Original Article

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Crush Injury: HBOT and Placebo Controlled Randomized Clinical Trail

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Abstract

Background: Hyperbaric Oxygen Therapy (HBO) is an established treatment modality, which is internationally practiced since a long time ago. International protocols for the practice of hyperbaric oxygen therapy have been established in the United States by the Undersea and Hyperbaric Medical Society (UHMS) and in Europe by the European Committee for Hyperbaric Medicine (ECHM). *Objective:* To look for outcome on Wound healing without tissue necrosis requiring surgical excision, new major surgical procedures in relation to progressive and massive revitalization after entry in trail, Time of healing and Length of hospitalization. *Study Design:* A prospective Randomized double blind placebo controlled trial performed to realize the aim and objectives of this study. *Place of Study:* The study was carried out at the Prana HBO Centre, which is owned by the Investigator and located in the Northern parts of Mumbai, in India. *Methods:* On receiving the patient to the HBO unit at Prana, patients were randomly assigned to receive HBO therapy or Placebo. HBO therapy was given with compressed with air at a pressure of 2.5 atmosphere absolute (ATA). At this pressure the patient breathed 100% oxygen via facial mask. The HBO therapy protocol included 90 minutes oxygen breathing at 2.5 ATA twice daily over 6 days as per study by G Bouachour et al. Placebo consisted of sessions in HBO chamber at a pressure of 1.1 ATA in order to stimulate compression and its effects on the ears, while the patient breathing normal air via facial mask. The placebo therapy included 90 minutes air breathing at 1.1 ata twice daily over 6 days. *Results and Discussion:* Total 60 patients completed the study period and no patient was excluded during the study analysis. The demographic profile was comparable in the two groups of HBO and Placebo group. It was observed in the study that complete wound healing without any tissue necrosis requiring any amount of surgical excision was observed in 24 patients in HBO group whereas only 13 patients were observed with complete healing in the Placebo group. There s a threefold effect of Hyper oxygenation in HBO Therapy, a typical treatment pressure of 2 ATA, the plasma and the tissue fluid oxygen tension increase 10 fold from about 100 and 30 mm hg respectively to more than 1000 mm hg in the plasma and more than 300 mm hg in the tissue fluids. *Conclusion:* HBO therapy is a very useful therapeutic adjunct especially in the management of severe trauma of the limbs in older patients with grade III soft tissue injuries. The side effects and complications of HBOT are so infrequent and/or minimal that contraindications for using this intervention as an adjunct in the management of crush injuries are almost nonexistent. However, in no situation should HBOT be used as a substitute for indicated surgical, orthopedic, and medical interventions.

Keywords: Crush Injuries; HBOT; Placebo; Clinical Trail.

Introduction

Spectrum of injuries to the body is the term used to explain Crush injuries. Soft tissues or the bony elements may be primarily involved in injuries often it's the combination of both. It is the severity of the injury which differentiates the crush injuries from other types of injuries of the musculoskeletal system. Injury severity may range from minor with minimal contusion of soft tissue with or without a related fracture of limb which may be

threatening with nonviable soft tissue and may be associated with complex fractures. The likelihood of successful outcome decreases as the severity of injury increases. Tissue damage at certain point is so great that successful healing is unlikely and leading to limb amputation is mandatory. As such no universal classification system is available to encompass the spectrum of crush injury but it was Gustilo and Williams [1] and Johansen and colleagues [2] generated classifications that predict outcomes for open fractures and limb survival, respectively, but clinical judgment remains the common final denominator for making decisions about the management of crush injuries.

Hyperbaric Oxygen Therapy (HBO) is an established treatment modality [3], which is internationally practiced since a long time ago. International protocols for the practice of hyperbaric oxygen therapy have been established in the United States by the Undersea and Hyperbaric Medical Society (UHMS) [4] and in Europe by the European Committee for Hyperbaric Medicine (ECHM) [5]. These are generally accepted as the standard of care in the western world and treatment protocols were developed for around 17 indications overall. However, additional indications are accepted by other hyperbaric medical societies. Approximately 53 indications are accepted in China [5,8] twenty in Japan6 and 72 in Russia [9].

Transcutaneous Oxygen Monitoring (TCOM) is advised (in international guidelines) in all peripheral non-healing wounds before treatment in the chamber [7]. The UHMS published standard protocols, which is based on the current available medical evidence. These protocols would typically prescribed the type of patients who should be selected (i.e. establishing a bona fide indication for therapy), and the typical work-up required for evaluation. This would for instance include the use of TCOM for diabetic ulcers of the lower limb [6,8]. The protocols also describe the range of treatment depth (while breathing 100% oxygen) that would yield a therapeutic tissue oxygen tension for the disease being treated. These typically range from 150 kPa to 280 kPa (depending on the disease being managed). Apart from the treatment depth, the report also describes the typical number of treatments to be provided for each indication, ranging from one session (e.g. for decompression sickness) to as many as 40 sessions (e.g. for radiation-induced lesions).

In present situation crush injuries are a big and significant challenge to our health care system, on both the front of management and expenditures. As a cause of trauma service hospital admission, one fifth of total admissions to level 1 trauma center diagnosis are crush injury [10]. For complex crush injuries, initial hospitalizations are typically prolonged and re-hospitalizations are frequently required to manage the residual complications. Significant challenge to health care system and devastating to the patient is the cost and period of convalescence. The leading causes of crush injury are motor vehicle accidents; gunshot/ munition, wounds, and falls [10]. Even with optimal management, outcomes of crush injury are frequently less than desirable with an inverse relationship between good outcomes and the severity of injury. This generates the question whether outcomes even with state-of-the-art surgical and orthopedic interventions can be improved in those patients who have such severe crush injuries that poor outcomes are the expectation.

Several studies and research on series of patients had suggested the importance of HBO therapy in crush injuries. Even the comparison was made between standard treatment and adjunct use of HBO therapy in management of several injuries of the limbs by G. Bouachour and his colleagues in 1996. In this study we are also doing the prospective and randomized study to evaluate the effect of HBO in crush injuries of the limb and it use as an adjunctive measure. Classification of soft tissue injuries were derived from Gustillo RB [11]. Type I: wound less than 1 cm long and clean. Type II: Laceration more than 1 cm long without extensive soft tissue damage, flaps or avulsions. Type IIIA: Adequate soft tissue coverage despite extensive soft tissue laceration or flaps, or high energy trauma irrespective of the size of the wound. Type IIIB: Extensive soft tissue injury with periosteal stripping and bony exposure. Type IIIC: Arterial injury requiring repair.

Patients and Methods

Study setting

The study was carried out at the Prana HBO Centre, which is owned by the Investigator and located in the Northern parts of Mumbai, in India. The center has one Sechrist Monoplace hyperbaric chamber and a TCOM machine with 3 electrodes. The oxygen gas supply is from oxygen cylinders of 7000 liters' capacity each. The center has all the requisite certifications and registrations as required by the local authority in Mumbai. Study was conducted over a period of 2 years and patient with severe limb injury referred to the Hyperbaric

Unit at Prana HBO center within 24 hours after the initial evaluation and surgical procedure were included. Written informed consent was obtained from the patient and patient's relative.

Surgical procedures performed were as per the requirement of the case and discretion of the operating surgeon, debridement, irrigation of wound, primary closure without tension with regard to severity of the fracture and soft tissue injury and stabilization procedures. Vascular reconstructions were done with available local soft tissue or muscle rotation flaps. Accordingly the patients were covered by appropriate antibiotics and preventive antithrombotic treatment.

On receiving the patient to the HBO unit at Prana, patients were randomly assigned to receive HBO therapy or Placebo. HBO therapy was given with compressed with air at a pressure of 2.5 atmosphere absolute (ATA). At this pressure the patient breathed 100% oxygen via facial mask. The HBO therapy protocol included 90 minutes oxygen breathing at 2.5 ATA, twice daily over 6 days as per study by G Bouachour et al. placebo consisted of sessions in HBO chamber at a pressure of 1.1 ata in order to stimulate compression and its effects on the ears, while the patient breathing normal air via facial mask. The placebo therapy included 90 minutes air breathing at 1.1 ATA twice daily over 6 days. It was a double blind study hence the patient as well the surgeons were not informed regarding the protocol of the treatment, whether HBO therapy or Placebo. After each session re-evaluation of the injured extremities was performed which included examination of motor, sensory functions, skin color, edema and palpation of peripheral pulses. In all cases wound dressings were performed in the surgical unit.

As per the study of Bouachour et al. [12], in our study too we made four primary study end points:

1. Wound healing without tissue necrosis requiring surgical excision
2. New major surgical procedures in relation to progressive and massive revitalization after entry in trail
3. Time of healing
4. Length of hospitalization.

Inclusion criterion

Based on following criterion the patients were included and enrolled in trial. Acute injury of the limb classified as type II or III depending on soft tissue injury as per Gustillo RB [11]. Surgical management within 6 hours after the injury; no history of peripheral arterial occlusive disease.

Exclusion criterion

Patients were excluded from the trail if the patient was enrolled in another trail, pregnant, Upper respiratory tract infection, neurologic or pulmonary or otorhinolaryngologic diseases contraindicating HBO therapy. In order to evaluate the effects of the treatment Transcutaneous Oximetry monitoring system was utilized for measuring tissue oxygenation ($TcPO_2$) in all the patients of both groups. Measurements were recorded on non inflamed skin 1 cm proximal to the upper margin of ulcer. $TcPO_2$ findings were recorded, and the findings were calculated by an electrochemical transducer, and it remains attached to skin and use of adhesive ring and contact liquid was used. The measuring site was cleaned carefully by a disinfectant (spirit). By analyzing and measuring the oxygen reduction current with the help of measuring cell it was concluded for skin oxygen partial pressure.

Ethics review

This study was performed within the scope of international ethical guidelines and legislation. Ethics review and approval was provided by Stellenbosch University (number: U16/06/015) and the ethics committee of the Hyperbaric Society in India

Statistical Analysis

Comparisons of quantitative data between the HBO group and placebo group were made with paired and unpaired t test. All data are presented by descriptive statistics and graphics. P value of less than 0.05 was considered significant.

Results

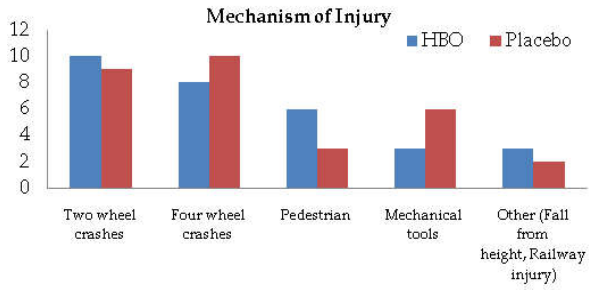

Fig. 1: Mechanism of Injury

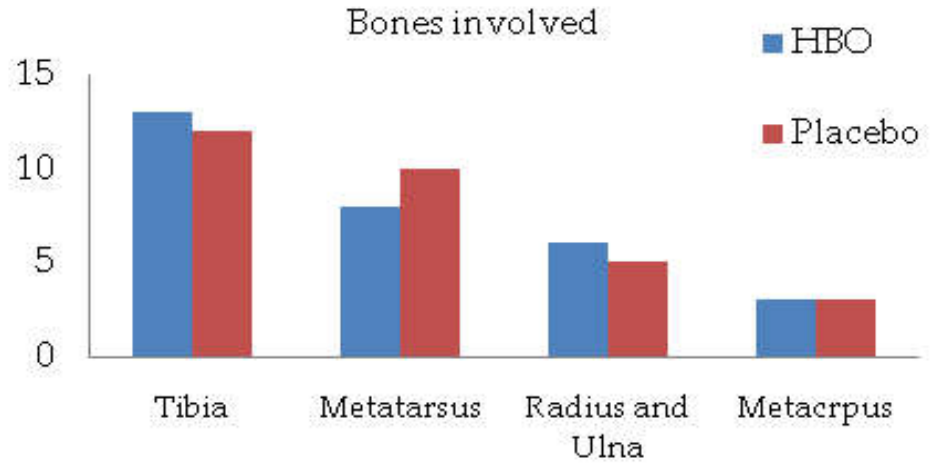

Fig. 2: Bones involved

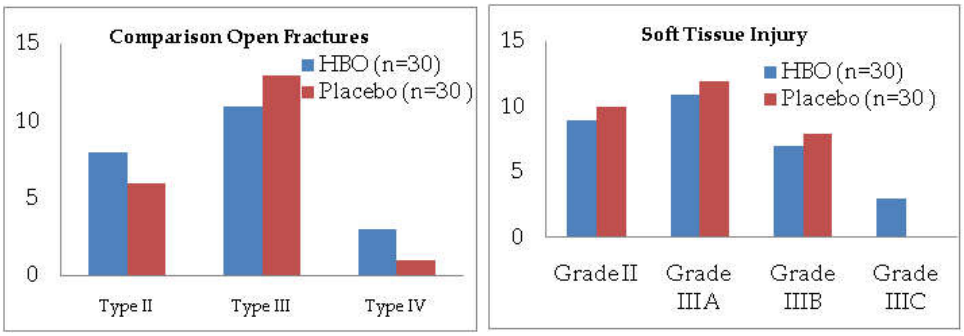

Fig. 3: Comparison Open Fracture and Soft Tissue Injury

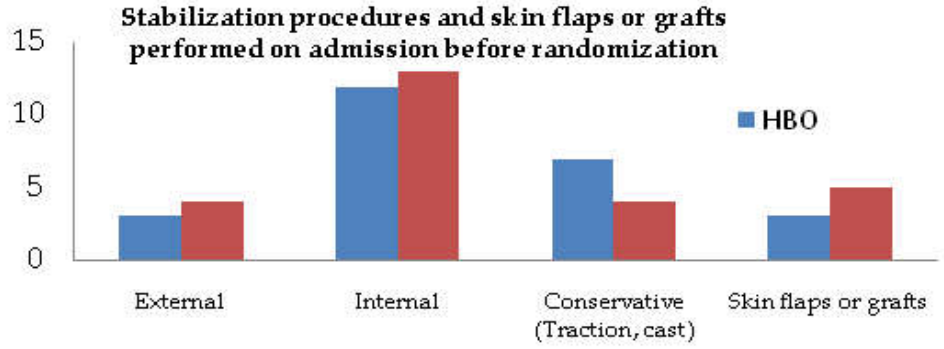

Fig. 4: Stabilization procedures and skin flaps or grafts performed on admission before randomization.

Table 1: Patients characteristic by treatment outcome

Groups	HBO (n= 30)	Placebo(n= 30)
Complete healing	24	13
Tissue Necrosis	2	12
New Surgical Procedures	3 (2)	10 (7)
Skin flaps and grafts	2	5
Vascular Surgery	1	0
Amputation	1	4
Wound dressings	17.3 (+ 6.41)	18.7 (+ 7.1)
Time of healing (days)	42.8 (+ 13.2)	49.3 (+ 11.7)

Table 2: Results of treatment in groups of patients matched for age and severity of trauma

	HBO Group				Placebo Group			
Age (Years)	**<40**		**>40**		**<40**		**>40**	
Soft tissue injury	**Grade II**	**Grade III**	**Grade II**	**Grade III**	**Grade II**	**Grade III**	**Grade II**	**Grade III**
Success	4	9	5	11	6	6	2	4
Failure	0	0	0	1	1	0	1	10
Totals	4	9	5	12	7	6	3	14

Table 3: Characteristics of the patients requiring new surgical procedures

Groups	HBO (n=2)	Placebo (n=7)
Age (Years)	52, 54	54.4 + 7.3 Range: 46 - 68
Diabetes Mellitus	1	3
Fractures	1	4
Soft Tissue injury*		
Grade IIIA	-	2
Grade IIIB	1	1
Grade IIIC	-	
Timing of new surgical procedures (Days)	5, 7	12.7 (+ 7.1) Range: 5-19

*Classification of soft tissue injuries derived from Gustillo

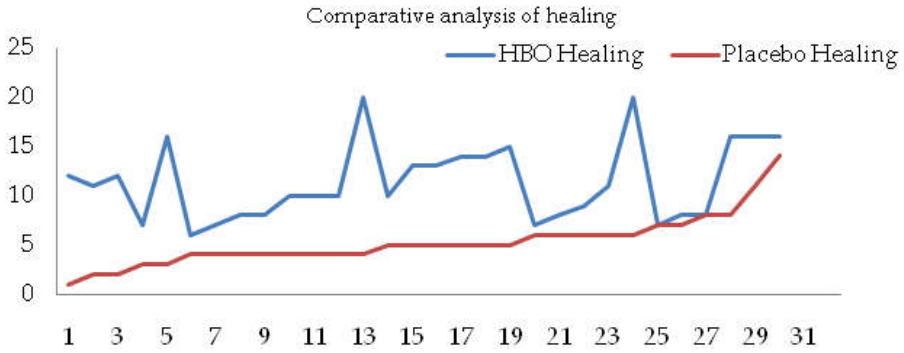

Fig. 5: Comparative analysis of healing

In the study total more than 69 cases were recruited and ended up with final 60 number of patient who fulfilled all the inclusion criteria for the study. Total 60 patients completed the study period and no patient was excluded during the study analysis. The demographic profile was comparable in the two groups of HBO and Placebo group. During the period of study neither of the group patient had any episodes of cerebral oxygen toxicity nor there were any adverse effects of pressurization observed. In study both the groups were relatively similar in terms of age 48.3 (+11.6) years for HBO group and 49.1 (+12.13) Years for Placebo group and to certain extent on risk factors. Total 7 patients were with Diabetes mellitus two and five respectively in the study in both groups. Mechanism of Injuries and bones involvement had been highlighted in Figures 1 and 2 respectively. As per Figures 2 and 3 differences was observed comparatively in severity of soft tissue injuries and fractures in both the group of study. Eight patients in the HBO group and ten patients in Placebo group had crush injuries without bony lesions. One patient in the HBO group required to have an end to end arterial repair for tibial artery. In HBO group one patient and in placebo group four patients were managed by primary amputation. In all the cases were required fracture stability was achieved as well stabilization procedures were achieved in both the group. In HBO group patients two cases and in Placebo group five patients' skin flaps and grafts were performed. Neurologic deficit in four patient of HBO group and three patient of placebo group was observed. As such surgical procedures and there timing and location, and types were not statistically varying from each other among both the group.

It was observed in the study that complete wound healing without any tissue necrosis requiring any amount of surgical excision was observed in 24 patients in HBO group whereas only 13 patients were observed with complete healing in the Placebo group.

Seven patients belonging to the placebo group were managed by repeated debridement as there was progressive necrosis of tissues observed, in all these patients secondary flap coverage was performed. Four patients from this placebo group had flap loss affecting fracture coverage and thus finally ended up with amputation. On the contrary in HBO group only two patients had to under gone surgical procedure due to ischemia and flap coverage of which one patient ended up with amputation.

On statistical analysis it was clearly observed that repetitive surgical procedures were common in placebo group in comparison to HBO group of patients. Both the patient group were not matched for age and severity of injury, but the result of outcomes were taken into consideration and summarized accordingly as shown in Table 2. In the observation o f subgroup of patient with more than forty years of age with grade III soft tissue injury, wound healing was obtained in eleven patients in the HBO group Vs four patients in the placebo group. By using paired t – test, In the HBO treatment the healing duration is reduced and the process of healing is faster with p value is 0.000001. Whereas in the placebo group healing duration and process of healing was delayed comparatively with p value of 0.0011. By using unpaired t – test it is evident that HBO treatment gives faster and efficient healing on the contrary in placebo group healing was delayed and less efficient with p value of 0.0000034.

Discussion

There is a threefold effect of Hyper oxygenation in HBO Therapy, a typical treatment pressure of 2 ata, the plasma and the tissue fluid oxygen tension increase 10 fold from about 100 and 30 mm hg respectively to more than 1000 mm hg in the plasma and more than 300 mm hg in the tissue fluids. Approximately 25% increased in oxygen carrying capacity is being observed as a consequence on 70 second of hyper oxygenation. There is threefold increase in the diffusion distance of oxygen through tissue fluids and relative barriers which includes ischemic margins of wounds. All these effects of hyper oxygenation is transient which last in the period of HBO therapy period and shall continue in the subcutaneous tissues for a around period of four hours, similarly for around one and half hours in the muscles [13]. Important consequences occurring due to hyper oxygenation enough oxygen is dissolved in plasma to meet tissue oxygen requirements even without RBCs, and transient increases of oxygen in the tissues triggering secondary mechanisms of HBOT to begin their actions. It has potential to provide an oxygenated environment to resume functions of wound healing and infection control. Hyperoxia acts against infection; it induces the production of toxic oxygen radicals which have a direct lethal effect of strict anaerobic organisms such as Clostridia species [14].

It leads to vasoconstriction which reduces inflow by 20%, whereas oxygenation is maintained through hyper oxygenation [15], with decreased inflow, yet maintenance of venous outflow edema is reduced [16,17]. Edema reduction in turn benefits into two fold increase of oxygen and reduce external pressure leading to improvised microcirculation. Hyperoxia causes enhanced oxygen dependent intracellular killing mechanism of ploymorphonuclear leukocytes and also affects bacterial clearance [18]. Depressed WBC killing capacity in infected ischemic tissues is reversed by oxygen tension of 4 mm Hg [19]. It is a mandatory requirement of hyper oxygenation t promote collagen production by fibroblasts in turn whose function are altered when an inadequate oxygen tension of less than 10 mm Hg is present in ischemic area [20]. Fibroblast differentiation collagen synthesis and angiogenesis is enhanced by HBO which ultimately leads to increased wound closure rate in hypoxic tissues [18,19,21].

HBO therapy to certain extent helpful to separate viable from nonviable tissues and thereby it helps to limit surgical excision. It also avoids soft tissue necrosis further preventing secondary exposure of joints, blood vessels, fractures and neural structures which radically modifies trauma prognosis [22]. The study made by Shupak A et al. in 1987 reported a clear improvement in prognosis in post traumatic acute ischemia in lower extremities after reconstructive surgery, in 8 cases out of total 13 studied cases complete limb salvage was accomplished and in three cases the level of amputation was lowered [23]. In our study it is clear evident that in patient with age more than forty years reduces the need for repetitive and aggressive debridement of tissues compromised by progressive necrosis in HBO group. HBO therapy is definitely helpful to segregate viable from nonviable tissues and thereby to limit the

surgical excision.

Recently study and experience from Chinese Shangahai which included 21 traumatic or near amputation of the limbs and fingers, of which 18 cases involved upper limb, 2 cases involved single fingers and one with lower extremity. The average time of limb ischemia before relplantation was around 16 hours with a range of 6 to 36 hours. In this study all the patients received HBOT after surgery. It was observed in the study, Limb survival occurred in 10 of 15 detached limbs, including 2 fingers that were ischemic for less than 10 hours, and in 4 of 6 patients with ischemic times greater than 20 hours. This study is noteworthy for the high survival rates observed in those patients with prolonged ischemia times [24].

Radonic and colleagues [25] describe their experience using HBOT as an adjunct for managing 28 patients with combat-related crural (lower extremity) vascular injuries during the Croatian War. All injuries were of the penetrating type. All patients had injuries that required vascular, orthopedic, and plastic surgery management in addition to fasciotomies. Thirteen patients who had a combination of extensive bony and soft-tissue injuries coupled with an ischemic time of greater than 6 hours received HBOT as an adjunct to their management. Good prognostic signs associated with HBOT included increase in blood pressure, improved skin color, increase in temperature on the injured side, and maintenance of temperature. Outcomes were assessed at discharge from the hospital and were described as "very good," "good," or "fair." The authors conclude that HBOT helped decrease the amputation rate.

Transcutaneous oxygen pressure is linked to oxygen delivery which is the result of oxygen content and blood flow. This noninvasive method of exploration was validated during HBO therapy [26]. It is possible to predict 100% sensitivity and 94% specificity whether or not secondary amputation of the traumatized limb should be performed, moreover during HBO therapy $PtCO_2$ monitoring seems to be useful to evaluate the evolution of the traumatized limb.

Conclusion

Although the evidentiary evidence supporting the use of HBOT for crush injuries is scant, the conclusions are consistent with our study which can be concluded with that HBO therapy is a very useful therapeutic adjunct especially in the management of severe trauma of the limbs in older patients with grade III soft tissue injuries. When the decision is made to use HBOT, current evidence suggests it should be started as soon after the injury as possible, preferably in the immediate postoperative period. If surgery is delayed, it is desirable to give HBOT while awaiting surgery. The side effects and complications of HBOT are so infrequent and/ or minimal that contraindications for using this intervention as an adjunct in the management of crush injuries are almost nonexistent.

Consequently, when pairing the clinical experiences and laboratory data, justification for using HBOT as an adjunct for managing crush injuries is strong. However, in no situation should HBOT be used as a substitute for indicated surgical, orthopedic, and medical interventions.

Conflict of Interest: The author declares no conflict of interest for this study.

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