The article was received on December 15, 2020, and accepted for publishing on March 22, 2021.

VARIA

A review of the need to provide hyperbaric medical research infrastructure for the treatment of combat-related injuries

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Abstract: *HBOT has been used quite extensively in the last couple of decades. But there are not many centers that offer this treatment, even in civilian situations. This review has described the rationale and clinical evidence for equipping medical centers with HBO systems, especially in military areas.*

A narrative review of all the literature available on HBOT in combat-related injuries, studies were retrieved from systematic searches on Science Direct, PubMed, SCOPUS, ISC, Google Scholar, and by cross-referencing until 2020.

First, the etiological mechanisms of action of HBOT were discussed. Furthermore, we have provided an overview of 117 studies that clinically investigated the effect of HBOT in the last couple of decades. Therefore, based on the number of studies showing a positive effect, to speed up the treatment process, especially in war-related injuries, it is better to provide its infrastructure and equip hospitals and centers with HBO.

Keywords: *hyperbaric, hyperbaric therapy, trauma, war trauma*

INTRODUCTION

The trauma of firearms has caused many casualties in human societies since world wars military facility up to date with the advancement of military facilities, and a large part of the medical staff has always been dedicated to treating and improving the disability of injuries caused by war trauma [1]. Many studies have been done in this regard, and the beneficial effect of hyperbaric treatment has been proven [2].

Hyperbaric Oxygen therapy is the treatment of patients with oxygen respiration in a high-pressure treatment room. Increasing oxygen and delivering it to tissues has beneficial effects for various diseases. Some of these injuries are related to combat-related injuries [3]. Although the number of hyperbaric oxygen therapy sessions varies depending on the type of disease, and there is no absolute definition for the duration or pressure of oxygen in each treatment session, when hyperbaric oxygen therapy timely and properly is done, the evolution and the final result will be improved [4]. However, due to the technical limitations of treatment such as the need for a high-pressure treatment room, adequate oxygen, and compressed air supply, medical and paramedical staffs, the centers that provide this treatment are not numerous, even in civilian situations [5]. Hyperbaric Therapy Working Group investigates the possible military applications of hyperbaric oxygen therapy and defines the terms of its use. The amount of damage caused by war traumas inside or outside the city varies depending

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on the geographical location, which necessitates a comprehensive study to provide a suitable solution to prevent trauma-related injuries [1]. Although it is not possible to set up hyperbaric treatment centers near the operation site, it seems possible to organize medical evacuation routes. It appears that this collection of information in the form of a review paper will benefit to help shorten the overall treatment time of combat-related injuries and optimize the final recovery by building the right infrastructure [6, 7]. It appears that this collection of information in the form of a review paper will benefit to help shorten the overall treatment time of combat-related injuries and optimize the final recovery by building the right

METHOD

To find available data and information in the literature on the role of Hyperbaric oxygen therapy (HBOT) induced combat-related injuries via vasoconstriction and Increase oxygen supply after trauma and we performed a search in multiples data banks such as Science Direct, PubMed, SCOPUS, ISC, Google Scholar, and the paper published Until 2020 were reviewed.

It should be mentioned that the search terms and keywords for evaluation of all published papers in this manner were "Hyperbaric Oxygen Therapy", "Refractory Osteomyelitis ", "Intracranial Abscess", "Radiation Injuries", "Burns", "Wound", "Traumatic Wound", "Traumatic Brain injury", "crush injury", "military Medicine" and "inflammation", "Acoustic trauma "Also, we used MESH term "OR" operator between synonyms keywords and "AND" operator between independent keywords for finding articles and papers as well as articles with the most consistency with our goal. For a review of all papers, we had inclusion criteria, and in 203 published papers which in them the hyperbaric oxygen therapy in combat-related injuries, 117 papers were selected for review and citation of all published papers.

DISCUSSIONS

The effects of hypoxia vary depending on the cause, whether the condition is acute or chronic, as well as the overall health of each individual. Cellular hypoxia may occur in multiple organ failure syndromes due to increased tissue oxygen demand or due to the ability of oxygen to break down at the cellular level; to repair, oxygen transfer and metabolic support are important components of treatment.

Definition and mechanism of action of HBOT

Since the 1960's HBO has been used for the treatment of various diseases and illnesses [8]. HBO involves the respiration of pure oxygen under high air pressure [8]. HBOT often use in complex trauma. Lamm [9] and Appaix [10] are credited for their pioneering work on the role of HBOT in these two conditions

According to the laws of physics and physiology, breathing oxygen at high pressure increases alveolar oxygen pressure and pharmacological effects with increased arterial O_2 content leading to improvement of ischemic state due to lack of oxygen such as chronic unhealed wounds, causes vasoconstriction and special antibacterial effect against anaerobic bacteria on the body [11].

In this procedure, the patient is completely enclosed in a special chamber, and by breathing 100% oxygen, the pressure inside the chamber gradually increases to more than one atmosphere [12]. So HBOT is a relatively time-consuming therapy for patients because patients must be physically present in the oxygen chamber [13]. HBOT is considered a safe therapy; however, side effects do occur in some studies. Contraindications to hyperbaric oxygen therapy are low, including untreated pneumothorax and some chemotherapy drugs such as bleomycin, which can lead to pulmonary fibrosis [14].

The effect of HBOT on the treatment of war traumas

Acoustic trauma

Acoustic trauma is damage to the auditory structures in the inner ear due to loud noise. Hearing loss and tinnitus are two of the most common disabilities caused by military veterans. Reports indicate a worrying increase in these complications in the military population [13]. Recent war scenes have seen soldiers face numerous dangers that lead to these effects, such as explosions, ototoxic chemicals, and loud noises [15]. Damage to the auditory mechanism can be caused by an explosion near the ear, shooting, or prolonged exposure to loud noises. Hearing loss, the fourth leading cause of medical visits to soldiers [16]. Of the more than 5,000 troops stationed in Iraq and Afghanistan who underwent audiometry, 1550 people have been reported to have been exposed to acute trauma of a sound explosion; of these, 72% have lost their hearing. Of all deployed personnel who underwent audiometry, 28% had a degree of hearing loss. More than two-thirds of English soldiers who have returned from Afghanistan, from injuries suffered severe and permanent hearing loss [5]. Animal experiments showed that 60 hours after acoustic trauma injury, the number of morphologically damaged inner ear sensory cells was lower in animals treated with HBO than in those treated without HBO [17, 18]. The best therapeutic effect on noise-induced hearing loss was obtained with a combination of HBO and prednisolone [19]. Animal studies in rats [20], pigs [18], and chickens [21] all showed that the HBO-treated group had a

significantly reduced signal-to-noise ratio. Also in human studies, victims of acoustic trauma in military operations were treated with HBO [22]. There was a significant improvement in hearing loss. Therapeutic results confirmed that 65% of patients who were not treated with various methods had improved hearing [23]. Based on studies performed at different times and conditions of hearing loss compared to other treatments, it can be concluded that HBO is recommended within 3 months after the onset of the disorder, and treatment with it is guaranteed [24].

Soft tissue infection

Soft-tissue infections, occur after trauma and around the foreign body, and even spontaneously [25]. A common factor, tissue hypoxia that suppresses the immune defense mechanisms [26]. In animal models (mice, rats, rabbits), mortality was significantly lower during treatment with antibiotics and HBO. But (depending on the specific type of bacteria) seen a series of adverse effects was treated with HBO, the streptococcal infection worsened [27]. The level of evidence for soft tissue infections and HBO is low. There are only case reports and retrospective studies, and no RCTs are available. Almost all patients studied were endangered hosts [28-30].

In the study of war-related organ injuries including type 3 combat fractures and the description of the effect of HBOT on wound healing and complications of infection, it was shown that the reduction of infectious complications in patients who have used HBOT in the treatment process (31). Recent studies aimed at determining the effect of HBOT in the treatment of acute surgical wounds and trauma have shown a lack of quality clinical trial studies and pointed to the need for further studies [32-34].

Crush Injury

Crushing causes severe tissue damage and calls into question tissue survival. These injuries lead to local hypoxia. Ischemia, on the other hand, causes edema due to direct vascular trauma, fluid secretion, or compartment syndrome. Edema is either vasogenic or cytogenic and increases the distance of oxygen delivery to the cells. Edema also leads to capillary collapse, thereby increasing the severity of hypoxia [35]. The main purpose of using hyperbaric oxygen in crushing injuries is to cause excessive tissue oxidation.

Animal models (rodents, dogs) Crush injury studies have shown significant effects of HBO treatment [36]. HBO also regulates inflammatory gene expression in endothelial cells and can reduce the expression of apoptosis.

In human studies, most data are obtained from case reports or series of up to 35 patients. And there is only one RCT that compares crush injuries with and without HBO treatment [37], which improved treatment and significantly reduced surgery. Patients over the age of 40, in particular, benefited greatly from HBO treatment. From the available data, experts conclude that the adjuvant use of HBO in crushing injuries may lead to a favorable outcome for selected patients [34, 38].

Burns

Burns are followed by hypoxia and tissue ischemia [39], which increase edema with loss of capillary wall integrity (endothelial cell contraction). This fluid loss, by changing the oncotic pressure gradient in the capillary wall, further reduces the intra-capillary fluid pressure and thus increases stasis [40]. As a result, areas of second-degree superficial burnt tissue (minor burns), develop in the first 24 hours after the burn, it progresses to a deep second or third-degree burn, which requires early surgery and a transplant to heal [41].

In all of these pathophysiological mechanisms, hypoxia plays a pivotal role. Oxygenation of ischemic tissues should be performed rapidly and in large volumes, to reduce tissue damage with ischemic-reperfusion. Hyperbaric oxygenation is the only treatment that can ensure that the treatment is successful [42, 43].

Several reports show the help of HBOT in the treatment of severe burns [44]. The use of HBOT in severe burns in a war scene may reduce the need for surgery and length of hospital stay [45], and possibly reduce mortality [46].

When soft tissues (such as skin and muscle) are burned, blood flow to the affected area is severely reduced. This causes the area to swell, and the swelling spreads from the affected area in all directions. The swelling may reach deep into the muscles and surrounding skin, causing more damage than the original injury. HBO should be used very soon to limit initial debridement and gradual tissue destruction [47].

The theoretical beneficial effect of HBOT on burn wounds is in the antibacterial effects of possible infections, in reducing edema and systemic inflammatory response, in limiting the size of burned tissue, and in increasing collagen formation. It seems that the best results from starting hyperbaric treatment in the first hours of injury. However, studies indicate a low and unclear role of HBOT in the management of severe burns. A randomized study supports the use of HBOT to evaluate the potential positive effects of HBOT on experimental burn wound healing [48]. In this study, the authors demonstrated a beneficial effect on HBOT wound healing and hypothesized that such an effect would be determined by reducing edema and maintaining

microcirculation. Although the quantity and quality of evidence-based studies on the potential benefits of HBOT in patients with burns are poor, its potential use in medicine, war is worthy of further investigation. To achieve the best result, careful selection and screening of patients are recommended [47].

Special attention has been paid to the use of HBO in respiratory injuries. There is currently concern that HBO may worsen lung damage, especially in patients with high levels of inhaled O_2 [49]. Studies have not reported any evidence of oxidative stress in HBO-treated burn patients who used lipid peroxidation exhalation products as a symptom [50].

However, a series of compelling prospective and retrospective studies have been published [47, 51] that show less need for surgery, reduced mortality, shorter hospital stays, and reduced treatment costs when using HBO concomitantly with conventional therapy. But so far no prospective placebo-controlled trials have been published that explicitly prove the effectiveness of HBO treatment [52, 53]. Therefore, acceptance of HBO as a valuable adjunctive therapy is limited to those burn centers that can provide early treatment of HBO without adding additional risks (infectious, hemodynamic) to the patient's condition [54, 55].

Frostbite

Frostbite-like thermal burns a profound impact on local microcirculation that it can be cold or an injury or an acute and prolonged exposure to cold be defined. It has been shown that after heating, a long-term damage phase occurs, which is very similar to the ischemia-reperfusion injury observed in thermal burns. At least, in theory, hyperbaric oxygen therapy could have the following benefits in frostbite injury.

Animal studies (especially rabbit studies) have been conducted sporadically over different years [56, 57], with each study showing different results [58-60]. These different results suggest that deep and rapid freezing damage can indicate several important differences in pathogenesis and tissue damage from slow to moderate freezing.

The experiments carried out on animals, the early application of HBO during or immediately after the heat re-use. Some sporadic case reports suggest that HBO may be helpful, even long after warming up. Because these are uncontrolled and isolated reports, the evidence supporting these claims is not very strong. In 2001, he reported a case in which HBO was used after only 4 days for a young boy who had both hands frozen, and was able to save all his fingers [61]. Similarly, cases have been reported, 12 and 22 days after frost damage and the use of HBO led to the rescue of the individual fingers [62, 63].

Although the experience is relatively limited because HBO is generally not recognized as a complementary treatment standard for frostbite; clinically, HBO appears to provide early, good and rapid separation of growing tissue from non-growing tissue. MR angiography, one week after the onset of the injury, looks promising in estimating the likelihood of resuscitation of the fingers [64].

Spinal cord injury

Many studies have examined the mechanism of action of HBOT in SCI [65, 66]. Some studies have shown the protective effect of HBOT in the treatment of SCI [67, 68] and others recommended a review of the care process [66]. The number of treatment sessions for patients with spinal cord injuries is determined by the patient's condition and response to treatment, but according to studies, at least 30 sessions of standard HBO treatment 5 sessions per week were recommended to begin treatment [69].

Carbon monoxide poisoning

Because lipid peroxidation is an important aspect of CO-induced neuronal damage, inhibition of neutrophil O_2 integrins at the cellular level by HBO therapy has been identified as a significant advantage of that treatment. HBO relieves cerebral edema through vasoconstriction [70]. HBO therapy is unique in increasing oxygen delivery while causing blood vessels to constrict.

Experimental studies have shown that HBO treatment restores mitochondrial oxidative metabolism in addition to eliminating tissue hypoxia [71] and prevent lipid peroxidation [72] and prevents endothelial leukocyte adhesion [73]. Although many studies have talked about the healing process and preventing the disease from getting worse [74-76], In some studies, the authors failed to demonstrate a significant advantage of an HBO treatment session over NBO treatment in patients with loss of consciousness. Similarly, treatment with two sessions of HBO showed no advantage over one session of HBO in patients who were in a coma [77].

Decompression sickness (DCS)

Decompression sickness (DCS) occurs when atmospheric pressure decreases too rapidly. During this syndrome, bubbles of inert gas dissolved in blood or tissues lead to blood supply blockage, direct mechanical damage, or biochemical actions. DCS can be expected after scuba diving, ascent with flying, or hypobaric or hyperbaric exposure [78, 79].

The endothelium of vessels can be injured by the bubbles causing DCS. This damage induces platelet aggregation, lipoproteins denaturation, and leukocytes activation. These events eventually lead to capillary leaks and proinflammatory events [80, 81].

Hyperbaric oxygen therapy (HBOT) by using an oxygen gradient and also through pressure is ale to reduce the size of the bubbles. According to Boyle's law, pressure increases can decrease the volume of the bubble. The bubble causing DCS is thought to be composed of nitrogen.

In the process of DCS, when a tissue ascends to a decreased atmospheric pressure, bubbles derived from nitrogen seep out of blood, tissue, or both. By breathing 100% oxygen in HBOT, the blood becomes rich in oxygen and poor in nitrogen that leads to a gradient of nitrogen between the blood and the bubble. So nitrogen goes from the bubble into the bloodstream which makes the bubble smaller [79].

Recompression is the choice of treatment. The greatest success from recompression, as the definitive treatment, occurs when treatment is done as soon as possible but no exclusionary time from symptom onset has been established [79, 81]. Assessment patient's symptom response to therapy determines the time a patient is kept at 60 or 30 fsw [82].

Recovery therapy

Military response is now accepted around the world to assist civil society in natural disasters. Most of the time, military support is provided only in large-scale disasters. In contrast, local resource capacity can be used in small-scale disasters.

On the other hand, due to the proposed vascular etiology, many other treatment modalities were proposed and experimentally tested. Examples of treatments are blood flow-promoting agents, dextran, vasodilators, and pentoxifylline. However, many of these studies have did not show effectiveness within the clinical setting [83-87].

According to some authors, contraction of the prostheses caused by HBOT treatment reduces tissue edema and secretion of acute post-traumatic inflammatory factors, which can have an analgesic effect on acute pain [88, 89]. So we conclude that, at least from a pathophysiological point of view, HBO should be started as soon as possible, so HBO delayed effects can be considered reasonable, even so, it is impossible to define a period in which HBO can be considered anything more than a tool [90].

Recommendations

For future studies, we recommend starting therapy as early as possible, preferably within 48 h and to use combination therapy. Furthermore, we recommend investigating the relationship between the effects of HBO and age, sex, and underlying disease. In future studies, randomization and having a control group also seem necessary.

CONCLUSIONS

HBOT has been used quite extensively in the last couple of decades. Even though most studies were not randomized controlled trials, we think that based on the number of studies showing a positive effect, HBOT should be discussed with patients (shared decision making) as optional therapy.

This narrative review has described the rationale and clinical evidence for equipping medical centers with HBO systems, especially in military areas. Equipping military hospitals with this treatment system can perform the first stage of treatment for the individual before the transfer and speed up the treatment process, especially in combination therapies.

Therefore, centers can be classified based on belonging to different categories of hospitals, and for each pathology, a suitable hospital category can be defined. Given that so far no formal coordination has taken place between the military hyperbaric centers of different countries, interoperability facilitated the organization of cooperation in the field of multinational operations.

We emphasize international cooperation on the applications of hyperbaric medicine in military medicine. At the International Congress of Military Medicine (ICCM) held in Iran in 2018, a panel on hyperbaric medicine was held with the participation of hyperbaric medical professors from the participating countries. In this research panel, Dr. Shahram Oliaei, hyperbaric medical researcher, emphasized research and educational cooperation to further coordinate the hyperbaric medical centers of the member countries.

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