Adjunctive hyperbaric oxygen therapy in the treatment of thermal burns

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ABSTRACT / RATIONALE

A significant and consistently positive body of evidence from animal and human studies of thermal injury support the use of hyperbaric oxygen as a means of preventing dermal ischemia, reducing edema, modulating the zone of stasis, preventing partial- to full-thickness conversion, preserving cellular metabolism and promoting of healing. The vast majority of clinical reports have shown reduction in mortality, length of hospital stay, number of surgeries and cost of care. Hyperbaric oxygen has been demonstrated to be safe in the hands of those thoroughly trained in rendering therapy in the critical care setting and with appropriate monitoring precautions. Careful patient selection is mandatory.

BACKGROUND

The National Burn Repository viewed the combined data of acute burn admissions for the time period between 2002 and 2011 in its 2012 report. Key findings were as follows: 91 hospitals from 35 states reported a total of 183,036 records. Seventy-five of the 91 hospitals contributed more than 500 cases. Seventy percent of burn patients were men with a mean age of 32 years in all cases. Children under the age of 5 accounted for 19% of the cases, whereas patients 60 or older represented 12%.

Seventy-two percent of reported total burn sizes were less than 10% total body surface area (TBSA), and these cases had a mortality rate of 0.6%. Overall mortality rate for all cases was 3.7%; flame burn mortality was 6.4%. The most common causes of burns were fire/flame and scalds, and these accounted for eight of 10 burns reported. Scalds are more prevalent in children, while fire and flame injuries dominated the remaining age category.

Most cases of burn injury (69%) occurred in the home. During the 10-year period from 2002 to 2011 the average length of hospital stay for both males and females declined from roughly 11 and 10 days, respectively, to eight days overall. The mortality rate decreased from 4.8% to roughly 3% for males and from 5.4% to 3% for females.

Deaths from burn injury increase with advancing age and burn size. The presence of inhalation injury in patients under the age of 60 and with a TBSA of 0.1-19.9% increased the likelihood of death by a factor of 16.

Pneumonia is the most frequently encountered complication and occurred at a rate of 6.1% for fire- or flame-injured patients and was more frequent among patients with four or more days on mechanical ventilation. For survivors, the average length of stay was slightly greater than one day per percent TBSA. For example, a 60% TBSA burn would be expected to be hospitalized for approximately 60 days.

Patients who died with burns below 70% TBSA usually did so within three weeks of admission. Larger burns were fatal in one week. The vast majority of burn cases admitted to burn units are 20% TBSA and less. Indeed, most are between 0.1% and 9.9%. Only 4% of cases present with burns greater than 40% TBSA.

The combination of thermal burn and concurrent inhalation injury or trauma increased mortality significantly. Overall, a 50-60% TBSA burn carries a mortality of approximately 37%. In the age group 20-29 years, mortality with a 60% burn is 19.5%. The same area of TBSA in a 60- to 69-year-old patient is 67%. Thus, age is an important factor in determination of outcome.

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Burn care is extraordinarily expensive. Charges for a 50-59% TBSA averaged $831,193 in 2012. A 60-70% burn incurs a cost of $851,970. Medicaid, Medicare or other government reimbursement represents 28.6% of burn patients; 31% is represented by private, commercial, charity or other; Workers Compensation or automobile insurance covers 9.9%; and "no information provided" or self-insured is indicated in 29% of cases.

Significant morbidity attaches to burn injury. Pneumonia, cellulitis, respiratory failure, urinary tract infection, wound infection and sepsis are the most frequently reported complications and significantly add to mortality [1].

Therapy of burns, therefore, is directed toward minimizing edema, preserving marginally viable tissue in the zone of stasis, protecting the microvasculature, enhancing host defenses and providing the essential substrate necessary to maintain viability. The ultimate goals of burn therapy include survival of the patient, rapid wound healing, minimization of scarring or abnormal pigmentation and cost effectiveness. Optimal outcome is restoration, as nearly as possible, to the pre-burn quality of life [2].

PATHOPHYSIOLOGY

Physiologic responses to a major burn include a fall in arterial pressure, tachycardia, a progressive decrease in cardiac output and stroke volume. Metabolic responses are complex and include metabolic acidosis and hyperventilation. Cellular adenosine triphosphate levels fall, resting cell membrane potential decreases, and an intracellular accumulation of sodium, calcium and water is paralleled by a loss of cellular potassium.

Immunologic responses include alteration of macrophage function and perturbation of cellular and humoral immunity [3]. The burn wound is a complex and dynamic injury characterized by a zone of coagulation, surrounded by an area of stasis, and bordered by an area of erythema [4]. The zone of coagulation or complete capillary occlusion may progress by a factor of 10 during the first 48 hours after injury. This phenomenon is three-dimensional; thus, the wound can increase in size and depth during this critical period.

Local microcirculation is compromised to the greatest extent during the 12 to 24 hours post-burn. Burns are in this dynamic state of flux for up to 72 hours after injury [3]. Ischemic necrosis quickly follows. Hematologic changes include platelet microthrombi and hemoconcentration in the post-capillary venules. Edema formation is rapid in the area of injury secondary to increased capillary permeability, decreased oncotic pressure, increased interstitial oncotic pressure, changes in the interstitial space compliance and lymphatic damage [5]. Edema is most prominent in directly involved burned tissues but also develops in distant uninjured tissue, including muscle, intestine and lung. Changes occur in the distant microvasculature, including red cell aggregation, white cell adhesion to venular walls and platelet thromboemboli [6].

Inflammatory mediators are elaborated locally, in part from activated platelets, macrophages and leukocytes and contribute to the local and systemic hyperpermeability of the microcirculation, appearing histologically as gaps in the venular and capillary endothelium [7]. This progressive process may extend dramatically during the first early days after injury [8,9].

The ongoing tissue damage in thermal injury is due to multiple factors, including the failure of surrounding tissue to supply borderline cells with oxygen and nutrients necessary to sustain viability [4]. Impediment of the circulation below the injury results in dessication of the wound, as fluid cannot be supplied via the thrombosed or obstructed capillaries. Topical agents and dressings may reduce but cannot prevent the dessication of the burn wound and the inexorable progression to deeper layers. Altered permeability is not caused by heat injury alone; oxidants and other mediators (prostaglandins, kinins and histamine) all contribute to vascular permeability [10].

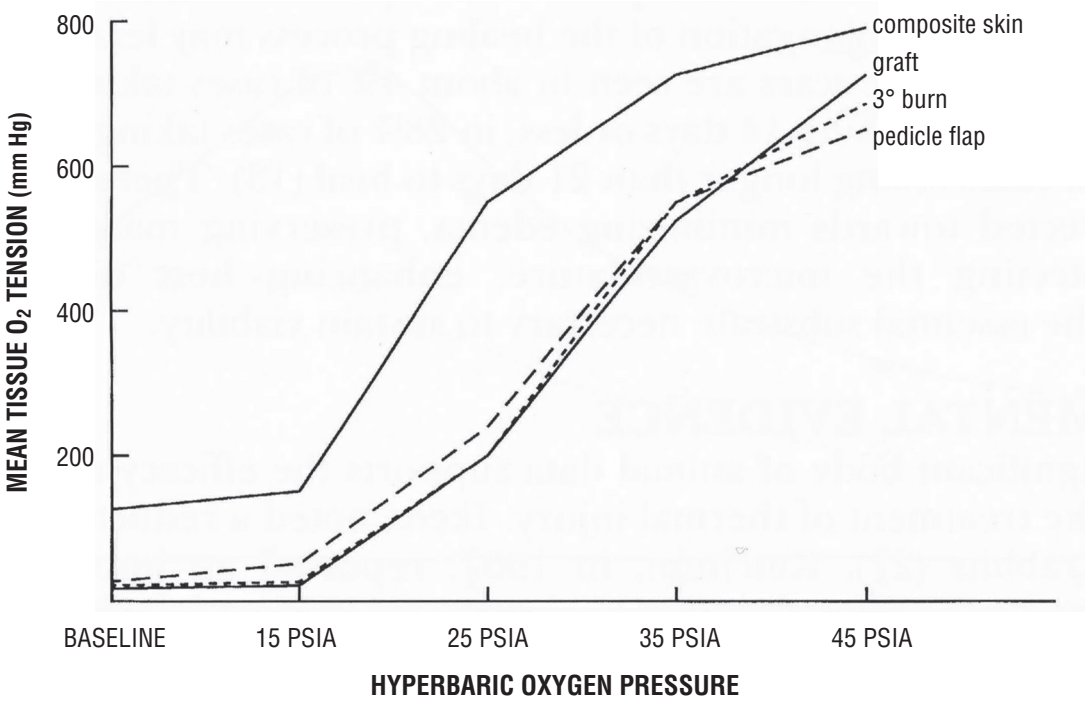
Neutrophils are a major source of oxidants and injury in the ischemia/reperfusion mechanism. This complex may be favorably affected by several interventions. Therapy is focused on the reduction of dermal ischemia, reduction of edema and prevention of infection. During the period of early hemodynamic instability, edema reduction has a markedly beneficial effect as well as modulating later wound conversion from partial- to full-thickness injury [11].

INFECTION

Infection remains the leading overall cause of death from burns. Susceptibility to infection is greatly increased due to the loss of the integumentary barrier to bacterial invasion, the ideal substrate present in the burn wound, and the compromised or obstructed microvasculature which prevents humoral and cellular elements from reaching the injured tissue.

Additionally, the immune system is seriously affected, demonstrating decreased levels of immunoglobulins, serious perturbations of polymorphonuclear leukocyte function [12,13], including disorders of chemotaxis, phagocytosis and diminished killing ability. These

FIGURE 1 – Tissue oxygen tension



Mean oxygen tension of normal skin and various hypoxic tissues as a function of hyperbaric oxygen pressure. Note: Oxygen tension rises in burned skin only with increasing pressure.

functions greatly increase morbidity and mortality. Certain patients with specific polymorphisms in the tumor necrosis factor and bacterial recognition genes may have a higher incidence of sepsis than the burn injury alone would predict [14]. More recently, fungal infections have become a therapeutic challenge [15].

Regeneration cannot take place until equilibrium is reached; hence, healing is retarded. Prolongation of the healing process may lead to excessive scarring. Hypertrophic scars are seen in about 4% of cases taking 10 days to heal, 14% of cases taking 14 days or less, 28% of cases taking 21 days to heal, and up to 40% of cases taking longer than 21 days to heal [16].

EXPERIMENTAL DATA

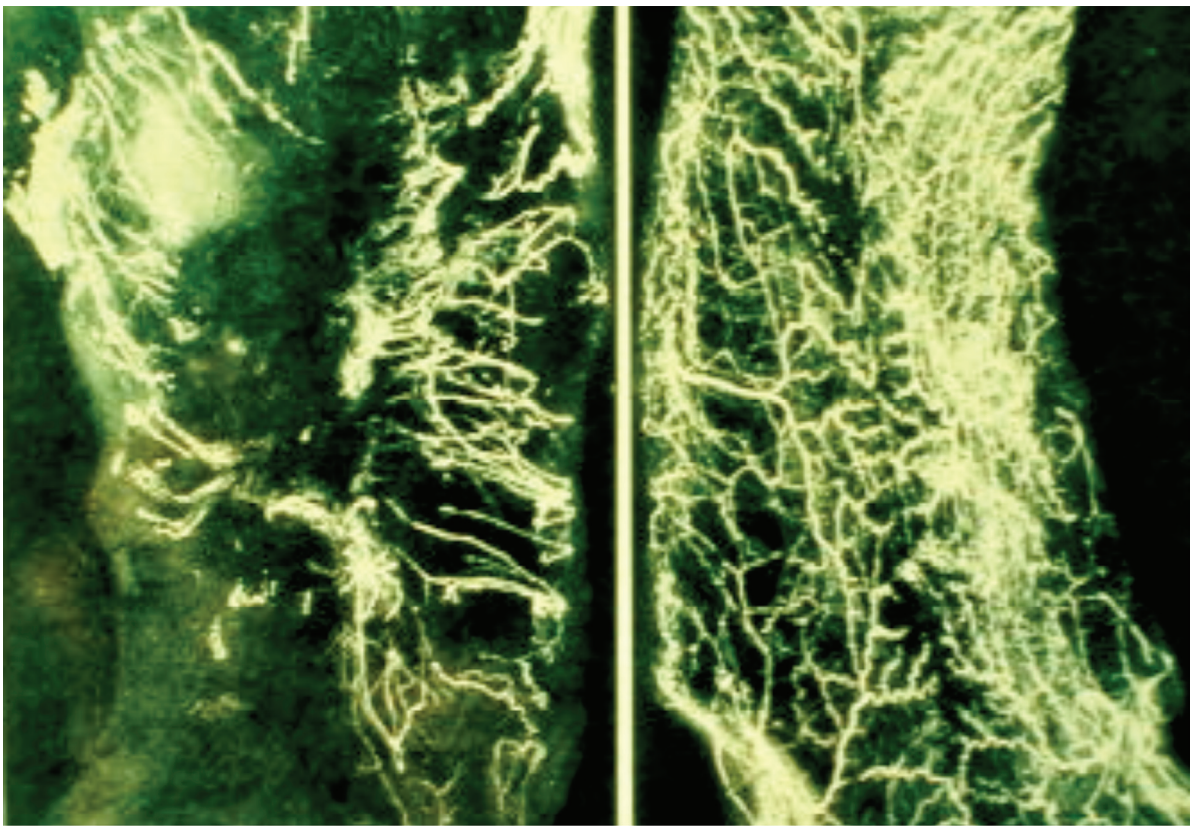
The efficacy of hyperbaric oxygen (HBO_2) in the treatment of thermal injury is supported by animal studies and human clinical data. Edema reduction with HBO_2 therapy has been demonstrated in burned rabbits [17], rats [18], mice [19] and guinea pigs [20,21]. Improvement in healing time has been reported in burned rabbits [22] and rats [23,24]. Decreased infection rates were an additional observation noted in these models [22,23].

In a seminal study in 1970 Gruber *(Figure 1)* demonstrated that the area subjacent to a third-degree burn was hypoxic when compared to normal skin and that the tissue oxygen tension could be raised only by oxygen administered at pressure [25]. Ketchum, in 1967, reported an improvement in healing time and reduced infection in an animal model [22]. He later demonstrated dramatic improvement in the microvasculature of burned rats treated with hyperbaric oxygen therapy [23] *(Figure 2)*.

In 1974, Hartwig [18] confirmed these findings and additionally noted less inflammatory response and suggested hyperbaric oxygen might be a useful adjunct to the technique of early debridement. Wells and Hilton *(Figure 3)*, in a carefully designed and controlled experiment, reported a marked decrease (35%) in extravasation of fluid in 40% of flame-burned dogs [26]. The effect was clearly related to oxygen, and not simply to increased pressure. A reduction in hemoconcentration and improved cardiac output were also noted.

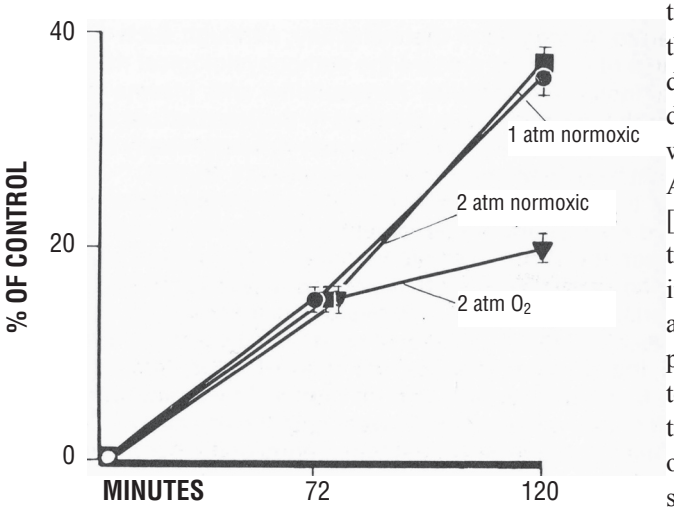
Nylander *(Figure 4)* [19] in a well-accepted animal model showed that hyperbaric oxygen therapy reduced the generalized edema associated with burn injury.

FIGURE 2 – Capillary state: Control *vs.* HBO_2



Left panel: Capillary disorganization, inflammation and leakage of contrast agent in control *vs.* **Right panel:** Restoration organized capillary arcades and intact circulation in HBO_2-treated animal.

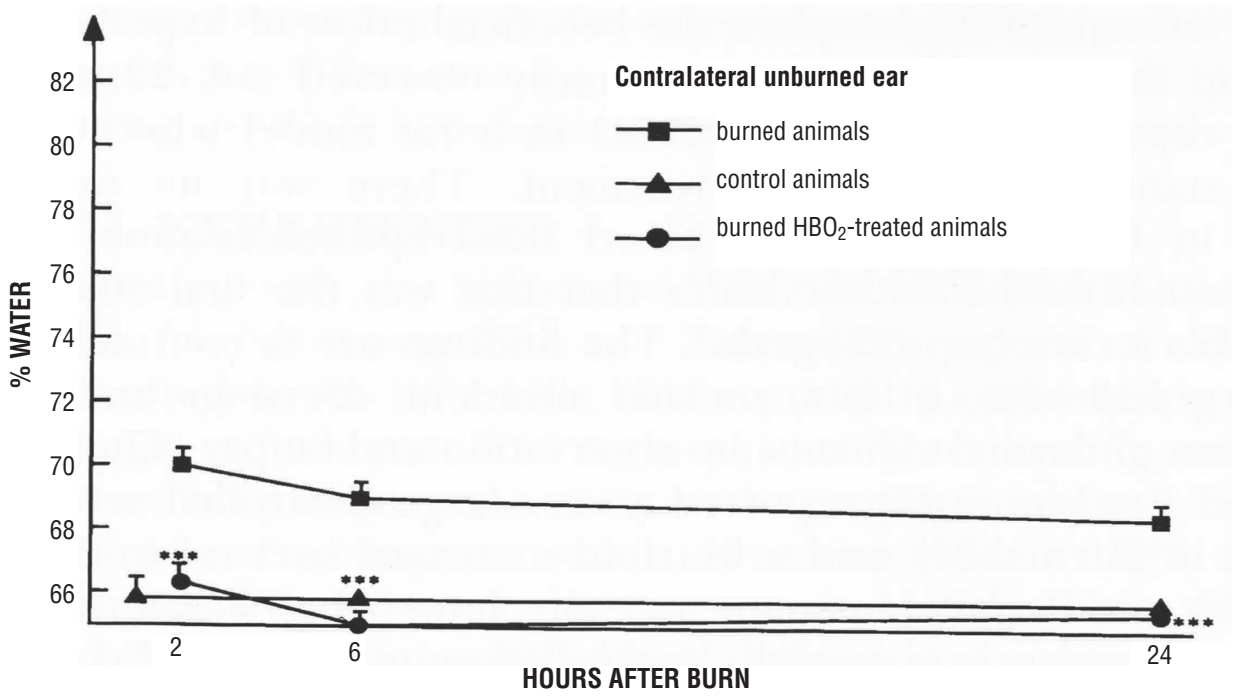
FIGURE 3 – Plasma volume losses



Plasma volume losses after burn in untreated animals (1 atm abs, normoxic), animals exposed to hyperbaric oxygen (2 atm abs, O_2) and to pressure alone (2 atm abs, normoxic).

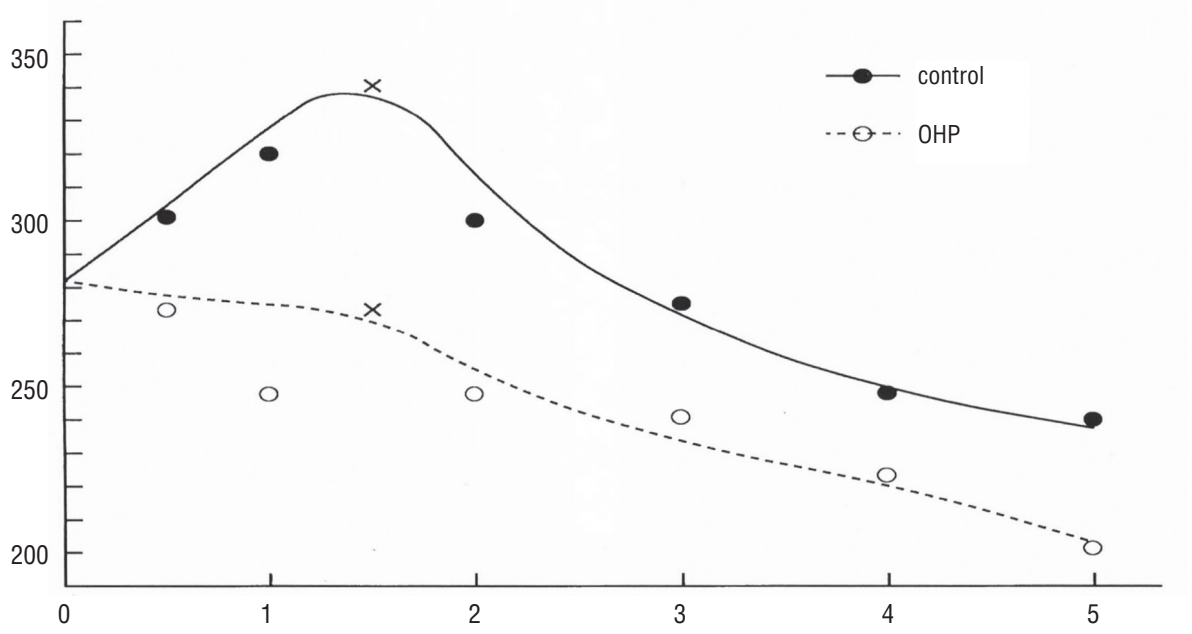
Kaiser *(Figure 5)* reported that hyperbaric oxygen treatment resulted in shrinkage of third-degree (full-thickness) injury in a rabbit model. Untreated animals demonstrated the expected increase in wound size during the first 48 hours. At all times treated animal wounds remained smaller than those of the controls. A reduction in subcutaneous edema was also observed [20,21]. Stewart and colleagues subjected rats to controlled burn wound resulting in deep partial-thickness injury. Both experimental groups were treated with topical agents. The hyperbaric oxygen-treated animals showed preservation of dermal elements, no conversion of partial- to full-thickness injury, and preservation of adenosine triphosphate (ATP) levels. The untreated animals demonstrated marked diminution in ATP levels and conversion of partial- to full-thickness injury *(Figures 6,7)* [27,28].

FIGURE 4 – Water content of the contralateral unburned ear



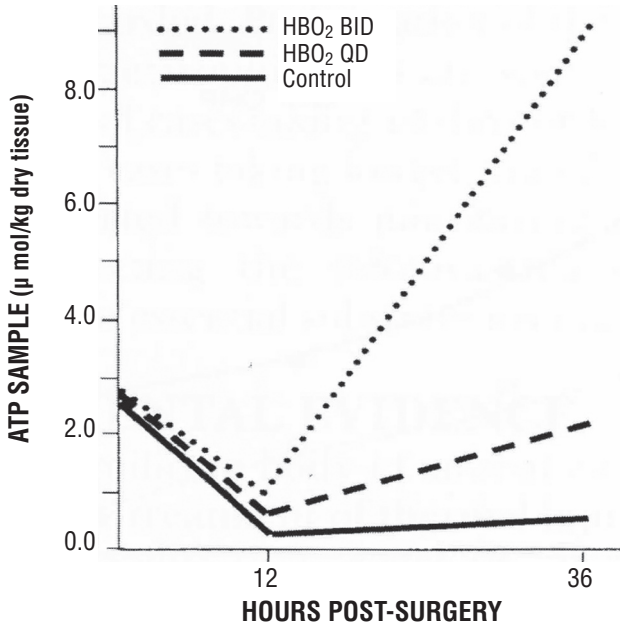
Water content (± SEM) of the contralateral unburned ear in burned animals with and without HBO_2 treatment.

FIGURE 5 – Tissue oxygen tension



Kaiser demonstrated in a full-thickness animal model a significant reduction of wound size in the hyperbaric-treated animals (open circles) *vs.* an increase in the control group, which remained larger at all times measured.

FIGURE 6 – Rats: burn with sulfadiazine dressing

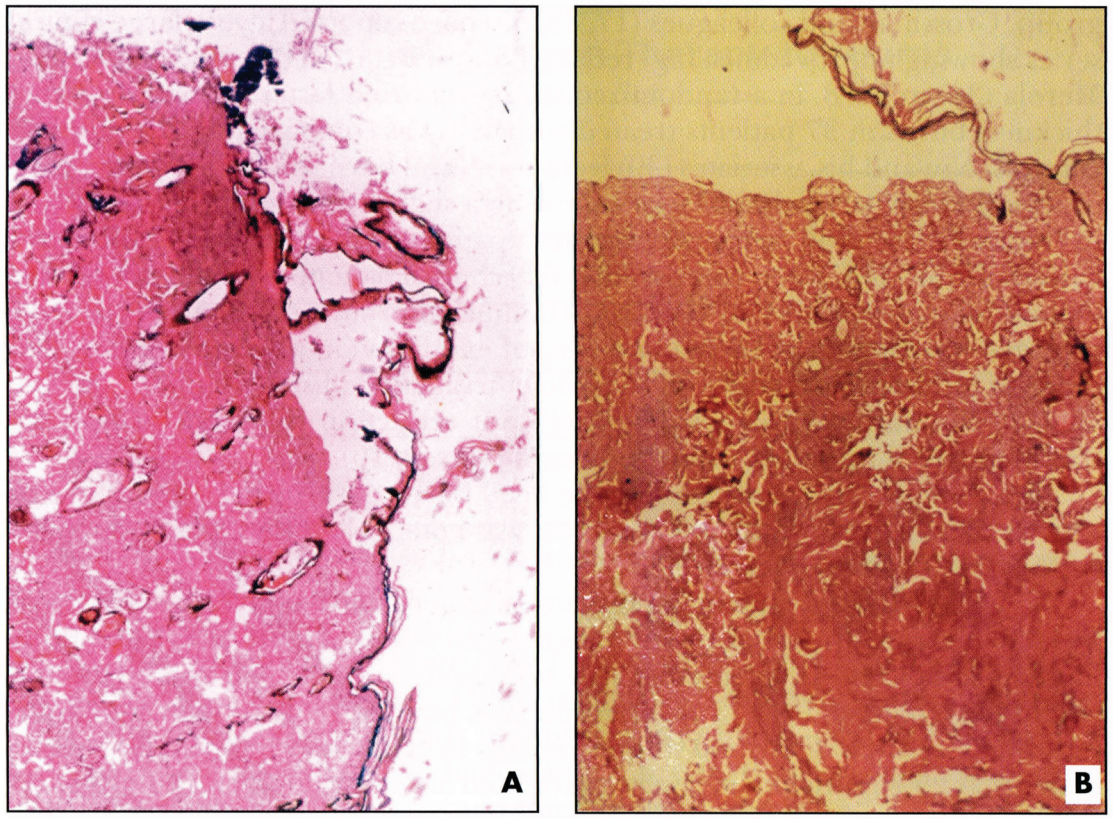


These studies may relate directly to the preservation of energy sources for the sodium pump. Failure of the sodium pump is felt to be a major factor in the ballooning of the endothelial cells, which occurs after burn injury and subsequent massive fluid losses [8]. Germonpré reported decreased extension of burn injury with HBO_2 [29]. HBO_2 has also been shown to dramatically improve the microvasculature of burned rats (Hartwig, Ketchum [18,23]). In guinea pigs, earlier return of capillary patency ($p<0.05$) was demonstrated using an India ink technique [30].

Miller and Korn reported faster re-epithelialization ($p<0.001$) from these regenerative sites in guinea pigs treated with HBO_2 *vs.* controls. The observed decrease in wound desiccation in the HBO_2-treated group was due to preservation of capillary integrity in the zone of stasis [10].

Saunders similarly reported improved dermal circulation, preservation of dermal elements, and less collagen denaturation with HBO_2 treatments [31]. Perrins, in a

FIGURE 7a-b – Partial-thickness burns



(A) Left: HBO_2-treated animals show preservation of the dermal elements.
(B) Right: Non-treated animals show coagulation necrosis.

porcine scald model, failed to demonstrate modification of progressive tissue destruction. However, oxygen was administered at 2 atm abs for only one hour, and treatment occurred over only a one-day period. No vascular studies were undertaken. It was also noted that the porcine model may not be appropriate given the fact that pigs are resistant to skin infection naturally, that pigs do not form a blister following scald wound injury and that pigs do not share many dermal elements with humans, including cutaneous sweat glands [32]. Niccole reported that HBO_2 provided no advantage in the treatment of full-thickness and partial-thickness burns alone or in combination with topical antibiotic therapy in controlling bacterial counts in a rat model. However, despite a treatment delay of 12 hours, hyperbaric oxygen significantly reduced the time to complete epithelialization in a partial-thickness burn injury [24].

The pathophysiologic changes within the burn wound show a striking similarity to those noted in the ischemia reperfusion injury, *i.e.*, depletion of ATP, production of xanthine oxidase, lipid peroxidation, activation of polymorphonuclear cells with subsequent endothelial adherence and generation of reactive oxygen species (ROS) [33-36].

Recent data regarding HBO_2 cardiac preconditioning (inducing cellular tolerance and protection from ischemia) and adaptive responses resulting in cardioprotection and attenuation of ischemia-reperfusion injury are mediated by HBO_2-induced ROS (*e.g.*, superoxide and hydrogen peroxide) that stimulate the production of nitric oxide. HBO_2-induced reactive oxygen species (ROS) are known to initiate gene expression and reduce neutrophil adhesion (via a decrease in CDl1a/18 function, *P*-selectin and down-regulation of intracellular adhesion molecule-1). HBO_2 also decreases lipid peroxidation, stimulates neovascularization and increases antioxidants, thus resulting in cardioprotection [37]. Elucidation of these mechanisms for cardioprotection may provide further understanding of the mechanisms whereby hyperbaric oxygen is of benefit in acute thermal injury.

In a model of reperfusion injury Zamboni demonstrated that hyperbaric oxygen is a potent blocker of white cell adherence to endothelial cell walls in skeletal muscle, interrupting the cascade that causes vascular damage [38]. The mechanism is felt to be an inhibitory effect on the CD18 locus [39]. As discussed by Wasiak *et al.* [40], inhibition of beta 2-integrin activation of intracellular adhesion molecule one (ICAM-1) [41] enables tissues to maintain microvascular flow in areas otherwise subject to the well-described "secondary injury" following a thermal burn [6]. This effect persists for some hours, as demonstrated by both Ueno [42] and Milijkovic-Lolic [43]; Germonpré's data support this observation and may explain the beneficial effect of hyperbaric oxygen therapy on the microcirculation previously observed [18,27-29,31].

Shoshani reported no benefit of HBO_2 in a rat burn model where all animals received standard sulfadiazine treatment [44]. There was no difference in burn wound size, re-epithelialization rate, Doppler blood flow or healing. In this report, the author erroneously stated that this was the first study utilizing standard burn care (topical agents). These findings contradict the earlier study by Stewart's group, who utilized silver sulfadiazine dressings and confirmed preservation of dermal elements [27,28] and might be explained by methodological differences.

Bleser and Benichoux, in a very large controlled study in a rat model of 30% body surface area (BSA) burns, reported reduced burn shock and a fourfold increased survival in HBO_2-treated animals *vs.* controls [45]. Tenenhaus and colleagues showed reduction in mesenteric bacterial colonization ($p<0.005$) in an HBO_2-treated burned mouse model [46]. Bacterial translocation is felt to be a major source of burn wound infection.

In 2005 Magnotti *et al.* proposed an evolution from bacterial translocation to gut ischemia-reperfusion injury after burn injury as the pathogenesis of multiple organ dysfunction syndrome. Systemic inflammation, acute lung injury and multiple organ failure after a major thermal injury are relatively common causes of morbidity and mortality. In the normal host, the intestinal mucosa functions as a major local defense barrier, a component of multiple defense mechanisms that helps prevent gut bacteria, as well as their products, from crossing the mucosal barrier. After a major thermal injury, and in other clinical and experimental situations, this intestinal barrier function becomes overwhelmed or impaired, resulting in the movement of bacteria and/or endotoxin to the mesenteric lymph nodes and systemic tissues, defined as bacterial translocation. The importance of this intestinal barrier function becomes clear when considering that the distal small bowel and colon contain 10^{10} concentrations of anaerobes and 10^5 to 10^8 each of Gram-positive and Gram-negative aerobic and facultative microorganisms per gram of tissue, and enough endotoxin to kill the host thousands of times over [47].

Loss of gut barrier function and a resultant gut inflammatory response lead to the production of proinflammatory factors; this can cause a septic state, leading

to distant organ failure. Splanchnic hypoperfusion leading to gut ischemia-reperfusion injury appears to be the dominant hemodynamic event, triggering the release of biologically active factors into the mesenteric lymphatics. The benefits of the early use of hyperbaric oxygen in burn victims may in part be mediated through amelioration of gut reperfusion injury.

The beneficial effects of HBO_2 in ischemic-reperfused tissues have been demonstrated in intestine [48], skeletal muscle [38,49], brain [50-52] and testicular tissue [53), and myocardium [54-57]. In a study of severely burned humans (>30% TBSA), HBO_2-treated patients compared to controls had increased levels of serum-soluble interleukin-2 receptor ($p<0.05$) and decreased plasma fibronectin ($p<0.01$), resulting clinically in a lower incidence of sepsis ($p<0.05$) [58].

Total enteral nutrition, starting as early as possible after thermal injury, is recommended for burn patients. It results in decreased morbidity and mortality, and supports intestinal structure and function. Studies of intestinal barrier function biology, pathophysiology and consequences of gut barrier failure demonstrate that the ischemic and/or stressed gut can become a proinflammatory organ [59], and gut-derived factors liberated after periods of splanchnic hypoperfusion can lead to acute distant organ, cellular dysfunction and activation of neutrophils and other proinflammatory cells [60].

Reduction of PMNL-killing ability in hypoxic tissue has been well documented [61,62]. The ability of hyperbaric oxygen to elevate tissue oxygen tension and the enhancement of PMNL killing in an oxygen-enriched animal model as demonstrated by Mader [63] suggest that this may be an additional benefit of HBO_2. Hussman and colleagues have shown no evidence of HBO_2-induced immunosuppression in a carefully controlled animal model [64].

In a 2005 randomized controlled study (Bilic) evaluated the effects of HBO_2 on burn wound healing. Standard deep second-degree burns were produced in male Wistar rats treated with silver sulfadiazine and then randomly assigned to either a normoxic, placebo gas or to 2.5 atmospheres absolute (atm abs) HBO_2 for 60 minutes for a total of 21 sessions. HBO_2 had a beneficial effect on post-burn edema ($p=0.022$), neoangiogenesis ($p=0.009$), numbers of regenerative active follicles ($p=0.009$), and time to epithelial regeneration ($p=0.048$). There were no significant differences in necrosis staging or margination of leukocytes. The authors conclude that the data support earlier conclusions that HBO_2 is of benefit in the healing of burn wounds [65].

Turkaslan *et al.* [66] reported that hyperbaric oxygen treatment reduced progression of the zone of stasis in the first 24 hours after injury and accelerated the healing process by supporting neoangiogenesis. Prevention of progression in the zone of stasis is a major goal in burn therapy. This report lends further credence to the previously cited work of Miller, Korn, Hartwig and Ketchum.

HBO_2 has been shown to mobilize stem/progenitor cells in both humans and mice by stimulating bone marrow stromal cell type 3 (endothelial) nitric oxide synthase [67-71]. Findings indicate that some of the mobilized cells will home to peripheral sites where they function as *de novo* endothelial progenitor cells (EPCs), contributing to wound vasculogenesis, a complement to local angiogenesis. Additionally, at peripheral sites HBO_2 stimulates stem cell growth and differentiation by engaging a physiological autocrine loop responsive to oxidative stress, much the same as lactate [72,73]. HBO_2 stimulates peripheral site EPCs recruitment and differentiation via a pathway involving thioredoxin-1, hypoxia-inducible factors-1 (HIF-1) and HIF-2. These findings provide new insight into possible mechanisms for the known clinical benefits of hyperbaric oxygen in burn injury.

The overwhelming body of evidence in a large number of controlled animal studies demonstrates that hyperbaric oxygen reduces dermal ischemia, reduces edema, prevents conversion of partial- to full-thickness injury, preserves the microcirculation, and preserves ATP and cellular integrity. Additional benefits may be enhancement of PMNL killing and modulation of ischemia reperfusion injury, resulting in improved survival.

CLINICAL EXPERIENCE

In 1965, Wada observed improved healing of burns in coal miners being treated for carbon monoxide poisoning with HBO_2. Later clinical series by Ikeda, Wada, Lamy, Tabor and Grossman [17,74-79) showed improved healing [74], decreased length of hospital stay [79], decreased mortality [79-80], decreased overall cost of care [79-81], improved morbidity [79), decreased fluid requirements (30-35%) [80], and decreased number of surgeries ($p<0.041$) [81]. Niu reported a very large clinical outcome series showing a statistically significant reduction in mortality ($p=0.028$) in 266 seriously burned patients who received HBO_2 when compared to 609 control patients [80]. He also observed a lower incidence of infection and stated that HBO_2 allowed the burn surgeon more time to more accurately define the extent of injury.

Cianci has shown a significant reduction in length of hospital stay in burns up to 39% TBSA [82]. Additionally noted was a reduction in the need for surgery, including grafting, in a series of patients with 40-80% burns when compared to non-HBO_2-treated controls. HBO_2-treated patients showed an average savings of 36% ($107,000) per case [81]. Adjusted for inflation, this would represent a saving of $203,000 per case in 2012 U.S. dollars.

Hart reported a sham controlled randomized series showing reduced fluid requirements, mean healing time (p<0.005), mortality and morbidity in 10-50% TBSA burn patients treated with HBO_2 when compared to controls and to United States National Burn Information Exchange Standards [84].

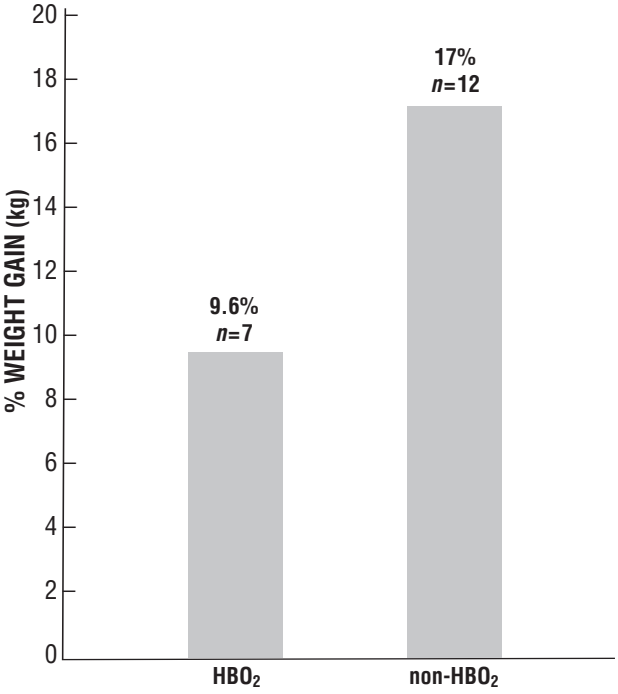
In a retrospective paired controlled series of burn patients treated with HBO_2, Waisbren reported increased sepsis, reduced renal function and decreased circulating white blood cells in HBO_2-treated patients. The author stated he could demonstrate neither a salutory nor deleterious effect on mortality [85]. While frequently cited as a negative study, there was a 75% reduction in the need for grafting (p<0.001) in the hyperbaric group. In a randomized controlled study of 37 partial-thickness burn patients treated with HBO_2 *vs.* 37 controls, Merola reported increased granulation, faster healing and decreased scarring [86].

Cianci observed similar results in a series of patients averaging 28% TBSA burns [87]. In a small blinded review, Cianci's group reported a 25% reduction in resuscitative fluid requirements (p<0.07) and maximum (and percent) weight gain (p<0.012) in seriously burned (40-80% TBSA) patients treated with adjunctive HBO_2 *vs*. controls at a regional burn center [81,83] *(Figure 8)* [88].

In a controlled pilot series, Maxwell reported reduced surgery, resuscitative weight gain, intensive care days, total hospitalization time, wound sepsis and cost of hospitalization in the HBO_2 group [89]. Cianci reported reduced surgeries (p<0.03), length of hospital stay (53%) and cost of care (49%) in 40-80% TBSA burns [90]. Hammarlund and colleagues showed reduced edema and wound exudation in a controlled series of human volunteers with UV-irradiated blister wounds [91] *(Figure 9)*.

In a subsequent similar study, Niezgoda *(Figure 10),* demonstrated reduced wound size (p<0.03), laser Doppler-measured hyperemia (p<0.05) and wound exudate (p<0.04) in the HBO_2-treated group. This study was the first prospective randomized, controlled double-blinded trial comparing HBO_2 with sham controls in a human burn model [92].

FIGURE 8 – Maximum weight gain / 3 days

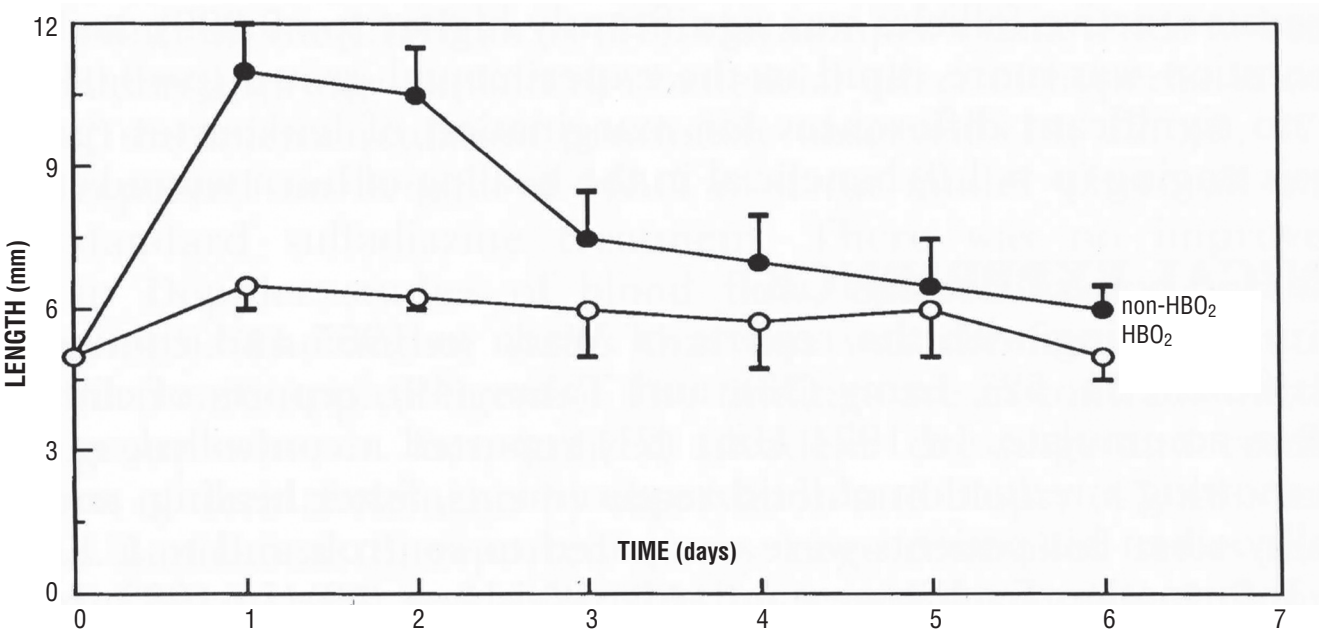


Maximum weight gain at three days expressed as percentage of admission weight. HBO_2-treated patients showed a 45 percent reduction in weight gain (p<0.03) [88].

Brannen *et al.* in 1997 [93] reported a randomized prospective trial of hyperbaric oxygen in the treatment of burn injury. Sixty-three patients received hyperbaric oxygen and 62 served as controls. One-third of the hyperbaric-treated patients received their first treatment within eight hours. However, the average time to treatment was 11.5 hours after the burn injury. The authors noted no difference in the outcome measures of mortality, number of operations, or length of stay and stated they were unable to demonstrate any significant benefit to burn patients from the use of hyperbaric oxygen.

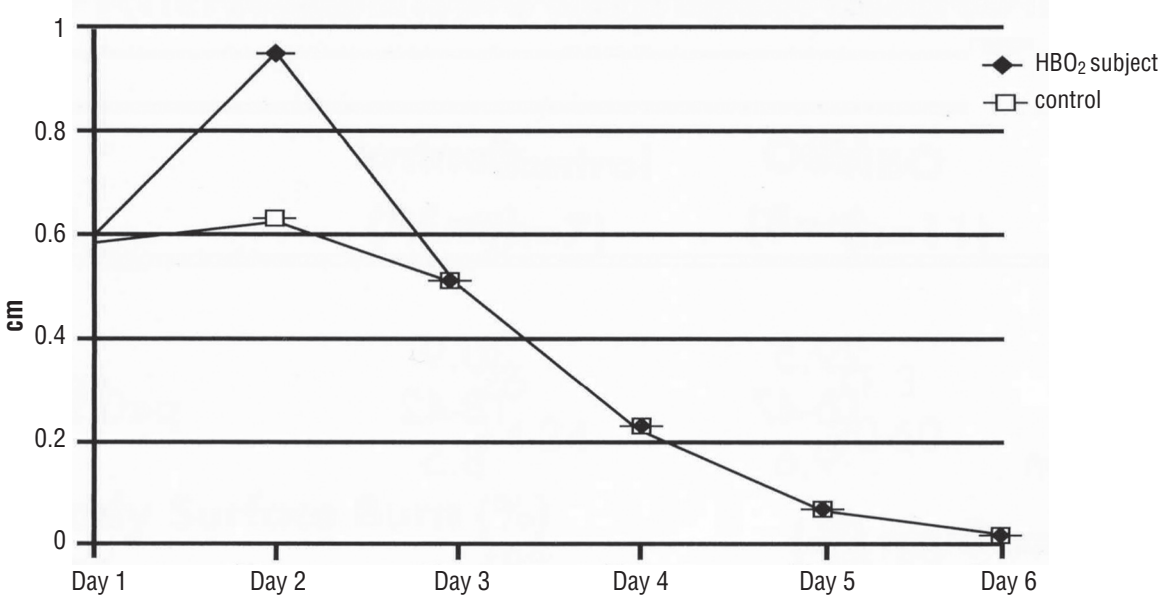
There were serious limitations in this study. Two-thirds of patients did not receive their first treatment until more than eight hours after burn injury, with a mean of 11.5 hours. Results in the subset of patients receiving earlier treatment were not examined separately. Important outcome measures not studied were functional and cosmetic aspects of facial, hand and perineal burns. Length of stay, number of surgeries, extent of grafting are subject to a variety of confounding influences, including economic (*e.g.*, hospital and insurance, utilization management, physician reimbursement) and social considerations (*e.g.*, lack of adequate housing, caregivers and rehabilitation efforts).

FIGURE 9 – Maximum length including edema



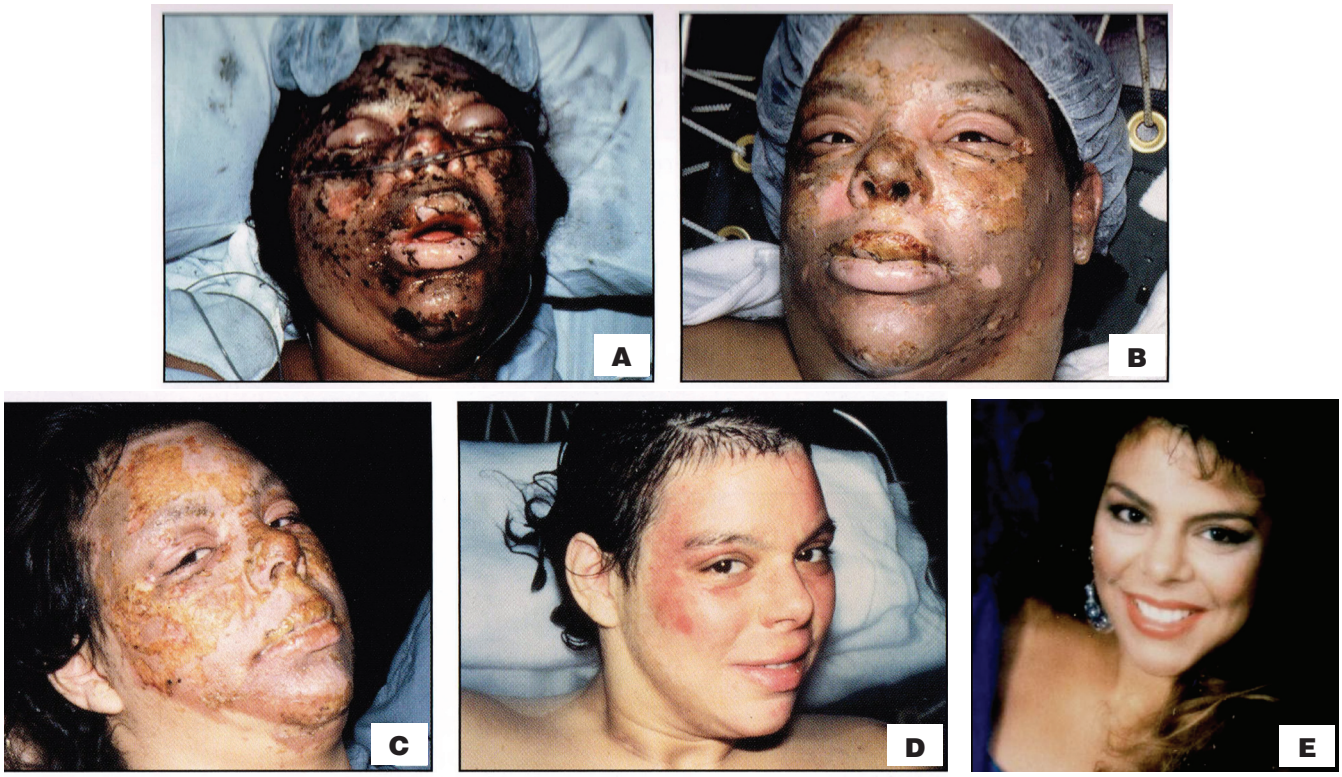
Maximum length (including edema adjacent to the wound) (mean ± SD) of UV-irradiated (•) and HBO_2-treated and UV-irradiated (○) blister wounds as a function of time. The value on Day 0 is approximately the diameter of the suction cup used to create the blister (p<0.05). GRAPH COURTESY OF DR. C. HAMMARLUND.

FIGURE 10 – Hyperbaric oxygen therapy for burns



Wound size measurements (cm) of ultraviolet-irradiated suction blister wounds in control group (❑) and hyperbaric oxygen group (■). GRAPH COURTESY OF DR. JEFFERY A. NIEZGODA.

FIGURE 11 – Burn victim's recovery



A. 23-year-old white female with facial burns from flaming gasoline and tar 12 hours after injury.
B. 24 hours later (36 hours after injury) after two HBO_2 treatments. Note resolution of edema.
C. 72 hours later (84 hours after injury) after six HBO_2 treatments.
D. Shortly before discharge.
E. Four years after discharge. *Note: Consent to use these photos was obtained prior to publication.*

Despite randomization for age, burn size and inhalation injury, the populations were still heterogeneous. Comorbidity was not examined, and all patients underwent exceedingly early and aggressive excisional therapy with rapid discharge to a lesser level of care. The authors did observe less fluid loss, drier wounds, which necessitated fewer dressing changes, and earlier healing. Further analysis showed a significant reduction in hospital costs in the hyperbaric group.

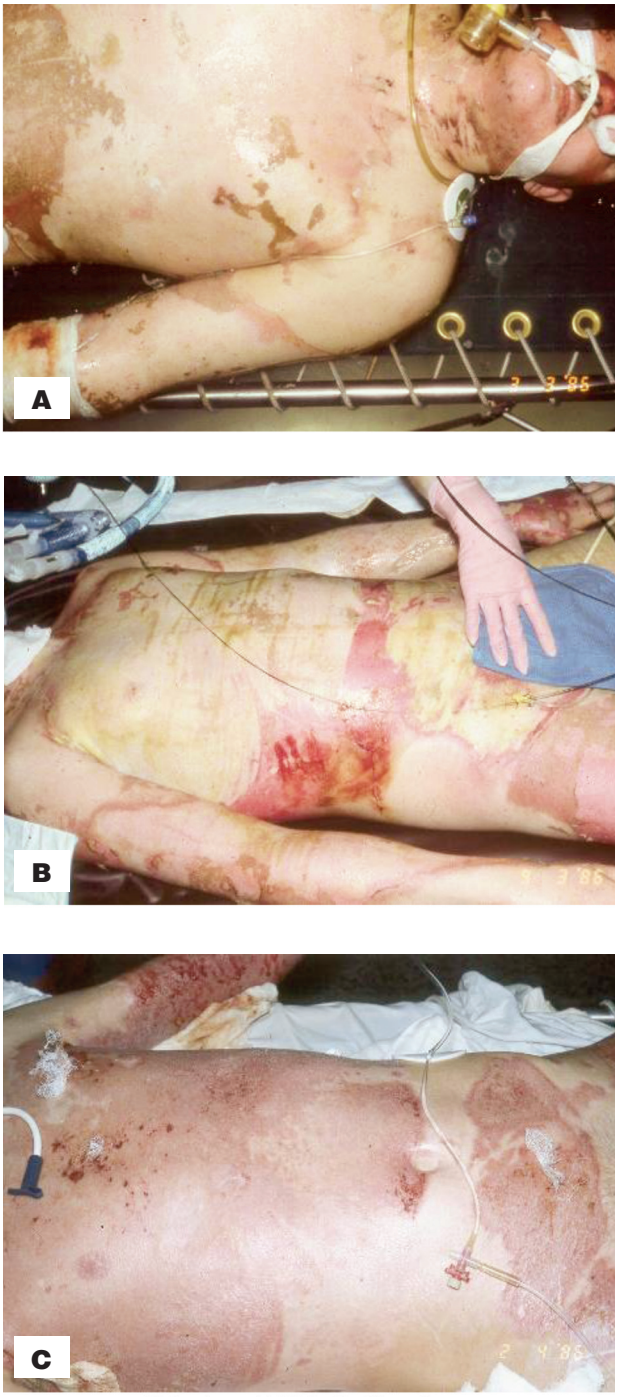
INHALATION INJURY

Considerable attention has been given to the use of HBO_2 in inhalation injury due in part to fear that HBO_2 may cause worsening of pulmonary damage, particularly in those patients maintained on high levels of inspired oxygen. The more extensive the burn injury, the higher the incidence of an inhalation injury [94]. Pulmonary injury caused by smoke inhalation is a major cause of fire-related deaths [95]. The airway injury can be worsened by a variety of chemical pyrolysis products, depending on the material burned [96].

Grim studied products of lipid peroxidation in the exhaled gases in HBO_2-treated burn patients and found no indication of oxidative stress [97]. In comparison with a comparable size burn alone, the combination of a body burn and smoke inhalation injury results in a marked increase in mortality and morbidity, in hemodynamic instability, in burn wound edema, a 30-50% increase in initial fluid requirements and an accentuation of lung dysfunction.

Ray analyzed a series of severely burned patients being treated for concurrent inhalation injury, thermal injury and adult respiratory distress syndrome [98]. She noted no deleterious effect of HBO_2, even in those 0 on continuous high levels of inspired oxygen. More rapid weaning from mechanical ventilation was

FIGURE 12 – Burn victim's recovery



A. 19-year-old white male with deep partial- to full-thickness burns from flame burn. TBSA 70%. Photo taken pre-HBO_2.

B. Patient six days later after HBO_2 twice daily.

C. 30 days later with HBO_2. No skin grafts required on chest and torso.

possible in the HBO_2-treated group (5.3 days *vs.* 26 days, $p<0.05$). There was a significant reduction in cost of care per case of $60,000 in the HBO_2-treated patients ($p<0.05$). Adjusted to 2012 U.S. dollars, this figure would be $108,000. There is no current evidence to controvert these studies.

In 2009, the Cochrane Data Base systemic review of the efficacy of HBO_2 for thermal burns, Villanueva *et al.* identified four randomized controlled studies, of which two satisfied their inclusion criteria [99].

In the first trial Hart in 1974 [84], as previously discussed, reported reduced fluid requirements and mean healing time ($p<0.005$) mortality and morbidity reduced when compared to controls. There was a reduction in mortality and morbidity when compared to the National Burn Information Exchange standards.

Because of heterogeneity, the studies could not be pooled, though Hart reported mean healing time significantly shorter – 19.7 *vs.* 43.8 days ($p<0.001$) – the authors suggested that the Hart study was particularly constrained by lack of power to detect useful clinical differences. The Brannen study [93], reporting no difference in mortality, length of stay or surgeries, was constrained by the previously mentioned limitations. The authors state that while there are promising results from non-random clinical reports, there is insufficient evidence to recommend or refute the routine use of hyperbaric oxygen for the treatment of thermal burns and suggest that large multicenter randomized study of sufficient power would be needed to address these shortcomings. The Cochrane report did not consider several outcome studies with matched controls showing reduced length of stay, reduction in fluid requirements and edema, reduction of surgery and cost effectiveness.

While these reports certainly had limitations, they represent valid analysis of the benefits of early treatment in thermal injury and underscore that the observations of skilled and experienced physicians remain an important component of determining therapeutic efficacy. A well-designed, randomized, blinded control study with sham treatment and sufficient power is certainly desirable yet remains to be performed. Most centers see very few large burns; only 4% of burn admissions are for burns >40% TBSA, certainly necessitating a multicenter format. Attempts at organized such a study have so far been unsuccessful.

PATIENT SELECTION CRITERIA

Hyperbaric oxygen therapy is recommended to treat serious burns – *i.e.*, greater than 20% total body surface area and/or with involvement of the hands, face, feet or perineum that are deep partial- or full-thickness injury. Patients with superficial burns or those not expected to survive are not accepted for therapy. Transfer of patients for HBO_2 treatment should be considered carefully and should be sent only to a facility that has both a hyperbaric chamber and a burn unit.

Burns related to methamphetamine manufacture can present to burn units in large numbers, typically involving the face and hands and are associated with a vague history of explosion. Costs for management of these patients are high, imposing significant financial burdens on burn unit hospitals [100].

CLINICAL MANAGEMENT

Surgical Perspectives

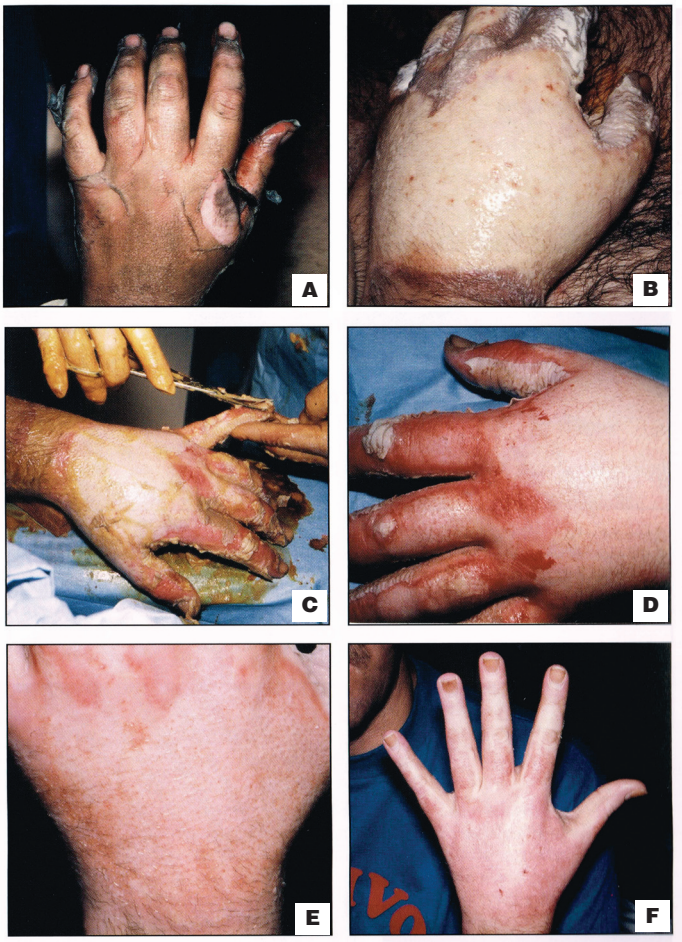
Over the past 30 years, the pendulum has swung to an aggressive surgical management of the burn wound, *i.e.*, early tangential or sequential excision and grafting of the deep second-degree and probable third-degree burns, especially to functionally important parts of the body [101,102]. Hyperbaric oxygen, as an adjunctive therapy, has allowed the surgeon yet another modality of treatment for these deep second-degree burns, especially including those to the hands and fingers, face and ears, and other areas where the surgical technique of excision is often imprecise and coverage is sometimes difficult.

These wounds, not obvious third-degree, are then best treated with topical antimicrobial agents, bedside and enzymatic debridement, wound care and adjunctive hyperbaric oxygen therapy, allowing the surgeon more time for healing to take place and for definition of the extent and depth of injury *(Figures 11-13)*.

Adjunctive hyperbaric oxygen therapy has drastically reduced the healing time in the major burn injury, especially if the wounds are deep second-degree [80-82,87]. There is theoretical benefit of HBO_2 therapy for obviously less well-defined third-degree burns [21]. Fourth-degree burns, most commonly seen in high-voltage electrical injuries, are benefited by reduction in fascial compartment pressures, as injured muscle swelling is lessened by preservation of aerobic glycolysis and, later, by a reduction of anaerobic infection.

Finally, reconstruction utilizing flaps, full-thickness skin and composite grafts, *i.e.*, ear-to-nose grafts, has been greatly facilitated using adjunctive HBO_2 [103].

FIGURE 13 – Burn victim's recovery



A. A deep partial-thickness burn to hand of 30-year-old male with 60 TBSA burn and inhalation injury. Taken on admission.

B. Patient six days later.

C. At surgery, light debridement.

D. Immediately after surgery. Note preservation of dermal appendages.

E. Two weeks after admission. Note re-epithelialization.

F. Appearance on discharge 25 days post-injury. Healed without grafting.

Often the decision to use HBO_2 therapy has been made intraoperatively when a surgeon is concerned about a compromised cutaneous or myocutaneous flap. Patients are, in many instances, prepared preoperatively about the possibility of receiving adjunctive HBO_2 therapy immediately postoperatively.

Units planning treatment of burn patients should be experienced in management of critical-care patients in the hyperbaric setting and to specific problems of

burn patients prior to initiation of a therapy program. Preferably personnel should be certified in burn care and hyperbaric oxygen therapy. The hyperbaric department should function as an extension of the burn unit and participate in the team approach to burn management.

Hyperbaric oxygen

Hyperbaric oxygen therapy is begun as soon as possible after injury, often during initial resuscitation. Treatments are attempted three times within the first 24 hours and twice daily thereafter on a regimen of 90 minutes of 100% oxygen delivery at 2.0-2.4 atm abs. Early experience in treating children recommended 45 minutes twice daily [79], but more recent extensive clinical use of HBO_2 in children demonstrates that adult protocols are safe.

Patients are monitored during initial treatment and as necessary thereafter. Blood pressure can be monitored via transducers or non-invasively using blood pressure cuffs designed for use in monoplace chambers. Patients can be maintained on ventilator support during treatment, which is frequently the case in larger burns with concurrent inhalation injury.

Careful attention to fluid management is mandatory. Initial requirements may be several liters per hour, and pumps capable of this delivery at pressure must be utilized in order to maintain appropriate fluid replacement in the hyperbaric chamber. In larger burn injuries, adequate fluid and electrolyte resuscitation during the first 24 hours can be problematic. Certain patients can develop hypotension shortly after exiting the chamber. Careful volume replacement and assessment of fluid status is mandatory prior to, during, and immediately after HBO_2 treatment. Increasing fluids during ascent may help compensate for any hypovolemia unmasked after hyperbaric oxygen exposure.

Maintenance of a comfortable, ambient temperature must be accomplished. Thermal instability may be a problem within one to two hours of burn wound cleansing and dressing change (depending on the methods used), especially in large TBSA burns. These patients should be carefully assessed prior to an HBO_2 exposure. Febrile patients must be closely monitored and fever controlled, as oxygen toxicity is reported to be more common in this group.

In large burns of 40% TBSA or greater, treatment is rendered for 10-14 days in close consultation with the burn surgeon. Many partial-thickness burns will heal without surgery during this time frame and obviate the need for grafting. Treatment beyond 20-30 sessions is usually utilized to optimize graft take. While there is no absolute limit to the total number of hyperbaric treatments, it is rare to exceed 40-50 sessions, and utilization review is recommended.

Concern has been expressed about the use of the carbonic anhydrase inhibitor mafenide acetate (Sulfamylon) and its removal recommended prior to HBO_2 treatment based on the potential for CO_2 buildup, which can lead to vasodilatation [104]. Sulfamylon is less frequently utilized in burn centers, and rarely used at our facility except in select cases (small TBSA, severe infection and/or contraindication to silver sulfadiazine). Its limited use in this setting has not resulted in any observed untoward effects [105]. Silver sulfadiazine is the most widely used topical therapy because of its relatively low toxicity and ease of use [7].

In larger TBSA burns, especially of the head and neck, otic barotrauma may be a problem, and careful attention should be given to this potential complication. The HBO_2 team should make use of early ENT consultation when indicated.

Patients may be treated in a multiplace or monoplace configuration. Movement over long distances is not recommended, and patients should not be transported to a hyperbaric chamber that is not within the same facility as the burn center [106].

EVIDENCE-BASED REVIEW

Twenty-one experimental animal studies cited in this report support the benefits of HBO_2 treatments in acute thermal injury. Mechanisms of action include edema reduction, amelioration or reduction in ischemia-reperfusion injury, enhancement of leukocyte killing, preservation of ATP, angiogenesis and maintenance of the microcirculation, and epithelial regeneration.

Twenty-two clinical series in this report meet AHA level of evidence criteria, 20 demonstrating benefit with the use of HBO_2 in thermal injury. Reported benefits include improved healing, and reductions in hospital stay, morbidity, mortality and hospital-related complications. HBO_2 therapy has been shown to be safe in these reports.

The American Heart Association (AHA) criteria classifies clinical studies according to the level of evidence.

Level	American Heart Association
1	Randomized, controlled trial, statistically significant
2	Randomized, controlled trial, statistically insignificant
3	Prospective, controlled, non-randomized
4	Historic, non-randomized cohort or case-controlled
5	Human case series

American Heart Association criteria

Seven human case series (AHA Level 5) show improved healing of burns, decreased hospital length of stay, mortality and overall costs in improved morbidity.

One of two studies that meet AHA Level 4 criteria noted statistically significant reductions in renal function, circulating leukocytes and an increase in positive blood cultures in the HBO_2 group [85]. However, there was a 75% decrease in the need for grafting in the HBO_2 group. The other, a small pilot study, reported reduced number of surgeries, resuscitative weight gain, intensive care unit days, total hospitalization time, wound sepsis and cost of hospitalization in the HBO_2 group [89].

Eight AHA Level 3 studies show statistically significant benefits with HBO_2 that include decreased mortality, lower incidence of infection, reduction in length of hospital stay, number of surgeries, wound size, wound exudation, resuscitative fluid requirements and maximum and percent weight gain. Cost savings were also demonstrated [80-89].

In patients with inhalation injury, HBO_2 did not cause oxidative lung injury as measured by arterial plasma and exhaled gases [97].

The two studies that meet AHA Level 2 criteria show benefit with HBO_2 [86,93]. For patients treated with HBO_2, findings include faster healing and a probable decreased incidence of sepsis ($p<0.05$) attributed to increased interleukin-2 receptor ($p<0.05$) and decreased plasma fibronectin ($p<0.01$) compared to controls [58].

Three studies meet AHA Level 1 criteria. A 1974 prospective randomized controlled double-blind series of four groups of patients stratified by percent TBSA burn showed reduced healing time ($p<0.005$) and reduced fluid requirements and mortality when the HBO_2-treated patients were compared to controls and to United States National Burn Information Exchange Standards [84].

A 1997 prospective randomized controlled double-blinded trial compared HBO_2 with sham controls in a human burn model. The HBO_2 group was treated at 2.4 atm abs (100% O_2) twice daily for three days, while the control group received a normoxic gas mix (8.75% oxygen) at 2.4 atm abs on the same schedule. Day 2 study outcome measurements revealed reduced wound hyperemia ($p=0.05$), wound size ($p=0.02$) and wound exudation ($p=0.04$), in the HBO_2-treated group. While wound hyperemia and size were not significantly different in the two groups by Day 6, wound exudation in the HBO_2 group remained lower than controls throughout the duration of the study [92].

In a prospective randomized clinical trial of HBO_2 in a referral burn center of 125 burn patients, the primary outcome variable of the study was length of stay, with secondary outcome measures of mortality and number of surgeries. The authors failed to show any reduction in length of stay, number of surgical procedures or mortality in the HBO_2 treatment group. These results were not unexpected, as both groups underwent very early and aggressive excision, thus invalidating not only this important study outcome parameter, but also potentially affecting length of stay. The authors state that they were very impressed when they began to use HBO_2, noting that these patients definitely had less fluid loss, were drier and appeared to heal earlier. These observations support the unreported reduction in overall cost of care in the group treated with HBO_2 [93].

Of the 22 clinical studies cited in this report, 20 show benefit of the use of HBO_2 for acute thermal injury. The AHA therapeutic intervention classification for thermal injury merits a designation as a Class IIa indication for HBO_2.

UTILIZATION REVIEW

Utilization review is recommended after 30 hyperbaric oxygen sessions.

COST IMPACT

Burn care is expensive. During 1997-98, in a Northern California regional burn center, hospital costs for 20 burn patients averaged $253,000 ($353,000 in 2012 U.S. dollars) [107]. This includes the cost of hyperbaric oxygen that averaged $6,360 ($9,000 In 2012 U.S. dollars) per patient.

Cost data from the 2012 National Burn Repository report indicate that for patients who survive 60% total body surface area burns, charges average $831,000 (in 2012 U.S. dollars) for the hospital stay alone. This does not include operating room time, surgeon's bills, artificial skin, rehabilitation and other costs that can reach $500,000 or more for burns over 80% TBSA [1].

Although not calculated, cost savings as a result of the use of HBO_2 in acute thermal injury are implied in all of the 22 clinical studies in this report by demonstrating reductions in healing time, hospital length of stay, and numbers of surgeries including grafting. In six of the studies, the authors specifically analyzed costs of care in thermal injury with and without adjunctive HBO_2, and estimates of average savings in patients treated with HBO_2 range from $60,000 to $107,000 per case.

DISCUSSION

Despite the many advances in burn therapy, including early excision, nutritional support, improved ventilation and infection control, there appears to have been little change in mortality except for patients over 65 with larger burns since the mid-1980s. Early excision seems to have decreased mortality and overall length of stay in smaller burns and those not suffering concurrent inhalation injury [108]. Engrav, in a review of 35 years' experience at the Harborview Burn Center in Seattle, Washington, reported that early excision did not decrease length of stay for larger burns and there has been little change since 1990 [109]. It has also been suggested that burn care may have already achieved "a floor of survival" [110]. Thus, further improvement in burn care, length of stay, mortality and cost containment must await future therapeutic developments. Adjunctive hyperbaric oxygen therapy has been shown to reduce length of stay and cost of care in conjunction with early excision and comprehensive burn management.

SUMMARY

Current data show that hyperbaric oxygen therapy when used as an adjunct in a comprehensive program of burn care can significantly improve morbidity and mortality, reduce length of hospital stay, lessen the need for surgery, and is cost-effective. It has been demonstrated to be safe in the hands of those thoroughly trained in rendering hyperbaric oxygen therapy in the critical-care setting and with appropriate monitoring precautions. Careful patient selection and screening are mandatory.

Given our current understanding of the uniquely beneficial effects of hyperbaric oxygenation on the cellular and molecular mechanisms of wound healing, it is suggested that the formal integration of hyperbaric oxygen therapy in early burn wound management be investigated by the use of well-designed multicenter studies that may provide data for burn wound healing and burn patient outcomes supportive of this role.

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Conflict of interest statement

The authors have no conflict of interest to declare.

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