Adjuvant Hyperbaric oxygen therapy (HBO_2)for treatment of necrotizing fasciitis reduces mortality and amputation rate.

S. J. ESCOBAR, J. B. SLADE, JR., T. K. HUNT, P. CIANCI

Department of Hyperbaric Medicine, Doctors Medical Center, San Pablo, CA; Department of Surgery, University of California, San Francisco, CA

Escobar S.J., Jr. Slade J.B., Hunt T.K., Cianci P. Adjuvant Hyperbaric oxygen therapy (HBO_2) for the treatment of necrotizing fasciitis reduces mortality and amputation rate. Undersea Hyperb Med 2005; 32(6):437-443. Objective: A retrospective analysis of 42 patients with necrotizing soft tissue infections treated with adjunctive HBO_2 to ascertain efficacy and safety. Overall mortality was 11.9% and morbidity 5%. Summary Background Data: Necrotizing soft tissue infections have historically high rates of mortality and morbidity, including amputation. Common misconceptions that prevent widespread use of adjunctive HBO_2 for this diagnosis include delays to surgery, increased morbidity, and significant complications. Methods: Forty-two consecutive patients (average age 56.1) with necrotizing fasciitis presenting to a major referral center were treated with adjunctive HBO_2 as part of an aggressive program of surgery, antibiotics, and critical care. Involved areas included the lower abdomen (15 patients), thigh and perineum (9 patients), flank (4 patients), lower leg (3 patients), and arm, shoulder, and axilla (2 patients). Co-morbidities included diabetes mellitus, chronic renal failure, intravenous drug abuse, peripheral vascular disease, and malignancy. Results: Mortality was 11.9% (5 patients). Both amputations (a finger and a penis), occurred prior to transport to our facility. The average number of surgical debridements was 2.8per patient; 1.25 performed prior to the start of HBO . The infectious process was controlled after an average of 7 HBO_2 treatments were administered to ensure successful wound closure. Complications consisted of only mild ear barotrauma in 3 patients (7%), and confinement anxiety in 17 (41%) but did not prevent treatment. Conclusion: Compared to national reports of outcomes with "standard" regimens for necrotizing fasciitis, our experience with HBO2, adjunctive to comprehensive and aggressive management, demonstrates reduced mortality (34% v. 11.9%), and morbidity (amputations 50% v. 0%). The treatments were safe and no delays to surgery or interference with standard therapy could be attributed to HBO_2.

INTRODUCTION

Necrotizing soft tissue infections encompass several previously named disease processes, including necrotizing fasciitis, Fournier's gangrene, necrotizing myositis (nonclostridial), and necrotizing cellulitis. There are approximately 1000 cases reported in the United States annually, making this a relatively rare disorder. The infections are usually polymicrobial and spread along subdermal fascial planes. Thrombosis of nutrient arteries to the skin may occur, thus producing areas of focal necrosis. The destruction of tissue is through liquefactive necrosis, which occurs as a result of many toxins, including hyaluronidase and lipase produced by the invading bacteria. "Walling off" of the infection by an inflammatory reaction does not occur. Clinically, these infections are marked by excruciating pain and the absence of clear local boundaries, and the visible degree

of involvement is substantially less than that of the underlying tissue.(1) In the early stage of necrotizing soft tissue infections, severe pain is disproportionate to the minor clinical findings.

Primary therapy consists of immediate and complete surgical excision of all nonviable tissue, broad-spectrum antibiotics, nutritional support, treatment of the underlying disorder, and continuous reevaluation of the wound. Most authors advocate routine surgical reexploration within 24 hours (2-4). Using the above therapeutic protocol, reported mortality rate remains high, ranging from 9-49%, with a cumulative average of 34% and a limb amputation rate reported as high as 50% (2,5). Several recent studies have demonstrated the most important factor in determination of mortality from necrotizing soft tissue infections is time from presentation to first surgery (2,3,5,6).

HBO_2 has been approved as adjunctive treatment for necrotizing soft tissue infections by the Undersea and Hyperbaric Medical Society (7) and is an accepted indication by the Center for Medicare Services (formerly Health Care Finance Administration/Medicare) and Medicaid (8). HBO_2 is defined as the intermittent systemic administration of 100% oxygen under pressure greater than atmospheric. The mechanism of action for treatment of the acute infectious process is through improvement of tissue oxygenation, enhancement of white blood cell oxygen dependent killing, reduction of edema, and enhancement of antimicrobial agents. Once the infection is halted, HBO_2 improves collagen formation and angiogenesis, thereby facilitating wound closure. Justification for hyperbaric oxygen use has been demonstrated through animal data, case studies, and retrospective clinical observations. A considerable body of basic data demonstrates the importance of oxygen for bacterial killing by leukocytes.(9-12) Still, its use has been controversial; several reports have suggested no benefit of adjunctive HBO_2.(13-15) Herein we report a low mortality and amputation rate in a relatively large experience of 42 patients.

METHODS

A retrospective analysis was performed of all patients treated with adjuvant HBO_2 at Doctors Medical Center in San Pablo, California (formerly Brookside Hospital), for necrotizing soft tissue infections between May 1983 and September 1997. This facility is a major referral center for HBO_2 in Northern California. A computer-generated search of an in-house database identified patients with the diagnosis of necrotizing fasciitis and/or necrotizing infection. Medical records were reviewed, and patients were identified with the diagnosis of necrotizing fasciitis, necrotizing process, Fournier's gangrene, and necrotizing myositis. Only patients with true necrotizing fasciitis were included in this study; the diagnosis of clostridial myonecrosis was excluded because this has been the convention developed by prior studies on the subject.

Factors analyzed were age, gender, co-morbid illness, site of infection, etiology of inoculation, white blood cell count, bacteria isolated, time from admission to operating room, time from admission to HBO_2, number of debridements total and prior to HBO_2, amputations, antibiotics, complications, number of hyperbaric oxygen therapies until process halted, and total number of therapies.

The patients included in this study underwent treatment from a multidisciplinary team approach involving surgery, infectious disease, critical care, and hyperbaric medicine. Early and aggressive surgery is the cornerstone of our protocol. The HBO_2 protocol involved successive treatments in a Sechrist monoplace hyperbaric chamber at pressures of 2.0-2.5 atmospheres absolute for a time period of 90-

120 minutes. Patients were treated on a twice daily regimen until progression of the infection was halted. Patients were then usually treated once daily for enhancement of wound healing at the request of the treating surgeon.

RESULTS

Forty-two patients underwent the treatment protocol. The average age was 56.1 years (range 22-84) and included 19 females and 23 males. Tables 1 and 2 demonstrate etiology of inoculation and co-morbid illness, respectively. Eighty-one percent of patients had white blood cell counts >12,000. Table 3 demonstrates site of infection. Polymicrobial organisms were isolated in 36/42 (85.7%) patients. Of the monomicrobial organisms, 2/42 (5%) patients isolated group A beta hemolytic streptococci, 1 patient grew Serratia sp., 1 Pseudomonas sp., 1 Staphylococcus sp., and 1 Enterobacter sp. All patients were placed on broad spectrum antibiotics until culture sensitivities were known. The average time from admission to the first operation was 56.8 hours, and included individuals transferred from other facilities to first debridement at this institution. The average number of debridements was 2.8 per patient; 1.25 performed prior to the start of HBO_2. The mean time from admission until initiation of HBO_2 was 69 hours; an average of 7 treatments was required to halt progression of the infection. The average total number of treatments per patient for enhancement of wound healing and preparation for split thickness skin grafts was 23.6. There were 2 amputations (one finger and one penis) which occurred prior to transfer to our facility and therefore prior to hyperbaric treatments. No amputations were required after the patients were in our care. Five of the patients succumbed to the disease for a mortality rate of 11.9%. Seventeen of 42 patients experienced mild confinement anxiety during the early course of their treatment. This was easily managed by mild sedation. Three of 42 patients experienced mild barotrauma of the ear.

DISCUSSION

A large body of experimental evidence ranging from animal models to basic data on intracellular killing of bacteria supports the use of HBO_2 (9-12). The mechanisms of action of hyperbaric therapy are primarily related to hyperoxygenation of tissues and are mediated via nitric oxide pathways. At 3.0 atmospheres absolute (the pressure equivalent of 66 feet of seawater) an arterial PO_2 of up to 2200 mmHg is achieved. This correlates to 6.9 volume percent dissolved oxygen in the plasma, a quantity sufficient to maintain life in the absence of hemoglobin (16). In this hyperoxygenated environment, appreciable diffusion of oxygen occurs up to 280 microns away from the capillary wall, which, under normobaric conditions, occurs out to only 30

TABLE 1

ETIOLOGY OF INOCULATION	NO. OF PATIENTS
Idiopathic	13
Abscess	9
Trauma	6
"Skin popping" illicit drugs	4
Surgery	4
Wound	3
Sepsis	1
Urethral	1
Condyloma accuminata	1

TABLE 2

CO-MORBID ILLNESS	NO. OF PATIENTS
Diabetes mellitus	18
Chronic renal failure	4
IV drug abuse	4
Malignancy	4
Coronary artery disease	3
Peripheral vascular disease	2
Sarcoidosis	2
Hamman-Rich syndrome	1
Cirrhosis	1
Nephritis	1

microns. In low oxygen tensions (5-15 mmHg) polymorphonuclear leukocytes demonstrate a decreased ability to kill organisms through the oxygen-dependent peroxidase systems. HBO_2 increases tissue PO_2 levels, thereby increasing the polymorphonuclear leukocyte's killing ability (9,12,17,18). HBO_2 has also been demonstrated to decrease edema and ameliorate ischemia-reperfusion injury (19). This may be accomplished by preventing or reversing the adherence of leukocytes to the endothelium and subsequent degranulation, thus reducing endothelial damage (20-25).

TABLE 3

SITE OF INFECTION	NO. OF PATIENTS
Perineum > abdomen	15
Thigh > perineum	5
Thigh	5
Arm	4
Neck	4
Thigh > flank	4
Leg	3
Arm > shoulder . axilla	2

Several studies have shown that increased oxygen tensions stimulate wound healing in ischemic tissues. Increased tensile strength in incisional wounds in rats with the administration of HBO_2 at 2 atmospheres absolute for 120 minutes twice daily has been demonstrated (26). The concentration of RNA/DNA ratio of connective tissue has been found to increase under hyperoxic conditions. Although mitogens, which stimulate fibroblast replication, and angiogenesis factor, which stimulates capillary budding, are released by macrophages in hypoxic environments, oxygen is essential for the synthesis of collagen by the fibroblasts (27-29). Recent evidence indicates that vascular endothelial growth factor is also stimulated by oxidants that are increased in the presence of hyperoxia (30,31). A minimum tissue PO_2 of 30 mmHg is necessary for collagen synthesis. HBO_2 administration allows for optimal oxygenation of tissue adjacent to and distant from capillaries and thereby enhances wound healing (32,33). Hirn demonstrated enhancement of wound healing and earlier wound closure in his animal model. After treating animals with experimental necrotizing infection with surgical debridement and antibiotics, it was noted that of the surviving rats, 82.5% of those who underwent hyperbaric oxygen treatment had complete healing of their wounds; whereas, only 12.5% of controls experienced complete closure (34).

Our series of patients demonstrates a remarkably low mortality in seriously ill patients, 11.9% (n = 42), from necrotizing fasciitis with the addition of HBO_2 to the "standard" regimen despite an average delay to surgery of 56.8 hours. A retrospective report by McHenry et al., found an overall mortality rate of 29% (n = 65) at a university center which did not utilize HBO_2, ostensibly to avoid delaying surgery, and has not been subjected to a randomized prospective controlled study. A metanalysis of 696 patients treated for necrotizing soft tissue infections without the use of HBO_2 demonstrated a cumulative mortality rate of 34% (2). Several other authors have also reported a reduction in mortality with the addition of HBO_2. Riseman found a 23% mortality rate versus 66% in the non-HBO_2 group (n = 29)(35). Hollabough et al., reported a 7% mortality rate in the hyperbaric oxygen-treated group versus 42% in the non-HBO_2 (n = 26) when adjunctive HBO_2 was used in the treatment of Fournier's gangrene (36). Patients receiving HBO_2 had an eleven times greater chance of survival. Whitesides et al., (37) and Scher (38) reported no deaths in a series of cervical necrotizing fasciitis patients treated with adjunctive HBO_2.

Limb amputation rate in necrotizing soft tissue infections has been reported as high as 50% without the use of HBO_2 (2). In our patients, two amputations were performed,

both of which occurred at transferring facilities where HBO_2 was not available. Two subsequent debridements along with HBO_2 were required after transfer of these individuals to our hospital, indicating continued progression of infection at the time of transfer to this facility. In his review of 198 consecutive patients with documented necrotizing soft tissue infections Elliott reported early wound closure in patients receiving HBO_2 – 28 days vs. 48 days – an average reduction in length of stay of 20 days (5). Length of stay is the major factor contributing to cost of medical care. In our series, continued hyperbaric oxygen was provided as an adjunct to wound closure and only when requested by the reconstructive surgeon. Closure of the debridement sites in the patient can be problematic, often necessitating rotation flaps (6).

Several authors argue that HBO_2 may adversely affect the care of the patient by causing a delay in surgical debridement while the patient is undergoing HBO_2 (2,39). We found no instances in our population where HBO_2 delayed definitive operative procedures. In many instances the patient was brought from the operative recovery room to the hyperbaric chamber. Such cooperation and coordination between the specialties is mandatory for a good outcome.

In our experience an average of seven treatments was given before we considered that the infectious process was halted. Cessation of the infection was determined by surgical tissue biopsy in most instances. In Brown's study, which found no statistically significant difference in hyperbaric oxygen vs. non-hyperbaric oxygen treatment (a 12% increased survival was reported in the hyperbaric oxygen group), 80% of those treated with hyperbaric oxygen received less than five treatments (13). The average time from admission to the first operation for our patients was 56.8 hours. This delay, commonly reported, is primarily due to late referral. McHenry found that the average time from admission to operation in nonsurvivors was 90 hours and in survivors was 25 hours (2). Surgical delay is a major factor affecting survival. A recent study showed 66.7% mortality when aggressive surgical debridement was delayed more than 48 hours (6).

The most common complication from HBO_2 was mild confinement anxiety in 40% of patients. In most cases this was easily managed with the administration of low doses of a benzodiazepine prior to entrance into the monoplace chamber. With the use of a larger multiplace chamber, the incidence of confinement anxiety is as low as 2% (40). The second most common complication found in this study was mild otic barotrauma, which occurred at a rate of 7%. The use of slow pressurization and depressurization rates (one pound per square inch per minute) aid in equilibration of air-filled cavities. Pressure equalization tubes through the tympanic membrane are recommended for individuals who have difficulty equalizing as well as the patient with an altered sensorium. There were no instances of pneumothorax or seizures in our study.

CONCLUSION

In conclusion, we found:

- No instances of delay or surgery
- A decrease in mortality vs. previously recorded series literature
- A decrease in morbidity (essentially no limb amputations) with the addition of HBO_2 to the standard therapeutic protocol for necrotizing soft tissue infections

Since it is not possible to create a prospective protocol in which "case severity" is

equally apportioned to each group, it is highly unlikely that a controlled comparison can be made. Only accumulated experience can be offered. We suggest that HBO_2 is a valuable adjunct in the treatment of this rare but serious disease, allowing more rapid control of the infectious process, a reduction in morbidity, and facilitation of earlier closure. These data are in agreement with recent cumulative reports showing a reduction in mortality, morbidity, and amputation rate when hyperbaric oxygen is utilized as part of an aggressive team approach to this difficult disease (41).

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