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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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