Case Report

Salvage Resolution in Sequence of Limb Salvage Surgery: Hyperbaric Oxygen Adjuvant in Musculoskeletal Oncology

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Background: For most sarcoma patients, limb sparing surgery is the standard of care. However, these salvage procedures may potentially result in complications such as post-operative wound problems owing to the reconstruction processes leading to difficulty in resolving and finding a suitable solution.

Objective: To report the cases and outcome after using a new treatment modality of hyperbaric oxygen therapy [HBO_2T].

Case Report: Four cases show the outcome after using HBO_2T in sequence of limb salvage surgery between December 2008 and December 2015 with evidence-based support. These cases had four different types of predictive major complication, 1) compromised flap with sign of necrosis subsequently attempting coverage after wide resection of the high grade spindle cell sarcoma on the knee, 2) chronic refractory osteomyelitis after wide excision and allograft reconstruction of osteosarcoma of the proximal tibia, 3) soft tissue necrosis subsequent to re-excision of previously irradiated recurrent myxofibrosarcoma, and 4) radiation injury of the cutaneous wound after wide resection and postoperative radiation after refractory wound dehiscence occurring in pleomorphic leiomyosarcoma left lateral ankle.

Results: Compromised flap after treating with HBO_2T application for 20 sessions, recovery of the viable tissues were achieved. Osteomyelitis after allograft reconstruction, infection was subsided then knee fusion was performed afterward. Healing enhancement in resected wound with previously irradiated area. Wound dehiscence was closed in postoperative radiation.

Conclusion: HBO_2T can be considered as an adjuvant therapy for problem cases in salvage resolution in sequence of limb salvage surgery and beneficial to enhance wound healing.

Keywords: Hyperbaric oxygen therapy, Chronic osteomyelitis, Compromised flap, Wound, Radiation injury, Salvage, Allograft infection, Sarcoma

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The standard of care for most sarcoma patient is limb sparing surgery. These salvage procedures need to remove the defect according to wide resection, which can be categorized into two types as followings bone and soft tissue. One of the common surgical methods utilized in reconstructive setting of the bone defect is allograft restoration. Unfortunately, infection was reported in 9% of the cases[1]. Additionally, using radiation in conjunction with surgery to eliminate tumor recurrence from close or positive margin can result in poorly oxygenated tissues and is associated with a high-risk of wound healing complication at 35% and 17% in cases treated with preoperative and postoperative radiotherapy, respectively[2]. On the other hand, dealing with the soft tissue loss with a flap coverage is an usual procedure. Nevertheless, the incidence of postoperative failure with partial and total flap loss approaches 7% and 3.5%, respectively[3]. Nowadays, the management sequence of limb salvage surgery, namely osteomyelitis are debridement, stabilization, and antibiotics, while management of compromised flaps are debridement and correction of mechanical causes. However, some results are not favorable.

Hyperbaric Oxygen Therapy [HBO_2T] has been focused on in recent years. The reason for the growing interest is the better understanding of the patho-physiology of hypoxia in wound healing. There is evidence of improving clinical outcome after HBO_2T when the traditional wound treatment is unsuccessful[4]. The potential of wound healing can be measured by periwound transcutaneous oxygen tension [$TcPO_2$], which is correlated with the initial rate of tissue repair

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and can be measured by transcutaneous oximetry [TCOM]. In case of low periwound $TcPO_2$ (<20 mmHg), the result of wound healing was associated with a 39 folds risk of early healing failure. This can prognosticate the outcome[4]. However, HBO_2T cannot solely replace quality of wound care. HBO_2T is a clinical treatment where patients breath 100% oxygen in a chamber with a pressure of more than 1 atmosphere absolute pressure [ATA]. In complex wound care, the wound is significantly reduced in size after using 100% oxygen for 90 minutes at 2.0 to 2.4 ATA after five sessions. Additionally, the first 10 sessions of HBO_2T should be uninterrupted[5].

Case Report

Between December 2008 and December 2015, there were four cases of failed limb salvage surgery, treated with HBO_2T as an adjunctive treatment. Final outcomes of such cases were considered as significant better results than those of the standard wound care. The four cases were described as follow, 1 compromised flap, 1 postoperative wound necrosis, 1 chronic refractory osteomyelitis, and 1 soft tissue radionecrosis of cutaneous wound.

Case 1: male 62-year-old with ischemic heart disease, non-smoker

Local recurrent myxofibrosarcoma with previous radiation therapy 60 Gy and adjuvant chemotherapy (doxorubicin and ifosfamide). A re-excision with tumor bed resection was performed subsequent to flap coverage. After 20 sessions of adjunctive HBO_2T applications, the patient showed significant improvement despite previous signs of wound healing problem. Improving result was shown with signs of viable tissues namely redness, increasing cellularity, and granulation. After that, skin coverage was performed with spilt thickness skin graft as shown in Figure 1.

Case 2: female 75-year-old with diabetes mellitus and smoking 10 cigarettes daily

She had a rapid growing mass on left knee. Biopsy result from the specimen showing high grade spindle cell sarcoma. Operation was done with wide resection and Vastus lateralis flap coverage as shown in Figure 2. Unfortunately, one week later, the flap was compromised with sign of tissue necrosis. Debridement result was not satisfactory. There was a significant improvement after 10 sessions of HBO_2T as shown in Figure 3.

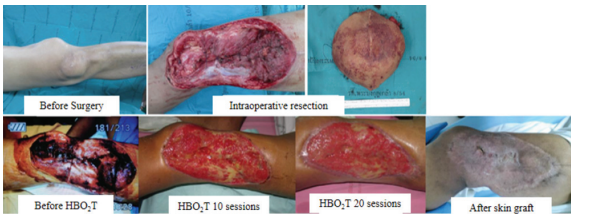

Figure 1. Compromised wound was getting better after using HBO_2T.

Figure 2. Intraoperative resection and flap coverage.

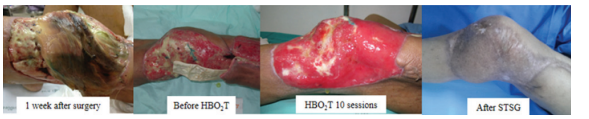

Figure 3. Improving result after HBO_2T.

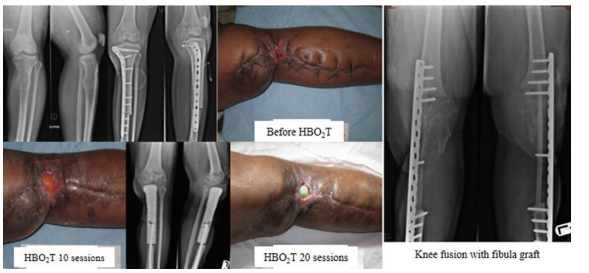

Figure 4. Chronic refractory osteomyelitis and HBO_2T.

Case 3: male 47-year-old, no underlying disease, non-smoker

This patient had high grade conventional osteosarcoma on the proximal tibia. He received treatment with wide resection and allograft reconstruction. Unfortunately, chronic refractory osteomyelitis had occurred despite of previous multiple debridement and intravenous antibiotics. The result was not satisfactory. The problem was resolved by using HBO_2T concurrent with debridement, removal of allograft, and the use of antibiotics cement spacer. Finally, infection was under controlled and limb salvage was done with knee fusion as shown in Figure 4.

Figure 5. Size of refractory wound was reduced significantly after using HBO_2T 20 sessions

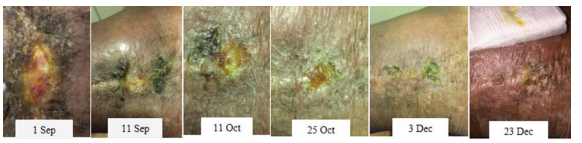

Figure 6. Home care dressing after HBO_2T.

Case 4: male 37-year-old, no underlying disease

This patient had leiomyosarcoma on left lateral ankle. Neoadjuvant chemotherapy was provided. Afterward, wide resection was performed, and then radiation was done. Due to closed margin of the neoplasm, it had negative margin and 10% tumor necrosis. Nevertheless, refractory wound dehiscence occurred. HBO_2T was then used for 20 sessions and wound healing improved significantly as shown in Figure 5. This was followed by standard normal saline solution wound care at home. Tissue recovery is shown in Figure 6.

Discussion

In the past, limb salvage surgery had often been troublesome and stood as a big challenge for orthopedic oncology. In recent years, a new treatment modality called hyperbaric oxygen was introduced as an adjuvant therapy to orthopedic surgery. It is achieving some results that could not be achieved with standard care such as compromised flap, chronic refractory osteomyelitis, and soft tissue radionecrosis, which occur often in limb preserving operation.

HBO_2T has been successfully utilized in non-healing wound repair by mechanism of elevating cellular oxygen levels following with increase neovascularization, or angiogenesis. It is the growth of new blood vessels from local endothelial cells[6] and vasculogenesis, which is the recruitment and differentiation in the wound bed of circulating stem/progenitor cells to form new vessels. Furthermore, it also stimulates collagen synthesis and fibroblast proliferation within the wound bed[7].

One of the most beneficial properties of HBO_2T is anti-inflammation. Clinical results have documented significant recovery with HBO_2T after extremity reimplantation, free-tissue transfer, and crush-injury/reperfusion. For example, after reattachment of flap, ischemic tissue will be reperfused more efficiently after using HBO_2T. The inflammatory cells paradoxically attack the ischemic tissue, which is known as ischemia-reperfusion injury. HBO_2T is believed to reduce the margination of leukocyte and porosity of endothelium, hence, reduce interstitial edema because HBO_2T regulates endothelial derived nitric oxide synthetase, which is the key mediator for epithelization, wound matrix formation, and neoangiogenesis.

Hyperbaric oxygen therapy and compromised flap

Flap reconstruction is a procedure commonly used for reconstructing the soft tissue defect. However, the incidence of partial and total flap loss approached 7% and 3.5%, respectively. With HBO_2T as adjunctive treatment, the compromised flap survival was dramatically increased to 73.3%, associated with a favorable treatment outcome including high percentage of treatment completion and high pretreatment transcutaneous oxygen measurements[3]. The criteria for selecting the proper patients are after corrected mechanical causes, etiology of flap compromised, and starting treatment as soon as signs of flap compromise appear[12]. Our experience with the HBO_2T overcoming the compromised flap situation was good.

Hyperbaric oxygen therapy and delayed radiation injury

HBO_2T has been used successfully for treating the complication of delayed radiation injury, which is usually seen six months or more after radiation. It is characterized by endateritis that creates tissue hypoxia, which inhibits the wound healing, hypocellularity, and severe secondary fibrosis. Historically, conservative management has been rather unsatisfactory. To achieve successful definitive treatment, major surgical intervention may be required, which may result in unfavorable outcomes. Delayed radiation tissue injury is one of the 14 approved indication for HBO_2T applications according to the Undersea and Hyperbaric Medical Society [UHMS]. This indication can be considered to be the American Heart Association [AHA] level IIb and "Likely to be beneficial" by the BMJ system as treatment for the extremities[8]. Furthermore, soft tissue injury resulting in cutaneous wound can be found in therapeutic radiation, with adjunctive HBO_2T showing 84% improvement[8,11]. The etiology of radiation injury arises from vascular changes, characterized by obliterative endarteritis and fibro-atrophic effect in the tissue. Increasing angiogenesis in hypoxic tissues has been shown after

using hyperbaric oxygen. The literature is supporting the application of HBO_2T prior to surgery in an irradiated field to prevent or decrease the incidence of catastrophic events such as wound breakdown or flap loss. Additionally, literature review of clinical reports, and animal studies showed no enhancement of cancer growth[11] after using HBO_2T.

Hyperbaric oxygen therapy and chronic refractory osteomyelitis

HBO_2T is a worthy option in cases of chronic refractory osteomyelitis. Many studies showed that increased oxygen tension in bone results in a decrease in bacterial number. Additionally, there is a proportional relationship between oxygen tension and polymorphonuclear leukocytes [PMN] killing ability and Vancomycin bactericidal activity[13]. HBO_2T can control infection by promoting the efficacy of leukocytes to kill pathogens by phagocytosis, which requires large quantify of oxygen to inactivate pathogens[9]. This mechanism is blunted in the hypoxic environment such as infected tissue or bone. The oxygen tension in osteomyelitic bone is low, rarely exceeded 25 mmHg of oxygen, whereas oxygen tension in the normal bone is 45 mmHg. Recent studies showed HBO_2T increase the oxygen tension to 104 mmHg in osteomyelitic bone, and to 322 mmHg in normal bone. Mader et al[10] showed a proportional relationship between oxygen tensions and phagocytic (PMN) killing ability. The study showed improved treatment of experimental Staphylococcal osteomyelitis with the adjunctive treatment of HBO_2T, likely as the result of enhanced oxygen-dependent killing mechanisms. Fibroblasts cannot synthesize collagen or migrate to the affected area when oxygen tension is below 20 mmHg. Elevating oxygen tensions to levels greater than 200 mmHg promotes fibroblasts to normal function. Following to the differentiation of fibroblast-like mesenchymal cells, osteoblasts deposit a layer of coarse immature fibrillar bone. This immature bone is then replaced by mature lamellar bone, which is functionally reconstructed by resorption and deposition by osteoclasts and osteoblasts. Vancomycin, quinolones, sulfomides, and the aminoglycoside class of antibiotics have been shown to be far less effective in the hypoxic environment. Eventually, Mader implied that with HBO_2T, the bactericidal activity of these group is enhanced.

Hyperbaric oxygen therapy and surgery

Based on the current research, the improved outcome of any major surgical procedure can be made with preoperative HBO_2T[11]. In series of patients for whom surgery was planned to repair radiation necrosis wounds or to resect recurrent cancer, a marked reduction of wound infection, wound dehiscence, and delayed healing was reported when adjunctive HBO_2T was applied before and after surgery, comparing with controls. HBO_2T is also used to treat the compromised flaps or grafts and irradiated wounds in treatment of sarcomas especially in case of previous unplanned excision. In this situation, wider resection is needed to receive a negative margin. Furthermore, HBO_2T can be initiated immediately after surgery without lingering for evidence of wound complications, which shows a greater reduction in complication. Clinical evidences of the efficacy of the HBO_2T are 1) high level evidence for decreasing risk of amputation in diabetic foot ulcer, 2) high level evidence for promoting healing of problem wounds, 3) low to moderate level for promoting salvage of the compromised flaps or grafts, 4) moderate level evidence in combination with surgery, antibiotics and HBO_2T promoting remission of refractory osteomyelitis, and 5) high level evidence TCOM prognosticates success of HBO_2T[6].

Safety

Serious adverse events are rare. Minor adverse events are reported such as cardiovascular effect, oxygen toxicity (central nervous system, pulmonary), barotrauma (middle ear, inner ear, sinus, dental, pulmonary), hypoglycemia, and confinement anxiety[6].

Conclusion

HBO_2T is considered as an adjuvant therapy and shall never replace the conventional standard of care. Nevertheless, it can offer great benefits in some situations such as compromised flap, radiation injury, and chronic refractory osteomyelitis. While evidence is limited due to the small number of studies, the successful outcome in experience from experts worldwide have been supported by the US FDA and CMS/Medicare as approved conditions for reimbursement. It is reasonable to state that HBO_2T is widely accepted and recommended for salvage resolution in failed limb salvage surgery.

What is already known on this topic?

Indications for using HBO_2T are chronic osteomyelitis, delayed radiation injury, and compromised flap, which have been approved with evidence-based from UHMS. The outcome after using HBO_2T is good

due to better understanding of healing process of wound and infection with oxygen therapy. Unfortunately, most of orthopedists do not have knowledge about the Underwater medicine and the Hyperbaric oxygen chamber is expensive. As a result, the number of cases treated with HBO_2T is very small even if it has a good outcome.

What this study adds?

In case of failed limb salvage surgery followed by chronic osteomyelitis, delayed radiation injury, and compromised flap, we demonstrated four clinical sarcoma cases using HBO_2T, which is extremely rare. The result after using the new form of adjuvant therapy, HBO_2T, is good, so it is reasonable to state that HBO_2T is recommended for salvage resolution in failed limb salvage surgery.

Potential conflicts of interest

The authors declare no conflict of interest.

References

1. Aponte-Tinao LA, Ayerza MA, Muscolo DL, Farfalli GL. What are the risk factors and management options for infection after reconstruction with massive bone allografts? Clin Orthop Relat Res 2016;474:669-73.
2. Moore J, Isler M, Barry J, Mottard S. Major wound complication risk factors following soft tissue sarcoma resection. Eur J Surg Oncol 2014;40: 1671-6.
3. Larson JV, Steensma EA, Flikkema RM, Norman EM. The application of hyperbaric oxygen therapy in the management of compromised flaps. Undersea Hyperb Med 2013;40:499-504.
4. Siegel HJ. Management of open wounds: lessons from orthopedic oncology. Orthop Clin North Am 2014;45:99-107.
5. Opasanon S, Pongsapich W, Taweepraditpol S, Suktitipat B, Chuangsuwanich A. Clinical Effectiveness of Hyperbaric Oxygen Therapy in Complex Wounds. J Am Coll Clin Wound Spec 2014;6:9-13.
6. Goldman RJ. Hyperbaric oxygen therapy for wound healing and limb salvage: a systematic review. PM R 2009;1:471-89.
7. Camporesi EM, Bosco G. Mechanisms of action of hyperbaric oxygen therapy. Undersea Hyperb Med 2014;41:247-52.
8. Feldmeier JJ, Hampson NB. A systematic review of the literature reporting the application of hyperbaric oxygen prevention and treatment of delayed radiation injuries: an evidence based approach. Undersea Hyperb Med 2002;29:4-30.
9. Lima AL, Oliveira PR, Carvalho VC, Cimerman S, Savio E. Recommendations for the treatment of osteomyelitis. Braz J Infect Dis 2014;18:526-34.
10. Mader JT, Brown GL, Guckian JC, Wells CH, Reinarz JA. A mechanism for the amelioration by hyperbaric oxygen of experimental staphylococcal osteomyelitis in rabbits. J Infect Dis 1980;142: 915-22.
11. Feldmeier JJ. Hyperbaric oxygen therapy and delayed radiation injuries (soft tissue and bony necrosis): 2012 update. Undersea Hyperb Med 2012;39:1121-39.
12. Baynosa RC, Zamboni WA. The effect of hyperbaric oxygen on compromised grafts and flaps. Undersea Hyperb Med 2012;39:857-65.
13. Mader JT, Shirtliff ME, Bergquist SC, Calhoun J. Antimicrobial treatment of chronic osteomyelitis. Clin Orthop Relat Res 1999;(360):47-65.