarkers as well as its asymptomatic nature, NASH is often under-diagnosed and most commonly found incidentally during routine Ultrasound of the abdomen [3]. No highly sensitive and specific tests are available to differentiate NASH from simple steatosis, but diagnostic accuracy can be improved by combining blood biomarkers [6]. It is an aggressive form of fatty liver disease, marked histologically by liver

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inflammation and may progress to advanced scarring (cirrhosis) and liver failure, which is similar to the damage caused by heavy alcohol use. The number of people at risk for NAFLD is even greater given the increasing prevalence of obesity, diabetes and metabolic syndrome [1]. Although steatosis can be a significant cofactor in progression of established CLD, or even hepatocellular carcinoma (HCC), only steatohepatitis indicates the presence of progressive liver disease in patients with NAFLD. Benign and malignant liver tumors have been more frequently reported with the increasing prevalence of obesity and diabetes [7]. Early identification and targeted treatment of patients with NASH are needed to improve patient outcomes, directing patients toward intensive lifestyle modification to promote weight loss as well as for referral for bariatric surgery as indicated [8]. In NAFLD, HCC frequently develops in a not-yet cirrhotic liver; ss there are no surveillance programs for these patients, diagnosis often occurs at a tumor stage beyond curative options, further marking the importance of its early diagnosis [9]. According to a recent study done by Edenvik et al. [10], NAFLD and alcoholic liver disease were more commonly associated with deficient surveillance for HCC, and therefore early diagnosis was missed.

Although liver biopsy is considered the gold standard to diagnose NASH, only those patients with a high risk of NASH or advanced fibrosis require this evaluation, since it is an invasive and potentially life threatening procedure. Non-invasive tools for diagnosis and disease staging are required, reserving liver biopsy for those patients where it offers clinically relevant additional information only [11]. The use of non-invasive tests to stage the severity of liver disease (ie. scarring) is now well established in the management of patients with chronic liver disease since the assessment of liver scarring provides prognostic information and establishes treatment priorities [12]. Techniques such as transient elastography, magnetic resonance elastography and acoustic radiation force imaging are becoming more established in detecting fibrosis in a variety of chronic liver conditions in addition to NAFLD, as reviewed by Fitzpatrick E et al. [13]

One such technique, transient elastography (TE), is a simple, safe and efficient way to estimate liver scarring which is done using FibroScan, and is the most popular non-invasive device used to assess liver 'hardness' (or stiffness) via TE. Liver hardness is evaluated by measuring the velocity of a vibration wave (also called a 'shear wave') generated on the skin [12]. The main clinical indication for liver elastography is fibrosis staging of chronic liver disease and detect advanced fibrosis. Histologic evaluation of a liver biopsy sample is an imperfect reference standard because some degree of sampling variability is inevitable due to the irregular distribution of fibrosis in chronic liver disease.

FibroScan can be easily performed at the bedside or in the outpatient clinic with immediate results for the diagnosis of significant fibrosis and cirrhosis in nonalcoholic fatty liver disease chronic hepatitis C, in recurrence of hepatitis C after liver transplantation, in co-infected HIV-HCV patients, in chronic hepatitis B, in chronic cholestatic diseases, in alcoholic disease [14]. FibroScan evaluates liver stiffness, inflammation and portal hypertension and the values have to be interpreted according to clinical, biological and morphological data. FibroScan® results range from 2.5 kPa to 75 kPa. Between 90–95% of healthy people without liver disease will have a liver scarring measurement <7.0 kPa (median is 5.3 kPa) [12].

The usual observed biochemical pattern in hepatic steatosis due to NAFLD is of increased levels of transaminases, with alanine aminotransferase (ALT) levels exceeding those of aspartate aminotransferase (AST). This classical pattern differentiates between hepatic steatosis from NAFLD and alcoholic liver injury, with the latter normally associated with a high AST/ALT ratio [15]. Generally, the AST to ALT ratio increases with the severity of the necroinflammatory and fibrotic changes [16].

Data validating the use of the AST/ALT ratio as a stand-alone scoring system in NASH is scarce. This study aims to establish a correlation between FibroScan values and AST/ALT ratio. Given the high prevalence of NAFLD in the general population, these noninvasive methods could be used in clinical practice to screen patients with NAFLD [17]. Lifestyle modifications to reduce weight are a major factor in the treatment of NAFLD. No pharmacological substances are as yet approved for the indication NASH [18].

MATERIALS AND METHODS

Out of a total of 2000 patients diagnosed with NASH over a period of 3 years (January 2017 to December 2019) in Amrita Institute of Medical Sciences and Research Centre, Kochi, 150 patients who underwent Transient Elastography Scan (FibroScan) is selected. Inclusion criteria consists of abnormal liver function tests, fatty liver infiltration on ultrasonography (US), undergone FibroScan etc. Exclusion Criteria are patients with a history of alcohol intake, hepatitis B and C, history of hepatotoxic drug intake and other liver diseases. Ethics Comittee of Amrita Institute of Medical Sciences has approved the study.

The mean of 10 elastography values is taken as the FibroScan value. Patient details like their demographics, USG findings, AST/ALT ratio, Neutrophil/Lymphocyte ratio, LFT etc were

obtained using their hospital numbers from Amrita Health Information System and recorded in MS Excel.

Pearson correlation of FibroScan values with AST/ALT ratio and splenic size and Receiver Operative Characteristic (ROC) is used to find out optimal cut off for AST/ALT and Splenic diameter, as well as their sensitivity, specificity, and predictive values, using SPSS.

RESULTS

The majority of cases were seen among males (Figure 1). 74% (111) of cases were above 40 years (Table 1 and Figure 2).

Table 1: Distribution of age

Age Group (years)	Frequency	Percent Distribution
11-20	1	0.6
21-30	15	10
31-40	23	15.3
41-50	38	25.3
51-60	48	32
61-70	22	14.6
71-80	3	2
Total	150	100

Figure 1: Distribution of gender

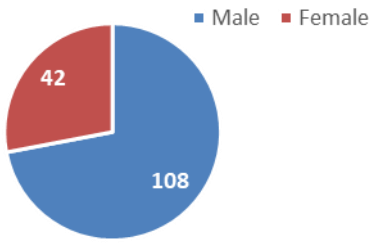
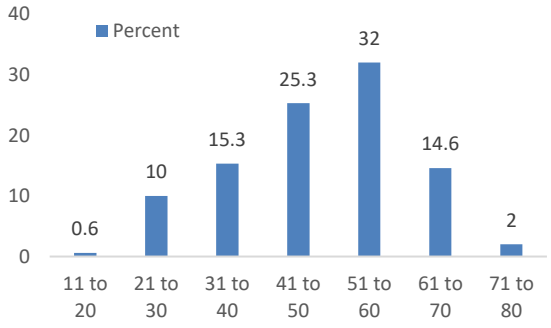


Figure 2: Distribution of age



Mean laboratory values are given in Table 2.

Table 2: Demographics and laboratory characteristics

Mean Age	48.4 years
Gender (Males)	108 (72%)
Mean HDL	46.68 mg/dl
Mean LDL	127.34 mg/dl
Mean TG	136.52 mg/dl
Mean AST	72.18 IU/L
Mean ALT	103.72 IU/L
FibroScan	7 kPa
Splenic Size	9.7 cm
Neutrophil	54.12%
Lymphocytes	35.5%
NEU/LYM	2.02

In order check the correlation between FibroScan and AST/ALT (Figure 3), Pearson correlation was used. Positive correlation of 0.245 with a statistically significant P value of 0.003 was obtained. Positive correlation of 0.298 with a statistically significant P value of <0.001 was obtained between FibroScan and Splenic Diameter (Figure 4).

Figure 3: Scatter Plot of FibroScan and AST/ALT

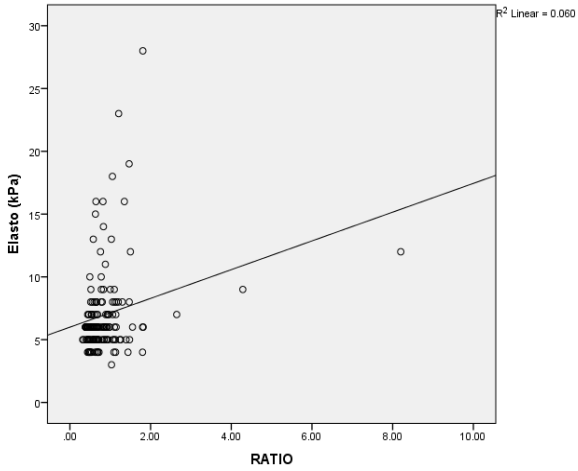


Figure 4: Scatter Plot of FibroScan and splenic size

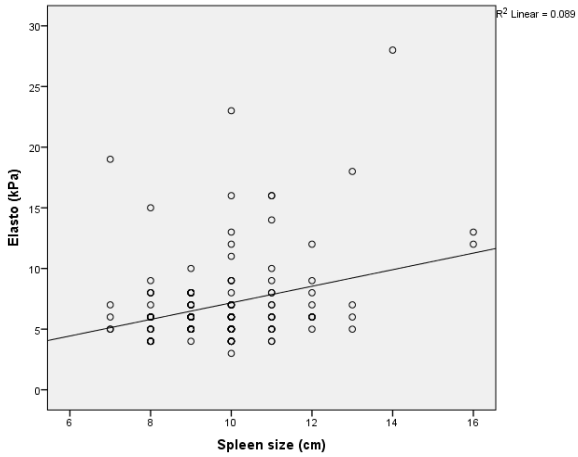
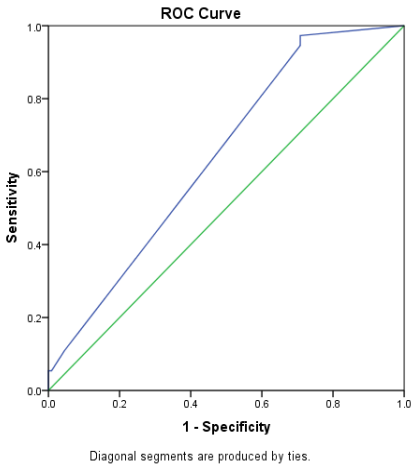


Table 3: Demographics and laboratory characteristics

		AST/ALT	Splenic size
Fibroscan	Pearson corrrelation	0.245	0.298
	p-value	0.003	<0.001

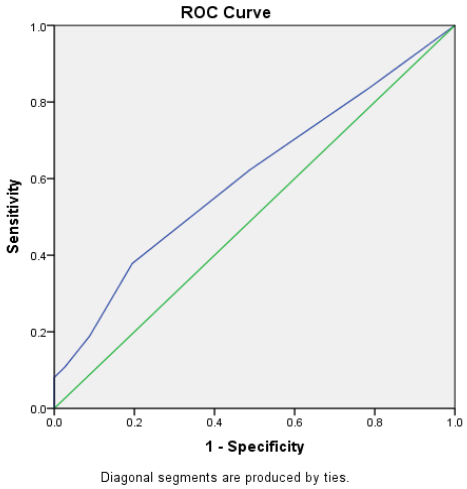
ROC curves were used to check the diagnostic accuracy of AST/ALT (Figure 5) which showed an AUROC of 0.641, ASTAST/ALT cut off 0.32 (P value 0.01), with a sensitivity and specificity of 97.3% and 29.2%. ROC for Splenic Diameter (Figure 6) showed an AUROC of 0.60, cut off of 9.5cm (P value 0.06), with a sensitivity and specificity of 62% and 51.3%.

Figure 5: ROC curve for AST/ALT



Area	0.641
AST/ALT	0.32
P value	*0.01*
Sensitivity	97.3%
Specificity	29.2%

Figure 6: ROC curve for Splenic Size



Area	0.603
SS	9.50
P value	*0.061*
Sensitivity	62%
Specificity	51.3%

CONCLUSION

Males of age more than 40 years had higher distribution of NASH, so middle aged males should be screened routinely as they are at a higher risk for developing NASH. FibroScan value with AST/ALT ratio and splenic size showed a statistically significant positive correlation, thus showing that AST/ALT ratio and splenic size increases with increase in liver stiffness. Thus our study shows that AST/ALT ratio can also be used for prompt diagnosis and management of NASH patients.

Contribution of authors

Varsha Somakumar, V S Srikanth, Cibi Manoharan – Concepts, design, definition of intellectual content, literature search, data acquisition, data analysis, Manuscript preparation, editing and review; Vishal Marwaha, VR Mujeeb, M.G.K.Pillai - Concepts, design, definition of intellectual content, Manuscript editing and review.

The manuscript has been read and approved by all the authors, and each author believes the manuscript represents honest work. There is no conflict of interest among the authors.

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ORIGINAL ARTICLES

The value of lipid profile in asthma-obstructive sleep apnea overlap

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Abstract: *The asthma obstructive sleep apnea overlap is a clinical entity relatively new and the association with a dysfunctional plasma lipid profile is not known.*

Aim. In this study, we compared the serum lipid profile in asthma-obstructive sleep apnea overlap syndrome to those in asthma and obstructive sleep apnea patients.

Methods. A cross-sectional study of 97 cases of which 26 patients had only asthma, 51 were diagnosed with OSA, and 20 were identified with A-OSA overlap. The lipid profile included the total cholesterol, HDL-cholesterol, triglycerides, the LDL-cholesterol. The Casteli indexes I and II and the atherogenic plasma index were calculated.

Results. The patients with asthma- obstructive apnea overlap were older (55.55 years vs 53,73 years in obstructive sleep apnea and 51,04 years in asthmatics), mostly obese (95%), and had a significantly higher average of BMI (38.11 vs. 35.64 and 28.8, respectively). Asthma- obstructive apnea overlap was at higher risk of cardiovascular disease than asthmatics, in respect to the lipid profile: the levels of HDL-cholesterol were lower, triglycerides were higher, and the values of Castelli index I and II were higher.

Conclusions. Based on our results, we confirm that age and BMI contribute to the risk of A-OSA overlap. The major differences in the common markers of the serum lipid profile are lower HDL-C and higher triglycerides. As a clinical implication, both Castelli indexes could provide additional value for cardiovascular risk and should be monitored in A-OSA overlap.

Keywords: *asthma, obstructive sleep apnea, HDL-cholesterol, triglycerides*

INTRODUCTION

The number of studies describing the asthma-obstructive sleep apnea overlap (A-OSA overlap), also known as "asthma-obstructive sleep apnea phenotype" is constantly increasing. The prevalence of obstructive sleep apnea (OSA) in asthmatic patients ranges from 19-60%. The prevalence is higher in older patients, with more than 10 years duration of asthma, in poorly controlled and in obese asthmatics [1, 2].

There is also a higher risk for the development of asthma in obese OSA patients. The coexistence of asthma in OSA aggravates the desaturation during the night [3].

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A pro-atherogenic serum lipoprotein profile in OSA, reported by many studies [4, 5], and broadly accepted is dyslipidemia, one of OSA's comorbidities [6, 7]. There is some clinical evidence that dyslipidemia improves after CPAP therapy [7]. The metabolic effects and, particularly, the lipid profile in asthma are less investigated. However, a systematic review showed an increased level of LDL-cholesterol in this category of patients [8].

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As more and more cases of A-OSA overlap are reported, the alterations of the lipid profile become more suggestive for additional cardiovascular comorbidity. In this respect, we developed a study to compare the serum lipid profile in patients with asthma-obstructive sleep apnea overlap syndrome compared to asthma and OSA, as a unique diagnosis.

METHODS

An observational, cross-sectional study was conducted in two Romanian centers from Bucharest and Constanta city.

From March to June 2019, patients with occupational asthma, that agreed to participate, were screened by Stop Bang and Epworth testing in the Clinic Department of Occupational Diseases in Colentina Hospital of Bucharest. Those asthmatics, with high scores, underwent a polygraphy test. OSA's diagnosis was based on apnea-hypopnea index (AHI) higher than 5/h.

The Constanta group of patients, previously diagnosed with asthma, were investigated by a similar methodology for OSA's diagnosis, in the Sleep Laboratory of Constanta Clinic Pneumophthisiology Hospital.

The study was approved by the Ethic Committee of the Constanța Clinic Pneumophthisiology Hospital.

Both research teams recorded data about demographics (age, sex), the body mass index (BMI), fasting glycemia, total cholesterol, triglycerides, high-density lipoprotein-cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) levels. BMI was calculated by dividing weight by the height squared. The current smoking habit was assessed. If the cessation of smoking was more than 1 year long, the subject was classified as a former smoker.

The blood profile of total cholesterol, triglycerides, and HDL-c cholesterol was directly measured by standardized methods, while LDL-C was calculated according to the Friedewald formula: LDL-C = TC − HDL-C − (TG/5).

The Castelli risk index I was computed by the ratio of total cholesterol/HDL-cholesterol. The risk values for primary prevention were considered (e.g. >5 for men and >4.5 for women) [9]. For the LDL-C to HDL-C ratio (Castelli risk index II), the levels associated with high were higher than 3.5 in men and 3 in women [9].

Atherogenic plasma index, as the cut-off for the cardiovascular diseases risk, was considered the logarithm of the ratio triglycerides/HDL-cholesterol higher than 0.5.10

Consolidated data were processed in a StatPLus for Mac software. Numerical data were compared by Kruskal Wallis test, while categorical ones required a Chi-square test. Regression was used to verify the relationship between variables. For the statistical significance, the threshold was set to estimate a 95% probability.

RESULTS

Among 97 cases, mean aged 53.38±6.76-year-old, mostly males (n=67), 26 patients had only asthma, 51 were diagnosed with OSA, without having a personal medical history of asthma, 20 were identified with A-OSA overlap, which made a point prevalence of asthma inside all OSA patients of 28.17%.

The main characteristics of these groups are presented in Table 1.

Table 1: Main characteristics of the patients

	All (mean ± SD)	**Asthma** (mean ± SD)	**OSA** (mean ± SD)	**Asthma-OSA overlap** (mean ± SD)
Age (years)*	53.38 ± 6.76	51.04 ± 4,87	53.73 ± 7.52	55.55 ± 6.16
Gender (F/M)*	30/67	13/13	12/39	5/15
Smoking (% active smokers/total)	17.53%	19.23%	23.53%	0%
BMI (kg/m^2)**	34.29 ± 7.06	28.8 ± 4.99	35.64 ± 6.59	38.11 ± 6.53
Total cholesterol (mg/dL)	210.78 ± 50.44	208.04 ± 28.27	207.82 ± 59.71	221.3 ± 43.66
HDL-cholesterol (mg/dL)**	50.2 ± 18,84	66.95 ± 25.76	44.42 ± 12.36	47.05 ± 13.44
LDL-cholesterol (mg/dL)	126.59 ± 42.99	116.9 ± 29.62	127.1 ± 51.22	135.5 ± 29.61
Triglycerides mg/dL)*	158.95 ± 142.03	122.45 ± 92.33	187.1±193.22	172.19 ±114.21
Castelli 1 index (TC/HDL)**	4.86 ± 2.8	3.51 ± 1.32	5.32 ± 3.27	5.14 ± 2.26
Castelli 2 (LDL/HDL)**	2.83 ± 1.4	2.04 ± 0.97	3.05 ± 1.53	3.12 ±1.18
API	0.48 ± 0.41	0.35 ± 0.31	0.6 ± 0.52	0.49 ± 0.32
Fasting glycemia (mg/dL)	118.06 ± 43.82	102.8 ± 16.5	125.65 ± 52.26	106.35 ± 18.62

*OSA = obstructive sleep apnea; F=female; M=male; BMI = body mass index; HDL cholesterol = high density lipoprotein cholesterol; LDL cholesterol = low density lipoprotein cholesterol; API= atherogenic plasma index; *statistically significant difference between all groups (p<0.05); ** high statistically significant difference*

between all groups (p<0.01)

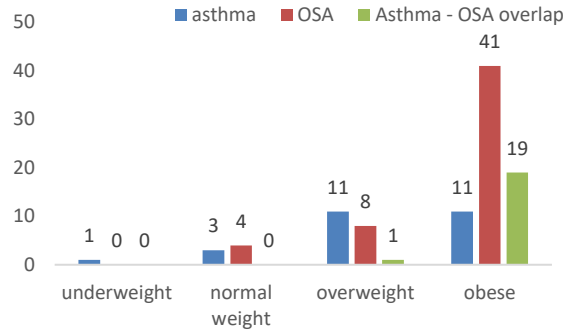
Most patients were in their 5th and 6th decade of age. The asthma-OSA association was significantly reported in the oldest patients than in the asthma group (H= 5.31, p = 0.02).

There was also a male predominance in the OSA group and A-OSA.

There was no difference by gender distribution between asthmatics and patients with A-OSA overlap (chi2 = 3.59, p=0.058).

The majority of patients were obese (73%) or overweighting (21%), especially in the A-OSA overlap group (38.11±6.53), with major differences among groups according to BMI categories (42% obese, 42% overweight, 12% normal weight, and 4% underweight, among asthmatics, compare to A-OSA overlap group with 95% obese and 5% overweight). The prevalence of obesity in the OSA patients was an intermediary between the prevalence encountered in the asthmatics and A-OSA overlap group (Figure 1).

Figure 1: Distribution of cases according to diagnosis and BMI categories



OSA= obstructive sleep apnea

Concerning smoking status, the highest percentage of active smokers was in the OSA group (23.53%), followed by 19.23% in asthmatics. However, this difference was not significant (chi2 =0.18, p=0.66).There were no active smokers in A-OSA overlap.

There was a direct correlation between BMI and triglycerides blood levels (Rho = 0.48, p=0.0001) and a reverse, significant correlation with HDL-C (Rho= -0.28, p=0.007).

The serum LDL-C showed no relation with BMI. However, the differences between groups maintained their statistical significance independent of the BMI.

The lipid profile was dominated by a high level of triglycerides and a low level of HDL-C in OSA and A-OSA overlap as compared to the asthma group.

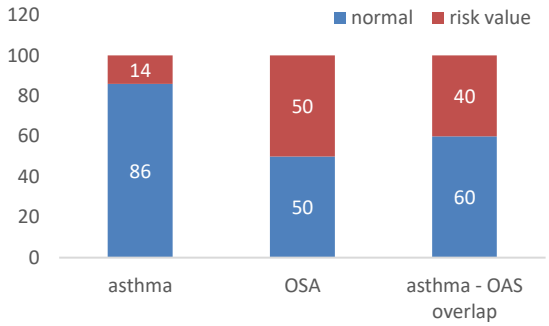
The LDL-C had the highest values in A-OSA-overlap.

The triglycerides and LDL-C were significantly higher in A-OSA overlap as compared to asthma (H=3.98, p=0.04, and H=4.52, p=0.03, respectively) while the HDL-C was significantly lower (H=8.31, p=0.003).

No significant differences were noted between the triglycerides, the LDL-C and HDL-C serum levels in OSA and A-OSA overlap (H=0.02, p=0.89; H=0.75, p=0.38, and H=0.25, p=0.62, respectively).

The average Castelli index was in the risk range values both in OSA and in A-OSA overlap groups. When measured individually, a few asthmatics had risk values than OSA patients. The highest percentage of risk values was found in the A-OSA overlap group (Figure 2).

Figure 2: Distribution of the Castelli index I among the patients with asthma, obstructive sleep apnea, and asthma-obstructive sleep apnea overlap



OSA= obstructive sleep apnea

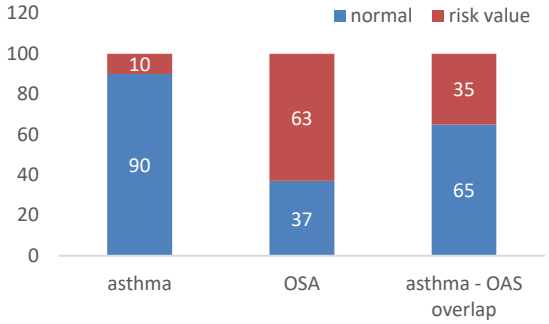
The number of patients with abnormal Castelli index in A-OSA overlap was higher than in the asthma group, but without statistical significance (chi2 =3.77, p=0.05), as the risk distribution between OSA and A-OSA overlap (chi2 = 0.21, p=0.65).

The majority (90%) of asthmatics had the ratio LDL/HDL in the normal values range.

The higher level of risk, according to this index, was among OSA patients, without significant difference compare to A-OSA overlap (chi2 = 0.02, p=0.89), as well as between asthma and A-OSA overlap (chi2 = 1.32, p=0.25) (Figure 3).

The percentage of patients with atherogenic plasma index (API) >0.5 was almost equally distributed among groups; 33% in asthma, 37% in OSA, and 38% in A-OSA overlap (chi2 =0.88, p=0.64). However, there is a significant difference between the API values in asthma as compared to the OSA group (H=3.89, p=0.04).

Figure 3: Distribution of the Castelli index II among the patients with asthma, obstructive sleep apnea and asthma-obstructive sleep apnea overlap



OSA= obstructive sleep apnea

DISCUSSION

In this study, we report differences in the serum lipid profile between asthma, OSA, and the co-existence of these two clinical entities referred to as asthma-obstructive sleep apnea overlap. The main findings are higher risk values for the Castelli index I and II in patients with A-OSA overlap compare to asthma patients.

Patients with A-OSA overlap were older, mostly obese (95%), with a significantly higher average BMI. These findings are from previous literature data [1, 2, 11]. The progression to A-OSA overlap requires a longer duration of time [12], considering the convergent effect of prolonged persistent chronic airways inflammation and aging.

Obesity contributes as well to the inflammatory status and increases the collapsibility of the upper airways and it is commonly accepted as a major risk factor for OSA [13]. In what concerns asthma, obese patients are reporting more severe symptoms, have a greater prevalence of co-morbidities [14], and a higher number of hospitalizations due to exacerbations [15]. The risk for A-OSA overlap might increase by higher corticoid doses that contribute to the deposition of fat in the neck region [1], another cause of upper airways resistance. OSA could be an explanation, as CPAP therapy in these patients reduces asthma reported symptoms [16].

Between the three groups, and between asthma and A-OSA overlap, the most significant difference in the serum lipid profile concerns the HDL-C. The presence of OSA seems to be the most important factor, as patients in this group had a lower blood level of HDL-C. Several studies have found the same reduction in HDL-C levels in OSA [4]. In asthma, a meta-analysis revealed no association between asthma and HDL-C levels in adults, but an increase in the LDL-C [17]. These studies support our hypothesis that the reduction in HDL-C levels in A-OSA overlap is mainly a consequence of the intermittent hypoxia related to chronic nocturnal repeated desaturation. As the A-OSA overlap is a relatively newly described entity, we could not directly compare our results with other studies. To the best of our knowledge, neither Medline nor Scopus databases give any result of a study specifically looking to this relation.

Despite the reproducible association in large cohorts of the increased cardiovascular risk related to low HDL-C level, the current clinical guidelines did not found enough evidence that raising HDL-C in serum would be of any benefit for these patients [18].

The latest evidence shows that not only the quantity but also the type of HDL particulate matters. The HDL particles are very heterogeneous and carry more functions than reverse cholesterol transport. Apolipoprotein A I and A-II are the major protein components in HDL. The HDL particle also contains a variety of lipids (phospholipids, cholesterol, in not esterified or esterified forms, and triglycerides) according to the maturation stage. It is a plasma vehicle for many other biologically active molecules, such as fat-soluble vitamins, steroid hormones, bile acids, bioactive lipids, haptoglobin, α-1 antitrypsin, transferrin, micro RNA) [19] and enzymes with antioxidant properties that would protect for reactive oxygen species and reactive nitrogen species damaging the endothelium [20]. To assure the esterification of the cholesterol, HDL contains lecithin cholesterol acyltransferase (LCAT) and to exchange esterified cholesterol and triglycerides with other lipoproteins, cholesteryl ester transfer protein (CEPT) [21].

The nomenclature of the HDL-C varies according to the method utilized for detection, and the degree of correspondence is far from perfect [22], leading to some confusion in the interpretation of results coming from different studies. Briefly, HDL is synthesized in the liver and the small intestines [23] as lipid poor preβ-HDL (the nascent HDL). In peripheral tissues, including macrophages foam cells, this particle interacts with ATP-binding cassette transporter A1 (ABCA1) to initiate the reverse transport of cholesterol to the liver and transforms to small HDL. Esterification of cholesterol inside the small HDL by LCAT and the exchange of esterified cholesterol with triglycerides from VLDL, IDL, and LDL-C, via the CEPT, end up in the formation of the mature HDL-C particle (the large HDL). Finally, HDL binds to the HDL receptor in the liver, and, through endocytosis, it is removed from circulation [24]. The triglyceride content of HDL promotes its clearance [23]. This permanent exchange, between the lipoproteins, in the bloodstream, influences the types of HDL particles in circulation.

In theory, both small and large particles might point towards a certain risk: the predominance of the small ones could show an ineffective/diminished potential for reverse cholesterol transport, while the predominance of the large ones could indicate a high burden of cholesterol in blood circulation. In epidemiological studies, a high level of large HDL seems to be protective for atherosclerosis [25], while, in already confirmed cardiovascular disease, high levels of small HDL are found [26] with a certain positive prognosis potential [27].

The techniques used to define the types of HDL particles are currently available mainly for research purposes, although their clinical value in assessing the risk and adapting therapy is of major value. Without this availability, different ratios of the commonly determined plasma lipoproteins and lipids were proposed to better characterize the atherogenic risk.

The estimation of the particle size is partially fulfilled by the API and the 2 Castelli indexes.

API was initially described to assess the atherogenic risk. Indeed, high levels were found in apparently healthy individuals in correlation with other biochemical markers of subclinical vascular diseases [28-29] and it was increased in subjects with cardiovascular disease compared to healthy controls [30, 31]. However, this marker was not confirmed as a predictable tool for stroke prediction [32]. In our study, the API did not have a discriminative value between the 3 groups. As there is no other study to compare with, this result should be cautiously interpreted and further investigated.

The Castelli risk I was a better estimation of the cardiovascular risk than individual lipoprotein particles measurement in the initial large cohort studies, as the Framingham study or the LRCP one [9], reflecting mostly the particles are responsible for the peripheral transport of cholesterol (the LDL and VLDL). It was, later, related to insulin resistance [33]. Even in normal weighted subjects, this marker had significant prognostic value for cardiovascular disease [34]. Castelli risk I show a direct relationship with the large HDL particles and indirect relation with the HDL 2b (small particles) and the small LDL [35].

Castelli index II describes the ratio between the HDL and LDL particles and is generally well associated with the Castelli index I and non-HDL cholesterol. It has been also used to differentiate the risk of atherosclerosis in chronic renal disease [36] or metabolic syndrome [37].

It is important to notice a high negative correlation between BMI and HDL with HDL-C in our study population. This finding is important, because, in certain circumstances, as in a chronic, persistent, inflammatory milieu that characterizes obesity, HDL particles become dysfunctional, losing their capacity for cholesterol efflux, and their anti-inflammatory and antithrombotic potential [38]

The low HDL-C and the high-risk Casteli index were not influenced by smoking, as all the A-OSA overlap patients were non-active smokers. It is assumed that, after smoking cessation, an improvement of the serum lipid profile manifests, mainly, on the elevation of HDL-C [39]. Even if the smoking effects would have been present, it was probably opposed by other pathogenic mechanisms. The groups of asthma and OSA had similar numbers of active smokers. Therefore, even if a certain influence of smoking on the lipid profile cannot be excluded, the significant difference in HDL-C noted between the groups should have another explanation.

We are aware of certain limitations of this study. Respiratory nocturnal polygraphy might underestimate the number of OSA patients inside the asthma population, because the majority of respiratory events are hypopneas, with arousals, that are more accurately counted only by polysomnography study [11]. Even so, the asthma patients were actively interviewed for OSA –related symptoms and none of them would clinically qualify for the diagnosis.

Another limitation of our study consists in the moderate number of patients, but from the perspective of no existing studies, we do consider that these results should be shared with the research community to promote further investigation in this domain. Despite these limitations, the results presented from this study add valuable information for the domain and substantiate the need for larger studies.

CONCLUSION

Based on our results, we confirm that age and BMI contribute to the risk of A-OSA overlap.

The major differences in the common markers of the serum lipid profile are lower HDL-C and higher triglycerides. As a clinical implication, both Castelli indexes could provide additional value for cardiovascular risk and should be monitored in A-OSA overlap.

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ORIGINAL ARTICLES

The effect of the transversus abdominis plane block on postoperative analgesia and patient comfort in patients having abdominal surgery with general anesthesia

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Abstract: *Background: This study aimed to investigate the effects of tranversus abdominis plane (TAP) block placed postoperatively using ultrasound guidance for patients with caesarean section, myomectomy, and hysterectomy under general anesthesia by eliminating additional pain caused by surgical incision.*

Methodology: The study has been planned to investigate the postoperative analgesia of 50 patients with TAP blocks applied and non-applied between the ages of 18-65, who will pass abdominal surgery. The study has been conducted in a prospective, randomized and controlled manner. Patients have been classified as those who have undergone TAP block (group: I) and those without block (group: II).

Results: Mean age of the patients in the TAP block group was 35.52 years, the mean age of the other group was 32 years and there was no statistically significant difference. The patients' visual analog scale (VAS) was evaluated at the 30th minute, 1st, 2nd, 6th, 12th, and 24th hours in the postoperative period. For patients with TAP blocks, the VAS score was found to be lower for all hours than patients without TAP blocks ($p<0.05$). Beginning at the 30th minute and 1st-hour analgesic needs of the block patients were compared with the other group ($p<0.05$).

Conclusion: TAP, that can be easily and safely placed provides effective analgesia and reduces the additional disruptions caused by the pain.

Keywords: *transversus abdominis plane block, postoperative pain, Bupivacaine, ultrasound-guided regional anesthesia*

INTRODUCTION

The transversus abdominis plane (TAP) block is a regional anesthesia technique described in recent years that provides analgesia for the anterior portion of the abdominal wall after abdominal surgery. With this method, local anesthetic injection of the area between the internal oblique and transversus abdominis muscles will block the afferent nerves of the abdominal wall.

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TAP is an attractive method of block simplicity and safety, and it has been shown to provide effective analgesia, reducing the response to postoperative stress and speeding up post-surgery improvement [1].

TAP block can be used in abdominal lower region operations such as hernia repair, appendectomy, abdominal hysterectomy. The most common operation where TAP is used is after cesarean operations. It is used for postoperative pain control in cesarean operations, reduction of analgesic drug consumption, reduction of side effects that may occur

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after the operation, and side effect profile due to analgesics used [2, 3].

The purpose of this study is to investigate the effects of the TAP block, which is performed with ultrasound after surgery, on patients with abdominal surgery such as cesarean, myomectomy, and hysterectomy under general anesthesia, on post-surgery pain and patient comfort.

MATERIALS AND METHODS

The study was conducted following the Helsinki Declaration Principles (rev.2013) and with the approval of the local ethical board. After the written and signed approval of the patients, it has been planned to investigate the postoperative analgesia and comfort of a total of 50 patients The study examined the postoperative pain levels after abdominal surgery with and without TAP block. Subjects were between the ages of 18-65 who will have abdominal surgery with transverse incision (cesarean section, hysterectomy (benign), myomectomy) and the American Society of Anesthesiologists Physical Status Classification System (ASA) I-II. Our study is planned to be prospective, randomized, and controlled. The individuals to be engaged were divided into two groups in a randomized form. Randomization was based on computer-generated code. In the first group, a total of 25 patients were admitted with 16 cesareans, 6 myomectomies, and 3 hysterectomies applied to the TAP block. In the second group, a total of 25 patients who did not undergo TAP block, no needle intervention, 18 cesareans, 5 myomectomies, and 2 hysterectomies were included as the control group. Those with skin infections, patients with organomegaly (hepatomegaly and splenomegaly), people who did not give consent to the method, and individuals with allergies to drugs to be used in the intervention area where Transversus abdominis plane is to be conducted were not included in the study.

0.9% NaCl solution at a rate of 2 ml/kg/hour was administered to the individuals whose oral intake was discontinued 8 hours before the surgery. The individuals to be included in the study were not given any sedative agent on the morning of their surgery. Before the procedure, 6-8 ml/kg volume of liquid replacement with crystalloid was applied to the individuals to be included in the study. 10 cm visual analog scale (VAS) for measuring the pain level was explained in detail to all patients before the procedure. All individuals to be included in the study were followed up with an anesthesia monitor, heart rate (CAH), electro-cardiography (ECG) (lead II), systolic blood pressure (SKB), and diastolic blood pressure (DBP) in the preoperative and preoperative period. After induction of anesthesia with 1 µg/kg fentanyl, 0.5 mg/kg rocuronium bromide, and 5 mg/kg thiopental sodium, 4-6% Desflurane and 50% N2O in Oxygen were used to maintain anesthesia following endotracheal intubation. Differently in general anesthesia management at cesarean operations, 5 mg/kg thiopental sodium and 0.5 mg/kg rocuronium bromide were administered in the induction and 4-6% Desflurane, (50% N2O+50% Oxygen) and 1 µg/kg fentanyl are added as inhalation anesthesia after umbilical cord clamping in maintenance. The maintenance dose of rocuronium bromide was 0.15 mg/kg for all cases. A necessary fluid replacement was performed during the operation. At the end of the operation, TAP blocks were placed on the 1st group of patients.

After the necessary sterilization conditions were established, the linear ultrasound probe was sterilely coated and placed in the middle of the iliac crest with the end limit of the ribs. Starting with skin, the layers in descending order, subcutaneous adipose tissue, external oblique muscle, internal oblique muscle, transversus abdominis muscle, and peritoneum were identified. As the tip of the 21Gx100 mm needle (visible cannula by ultrasound, with facet tip) passed through the muscular layers and fascia, a fascial click was felt and the needle was advanced with ultrasound in a controlled manner. After receiving the second click sensation (passage of the fascia of the internal oblique muscle), after a 0.5-1 ml test dose, the location of the needle was fixed and frequently aspirated and applied to the bilateral neurophysical plan so that 20 ml of 0.25% bupivacaine was applied to one side.

The first group of patients was awakened after TAP block treatment and reversal of muscle relaxant with atropine sulfate and neostigmine; the control group was awakened after reversal of muscle relaxant with atropine sulfate and neostigmine at the end of the operation. When VAS>3 in the postoperative period, 1g of paracetamol was administered as an intravenous infusion over 10 minutes in terms of the first analgesic requirement.

Systolic and diastolic arterial pressures, heart rates of all patients were monitored immediately before and postoperatively at 30th minute and 1st, 2nd, 4th, 6th, 12th, and 24th hours after block administration. The pain levels of the patients were measured at the 30th minute, 1st, 2nd, 4th, 6th, 12th, and 24th postoperative VAS values. The need for nausea, vomiting, and initial analgesia was recorded. In this study, none of the patients underwent any invasive procedures other than routine procedures.

When parametric test counts were fulfilled (Kolmogorov-Simirnov) by uploading the data obtained from our study to SPSS (ver:22.0) program, significance test of the difference between the two averages, variance analysis in repeated

measurements, Bonferroni test, Mann Whitney U test, Wilcoxon test, Freidman test, and Chi-square test were used when parametric test assumptions were not fulfilled. When α is taken as 0.05, β: 0.10, 1-β: 0.90, 25 individuals were included in each group and the strength of the test was p= 0.90388.

Our data were reported as the arithmetic mean, standard deviation, several individuals, and the level of error was taken as 0.05.

RESULTS

The age of the patients who underwent the TAP block was 35.52 ± 9.60 years; the age of the patients in the group without block was 32.00 ± 8.10 years. There was no difference in age compared to both groups (p>0.05). The duration of the case was 43.60 ± 11.41 minutes in the block group and 45.00 ± 12.24 minutes in the group without block. The difference between the groups in terms of case duration is insignificant (t: 0.41, p<0.678, p>0.05).

When the heart rate values of the groups were compared; the difference between the groups at 30th minute, 1st, 2nd, 4th, 6th, and 24th postoperative hours was found to be significant and the heart rate was lower in the block group compared to the other group (p<0.05) (Table 1).

Table 1: Comparison of groups in terms of heart rate (times/min)

Postop. time (hour)	**TAP group** (mean ± SD)	**Control group** (mean ± SD)	**Result**
0	80.50 ± 15.29	80.12 ± 13.85	t: 0.48 p: 0.96
½	86.84 ± 12.09	94.52 ± 14.42	t: 2.04 p: 0.047*
1	81.80 ± 9.30	92.72 ± 9.96	t: 4.00 p: 0.001*
2	80.44 ± 5.60	86.84 ± 6.74	t: 3.64 p: 0.001*
4	78.56 ± 6.31	86.48 ± 7.56	t: 4.01 p: 0.001*
6	77.0 ± 5.82	81.28 ± 5.19	t: 2.74 p: 0.009*
12	75.64 ± 7.40	78.44 ± 5.21	t: 1.54 p: 0.129
24	73.72 ± 4.71	76.56 ± 5.14	t: 2.03 p: 0.047*

**p<0.05 significant; SD – standard deviation*

When comparing the rest Visual Analogue Scale (VAS) values assessed at various times of patients in the two groups of study, the difference was significant (p<0.05). The resting VAS values measured at different periods of the individuals in the TAP block group were lower (Table 2).

Table 2: Comparison of resting values of groups

Postop. time (hour)	**TAP group** (mean ± SD)	**Control group** (mean ± SD)	**Result**
½	5.04 ± 1.59	8.88 ± 0.83	p: 0.001*
1	4.36 ± 0.86	8.12 ± 0.66	p: 0.001*
2	4.0 ± 0.95	7.40 ± 0.81	p: 0.001*
4	3.20 ± 0.95	6.92 ± 0.90	p: 0.001*
6	2.80 ± 0.76	5.64 ± 0.81	p: 0.001*
12	1.84 ± 0.74	4.0 ± 0.85	p: 0.001*
24	1.24 ± 0.43	3.44 ± 0.76	p: 0.001*

**p<0.05 significant; SD – standard deviation*

When the systolic blood pressure (SBP) values measured at different times were compared, the difference was found to be significant when the individuals in both groups were compared at the 1st hour and 4th hour postoperatively (p<0.05). SBP values of the individuals who received block at 1st and 4th hours are lower. A significant difference between the groups at 30th minute, 2nd, 6th, 12th, and 24th postoperative hours was not found (p>0.05) (Table 3).

Table 3: Comparison of groups in terms of systolic blood pressure (mm/Hg)

Postop. time (hour)	**TAP group** (mean ± SD)	**Control group** (mean ± SD)	**Result**
0	112.4 ± 10.9	111.24 ± 10.94	t: 0.48 p: 0.96
½	128.4 ± 15.18	137.2 ± 19.26	t: 1.79 p: 0.079
1	122.8 ± 10.21	132.8 ± 14.86	t: 2.77 p: 0.008*
2	119.6 ± 10.59	126.8 ± 14.92	t: 1.96 p: 0.055
4	115.6 ± 10.83	126.0 ± 12.24	t: 3.18 p: 0.003*
6	114.4 ± 11.93	113.24 ± 23.92	t: 0.21 p: 0.829
12	116.0 ± 9.57	110.8 ± 10.37	t: 1.84 p: 0.072
24	116.6 ± 7.57	112.8 ± 9.79	t: 1.45 p: 0.429

**p<0.05 significant; SD – standard deviation*

When comparing the diastolic blood pressure (DBP) values of the patients with and without TAP block, a statistically significant difference was found between the two groups at the 30th minute, 1st, 2nd, and 4th hour postoperatively (p<0.05). DBP values of the individuals who received block at these hours are lower. No difference between the two groups at the 6th, 12th, and 24th hours was found (p>0.05) (Table 4).

Table 4: Comparison of groups in terms of diastolic blood pressure (mm/Hg)

Postop. time (hour)	**TAP group** (mean ± SD)	**Control group** (mean ± SD)	**Result**
0	65.4 ± 8.1	67.8 ± 9.27	t: 0.77 p: 0.335
½	76.4 ± 8.6	83.8 ± 11.03	t: 2.77 p: 0.009*
1	77.2 ± 7.37	84.0 ± 10.0	t: 2.73 p: 0.009*
2	71.6 ± 6.87	80.0 ± 10.4	t: 3.36 p: 0.002*
4	70.8 ± 8.12	78.8 ± 11.66	t: 2.81 p: 0.007*
6	70.8 ± 7.59	72.8 ± 8.42	t: 0.88 p: 0.382
12	71.2 ± 8.32	71.6 ± 8.5	t: 0.16 p: 0.867
24	66.4 ± 8.10	68.8 ± 9.27	t: 0.77 p: 0.335

**p<0.05 significant; SD – standard deviation*

When comparing the need for analgesic drugs for the groups in the first 30 minutes, the difference was significant (p<0.05). Fewer patients in the TAP block group reported the need for analgesic drugs. When comparing the need for analgesic drugs for the groups at 1st hour, the difference was found to be significant (p<0.05). As can be seen, 8 patients in the TAP block group within the first postoperative hour and 25 patients in the control group within the first postoperative hour stated that they needed analgesics. Individuals without block application stated that they needed analgesics at the 30th minute and 1st hour, while two people in the block group needed analgesics at later hours (Table 5).

Table 5: Comparison of resting values of groups

Postop. time (hour)	**TAP group** (mean ± SD)	**Control group** (mean ± SD)	**Result**
½	8 patients (32%)	16 patients (64%)	p: 0.024*
1	0 patient (0%)	9 patients (100%)	p: 0.001*
12	2 patients (11.7%)		p: 0.49

**p<0.05 significant; SD – standard deviation*

When comparing postoperative nausea and vomiting (PONV) according to the groups, a statistically significant difference was found between the two groups at the 30th minute postoperatively ($p<0.05$). Nausea was never seen in the block group, whereas nausea was seen in 10 of the individuals who did not receive the block. No difference in nausea compared to both groups at the first hour was found ($p>0.05$). 4 patients (%16) in the non-block group indicated they had nausea. While 100% of the two groups did not have nausea at the 2nd hour, no difference was found between the two groups at the 4th hour ($p>0.05$). Nausea was observed in two individuals who did not receive block at the 4th hour. Individuals in both groups did not experience nausea at the 6th, 12th, and 24th hours.

When comparing the two groups in terms of vomiting, the difference at the 30th minute was significant ($p<0.05$). No vomiting was observed in the TAP block group, while vomiting was observed in 9 patients (36%) in the non-TAP group. No difference in vomiting compared to both groups at the first hour was found ($p>0.05$). Vomiting was observed in 4 patients (16%) in the non-block group, while no vomiting was observed in the other group. No vomiting was observed at the 2nd, 6th, 12th, and 24th hours. There was no difference between the groups at the 4th hour ($p>0.05$). Vomiting was observed in 2 patients (8%) without block application.

DISCUSSION

Today, pain is one of the frequent causes for doctor visits and is held responsible for a significant part of the loss of the labor force [4, 5]. Among the negative effects and complications; pain includes thromboembolic complications due to immobility and prolonged hospitalization time [4, 5].

It has been reported that with postoperative pain treatment using regional anesthesia methods, analgesic drug need is reduced and the recovery process of patients is faster [6]. The use of effective regional anesthesia methods in postoperative pain treatment also reduces the side effects of systemic analgesic drugs [7, 8].

TAP block is a regional anesthesia technique performed to provide analgesia after abdominal operations [9]. TAP block is used for retropubic prostatectomy [10], abdominal operations with bowel resection [11, 12], gynecological malignancy operations, total abdominal hysterectomy operations [13], cholecystectomy [14], and appendectomy operations [15] postoperative analgesia. Some of these studies were performed using the TAP block, a petite triangle, and a part of the study using the loss of resistance technique, followed by ultrasound. During the TAP block, the literature has been reported to damage the inner body of the abdomen, both in blind technical blocks and in blocks in the ultrasound guide [16]. Intraperitoneal injections, hematoma in the intestines, and temporary femoral nerve damage are among other complications [17]. It is important to remember the local anesthetic toxicity due to the increased local anesthetic volumes after bilateral TAP block placement. Therefore, careful aspiration is required to avoid intravascular local anesthetic injection [17]. Our study did not show any complications to the group where bilateral TAP block was applied.

Pain evaluations of the individuals included in the study were evaluated with VAS scoring at 1st, 2nd, 12th, and 24th hours. VAS score was found to be significantly lower in the TAP group compared to the control group at all evaluation times. With these results, very close results were obtained when compared to a study describing the petite triangle in TAP block [11]. In our study, unlike this study, the first analgesic needs of the patients were evaluated and it was determined that the TAP block group needed the first dose analgesic less frequently. Also, our study addressed additional complaints such as nausea and vomiting of patients.

The most commonly used local anesthetics in TAP block administration are Bupivacaine [10, 15, 18], Ropivacaine [13], and Levobupivacaine [9]. In our study, TAP block was applied to each site as 20 ml with 0.25% Bupivacaine, which we think has a longer duration of action. This application we made in our study complies with the current literature.

A study [12] included 40 patients who underwent colorectal surgery under general anesthesia, applied 0.25% Bupivacaine to the TAP group and SF to the control group as 20 ml bilaterally at the end of the surgery. A 65% decrease was observed in total morphine consumption for 24 hours compared to the control group in the TAP group. Although the need for initial analgesia was similar in both groups, subsequent doses were required longer in patients in the TAP group [12]. Another study [14] divided the patients including 54 patients that have undergone laparoscopic cholecystectomy as randomized 3 groups. The first group was the control group, the second group was the TAP group with 0.25% levobupivacaine and the third group was the TAP group with 0.5% levobupivacaine. The need for postoperative analgesia was found to be lower in the TAP groups. No significant difference was found between the 2nd and 3rd groups, and no complications related to TAP block were observed [14].

According to a study [15], 52 patients who underwent appendectomy under general anesthesia, divided the patients into two groups as randomized double-blind and

applied TAP block with Bupivacaine accompanied by ultrasound to the second group. Total morphine dose and VAS scores for the first 24 hours were found to be significantly lower in the TAP group and no complications occurred in the TAP group [15]. In contrast to these studies, a conducted research [13] on 13 patients who underwent gynecological cancer surgery in 2010; no difference was found between the groups with and without TAP block in terms of analgesic drug consumption and patient comfort. In our work, the TAP block was applied to individuals after the end of the operation.

In a meta-analysis examining the studies for postoperative pain control after cesarean section, 524 patients were evaluated in a total of 9 studies, and the main purpose of these individuals who underwent TAP block after spinal anesthesia (7 studies) and general anesthesia (2 studies) is to investigate pain control and analgesic consumption. It has been emphasized that after spinal anesthesia, TAP block application without intrathecal opioid is a significant contribution to the control of postoperative pain and that after spinal anesthetic using opioid, you need to work further, although unclear [19].

Some studies have compared TAP blocks to epidural analgesia. Recently, a group of researchers conducted a retrospective matched case-control study comparing continuous TAP block catheters (posterior and subcostal approaches; n = 15) to thoracic epidural analgesia (n = 15) [20]. Except for assessments in the post-anesthesia care unit, there was no appreciable difference in pain scores between the two groups over a 3-day follow-up period. While patient satisfaction was similar between groups, the TAP block group required a significantly higher amount of breakthrough fentanyl over the study period. The therapeutic failure rate was higher in the epidural group (patchy block in 4 patients) versus the TAP catheter group (unilateral block in 2 patients). Hypotension was reported in 2 patients from the epidural group [20].

Also, an increasing number of reports indicate that TAP blocks can be a safe alternative to neuraxial blockade in patients with coagulation disorders [21, 22].

In our study, postoperative patient-controlled analgesia was not studied as a dose and the first analgesic requirement was recorded as time; heart rate, systolic, and diastolic blood pressure were found to be lower in the patient group who underwent TAP block compared to the other group. No nausea-vomiting was observed in the TAP block group. Thus, we believe that the likelihood of nausea-vomiting complications is reduced.

CONCLUSION

In our study by applying TAP blocks, the need for the first postoperative supplemental analgesia was delayed in the TAP group, thus reducing any side effects that may develop due to these analgesics. Although in our study, in the patient group who underwent TAP block; we have achieved significant and positive results, such as less postoperative pain, less initial analgesic need and additional convergence, more stable vital signs, more comprehensive investigations are necessary to routinely implement this practice.

Tap blocks are relatively easy to place and appear to be associated with little risk when placed with ultrasound guidance by trained practitioners. This kind of block provides effective analgesia and reduces the additional disruptions caused by the pain.

Contribution of authors

Study Design: Nagihan Yuksek, Ahmet Cemil Isbir; Data Collection: Nagihan Yuksek; Statistical Analysis: Iclal Ozdemir Kol; Data Interpretation: Ahmet Cemil Isbir; Manuscript Preparation: Onur Avci, Ahmet Cemil Isbir; Literature Search: Kenan Kaygusuz, Sinan Gursoy

Registered at ClinicalTrials.gov, ID: NCT04364477.

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ORIGINAL ARTICLES

Assessment of complications and outcomes of mechanical bowel obstruction in a military hospital

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Abstract: *Aims: Mechanical bowel obstruction is a frequent surgical emergency and a frequently confronted burden in abdominal operation. This study aimed to find out the model of mechanical bowel obstruction in the Iranian population.*

Methods and materials: In this study, all patients with clinical and radiological evidence of mechanical bowel obstruction that admitted to the Department of Surgery of Baqiyatallah Hospital with a diagnosis of mechanical bowel obstruction from January 2012 to December 2015 were included. The age, gender, symptoms operative details, postoperative complications, outcome, and mortality, were recorded.

Results: 193 patients with mechanical bowel obstruction were admitted in our study. Regarding the clinical presentation of the patients, the absence of passage of flatus and/or feces with abdominal pain (65.8%) were the most common presenting symptoms. Adhesions, colonic volvulus, hernias, different types of colorectal cancer were the most frequent causes of obstruction (54.9%, 15.54%, 7.2%, and 9.8%, respectively). Twenty-one patients died, resulting in a mortality rate of 10.9%. In the 19 patients with colorectal cancer, 7 (31.6%) patients have died and cause of death in all them related to cancer disease.

Conclusion: The results showed that the most common mechanisms of intestinal obstruction were adhesions, volvulus, cancers, and hernias, respectively, and the most common risk factors were appendectomy history, herniation surgery history, and cholecystectomy history, respectively. About 21 patients (10.8%) underwent obstruction surgery with a diagnosis of malignancy, which was confirmed in 19 cases of tumor pathology, of which about one third had recurrence within 3 years.

Keywords: *mechanical bowel obstruction, adhesions, colorectal cancer*

INTRODUCTION

Mechanical bowel obstruction is a frequent surgical emergency and a frequently confronted burden in abdominal operation [1-3]. Intestinal obstruction relates to extremely severe circumstances, demanding a fast and accurate diagnosis as well as critical, rational, and efficient treatment [4].

The diagnosis of mechanical bowel obstruction is not always simple, and an implication of operation requires a vast indication of suspicion [5, 6]. Comprehensive past and precise clinical exams are important to obtain a practical diagnosis and preparation therapy [7]. There are several cardinal characteristics, i.e. colic, distension, vomiting, and constipation, but the influence of each of these is affected by the position and kind of obstruction [5-9]. The administration needs early diagnosis and therapy with meticulous fluid, electrolyte balance, and timely operational intervention [10]. The complications can be decreased by

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early diagnosis and immediate surgical intervention [11].

Emergency surgery for malignant bowel obstruction is correlated with a mortality incidence of up to 30 percent [12]. It also results in considerable morbidity with prolonged hospital stay, delay at the beginning of chemotherapy and many stoma organizations, with a disorder of quality of life [12-14].

Also, malignant bowel obstruction has a major affected on health costs given that these cases are hospitalized and may need multiple mediations [13]. Medical administration has lower short-term mortality but may be correlated with low resolve or recurrence of the obstruction [14]. Because of the enormous problem of MBO in cases with cancer and the meaningful discrepancies in the morbidity of surgical versus medical treatments, it is necessary to characterize the predictors of survival and the impact of therapy modality on case results [15]. However, MBO may be due to the primary tumor, metastatic disease, or past surgical intervention leading to adhesions or an internal hernia [16, 17]. Albeit, many studies showed that MBO in the setting of colon cancer, the actual incidence, and the results remain unknown [9, 12-16].

In a study showed that 10-50% of patients with advanced cancer stage would develop MBO during their illness and experience from intractable abdominal pain, vomiting, which result in a decreased quality of life, mental and emotional problems [18]. Various therapies, including operation, palliative radiotherapy, chemotherapy and total parenteral nutrition formulas, may be used to reduce the symptoms in MBO patients; however, there is currently no agreement about the optimal treatment approach and no substantial evidence supporting the effectiveness of any treatment in enhancing the quality of life and prolonging survival [16-18]. Varying the pattern of the disease from time to time needs periodic studies to assess the etiological factors and behavior of the disease [12-18]. Also, as well as regional differences in the pattern of bowel obstruction and changes in the illness pattern over the years, are well documented in the previous studies [18]. This study aimed to find out the model of mechanical bowel obstruction in the Iranian population.

METHODS AND MATERIALS

In this study, all patients with clinical and radiological evidence of mechanical bowel obstruction that admitted to the Department of Surgery of Baqiyatallah Hospital with a diagnosis of mechanical bowel obstruction from January 2012 to December 2015 were included. The enrollment of the patients in the study was approved by the ethics committee of the Baqiyatallah University of Medical Sciences and written informed consent was obtained from all patients. Patients with paralytic ileus were excluded from our study.

The age, gender, symptoms operative aspects, post-operative complications, result, and death were recorded. Following clinical investigations, every six hours with the same attending surgical unit were conducted in all cases to assess the patients' symptoms. All cases had been operated on by the authors in the general surgery departments of the Baqiyatallah hospitals.

The diagnosis was based on clinical judgments, history, and supported by ultrasonography and radiological studies (plain x-rays) in all cases. The final diagnosis was presented at exploratory laparotomy, which was endeavored following thorough first evaluation, examinations, and resuscitation. The operation was determined as required in those patients where the operation was conducted in thirty-six hours.

Chi-square test and Fisher's exact test was utilized for the relationship between qualitative variables. The non-parametric Mann-Whitney test made a comparison among the groups. The Kolmogorov–Smirnov test was used for the normality of the data. The data was used by SPSS 20 software. The significance level for the tests was considered less than 0.05.

RESULTS

193 consecutive patients with mechanical bowel obstruction were included. The average age was 58.1 ± 19.0 years while women comprised 32.64% of the group. The most of the patients (60.1%) presented in above 59 years old.

Regarding the clinical presentation of the patients, the absence of passage of flatus and/or feces with abdominal pain (65.8%) were the most common presenting symptoms, only abdominal pain (27.5%) was the second frequent physical finding on clinical examination abdominal.

Regarding the types of previous operations, 35 patients (23.33%) had undergone an appendectomy, 27 (18.0%) hernia procedures, 24 (16.0%) had a cholecystectomy, and 86 (43.3%) had other surgical procedures.

Adhesions, colonic volvulus, hernias, different types of colorectal cancer were the most frequent causes of obstruction (54.9%, 15.54%, 7.2%, and 9.8%, respectively). There was no significant difference in the cause of obstruction regarding gender and age levels. An evaluation of 193 cases of mechanical bowel obstruction from the standpoint of etiology, age, and sex distribution, is presented.

Types of colorectal cancer were overrepresented accounting for 8 (42.1%) with obstruction due to sigmoid cancer, whereas six (31.6%) patients had a colon cancer, 3 (15.8%) had a cecum cancer, and one (5.2%) had a rectum cancer.

Regarding the clinical presentation of the patients and cause of obstruction, Adhesions and abdominal pain (56.08%) with were the most common presenting symptoms and cause of obstruction. The absence of passage of flatus and/or feces and Adhesions (33.9%) were the second frequent presenting symptoms and cause of obstruction.

There was a significant association between the cause of obstruction and history of surgery (P<0.001).

109 patients (56.4%) of the total study group were safely and more efficiently treated.

Eighty-four cases of the 193 patients sustained complications; 28 (33.3%) suffered from recurrence adhesion along with obstruction, 15 (17.9%) had abdominal pain, 15 (17.9%) had constipation. In the 19 patients with colorectal cancer, six (31.6%) patients had a recurrence.

Twenty-one patients expired, following in a death rate of 10.9%. In the 19 patients with colorectal cancer, 7 (31.6%) patients have died and cause of death in all them related to cancer disease.

DISCUSSIONS

In the past, the most common cause of intestinal obstruction was a strangulated hernia, but today, due to the higher prevalence of surgery than in the past, the most common cause of intestinal obstruction (75-80% of cases) is adhesions due to previous surgeries [7, 9, 11, 12]. These patients present with clinical signs of obstruction including colic abdominal pain, abdominal distension, and nausea and vomiting, and constipation. The complete obstruction causes intestinal dilation with an accumulation of water and gas. Radiological signs are visible 3-5 hours before obstruction [11-13]. In the present study, the most common postoperative diagnoses were adhesions in 106 patients (54.9%), volvulus in 30 cases (15.5%), colorectal cancers in 19 patients (9.8%) and hernias in 14 patients (7.2%), respectively. While in the study of Saber, the diagnosis of the cause of obstruction was observed in most cases with sigmoid volvulus and inguinal hernia, each with 18% and the site of obstruction in the small intestine with 55%. The most common symptoms in the present study were abdominal pain, which was seen in more than 95% of cases, and the second most common symptom was lack of gas or stool, which was seen in more than 65% of cases. In the study of Markogiannakis et al., the most common symptoms were flatulence (90%) followed by bloating and abdominal pain (65.3%). Adhesion was observed in 64.8% of cases, incarcerated hernia in 14.8%, and colon cancer in 13.4% [3].

Füzün et al. (2005), which looked at the causes of mechanical intestinal obstruction, found that intestinal adhesions were the most common cause of obstruction with 44%, followed by hernias with 23.9% and volvulus with 12.7%. Colon carcinoma was 10.1% of the causes of intestinal obstruction [9]. Our study is consistent with the above study in terms of 4 common factors and only slightly different in order after the most common cause, which is adhesion in both studies. The prevalence of colorectal cancers is very close in the two studies.

Regarding the clinical presentation of our cases, the lack of passage of feces or/and flatus with abdominal pain were the many common presenting symptoms and abdominal pain was the second most prevalent physical conclusion on clinical research [12-14]. The results, even though some variations are marked, are in agreement with the studies. Especially, Cheadle et al. showed abdominal vomiting 82%, pain 92%, distention 59%, and abdominal tenderness 64% as the most frequent signs [19]. While abdominal distension, bilious vomiting, absolute constipation, and abdominal pain were the main signs and symptoms in another study. In research on 100 patients with adhesive small bowel obstruction and recognized that the most common symptoms were vomiting 77%, colicky abdominal pain 68%, and absence of passage of flatus and/or feces 52% while abdominal distension developed the most common clinical symptom with a rate of 56% [20]. In a study of patients with bowel obstruction due to large bowel volvulus, the most common symptom of sigmoid volvulus was distension 79% and the most common symptoms were pain 58% and obstipation 55%, while most patients with cecal volvulus presented with pain 89% [21]. Moreover, in a review study of patients with obstruction because of small and large bowel intussusception, abdominal pain, nausea, vomiting, and abdominal distension were the frequent symptoms and signs, respectively [22].

Adhesions, colonic volvulus, hernias, different types of colorectal cancer were the most common causes of obstruction [23]. These results were also mentioned in the current research.

Furthermore, adhesions were the most common etiology of obstruction in and the total study group. Several studies propose that adhesions are responsible for 32%-74% of bowel obstruction and are the leading cause of small intestinal obstruction representing 45%-80% of it [20-23]. The large majority of the cases with adhesive obstruction

have experienced previous abdominal procedures [23]. In the present study, this was agreement with previous studies.

The model of mechanical intestinal obstruction shows a difference in various areas. The obstructed herniae were observed as the 3rd common condition in the current research, whereas it was the second common condition of the other research, which almost is comparable with the other investigations carried in the country [14-15]. As for the types of surgeries in our cases, appendectomies, and hernia surgeries, cholecystectomies were more prevalent. This results also in agreement with the literature [9, 16].

However, the proper administration of adhesive obstruction is still uncertain, a large portion of these cases, varying from 35% to 65% in some investigations, can reliably and efficiently be managed with operation administration as it was also noted in our cases [23, 24].

The growing performance of adhesions as a condition of acute intestinal obstruction requires a higher requirement for regular precautionary standards toward adhesion formation [25]. Some effective actions are now supported through elective abdominal surgery to reduce the increase of adhesions that might consequently produce intestinal obstruction [26].

In previous studies showed sigmoid cancer is the etiology of obstruction that cases with high intestinal obstruction with a percentage of 40%-90% [27]. A study by Baloch et al., of 252 patients with mechanical bowel obstruction, showed due to the regional epidemic, the most common cause of obstruction was abdominal tuberculosis, which was observed in 30% of cases, and unlike our study and most other studies, adhesion was the second most common cause of obstruction. Also, in this study, the hernia was observed in only 17.5% of patients [15].

In our research, complication and mortality percentage were almost small. In the previous studies, complication proportion varies from 6 to 47 percent while death ranges from 2 to 19 percent [25, 28]. In our study, there was the association between mortality rate and colorectal cancer disease.

CONCLUSION

The results showed that the most common mechanisms of intestinal obstruction were adhesions, volvulus, cancers, and hernias, respectively, and the most common risk factors were appendectomy history, herniation surgery history, and cholecystectomy history, respectively. About 21 patients (10.8%) underwent obstruction surgery with a diagnosis of malignancy, which was confirmed in 19 cases of tumor pathology, of which about one third had recurrence within 3 years.

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VARIA

The nuclear accident at Chernobyl: Immediate and further consequences

Symeon Naoum[1], Vasileios Spyropoulos[1]

Abstract: *The accident at Chernobyl occurred in April 1986 at the Chernobyl Nuclear Power Plant in Soviet Union. The incident occurred during a scheduled safety test. A combination of inherent reactor design flaws and operators' mistakes resulted in reactor's No.4 disaster and the emission of a large quantity of radiation. The immediate actions involved the fire extinguishing, the cleanup of radioactive residues and the prevention of a new explosion. For this purpose, plenty of people worked with self-sacrifice. The people who lived nearby were removed. As far as the socio-economic impact for the Soviet Union is concerned, it was quite serious. Moreover, the environmental and human health consequences were also alarming with thyroid cancer being the most studied. Useful conclusions, especially for the safety both of reactors and nuclear power, as well as for the impact of radiation at ecosystems have been drawn. The debate about the use of nuclear power has remained open ever since.*

Keywords: *nuclear power, thyroid cancer, RBMK reactor, radiation, radioactivity, liquidators*

INTRODUCTION

The Chernobyl nuclear accident occurred on 26 April 1986 in the light water graphite moderated reactor No 4 at the Chernobyl Nuclear Power Plant, close the town of Pripyat, in Ukrainian Soviet Socialist Republic Soviet Union, roughly 100km of the city of Kiev [1].

The reactor exploded during a safety test that was inappropriately made, with the operators losing control. This was due to a design defect of the RBMK reactor, which made it unstable when performed at low power. The outcome was the destruction of the reactor and the leakage of a huge amount of radiation into the environment [2, 3].

During the accident two deaths were caused because of explosion. Over the coming weeks a number of emergency staff was hospitalized with acute radiation sickness (ARS), while 28 firemen and employees finally died. The Chernobyl accident is considered the most damaging nuclear power plant accident in history. The Chernobyl and the Fukushima accident are the two nuclear accidents classified as a level 7 (the maximum classification) on the International Nuclear Event Scale [4].

CHRONOLOGY

The city of Chernobyl is located in Ukraine at a distance of 104km northeast of Kiev and 16km from the border with Belarus. Before the evacuation, it had about 14,000 inhabitants. Closer to the plant was the larger city Pripyat (about 49,000), which was built to accommodate the employees of the nuclear plant and their families [1]. The Chernobyl Nuclear Power Plant began to operate in 1977 with the first reactor of a total of four. Gradually, three more

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reactors began to operate by 1983. They were boiling water reactors with enriched uranium, type RBMK. The plant had a total capacity of 4000 MW electric power. The combination of graphite as a moderator and water as coolant is not found in other types of reactors [5].

THE ACCIDENT

When the reactor operates, it has an integrated cooling system. When it is shut down, the radioactive decay continues and heating of the reactor continues too. As a result, further cooling is required even after the reactor has been switched off. However, the three diesel engines which were used for this purpose needed 60-75 sec interval to achieve the required performance. In case of emergency, the reactor would be left without adequate cooling for this period, which was a very serious risk [6]. To remedy this problem, it was suggested the use of the kinetic energy of the steam turbine which was produced during the deactivation of the reactor.

After three failed tests (1982, 1984 and 1985) and some changes in design, a new test was designed to become in April 1986, when the Reactor No 4 was deactivated for scheduled maintenance. The test ended up in the tragic accident that occurred in 01:26 on Saturday, April 26, 1986. After a sequence of events during the test (which are not relevant to the present paper) it finally resulted in an uncontrolled increase of power. Simultaneously, the steam pressure in the reactor increased which eventually led to the first burst. The reactor's building was destroyed and a significant amount of radioactive materials were released into the atmosphere. A few seconds later, a second stronger explosion followed. Several fires broke out while the reactor itself started to flare [7].

Causes of the accident

The accident at Chernobyl was the result of a combination of unauthorized manipulations, human errors and design imperfections of the type RBMK reactor. According to the reappraisal of the accident by International Nuclear Safety Advisory Group at 1997 [8] the factors that contributed were:

- Unlike to most nuclear reactors which have a negative void coefficient, the RBMK had a dangerously high positive void coefficient.
- The use of graphite at the end of the control bars resulted in lowering the reactor power, had as a result the reactor power to be increased for a few seconds. This behavior is counter-intuitive and was not known to the reactor operators.
- The design of RBMK reactor had also other defects and was not consistent with the minimum acceptable safety rules for nuclear reactors.
- There was deficient safety culture in the design, organization and operation of nuclear power by the Soviet Union.
- There was inefficient and inadequate transmission of important information, both between operators and between operators and designers.
- There was inadequate safety analysis.
- The test was scheduled to take place before the night shift from well informed and familiar with the process employees. However, due to an unexpected ten-hour delay, the test was made during the night from less experienced staff.

The first hours

During the accident two workers were killed because of the explosion. There have been many fire focuses, the main of them were on the roof of the station and the reactor No 4. Initially, firemen were unaware of the risk of smoke and debris and did not receive any additional protection measures. So they received high doses of radioactivity. Although the fire on the roof had extinguished until 05:00 o'clock, the fire inside the reactor was still active. Within the next few days about 5,000 tons of chemical materials and sand were thrown by military helicopters to absorb the radiation.

The levels of radioactivity reached 20.000 Roentgens (R) per hour (the leather dose is 500R within 5 hours). In the first hours, both workers and supervisors in the control room were unaware of the actual levels of radioactivity. The one dosimeter did not work and the second one was not accessible due to the explosion. The remaining dosimeters had a measurement limit of 0,001R/s, so they showed "off scale" [9]. Due to faulty readings, the head of the station, Alexander Akimov, believed that the reactor was not affected by the explosions. Akimov and his assistants remained in the reactor building until the morning without taking any protection measures. Most of them, including the Akimov, died from exposure to radiation within the next three weeks.

IMMEDIATE CONSEQUENCES – CRISIS MANAGEMENT

After the extinguishing of fireplaces, a number of problems and potential risks had to be addressed:

I. Steam explosion risk

The floors under the reactor were filled with water. At the same time, smoldering graphite, fuel and other materials fed to the reactor began to mix with molten concrete from the

reactor walls resulting in a semi-liquid material that resembled a lava [10]. If this mixture succeeded in penetrating the reactor floor and coming into contact with water, it could cause a more disastrous explosion. To prevent this danger it was considered necessary the water pools to be drained. This hazardous mission was carried out by engineers Alexei Ananenko and Valeri Bezpalov and the shift supervisor Baris Baranov. After the valves had been opened a large amount of extremely radioactive water was pumped.

II. Radioactive debris removal

The next challenge was the removal of the radioactive particles which were dispersed around. The main part of this effort shouldered the army. The plan included the transport and disposal of radioactive materials within the reactor core. Wearing lead protective clothing, the "liquidators", as the workers were called, either transplanted radioactive materials manually, or handled heavy machines which did the same job. Many of them received cumulatively high doses of radiation throughout the procedure [11]. Furthermore, a large number of remote-controlled machines were used in order to be avoided the exposure of workers to high doses of radioactivity.

III. Announcement of the accident

At 21:02 on 28 April, about 67 hours after the accident, a 20-second announcement was read on a TV news program: "There has been an accident at the Chernobyl Nuclear Power Plant. One of the nuclear reactors was damaged. The effects of the accident are being remedied. Assistance has been provided for any affected people. An investigative commission has been set up". However, attempting not to hurt the prestige of the regime, the Soviet authorities initially had tried to hide the incident. The above announcement occurred only when the morning of the 28 April, in routine control, personnel of the Swedish Nuclear Power Plant at Fosmark recorded high levels of radioactivity. The Swedish government came into contact with the Soviet Union and the latter was forced to admit that an accident had occurred [12]. Although, the Soviet government, attempting to downplay the event, issued a statement that there was no reason to postpone the celebrations and parade for the 1 May International Worker's Day in Kiev.

IV. Evacuation of Pripyat

After the incident, the residents of Pripyat, completely ignored what had happened. A special committee was created a few hours later to investigate the accident. The committee arrived at the plant on the afternoon of April 27 and soon had enough evidence of the seriousness of the situation seriousness. So, in the early hours of April 27, 36 hours after the accident, they decided to evacuate Pripyat. It was initially decided that the evacuation would only be for 3 days but shortly was decided the permanent implementation of this measure.

With a statement issued by the city council the residents were informed that they would displace the city for 3 days by buses started at 14:00, on 27 April. The evacuation would be under the supervision of the police and the city officials. The residents had also been informed to take with them only their documents and entirely essential personal belongings. It was also announced that all assets would be kept by the police after the evacuation. Except for the police officers who would remain in the city for safety, there was a list of employees who were required to remain for the continuity of the plant operation. Around 15:00 a total of about 45.000 residents were transferred to different villages in the Kiev region [12].

V. Set up of exclusion zone

On May 2, a government committee decided –rather arbitrarily- a 30km area from the damaged reactor as the designated evacuation zone. This area was also divided into three sub-zones in which, both the protection measures of those who arrived, and the activities which took place, were different: The area around the reactor, a second with a radius of about 10km, and the rest zone until the 30km.

Later, this distinction was made according to the revised dose limit of 100mSv [13]. So there were:

- the "Black Zone" (over 200 μsv/h)
- the "Red Zone" (50-200 μsv/h)
- the "Blue Zone" (30-50 μsv/h)

In the first place the inhabitants would never return. In the second they may be back when the radiation levels would be reduced. In the third only children and pregnant women would have to be removed. Although the evacuation of these areas was not immediate, a total of 116,000 people were eventually removed. However, there were few residents, mainly elderly, who refused to remove. After repeated efforts at expulsion, authorities finally accepted their presence giving them an unofficial permission to stay.

The boundaries and the status of the zone and sub-zones have been amended many times in the coming years.

FURTHER CONSEQUENCES

I. Financial consequences

It is very difficult to determine the total cost of the Chernobyl accident. It afflicted, and continues to, both the Soviet Union

(and the countries which have arisen since its breakup), and many other countries. According to the Chernobyl Forum Report (2005) the 22% of the national budget of Belarus in 1991 was connected to Chernobyl (decreased at 6% in 2002), while in Ukraine 5-7% of the government spending continues to be related to the accident [14]. A great part of the cost is still about Chernobyl-related social benefits in approximately seven million people in Russian, Ukrainian and Belarus. Another important economic factor for the years after the accident was the removal of 1,900,000 acres of agriculture land, as well as 1,700,000 acres of forest from production.

Finally, a large number of countries, mainly Europeans, have been forced to spend resources to check the amount of radioactivity in soils, food and water, while International Organizations, such as the World Bank, have financed both the rehabilitation work and the building of the new reactor shelter (New Safe Confinement).

II. Political and social consequences.

Before the accident M. Gorbachev had implemented the political "glasnost" with purpose to enhance the transparency of politics. However, the accident led to return to past secretive politics. At the same time, distrust of international community against the Soviet regime was grown up. The mistrust of the citizens towards the regime was also high enough, especially among nearby areas residents and those who needed to move.

Combined with the economic consequences, the lack of confidence, both in international and national level, is believed to have contributed to the fall of the Soviet Union, a few years later. Apparently, except for economic impact, political and social consequences continued to affect the 3 countries in this region, even the fall of the Union [14]. On the other hand, the need for bio-scientific cooperation helped forge closer relationship between Soviet Union and US at the end of the Cold War.

III. Environmental effects:

a) Spread of radioactive substances

It is estimated that Chernobyl released about four times the amount of radioactivity of the two atomic bombs in Hiroshima and Nagasaki. More than 100,000 km^2 were significantly contaminated even though the areas around the plant were the most overburdened. Lower levels of radiation were detected in different regions in Europe. The radioactivity dispersion was incongruous since it depended on both weather conditions and water paths. Soviet and Western scientists claim that 60% of radioactivity contaminated Belarus. Also, according to the 2006 TORCH report, half of the volatile particles came out of the Soviet Union [15].

b) Residual radioactivity

The Chernobyl Nuclear Power Plant is located next to the river Pripyat, which at that time was watering the broader area of Kiev. Although water purification measures were initially taken, the supply of water to Kiev began to become from the river Desna, two months later. Also, in some lakes in Russia and Belarus the concentrations of radioactivity in certain species of fish far exceeded the acceptable limits, even the period 1990-1992 [16]. On the contrary, excluding the exclusion zone, the groundwater does not seem to be affected.

c) Flora and fauna

After the accident, 4 km^2 of the neighboring pine trees were died, giving a characteristic red color that gave the name of the "Red Forest". Several of the wild animals in the most affected areas, either died or stopped breeding (most of the domestic animal in exclusion zone were removed) [17]. A typical example was the animals of a small island in the river Pripyat, where, the horses died and the beasts either died or were extremely weak. All of them due to significant thyroid malfunction.

In the following years, increased levels of radioactivity were detected in domestic animals both inside and outside of the Soviet Union. Several European countries have carried out checks on animal products in order to ensure consumer safety, for many years after the accident. As reported, were contaminated in total over 19.000 km^2 of agriculture land. Of these 2.640 km^2 will never be cultivated. Also about 17.000 km^2 of forest, mainly in the Ukrainian lands, were infected [14].

IV. Human impact

a) General

After the accident, totally 273 people suffered from acute radiation sickness, 31 of whom were died within the next three months. According to the Chernobyl Forum Report (2005), 28 of the "liquidators" died of Acute Radiation Syndrome, while 15 died of thyroid cancer within the coming years [14].

The same report states that it is extremely difficult to be calculated the total number of cancer due to the Chernobyl accident. The four most harmful radionuclides spread from Chernobyl were iodine-131 (half-lives: 8.02 days), caesium-134 (2.07 years), strontium-90 (28.8 years) and caesium-137 (30.2 years). Iodine, despite the small half-life, is the most unstable and appears to have caused the most important

health problems up to now [18]. It tends to become concentrated in thyroid and milk glands and cause thyroid cancer. Caesium tends to accumulate in vital organs such as the heart. Finally, strontium accumulates in bones increasing the risk of cancer.

According to WHO and independent researchers who studied the children of emergency workers, there was no statistically significant difference in mutation frequencies among children conceived before and after their father's exposure [19]. However, due to fear, distrust to the authorities and poor media information, an increase in the number of abortions in -other normal- pregnancies has been observed in some European countries. In Greece, although radioactivity measurements did not exceed the safety limits, there was an observed 2,500 excess of otherwise wanted pregnancies being terminated [20]. Furthermore, in countries such as Sweden and Finland, where there were not noticed more abortions, there was not increase in the incidence of congenital malformations [21]. The same conclusion is reached by Frank Castranovo study, of the Harvard Medical School in 1999, which has, among other things, analyzed the data from the two largest maternity clinics in Kiev [22]. He says that there is no evidence that the accident has increased the rate of birth defects.

b) Cancer assessments

The estimates of the number of cancers that have occurred or will arise in the future as a result of the accident vary enormously. This is due to both the lack of solid scientific data and the different methodologies used to quantify mortality. The Chernobyl Forum predicts that the total number of deaths could reach 4,000. However, these deaths are expected to be mainly among the most exposed people (emergency workers, evacuees, residents of the most contaminated areas) [14]. The Risk Projection suggests that Chernobyl can be responsible for about 1,000 cases of thyroid cancer and about 4,000 cases of other cancer, in Europe (0.01% of all cancer after the accident) but, as stated, the estimates are subjective. The most tightly associated with the accident cancer is thyroid cancer, due to the well-documented influence of the iodine on this gland.

According to the Forum, thyroid cancer is one of the main health impacts from the Chernobyl. On the contrary there has not been evidence for an increase of the number of other kinds of cancer or leukemia. The United Nations Scientific Committee on the Effects of Atomic Radiation ends up to similar conclusion. It finds an increase in the incidence of thyroid cancer, particularly among children and adolescents exposed to radiation, but no other indications of major health impacts [23].

Finally, the International Atomic Energy Agency indicates that there has been no increase in the incidence of solid cancer as a consequence of Chernobyl accident [14]. On the contrary, there are estimates such as the International Physicians for the Prevention of Nuclear War that refers to about 10.000 cases of thyroid cancer and 50.000 cases which are expected in the future [24].

c) Health disorders

One other important impact of the accident, especially among the directly involved populations, has to do with mental health. Both the incident itself and the initial attempt to be downgraded it had as a result to create exaggerated fears about the risks of radiation exposure. The IAEA supports that the designation of the affected people as "victims" rather than "survivors" has fed them to perceive themselves as weak, helpless and lacking control over their future [14]. Further health effects may have been caused due to this belief.

Other surveys show that humans remain largely unsure of what the effects of radiation actually are. For example, some teenagers or young adults who had received modest or small amount of radiation feel condemned to be ill and thus believe that there is no downside to have unprotected sex or use drugs.

The research and assessment of long-term effects of radiation on human health are continuous by many organizations, such as the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) [25].

DISCUSSION

The review of the causes and consequences of the Chernobyl accident had as a result many important conclusions to have drawn and, at the same time, there was a matter of intense concern.

The weaknesses and pathogens of the Soviet regime were clearly showed up. The authorities initially tried to conceal and then to devalue the gravity of the incident. For this reason, the decision to evacuate the much burden areas was delayed. This has resulted in the distrust and dispute of the citizens towards the authorities, which had as a result the citizens not to comply with the instructions of the following period.

Questions have also been raised about the safety, both the RBMK reactor and the nuclear reactors in general. The accident led to be made corrections to the design and operation of Soviet reactors but also of the reactor in West [26]. Simultaneously, a culture of safety was dealt with in the

handling of nuclear energy. The combination of reactor faulty manufacturers and human errors that led to the Chernobyl accident resulted in the persistence in safety of both governments and scientists as well as the leaders and staff of the nuclear power plants. A repetition of the Chernobyl accident is now virtually impossible, according to report of the German Nuclear Safety Agency [27].

Furthermore, cooperation between East and West has improved in terms of reactor improvement and safety. Since 1989 there have been many reciprocal visits from the former Soviet Union and the West. In 1989 the World Association of Nuclear Operators (WANO) was founded, which has under the auspices 130 operators of nuclear power plants in more than 30 countries [26].

The Chernobyl nuclear accident also helped to understand the impact of radiation on the environment, ecosystem and humans. Scientists had the opportunity to study short and long term radioactive contamination as well as to relate specific exposure levels with corresponding results. Also, knowledge and experience on the appropriate measures to protect against radioactivity have increased.

Despite the intense fear and concern it seems that the only sufficiently documented impact that accident had at the human health (excluding emergency workers who have received high doses of radiation during the first days from the accident) was thyroid cancer [28].

Finally, the debate on the use of nuclear energy remains open. There is a continuing dispute between those who argue that the use of nuclear power is dangerous, and those who claim it is necessary and sufficiently secure. The growing public awareness about climate change and the critical role that carbon dioxide and methane emissions play have increased the intensity of the debate. The use of nuclear energy is environmentally friendly and reduces fossil fuel consumption. However, if anything goes wrong the consequences can be devastating to humans and to the environment. The debate remains open today between those who fear the power of nuclear and those who fear what will happen to the planet if humanity does not use nuclear power.

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VARIA

Comparative study on the independent learning activity of young people in the bachelor's and master's programs

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Abstract: *During the late adolescence, it can be reached the highest level of mental operative functions and other intelligent human manifestations. Abstract mental operations can be done at this level: synthesis of syntheses, generalization of generalizations, abstraction of abstractions. Students go through many attempts to find which is their personal style of learning new materials, new contents. The study was conducted on a number of 31 participants. The group was divided into two subgroups: 16 students in the 5th year at Faculty of General Medicine and 15 master students in the second year at University of Sports, Sports Performance program. The used instrument consists of 21 questions (11 questions are about the individual studying process of the participants and 10 are about their beliefs about the teaching process of academics in courses), along with 4 more questions related to personal data. It is an opinion questionnaire. The teaching style of academics differs: those of Faculty of General Medicine are focusing on a lecture type style (75%), and University of Sports on an interactive style (67%). We discovered differences in the process of self-learning: between continuous and discontinuous style. For medical students, there was a longer distribution of the self-taught learning process; instead, University of Sports students organize their learning time in the last part of the semester. University of Sports students are more concerned with on the development and refinement of their personal practical skills, but also of the subjects they work with (kids or athletes), their goal being to accumulate their own experience as rich as possible from working with as many individuals and less to take from the experience of other colleagues. The coach-athlete/sports teacher-pupil relationship is more personalized and longer-lasting than the doctor-patient relationship.*

Keywords: *laser Doppler vibrometry, middle ear*

INTRODUCTION

1. Learning activity and its role in summative assessment

1.1. Learning activity for young people - generalities

During the adolescence period (considered between 14/15 and 20 years), the individual seeks his own identity and begins the stage of abstract thinking. Hayford [1] highlights the student period of 18/20-24/25 years as a prolonged adolescence. The young adult age is between 20-40 years and assumes that the most important aspects are the intellectual skills that will be used in professional life and the foundation of intimate and personal life.

Around the age of 17-18, the highest level of mental functioning and the manifestation of human intelligence is reached. The operations of thinking are fully liberated from the informational contents to which they were initially applied, they are generalized, they are transferred and they become formal. Thus, the second-degree operations are

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successful: syntheses of syntheses, generalizations of generalizations, abstractions of abstractions.

Piaget describes the stage of concrete operations as ending around the age of 12-13 years old, when adolescents are able to perceive the constancy of objects in terms of transformations, regarding structure, volume, in a nutshell, the ability to understand the fact that objects are constant in relation to the notion of flexibility. After the age of 13, up to 17-18 years, the stage of formal operations is completed, when young people manage to think inferentially, including the possible, with the issuance of assumptions and the definition of specific pathways for each option seen separately. It defines the logic, the concepts of contradiction, certain grammatical structures of the "double negation" type, the detection of the grammatical concepts of circumstantiality and attributiveness and the optional-conditional, which could be seen differently. Also, an important role is played by the concept of "perceiving the absurd" or of the possibility to operate on the determinants, of the empty set, in the sense of superior mathematics.

During late adolescence, there is a strong conflict related to the balance between maturity and childhood, the balance between needs and how to meet them, due to the relationship between aspirations and possibilities and the conflict between dependence and independence.

Some authors [2] consider that adolescence is a period of confusion, but also a period of future projections that the adolescent makes. The desire for self-improvement appears, emotions and feelings are amplified, moral autonomy and self-awareness are developed, the adolescent has the feeling of independence. There are feelings of disagreement and rejection of ideas imposed by other people.

The period of youth, between 20-24 years [3] is considered a period of transition to adulthood. The acquisition of economic autonomy begins, leading to greater independence. Levinson [4] calls the period from 17 to 22 years - the period of young adulthood and considers that it is characterized by the coexistence of the adolescent and the young adult status. He considers that it is a period of transition dominated by the transition of the young man from the state of child-man to that of young man.

Young people begin to become autonomous, move away from the family environment, from the model imposed by their childhood, create their own social system and thus structure themselves as individuals and part of their generation. The aspirations, the ideal about the world and life, the value system begin to particularize and become constant, proper in the young person's life, giving coherence to his/her actions.

Learning is the main activity of young people. They have a very high capacity to assimilate information, to incorporate it. They also show an increased availability for this activity. The preoccupation for learning comes from an internal motive towards self-improvement, continuous development, search for existential meanings and senses. They are beginning to lose the importance of the school assessment, grading and ranking component, focusing on the activity of acquiring the necessary knowledge in the desired field. According to Erikson [5], the adult stage involves: amplifying social identity, employment and involvement in social life, intense feeling of love, the beginning of family life and the development of intimacy, the oscillation between isolation – intimacy - the tendency to link relationships with others groups.

Knowledge and, in general, the intellect has a wider notional area than the psychic process of memory. In turn, memorization is only the first part that defines memory as a high psychic function, the other two aspects being the preservation of information and updating (which can be in the form of recognition or reproduction). The intellect is the superior form to which the definition of the personality of young people accesses, this including the peaks of the "iceberg" represented by each function or psychic process. In the absence of memory, life would be a "ball of sensory impressions", structuring the continuity of the psyche leaving "gaps" in the network in which students submit their information. If we refer strictly to the psychic process of memorization, we can describe the concept of "buffer", in which many students run, more or less information, depending on individual abilities, some being those who learn early and cope with information exams stored in long-term memory, others having as a favorite profile the loading of the buffer (this being a capacity, an ability in itself) and having remarkable results with the information stored here. The persistence over time and the effectiveness of this type of long-term learning in relation to valid and valuable expression in the future profession is to be discussed.

The overall mental operations are developed and many specific algorithms are formed. The motivation for vocational learning is strong, especially practical work-related learning. Another important aspect is that learning becomes strongly selective, conscious and voluntary. The formation of hypothetical-deductive thinking appears when the young person has the capacity to abstract, to separate the notion of object from a concrete reality and the possibility to analyze his own thoughts. He/she begins to understand and deduce the cause-effect, singular-particular-general connections. The ability to apply in practice with an individual character is also formed - the young person has

the tendency and ability not only to acquire new knowledge, but also to use it to create something new, integrates it much better [6].

Young people go through new challenges once they enter the university/vocational education system related to important exams, different classification system, different grading system, different type of examination, university structure and so on.

1.2. Self-training

Youth has an emphasis on the need and desire to learn more on their own, with autonomous effect. A style that focuses on the need for continuous renewal of one's knowledge through a constant personal effort is preferred, an effort that opens the perspective of developing the skills to learn alone, of autonomous and independent training. These self-taught systems will gain ground, because they respond better to self-motivations, an internal motivation for self-improvement and training, for self-completion, each individual having the opportunity to cultivate and better value their own abilities. and skills. Thus, the individual becomes his own "manager" of his intellectual, cultural and professional progress and plays an active role in the development of his cognitive function and his own training.

Self-training is defined as an integral part of self-education [7], which refers to the enrichment of knowledge and independent intellectual training. It involves a motivational impulse and the acquisition of tools of independent intellectual work. Individuals create their own self-training system, with personal, adapted techniques, which are based on his style. These involve: choosing the necessary information, systematizing it, processing the learning content, using the content to solve some learning tasks (exercises that help to integrate the learned content), self-control and so on.

Self-training is considered a form of manifestation of cognitive activism [8], a difficult and complex process that is not summarized only during university studies, but throughout the life of the individual. It is considered that the self-taught activity requires great efforts, ability to organize, to organize his/her own personal space, concentration on the task, developed motivational sphere, permanent control and self-improvement. This type of learning is common in high school. It is based on awareness and formation of personal appreciation of the domain taught. Metacognition is the theoretical foundation behind self-training. Self-regulated learning is based on self-responsibility.

The following question also arises: why a person cannot have a self-regulated learning throughout all learning experiences. Other theorists [9] believe that, when they are young, children cannot be self-regulators during learning in any formal way. In addition, comes Piaget's theory [10] that explains that against self-learning learning comes the egocentrism of the young child. And Vygotsky [11] emphasizes the importance of young children's inability to use inner language in guiding roles.

It is important to mention that the self-training activity must in turn be learned and repeated. Students go through many attempts in order to find out what is their personal style of deepening the teaching courses, their contents. Dordea [12] states that there are three sub-competencies that students must master in order to succeed in the process of self-teaching: self-appreciation of the personalized strategy, realization/implementation of that strategy, self-evaluation of results. Basically, the student has to "learn how to learn".

The individual learning project can be improved through two main ways: 1) indirectly, through experience; and 2) directly, through training. Thus, individual study can be encouraged through recurrent positive experiences (students notice that self-assessment is positive and that self-instruction increases the accuracy of learning), similar to the theory of positive reinforcement.

It is important that adolescents and young people acquire self-regulatory skills during their development. As the time passes, they need to process an ever-expanding volume of information and operate with knowledge at increasingly abstract levels. An essential feature of self-regulated learning is the dynamic approach of the topics to be learned. Thus, the student can analyze the teacher's comments and compare them with his own perceptions of the learning situation. Can self-learning lead to a burn-out syndrome due to the pressure and informational volume? Recent scientific research based on evidence-based medicine is highlighting the increased number of young people that are developing burn-out syndrome, sometimes due to medical conditions (neuroendocrine for example) that leads, in the severe form, up to depression [13].

The situation of students who become pregnant at a young age should also be discussed as a separate perspective (even if they have a lower frequency in the University of Medicine or Sports, given the specifics of learning or activities/ practical works). However, their number should not be neglected, especially in terms of pregnancy hormones, which cause mood swings, which can influence the ability of learning, given the motivational-volitional links with those of mnesic-prosexic processes and learning, especially in the amygdala area and the hippocampus area, brain areas significantly involved in both emotional motivational

regulation and superior gnostic functions, so that they are active at the optimal level in terms of supporting the effort to complete a university curriculum [14, 15].

1.3. Adult education

The educational process of adults must respond to the challenges posed by today's society, which is changing its rhythm very quickly. Giddens [16] proposes a series of characteristics of late modernity, as typical elements for contemporary western society: industrial capitalism, reflexivity, individual responsibility. Modernization has accentuated digital education, with the help of digital technologies in many fields, from trade to education, medicine, teachers [17].

Adult education in Romania takes place in the context of another type of modernity than that of the western countries, namely tendentious modernity [18]. This concept refers to the fact that there are differences between the style in our country and the western one, due to some older concepts in our system, which makes the modernization to be partial and unfinished.

Adult education occurs only by virtue of personal own vision of the project of developing society, with all the implications of the coexistence of the old with the new, of progress with conservatism, of the modern with the traditional. It aims to improve existing skills and/or acquire new ones. It also aims to assimilate system values that have previously proven social performance and put them into practice. Adult education asserts itself in different forms of education: continuing education, non-school education, non-formal education.

There are a number of phenomena that prevent the formation of adults: inequality of opportunities in education, inequalities between levels of education (between educational units from the same area, between students), inequalities of access between faculties. In several cases these inequalities have a huge impact on the developing personality of an adult person even more if this personality closes the borderline type or reaches the psychiatric connotations [19]. There are several causes that are against unitary access to educational levels: poor material endowments, underfunding of educational units, differences between schools in urban and rural areas, problems related to human resources in schools, school dropout, repetition, the existence of a segment of the population that does not take advantage of the educational system. The higher the level of schooling, the higher the value of the additional costs of education that the family has to cover, discussing here for example: the fee for college, food expenses, textbooks, rent [20]. Nowadays, recent strategies involving the cost of education are trying to keep the step with full on-line education system, additional costs covered by the family have changed their levels: for example, a higher investment in modern communication devices. In the same time, the educational system redirects its costs based on this new on-line strategy.

Lifelong learning involves everything a person does throughout life to complete his/her knowledge, learn new things, acquire skills or develop his/her talents in formal, non-formal and informal contexts.

It is important to note that education, from one level onwards, is optional. Post-school training is often a personal choice. Unfortunately, there are no mechanisms in society to encourage adults to learn continuously. They may limit themselves to the knowledge gained in school due to routine, inability to cope with change, difficulty in economic and financial management, disinterest in performance.

It is observed that young people who have obtained a higher education have: information processing capacity that can be extended to other cognitive areas, the operability of thinking is kept at high levels, the young person's thinking is wide, deep, systematic, rigorous, very good mental adaptability to specific professional. Young people have critical thinking [21].

1.4. Evaluation - types of evaluation

Evaluation is a component part of the educational process. It informs us about the effectiveness of teaching-learning strategies and methods and appreciates the correct choice of operational objectives on lessons. The teaching-learning-evaluation relationship presupposes a cause-effect circle, in which each component conditions the other. If we are thinking at the western model, the evaluation should not be considered a control method that would punish those who fail it. Students must understand the learning content, not only memorize it, and the given task must be contextualized, in which the subject can express his/her learning style.

Evaluation can be of several types. It differs depending on the type of classification. According to the criterion of the moment at which it is performed, the evaluation can be:

- initial (in the initial phase of the instructive-educational process) - aims to see what is the level from which to start,
- continue (throughout the training program) - aims to observe the improvements along the way and to achieve the optimization of the educational process,
- summative (at the end of a session/module).

The evaluation can also be: formal and informal. The formal one presupposes well-defined criteria, previously outlined and it is associated with standardized tests, it presupposes a

certain level of expertise of the one who performs it (License type exams, Baccalaureate, National Assessment etc.). Informal assessment is based on intuitive criteria and involves tests created by the teacher.

There is another classification of evaluation: internal or external. The internal one is made by the internal teacher (the one who designed the learning content is the one who evaluates it). In this case, the evaluator knows the particularities of the students, is familiar with them, knows their progress along the way. The external evaluation is performed by a teacher who has not been involved in the instructional-educational process and has the advantage that it is objective.

The evaluation can also be of normative and criterion type. The normative one has the following characteristics: the performance of the subjects is related to the group norm, to the reference group (class, year, respective series) and compares the students, it ranks them. Criterion evaluation presupposes that performance is related to an absolute criterion, to a standard. Evaluate absolute success in evaluation.

According to some other authors [22-24], evaluation can be: comparative (has the role of classifying subjects, relating them to each other, according to their level of success), based on a criteria (has the role of providing functional information, allowing subjects to be in in relation to achieving the objectives common to all subjects), corrective (wants to provide the subject with additional information depending on the difficulties he encountered), conscious or formative (oscillates between cognition and metacognition and promotes active participation and autonomy of the subject so that he/she, subsequently, takes control of his/her own transformation, becoming aware of its shortcomings and difficulties).

The traditional assessment methods are: oral tests, written tests and practical tests. There are also complementary, more modern methods, among which: systematic observation of behavior, investigation, project, portfolio, self-assessment [25].

Sometimes the psychological and physical overload based on a frail personality structure could lead to an interpretative phenomenon of key components of an evaluation, that, for the student, seems to be debatable. Risks will lead later on to anxiety and depression sometime at psychiatric levels [26, 27].

1.5. Summative evaluation

It is also called cumulative evaluation. The act of evaluation involves three stages: measurement, assessment of results and adoption of improvement measures [28]. It is performed at the end of a session/module. It has the purpose of accreditation/decision to improve future activities. It is performed by an internal or external evaluator, is done at long intervals and aims to see the final results of the students. It tries to test the final and accumulated knowledge that the students have acquired. It is important because of its dual role. It is useful for the trainer, to see if the chosen means and methods are useful, effective, if the information has arrived correctly and as quantitatively as possible. It is the feedback he receives from students. It is also useful for students to objectify what information they understood, what should have been clarified in more detail, etc.

It is a type of balance sheet assessment, global, at the end of relatively large activity segments. The disadvantage of this type of evaluation is that it does not allow the regulation/improvement of the didactic process; it is possible only after relatively long periods or never. Thus, trainers cannot change the teaching-training style to improve the results of their students, because they cannot make a second summative evaluation. However, it highlights the level at which the activity took place and its results, recognizes the efforts made by the subjects and the interest shown by them. It also offers the satisfaction of the social recognition of the subjects' competencies. At the level of society, these cumulative assessments certify that subjects are able to cope with certain tasks and requirements and that they can play certain roles in social life.

It is well known that grades, often, do not exactly reflect the true level of performance of the subjects and as a result, are not stimulating and do not provide sufficient data on the effectiveness of the training program. It is advisable to use it together with other types of assessment, such as continuous assessment, to rely on continuous feedback to cooperate the teacher with the students [29].

MATERIALS AND METHODS

The present research aimed to highlight some differences in the learning-teaching process of young people at the level of students at the Faculty of General Medicine, compared to those at the National University of Physical Education and Sports. We tried to observe what is the time that young people aged 18-25 allocate for individual study in their preparation for the summative assessment and the level of awareness of the need to be involved in the self-taught process. We highlighted the perception of students in relation to the teaching style of academics. We also sought to highlight possible psychological motivational explanations for interpreting the results.

The tool used was a questionnaire that consists of 21 questions (11 questions are related to the individual study process of young people in the group, and 10 are about the teaching process sustained by the professors at courses), along with four more questions to highlight the factual data. It is an opinion questionnaire. The participants received the appropriate training to complete the answers and were assured of the confidentiality of the data, their results being used only for the purpose of this research. The questionnaire took about two minutes to complete.

The tool was uploaded in google forms and sent to the participants to form the database. The data were collected between April 15-25, 2020.

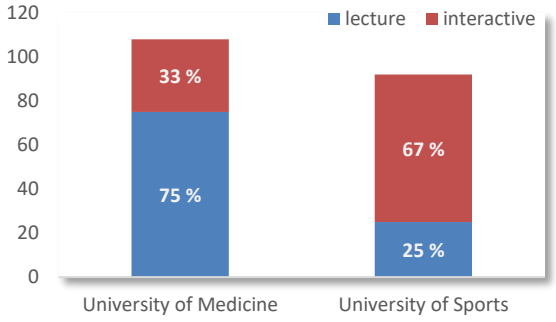
The study was performed on a number of 31 participants. The group was divided into two groups: 16 students in the 5th year at the University of Medicine and Pharmacy- Faculty of General Medicine and 15 master students in the second year at The National University of Physical Education and Sports, the Motor Performance program.

The ages of the participants ranged from 22 to 26 years. There was female (18) and male (13) participants.

RESULTS

Regarding the methods of education and training in young people, we highlighted the teaching style of the university staff from the two faculties and we noticed differences between the style of them, one activating in the field of health and the other one in the field of sports (Figure 1).

Figure 1: Teaching style of academics (percentage of teachers)

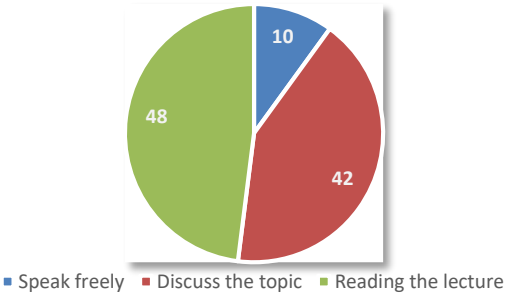


Although, currently, the teachers from the medical university are increasingly open to a more interactive teaching style, it is important that a well-structured lecture is based on a diagnostic tree, and the mastery of logical thinking by the medical student implies, in for the most part, the acquisition of diagnostic tree-type thinking. This is the reason why many medical teachers prefer a lecture style because it is better suited to the large learning content, compared to those in the field of sports that emphasize the practical part of the theorized content.

Medical professors focus more on teaching "thick materials" in a lecture-style method when they are addressing to a homogeneous group of young people, with preliminary and extensive concepts from the pre-clinical years and for whom the information presented makes sense and it is easy to understand. For more difficult subjects, students prefer a direct teaching method, in which they manage to write down the information as accurately as possible, in order to have the chance of a second or third passage through the materials represented by their own notes, in the idea that the information it was so abundant that the student (less familiar with information gaps from previous years) could not be assimilated. For such students, who have become more accustomed to the learning required to go to the University of Medicine, the lecture-method makes it less difficult for students to be less thorough, as they need accurate exposure of information and at a slower pace, so that the lesson can be more easily assimilated.

Regarding the presentation style of the information in the courses, the total distribution at the level of both faculties is presented in Figure 2 – presentation style. We consider that it is a too high percentage of teachers who read the presentations in the courses, being more a monologue type course, than a bidirectional one in which the information is incorporated by the student. It is true that of this 48%, 66% of respondents were medical students. This suggests, again, that the need for knowledge, the dictionary that future doctors must master, is much greater than that of sports specialists. Thus, it is absolutely necessary for health teachers to exhaustively expose, perhaps sometimes arid and dull, medical terms that students must master.

Figure 2: Presentation style



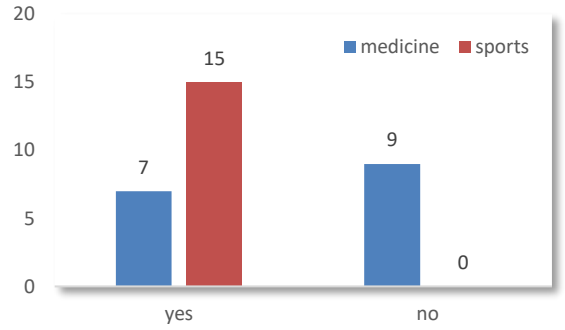
This research can show the need for certain teaching materials that must be presented in a readable and slow tempo. This need is related to a psychological concept regarding the teacher's ability to establish a connection between the unconscious mind of the students (who

gradually enter in a learning state) and the unconscious mind of the teacher (the later having a more systematized information). The slow tempo prepares the student to enter the scientific atmosphere in a preliminary psychic state, kind of an awaiting state of mind for the "key" information, which comes gradually. The student must receive the information with the same curiosity, interest and respect for the simple information. These will represent clues for the future job, because the causal links cannot be understood exactly if the students expect only interesting and spectacular information and they pay attention only when these are exposed.

Most students (81%) of both groups estimated that a course has about 10-20 pages. All subjects accepted that they reopened the materials for the information taught in their practice.

To the question that probed the need to individually read and understand the content of the courses, the students from the sports university answered, in a percentage of 100%, yes. On the other hand, in the group of medicine students, the distribution was uneven. This shows us that at the university of medicine is a much more detailed and exhaustive content that requires explanations from teachers, while at the sports university is more emphasis on the practical side, students having the necessary knowledge to understand the content of the courses. The explanation can be seen in the Figure 3.

Figure 3: The need to extract the main information individually from the course content (number of students)



Regarding the information presented at either of the two faculties, if we refer to the high-level learning, more exactly, the preparation for master's or doctorate for UNEFS students versus the preparation for bachelor's or residency for medical students, it is necessary to explain the detailed information in time, for longer periods in terms of dosing effort. It is well known that for grade 7, students must go through the subject once, for grade 9, twice, and for grade 10, three times. This is especially important for difficult materials, which include arid parts (and less practical demonstrations), the preclinical subjects in the first years of the Faculty of Medicine or the theoretical parts of some less publicized sports. Also, the preparation of any important exam involves dosing the effort, thus, in the first days one learns about four-five hours a day, and in the last ten to fourteen days, in the memory has to run for the last time the whole subject, with the intelligence to focus on the key concepts and logical causal links.

The results showed that most medical students' courses have more than 7 pages, which makes them spend more time learning the content needed for summative assessment. It should be noted that the material to be learned from the Faculty of General Medicine follows a general pattern that involves a predetermined order: prevalence and incidence of the phenomenon/disease, etiological aspects, pathophysiological aspects, characteristic symptoms, their grouping in syndromes, main diagnosis, differential diagnoses, evolution and prognosis (positive factors, negative factors), treatment options. It is known that most of the time is spent understanding the pathophysiological mechanisms behind the diseases, but in the field of health it is absolutely necessary to go through these arid mini-chapters to understand the phenomenon in full, compared to specialists in sports, where the accent is on practical application. In addition to changing/developing learning skills in relation to the age and experience in student years, learning styles also change in relation to the years spent in a particular faculty, with the involvement in adapting to the specifics of that faculty. This capacity of adapting involves flexibility of thought and intellect and, of course, experience. Once familiarized with the most important concepts in the field of activity, after about five years in a faculty, students, master students, doctoral students or residents achieve the performance of reading about 20-30 pages of scientific content with which they are familiar, without feeling the effort, with pleasure, interest and the possibility of thinking in parallel for developing their own opinions. In the last category, the teaching-learning mechanism is reversed, starting from practice to conceptualization, which is more attractive for students because they enjoy the results of concrete work faster (Figure 4 – the learning processes).

At the level of both educational structures, students similarly reported the need to take notes during the courses, but two respondents from the medicine university noted that most courses receive written support which made them not need to take notes. We emphasize here the importance of distributing written course support to students.

Figure 4: The learning processes.

We consider that the educational instructional process is much more effective in the case of the existence of written materials after which the student can be guided later, during the individual study process. The main activity of the student during the course should be to focus attention on the topic of the course, on the information that the teacher has to offer. We are trying to adhere to a western education system, in which the modernization of the process with the help of technologies is desirable. We consider it appropriate to emphasize the link between taking notes and the facilitation of the active memorization, later learning and reproduction the material. There are students who manage to go through large materials (hundreds or thousands of pages) through active learning and using a specified type memory, the one from which the information drains unconsciously in a passive way. Others are focused on compiling their own notes, on taking notes, failing to store information if it is not processed and systematized in their personal way. We do not comment on the superiority of any of these techniques, but we want to emphasize different ways of how the mind function. The personal notes, as the individual dedicates himself to the profession, can become more and more schematic, becoming understandable only by the one who writes them. These personal notes can exclusively define causalities, "key" concepts, inferences, connections and fewer mnemonic formulas (these being typical for an earlier stage learning).

Another aspect to note is the desire for the lecture not to be completely similar to the course support and it proved to be more efficient to listen to the lecture, when the student does not focus on finding those notions in the written material, but on understanding the explanations given by the teacher and following the logical thread of the lecture, proving much more effective than the situation in which the student reads the learning content beforehand. The notions described in medical courses are difficult, imply new and unknown terms to the student, which makes it important to lecture and especially to be accompanied by explanations, examples that make the learning content more accessible. That said, the lecture is a material more understandable to the student than some course notes in medical terminology. In this case, the role of the lecture is to lower the level of understanding from abstract to concrete, from general to particular. Instead, in the sports environment, the provision of specialized materials is more easily accessible at first reading even to an audience unfamiliar with the field, but the difficulty lies in the practical applicability of the theoretical content.

In both Universities, students rated similarly on a Likert scale from 1 to 10 the "weight" – the difficulty of a course, somewhere at a grade of 7-8. This suggests that the teaching content is reported to the type of students taking part in the course. Thus, the participants do not have a comparison model, all the courses are of the same similar level within his university. At the both faculties we suggest the need to introduce courses with graded difficulty, thus the difficult subject is exposed at the, approximately, seventh-eighth meeting with students, after they have acquired interest in the studied information and have sufficient knowledge to be interested in deepening the subject.

We wanted to probe the students' conscientiousness about the self-instruction process for summative assessment. The Figure 5 shows the difference between continuous learning (throughout the year) and discontinuous learning (exhaustive period during the session, in which they only prepare for assessments). For medical students, there was a longer distribution of the self-taught learning process, instead, the sport university students organize their learning time in the last part of the semester.

Figure 5: Distribution of the self-training process over a longer period of time (number of students)

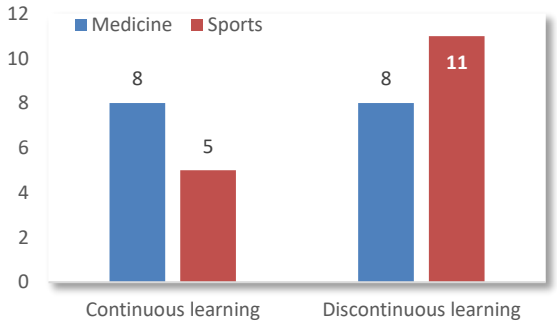


Figure 5 shows that the distribution of medical students' conscientiousness is divided equally between those who study continuously and discontinuously, while in the category of students at sports university, most of them learn the theory for the exam shortly before it.

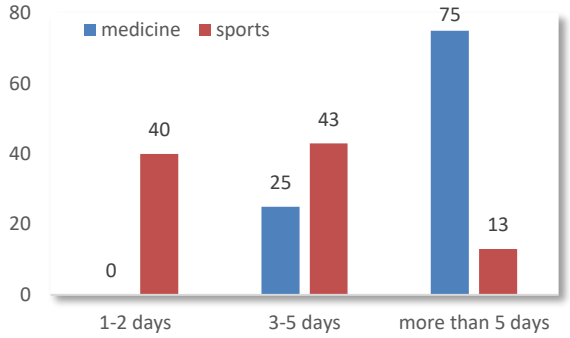
Among the explanations, we thought about the aspect that, in both situations, the practice of that profession has two components: the practical part (working with patients versus working with students) and the conceptualization part which

involves talking and theorizing what you do. For the doctor, we refer to the composition of the observation sheet, the possibility to explain the case and the scientific research; and for sport coaches and teachers, it involves the lesson plan, the training plan, the monitoring through observational feedback. Medical students, from year 3, go to hospitals, see clinical cases that arouse their interest, receive partial or incomplete explanations from their seminarians about solving the case. Thus, the interest to learn more is aroused, and with the help of modern forms of learning (internet, for example), their curiosity makes them look for information and learn more constantly through the challenges from practice to theory. This learning is not necessarily a systematized one, but it puts the student in a greater contact with the learning content.

The students at the sport University are concerned with everything related to the development and refinement of personal practical skills, but also of the subjects they work with, their goal being to accumulate their own experience as rich as possible from working with as many individuals and less to take from the experience of other colleagues, because the coach-athlete/teacher-student relationship is more personalized and longer lasting than the doctor-patient one (especially in the emergency medical branches and not in chronic diseases). However, there are also some long-term doctor-patient relationships, such as these in chronic diseases (such as psychosomatic, rheumatological, oncological diseases, which require time dosing the treatment regimens and proper management, both somatic and psychological). Such relationships are of the adult to adult type (when the patient is responsible for dose adjustment depending on the acute symptoms present), parent to child relationships (which are sometimes necessary when the patient himself is a doctor and such an attitude becomes useful for making the patient in question listen), friendship-type relationships (where the doctor goes from being an “enemy of the disease” to being a friend of the patient, a counselor, a trusted person who helps the patient not feeling the limitations imposed by disease). Similarly, the athlete-coach relationship can: define the coach’s domination (in terms of his personality and executive function) or transform the coach into an advisor of training, shifting the responsibility to the athlete. In the later type of relationship, the coach becomes guide for optimal and efficient development of his athlete. The coach can be a mentor, a friend, an advisor, an authoritarian superego, who controls the desires and objectives of his athlete and the dosage of efforts, but always maintains the high-performance standard.

We objectified that most medical students give for the learning process over 5 days before an exam, while those at the sports University give 1-5 days. The uneven distribution can be seen in the Figure 6.

Figure 6: Distribution of days granted for learning process, compared between the two universities (percentage of the students)



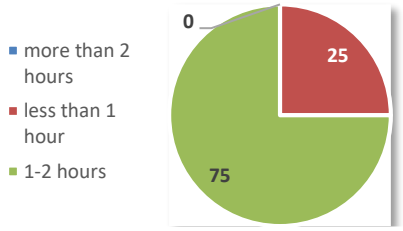
An explanation of the phenomenon could be that those medical students who give more than 5 days are those who, over time, have formed a structured thinking, to learn in steps, from micro aspects, to macroscopic aspects, from pathophysiology and etiology towards the logical understanding of the formation of the symptoms characteristic of the respective disease. In another category are those medical students who believe that diseases should be acquired from the clinic to understand the etiology and thus, they intentionally omit the arid part of the learning content, believing that it operationalizes learning. Many of these "more efficient" students can get high grades in practical exams, maybe even at oral ones, where the teacher requires only the clinical conceptualization of the case, but still a deeper approach will reveal the gaps in understanding the etiopathogenic phenomenon

We sought to probe the maximum time a young person can stay focused in a learning activity in late adolescence and whether there are differences between the training and the profession they choose, differences that will influence their ability to concentrate. From the collected data, we did not discover significant differences, which leads us to think that this capacity depends on certain internal factors and on the stage of personal development. This can be seen in the Figure 7.

The psychological explanation of this phenomenon can be in the concept of endurance and the development of long-term endurance in terms of staying longer and longer in contact with notions, concerns, problems, conceptualizations of the chosen profession. The faculty and the acquisition of information during it are only the preamble, endurance itself is obtained with the practice of the profession, important roles having curiosity, self-improvement, desire to be up to

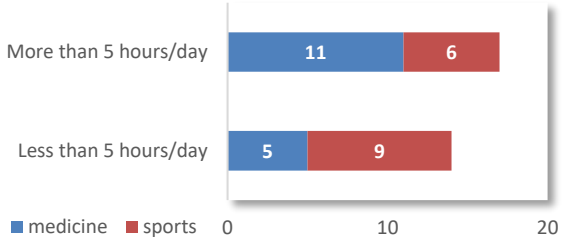
date with news, desire to interact and exchange information with other professionals. We consider that the age range of 18-25 years is the one in which the foundations of endurance are barely laid and still different students are looking for the right techniques for acquiring information, sweeping between what would be easy from theory to practice or to practice in theory ("learning to learn").

Figure 7: Concentration endurance



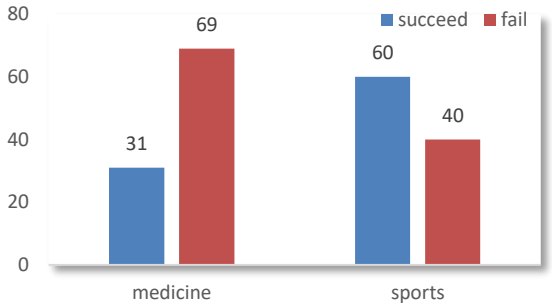
We found that there are significant differences between group samples in terms of the maximum number of hours per day spent for individual study. The percentage of those who spend more than 5 hours a day for individual study is in medical students' area. This demonstrates that they make greater efforts to self-train, have a greater ability to organize, focus on the task, a higher motivational motive, but also the desire for self-improvement more developed than in the field of physical education. The distribution can be seen in the Figure 8.

Figure 8: The maximum number of hours per day spent for self-training (percentage of the students)



We also probed the importance of the self-taught process, by asking the need to study at home the material presented in the course to pass the final exam. We wanted to emphasize that medical students need a period of self-improvement, a period of in-depth assimilation of the information presented to the course or practical work, compared to those from a sports University, who managed to pass the exams based only on the knowledge assimilated to the courses (Figure 9).

Figure 9: The process of passing the exams based only on the knowledge assimilated to the course (percentage of students)



DISCUSSION

There is a major difference between the style of teaching knowledge for students in the two faculties - the mechanism for medical students is from theory to practice; while for students in the field of physical education, the learning mechanism is reversed, from practice to the formulation of theories.

The field of medicine has been developed for thousands of years, and during all this time, specialists have learned to work simultaneously: in one plan to diagnose and treat, and in the other to make explicit, theorize, generalize, argue, and develops an inferential and dichotomous thinking. They have developed their own style of communication between specialists to convey key information in operationalized and synthetic concepts. Thus, 66% of medical students perceive that the teaching style of teachers regarding the medical dictionary must be mastered as being much focused on the presentation of information and less on practical applicability. Instead, sports coaches or teachers have recently started to focus on the conceptualization of their work, on quantification, on operationalization, on ways of exchanging information (to external sources such as: psychologist, athlete's family, school leader, etc. or between them as specialists).

100% of the students from the sports University consider that they need to inspect the learning material themselves, but it is very important that they have the necessary information to understand it individually. In the field of coaches and sport teachers, the emphasis was on the practical side, on streamlining the educational-instructional process, on refining personal skills, on developing the means and methods of teaching the learning content.

Teachers in both faculties should focus on lecture-type teaching, but not identical to the written material; they have to include examples, follow a red thread (message to take home) and ensure that it has been passed on to the student.

Along these lines, students should be considered active partners in the teaching process even if their level of instruction is much lower than the teacher's one and even if there are significant differences between participating students in terms of previous level of knowledge, involvement, curiosity and motivation. The teacher's role is to modulate the "global intelligence of the audience", encouraging the obviously participatory students and stimulating the less interested ones. It would be a didactic mistake to have the preconception that the overall intelligence of the audience is low, which may lead the teacher to lower the level of the lecture or consider that it is no longer necessary to provide complete information, omitting examples and features or not presenting parts considered more difficult. Students similarly rate the weight of the courses on grades 7-8, which demonstrates that the learning material is hard enough to keep them focused and grasp in their understanding, but easy enough not to lose them and to be at their level of knowledge.

Among the teacher's tasks should be to increase the student's endurance (making him forget how time passes), involving him in active listening in which the student's thinking becomes a partner of the teacher's thinking in understanding the chain of information explained (even if it not perceived). We notice that in young people aged 18-25, endurance is limited to 1-2 hours mostly, but it is acquired by stimulating logical thinking, memorization through vivid representations with reference to clinical cases and practical applications. It is also known that during this period, students are still learning how to improve themselves, how to learn information more effectively, learn how to learn. At the end of the lecture, the student must remain in a still active state, with the desire and curiosity to look for a minimum of personally discovered information regarding the topic of the course presented. Also, the student's thinking must remain during the lecture able to compare the newly received information with a previous knowledge database, which helps him to make his entire previous notional system richer and supported on a more solid basis.

According to the scientific literature, the period of late adolescence is considered a maximum in terms of the ability to assimilate new information, as well as curiosity and openness to it, the desire to filter and systematize it according to personal experience. Therefore, the teacher must teach them a material appealing to the maximum capacity that he intuits as being present in these young people, crediting them with motivation, life choices, determination for the profession, the belief that they will never give up self-improvement.

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Authors' contribution:

AIT and RTB contributed in all the stages of the article, they designed the article and revised the manuscript for important intellectual content. AIT acquired the data and AIT and RVC drafted the work. RVC contributed to the conception of the work and revised the language.

All authors read and approved the final manuscript.

Ethics approval and consent to participate:

For this study, the agreement was obtained from the Ethics Committee of Teaching Staff Training Department of The National University of Physical Education and Sports. The subject data were completely confidential and they approved the publication of data.

Patient consent for publication: Not applicable.

Competing interests:

The authors declare that they have no competing interests.

Availability of data and materials:

The information generated and analyzed during the current study is available from the corresponding author on reasonable request.

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VARIA

Evaluation of systemic second-line therapy in recurrent or metastatic esophageal cancer

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Abstract: *Background: More than half of patients with locally advanced esophageal cancer are unresponsive to first-line chemotherapy. To date, there is no standard second-line regimen; new agents, such as immune-checkpoint inhibitors or anti-Neurotrophic Tropomyosin-Related Kinas agents, have only been recently recommended. This study aimed to assess the benefits of classical second-line chemotherapy in terms of survival and tolerance. Materials and Methods: This retrospective analysis assessed the benefits and tolerance of different second-line regimens of chemotherapy in progressive, locally advanced or metastatic oesophageal cancer treated at the department of Radiotherapy-Oncology at the Institute of Oncology between January 2011 and January 2017. Results: The analysis found 87 patient files with a median age 59.5 years (ranging between 41 and 84), of which 40.2% (35 patients) failed the first-line platinum and 5-fluorouracil combination. Histology favoured adenocarcinomas (63.2%). The patients were in good clinical condition, with ECOG 0–1 in 86.1% (74 patients), and less than five percent had more than three metastatic sites (3.4%, 3 patients). The regimens were mostly two-drug cytotoxic (53.9%, 47 patients): FOLFIRI in 18 patients (20.7%), FOLFOX in 18 patients (20.7%), vinorelbine–platinum combination in 11 patients (12.6%), and docetaxel in 40 patients (38.7%). The median treatment duration was 7.74 weeks (range 1 to 12). The general response rate was 47.1% (41 patients), including stable disease. The median time to progression was 7.61 weeks, with a range between 1.6 and 8.6 weeks, with no differences in this respect among the fourth type of treatment received (p = 0.170). Grade 3–4 toxicities, including neutropenia, gastrointestinal problems, and metabolic disorders, were observed in 44 patients (50.6%). The median event-free survival was 2 months (range between 1 and 6.3), and 63.2% (55 patients) subsequently received a third line of chemotherapy. Conclusion: Second-line chemotherapy is still the first-choice recommendation in all fit patients with advanced oesophageal cancer. The new agents are efficacious only in cases with PD-L1 positive or high microsatellite instability.*

Keywords: *second-line chemotherapy, locally advanced/metastatic oesophageal cancer, survival benefit, toxicity*

INTRODUCTION

Esophageal cancer has two histopathological subtypes: squamous carcinoma found in the superior and upper-two-thirds regions [1], and adenocarcinoma, which develops at deep inferior and junctional mucosal glands. Both have high similarities in their pattern of metastasis [2]. Esophageal cancer is the sixth most common cause of specific deaths worldwide [3]. The peak of incidence is reported in the sixth decade of age, and cancer occurs more frequently in men [4].

Approximatively half of the patients have advanced disease at diagnosis. Three-quarters of resectable disease will relapse, of which more than half will be candidates for

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second-line systemic therapy [5]. Overall five-year survival is less than 10% [3].

Regarding the first line, for adenocarcinoma, the regimen used is similar to those used in gastric cancer, fluoropyrimidine-based chemotherapy while in squamous esophageal cancer the regimen is cisplatin-based and in general, regardless the histology, the median overall survival (OS) does not exceed nine months [6].

Currently, there is no established second-line systemic treatment for esophageal cancer [7]. Subsequent lines of chemotherapy have recently been proposed by NCCN (National Comprehensive Cancer Network) guidelines for locally advanced or metastatic esophageal and oesophagogastric junction cancer [8]. New treatment options include ramucirumab and paclitaxel which give a 2-month benefit in median overall survival (9.6 months versus 7.4 months for paclitaxel only, p = 0.017) [9]. Pembrolizumab is a category 1 recommendation anti-PD1 (programmed cell death protein) antibody for esophageal PD-L1 (programmed death-ligand 1) positive or for any histology displaying MSI-H (microsatellite instability-high) or d-MMR (deficient mismatch repair) status [8] based on a benefit of 1 month (8.2 vs. 7.1 months, HR = 0.78, P = 0.0095) versus classical chemotherapy taxanes or irinotecan in the squamous cell carcinoma subgroup [10]. With a 2B level of recommendation, entreticnib is proposed for a median 10 months' duration of response, 95% CI [7.1 - NE] [11], and larotrectinib is proposed in NTRK (Neurotrophic Tropomyosin-Related Kinase) fusion-positive esophageal tumours [12].

MATERIALS AND METHODS

Medical files from the institutional database of patients diagnosed with metastatic invasive esophageal squamous cell carcinoma (SCC) or adenocarcinoma (AC), referred to our institution for second-line chemotherapy were analysed. The main inclusion criteria were age >18 years, clinical-stage IV according to AJCC 8th edition [15], treatment by at least one regimen of chemotherapy or radiotherapy and assessed for response.

Patients were excluded if they were eligible for salvage surgery or had synchronous cancer or severe comorbidities that might impair our results. The study was approved by Ethycal Committee of Insitute of Oncology "Prof. Dr. Alexandru Trestioreanu", Bucharest, Romania no 1597/17th December 2010.

The primary outcome was time to progression, evaluated between the start of second-line chemotherapy and first progression or death by any cause. Secondarily, treatment benefit was evaluated using CT scan, and, in terms of tolerance, the rate and duration of grade III-IV adverse events (AE) classified according to CTCAE v. 4.03 [16].

Data were analysed using SPPS version 23 (IBM Corporation, Armonk, NY, USA). Non-parametric tests were used to compare subgroups. The chi-squared test determined the correlation between response to treatment and demographic and clinical variables. Fisher's exact test was employed when there were fewer than five cases in any cell of the 2×2 table. The associations between variables and survival parameters were analysed by logistic regression analysis, and survival curves were generated using the Kaplan–Meier method and compared using the log-rank test. Hazard ratio (HR) and 95% confidence interval (CI) for variables were calculated using the Cox proportional hazard model. All statistical tests were two-sided, and a p-value < 0.05 was considered significant.

RESULTS

3.1. Patient characteristics

During the period of analysis, a total of 87 patients were treated in our department by chemotherapy for esophageal cancer, with a mean age 59.5 (range between 41 and 84). Among them, 37 patients were treated for recurrent disease, 29 patients had metastatic disease at initial presentation, and 21 patients received the second-line treatment for a locally advanced disease with no indication of surgery or radiotherapy.

The principal histology was adenocarcinoma (63.2%, 55 patients), and the primary lesion was typically situated in the lower and junction of the esophagus (48.9%, 51 patients). One-third of patients had liver metastasis, but almost all had no more than two sites of secondary lesions (96.6%, 84 patients) and were in generally good condition, with ECOG 0–1 in 85.1% (74 patients) (Table 1).

Table 1: Patients characteristics in target population

Characteristics	n	%
Age (years): median 59.5; range [41–84]		
40–50	14	16.1
51–70	63	72.4
>70	10	11.5
Gender		
Male	58	66.7
Female	29	33.3
Location of primary lesion		
Upper	14	16.1
Middle	22	11.5
Lower	25	35.6
Junction	26	33.3

Characteristics	n	%
Histopathological sub-type		
Squamous cell carcinoma	32	36.8
Adenocarcinoma	55	63.2
The initial stage of disease		
I	17	19.5
II	10	11.5
III	31	35.6
IV	29	33.3
Metastatic site		
Lymph node	18	20.7
Lung	18	20.7
Liver	30	34.5
Bone	12	13.8
Other	9	10.3
Number of metastatic sites		
1	50	57.5
2	34	39.1
3 and more	3	3.4
ECOG		
0	44	50.6
1	30	34.5
2	13	14.9

Abbreviations: CHT = chemotherapy, ECOG = Eastern Cooperative Oncology Group Performance Status, FU-PI: 5-fluorouracil–platinum regimen, LV5FU2CDDP =5-fluorouracil 1600 mg/m2 + leucovorin 200 mg/m2 + cisplatin 50 mg/m2q2w, 5FU-CDDP=5-fluorouracil 1000 mg/m² day 1-4 + cisplatin 100 mg/m² day 1 q3w, PR = partial remission , PD = progressive disease, SD = stable disease.

3.2. Treatment characteristics

The first-line combination of cisplatin plus 5-FU (5-fluorouracil) was most typical in localized and metastatic esophageal cancer (40.2%, 35 patients). This combination involves 5-fluorouracil 1000 mg/m² per day for 4 days and cisplatin 100 mg/m² on day 1 every 21 days (17) or, in the so-called LV5-FU2 – cisplatin two-week regimen, cisplatin 50 mg/m², calcium folinate 200 mg/m², 5-FU 400 mg/m² on day 1 and 5-FU 1200 mg/m² over a 46-hour continuous infusion (18). Other protocols used were FOLFIRI (39 pts, 44.8%) vinorelbine-cisplatine based (10 pts, 11.5%) and taxane based (3 pts, 3.4%).

Patients who received FOLFOX regimen, as second line treatment modified they represented 20.7% (18 patients), 46% (40 patients) received a docetaxel regimen, 20.7% (18 patients) received a FOLFIRI regimen, and 12.6% (11 patients) received a vinorelbine–cisplatin regimen. Details regarding the protocols used in second line are listed in the Table 2.

Table 2: Second line chemotherapy protocols summary.

Second line regimen	Protocol summary	Number patients	Response rate	Reference
FOLFOX6	oxaliplatin 85 mg/m², leucovorin 200 mg/m², 5-FU push 400 mg/m², 5FU 2400 mg/m² for 46 hours, q2w	18 (20.7%)	83.3% (15 pts)	(19)
NVB-CDDP	vinorelbine 25 mg/m² day 1+ 8, cisplatin 80 mg/m² q3w	11 (12.6)	45.5% (5 pts)	(20)
FOLFIRI	irinotecan 150–180 mg/m², 5-FU 400 mg/m² push, leucovorin/ calcium folinate acid, 125mg/m², 5-FU 2400 mg/m²/46 hours, q2w	18 (20.7%)	50% (9 pts)	(21)
DTX	docetaxel 75mg/m², q3w	40 (46%)	12 (30%)	(22)

Abbreviations: FOLFOX6 = Oxaliplatin 85 mg/m²+ leucovorin 200 mg/m² + 5 FU 2800 mg/m² q2w, FOLFIRI = Irinotecan 150–180 mg/m² + leucovorin 125 mg/m² + 5-FU 1600 mg/m² q2w, NVB-CDDP = Vinorelbine 25 mg/m² day 1 + 8 + cisplatin 80mg/m² q3w, DTX = docetaxel 75 mg/m² q3w.

The median time of chemotherapy was 7.74 weeks, with a range between one and twelve weeks. The mean number of cycles was 2.36, with a range between one and seven cycles and no significant differences was registered between the medians of any regimen (p = 0.065). Choice of chemotherapy regimen was correlated with the initial stage of disease, histological subtype, the number of metastatic sites, site of metastasis and performance status (p < 0.0001). More than half of the patients included in the study were able to benefit from the third line of treatment (55 pts, 63.2%) (Table 3).

3.3. Benefit

The response rates that were obtained were as follows: 28.7% (25 patients) had partial remission, 18.4% (16 patients) stable disease and 52.9% (46 patients) recorded either clinical or radiological progression.

Table 3: Second line chemotherapy protocols characteristics and toxicity.

Characteristics	n	%
Number of cycles: median 2.87, range [1–7]		
< 2	28	32.2
2–4	45	51.7
> 4	14	16.1
CHT duration (weeks): median 7.74, range [1–12]		
< 6	20	22.9
6–8	52	59.7
> 8	15	17.3
Grade 3–4 toxicities		
Without	44	50.6
Haematological	30	34.5
Gastrointestinal	10	11.5
Metabolic disorders	3	3.4

The difference between the response to different second line regimen of chemotherapy were not statistically significant (p=0.042).

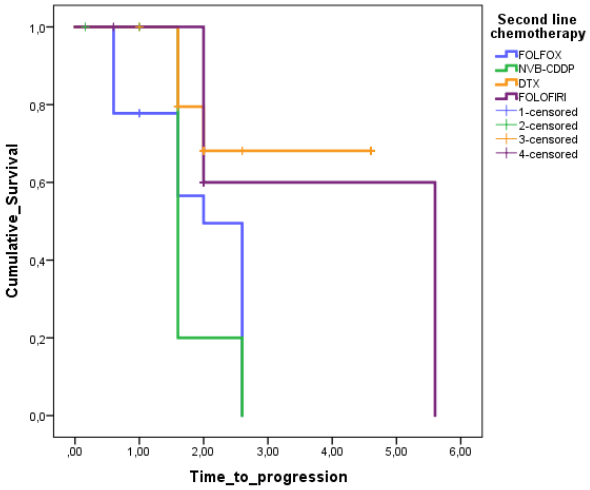
We estimated that the median OS on the basis of the results of several studies of second-line chemotherapy [26-29].

Response was directly correlated with primary tumour location (p = 0.022) and histopathological subtype (p = 0.017) and with tumour burden and type of chemotherapy regimen (p < 0.0001).

The median time to progression was 7.61 weeks, ranging between 1.6 and 8.6 weeks, with no statistical difference between the fourth type of treatment received (p = 0.170).

Time to progression was associated with the number of metastatic sites (HR 2.886, p = 0.004) but not with the type of chemotherapy regimen (p = 0.373). By contrast, the log-rank test showed significant differences in time to progression by type of chemotherapy (chi-square 22.1852, p < 0.0001) (Figure 1).

Figure 1: Kaplan–Meier curves in locally advanced or metastatic oesophageal cancer patients according to the second-line chemotherapy regimen.



Fifty-five patients (63.2%) could benefit from a subsequent, third line of chemotherapy.

The median event-free survival for all patients was two months, with a range between 1 and 6.3 months.

3.4 Toxicity

Forty-four patients (50.6%) displayed no grade III-IV toxicities. Seven patients displayed haematological and gastrointestinal disorder together, and all patients presenting metabolic disorder also had febrile neutropenia.

DISCUSSION

Esophageal cancer are a challenging disease for which there are limited treatment effective options. Despite research, the only treatment with clinical benefit and more accessible in the second-line setting remains chemotherapy.

The population in our study was in relatively good clinical condition: 85.1% with ECOG 0 or 1, almost all without more than two sites of metastasis (96.6%), younger than 70 and, in more than 60%, bearing adenocarcinoma as histological subtype. In this analysis, the most-used (53.9% of cases, 47 patients) were two-agent regimens: FOLFIRI, or cisplatin–vinorelbine, and FOLFOX. The median treatment duration was 7.74 weeks, and most had received 5-fluoropyrimidine in the first line (85.1%, 74 patients).

The general benefit was reflected by a 47.1% (41 patients) response rate, including cases with disease stabilisation, the median time to progression of 7.61 weeks (range 1.6 to 5.6 weeks) and a median time to death of 2 months (range 1 to 6.3 months). Chemotherapy was generally tolerated, though almost half of patients developed grade III-IV toxicities; one-third of these were mostly non-complicated grade III anaemia or thrombopenia.

Several earlier retrospective or phase II studies have evaluated whether second-line chemotherapy might be useful for oesophageal cancer patients.

Regarding irinotecan, in a small phase II study, 29 patients (27 with adenocarcinoma) were given capecitabine 2,000 mg/m2 day on days 1–14 and irinotecan 250 mg/m2 every 3-week cycle. The study showed an objective response of 17% (five patients) and median progression-free survival of 3.1 months 95% CI [2.2–4.1] and median OS of 6.5 months 95% CI [6–7.1] with a 10% rate of febrile neutropenia [24].

In another phase II study, irinotecan combined with cetuximab in 63 cases of platinum-refractory gastro-esophageal carcinoma, led to an 11% (6 patients) partial response rate and 37% (23 patients) rate of stabilization, with median progression-free survival of 2.8 months, median overall survival of 7.1 months and a 32% rate of grade III-IV toxicities [25].

Even as a single agent, irinotecan showed a survival advantage, compared to best supportive care, in 40 patients with metastatic or locally advanced adenocarcinoma gastro-esophageal of the junction. Irinotecan given of 250 mg/m2 with the possibility of an increase to 350 mg/m2 if well-tolerated, gave a 53% rate of stable disease and 50% clinical benefit versus 7% and a median survival of 4 months 95% CI (3.6–7.5) versus 2.4 months 95% CI (1.7–4.9) and 0.48 HR for death 95% CI (0.25-0.92) [26].

In untreated metastatic gastro-esophageal adenocarcinoma (N = 220 patients), by substituting oxaliplatin for cisplatin in a FOLFOX-like regimen (fluorouracil 2,600 mg/m^2 over 24-hour infusion, leucovorin 200 mg/m^2 and oxaliplatin 85 mg/m^2 every 2 weeks) there was no statistically difference in terms of progression-free survival (5.7 vs. 3.9 months, p = 0.077), response rate (35% versus 20%) or median overall survival (10.7 vs. 9.8 months). Adverse events were significantly fewer (9% vs. 19%) and treatment showed better responses in patients aged over 65 years old compared to cisplatin: 41.3% response rate versus 16.7% (p = 0.012), time to treatment failure of 5.4 versus 2.3 months (p < 0.001) and progression-free survival of 6.0 versus 3.1 months (p = 0.029) [19]. A later meta-analysis (N =1294 patients in three randomized trials), regarding the meme subject, showed improved progression-free survival (HR = 0.88, p = 0.02) and overall survival (HR 0.88, p = 0.04) in advanced, unresectable gastric cancer [27].

In a monocentric retrospective study of 94 patients with metastatic esophageal cancer, a modified FOLFOX 6 regimen comprising fluorouracil 2400 mg/m^2 over 48 hours after a bolus of 400 mg/m^2, leucovorin 400 mg/m^2 and oxaliplatin 85 mg/m^2 gave an objective response rate of 41.4% (39 patients), of whom 6.3% (6 patients) with a complete response and 21.3% (20 patients) with stable disease. Any grade of hematologic toxicity was found in 69.1% of cases [28].

Regarding taxane-based chemotherapy, the UK COUGAR-2 phase III study(N=168) confirmed the benefit of second-line chemotherapy by docetaxel 75 mg/m^2 every 3 weeks compared to best supportive care by a median OS of 5.2 versus 3.6 months (HR 0.67, 95% CI [0.49–0.92]; p = 0.01) in patients with a good performance status [22].

In a retrospective study which assessed in 163 patients the clinical benefit of second-line taxane therapies, docetaxel at 70 mg/m^2 every 3 weeks versus paclitaxel 100 mg/m^2 weekly for 6 weeks of 8 weeks cycle, survival without progression was identical (2.3 months) for both regimens the overall survival was 6.1 versus 5.3 months, with 32.6% and 16.1% rates, respectively, of grade III-IV toxicities [29].

Only a few randomized studies have compared the benefits of different second-line chemotherapy regimens, mainly in gastric cancer and in Asian patients.

In 202 Korean patients with less than two prior lines of chemotherapy, randomized in a 2:1 ratio treated with docetaxel or irinotecan compared with supportive treatment,was recorded a superior overall survival (5.3 vs. 3.8 months; HR 0.66, p = 0.007) while no survival difference was recorded between docetaxel and irinotecan. The tolerance was good, the hematologic toxicities manageable and the rates of non-haematologic toxicities were comparable in both groups but there was with no significant differences in terms of survival between two regimens of chemotherapy [30].

In another Asian study, in 223 Japanese patients randomized to received paclitaxel alone or irinotecan alone as second line treament, the median overall survival was comparable (9.5 vs. 8.4 months, p = 0.38), although less toxicity appeared in the paclitaxel arm and more of those patients went on to receive third-line chemotherapy [31].

In a meta-analysis of 28 studies (N = 4810 patients), mostly retrospective, the second line showed no difference between taxane- and irinotecan-based regimens in terms of overall survival (HR 0.94, CI [0.78–1.13]) or survival without progression (HR 0.84, CI [0.69–1.03]), nor was there any difference for any single-agent regimen compared to best supportive care (HR 0.65, 95% CI [0.53–0.79]. Median survival gain ranged from 1.4 to 2.7 months among the individual studies considered. Doublet chemotherapy based on taxane or irinotecan plus platinum and fluoropyrimidine did not display different survival but showed increased toxicity compared to taxane or irinotecan monotherapy [6].

As far as new agents, despite the failures of several clinical trials involving molecularly targeted agents, several have shown some benefits worth mentioning that represent the basis of NCCN recommendations [8].

Ramucirumab, an antibody that targets the vascular endothelial growth factor receptor 2, the expression of which might be a mechanism of the aggressiveness of gastric and gastro-esophageal junction adenocarcinoma, led in pre-treated patients with esophagogastric cancer significant survival benefit, 5.8 months compared with 3.8 months for placebo (HR 0.776, 95% CI [0.603–0.998]), a similar benefit were seen in the COUGAR-02 trial assessing the benefit of docetaxel [32].

By adding paclitaxel to ramucirumab, in another phase III trial, it was reported a significant benefit in terms of median OS 9.6 months versus 7.4 months, HR 0.807, 95% CI [0.678–0.962] (p = 0.017). In terms of adverse events, the association was mainly marked by hypertension (14%, 46 patients vs. 2%, 8 patients), fatigue (12%, 39 patients vs. 5%, 18 patients) and abdominal pain (6%, 20 patients vs. 3%, 11 patients) [9].

Regarding the role of immune checkpoint inhibitors, in the KEYNOTE 181 trial (N = 628 patients), the response rates with pembrolizumab were double or even triple those achieved with chemotherapy at the investigator's choice (paclitaxel,

docetaxel, or irinotecan), though the median duration of response was longer in the group with PD-L1 CPS (Combined Positive Score) equal or higher than 10 (9.3 vs 7.7 months with chemotherapy HR 0.69; 95% CI [0.52–0.93]; p = 0.0074); 12-month overall survival rate in CPS ≥10 patients was 43% compared to 20%. With pembrolizumab, fewer patients had drug-related adverse events of any grade (64% vs. 86%) or grades 3 to 5 (18% vs. 41%) compared with chemotherapy. The most common events were fatigue (11.8%), hypothyroidism (10.5%), loss of appetite (8.6%), nausea (7.0%) and diarrhoea (5.4%) [10]. The phase III KEYNOTE-590 study (ClinicalTrials.gov identifier NCT03189719), assessing the efficacy and tolerance of pembrolizumab plus chemotherapy as first-line therapy for locally advanced or metastatic esophageal carcinoma, is ongoing [33].

HER 2 (human epidermal growth factor receptor) expression was not considered in the study due to the fact that it was not frequently found in the study population, and Trastuzumab treatment is not approved in Romania for second-line treatment [23, 34].

The time to disease progression was quite difficult to track due to the fact that several patients have continued their treatment at other institutions or have been transferred to a palliative care unit without the possibility to obtain their date of death, because in Romania there is not a computerized death reporting system and this is a limitation of the study.

The limitations of our study were the retrospective character, small number by each subgroup of treatment patients and lack of the subgroup of patients treated with both active and passive immunotherapy.

CONCLUSIONS

Immunotherapy using immune checkpoint inhibitors has revolutionized the cancer treatment and becomes the new standard of second line treatment in non-operable advanced or metastatic esophageal cancer.

Moreover, the new agents seem to be efficacious only in cases where the expression PD-L1 is positive or high microsatellite instability is present.

The old chemotherapy regimen has a similar efficacy and relatively good tolerance and still might the first-choice recommendation in fit patients

This analysis showed a generally good response to systemic treatment, comparable to the responses reported in other studies.

Our study did not show a difference in clinical benefit depending on the treatment regimen.

Moreover, the incidences of adverse events such as grade 3 or higher leukopenia and febrile neutropenia was observed in all patients. Forty-four patients (50.6%) displayed no grade III-IV toxicities. Seven patients displayed haematological and gastrointestinal disorder together.

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Competing interests:

The authors declare that they have no competing interests.

Availability of data and materials:

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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VARIA

Therapeutic decision of laparoscopy and its benefits as a gold standard in acute cholecystectomy

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Abstract: *Background: Acute cholecystitis is the most frequent complication of cholelithiasis and counts for one third of surgical emergencies.*

Aim: The study evaluates the outcomes and limits of laparoscopic cholecystectomy in acute cholecystitis.

Materials and methods: A retrospective study was performed for 2 years, between 01.01.2016-31.12.2017 in the 2nd Surgery Department of the Sibiu County Emergency Clinical Hospital, on hospitalized patients with acute cholecystitis, who underwent surgery. The severity of acute cholecystitis was analyzed using the Tokyo Guidelines (TG13 / TG18) severity risk scale. The preoperatory evaluation of the anesthetic-surgical risk was based on American Society of Anesthesiologists Physical Status Classification (ASA PS) and Charlson Comorbidity Index (CCI) (9). Statistical analysis was performed to analyze the outcomes and limits of laparoscopic cholecystectomy and the risk factors for conversion and open surgery.

Results: Out of the 262 patients in the study group, most of the patients (61%) were diagnosed with moderate acute cholecystitis, while 67 patients (26%) were diagnosed with mild form and 34 (13%) with severe acute cholecystitis. Laparoscopic cholecystectomy was performed in 96.1% of cases with no conversion to open surgery. The postoperative complications were ligature slippage (1.9%), main bile duct injury (1.9%), postoperative hemorrhage (3.9%) and surgical site infections (2.4%), most of them being managed conservatory.

Conclusions: Laparoscopic cholecystectomy can be performed nowadays with minimal morbidity in acute cholecystitis. Knowledge of various factors predicting possible conversion helps in adequate pre-operative selection and counseling for open procedure with further reduction in the overall morbidity of laparoscopic cholecystectomy.

Keywords: *laparoscopic cholecystectomy, acute cholecystitis, risk factors, inflammation*

INTRODUCTION

Acute cholecystitis is the most frequent complication of cholelithiasis and counts for one third of surgical emergencies. Blocked stones at the level of the infundibulum or cystic duct generate inflammatory phenomena of variable intensity, from mild to severe, with organ failure and septic condition. It is considered to be the second source of complicated intra-abdominal infection (18.5%), according to the World Society of Emergency Surgery complicated intra-abdominal infections Score study [1]. Laparoscopic cholecystectomy has become the "gold standard" in treatment of biliary lithiasis due to its undeniable advantages in reducing pain and postoperative complications. However, there are still controversies regarding the management of patients with acute cholecystitis. In the early days, after the first laparoscopic

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cholecystectomy, acute cholecystitis was considered as an absolute and later, a relative contraindication for this surgery [2] due to the possible risk of increased morbidity, especially common bile duct injuries [3].

The current concept is in favor of emergency intervention in the first 72 hours after hospitalization, as there is no evidence that delaying the intervention after resolving the acute outbreak would benefit in reducing intraoperative complications, especially major biliary tract injuries, due to local fibrous remodeling [4-7]. The current guidelines recommend surgery as soon as possible because evidenced-based clinical studies confirmed that an early treatment reduces the total hospital stay and does not increase the complication or conversion rates [8].

The study evaluates the outcomes and limits of laparoscopic cholecystectomy in acute cholecystitis.

MATERIALS AND METHODS

A retrospective study was performed for 2 years, between 01.01.2016-31.12.2017 in the 2nd Surgery Department of the Sibiu County Emergency Clinical Hospital, on hospitalized patients with acute cholecystitis. The inclusion criteria were:
- hospitalization diagnosis of "Acute non-/lithiasis cholecystitis"
- histopathological confirmation of the acute character of the inflammation of the gallbladder wall;
- surgical treatment of the pathology during hospitalization.

Patients with acute biliary pathology, but who were not treated surgically, and patients who did not show acute inflammatory signs in the gallbladder were excluded.

Observation sheets and operating protocols were analyzed. The collected data documented age, sex, associated pathology, preoperative clinical and paraclinical data (hemoleukogram, fibrinogen, AST, ALT, bilirubin, amylase, INR, urea, creatinine, abdominal ultrasound), type of intervention, postoperative complications, appearance histopathological examination of the gallbladder specimen, duration of hospitalization. The severity of acute cholecystitis was analyzed using the Tokyo Guidelines (TG13 /TG18) severity risk scale. According to this classification, Grade III (severe acute cholecystitis was considered the acute cholecystitis associated with organ/system (renal, cardiovascular, hepatic, respiratory, neurologic, hematologic) dysfunction, Grade II (moderate) acute cholecystitis associates clinical signs of acute cholecystitis with white blood cells (WBC)>18000/mmc, palpable tender mass in the right upper abdominal quadrant, marked local inflammation and the onset of symptoms of more than 72 hours before presentation. Grade I (mild) acute cholecystitis is defined as acute cholecystitis which does not meet criteria for grade II or III [7, 8].

The preoperatory evaluation of the anesthetic-surgical risk was based on American Society of Anesthesiologists Physical Status Classification (ASA PS) and Charlson Comorbidity Index (CCI) [9]. Statistical analysis was performed to analyze the outcomes and limits of laparoscopic cholecystectomy and the risk factors for conversion and open surgery.

Table 1: Preoperatory evaluation of the patients in the study group: demographic data and associated comorbidities

General characteristics in the study group	
	Total (n=262)
Gender	
Female	171 (65.26%)
Male	91 (34.73%)
Age	
21 - 30 years	20 (8%)
31 – 40 years	44 (17%)
41 – 50 years	68 (26%)
51 – 60 years	47 (18%)
61 – 70 years	34 (13%)
71 – 80 years	31 (12%)
>80 years	18 (7%)
Comordibities	
Diabetes mellitus	29 (11.06%)
Hypertension	120 (45.8%)
Coronary diseases	70 (26.7%)
Valvular diseases	7 (2.6%)
Respiratory diseases	22 (8.3%)
Obesity	41 (15.6%)
Previous abdominal surgery	9 (3.4%)
CCI*	
0	107 (41%)
1	73 (28%)
2	23 (9%)
3	23 (9%)
4	16 (6%)
5	10 (4%)
≥6	10 (3%)
ASA PS**	
I	59 (22%)
II	92 (25%)
III	75 (29%)
≥IV	36 (14%)

**CCI: Charlson comorbidity index*
***ASA PS: American Society of Anesthesiologists Physical Status Classification*

RESULTS

Of the total number of patients (361) who presented at the Sibiu County Hospital, Surgery Clinic, with acute biliary pathology during the analyzed period, 262 (73%) presented inclusion criteria in the study. Demographic characteristics

of the study group (Table 1) confirm the predominance of pathology in females (65.26%), and middle adulthood (40-60 years). In 73% of cases, the presentation was late, after more than 72 hours after the onset of painful abdominal symptoms.

The main associated comorbidities were: cardiovascular disease, obesity and diabetes. Assessment of surgical anesthetic risk by calculating the Charlson comorbidity score (CCI) and placing it in the risk classes of the American Society of Anesthesiologists Physical Status Classification (ASA PS) system (Table 1).

Routine preoperative evaluation consisted of clinical evaluation, abdominal ultrasound, chest X-ray, EKG, as well as evaluation of biochemical and hematological parameters, characteristics to assess the severity of infection (hemoleukogram, fibrinogen, ESR), but also liver function (AST, ALT, bilirubin), renal (urea, creatinine), coagulation (INR). According to TG13/TG18 severity risk scale, most of the patients (61%) were diagnosed with moderate acute cholecystitis, while 67 patients (26%) were diagnosed with mild form and 34 (13%) with severe acute cholecystitis.

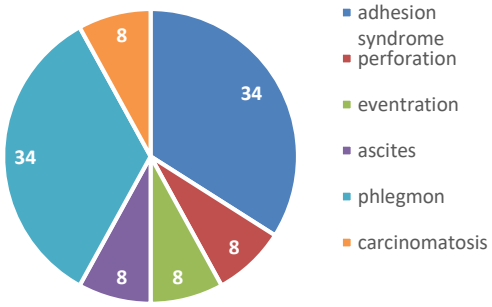
The management of acute cholecystitis was according to Tokyo Guidelines, based on the severity of symptoms, ASA and CCI index. Patients with ASA≥3 and CCI≥6 or sepsis, underwent fluid rebalance and general supportive care before surgery could be performed safely. Emergency laparoscopic cholecystectomy in the first 72-96 hours after admission was performed. Large spectrum intravenous antibiotherapy was used in all cases.

The operative moment was carefully planned after attentive clinical and paraclinical evaluation of the patient and rebalancing of associated comorbidities. Most of the patients (252; 96%) underwent laparoscopic cholecystectomy. Open surgery was used in 10 patients. There were no conversions in the study group, all intraoperative incidents and accidents were managed by laparoscopic approach.

The main reason for deciding from the beginning the classic intervention is the complex adhesion syndrome, but also the suspicion of phlegmon, representing 34% of the number of patients in this category (4 patients). Others include perforation, with biliary peritonitis, postoperative eventration, ascites and peritoneal carcinomatosis associated with colon neoplasm (1 patient each) (Figure 1).

A comparative analysis of the histopathological aspect of the gallbladder for the 2 groups in the study group (laparoscopic and classic) shows that the form of catarrhal inflammation of the gallbladder wall was 87% in the laparoscopic group and 60% in the classically operated group.

Figure 1: Factors for open cholecystectomy in the study group (percentages)



Although less frequent in the laparoscopically operated group, the presence of the difficult forms, such as gangrenous cholecystitis, piocholecystitis, pericholecystic plastron, is not a contraindication for the laparoscopic approach being successfully resolved in this way. On the other hand, the presence of peritoneal carcinomatosis, ascites, eventration, or extensive postoperative adhesions in the upper abdominal floor are absolute or relative contraindications for laparoscopy (Table 2).

Table 2: Histopathological aspects of the removed cholecyst: laparoscopic vs open cholecystectomy

Histopathological aspect of the removed cholecyst	Laparoscopic Cholecystectomy	Open Cholecytectomy
pericholecystic plastron	1 (1%)	1 (10%)
piocholecystitis	3 (1%)	0
pericholecystic fibrosis	5 (2%)	1(10%)
gangrenous cholecystitis	17 (7%)	1(10%)
hydrops	6 (2%)	1(10%)
cataral inflammatory changes	220 (87%)	6 (60%)

A particular aspect as a difficulty in surgical tactics is the association of acute cholecystitis with primary gallstones in 13 cases and angiocolitis in 2 cases.

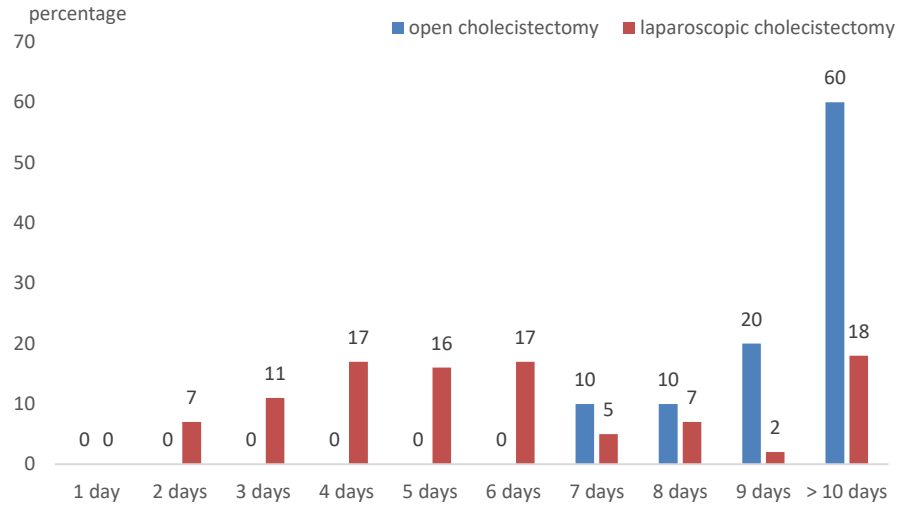
Main bile duct lithiasis resolution was achieved by ERCP, in 15% preoperatively and in 85% postoperatively.

The outcome was favorable with no complications, in most cases (88%) operated laparoscopically and in 50% of cases operated classically, which is correlated with the degree of difficulty and associated comorbidities increased in the group of 10 patients who were treated by classic cholecystectomy.

The average hospital stay was 5.7 days in the laparoscopic

group and 11.2 days in the classically operated group (Figure 2).

Figure 2: Postoperative hospital stay in open and laparoscopic cholecystectomy



The postoperative complications are presented in Tables 3 and 4. Following the study we determined the most common postoperative complications due to the surgical technique, these being: ligature slippage, main bile duct injury, postoperative hemorrhage and surgical site infections. It can be seen that the most common complication in the study is postoperative hemorrhage, caused by: either skidding of the cystic artery ligation, or by inefficient hemostasis (3.9%), followed by skidding of the cystic ligature (1.9%).

Table 3. General postoperative complications in open and laparoscopic cholecystectomy

General postoperative complications	Open cholecystectomy		Intervenție laparoscopică	
	No	*percentage*	*No*	*percentage*
Death	1	10 %	5	2 %
Stroke	0	0 %	1	1 %
Acute miocardial infarction	0	0 %	4	2 %
Malign arterial hypertension	0	0 %	2	1 %
Ascitis	1	10 %	3	1 %
Nosocomial infection	3	30 %	5	2 %
Sepsis	0	0 %	3	1 %
Others	0	0 %	6	2 %

The reasons for the skidding of the ligature are multiple and we will give some examples: the skidding of the metal clip, being the edematous and friable cyst, the skidding of the metal clip being cut to its laughter, etc. On the 3rd place, but very important due to their severity, is the damage of the main bile duct during the maneuvers (1.9%) (Tables 3, 4).

Table 4. Surgery related postoperative complications in open and laparoscopic cholecystectomy

Surgery related postoperative complications	Open cholecystectomy		Intervenție laparoscopică	
	No	*percentage*	*No*	*percentage*
Skidding of the cystic ligature	2	20 %	5	1.9 %
Lesions of the main bile duct	0	0 %	5	1.9 %
Postoperative hemmorhages	1	10 %	10	3.9 %
Surgical site infections	3	30 %	6	2.4 %

The resolution of surgical complications was done in most cases by conservative management, 2 cases requiring reintervention, 1 for postoperative hemorrhage and resolution by ERCP approach of CBP lesion.

DISCUSSION

Laparoscopic cholecystectomy has become the "gold standard", due to its undeniable advantages in reducing pain and postoperative complications, as well as the length of hospital stay. Even during the COVID-19 pandemic era, when laparoscopy was firstly regarded with extreme prudence, the general surgical opinion was that we must not step back from the achievements of modern surgery, but reinforce the

safety measure regarding the ultrafiltration of pneumoperitoneum [10].

Together with the development of anesthesia and intensive care skills and techniques, the safety limit for performing laparoscopy also increased nowadays towards the age of 80-85 years [8, 11], and even of 91 years old in our study group, if not severe ASA risk is associated. In the study group there was no case of conversion. Careful preoperative assessment of the comorbidities and attentive patient clinical evaluation is extremely important before choosing between open and laparoscopic surgery. Conversion to open surgery is associated in several studies with negative effects, including prolonged operation time and increased bleeding which is particular important in patients with increased anesthetico-surgical risk [12].

Another conclusion in the study was that the surgeons should be aware of the significant risk of severe cardiovascular acute events following both laparoscopic and open cholecystectomy, especially in cases with severe sepsis and inflammation or high risk associated comorbidities. These complications should be included in the reasonable disclosure, when the patient is informed about the procedure and the associated possible risks and complications. Informed consent process must be the base of a partnership between doctor and patient, in sharing the inherent risks associated to surgical procedures and understanding what the expectations should be [13].

The severity of local inflammatory changes is a major risk factor for intra operatory and postoperative associated complications. Hyperbilirubinemia significantly increases the likelihood of finding common duct stones in patients with acute cholecystitis, but it also occurs in patients with acute cholecystitis without common duct stones [8]. Hyperbilirubinemia is also a biomarker of intraperitoneal inflammation, along with lipopolysaccharide binding protein (LBP) and Il-6, which increase as a response of liver disfunction associated to bacterial aggression. There are evidences that Escherichia coli and Bacteroides fragilis, common pathogens of the biliary and intestinal wall, were supposed to interfere with hepatocyte microcirculation, inducing sinusoidal lesions. LPSs activate monocytes and macrophages to secrete inflammatory cytokines (tumor necrosis factor alpha (TNF-α) and IL-1, etc.) and other potent mediators [14] by an intracellular signal amplification pathway. These mediators, in turn, act on additional target cells to produce cardiovascular shock, multisystem organ failure, and septic shock [15], one of the major causes of death in intensive care units [16]. In recent studies, a raised concentration in bile but also a more pronounced immunohistochemical expression of cytokines, likeTNF-α, IL-1α, IL-6 was found in the cholecystic wall in both acute and chronic cholecystitis, which may suggest the role of these cytokines in pathogenesis of inflammation and cholelithiasis [17, 18].

Severe inflammation is associated with increased risk of main bile duct during laparoscopic dissection of gallbladder, one of the most serious complications of cholecystectomy. Recently, near infrared (NIR) fluorescence Indocyanine Green was employed in challenging cases to allow a better visualization of the biliary tree. The molecule of ICG is a polymethylic cianyne, which can be administered intravenously, with an excellent safety profile. It binds with circulating albumins and lipoproteins and is excreted into the bile almost unchanged after hepatic extraction [19]. Several studies proved the beneficial use of ICG, which may ensure the surgeon to perform LC with confidence, even in the presence of severe inflammation [20, 21].

Laparoscopic cholecystectomy can be performed nowadays with minimal morbidity in acute cholecystitis [23]. Knowledge of various factors predicting possible conversion helps in adequate pre-operative selection and counseling for open procedure [24] with further reduction in the overall morbidity of laparoscopic cholecystectomy.

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VARIA

Medical causes and diseases leading to early permanent disqualification in IRIAF pilots based on their service categories

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Abstract: *Background and Aim: Efficient manpower is the most important capital and studies have shown the relationship between health and performance.Understanding the factors leading to disability has preventive importance.Our aim is determine the causes and diseases leading to early permanent medical disqualification of the Islamic Republic of Iran Air Force pilots based on their service categories.*

Methods: This is a descriptive, cross-sectional, retrospective study with target population of the Islamic Republic of Iran Air Force pilots with early and permanent medical disqualification from 1986 to 2016.

Results: Out of 508 cases of early medical discharges, 239 items were considered medical disqualification, 17 war captives, 34 service exchange and the remaining 218 was for on service killed or missed persons.The main medical causes were neurosurgery, cardiovascular and psychiatric, while common diseases include lumbar discopathy, myocardial infarction and cardiac arrhythmia.The lost service years was 3233 person year and the average was 12.63 person year per individual.

Conclusions: Based on the previous similar studies, it was expected that the common cause include neurosurgery, cardivascular and psychiatric with more prevalence in fighter, transportation, and helicopter service categories.At the end, we found that our results were in line with initial expectations.

Keywords: *disabilities, medical disqualification, health, prevention, performance*

INTRODUCTION

Human resources are the most important capital of armed forces, and many studies have shown the strong links between personal health and organizational performance. In order to increase productivity, organizations have adopted numerous measures not only to evaluate pre-employment health status, but also monitor staff health during their service life. Nonetheless, health risks remain the most important reducing factor of personal productivity. Disability is defined as the effect of a disorder on physical, mental, and social activity of a person where the work environment and the family status are also effective elements [1, 2, 3, 4]. According to statistics, effective prevention of cardiovascular risk factors in aviation population has a significant role in improving the professional health index of aviators (pilots). The study of aviator's work environment and their lifestyle, active intervention, periodic regular examinations and screening tests for early detection of diseases are among the basic measures [10].

These days, the economic, mental and social problems caused by disability in armed forces are critical burdens. Regardless of the huge cost to run and maintain a powerful army, the supportive burden of victims can be devastating for any society [22]. In 1993, the United States (U.S) army paid 500 million dollars to compensation newly recruited armed forces [7, 8] In a study between 1980 and 1994 on the

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causes of disability in U.S. air and sea forces, it has been shown that disability in armed forces had led to an excessive cost of about 1.5 billion dollar in form of a compensation [2].

The preparation of military pilot volunteers to enter professional trainings and the provision of optimal services in the form of well-trained pilots require a huge amount of resources, both physical and intellectual [1]. The ultimate goal of present study was to determine the causes and diseases which led to early permanent medical disqualification (EPMD) of Islamic Republic of Iran Air Force (IRIAF) pilots based on their service categories from 1986 to 2016. Other objectives include; determine the causes and diseases which led to EPMD in IRIAF pilots who captured during the war, killed or missed in actions or have been forced to change their service category due to medical reasons, their lost service years (LSY) and its average and provision of scientific and practical solution to prevent the EPMD of IRIAF pilots, all based on their service categories.

METHODS

This is a descriptive-cross sectional-retrospective research which ethically approved by the ethics committee of the Aerospace and Sub-aquatic Medical Faculty in Aja University of Medical Sciences (with registration No# 10167118) and was conducted by the personal expenses of the corresponding author. However, like other up-to-date military articles, we are reluctant to disclose a number of military confidential information (i.e. total number of assessed cases).

All the IRIAF pilots(which all are male) with EPMD who had relevant official records from 1986 to 2016 was included in the study and those who had medical disqualification due to physical or mental illness and death in non-occupational accidents, non-medical reasons, personal requests or disciplinary punishments were excluded. In this study, all pilots were captured during the war, killed or missed in actions, and those who confronted with service exchange were classified as permanent disqualification. However, this is one of the study advantages and all data was illustrated in detail separately. In order to observe the principle of confidentiality a non-disclosed random ID code were assigned for every person.

Main disease of the participants was classified based on the ICD-10 (10th version of international classification of diseases) and registered in to the Microsoft excel-based pre-designed electronic data sheet. Other recorded information included; date of entry into the service, date of departure from the service and service categories. Indeed, the total lost service years and average lost service years were calculated for each service category. Finally, this data was analyzed and displayed as graphs and figures for better presentation.

RESULTS

During the period of 1986 to 2016, 508 cases of early permanent discharges occurred in IRIAF pilots which contained; 239 medical disqualification, 218 killed or missed in actions, 34 service exchange and 17 war captives (Table 1).

Table 1: Study data

Service pilots categories / Status	Fighter	Transportation		Helicopter	Total
		light	heavy		
Medical disqualification	171	20	26	22	239
War captives	16	0	0	1	17
Killed or missed in actions	159	7	30	22	218
Service exchange	28	0	3	3	34
	374	27	59	48	508
		86			

The most prevalent medical causes of EPMD in IRIAF pilots were neurosurgery, cardiovascular and psychiatric (Figure 1).

A gynecological and urological consultation was requested for a non-functioning urethral-vesical catheter of a 60 years-old female patient admitted in the Orthopedic Department that underwent surgery with external fixation 2 days prior for a complex pelvic fracture (transverse fracture of the right acetabulum, left obturator ring fracture, left sacral fracture, fifth lumbar transverse apophysis fracture with paralysis of the external left sciatic nerve) (Figure 1).

The most common diseases led to EPMD in IRIAF pilots included; lumbar discopathy, myocardial infarction, cardiac arrhythmia, generalized anxiety disorder and post-traumatic stress disorder (Table 2).

Figure 1: Causes lead to the EPMD of IRIAF pilots based on their service categories

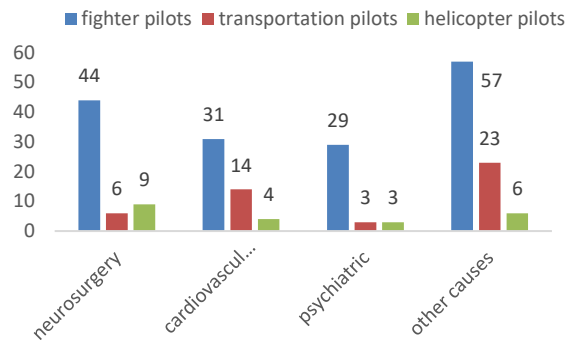
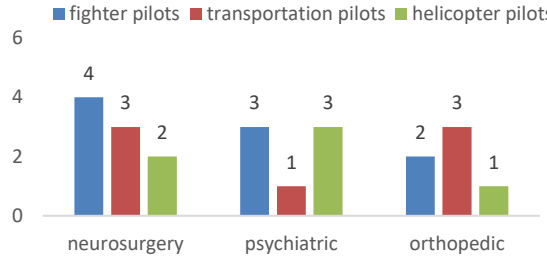


Table 2: Diseases lead to the EPMD of IRIAF pilots based on their service categories

Service pilots categories / Status	Fighter	Transport	Helicopter
Lumbar discopathy	18	5	5
Myocardial infarction	12	6	2
Cardiac arrhythmia	10	2	1
Generalized anxiety disorder	10	0	1
Post-traumatic stress disorder	10	0	0
Other diseases	111	33	13

The most prevalent medical causes of EPMD in war captive IRIAF pilots were neurosurgery, psychiatry and orthopedics (Figure 2).

Figure 2: Causes lead to the EPMD of war captive IRIAF pilots based on their service categories.



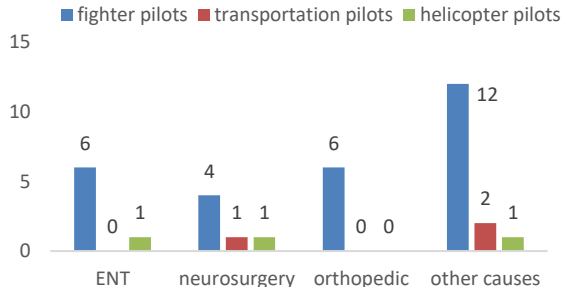
The most common diseases led to EPMD in war captive IRIAF pilots included; post-traumatic stress disorder, lumbar vertebral fracture with fusion and complicated bone fracture (Table 3).

The most prevalent medical causes of permanent medical service exchange (PMSE) in IRIAF pilots were ear, nose and throat (ENT), neurosurgery and orthopedics (Figure 3).

Table 3: Diseases lead to the EPMD of war captive IRIAF pilots based on their service categories

Service pilots categories / Status	Fighter	Transport	Helicopter
Post-traumatic stress disorder	3	1	1
Lumbar vertebral fracture with fusion	2	0	1
Complicated bone fracture	1	0	1
Lumbar discopathy	1	1	0
Cervical discopathy	1	0	1
Other diseases	3	0	0

Figures 3: CT-scan showing complex pelvic fracture and the communication between the bladder and the left labia.



The most common diseases led to PMSE in IRIAF pilots included; motion sickness, complicated bone fracture, lumbar discopathy (Table 4).

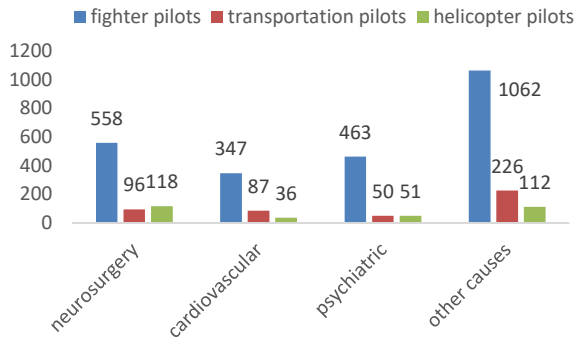
Table 4: Diseases lead to the PMSE in IRIAF pilots based on their service categories

Service pilots categories / Status	Fighter	Transport	Helicopter
Motion sickness	6	0	0
Complicated bone fracture	4	0	0
Lumbar discopathy	2	1	0
Cervical discopathy	2	0	1
Generalized anxiety disorder	2	0	0
Other diseases	12	2	2

As 3233 LSY, 2457 (%76) was belong to fighter pilots, 459 (%14.4) to transportation pilots and 317 (%9.8) to helicopter pilots. The most prevalent medical causes of LSY in IRIAF pilots with EPMD were neurosurgery, psychiatry and cardivascular (Figure 4).

The most LSY in IRIAF pilots with EPMD were belong to lumbar discopathy, generalized anxiety disorder and cardiac arrhythmia (Table 5).

Figure 4: Causes lead to the most LSY in IRIAF pilots with EPMD based on their service categories.



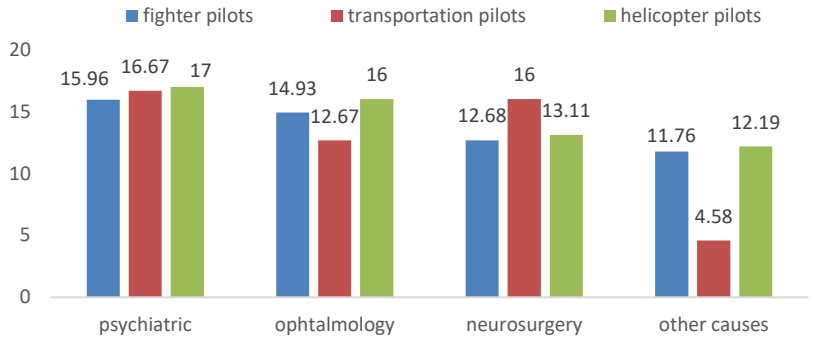
The average of LSY in IRIAF pilots with EPMD was 12.63 person year per individual (13.14 in fighter, 9.98 in transportation and 13.78 in helicopter pilots).

The most prevalent medical causes of LSY average in IRIAF pilots with EPMD were psychology, ophthalmology and neurosurgery (Figure 5).

Table 5: Diseases lead to the most LSY in IRIAF pilots with EPMD based on their service categories

Service pilots categories / Status	Fighter	Transport	Helicopter
Lumbar discopathy	225	80	56
Generalized anxiety disorder	187	0	12
Cardiac arrhythmia	136	19	18
Complicated bone fracture	151	0	0
Post-traumatic stress disorder	151	0	0
Other diseases	1067	360	231

Figure 5: Causes lead to the most LSY in IRIAF pilots with EPMD based on their service categories.



The diseases resulted in the highest average of LSY in IRIAF pilots with EPMD included; migraine, cardiac arrhythmia and lumbar discopathy (Table 6).

Table 6: Diseases lead to the most LSY average in IRIAF pilots with EPMD based on their service categories

Service pilots categories / Status	Fighter	Transport	Helicopter
Migraine	13	16	23
Cardiac arrhythmia	13.6	9.5	18
Lumbar discopathy	12.5	16	11.2
Generalized anxiety disorder	18.7	0	12
Epilepsy	14	12	0
Other diseases	11.92	6.58	11.56

DISCUSSION

In the study of Whitton-1984 on United State Air Force (USAF) pilots and navigators, the common causes were cardivascular and neurologic [17], while in the same study of Mc Crary-2002, the most common causes in 1995 to 1999, include cardivascular, musculoskeletal, neurologic and endocrinology [12]. Also, in the study of Montazeri-2005, the most common causes of EPMD in IRIAF pilots included cardivascular and musculoskeletal [20]. In the study of Ghazizade-2010 on the same population in 1992 to 2003, cardivascular, nervous-skeletal and gastrointestinal were the most common causes [19].

In the study of Dark-1986 with the help of The Federal Aviation Administration (FAA), on medical disqualification of American airlines pilots in 1983 and 1984, the most commonly reported causes were cardiovascular and Neuropsychiatric events [18]. In the Nakanishi study on permanent disability of 260 Japanese crews, significant causes include malignancies, neurodegenerative, cardiovascular, gastrointestinal and musculoskeletal disorders [9]. In the review of trained pilots on Commonwealth countries from 1994 to 2004, the causes of cardiovascular were prevalent [19]. In the Arva study on 257 Norwegian civil pilots, the main causes were cardiovascular,

neurologic, musculoskeletal and psychiatric disorders [11]. In the studies of Mitchell-2004 and Evan-2006 on sudden incapacitation of British civil pilots, 36 cases have been diagnosed and half of them were due to cardiovascular, cerebrovascular and psychiatric disorders [13, 14]. In the Nezami study on 200 civil pilots of Vnukovo airport in Moscow, cardivascular, neurologic and digestive have been the main causes of medical disqualification [10].

In the Mc crary's study, the more common diseases were ischemic heart diseases, high blood pressure, back pain, inter vertebral disc disorders and migraine [12]. In the study of Nezami, ischemic heart diseases, myocardial infarction, high blood pressure, cerebrovascular sclerotic lesions and peptic ulcer have been common [10]. FAA has conducted a great comprehensive study in 2014 on the causes of medical disqualification of pilots listing fifteen major causes, including; pectoris angina, bipolar mood disorder, cardiac valve replacement, coronary artery diseases, diabetes mellitus, loss of consciousness with unknown reason, seizure, cardiac replacement, myocardial infarction, permanent pace maker, disabling personal disorder, psychosis, drug abuse and dependency and lack of neural control, in order of significance [16].

In the study of Montazeri, the mean LSY of IRIAF retired with EPMD was 6.5 person year per individual [20]. In the Ghazizade study, the mean LSY was 6.14 and the highest was 10 person year per individual [19].

The present study has limitations that include: 1) missing details due to the lack of presence of a comprehensive electronic system for recording personal medical records; 2) the possibility of oriented malingering in disorders where specific objective diagnostic methods are not available and were mostly diagnosed subjectively, such as motion sickness, migraine and etc, and 3) flying device factors (ergonomics and exhaustion), operational and airbase factors (work and rest schedule), Personal factors (life style, physical and psychological capabilities, socioeconomic state, use of legal and illicit drugs and habits), medical factors (medical and psychological advices and hygiene education) are important items which have effective influence on pilots health.

The current investigation has important advantages such as: 1) so far, in terms of quantity and quality, there is a limited number of similar studies have been conducted about military pilot's health; 2) it has the longest cross-sectional period (35 years), the closest was performed during a 10-years period [18]; 3) express the statistics of IRIAF pilots which captured during the war, killed or missed in actions and those who confronted with service exchange, and 4) Records given were sorted according to the service categories.

CONCLUSIONS

More studies should be conducted on military and civil aviator's (pilots) health in the future. We believe that the life style modifications, regular fitness training, hygiene and health education and use of medical and psychological counseling for preventing the EPMD in military pilots are necessary preventive steps to take. Also, use of up-to-date comprehensive electronic system, upgrading on-the-job examinations, sufficient periodic in-service examination in occupational health centers are recommend by authors.

List of Abbreviations

U.S = United States; IRIAF = Islamic Republic of Iran Air Force; EPMD= Early and Permanent Medical Disqualification; LSY= Lost Service Years; ICD-10 = 10th International Classification of Diseases; PMSE= Permanent Medical Service Exchange; ENT = Ear, Nose and Throat; USAF= United State Air Force; FAA= Federal Aviation Association

Authors' contribution:

MD – data collector and supervisor, statistical analyzer and literary editor; HS – main owner of the idea, scientific supervisor, executive author and editor.

Ethics approval and consent to participate:

The ethical approval of this study was issued with registration No#10167118 by the ethics committee of the Aerospace and Sub-aquatic Medical Faculty in Aja University of Medical Sciences.

Patient consent for publication: Not applicable.

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Competing interests:

The authors declare that they have no competing interests.

Availability of data and materials:

All the data of this study is available and could be accessible for publication by that valuable military journal.

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VARIA

Golden hour of sepsis: Can we do more?

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Abstract: *Introduction: Sepsis is a life-threatening organ dysfunction due to a dysregulated host response to an infection1 and also an important worldwide health problem. Recent progresses in understanding pathogenesis are reflected in increasing emphasis put on time (Sepsis Update 2018 decreased the time for diagnosis and treatment from 3- 6 hs Sepsis-2 to 1 hour). The aim of the study was to combine an early warning score (increased sensitivity- NEWS2) and a biomarker (increased specificity- presepsin) in order to detect earlier an acute illness (infection) before becoming life-threatening.*

Materials and methods: It was a retrospective, single-center observational cohort study of 125 consecutive patients who were diagnosed with systemic inflammatory response syndrome between July 2016 and July 2018 at Emergency Department of "Dr. Carol Davila" Central Military Emergency University Hospital, Bucharest, Romania in order to determine sooner, which patient will further develop a sepsis. We used the area under receiver–operator characteristic curves (AUC) to assess the overall discriminatory power of NEWS2, MEDS and presepsin in detecting sepsis, septic shock and the probability of death on admission and compared them with combined scores between NEWS2 and presepsin.

Results: Using a combined score and a simple algorithm, the NEWS2 score had changed (12,8%) for 16 patients. For 10 out of 95 (10,52%) without sepsis and 6 out of 30 (20%) of septic patients, more points were added to NEWS2 meaning that more septic patients were diagnosed before an infection become life-threatening

Conclusions: In the present study, we have tried to assess the impact of a monitoring score and a rapid POCT biomarker, in a condition when time is of critical importance. Using a verified early warning score, NEWS2, with increased sensibility and low specificity and presepsin, POCT biomarker with increased specificity, we diagnosed sepsis earlier in a number of cases.

Keywords: *sepsis, early warning score, NEWS2, combined score, presepsin*

INTRODUCTION

Sepsis is a life-threatening organ dysfunction due to a dysregulated host response to an infection [1] and also an important worldwide health problem. Nowadays the global sepsis estimates are more than double than previous calculations, with 11 million sepsis deaths and 48.9 million incident sepsis cases in 2017 with a global trend of decreasing sepsis [2]. Although Sepsis-3 definition is designed to put a diagnosis in prehospital settings, battlefield and Emergency Department (ED) on arrival there is much to be done to further improve diagnostic of patients with sepsis. The specificity of the Sepsis-3 criteria is great, but sometimes the sepsis diagnostic is put too late for a specific patient.

Rapid clinical evaluation on arrival in ED and as soon as possible paraclinical evaluation are realized with POCT (point of care testing) devices which allow a more rapid targeted response (complete blood count, acid-base analysis, targeted biomarkers, etc.) to gain time for the patient and to prevent and fight against further deterioration of a patient in a not an optimal state. Sepsis-2 [3] emphasized the fact

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that time management is of critical importance. Early targeted therapy and management bundle put an algorithm at hand for doctors and 2018 Sepsis update [4] indirectly stressed out that rapid medical intervention is paramount because what it should have been done in the first 3-6 hours, from that moment on, it must be done in one hour. For greater accuracy and tailored treatment more exhaustive laboratory analysis usually arrive in at least 30-40 minutes.

By 2015 over 36 Early Warning Scores were used and evaluated for accurately forecast the prognosis [5]. Developed as specific tools, in different environments (different wards, ED, ICU), some scores are nowadays obsolete or of limited use [5, 6] but some are still used and revised (NEWS2).

A possible research direction in sepsis might be to combine an early warning sign/score with increased sensibility, low specificity and a specific biomarker which will increase the specificity to buy time for the patient and ultimately to save more lives with increased cost-results efficiency.

Conceived in 2012, verified on different wards for several years and revised in 2017, National Early Warning Score 2 is nowadays used in United Kingdom with great success [7].

Used in different environments, presepsin is one of the biomarkers which passed the proof the time, as a valuable tool in POCT, being used for more than a decade now [8, 9, 10, 11, 12, 13]. Presepsin increases in patients developing infections in a severity-dependent manner [14, 15, 16]. Previous studies showed that presepsin levels performed when used for early diagnosis, risk stratification and prognosis [17, 18].

The aim of the study was to find new ways in which to combine these recently developed tools, an early warning score (NEWS2) and a specific biomarker (presepsin) in order to diagnose more cases of severe infections, before developing sepsis, preventing further deterioration of an already altered patient with multiple comorbidities. The proposed score is easy to calculate, rapidly available and allowed us to markedly decrease the time for intervention for patients with altered medical status before becoming life-threatening.

MATERIAL AND METHODS

Study design

This was a retrospective, single-center observational cohort study of 125 consecutive patients who were diagnosed with systemic inflammatory response syndrome between July 2016 and July 2018 at Emergency Department of "Dr. Carol Davila" Central Military Emergency University Hospital, Bucharest, Romania in order to determine sooner, which patient will further develop a sepsis. We developed a simple algorithm for earlier diagnose of sepsis and compared the results with Sepsis-3 criteria, NEWS2 and MEDS scores. All patients were above 18 years old and have agreed to sign the informed consent. The study was approved by the ethical committee at "Dr. Carol Davila" Central Military Emergency University Hospital, Bucharest, Romania.

Blood sample analysis

Presepsin concentrations were measured using a chemiluminescent enzyme immunoassay (PATHFAST™ Presepsin), performed on the PATHFAST point-of-care analyzer (Mitsubishi Chemical Medience Corporation, Tokyo, Japan). Measuring range is 20–20,000 ng/L; manufacturer's URL (95th percentile) is 320 ng/L. Correlation between heparinized and EDTA plasma was Y = 1.00× + 1.53 (r=0.999, n=23) [19].

Developing a tool for earlier diagnosis of sepsis

National Early Warning Score (NEWS) 2 is recommended by the NHS (National Health System) UK to determine the degree of illness of a patient, to prompt critical care intervention and recommends the NEWS 2 in the following settings: Emergency (for initial assessment, serial monitoring and assessment for triage), ward (for initial inpatient assessment and serial monitoring), prehospital (for communication of illness severity to receiving hospitals). Respiratory rate, hypercapnic respiratory failure/room or supplemental O_2, temperature, systolic BP (mmHg), pulse (beats per minute) and consciousness are assessed.

In order to try other combination of NEWS2 and PSP we have obtained other scorings to better predict the prognosis and earlier detection of sepsis.

We have created a new score NEWS2PSP: for PSP between 0-1000 pg/ml we granted 1 point; between 1000-2000 points=2 points, and so on. Adding those values to NEWS2 score lead us to the new score NEWS2 PSP.

Another compounded score was tested: for PSP<200 pg/ml we have given 1 point, 2 points for PSP=200- 300 pg/ml, 3 points for PSP=300-500 pg/ml, 4 points for PSP=500-1000 pg/ml and 5 points for PSP>1000 pg/ml. The new score was NEWS2PSP2.

NEWS2PSP3 resulted from granting 1 point if PSP>1000 and 0 points if PSP<1000.

Granting 0 points for PSP<5000 pg/ml, 1 point for PSP=5000-10000 pg/ml and 2 points for PSP>10000 and adding these points to NEWS2 lead us to NEWS2PSP4.

Statistical analysis

Descriptive statistics was used to summarize the study population. Baseline and follow-up characteristics were described by means and standard deviations (SD) or by median and interquartile range (IQR) for continuous variables, as appropriate, and by percentages for categorical variables. We performed Chi2 statistics or Fisher's exact tests when appropriate for qualitative variables, and the Wilcoxon/Mann–Whitney test for continuous variables with skewed distributions to compare baseline patient characteristics and study outcomes. Categorical variables are presented as counts and percentages. We used the area under receiver–operator characteristic curves (AUC) to assess the overall discriminatory power of NEWS2, MEDS and presepsin in detecting sepsis, septic shock of the probability of death on admission. The IBM SPSS version 20.0 software (IBM Corp., Armonk, NY, USA) was used for statistical analysis.

RESULTS

There were 125 consecutive patients which were considered to have SIRS (systemic inflammatory response syndrome) and included in the study. When 2 or more SIRS criteria were found, presepsin (PSP) was assessed. From these 30 were diagnosed as having sepsis (Sepsis-3 definition, with 2 or more qSOFA criteria) and 11 were diagnosed as having septic shock. During the study 27 patients have died from different causes, some of them being sepsis or septic shock. The mean age was of 70.88 years with standard deviation of 15.74 years; they ranged from 18 to 96 years. Of the total study population, 79 (63.2%) were men. Table 1 provides the baseline characteristics demographic data, the calculated scores, selected comorbidities and the site of infection.

Table 1: Baseline characteristics, used scores, selected comorbidities and the site of infection

Demographics	All patients (n=125)	Sepsis (n=30)	Septic shock (n=11)	Exitus (n=27)
Age (mean, SD)	70.888 (15.74406)	73.4666 (15.3139)	72.2727 (15.3391)	75.6296 (14.4277)
Sex (male, %)	79 (63.2)	23 (29.11)	10 (12.65)	20 (74.07)
Weight (mean, SD)	71.472 (12.6835)	70.7333 (9.2805)	72.2727 (9.3525)	70.5185 (15.8637)
GCS (mean, SD)	14.264 (2.1841)	12.8666 (2.9970)	12.4545 (2.6064)	13.8148 (2.4651)
QSOFA (mean, SD)	0.672 (0.9779)	2.2666 (0.4422)	2.5454 (0.4979)	1.1481 (1.1123)
NEWS2 (mean, SD)	4.768 (3.6532)	9.7333 (2.8511)	12 (2.3741)	6.5925 (4.0208)
MEDS (mean, SD)	9.568 (4.3512)	14.0333 (2.9606)	15.8181 (2.5873)	12.9259 (4.2681)
PSP (mean, SD)	2594.608 (3063.226)	3582.8 (4306.524)	2961.545 (2163.594)	3272.593 (4373.756)
Selected comorbidities				
Malignancy (%)	35 (28)	10 (28.57)	2 (5.71)	8 (22.85)
Diabetes melitus (%)	27 (21.6)	9 (33.33)	4 (14.81)	6 (22.22)
Cardiac failure (%)	49 (39.2)	9(18.36)	4 (8.16)	13 (26.53)
Kidney failure (%)	36 (28.8)	7 (19.44)	3 (8.33)	11 (30.55)
Respiratory failure (%)	20 (16)	8 (40)	3 (15)	8 (40)
Institutionalized patient (%)	7 (5.6)	3 (42.85)	1 (14.28)	6 (85.71)
Site of infection				
Abdominal (%)	26 (20.8)	6 (23.07)	3 (11.53)	8 (30.76)
Cutaneous (%)	15 (12)	1 (6.66)	0	3 (20)
Endocard (%)	1 (0.83)	0	0	1 (100)
Pulmonary (%)	20 (16)	6 (0.3)	2 (10)	5 (25)
Kidney (%)	28 (22.4)	11 (39.28)	5 (17.85)	5 (17.85)
Unspecified (%)	35 (28)	6 (17.14)	1 (2.85)	5 (14.28)

GCS= Glasgow Coma Scale, qSOFA= quick Sequential Organ Failure Assessment, NEWS2= National Early Warning Score 2, MEDS= Mortality in Emergency Department Score, PSP= presepsin

Patients who met the Sepsis-3 criteria (2 or more qSOFA points) were treated accordingly to the current guidelines for sepsis. Only 30 patients were diagnosed with sepsis and 11 with septic shock.

Table 2 shows the Area Under the Receiver Operating Characteristics and confidence intervals for the different scores and compound scores.

NEWS2 9.7±2.9, MEDS 14.0±3.0 and PSP (presepsin) 3582.8±4380.1 showed increased values for sepsis with statistical significance for NEWS2 p<0.001 MEDS p<0.001; of note the statistical significance for PSP was p=0.043. For sepsis NEWS2 has the best AUROC (Area under ROC) 0.962

(95%CI 5.54-7.51), MEDS 0.875 (95%CI 4.39-7.36), PSP 0.603(95%CI 41.32-2559.17) according to Sepsis-3 criteria as depicted in Figure 2. ROC curves are the same for septic shock NEWS2 0.974 (95%CI 6.11-9.74), MEDS 0.913(95%CI 4.39-9.3) and respectively for PSP 0.626 (95%CI 1526.19-2330.88) (Figure 3).

Table 2: AUROC and 95%CI calculated for different combined scores in sepsis, septic shock and mortality

	Sepsis		Septic shock		Mortality	
	AUROC	**95%CI**	**AUROC**	**95%CI**	**AUROC**	**95%CI**
NEWS2	0,962	5,54- 7,51	0,974	6,11- 9,74	0,670	0,79- 3,85
MEDS	0,875	4,39- 7,36	0,913	4,39- 9,3	**0,762**	2,55- 6,01
PSP	0,603	41,32- 2559,17	0,626	-1526,19- 2330,88	0,561	-454,79- 2184,34
NEWS2PSP	0,z924	6,36- 9,45	0,949	5,66- 11,20	0,656	1,21- 5,39
NEWS2PSP2	0,953	5,69- 7,84	**0,975**	6,31- 10,19	0,676	0,94- 4,17
NEWS2PSP3	0,956	5,95- 7,65	**0,975**	6,22- 9,96	0,672	0,90- 4,03
NEWS2PSP4	**0,971**	5,69- 7,65	0,972	6,07- 9,76	0,670	0,82- 3,91

Figure 1: Receiver-operating characteristics (ROC) curves for NEWS2, MEDS, PSP and for derived scores (NEWS2PSP, NEWS2PSP2, NEWS2PSP3, NEWS2PSP4) in sepsis (AUROC 0,971 %95 CI 5,69- 7,65 for NEWS2PSP4)

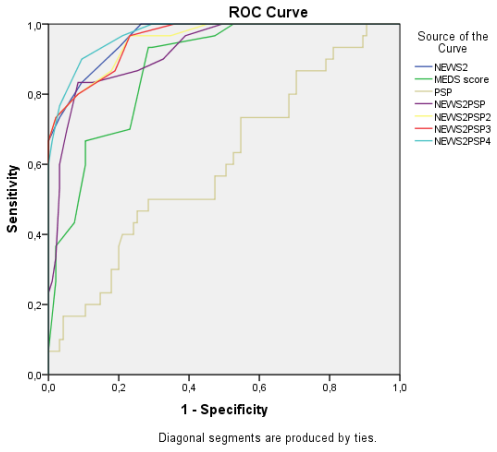


Figure 2: Receiver-operating characteristics (ROC) curves for NEWS2, MEDS, PSP and for derived scores (NEWS2PSP, NEWS2PSP2, NEWS2PSP3, NEWS2PSP4) in septic shock (AUROC 0,975 %95 CI 6,31- 10,19 for NEWS2PSP2 respectively AUROC 0,975 %95 CI 6,22- 9,96 for NEWS2PSP3)

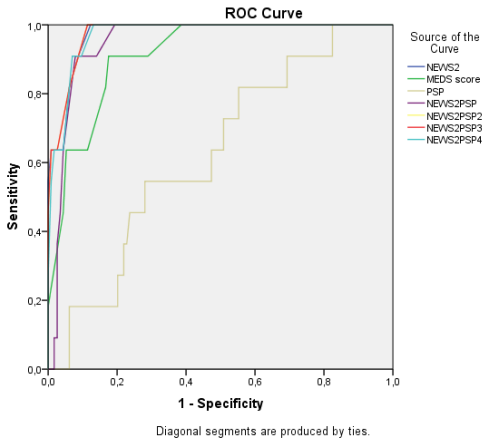
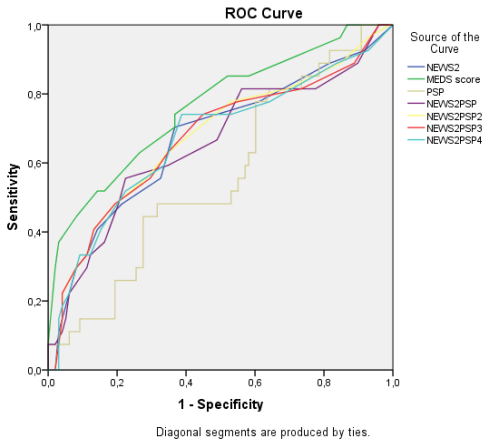


Figure 3: Receiver-operating characteristics (ROC) curves for NEWS2, MEDS, PSP and for derived scores (NEWS2PSP, NEWS2PSP2, NEWS2PSP3, NEWS2PSP4) in mortality (AUROC 0,762 %95 CI 2,55- 6,01 for MEDS score)



We created a new score, NEWS2PSP, transforming PSP values as follows: between 0-1000 pg/ml = 1 point; 1000-2000 pg/ml = 2 poits, and so on; adding these points to NEWS2 score resulted the new score NEWS2PSP; AUROC for

sepsis and septic shock were not superior to NEWS2: AUROC NEWS2PSP in sepsis 0.924 (95%CI 6.36- 9.45), in septic shock 0.949 (95%CI 5.66-11.20), compared to AUROC NEWS2 in sepsis 0.962 (95%CI 5.54-7.51) or in septic shock 0.974 (95%CI 6.11-9.74). MEDS, a specific designed score was superior to NEWS2PSP in predicting mortality AUROC MEDS 0.762 (95%CI 2.55-6.01), AUROC NEWS2PSP 0.656 (95%CI 1.21-5.39).

Another compounded score was tested: for PSP<200 pg/ml we have given 1 point, 2 points for PSP=200- 300 pg/ml, 3 points for PSP=300-500 pg/ml, 4 points for PSP=500-1000 pg/ml and 5 points for PSP>1000 pg/ml. Those values were added to NEWS2 and formed NEWS2PSP2 which has no more added value to NEWS2 for predicting sepsis (AUROC NEWS2 0.962 (95%CI 5.54-7.51), AUROC NEWS2PSP2 0.953 (95%CI 5.69-7.84), minimal in septic shock (AUROC NEWS2 0.974 (95%CI 6.11-9.74), AUROC NEWS2PSP2 0.975 (95%CI 6.31-10.19). MEDS kept an advantage in predicting death over NEWS2PSP2 (AUROC MEDS 0.762 (95%CI 2.55-6.01), AUROC NEWS2PSP2 0.676 (95%CI 0.94-4.17).

NEWS2PSP3 resulted from granting 1 point if PSP>1000 and 0 points if PSP<1000- with no better prognostic value over NEWS2 for predicting sepsis ((AUROC NEWS2 0.962 (95%CI 5.54-7.51), AUROC NEWS2PSP3 0.956 (95%CI 5.95-7.65) and kept a slightly advantage over NEWS2 in septic shock AUROC NEWS2 0.974 (95%CI 6.11-9.74), AUROC NEWS2PSP3 0.975 (95%CI 6.22-9.96). MEDS kept an advantage in predicting death over NEWS2PSP3 (AUROC MEDS 0.762 (95%CI 2.55-6.01), AUROC NEWS2PSP3 0.672 (95%CI 0.90-4.03).

Granting 0 points for PSP<5000 pg/ml, 1 point for PSP=5000-10000 pg/ml and 2 points for PSP>10000 and adding these points to NEWS2 lead us to NEWS2PSP4 which is superior to NEWS2 (AUROC NEWS2PSP4 0.971 (95%CI 5.69-7.65) compared to AUROC NEWS2 0.962 (95%CI 5.54-7.51). Using a cut-off value of 9.5 for NEWS2PSP4 we can diagnosis of sepsis with a sensitivity of 60%. (for a NEWS2PSP4 compound score >6.5 sepsis is diagnosed with a sensitivity of 90% and 90.5% specificity).

Using this simple algorithm, for 16 patients the NEWS2 score had changed (12.8%). For 10 out of 95 (10.52%) without sepsis and 6 out of 30 (20%) of septic patients, more points were added to NEWS2 meaning that more septic patients were diagnosed before an infection become life-threatening.

For septic shock NEWS2PSP4 was a reliable score; AUROC values were as follows: AUROC NEWS2 0.974 (95%CI 6.11-9.74), and NEWS2PSP4 0.972 (95%CI 6.07-9.76) (very close), while MEDS kept the advantage in predicting mortality (similar AUROC for NEWS2 and NEWS2PSP4) (AUROC NEWS2 0.670 (95%CI 0.79-3.85), MEDS 0.762 (95%CI 2.55-6.01), NEWS2PSP4 0.670 (95%CI 0.82-3.91). Figures 1, 2 and 3 represent receiver-operating characteristics (ROC) curves for NEWS2, MEDS, PSP and the derived scores for sepsis/ septic shock/mortality as above.

DISCUSSION

In our study we proved that adding a specific biomarker, presepsin, to NEWS2 we can put a sepsis diagnosis earlier, reliable, with increased accuracy, avoiding further deterioration. Studies have proved that clinical deterioration is often forecasted by changes in vital signs up to 6 to 24 hours [20, 21]. This can buy time for a specific patient, but in fact also for the system to recover.

To be remembered, although an increased specificity sign, ST elevation, did not decrease mortality per se. Only after angina pectoris was combined with a specific biomarker, troponin, combined with proactive actions, coronary stenting, markedly decreased the mortality.

Immunity against a microorganism relies primarily on the activity of monocytes, macrophages and granulocytes that recognize pathogen-associated molecular patterns that activate downstream pathways and participate to bacteria clearance. This is partly done through a cluster-of-differentiation marker protein 14 (CD14), which has an immediate response against lipopolysaccharides (LPS) [14, 22]. After binding of LPS to CD14 through the LPS-binding protein (LBP), a subtype of soluble CD14 (sCD14-ST, or presepsin, a 13 kDa protein that is a truncated N-terminal fragment of CD14 [15, 16] is released to the blood flow.

Different scores were used as specific tools in specific circumstances. The more versatile ones are the ones that can be used in as many as possible situations, with minimum of resources, as fast as possible. National Early Warning Score 2 (NEWS2) is released after 5 years of trials after the first version of evaluation in hospitals in UK. This score advocates a system to standardize the assessment and response to acute illness and its efficacy was proven in time. Using six simple physiological parameters already recorded in routine practice, NEWS2 is a pragmatic approach with a key emphasis on system-wide standardization

Rapid diagnostic on ED saves lives. Acute myocardial infarction, stroke and sepsis are medical conditions when short time to diagnosis is of paramount importance, that cannot be overemphasized.

NEWS2 can be used as a point of departure for assessing an acute medical illness, but to accurately diagnose a patient a specific tool is needed (ST elevation for acute myocardial

infarction on EKG, CT scan for stroke and nowadays qSOFA criteria for sepsis).

As Sepsis-3 stated, a sepsis is declared when an infection becomes life-threatening. This puts a rapid diagnose with minimal resources. Having some preliminary results can gain time to earlier diagnose a life-threatening condition and to prevent further deterioration. When we have the Sepsis-3 criteria, the diagnosis is obvious.

We proved that with minimal resources, monitoring vital parameters and assessing a score and when suitable a POCT biomarker, in 15 minutes we raised the suspicion of sepsis, before becoming manifest, with increased accuracy, gaining at least 45 minutes. We found that a biomarker, presepsin, can accurately earlier diagnose sepsis used in correlation with a verified score, NEWS2 which is used for a patient to access the appropriate level of care at a certain moment. We also took into account MEDS as a level of reference, for its power to predict the prognosis due to sepsis (Mortality in Emergency Department Score).

Of note is that the presepsin values were used to help diagnose sepsis after Sepsis-2 definition, but in our study, we tried to use the presepsin for earlier detection of sepsis, after Sepsis-3 definition, before the clinical life-threatening criteria to become manifest (SBP≤100 mmHg, ≥22 breaths per min, GCS<15).

With an altered mental state, incomplete anamnesis to be taken from relatives or the lack of proper documents, increasing number of patients on admission and too often not enough personnel, an accurate, proper assessment on admission is mandatory. After the initial evaluation, vital functions monitoring and blood samples are taken, before more complete laboratory analysis to be available – with a median of one hour, the Point-Of-Care-Testing devices can give you a more comprehensive understanding of the actual medical state in approximatively 15 minutes. POCT biomarkers, arterial gases analysis and complete blood count with multiple scores applied, offer a more comprehensive assessment of a patient and sometimes prioritize the subsequent investigations. While a MEDS score needs not so easy to get information (rapid terminal comorbid illness, neutrophil bands, lower respiratory infection or nursing home resident) NEWS2 is a reliable, verified score intended to be used for monitoring, with increased sensitivity. Based on initial evaluation, taking presepsin (available in 17 minutes) only to patients with SIRS and NEWS2 assessment, taken together increased the number of the patients to be earlier diagnosed with sepsis with 10%. Presepsin was the ideal biomarker due to the fact that it has earlier response compared with procalcitonin after the onset of an infection (peak level<2 h) plus a short half-time (0,5-1 h) compared with those of procalcitonin (2-3 h and 20-24 h, respectively) and CRP (6 h and 4-6 h, respectively) lead us to use this biomarker. The lack of specificity as procalcitonin increases also in surgical interventions, cardiogenic shock, thermal shock, graft-versus-host disease, immunotherapy, burns, acute pancreatitis lead us to consider using presepsin as specific biomarker [21, 23, 24].

To our knowledge this was the first report of PSP and NEWS2 score used in combination for sepsis diagnosis. Nevertheless, although this association is better for earlier detection of sepsis, there no added advantages in predicting septic shock or mortality.

Sepsis is not a completely understood pathology. Surviving Sepsis Campaign with the periodic reevaluation (even the Sepsis, Sepsis-2, Sepsis-3 definition suggests the dynamics and the major concern involved) still leaves room for refinement and improvement. Our study reflects our approach for earlier diagnose of sepsis. Having a patient with clear criteria for sepsis accordingly to qSOFA leaves no room for doubts and the nowadays guidelines stress the importance of earlier diagnosis and rapid measurements to be taken (2018 Sepsis Uptated) in the first hour.

Sepsis defined as life-threatening organ dysfunction caused by a dysregulated host response to infection does not shed light over the dysregulation. Is it due to the increased aggressivity of the pathogen, to the amount of the pathogen, to the particularities of the injured organ/system, of the comorbidities which decrease the defense mechanisms, of the defense of the defense mechanisms itself? In order to achieve timely treatment for a possible lethal condition, a sensitive screening tool is more important than a specific one [25, 26] and identifying the poor prognostic factors may have a role [27].

Although qSOFA has an increased specificity and minimal resources to be used, lacks the sensibility and consequently the diagnosis of sepsis is often put too late. Even one point granted on initial evaluation does not imply that subsequent evolution is not going to be worse, to further deteriorate without becoming life-threatening. So, more refined approach is sometimes necessary.

Study limitations and strengths.

The present study has some limitation. First, being a single center retrospective, observational study we may not have a comprehensive view of this complex pathology. Second, being a tertiary hospital, may have had more complex patients which may have biased in generalizing the

conclusions. Future studies should include more patients from different sites. Third, sepsis defined as life-threatening condition, may alter the health status by itself- an out-control infection might bias the renal function by itself or by aggravation of an already altered renal function as a comorbidity in a more general health status. Fourth, the limited number of patients studied, although significant, are a mere part of the patients with sepsis, so the drawn conclusions should be further verified. Fifth, the size of the cohort might have not enough power requested to draw final conclusions. Finally, although already described in literature, the correlation between presepsin/ biomarker with renal clearance levels and kidney function in patients with life-threatening condition should be studied further.

As strengths in our study we assessed the impact of an earlier intervention over a life-threatening condition in which time is of critical importance. Although widely used, the scores are sometimes inadequately applied. Making distinction between the goals and the moment to be applied to, a score is not a goal in itself. Using a monitoring, verified score as NEWS2, high sensitivity, low specificity combined with a specific biomarker with short time until peak values are attained, lead us to suggest that before becoming dysregulated and life threatening, the sepsis might have an earlier, more optimized approach.

CONCLUSIONS

In the present study, we have tried to assess the impact of a monitoring score and a rapid POCT biomarker, in a condition where time is of critical importance. We acknowledged that in a not completely understood lethal pathology as sepsis, different approaches might be tried in order to earlier detect a life-threatening condition. Using a verified monitoring score, NEWS2, with increased sensibility and low specificity and presepsin, POCT biomarker result within 17 minutes, we diagnosed sepsis earlier.

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VARIA

The effect of multimedia training on social function of burn patients in Shahid Motahhari Hospital, Tehran: A clinical trial study

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Abstract: *Introduction: Burn is a tissue injury and affects social functioning and relationships. Complications of burns lead to disruption of social relationships and consequently social dysfunction.*

Objective: Aim of this study was to determine the effect of multimedia training on social functioning of burn patients in Shahid Motahhari hospital in Tehran.

Methods: This clinical trial study was performed on 100 burned patients. The intervention group received a multi-media self-care discharge training on a CD in addition to the common education. Social function of quality of life was examined in both groups before intervention, 3 months and 6 months after intervention.

Conclusion: Results showed that before intervention the mean score of social function of quality of life in intervention and control group was 1/55± 0/46, 1/92± 0/6 respectively which was statistically significant (p <0.001). Mean and standard deviation of social function of quality of life in the intervention and control groups three and six months after intervention were 2/47± 0/56, 4/05± 0/77, 2/15±0/39, 3/29 ± 0/95 respectively which was statistically significant (p <0.001).

Keywords: *self-care, multimedia, patient discharge, social adjustment, burns*

INTRODUCTION

Burn have been described as one of the most devastating disasters on the human body [1] which seriously damages one's life and health and is considered to be the fourth most common injury [2]. The World Health Organization estimates that the incidence of burns Severe is one percent of life expectancy and more than 300,000 people die from burns worldwide each year [3]. According to the Forensic Medicine Organization statistics, in the first quarter of this year, 379 people died from burns in the country. Of these, 213 were men and 166 were women [4], so burn injuries are one of the most dangerous health incidents in Iran. Over the past decade, advances in health care have made patients with more severe burns survive [5]. Even if urgent management is successful, burn injuries can create many obstacles for patients. In addition to their physical problems, they also suffer from social problems and ultimately their quality of life is affected [6]. Patients suffer from severe seizures at the gate, which can live longer. High-end living is particularly attractive in most places where a lot of space for cabins can be attractive. And the place of marriage, relationships, places of residence, in their lives, and ultimately cause them to become overwhelmed by anxiety and anxiety [7]. People

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have trouble meeting new people and dating, worrying about developing relationships and exhibiting various reactions, such as shyness, aggression, or extreme social avoidance. Therefore, it is necessary to design appropriate supportive programs to improve their quality of life [8]. The only thing that will help the patient is how to live with this situation and learn to meet their own needs and to be less in need of others and to have the attitude that they can play with these shortcomings and that It will be nothing but training and learning and rehabilitation [9]. The philosophy of patient education is to apply the information and skills learned to control and cope better with the disease performed by the care team, especially the nurses [10]. The role of nurses in the last few years as the most important member of the health care team has undergone a historical transformation, from promoting patient-centered health education to empowering patients to self-care and achieve health. Informing the patient and contributing to decision-making speeds recovery and reduces hospital stay and reduces hospital readmission [11]. This is a key challenge here in achieving donation. Education is a traditional teaching tool and disability [12], because lecture-based training requires a great deal of time and expense and, on the other hand, a patient with a burn accident during hospitalization due to mental and physical injuries, physical injuries. Physical weakness, painful daily activities, intellectual discomfort, and lack of focus on decision making may make you less prepared to learn and remember education. The empowerment and self-care is not [9]. In recent decades, traditional approaches to learning with the advent of new technologies such as multimedia virtual education have undergone dramatic changes [13]. The purpose of multimedia application is to make meaningful learning happen, and meaningful learning occurs when the learner can make meaning to the material presented by constructing a coherent mental image from multiple sources of information [14]. It seems that learning will be better if the patient is able to carry out a self-care program using a comprehensive audiovisual CD to suit any time and circumstances they wish [9]. Also, due to the gradual process of rehabilitation in patients, education during discharge for these patients to return to the community must be sufficient and carefully planned [15].

OBJECTIVES

Since humans are social beings and communicating with others is an important factor in life and patients with burns suffer from this, the researchers sought to investigate the impact of multimedia training on the social functioning of burn patients. At the Shahid Motahhari Hospital in Tehran.

MATERIALS AND METHODS

Setting

This research was a randomized clinical trial with a control group that was conducted in the hospitalization wards of Shahid Motahari Burn Center, Tehran, Iran in from 2016 to 2017. The study population consisted of all burn patients who were admitted to Shahid Motahari Burn Center and were participated in the study based on the inclusion criteria.

Inclusion and exclusion criteria

The criteria for participating in the study were the patients` age, people who were between 18 to 60 years, and had the ability to use audiovisual compact discs (CDs), their burning percentage to be 10-45%, degrees of 1, 2 and 3, those having a minimum reading and writing literacy, and understanding of Persian language. Also those who lacked sensory and motion problems and brain and mental disorders, mental retardation, those who were living in Tehran and the suburbs of Tehran, people whose burns were due to accident and non-self-immolation, non-burning with electricity were included in the current study. The exclusion criteria were the withdrawal of continued study and severity of disease, disability and death of patient.

Sampling method

The sampling method was at convenience and continuous study; the patients were randomly assigned into intervention and control groups. According to the studies carried out in this regard, the effect of educational interventions with 95% of confidence and 80% of test capacity was considered on the number of samples needed for each group and taking into account 10 scores of difference in the quality of the psychological dimension of life of the two groups. So the population was estimated to be 55 people based on the following formula in a way that each group included 50 subjects, considering 10% of the probability of not participating. Finally, 100 samples were considered to be participated in the study with the formula $n=2(z1-\alpha/2+z1-\beta)2s2/(\mu1-\mu2)2$. In this formula $z1-\alpha/2=1.96$, $z1-\beta=0.84$, $s=9$ and $\mu1-\mu2=5$.

Measures

Two questionnaires were used in the recent study. The demographic information questionnaire and the status of the disease including some questions about gender, age, occupation, marital status, burning agent or source of heat (gasoline, gas, flame, hot liquids, oil, hot food, etc.), level of education, grade and percentage of burns, burning area, city, location of incident and economical status. This

questionnaire was selected by the patient and a research associate on the first day so that the samples inclusion in the study was completed. The next instrument was a questionnaire of burn patient's Quality of Life [BHS-B (Burning Specific Health Scale). The social dimensions of this questionnaire were used.

The questionnaire included 40 questions about skin sensitivity to heat, body image, hand performance, care for burnt areas, communication, ability to perform simple activities, sexual function and psychological dimension with the options of high, moderate, low and never, which had been scored from 1 to 5, respectively. Each questionnaire had at least one and maximally five scores. Based on this questionnaire, the quality of life in each dimension or domain was determined separately and in all domains. From 40 questions of the questionnaire, 18 questions were related to the physical dimension of quality of life, 11 questions were about the psychological dimension of quality of life and 11 questions revealed the social dimension.

Demographic and disease information questionnaire was given to 10 faculty members of the faculty of medical sciences in terms of validity and content validity, and then their opinions were applied as the reliability and validity of the BHS-B were measured by Kildal et al. in 2001 using its dimensional analysis [16] In Iran, Pishnamaazi et al. (2009) had measured its validity and reliability by Alpha Cronbach of 94% in the burn patients in Shahid Motahari and Hazrat Fatemeh hospitals [17] and at Qotboddin Shirazi Hospital [18], calculated the reliability of this tool with Alpha Cronbach of 98%. In our study, Alpha Cronbach was measured 94%.

Education and treatment program

Based on the implementation of this method, the researcher referred to the Burn Medical Educational Center of Shahid Motahari Hospital after receiving the study confirmation from Iran University of Medical Sciences and the ethical code from the university's ethics committee (93-02-28-24922-106366 on 8/12/2014 and registered in a clinical trial with the code IRCT 2014112920145).

After introducing the principal investigator and the collaborators of the research and the research objectives to the hospital's officials and obtaining permission, he referred to the departments and, while introducing himself and the colleagues of the research and the study objectives to the departmental authorities, the samples were randomly provided according to the conditions of inclusion as the control or intervention group. After explaining the procedure and ensuring the anonymity of the samples, a written informed consent was obtained from each participant. They were announced that the transportation cost and the cost of left work to be compensated at 3 and 6 months by the researcher. Before the intervention, the demographic information and burn characteristics questionnaire was completed by the patient with the help of a research associate and using medical records. Then the intervention and control groups received face-to-face routine trainings, however, the intervention patients, in addition to routine trainings, received the self-care discharge education of a burnt patient given at the time of discharge in an educational CD containing text, slide, film and recorded sound; then the researcher gave this CD to the patients to perform at home. In educational session they used CDs and answered questions for 30-60 minutes at the time of discharge.

Educational content was prepared based on the sources of self-care educations of the burn patients. The questionnaire of the quality of life of burnt patients in the psychological, physical and social dimensions was completed by the patient before the intervention on the day of discharge and 3 and 6 months after the intervention; the telephone number, email address, researcher's telegram number were given to patients to call if necessary. The researcher conducted a weekly phone contact with the patients in the intervention and control groups to follow up and ensure the preservation of the samples. After 3 and 6 months of intervention, the patients in both the control and intervention groups were contacted by phone to complete the questionnaire. Patients completed the questionnaires in the manner of the self-report. At the end of the research, the educational CD was provided to the control group for observing ethics in the research.

Ethical consideration

This study was approved by the Ethics Committee of Iran University of Medical Sciences and the Ethics Committee of the place where research was conducted (Ethic code: 93-02-28-24922-106366).

The clinical trial was approved by the Iranian Registry of Clinical Trials (IRCT) under No: IRCT2014112920145N1. The CONSORT checklist was used to report the study.

Statistical analysis

After collecting raw data for the analysis, the descriptive and inferential statistics (Chi-square and independent and paired t tests for the distribution of normal variables), Fisher's exact test, nonparametric tests such as Mann-Whitney, Wilcoxon and Friedman test and Dunn test, with Bonferroni's correction, Spearman correlation coefficient were used by SPSS software (version 21, Chicago, IL, USA). It should be

noted that all of the participants were included in the process and no one was excluded during the investigation.

RESULTS

Among the participants of this study, 56% of the subjects were male and 56% were female. Only 34% of them in the intervention group were in the age range of 39-48 years and 44.9% of the control group`s members were in the age range of 29-38 years.

According to the statistics, most of them (44% in the intervention group and 79.6% in the control group) were married. In the intervention group, 48% and in the control group, 62.5% were employed; 52.1% had diploma in the intervention group and 66.7% had diploma educational level in the control group.

Moreover, 36% in the intervention group and 34% in the control group were burned by fire flame and 60% in the intervention group and 64% in the control group had a degree of burns of 1, 2 and 3. Furthermore, 24% in the intervention group had burning percentage of 15-20% and in the control group, 36% had burning percentage of 21-26%. About 46% in the intervention group had burn in the trunk, hand, and foot and 47.9% in the control group had burn in the whole body.

The majority of patients in the intervention and control group (58.1%, 79.2%, respectively) were resident in Tehran. The majority of patients in the intervention and control group (58.1% and 53.5%, respectively) were burned at home. In the intervention group, 56.5% were on average economical level and 37.8% were in weak economic level.

The Mann-Whitney test showed that before intervention, the mean of social function in intervention and control groups was 1.92±0.6 and 1.55±0.46, which was statistically significant (p<0.001). The mean difference of the score of social function in both intervention and control groups at the time before intervention was statistically significant and the mean score of social dimension in the intervention group was slightly higher than the control group.

Mean and standard deviation of social function score in intervention and control groups three months after intervention were 3.29±0.95 and 2.15±0.39, respectively and six months after intervention, the mean and standard deviation of intervention and control group were 4.05±0.77and 2.47±0.56, which were statistically significant (p<0.001) (Table 1).

Table 1: Comparison of mean and standard deviation of social function score in intervention and control groups one month before and three and six months after intervention

	Intervention group	Control group
Mean and standard deviation before intervention	1/92 ± 0/6	1/55 ± 0/46
Test result	Z = -2/98 P value < 0/001	
Mean and standard deviation three months after intervention	3/29 ± 0/95	2/24 ± 0/4
Test result	Z = -6/83 P value < 0/001	
Mean and standard deviation six months after intervention	77/0 ± 05/4	2/75 ± 0/58
Test result	Z = -7/74 P value < 0/001	

Considering the chi-square value (=95.14) and the value of significance level (p<0.001) in Table 2, since the level of significance was less than 0.05, the assumption of the equality of the mean scores of social function during three periods was rejected statistically, that is, the average score of social function varied at least in two periods of the three ones. Therefore, in order to determine which of the two periods had a significant difference, the Dunn follow-up test was used.

The results of the test were presented in Table 2 and 3, while the mean score of each period had significant differences with other periods because the corrected significance level value was less than 0.05.

Figure 1 shows that the social dimension score before intervention in the intervention group was slightly higher than the control group, but after 3 and 6 months of intervention, the social function score of the intervention group demonstrated a significant difference compared to the control group (p<0.001).

Table 2: Results of comparison of mean and standard deviation of social function score before intervention, 3 and 6 months after intervention in intervention group using Friedman test in intervention group

Time	Number	Mean	Standard deviation	Test result
Before intervention	50	1/92	0/6	Chi-square = 95/14 df = 2 p-value<0/001
Three months after intervention	50	3/29	0/95	
Six months after intervention	50	4/05	0/77	

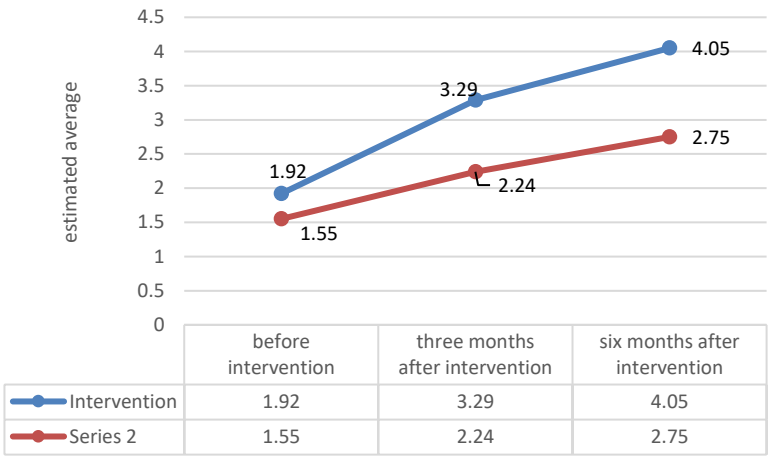
Table 3: Comparison results of social function score in 3 periods with Dunn pairwise test with Bonferroni's correction in intervention group

Difference	Standardized test statistic	Corrected significance level
Before intervention - 3 months later	-5/4	<0/0.001 adj. p-value
Before the intervention - 6 months later	-9/45	<0/0.001 adj. p-value
3 months later - 6 months later	-4/05	<0/0.01 adj. p-value

Table 4: Comparison results of social function score in 3 periods with Dunn pairwise test with Bonferroni's correction in control group

Difference	Standardized test statistic	Corrected significance level
Before intervention - 3 months later	-5/25	<0/0.001 adj. p-value
Before the intervention - 6 months later	-8/4	<0/0.001 adj. p-value
3 months later - 6 months later	-3/15	<0/0.01 adj. p-value

Figure 1: Comparison of the trend of changes in the mean score of social function 3 and 6 months before and after intervention in two groups



DISCUSSION

The results of this study showed that multimedia virtual self-care discharge education improves social functioning of burn patients. This finding is consistent with the study by Li et al. In their study, they found that social functioning of burn patients 5 weeks after rehabilitation was better than the control group [19]. Tang et al. (2015) study also showed that the use of rehabilitation interventions and self-care measures increased the social function dimension of patients three months after intervention, which is consistent with the present study [20]. Radwan et al. (2011), who found that running a 7-day rehabilitation program for 2 weeks improved social performance in the experimental group, also consistent with our study [21]. Burn injuries affect one's ability to cope with life's stresses and interact with the outside world [8]. These people feel ashamed and embarrassed about being in the community and communicating with others due to the apparent changes caused by burns and burns, and the look and sometimes excitement of others suggests that they feel compassion and compassion. For this reason, they lack communication and social skills and require intervention [23]. Hojati et al.'s study showed that psychosocial interventions had a significant effect on life satisfaction, occupational activity, mental health, physical health, quality of life, and social

relationships.

Therefore, these interventions increase patients' life satisfaction and social relationships [24]. The results of the Fatimid study showed that patients' quality of life in the social dimension was relatively undesirable, so it recommended that patients be taught communication skills [25]. The consequence of education in the community is maintaining and promoting health and will have many benefits, including reducing the duration of illness, accelerating client independence and maintaining self-confidence in self-care [26]. A study by Elalem et al. (2018) showed that self-care nursing intervention was effective in burn patients.

And self-care intervention led to active participation of patients in their treatment and led to a significant improvement in quality of life as well as self-esteem, which is consistent with the present study which correlates with self-esteem and quality of life later. Social has had a significant impact [27]. Hospital discharge is associated with stress and anxiety and an increased need for patients to receive information. Information training is essential for the well-being of patients because patients experience discomfort after awareness discharge [28]. Discharge does not mean the end of treatment for burn patients, but discharge means that the patient and his or her family must resume the responsibility of managing their lives without assistance from hospital staff. Burn patients need to adapt to new situations that include self-care at home, lifestyle change and return to society [29].

Limitation and recommendation

One of the limitations of the present study was the mental state of the patient which could be effective in answering the questions. It was the researcher who emphasized the importance of the subject in the result of the research and asked the samples to fully comply with the CDC's recorded care instructions and followed up the samples by telephone.

CONCLUSIONS

Given the findings of the present study, it is important to provide virtual and multimedia education and to institutionalize a self-care culture. This allows the patient to self-care and engage in self-care. Nurses and caregivers in burn centers need to know that these patients will be socially isolated and isolated, and that they need to return to the community, and nurses are one of those who treat patients' behaviors and attitudes more than others. So they can help them get back into the community with proper education, but education through lectures does not meet their educational need because they are involved in the mental illness of their illness and burn accident, especially while they are still in hospital. And maybe the ability to understand and learn training in that situation So they need virtual training to use it in the right conditions and in a comfortable place. That is, self-care education should be continuous, accessible, follow-up, and economically viable. So using educational CDs, which is a virtual teaching method, can be a good option. It is recommended that nurses use this method in clinical centers.

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Conflict of interests

It is not declared by the authors.

Ethics approval and consent to participate

Clinical trials with the issue number IRCT 2014112920145, ethical code number 93-02-28-24922-106366 on 18/09/1393.

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VARIA

The use of IPACK and the continuous adductor canal block in the perioperative management of total knee prosthesis

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Abstract: *Background: Although locoregional anesthesia techniques in total knee arthroplasty (TKA) have progressed steadily, the emergence of the adductor canal block representing a step forward for postoperative evolution in preservation of the quadriceps muscle strength, analgesia of the posterior territory of the knee still remains a challenge. The emergence of IPACK, in association with earlier techniques, offers promising preliminary results in terms of its contribution to a favourable evolution and to the satisfaction of TKA patients.*

Materials and methods: Prospective trial performed on a group of 28 patients undergoing a total knee arthroplasty intervention; analgesia control in the postoperative period was performed either with opioid and nonopioid systemic analgesics, or by associating the continuous adductor canal block with IPACK and systemic analgesics. The primary objective is pain control at rest/on mobilization, while the secondary purpose is analysis of opioid use, their side effects and recovery of joint mobility.

Results: There is a significantly better pain control in the group of patients with locoregional anesthesia, both at rest and on mobilization ($p<0.005$), accompanied by a decrease in opioid use ($p<0.00001$) and the related adverse reactions; at the same time, there is an improvement in the functional recovery of the knee joint, quantified by the flexion degree at 24 and 48 hours after surgery (61.5/71.12 degrees for continuous adductor canal block with IPACK versus 45.14/55.42 degrees for general anaesthesia)

Conclusions: The introduction of peripheral nerve blocks in the multimodal analgesia regimen after TKA results in better control of postoperative pain, both at rest and on mobilization, in a decrease in opioid use and their related adverse reactions and in an improved recovery of joint range of motion, as well.

Keywords: *continuous adductor canal block, IPACK, VAS, TKA*

INTRODUCTION

Total knee prosthesis is currently one of the most common surgeries in the field of orthopedics, the number of such interventions performed annually being on an accelerated upward trend. On the other hand, the pain stimulus that occurs in total postarthroplasty of the knee is often very intense, TKA being known as one of the most painful orthopedic surgeries , pain control is a major component in perioperative management of TKA [1].

The pain occurring in the postoperative period, as well as the systemic inflammatory response initiated following the tissue trauma will have significant consequences for the

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postoperative evolution of the patients, including prosthesis infection which can compromise the joint functionality and complicate postoperative evolution [2]. It has been shown that activating an exacerbated systemic inflammatory response leads to increased rates of local and systemic complications, increased perioperative morbidity and mortality, increased length of hospitalization and patient dissatisfaction. In view of the above mentioned, the existence of a standardized and complex protocol for the perioperative management of patients with TKA becomes an absolute requirement in order to improve the postoperative evolution, decrease the duration of hospitalization and increase patient satisfaction [3]. The multidisciplinary approach is decisive in determining the prognosis both in case of primary TKA, as for modular endoprosthetic reconstruction, as well [4].

MATERIAL AND METHOD

After getting the agreement of the Ethics Commission of the Bucharest University Emergency Hospital (SUUB), a prospective monocentric trial was performed on 28 patients undergoing unilateral total knee arthroplasty surgery in the SUUB Orthopedics and Traumatology Clinic between May 2020 and March 2021.

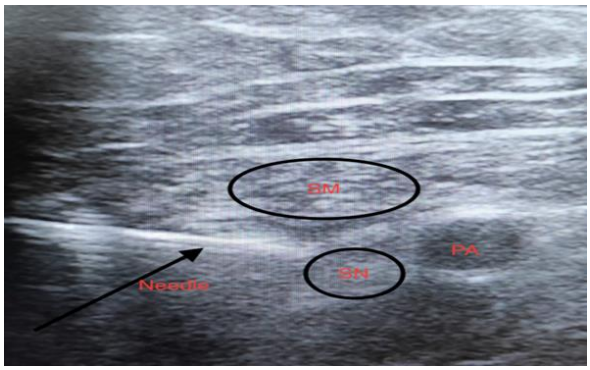
The patients included in the trial belonged to ASA risk classes 1-3; patients with ASA risk class > IV, chronic opioid users prior to presentation, obese patients with BMI>40 kg/sq.m., known allergies to analgesic medication included in the protocol, contraindications for neuraxial anesthesia, chronic kidney disease or pre-existing peripheral neuropathy were excluded from the trial. Prior to surgery, patients were informed extensively with regard to the protocol, the technique of anesthesia and analgesia, the related risks and benefits, and the patients gave their informed consent.

The total knee prosthesis surgery was performed by experienced surgeons of the Orthopedics and Traumatology Clinic of SUUB with a parapatellar anteromedial approach, with bicompartmental prosthesis and using the hemostatic band [5].

The trial was performed on 2 groups of 14 patients each, divided according to the anesthetic management and the perioperative analgesia approach. The first group comprised of patients that received balanced anesthesia with volatile pivot and intravenous multimodal postoperative analgesia. In the second group, the anesthetic technique consisted of spinal anesthesia associated with IPACK and the continuous adductor canal block. All patients (both group 1 and group 2) received preemptive analgesia, paracetamol 1 g, Gabaran 300 mg and Celecoxib 200 mg one hour before surgery; the treatment was continued for the first 72 hours postoperatively (paracetamol 1 g every 6 hours under ASAT/ALAT control, Gabaran 600 mg/day in 2 doses, Celecoxib 200 mg twice daily). The locoregional anesthesia maneuvers were performed by anesthetists of the Anesthesia-Intensive Care Department of SUUB.

Patients in group 2 were admitted to the preoperative ward approximately one hour before the time of surgery for performing the 2 peripheral nerve blocks. The patient is placed in supine position, a peripheral venous line is inserted and the patient receives standard monitorization (according to the standards required by the Romanian Anesthesia and Intensive Care Society). To perform the adductor canal block, the patient is positioned with the thigh in slight abduction and external rotation; the patient's thigh is disinfected with 2% chlorhexidine solution, the high frequency linear probe (Philips Cx50 transducer L 12-5 50 mm) is used, which is placed transversely on the thigh in its anteromedial portion approximately at the junction between the medial and distal thirds of the thigh, and the saphenous nerve located anterolaterally to the femoral artery, under the sartorius muscle is identified; under ultrasound guidance (the in-plane approach) the Touhy needle from the Contiplex Touhy Ultra-B. Braun set is advanced under careful ultrasound visualization, from the lateral to the medial area up to the vicinity of the femoral artery. After aspiration and the prior injection of 1-2 ml in order to check the position of the needle, 20 ml of ropivacaine 0.5% is infiltrated into the upper part of the artery (Figure 1).

Figure 1: Infiltration area



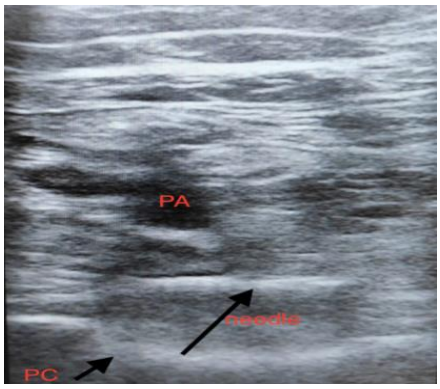
SM sartorious muscle, SN safenous nerve, PA popliteal artery

A plexus catheter is inserted in the adductor canal; the catheter is secured at 11-13 cm with Histoacryl and Tegaderm to prevent dislocation and extravasation of local anesthetic. A mixture of ropivacaine 0.2% with Fentanyl 2-gamma/ml with Easy Pump B. Braun, with a volume of 125 ml and a constant administration rate of 5 ml/hour, is administered postoperatively, allowing for the easy

mobilization of the patient. The catheter is retracted 72 hours postoperatively.

The second peripheral nerve block performed is IPACK. The patient is in a supine position with his knee slightly bent. The high frequency linear probe (Philips Cx50 transducer L 12-5 50 mm) is used, which is positioned transversely in the popliteal fossa for the visualization of the femoral condyles, the popliteal artery, the tibial nerve and the common peroneal nerve; the transducer is advanced slightly proximally until the posterior edge of the femur is visualized. After local anesthesia with 1-2 ml of lidocaine 1%, a Stimuplex Ultra 360 20G-100 mm needle is inserted, under ultrasound guidance (the in-plane approach), in the space between the popliteal artery and the posterior edge of the femur, from the lateral to the medial area, and the local anesthetic is infiltrated, 20 ml of ropivacaine 0.5% in a single injection (Figure 2).

Figure 2: Infiltration area for second peripheral nerve block



PA popliteal artery, PC posterior capsule

Postoperatively the patients are admitted to the postoperative intensive care unit for the first 24 hours. The patients in group 1 (general anesthesia) enter the multimodal analgesia protocol with morphine combined with paracetamol 1 g/6 hours, Gabaran 300 mg/12 hours and Celecoxib 200 mg/12 hours. Postoperative analgesia of patients in group 2 (spinal anesthesia with peripheral nerve blocks) is ensured by the administration of local anesthetic via adductor canal catheter, supplemented by the administration of paracetamol 1 g/6 hours, Gabaran 300 mg/ 12 hours and Celecoxib 200 mg/12 hours.

The primary objective of the trial is to record the pain score by means of the visual analogue scale (VAS) both at rest and in activity, while the secondary objectives that we followed are the consumption of opioids in the two groups, their adverse effects and the degree of mobility of the joint that correlates directly with a quick postoperative rehabilitation of the joint.

Statistical analysis

The data recorded is processed using descriptive statistics, Student t-test. The nature of the hypotesis testing was two-tailed, and P<0.005 was considered statistically significant.

RESULTS

From a demographic point of view, no significant differences are observed between the two groups of patients (tabel 1). The preoperative pain score at rest is also comparable, and in terms of chronic analgesic use it is observed that only 4 patients in group 1 and 3 patients in the group 2 were chronically using analgesics of the NSAID category (in the last 3 month) and one patient analgesics of the weak opioids class.

Table 1: Demographic data, surgical information (values are presented as mean or number and percent)

Treatment group	General anesthesia n=14	IPACK/cACB n=14
Age(y)	62 (49-70)	68 (59-74)
Gender, male, n	4 (14)	5 (14)
BMI (kg/m²)	34 (25-39)	32 (25-38)
Surgical time(min)	117 (70-170)	130 (80-180)
VAS rest at home	3 (3-4)	4 (3-5)
NSAID consumption at home (last 3 month)	4 (14)	3 (14)
No opioid consumption at home	13 (14)	14 (14)

IPACK, infiltration of local anesthetic between posterior artery and capsule of the knee; cACB, continuous adductor canal block; BMI, body mass index; VAS, Visual Analogue Scale ; NSAID, Nonsteroidal anti-inflammatory drugs

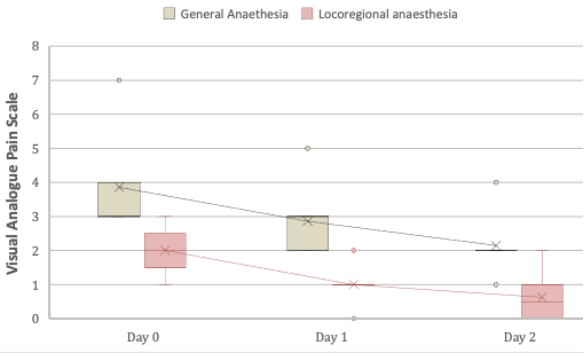
VAS score at rest and at work on day 1 and day 2 showed significantly (p<0.005) better values in locoregional anaesthesia group (lot 2) compared to general anaesthesia group (lot 1). VAS score at rest after 8 hours postoperatively also showed significantly (p<0.025) better values in locoregional anaesthesia group compared to general anaesthesia (Figure 3).

The mean ranges of movement on days 1 and 2 postoperatively for locoregional anaesthesia group (61.5 degrees and 71.12 degrees, respectively) were significantly better (p< 0.0005) than ranges of movement on day 1 and 2 for group with general anaesthesia (45.14 degrees and 55.42 degrees).

Similary, the opioid usage was lower (P<0.00001) on day 1

for pacients who received adductor canal blockade combined with IPACK.

Figure 3: Pain numerical rating scale at rest



Boxes represent 25th-75th percentiles interval. X marks mean value

DISCUSSION

Because effective analgesia is largely responsible for blocking this metabolic breakdown called systemic inflammatory response, much of the efforts undertaken by clinicians have focused on controlling postoperative pain [6]. Recent decades have witnessed the wide implementation of the concept of multimodal analgesia, a protocol in which, in order to ensure effective analgesia, conventional analgesia methods (administration of opioids, paracetamol, nonsteroidal anti-inflammatory drugs, etc.) are associated with new locoregional anesthesia techniques. This makes it possible to reach an effective analgesia threshold while significantly reducing the use of opioids and analgesic drugs, therefore decreasing the adverse reactions related to their excessive consumption [7].

The role of locoregional anesthesia in the management of the TKA patient is already well established. Numerous studies have shown that the association of different peripheral nerve blocks with the administration of systemic analgesics in the multimodal analgesia protocol (the femoral nerve block and more recently the adductor canal block) makes an important contribution to the perioperative management of such patients [8, 9]. Unlike the femoral nerve block, which often results in quadriceps muscle fatigue and increases the perioperative risk of accidental fall, the adductor canal block preserves the muscular strength of the quadriceps muscle, reduces the risk of in-hospital fall and significantly improves the functional recovery of the joint [10-12]. However, it seems that the inclusion of the femoral nerve block or the adductor canal block in the perioperative management plan does not necessarily eliminate the need for opioid administration in the perioperative period [13]. This can be explained by the fact that both variants of the femoral nerve block – the classic one and the adductor canal block – will ensure the analgesia of the anterior and mediolateral territory of the knee joint, so that the posterior area innervated by branches detaching from the sciatic nerve is completely free of analgesia, hence the need to supplement with analgesics postoperatively [14].

In this sense, different solutions have been searched to ensure efficient analgesia in this territory, without affecting the motor performances that play an important role in the rapid postoperative functional recovery. Thus, the emergence of the IPACK block (infiltration between the popliteal artery and the capsule of the posterior knee) appears as a promising solution in terms of ensuring analgesia for the posterior territory of the knee joint [15, 16]. The innervation of the posterior territory of the knee joint is ensured by articular branches detaching from 3 main trunks: the tibial nerve (whose branches represent the main source of innervation of the knee posterior capsule), the common peroneal nerve (that sends terminal branches to the anterolateral and posterolateral portion of the capsule) and the obturator nerve (3 branches ensuring the innervation of the superomedial portion of the capsule) [17]. In essence, IPACK blocks the terminal sensitive branches detached from the popliteal plexus and the obturator nerve, thus ensuring analgesia of the posterior capsule of the knee, without involving motor branches and therefore without affecting the process of functional recovery of the joint. Sparing the motor branches of the common peroneal and tibial nerves and covering the posterior territory of the knee joint are two features that can make IPACK the ideal solution, along with the adductor canal block, with a view to ensuring effective analgesia of the knee joint in the postoperative period [18, 19]. From a technical point of view, this is achieved by the infiltration of a local anesthetic into the area located between the popliteal artery and the posterior capsule of the knee, an ultrasonographically guided maneuver. So far, experience with the use of the combined technique consisting in locoregional anesthesia, adductor canal block associated with IPACK, has been limited in terms of the functional recovery of the joint, the analgesic efficiency and the opioid use.

Starting from the idea that the new techniques described in locoregional anesthesia represent a major step forward in the perioperative management of TKA patients, the trial described here will analyze the efficacy of the continuous adductor canal block associated with IPACK in improving pain control and functional recovery, in reducing opioid use and the incidence of side effects, as well as in reducing the duration of hospitalization [19].

From a demographic point of view, no significant differences

are observed between the two groups of patients. The preoperative pain score at rest is also comparable, and in terms of chronic analgesic use it is observed that only 4 patients in group 1 and 2 patients in the group 2 were chronically using analgesics of the NSAID category and one patient analgesics of the weak opioids class.

As regards the intensity of pain on the day of surgery, patients in the group with postoperative analgesia based on the combination of analgesics of the opioid class and nonopioids had a higher VAS score than those for whom locoregional anesthesia with systemic analgesics of the weak opioids class and nonopioids was used in the multimodal analgesia protocol. Also, there is a better control of pain in group 2, including days 2 and 3 postoperatively, both at rest and when mobilizing the knee joint with the help of kinetics.

Following the functional recovery of the joint, we notice that the patients in group 2 were able to suffer a higher degree of flexion of the joint in terms of pain, compared to patients without locoregional anesthesia. At the same time, the use of opoids was significantly higher in patients with systemic analgesia only.

During the trial, only one major adverse event occurred, namely one case of respiratory depression following opioid administration; adverse reactions such as nausea and vomiting were more common in patients with opioids, while in the group of patients with locoregional anesthesia no adverse effects were reported of the type systemic toxicity of the local anesthetic, extravasation of the anesthetic at the site of catheter insertion or in-hospital fall due to decreased muscle strength of the quadriceps muscle.

Although locoregional analgesia in the perioperative management of TKA is supported by the results of the trial, it has certain limitations. First of all, the trial is not a randomized one. Secondly, the follow-up of the patients was performed only in the first 72 hours postoperatively, until the removal of the adductor canal catheter, therefore we cannot provide any data on the further developments in terms of pain intensity and analgesic requirements after locoregional analgesia is suppressed. Further studies are needed in order to determine whether the benefit of locoregional anesthesia (joint mobilization, pain score) is maintained after its discontinuation. Thirdly, despite significantly higher opioid use in patients in group 1, postoperative pain is more difficult to control, therefore comparing the degree of joint mobility of the two groups may not be relevant, the intensity of the pain being an important limiting factor of the mobility degree.

In a prospective, triple-blind trial conducted by Kim D. et al in 2017 on a group of 86 patients undergoing primary unilateral knee arthroplasty, the association between IPACK and the adductor canal block at the periarticular infiltration of the local anesthetic provides a high level of analgesia and helps reduce opioid use compared to the joint infiltration associated with the systemic multimodal analgesia regimen. This trial supports the introduction of IPACK and the adductor canal block in a standardized multimodal analgesia protocol for patients undergoing orthopedic knee joint prosthesis surgery [20].

Another prospective trial by Patterson ME. et al. on 69 patients enrolled during the period 2016-2018 shows that the association of IPACK with the multimodal analgesia regimen improves pain control at rest in the postoperative period, but without bringing a significant clinical improvement (no significant differences were found between the pain in conditions of physical exertion, distance walked, length of hospitalization or opioid use), therefore the trial did not recommend the introduction of IPACK in the routine management of knee arthroplasty [21].

CONCLUSIONS

Although the results of the clinical trials conducted so far are controversial and long-term research is needed on this topic, the trial conducted in our center supports that the introduction of peripheral nerve blocks in the multimodal analgesia regimen after total knee prosthesis results in a better control of the postoperative pain both at rest and on mobilization, in the decrease of opioid use and implicitly of the incidence of the related adverse reactions. Moreover, the IPACK association seems to bring an additional benefit consisting in the control of the painful stimuli at the back of the knee joint, with a faster rehabilitation and increased joint mobilization, which in the long run will lead to a lower rate of complications caused by prolonged immobilization and to a higher degree of patient satisfaction.

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VARIA

Couvelaire-Uterus: literature review and case report

Ionut M. Cobec[1], Andreas Rempen[1]

Abstract: *Uteroplacental apoplexy or Couvelaire uterus is a rare complication in the spectrum of the life-threatening placental abruption.*

We report a 29-year-old pregnant woman who had a placental abruption complicated with the rare condition of Couvelaire uterus, with an delivery per uterus-sparring cesarean section.

The early diagnosis and proper medical management of placental abruption through uterus-sparring cesarean section present the best outcome for mother and child.

Keywords: *uterus Couvelaire, placental abruption, uteroplacental apoplexy*

INTRODUCTION

Utreroplacental apoplexy or Couvelaire uterus is a rare manifestation which complicates aprox. 5% of placenta abruptions and was described for the first time in 1911 by French obstetrician Dr. Alexandre Couvelaire [1, 2]. The placenta abruption complicates ~1% of pregnancies [3] and the maternal mortality can reach up to 5%. The uteroplacental apoplexy is a rare, nonfatal complication of the placenta abruption [4].

A literature search for the last 10 years was conducted on 25.11.2020 using the PubMed database and having the key words 'Couvelaire uterus'. This resulted in 27 articles published in the last 10 years. The Couvelaire uterus is often underreported and underestimated. The etiology is unknown and the diagnosis is done through inspection or histological examination [4].

This mechanism of placenta abruption can be seen as physiological after the fetus delivery and as pathological in the pregnancy with the fetus still in uterus. The acute condition of placenta abruption is the result of a compromise of the vascular structures supporting the placenta, having as outcome a retroplacental hematoma. This process may represent the starting point for Couvelaire uterus. The hemorrhage from pathologic vascular damage within the placenta seeps into the decidua basalis causing a separation of the placenta. Before the second stage of labour is finished, the blood created by bleeding resulting from the early placenta abruption infiltrates into the myometrium finding its way into the peritoneal cavity. Occasionally, such effusions of blood extend in the parametrium. As a result of the described mechanism we notice the macroscopic aspect of Couvelaire uterus which displays lesions characterized by violet to black ecchymoses [5, 6, 7]. The Couvelaire uterus sometimes loses its contractile power but usually responds well to intravenous oxytocin [6, 8]. The uterine ability to contract is preserved, particularly after amniotomy and decompression to allow constriction of spiral arteries [9].

Among the risk factors for placenta abruption are early

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pregnancy bleeding, hypertension or thrombophilia, or abdominal trauma [10]. The diagnose of placenta abruption is made clinical and is completed by the ultrasound scan and CTG. The patients present a painful, tender and rigid uterus, may have uterine contractions, vaginal bleeding is also common. The finding of a retroplacental clot on ultrasound scan is a risk factor for placenta abruption, the ultrasound scan plays an important role correlated to the clinical situation in the diagnose of the placenta abruption [3, 10, 11].

The delay of the diagnose of placenta abruption increase the risk of intrauterine fetal death, hypoxic brain injury, bleeding, coagulopathy with increased maternal and fetal morbidity and mortality [12, 13]. The incidence of coagulopathy in placenta abruption is reported to be 5.8% [3]. In the case of Couvelaire uterus the disseminated intravascular coagulation can be induced through the infusion of thromboplastic material in maternal circulation [14].

Couvelaire uterus was associated in different reports with placenta abruption, placenta previa, amniotic fluid embolism, and preeclampsia [4, 15]. Cesarean section in the patient's history is a risk factor for uterine rupture, abnormal placental implantation, placental abruption and uterine scar dehiscence in subsequent pregnancies [16]. Some authors consider that the incidence of Couvelaire uterus is increased by the increase in cesarean deliveries [4].

The management of the antenatal and postpartum hemorrhage plays a key role, on one side in the control of the bleeding and blood transfusion, and on the other side aims to reduce fetal and maternal morbidity and mortality [4].

In the past hysterectomy was performed as a routine therapy of Couvelaire uterus. Nowadays, is recommended to opt for the conservative management [4, 8]. The proper management of this pathology reduces the high maternal and fetal risks. The literature reports cases of fetal demise, but also hysterectomy as a result of severe disseminated intravascular coagulopathy [3, 4, 17]. The early decision to perform a hysterectomy taken before the patient's condition is extreme serious is required in order to minimize the morbidity and mortality [18, 19]. On the other hand, before deciding for more aggressive procedures, like hysterectomy, B-Lynch technique should be taken into consideration in cases of postpartum haemorrhage as a result of abruptio placentae followed by development of Couvelaire uterus [19, 20].

In a study on placenta abruption poor perinatal outcome associated with Couvelaire uterus, pregnancy induced hypertension and disseminated intravascular coagulopathy is reported [18].

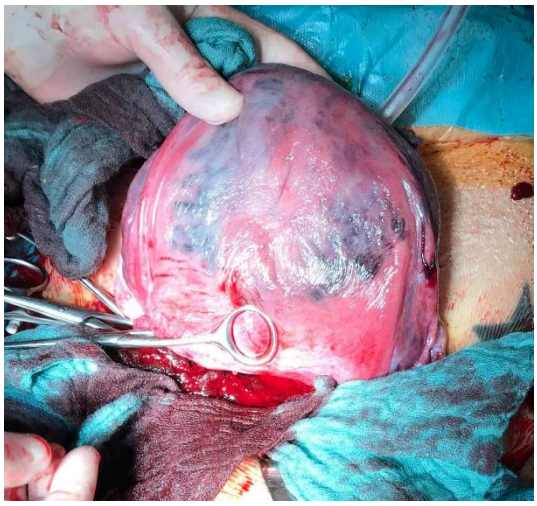
CLINICAL EXAMPLE

A 29-year-old gravida two, para one, in the 37th (36+6) week of an uncomplicated pregnancy, with a history of an uneventful spontaneous delivery, was admitted to the obstetric ward with symptoms of nephrolithiasis and urinary infection for further therapy. The obstetrical check-up was uneventful. The admission symptoms were alleviated, discharge could have been possible but she developed irregular and poorly coordinated uterine contractions. She developed uterine tenderness without relaxation between contractions, with wooden hardness by palpation. Vaginal examination revealed acute hemorrhage from the uterine cavity. The patient was hemodynamically stable. The cervix was 2 cm long and 1 cm dilated. CTG was normal. Cesarean delivery was indicated by suspicion of placental abruption. Intraoperatively massive hemoperitoneum and the diagnose of placenta abruption with Couvelaire uterus was confirmed (Figure 1).

A healthy boy was delivered. Uterus-sparring surgery was performed.

Postoperative recovery was uneventful.

Figure 1: Couvelaire uterus as a result of acute intradecidual hemorrhage produced by the rupture of the uterus–placental spiral arterioles which produces ecchymosis discoloration, secondary to extravasation of blood into the myometrium and serosa, can lead to hemoperitoneum.



DISCUSSION AND CONCLUSION

Placental abruption represents the early separation of the placenta from the uterus wall developing a retroplacental hematoma which is an acute intradecidual hemorrhage

produced by the rupture of the uterus–placental spiral arterioles. Couvelaire uterus or uteroplacental apoplexy is the result of blood extravasations in the tissues, occasionally the infiltrations which reach the peritoneal cavity creating hemoperitoneum [1, 2, 5].

In our case, the first intraoperative view after opening the peritoneal cavity was the massive hemoperitoneum and Couvelaire uterus with dark purple and copper color patches with ecchymosis discoloration and hemorrhagic infiltration in the lateral portions of the uterus.

Diagnosis is made through direct inspection or histological examination [2]. The management of this complication of the placenta abruption is conservative through uterus-sparring surgery, hysterectomy is usually not required and should be discouraged [2, 6]. Couvelaire uterus is a rare complication of placental abruption, with an underreported incidence and it is often associated with placenta previa, amniotic fluid embolism, and preeclampsia [4, 15] .

Often Couvelaire uterus is reported with massive placenta abruption requiring blood transfusion [4]. In our reported case blood transfusion was not required. Antenatal fetal and maternal monitoring, but also the delivery on time, plays an important role in the delivery outcome, otherwise due to bleeding it can come to fetal demise [15, 21]. Placental abruption has an increased maternal morbidity risk of haemorrhage, hysterectomy and consumptive coagulopathy [3]. The life-threatening condition of disseminated intravascular coagulation should not be underestimated [3, 18] .

In the reported case the patient was in the hospital under monitoring and the prompt medical decisions reduced the maternal and fetal risks.

The early diagnosis and proper medical management of placental abruption through the uterus-sparring cesarean section provide the best outcome for mother and child.

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VARIA

The role of the communication in changing health behaviors

Dodu G. Petrescu[1], Raluca Răducu[1], Cristina Soare[1], Victor L. Purcărea[1]

Abstract: *The communication in the field of health can be defined as a communication strategy used to inform and influence individual and community decisions with the aim of improving and enriching personal and community behaviors and public health practices. It includes studying public health attitudes and behaviours to determine the type, frequency and format of the messages.*

Keywords: *attitudes, behavior, change, communication, health*

Social communication and behavioral change are at the heart of any successful public health initiative. The purpose of communication is to make someone to think in a certain way, to do something or to act, in other words is the exchange of emotions, ideas and opinions in the form of information between sender and receiver [1]. It is the most important aspect of the educational process aimed at changing behaviour and attitude and improving the level of knowledge [2].

The communication has several functions [3]:
- instrumental function – to achieve something;
- information function – to find out or explain something;
- social contact function – to make a pleasant environment;
- control function – to cause someone to behave in a certain way;
- expression function – to express feelings or to present themselves in a certain way;
- role-related function – for the given situation;
- educational function – to convey knowledge;
- stimulation function– to bring interest;
- entertainment function – to provide leisure activity;
- cultural promotion function – to strengthen cultural rites.

According to John Fiske-1982, [4] there are two complementary schools with different approaches, in the study of the communication, the school "process" (communication as a transmission of messages; communication analysis models: Lasswell - 1948, Shannon and Weaver - 1949, Newcomb - 1953, Gerbner - 1956, Westley and MacLean - 1957, Jakobson - 1960, etc.) and the semiotian school (communication as production and exchange of meanings; founders and contributors: Charles S. Peirce and Ferdinand de Saussure , as well as C.K. Ogden and I.A. Richards, Louis Trolle Hjelmslev, Roland Barthes, Pierre Gouriaud); There are many schemes of the communication process, but the most complete belongs to Philip Kotler, who managed to integrate all the elements of the process, as can be seen in the Figure 1.

The Healthy People 2010 Report defines the communication in public health as "the art and technique of informing, influencing and motivating individuals, institutions, general public on the important public health issues [6].

The term health communications was first used in 1961, when the U.S. National Health Council held a National Health Forum to discuss the challenges facing health intelligence communications [7]. The term was used again in 1962, when the surgeon Luther Terry organized a conference on health

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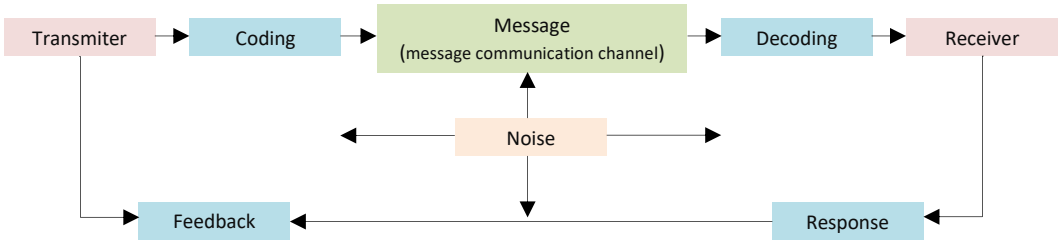
communications to discuss how different communication techniques can be used to make health information available to the public [8]. The term was adopted by members of an interest group at the International Communication Association (ICA) in 1975 [9].

Figure 1: Kotler's model.



Source: Adaptation by Kotler, Ph., Principles of Marketing, III. Developing the Marketing Mix. 13. Integrated Marketing Communication Strategy, Pearson, Canada, pag. 546, accesibil online la: http://www.pearsoned.ca/highered/divisions/virtual_tours/kotler/kotler_ch13.pdf [5]

Health communication is a hybrid field that derives from communication, marketing, journalism and public relations studies and overlaps with health education and health promotion [10].

The health education is used to make people aware of the patterns of healthy behavior and its importance. The health education programmes related to behavioral change are considered to be a pillar of medical activity [11].

The health education is a social science that relies on medical, biological, physical, environmental and psychological sciences to prevent the occurrence of the diseases and promote health through behavior-changing activities based on the education.

Health campaigns for the prevention of the communicable diseases, for the promotion of maternal and child health, for the promotion of the immunisation, for education about family planning methods and other preventive health services have a long history [12].

The health education is linked to changes in people's feelings, knowledge and behaviour. It is the process carried out by actively involving people who aim to initiate healthy behavior and to know the prejudices and practices of people who are discouraged towards health in order to achieve the health goal [13].

The health communication is an extensive area that includes health education, risk communication, health and policy promotion, focus communication, patient and supplier communication and health literacy. Health communication strategies enable to the doctors and nurses, community health centres, hospitals and hospital administrators, nursing homes, health educators, non-profit organisations, government agencies and others to disseminate information that can positively influence personal health behaviors and choices.

Using informed marketing tactics and sociological data to lead to decision-making, the health communication is used to promote health campaigns in order to influence and educate the public on health issues [14].

The success of the health communication or health education programmes depends on people's interest. It is important for them to be actively involved, the change cannot be imposed, people must be motivated to adopt healthy behavior [15].

Communication related to the behavior change can take different forms, to appeal at the individual or group level, in order to change behavior towards a specific health problem. Health communication includes interpersonal communications, such as individual meetings between a healthcare provider and the patient [16], as well as community-focused communications such as public meetings, advertisements in local newspapers, the distribution of brochures and leaflets or educational events.

The media plays a key role in health communication, serving as a channel of health information from the government and specialized health organizations to the public. With their extensive coverage through radio and television commercials, the media can persuade the general public to adopt new healthy behaviors and recall information on preventive health care, disease prevention and treatment, immunizations and more.

The Internet is now disseminating information on an unprecedented scale, but at the same time, false and unsafe information has become more common than ever, posing risks to the health of uninformed users. This situation can cause an unjustified panic among those who receive the messages and can be a problem as technology continues to move forward. Therefore, public health providers must communicate the risks to the public in a responsible and transparent way and identify and eliminate misleading notions [17].

The decision to choose a particular communication channel must be based first on the research of the target audience and then on its usefulness and coverage. Thus, some technologies are not particularly effective when used by a small number of people or are too complicated to be operated by ordinary people.

Health communication issues have become a major topic of large-scale research programs sponsored by various foundations, health care corporations and government agencies.

Communication to change behavior is based on research and involves interaction with individuals and communities and personalizes messages that meet the needs of a particular target audience. Messages are then disseminated through different communication channels to bring about behavioral changes in specific problems and achieve the desired positive results.

The message must have an impact and it should disseminate appropriate health content defined by [6] :

- accuracy (the content is valid and without errors of interpretation or judgment);

- availability (the content must be placed where the public can access it);

- balance (to present both the benefits and risks of potential actions);

- consistency (remains consistent over time and it is consistent with information from another source);

- cultural competence (it must take into account ethnic, educational, linguistic issues); - relevant scientific evidence;

- coverage (to be available to the largest possible number of people in the target population);

- reliability (the source of the content is credible and the content is up-to-date);

- repetition (the delivery of the message must be continuous and repeated over time).

The development and management of social and behavioral change programmes involves the building of the partnerships at the national and local level, using new technologies and techniques of social and behavioral change and the incorporating of the social and behavioural change activities into programming the provision of services.

The utilisation of the new communication technologies for processing and dissemination of the health information has given rise to a new field, called health informatics. As information technologies advance, there are a variety of the new tools and information media for disseminating and accessing health information.

The access to relevant and in useful time at health information can help consumers participate in decision-making and encourage cooperation and collaboration between providers and consumers.

The health communication can help solve ways in which consumers and providers can most profitably inform themselves about relevant health problems, identify the best ways to develop and present high-quality health information to the target audience, and encourage decision-making in modern efforts to adopt healthy behaviors.

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VARIA

Planning a hospital to respond to the COVID-19 outbreak: experience from a Romanian reference unit

Gabriela Hofer[1], Dodu G. Petrescu[1], Victor L. Purcărea[1]

Abstract: *During the COVID outbreak, many hospitals were nominated as a support hospital for the treatment of positive tested patients infected with SARS CoV-2 virus. "Dr. Nicolae Ruşdea" Pneumophtiziology Hospital Baia Mare carried out an exceptional activity compared to the previous year considering the current epidemiological context. Major changes were made in strategies, procedures and protocols. The staff had to adapt to the new epidemiological situation through dedication and devotion. In 2020, there were no COVID outbreaks within the unit, as separate compartments were made, intended to protect the medical personnel, but also to ensure the health of the patients.*

Keywords: *COVID plan, hospital, Romanian reference unit*

INTRODUCTION

"Dr. Nicolae Ruşdea" Pneumophtiziology Hospital Baia Mare is a specialized hospital providing medical services in the specialties of pneumology for adults and children. Starting with April 2020, it provides hospital care for patients tested positive for the SARS-CoV-2 virus, including intensive care. In 2020, the hospital served the entire county of Maramureș for patients tested positive for SARS-CoV-2 virus. In the intensive care department, patients from Maramureș County received health care, mainly from the country, depending on the places available at the request of the Committee for Emergency Situations. Throughout this period, the fight against pulmonary tuberculosis continued through the national control and surveillance program as well as ensuring the continuity of integrated ambulatory care services for patients with non-Covid pneumological diseases and the follow-up of post-Covid patients. Compared to the previous year, considering the current epidemiological context, which led to major changes in the way of working, procedures and protocols. In order to provide the resilience of health systems during the COVID-19 pandemic, we describe, at the hospital level, the key elements to provide the medical staff sand patients safety, including the challenges and issues to anticipate following the experience of our center

CLINICAL EXAMPLE

The aim was to establish synergies between health worker safety and patient safety policies and strategies, developing linkages between occupational health and safety, patient safety, quality improvement, infection prevention and control programmes [1]. It was necessary to review and upgrade the standards, guidelines and codes of practice in order to assure the health worker and patient safety [1]. The executive board consisting of a multidisciplinary team: general manager, epidemiologist and the technical-administrative staff, planned the separation of the hospitals' circuits in COVID and NON-COVID. During the pandemic, the hospital changed his usual structure, consisting of 2 departments of medical specialties (pneumology, intern medicine, cardiology, urology, metabolic diseases,

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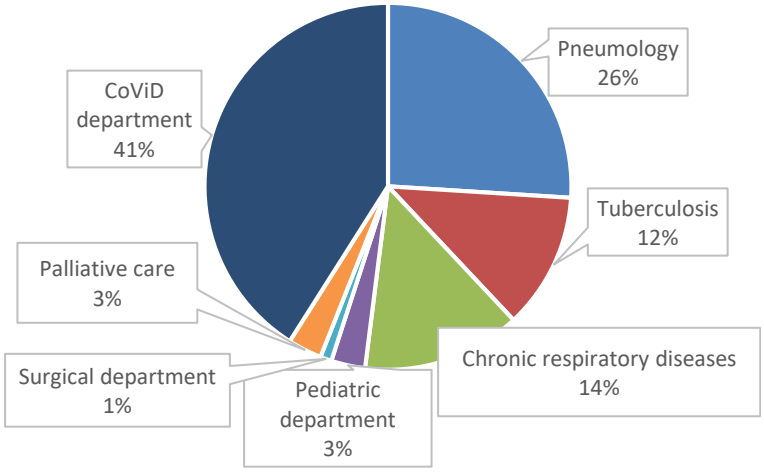
neurology), one section of surgical specialties, one pediatric department, a department ICU (intensive care unit), blood transfusion units, palliative care and an operating room. The rest of the structure was maintained: farmacy, sterilization, medical analysis laboratory, radiology department, tuberculosis dispensary, reception desk, evaluation and medical statistics department (Figure 1).

Figure 1: Plan for new structure of the hospital to augment the health system during the pandemic.



After the State of emergency in the coronavirus pandemic, depending on the local epidemiological evolution, the hospitalizations and the scheduled surgical interventions can be resumed, as well as the activity in the outpatient clinics. Being a 4-storey Hospital, a level was created for the green zone, non-COVID, and the 2nd and 3rd floor were allocated for the COVID section - red zone, served by an elevator: at each level a separate filter for dressing and undressing the protective equipment; the 4 elevators and 6 exits of the hospital had separate destinations: a red zone entrance, one for staff, one for drugs and one for food. A special elevator for patients, one for the staff and the elevators on the opposite side of the building are used for waste and medical staff. A separate circuit was intended for the ICU section, and a separate one for the rest of the staff. In the green area, the staff was separated, depending on the section, so as not to be conglomerated by people. Radiology department: provides a separate circuit for non-COVID patients hospitalized, and a dedicated department for tuberculosis dispensaries. Also a sequential circuit for computer tomography access. The organization of the COVID departments provides a separate circuit for access to the Covid patients section with a dedicated elevator only for COVID-positive patients. The medical personnel circuit with clothing filter area, decontamination area, green area for rest and document preparation (common for COVID and ATI section). The contaminated waste had a special circuit - collection and transport on a circuit intended only for waste (all waste generated in the COVID section are considered hazardous waste). The food circuit, consisting in disposable dishes, are collected as infectious medical waste. Assistance to acute and chronic non-COVID pneumology patients was assured. When entering the hospital, all people will go through an epidemiological triage, depending on the symptoms presented, the suspicious cases will be hospitalized in special isolation areas (buffer-zones), organized at the 1st floor, to be tested by RT-PCR for SARS-CoV-2 infection (according to the recommendations of the National Institute of Public Health). Separate circuits are provided for these patients.

DISCUSSIONS

With all the circuits, red-zone and green-zone, the hardest part was teaching the staff to overcome fear, but the idea that you have some completely separate safe circuits made the staff trustful and work, and accept the new rules imposed. Moreover, having 4 training teams that teaches the use of the protective equipment, the existence of a supervisor in the first 3 months to monitor the dressing and undressing the equipment, in order to avoid mistakes. As a result, there was no outbreak in the hospital for 12 months, with only isolated cases coming from outside of the hospital.

CONCLUSIONS

The coronavirus disease (COVID-19) outbreak is a global public health problem. Medical personal is an important at-risk population that can get COVID-19 due to close contact with patients2. The healthcare reform, with subsequent amendments and additional changes, caused a new reorganization and restructuring of health units, depending on the needs, in order to ensure the isolation conditions and

the functional circuits that aim at the prevention and control of the SARS-COV-2 infection3,4. The reorganization and restructuring of the health units subordinated to the local public administration authorities will be done with their consultation. The reason for these changes is mostly because of the epidemiological evolution of the SARS-COV-2 virus pandemic. In addition, there is an increased addressability of patients with pneumological problems including patients with pulmonary diseases after SARS-COV-2 infection that need recovery. Also, the need to carry out the activities of the tuberculosis prevention and control programs.

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VARIA

Copper and its role in the human body – the importance of establishing copper concentrations in the body

Oana R. Avram[1], Genica Caragea[2], Camelia A. Varzaru[2]

Abstract: *Copper is essential to all living beings, as a food mineral, being an essential component of the cytochromoxidase enzymes complex. It is also an essential component of several systems involved in the production of hemoglobin, of sugar metabolism, of catecholamines' synthesis and in the formation of cross-links between collagen, elastin and keratin fibers within the hair. The dysregulation of copper through impaired absorption or excretion, either genetically based or in acute or chronic poisoning, results in deficiency or toxicity. For this reason, the measurement of copper levels in various biological samples: urine, blood, or hair, provides the physician with information regarding contamination, poisoning, or a metabolic disease. Due to low concentrations in most heavy metals' and metalloids' cases, finding traces in biological samples is a difficult problem. Classical methods (staining, flame photometry, reagent kits, electrochemical methods) can only be used for a limited number of elements, such as sodium, potassium, calcium, magnesium, copper, iron and zinc. The analysis of biological samples is the most important use of graphite furnace atomization. The advantages of using this technique are its great sensitivity and the very low quantity of sample necessary for performing the measurement.*

In modern medicine, determining microelements is very important in diagnosing diseases and/or in treating them. The GF-AAS method is quick, reproductible and has very good sensitivity.

Keywords: *copper, toxicity, metabolism disorders, Wilson disease, determination methods, spectrophotometry, GF-AAS*

INTRODUCTION

A great number of chemical elements in nature are present in the body, either as standalone components, or bound one to another, forming organic and inorganic substances that facilitate or create various disorders in the human body. A part of them (Co, Cr, Cu, Fe, Mg, Mn, Mo, Ni, Se, Sr and V) are essential to life.

Other elements (As, Ba, Be, Cd, Li, Hg, Pb, Sb, Sn) are considered toxic, and their concentrations in any given biological product is preferred to be close to nil. When such concentration is different from zero, the value is considered normal if it is lower than the limit established by toxicology authorities around the world.

Copper is a chemical element that has been used for thousands of years in alloyes. Its compounds are frequently found as copper (II) salts, which usually yield the blue or green colours of minerals, such as azurite or turquoiuse, and have been largely used as pigments. Copper sulfate forms are bright blue crystals containing five molecules of water [$CuSO_4 \cdot 5H_2O$]. It is commonly known as the "Blue Vitriol" or "Blue Stone" [1] and it is used mainly for agricultural purposes as a pesticide, and in the leather industry [2, 3].

Biological Roles of Copper

Copper is essential to all living beings, as a food mineral, as

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it is an essential component of the cytochromoxidase enzymes' complex. It is found in the liver in vertebrates. In high concentrations, copper compounds are toxic for evolved organisms, and are used as bacteriostatics and fungicides.

Copper alloys have intrinsical natural properties that kill a large number of microorganisms, such as E. coli O157: H7, methicillin-resistant Staphylococcus aureus (MRSA), Clostridium difficile, influenza virus A, adenovirus, fungi [4, 5]. Some copper 355 alloys have been shown to kill more than 99.9% of germs within two hours, when properly cleaned [4]. The United States Environment Protection Agency (EPA) has authorized these copper alloys as „antimicrobial materials with public health benefits" [4]. Recent biotechnological researches use copper ions coupled with indocyanine and proteins in targeted cancer treatments [6].

Proteins which contain copper have several biological roles in electron and oxygen transport, processes in which interconversion of Cu (I) and Cu (II) easily takes place [7]. The biological role of copper began the moment oxygen appeared in our planet's atmosphere [8].

In the cytochrome-c oxidase, which is necessary for aerobic respiration, copper and iron work together to reduce oxigen. Copper is found in superoxide-dismutase, which catalyzes the breakdown of superoxides, through conversion to oxygen peroxide and hydrogen:

$$2\ HO_2 \rightarrow H_2O_2 + O_2$$

Copper is an essential component of several systems involved in the production of hemoglobin, in sugar metabolism, in catecholamine biosynthesis, and in forming cross-links between collagen, elastin and keratin fibers within hair.

Copper deficits leads to growth and behavioural disorders, especially in children [9]. Copper deficiency is an etiology of anemia, neutropenia, and bone marrow dysplasia that may be under-recognized, being a possible cause of medical errors in clinical practice [10, 11]. The mechanism of anemia in copper deficiency may be related to the role of copper-dependent enzymes, such as ceruloplasmin and cytochrome-c oxidase, in iron metabolism and transportation [12]. Bone marrow findings of marked vacuolization of both erythroid and myeloid precursors have been consistently reported, and ring sideroblasts are also occasionally reported [13].

Kinetics of Copper

Copper intake is mainly achieved through diet : it is easily absorbed, but its absorbtion is limited by homeostatic mechanisms, after requirements have been met. The human body contains aproximately 1.4-2.1 mg/kg of copper [14]. Copper is absorbed in the gut, then transported to the liver bound to albumin [15]. After being processed in the liver, it is then distributed to other tissues. Copper transportation involves a protein called ceruloplasmin, which also transports copper excreted in milk [16]. The body is able to excrete excessive levels of copper, if necessary, through the bile. The excreted excess is not reabsorbed by the intestine [17, 18]. In catalytic oxidation processes, metalloproteins containing copper are also necessary, as they intervene in oxygen metabolism. Also, copper also acts in oxidative phosphorylation reactions. Copper intake from food can also prevent certain diseases or deficiencies, such as allergies, hair loss, AIDS, leukemie, osteoporosis and gastric ulcer. Together with iron, copper helps in red blood cells' synthesis.

Copper metabolism disorders

The dysregulation of copper through impaired absorption or excretion results in deficiency or toxicity, as illustrated by two rare genetically based diseases.

Wilson's disease was first described in 1912 by Kinnear Wilson as "progressive lenticular degeneration". Wilson's disease can manifest itself at birth, but signs and symptoms only appear when copper accumulates in the brain, liver, or another organ. The signs and symptoms vary with the body part that is affected by the disease and can include fatigue, loss of appetite or abdominal pain, jaundice, brown-golden Kayser-Fleischer rings, muscular stiffness, lack of motor coordination, speech impairment and others.

Menkes' disease, when the body cannot stock copper, leading to its deficiency; it is also known and the uncombable hair syndrome (hair lacks in color, is sparse, wiry and rough, with occasional nodosities) or Menkes' kynky hair disease. It is a rare hereditary X-linked transmitted disease, described by Menkes in 1962 as a severe degenerative disease of the nervous system. Biologically, serum copper and ceruloplasmin levels markedly decrease. Some of the clinical manifestations pertaining to this disease are facial dysmorphia, signs of neuropsychic involvement, hypothermia, skeletal manifestations similar to those in scurvy, and the irregular lumen of blood vessels.

Clinical signs in copper intoxication

In acute intoxication, serum copper reaches very high values, ceruloplasmin and hepatic copper are within normal limits, and urine copper is increased.

In chronic intoxication, serum, urinary copper and

ceruloplasmin are increased, and hepatic copper reaches very high values. The acute toxicity of copper in humans is likely due to the generation of reactive oxygen species, which deteriorate DNA [10]. A minimal dietary value of at least 3 ppm was reported for healthy growth in rabbits [20]. However, high concentrations of copper (100 ppm, 200 ppm, sau 500 ppm) in their diets can favorably alter their growth rates [21].

Copper toxicity is determined by the balance between copper intake and excretion. Voluntary copper salts intake, copper intake from food and beverages, inhaling dust which contains copper or aerosols which contain copper salts, through manual spraying of insecticides or fungicides, represent the main risks of exposing the human body to copper contamination.

The main actions of copper on the human body are gastrointestinal irritation, liver and renal disorders, intravascular hemolysis and shock. Acute intoxication following ingestion of copper salts targets the GI tract, cardiovascular and circulatory systems, hematopoietic system, liver, kidneys and nervous system.

The respiratory effects following inhalation are: acute exposure to copper vapors targets the respiratory pathways and chronic exposure to copper salts, seen in those who spray plants, targets the lungs.

The local, irritating effects, through cutaneous or eye contact with copper salts, are seen at skin and eye level.

Other diseases in which abnormalities in copper metabolism appear to be involved include Indian childhood cirrhosis (ICC), endemic Tyrolean copper toxicosis (ETIC), and idiopathic copper toxicosis (ICT), also known as non-Indian childhood cirrhosis. ICT is a genetic disease recognized in the early twentieth century primarily in the Tyrolean region of Austria and in the Pune region of India [22].

DETERMINING COPPER CONCENTRATIONS IN BIOLOGICAL PRODUCTS

Due to low concentrations in most heavy metals' and metalloids' cases, finding traces in biological samples is a difficult problem. Classical methods (staining, flame photometry, reagent kits, electrochemical methods) can only be used for a limited number of elements, such as sodium, potassium, calcium, magnesium, copper, iron and zinc.

Modern methods replace these types of tests. Elements can be determined through atomic absorbtion spectrometry AAS with flame atomization FAAS or graphite furnace atomization GTAAS, inductively coupled plasma and atomic emission spectrometry ICP-AES or inductively coupled plasma and mass spectrometry ICP-MS. ICP-MS is the most sensitive method for determining metals and metalloids, but it also has the highest cost. For determining metals and metalloids in biological samples, the GTAAS method is recommended. For Na+, K+, Cl-, Ca2+ it is much more cost effective to use machines which only measure blood or urine concentrations of these ions, through electrochemical methods.

The analytical method used to determine the concentration of studied elements, from the analyzed matrices, is the atomic absorbtion spectrometry coupled with graphite furnace atomization GF-AAS (Graphite Furnace Atomiser – Atomic Absorbtion Spectrometry). Atomic absorbtion spectrometry is an analytical method used to quantitatively measure metals or metalloids in a sample, based on the quantity of light that is absorbed or emitted by atoms, from a line that is characteristic for the specter of light the atom emits in an excited state.

The first method that was used to bring atoms to an excited state was heat emanated by a flame. The temperature of this flame is approximately 1200 – 13000C. Due to the low temperatures that can be achieved with this method, the sensitivity of this type of atomization is not useful in determining the majority of elements in biological samples.

Graphite furnace atomization has become very useful in analytical chemistry, as a technique which is very good for determining trace elements in a wide variety of sample types. The principle of this method, of achieving a controlled temperature, using electrical current, makes it perfectly reproductible, compared to flame atomization. The greatest advantage, however, consists in the high atomization temperatures, which can never be attained with a flame, which makes analyzing trace elements in biological samples possible.

The number of replicates (repeatedly performing the same determination) is very important for obtaining quality results. Thus, the working program allow real-time quality control of obtained results, by verifying the standard deviation of replicates. If the value of the square mean deviation (standard deviation) of values measured in the same sample exceeds the pre-established value, the system performs the determination once more. The usually admitted standard deviation is 4-5%. The increase of replicates' number increases the duration of a given determination, wears down the graphite furnace, but improves the accuracy of the results. Due to the marked stability of the machine, it is possible to use the minimum number of two replicates.

The absorbance signal has its own noise due to the variations in emitted light, due to its transmission through the optical chain, due to variations caused by the photomultiplier and the electronic system which amplifies the electric signal. This type of noise can be removed by mathematical methods. The methods which may be applied are either in 3, 5, or 9 points. The calibration method is extremely important for the accuracy of the results. For this reason, choosing an optimal calibration method is one of the most important decisions in establishing the method. For standard calibration, the software automatically chooses the liniar calibration. The calibration curbe may or may not pass through point zero. When measured levels are very low, this curve must pass through point zero. Quality control is mandatory to establish the accuracy of the obtained results. Quality control also involves checking: the standard deviation of replicates; the correlation coefficient of the calibration curve; the detection limit of the method and the apparatus.

Table 1: Concentrations of some essential trace elements in blood and urine (mg/l).

Element	Serum (µg/L)	Blood (µg/L)	Urine (µg/L)
Chromium	0.5	0.5	10
Cobalt	0.2	2.0	100
Copper	1100	1200	60
Iron	1200	-	180
Magnesium	0.5	5	300
Molibdenum	1.0	100	100
Nickel	5.0	5.0	85
Selenium	100	100	30
Strontium	50	-	150
Vanadium	0.5	4.0	16

In urine spot samples, there was a great variation in copper content, which is why collecting 24h urine and sampling from the total volume is recommended. The conventional level taken as diagnostic of Wilson's Disease is >100 mg/24 hours in symptomatic patients [23].

A method to determine the concentration of an element in the matrix involves establishing the working conditions of the spectrometer, of the graphite furnace atomizer, of the sample dispenser and the conditions for the automatic quality control of the test.

The calibration curves of the elements, absorbance as a function of concentration, are calculated with the following equation:

$$A/C = a + b * A + cA^2$$

where: A – is the sample absorbance, C – is the sample concentration, A, b, c, d – are coefficients of the calibration curve.

The determination of copper in biological samples is usually carried out for diagnosing Menkes or Wilson disease or for monitoring the distribution and the amount of copper removed during dialysis procedures of patients with chronic renal disease [24, 25].

In order to develop a method for determining direct GF-AAS copper in biological samples (blood and urine) the establishment of operating parameters for atomic absorption spectrometer system – AAS 880 Spectra Varian and for graphite tube atomizer – GTA 100 is of major importance.

The utilized wavelength must be a part of the absorbtion specter of copper and depends on the type of sample. It may be 327.4 nm or as alternative wavelengths, 324.8 nm or 217.9 nm or 218.2 nm. The correct choice is made with the purpose of eliminating the non-atomic absorbtion which may appear during sample analysis. The width of the used diaphragm is of 0.2 or 0.5 nm and its size depends on the type of analyzed sample.

Method for determining the level of copper in whole blood samples

The samples were analyzed with a system formed from the following components:

- Atomic absorbtion spectrometer AAS-880.
- Graphite tube atomizor GTA-100.
- Programmable sample dispenser – PSD.
- Water cooler – Neslab CFT 22.
- Nitrogen generator - Dominick Hunter.
- Gas cylinder (Argon) 99.9999% purity

Optimized working parameters for determining copper levels in whole blood

In order to determine the Cu concentration in the blood samples taken from patients (2 ml of venous blood, taken on anticoagulants), the following method was used:

- Pipetting method – automixing;
- Quantity of injected sample – 10 µl;
- Measurement method – peak height;
- Concentration calibration;
- Smoothing – 9 points;
- Number of replicates - 2 for standard and for sample;
- Cathode tube current – 4 mĂ;

- Wavelength – 327.4 nm;
- Slit width - 0.5 nm;
- Background correction – deuterium lamp;
- Drying – 1200C;
- Calcination - 8000C;
- Atomization - 23000C;
- Cleaning - 25000C;
- Three-point calibration curve – 0, 50 and 100 µg/l;
- Recalibration rate – 15;
- Method detection limit <1.0 µg/l.
- Apparatus detection limit <0.04 µg/l.

Automatic quality control – dispersion <10 %; correlation coefficient of calibration curve >0.998.

The optimization of the temperature program must provide optimal conditions for the measurement of Cu signals by GF-AAS, free of interferences from the background which is a very common problem in the analysis of biological samples (26). The application of the optimized temperature program made possible to eliminate the whole matrix of the sample before the atomization step, as confirmed by the low background signals observed in the measurement of Cu. No chemical modifiers were added. However, biological samples must undergo a deproteinization process, which is meant to eliminate non-atomic absorbance.

Table 2: Established and optimized steps for GTA 100

Step	Temp C	Time s	Flow L/min	Gas Type	Read	Signal Storage
1	40	5	3	N_2	No	No
2	80	10	3	N_2	No	No
3	105	5	3	Ar	No	No
4	105	10	3	Ar	No	No
5	800	20	3	Ar	No	No
6	800	5	3	Ar	No	No
7	800	2	0	Ar	No	Yes
8	2650	0.9	0	Ar	Yes	Yes
9	2650	2	0	Ar	Yes	Yes
10	2650	3	3	Ar	No	Yes
11	40	30	3	N_2	No	No
12	40	5	0	N_2	No	No

Copper stock standard solution containing 1000 mg/L copper was diluted with a premixed solution of distilled water and analytical grade concentrated nitric acid to provide working standards of various concentrations in 0,1% (w/v) HNO3. The calibration blank solution used throughout was a 0.1% w/v HNO3 solution. For copper, the working standards were 100 and 50 µg/L.

Table 3: Performance parameters of linear regression analysis

Conc. ug/L	Abs	Abs. Average	STDEV	RSD %
0	0.0193	0.0183	0.0014	7.55
0	0.0167			
0	0.0188			
50	0.3996	0.4001	0.0009	0.23
50	0.4012			
50	0.3996			
100	0.7214	0.7178	0.0034	0.47
100	0.7147			
100	0.7174			

The whole blood sample (200 µL) was treated with 800 µL solution 5% antifoam B (Sigma) and with 1000 µL of 1.6 M HNO3 solution. The mixture was maintained for 20 minutes and centrifuged with 5000 rpm for 5 min. The supernatant was analyzed by GF-AAS. The results are obtained in µg/dL. A linear relationship was found between the absorbance at 327.4 nm and the concentration of cooper in the range of 0.0 to 100 µg/L. The representative linear equation was y = 0,007x + 0,029 where: y is the absorbance, x is lead concentration (µg/L), calculated by the least squares method. The regression coefficient (r) standard curve was 0.9972, indicating good linearity (r > 0.99).

The performance parameters of linear regression equation are presented in Table 3. The parameters of the GF-AAS analysis method of lead are presented in Table 4. LOD and LOQ were calculated based on the standard deviation and the slope of the regression line.

Table 4: Validation parameters

Standard error	0.0173
R Square	0.9972
Intercept	0.0290
Slope	0.0070
SE of intercept	0.0091
LOD (µg/L)	***4.29***
LOQ (µg/L)	***13.01***

LOD is the lowest concentration of an analyte that can be detected while LOQ is defined as the lowest concentration

of an analyte that can be determined at the acceptable level of precision and accuracy and were calculated according to the formula below: LOD = 3,3*(SD of intercept/Slope) and LOQ = 10*(SD of intercept/Slope)

The established method can be easily used to perform copper measurements in the laboratory, both in urine and blood samples taken from patients suspected for copper intoxication. Copper deficiency and toxicity can be either of genetic or non-genetic origin. The study of copper's genetic diseases, which are the focus of intense international research activity, has shed insight into how human bodies use copper, and why it is important as an essential micronutrient.

The evolution of the copper concentration in urine or whole blood provides very useful information for poisoning diagnostic when the history is not clear [27, 28].

CONCLUSIONS

Microelements play an important role in the normal course of life. The variation of their blood levels within the body can lead to metabolic disturbances. For example, copper deficiency is found in Menkes syndrome or ,,uncombable hair disease", and copper excess leads to Wilson's disease. The rise in blood levels of copper can also be due to acute intoxication, for example, as a result of spraying plants with copper sulphate.

For these reasons, measuring Cu concentrations in various biological samples, urine, blood, or hair, provides the physician with information regarding contamination, intoxication or the existence of a metabolic disease.

The analysis of biological samples is the most important use of graphite furnace atomization. The advantages of this technique are its high sensitivity and the very low quantity of sample necessary for the measurement.

In modern medicine, determining trace elements is very important in diagnosing various diseases and/or in treating them. The GF-AAS is a quick, reproductible and highly sensitive method.

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