Treatment of Frostbite With Hyperbaric Oxygen Therapy: A Single Center's Experience of 22 Cases

Ammara Ghumman, MD[1]; Hannah St. Denis-Katz, MD[1]; Rosalind Ashton, MD[1]; Christopher Wherrett, MD, FRCPC[2]; and Claudia Malic, MD, MRCS(Eng), FRCS(Plast), FRCSC[1,3]

ABSTRACT

Introduction. Frostbite is well documented in the military and countries with extreme temperatures, and it is most likely due to increased exposure to cold temperatures and/or risk-taking behavior. Severity of injury depends on absolute temperature, wind chill, duration of exposure, wet or dry cold, immersion, clothing quality, and substance use. Hyperbaric oxygen therapy (HBOT) has been described as a treatment option but only in small case series. **Objective.** The aim of this retrospective study is to describe the usage patterns, side effects, and outcomes of HBOT used as an adjunct to wound care at a single major Canadian university hospital. **Materials and Methods.** A retrospective review of patients with frostbite injury admitted and treated with HBOT between January 2000 and March 2015 was performed. A total of 22 patients were studied. Available data included patient demographics, duration of exposure to cold temperature, severity of injury, time to HBOT, duration of therapy, side effects of therapy, concurrent therapies (dressing, anticoagulation, antibiotics), bone scan results, and consequent level of amputation. **Results.** The cohort consisted mostly of men (18, 81.8%) and patient mean age of 40 years (range, 13-70 years). Ten patients (45.5%) were intoxicated at the time of injury, and psychiatric illness was implicated in 9 (40.9%) patients. Of the presented injuries, 17 (77.3%) had frostbite to the upper extremity. Bone scans were performed on 16 (72.7%) patients. In 4 patients, the absence of radiotracer activity correlated with a protective effect on subsequent amputation levels. All patients received anticoagulant therapy. Of the 22 patients, 16 (72.7%) experienced at least 1 side effect of HBOT, including otologic barotrauma, nausea, vomiting, anxiety, oxygen toxicity seizure, and myopic changes. All study patients recovered without permanent sequelae; it is unclear whether HBOT reduced soft-tissue damage or amputation rates. **Conclusions.** This is the largest cohort reported in the literature of patients with frostbite injuries treated with HBOT. Hyperbaric oxygen therapy may show positive impact on the demarcation level of frostbite and, despite the common side effects, it generally causes no long-term sequelae.

KEY WORDS

frostbite, burn, cold burn, hyperbaric oxygen therapy, HBOT, amputation, acute wound

INDEX

Wounds 2019;31(12):322–325. Epub 2019 September 30

Frostbite is a localized cold thermal injury from exposure to temperatures low enough to cause ice crystal formation in tissues, resulting in damage to cell membranes and osmotically dehydrated cells.[1] The feet and hands are the most commonly affected areas and account for 90% of frostbite injuries.[2] Historically, frostbite was primarily seen in military populations, but it has become increasingly prevalent in homeless people, who are vulnerable to cold injuries.[2] Additionally, a growing interest in outdoor activities, such as skiing, hiking, and mountaineering, has contributed to an increased prevalence of frostbite injuries in the general population.[2]

Frostbite occurs because of 3 interlinked processes: (1) extracellular ice crystal formation as a direct injury, which (2) leads to oncotic fluid shifts and intracellular dehydration, and (3) ultimately cell death. The indirect injury by cold-induced vasoconstriction increases blood viscosity, microvascular thrombosis, and resultant tissue hypoxia, and this begets the final process of the release of potent inflammatory hypoxia-related mediators during the hunting reaction and with tissue reperfusion. These mediators, such as prostaglandin $F_2\alpha$ and thromboxane A_2, trigger further vasoconstriction, platelet aggregation, and blood vessel thrombosis, leading to more endothelial cell damage and further hypoxia and cell death.[3-5]

The mainstay of frostbite treatment protocol is derived from McCauley et al,[4] which prescribed admission to hospital, rapid rewarming with water immersion at 104°F to 108°F (40°C to 42°C), tetanus prophylaxis, ibuprofen for anti-inflammatory properties, narcotic analgesics

for pain control, smoking cessation, limb elevation, rest, and splinting. Since then, few major modifications in frostbite management have been introduced. Adjunctive therapies, such as early intra-arterial thrombolysis, have recently come into favor with promising results. Thrombolytic therapy has been used in frostbite injuries to limit ischemic effects by improving perfusion to affected tissues. This therapy has been shown to be effective if administered within 24 hours after rewarming frostbitten tissue.[6]

Hyperbaric oxygen therapy (HBOT) treats patients with 100% oxygen at greater than 1.0 atmosphere (atm). It can be used to treat selected ischemic problem wounds, wounds caused by radiation, compromised flaps and grafts, and ischemia-reperfusion disorders.[7] Hyperbaric oxygen therapy in a delayed setting (>24 hours) prevents complications of nonhealing wounds (eg, infection) and aids in demarcation.[8] Studies have demonstrated improvement in graft survival from administration of HBOT before and after skin grafting.[7] Other animal studies also support the use of HBOT in flap and graft compromise.[7]

Hyperbaric oxygen therapy has been shown to mitigate reperfusion injuries by temporarily inhibiting neutrophil β2 integrins and inducing activity of antioxidant enzymes and anti-inflammatory proteins.[6] As a therapy for frostbite, HBOT compensates for some microcirculatory failure and tissue hypoxia by increasing oxygen delivery to ischemic tissues directly via elevated arterial oxygen concentration and indirectly via angiogenesis and resolution of tissue edema.[6] It also has demonstrated additional physiologic effects that may promote healing of frostbite injuries.[9]

Hyperbaric oxygen therapy has been used as an adjunctive therapy for frostbite for more than 50 years.[10] Both animal studies and human case reports have described favorable results with the use of HBOT in frostbite injuries.[11-15] However, previous reports of HBOT for this indication have been limited by small sample sizes, with the highest reported cohort being 10 patients.[15] To further the research in this area, the authors aimed to describe the usage patterns, side effects, and outcomes of HBOT at the pediatric and adult institutions of a major Canadian university hospital.

MATERIALS AND METHODS

Both adult and pediatric Institutional Review Board approvals were obtained at the authors' institutions (Ottawa Hospital, Ottawa, Canada; Civic and General Campus and Children's Hospital of Eastern Ontario, Canada). A retrospective review of medical records of patients admitted with a frostbite injury and treated with HBOT at the authors' university hospital between January 2000 and March 2015 was performed. Data collected included patient demographics, duration of exposure to cold temperature, severity of injury, time to HBOT, duration of therapy, side effects of therapy, concurrent therapies (dressing, anticoagulation, antibiotics), bone scan results, and consequent level of amputation.

Protocol

All patients underwent a modified McCauley et al[4] protocol with rapid rewarming, tetanus prophylaxis, nonsteroidal anti-inflammatory drugs, pain control with multimodal analgesia, and antiplatelet or anticoagulant treatment. In situations in which the patient was not already on anticoagulation or antiplatelet medication, aspirin was used rather than ibuprofen as a single agent for dual anti-inflammatory and antiplatelet effects. The authors' institution does have established protocol for arranging intra-arterial tissue plasminogen activator; therefore, this was not part of the standard management. Blister management with debridement was instituted at the first assessment by plastic surgeons. Adjuvant investigations (eg, bone scans) and further treatments (eg, HBOT) also were initiated at the first assessment by a plastic surgeon. Bone scans were used as an adjuvant tool in this study and did not impact the initiation of HBOT.

RESULTS

A total of 22 patients were identified from the hyperbaric unit medical records. Of the 22 patients included, 18 were male (81.8%) and 4 were female (18.2%). Patients ranged in age from 13 years to 70 years (mean: 40 years). The 2 predisposing factors, alcohol intoxication and psychiatric illness, were present in 10 (45.5%) and 9 (40.9%) patients, respectively.

By anatomic site of injury, the upper extremities were involved in 17 patients (77.3%). There were 9 (40.9%) patients with upper extremity (ie, hand, arm) frostbite and 5 (22.7%) with lower extremity (ie, foot, ankle) frostbite. Eight (36.4%) patients had multiple injury locations, with 2 (9.1%) suffering head and neck injuries in addition to extremity injuries. Third-degree frostbite injuries were the most prevalent injuries recorded (11, 50%), followed by injuries of unknown depth (6, 27.3%) and second-degree injuries (3, 13.6%). Time of cold exposure was less than 4 hours in 10 patients (45.5%), 4 hours to 8 hours in 3 patients (13.6%), 8 hours to 12 hours in 2 patients (9.1%), and unknown in 7 patients (31.8%). Time from presentation to HBOT was 4 hours to 8 hours in 2 patients (9.1%), 8 hours to 12 hours in 3 patients (13.6%), 12 hours to 24 hours in 5 patients (22.7%), and more than 24

Table 1. Hyperbaric oxygen treatment (HBOT)

HBOT	NO. OF PATIENTS (N=22; %)
Treatment sessions	
≤5	9 (40.9)
6–10	4 (18.2)
11–15	3 (13.6)
16–20	4 (18.2)
≥21	2 (9.1)
Total days treated	
≤5	10 (45.5)
6–10	10 (45.5)
11–15	1 (4.5)
16–20	0 (0)
≥21	1 (4.5)

Table 2. Incidence of adverse effects

ADVERSE EFFECT	NO. OF PATIENTS (N=22; %)
None	5 (22.7)
Overall	17 (77.3)
Seizure	2 (9.1)
Nausea/vomiting	5 (22.7)
Anxiety/claustrophobia	5 (22.7)
Visual changes	1 (4.5)
Otologic barotrauma	8 (36.4)
Teed 1	4 (18.2)
Teed 2	2 (9.1)
Teed 3	2 (9.1)

hours in 12 patients (54.5%). All patients (100%) received either antiplatelet or anticoagulant therapy. Patients were started on aspirin 325 mg once daily, and 8 patients (36.4%) were already on an antiplatelet or anticoagulant treatment for another indication. Patients continued their regular antiplatelet or anticoagulation therapy and were not provided the additional aspirin.

Hyperbaric oxygen therapy was administered at a pressure of 2.5 atm absolute (49.5 feet seawater) in 3 cycles of 30 minutes separated by 2 air breaks of 10 minutes. Sessions were initially conducted 2 to 3 times daily, as indicated by the treating physician and resource availability of therapy, and then tapered to completion. Total treatment sessions ranged from 3 sessions to 43 sessions (**Table 1**). Bone scans were performed within 2 to 6 days of presentation on 16 (72.7%) patients. Of these patients, 8 experienced subsequent amputation, usually 5 weeks to 6 weeks following the initial injury. Data were available to correlate bone scan radiotracer activity with amputation level after HBOT in 7 patients. In 2 patients, the ultimate amputation level was proximal to that indicated by bone scan; in 1 patient, the amputation level was at the level indicated by bone scan; and in 4 patients, the definitive amputation level was distal to that initially indicated.

Side effects occurred in 17 (77.3%) patients, with some patients experiencing multiple effects; the remaining 5 (22.7%) patients experienced no effects at all. The most common side effect was otologic barotrauma, as defined by the Teed score,[16] followed by nausea/vomiting and anxiety/claustrophobia (**Table 2**). Myringotomy tubes were placed in 6 patients. All side effects completely resolved after treatment.

DISCUSSION

This is the largest case series to date of patients with frostbite treated with HBOT. Epidemiologically, this study corroborates previously published literature indicating predominantly male patients sustain frostbite injuries and predisposing factors include alcohol intoxication and psychiatric comorbidity.[17] This study also supported a previously published study regarding anatomic distribution of frostbite injuries, with most patients sustaining frostbite to upper or lower extremities.[17]

Bone scans were performed in 16 (72.7%) patients and did not correlate with the final amputation levels. Amputation levels were determined clinically. In 50% of cases requiring amputation, there was a possible beneficial effect of HBOT, because the final amputation level was distal to the predicted level from pretreatment bone scans.

Hyperbaric oxygen therapy has been posited to work through a variety of mechanisms related to increased arterial oxygen concentration. It has been shown to increase oxygen-sensitive fibroblast proliferation, angiogenesis, and capillary density; decrease tissue edema by promoting intermittent vasoconstriction; and modulate leukocyte bactericidal and proinflammatory activity.[7,18-20]

In the frostbite literature, several studies have examined the utility of HBOT. Hyperbaric oxygen therapy was first reported in frostbite injuries in 1963 by Ledingham.[10] Since that time, both animal studies and clinical reports have been published on this topic.

Animal studies have been equivocal. Studies by Okuboye et al[11] and Uygur et al[12] demonstrated beneficial effects of HBOT in rabbit models with frostbite injuries. However, Gage et al[9] reported no additional benefit of HBOT in a leporine model and Hardenbergh[13] found no additional benefit of HBOT in a murine model. Germonpre[14] suggested HBOT may be better suited to treat slowly acquired, less extreme cold injuries.

Multiple human studies have been published in the form of case reports with positive outcomes using HBOT.[6,15] Although early initiation of HBOT in frostbite injury is advocated, research suggests there are protective effects of HBOT even when initiation is delayed, including antibacterial action and angiogenesis effect.[6,8,14] This study demonstrated the use of HBOT in a delayed fashion (after 24 hours) in 54.5% of patients.

Hyperbaric oxygen therapy is a relatively well-tolerated procedure.[21] In a large retrospective review of 2334 patients, side effects from HBOT were reported to occur in 17.4% of patients.[16] The most common side effect in this study was middle ear barotrauma,[16] which was evaluated according to the Teed classification on otoscope examination.[16] Other rare barotrauma-related side effects include sinus/paranasal, dental, and pulmonary barotrauma. Central nervous system (CNS) oxygen toxicity from HBOT can cause grand mal seizure activity. Several risk factors have been identified, including higher treatment pressures, hypoglycemia, CNS tumors, lack of air breaks, carbon monoxide poisoning, and opioid use.[22-25] Ocular side effects of HBOT can include cataract formation and temporary myopic refractory lens changes.[21] Claustrophobia or anxiety related to confinement within the hyperbaric chamber also can manifest in patients.[21]

This study is the first to report nausea and vomiting as a side effect in the frostbite HBOT population. This side effect in HBOT for emergency indications may limit the ability to complete the desired or recommended number of treatments. Most of the patients received opioids at some point

during their treatment; this likely is a major predisposing factor to this side effect. As a result, the present rate of side effects is 77.3%; however, majority of the side effects found were minor and successfully managed with no long-term sequelae.

LIMITATIONS

There are several limitations to this study. The study is retrospective with a limited sample size and short follow-up. Additionally, the bone scan was used as an adjunctive tool only and not to monitor the effect of HBOT with pretreatment and posttreatment scans. Thus, this study was unable to determine a correlation between the adjunctive use of HBOT to bone scans. Further research also needs to be conducted to assess the effectiveness of early (< 24 hours) versus delayed (> 24 hours) HBOT.

CONCLUSIONS

Frostbite injuries result from localized cold thermal injury and commonly result in long-term disability, particularly in those of low socioeconomic status. Adjunctive therapies are becoming more popular for treatment of these injuries. This is the largest series (22 cases) in the literature of patients with frostbite treated with HBOT as an adjunct to wound care. In half of the cases requiring amputation, there was an observed possible beneficial effect of HBOT, because final amputation level was distal to predicted level from pretreatment bone scans. Hyperbaric oxygen was relatively well-tolerated despite the high incidence of side effects. These side effects were successfully managed, resulting in full recovery, further adding to the literature in support of the safety of HBOT to treat frostbite.

ACKNOWLEDGMENTS

Affiliations: [1]Division of Plastic and Reconstructive Surgery, Department of Surgery, University of Ottawa, Ontario, Canada; [2]Department of Anesthesiology, University of Ottawa, The Ottawa Hospital General Campus, Ottawa, Ontario, Canada; and [3]Children's Hospital of Eastern Ontario, Ottawa, Ontario, Canada

Correspondence: Claudia Malic, MD, Children's Hospital of Eastern Ontario, 401 Smyth Road, Ottawa, Ontario K1H 8L1 Canada; cmalic@cheo.on.ca

Disclosure: The authors disclose no financial or other conflicts of interest.

REFERENCES

1. Millet JD, Brown RK, Levi B, et al. Frostbite: spectrum of imaging findings and guidelines for management [published online August 5, 2016]. *Radiographics.* 2016;36(7):2154–2169.
2. Haik J, Brown S, Liran A, et al. Deep frostbite: the question of adjuvant treatment. *Isr Med Assoc J.* 2016;18(1):56–57.
3. Hallam MJ, Cubison T, Dheansa B, Imray C. Managing frostbite. *BMJ.* 2010;341:c5864. doi: 10.1136/bmj.c5864.
4. McCauley RL, Hing DN, Robson MC, Heggers JP. Frostbite injuries: a rational approach based on the pathophysiology. *J Trauma.* 1983;23(2):143–147.
5. Mohr WJ, Jenabzadeh K, Ahrenholz DH. Cold injury. *Hand Clin.* 2009;25(4):481–496.
6. Higdon B, Youngman L, Regehr M, Chiou A. Deep frostbite treated with hyperbaric oxygen and thrombolytic therapies. *Wounds.* 2015;27(8):215–223.
7. Thom SR. Hyperbaric oxygen: its mechanisms and efficacy. *Plast Reconstr Surg.* 2011;127(Suppl 1):131S–141S.
8. Kemper TC, de Jong VM, Anema HA, van den Brink A, van Hulst RA. Frostbite of both digits of the foot treated with delayed hyperbaric oxygen: a case report and review of literature. *Undersea Hyperb Med.* 2014;41(1):65–70.
9. Gage AA, Ishikawa H, Winter PM. Experimental frostbite. The effect of hyperbaric oxygenation on tissue survival. *Cryobiology.* 1970;7(1):1–8.
10. Ledingham IM. Some clinical and experimental applications of high pressure oxygen. *Proc R Soc Med.* 1963;56:999–1002.
11. Okuboye JA, Ferguson CC. The use of hyperbaric oxygen in the treatment of experimental frostbite. *Can J Surg.* 1968;11(1):78–84.
12. Uygur F, Noyan N, Sever C, Gümüş T. The current analysis of the effect of hyperbaric oxygen therapy on the frostbitten tissue: experimental study in rabbits. *Cent Eur J Med.* 2009;4(2):198–202.
13. Hardenbergh E. Hyperbaric oxygen treatment of experimental frostbite in the mouse. *J Surg Res.* 1972;12(1):34–40.
14. Germonpre H. Hyperbaric oxygen in the treatment of burns – frostbite. 2014. Available at: https://www.sto.nato.int/publications/STO%20Educational%20Notes/STO-EN-HFM-245/EN-HFM-245-09.pdf.
15. Mekjavic IB, Gorjanc J, Mekjavic PJ, Bajrovic F, Milcinski M. Hyperbaric oxygen as an adjunct treatment of freezing cold injury. *Prev Cold Injuries.* 2005;16:1–4.
16. Hadanny A, Meir O, Bechor Y, Fishlev G, Bergan J, Efrati S. The safety of hyperbaric oxygen treatment – retrospective analysis in 2,334 patients. *Undersea Hyperb Med.* 2016;43(2):113–122.
17. Valnick S, Chasmar L, Clapson JB. Frostbite in the prairies: a 12-year review. *Plast Reconstr Surg.* 1993;92(4):633–641.
18. Tandara AA, Mustoe TA. Oxygen in wound healing–more than a nutrient. *World J Surg.* 2004;28(3):294–300.
19. Hopf HW, Gibson JJ, Angeles AP, et al. Hyperoxia and angiogenesis [published online February 17, 2004]. *Wound Repair Regen.* 2005;13(6):558–564.
20. Nylander G, Lewis D, Nordström, Larsson J. Reduction of postischemic edema with hyperbaric oxygen. *Plast Reconstr Surg.* 1985;76(4):596–603.
21. Heyboyer M 3rd, Sharma D, Santiago W, McCulloch N. Hyperbaric oxygen therapy: side effects defined and quantified. *Adv Wound Care* (New Rochelle). 2017;6(6):210–224.
22. Heyboer M 3rd, Jennings S, Grant WD, Ojevwe C, Byrne J, Wojcik SM. Seizure incidence by treatment pressure in patients undergoing hyperbaric oxygen therapy. *Undersea Hyperb Med.* 2014;41(5):379–385.
23. Banham ND. Oxygen toxicity seizures: 20 years' experience from a single hyperbaric unit. *Diving Hyperb Med.* 2011;41(4):202–210.
24. Hadanny A, Meir O, Bechor Y, Fishlev G, Bergan J, Efrati S. Seizures during hyperbaric oxygen therapy: retrospective analysis of 62,614 treatment sessions. *Undersea Hyperb Med.* 2016;43(1):21–28.
25. Seidel R, Carroll C, Thompson D, et al. Risk factors for oxygen toxicity seizures in hyperbaric oxygen therapy: case reports from multiple institutions. *Undersea Hyperb Med.* 2013;40(6):515–519.