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HYPERBARIC OXYGEN THERAPY IN ACUTE TRAUMATIC ISCHEMIC INJURIES OF THE EXTREMITIES: MECHANISMS, TIMING, AND CLINICAL EVIDENCE - A NARRATIVE REVIEW

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ABSTRACT

Background: Acute traumatic ischemic injuries of the extremities, including crush injuries, compartment syndrome, and vascular trauma, remain associated with substantial morbidity, tissue necrosis, and risk of limb loss despite advances in surgical and reconstructive management. Increasing evidence suggests that ischemia-reperfusion injury and microvascular dysfunction contribute substantially to secondary tissue damage following severe extremity trauma.
Aim: The aim of this narrative review was to summarize and critically evaluate the current evidence regarding hyperbaric oxygen therapy (HBOT) in acute traumatic ischemic injuries of the extremities, with particular emphasis on pathophysiology, biological mechanisms, treatment timing, and clinical outcomes.
Methods: A narrative literature review was conducted using PubMed/MEDLINE and Google Scholar databases. Randomized clinical trials, observational studies, systematic reviews, and mechanistic studies evaluating HBOT in crush injuries, compartment syndrome, traumatic ischemia, and severe extremity trauma were analyzed.
Results: Available evidence suggests that adjunctive HBOT may reduce tissue necrosis, wound-related complications, edema formation, and repeated surgical procedures in selected patients with severe traumatic ischemic injuries. The most consistent findings involved preservation of marginally viable tissue and attenuation of secondary ischemic progression rather than definitive prevention of amputation. Experimental studies additionally demonstrated improved tissue oxygenation, modulation of inflammatory activation, and support of microvascular perfusion.
Conclusions: HBOT appears to represent a promising tissue-preserving adjunct in selected patients with acute traumatic ischemic injuries of the extremities. However, current evidence remains limited by methodological heterogeneity and relatively small study populations.

KEYWORDS

Hyperbaric Oxygen Therapy, Crush Injury, Compartment Syndrome, Ischemia-Reperfusion Injury, Limb Salvage, Traumatic Ischemia

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1. Introduction

Acute traumatic ischemic injuries of the extremities, including crush injuries, compartment syndrome, vascular trauma, and mangled extremities, remain a major challenge in contemporary trauma and reconstructive surgery. Despite advances in vascular repair, microsurgical reconstruction, and critical care, these injuries continue to be associated with substantial morbidity, high rates of tissue necrosis, prolonged disability, and risk of limb loss [1–4]. In severe extremity trauma, restoration of macroscopic blood flow does not necessarily translate into recovery of tissue viability, as persistent microcirculatory dysfunction and secondary ischemic injury may persist despite technically successful surgical intervention [1,3,5]. Moreover, severe skeletal muscle injury may result in rhabdomyolysis, acute kidney injury, systemic inflammatory response syndrome, and multiple organ dysfunction, further contributing to poor clinical outcomes [3,6].

An increasing body of evidence suggests that ischemia-reperfusion injury (IRI) plays a central role in the progression of tissue damage following acute traumatic ischemia [7–10]. Reperfusion, although essential for restoring oxygen delivery and metabolic support, may paradoxically exacerbate tissue injury through activation of inflammatory and oxidative pathways [7,8]. Experimental and preclinical studies have demonstrated that reperfusion is associated with reactive oxygen species generation, endothelial dysfunction, leukocyte activation, increased vascular permeability, and microvascular flow impairment [7–10]. These mechanisms contribute to the development of tissue edema, impaired capillary perfusion, and progressive deterioration of local oxygen delivery despite restoration of arterial inflow [7,9]. Persistent microcirculatory

dysfunction and the no-reflow phenomenon are currently recognized as major contributors to ongoing tissue hypoxia and secondary necrosis in severe extremity trauma [7,8].

In crush syndrome and compartment syndrome, ischemia and edema may create a self-perpetuating cycle of progressive tissue injury [3,4,11]. Increased intracompartmental pressure impairs capillary perfusion, leading to worsening hypoxia, collapse of the microcirculation, and further edema formation [3,11]. In addition, skeletal muscle tissue is highly susceptible to ischemic damage because of its high metabolic demand, and irreversible injury may develop rapidly if tissue oxygenation is not restored within a critical time window [7,8]. Consequently, early therapeutic strategies aimed at preserving microcirculatory integrity and limiting secondary tissue injury may play an important role in limb salvage and functional recovery.

Hyperbaric oxygen therapy (HBOT) has emerged as a potential adjunctive treatment modality in acute traumatic ischemic injuries of the extremities [2,4,9,12–15]. HBOT involves the administration of 100% oxygen under increased atmospheric pressure, resulting in markedly elevated oxygen tension in plasma and enhanced oxygen diffusion into hypoxic tissues [9,11,13,14]. Beyond its effects on tissue oxygenation, HBOT has been proposed to influence several biological processes relevant to traumatic ischemia, including edema reduction, modulation of inflammatory responses, improvement of microvascular perfusion, and attenuation of reperfusion-associated tissue injury [7,9,13–15]. Available experimental and preclinical studies suggest that HBOT may support tissue repair by improving cellular survival and promoting favorable conditions for wound healing and microvascular recovery [9,15].

Although HBOT has been increasingly utilized as an adjunctive therapy in crush injuries, compartment syndrome, traumatic ischemia, and severe lower limb trauma, the available clinical evidence remains heterogeneous [1,2,16–18]. Variability in injury patterns, timing of intervention, treatment protocols, and study design has contributed to ongoing uncertainty regarding optimal patient selection and therapeutic efficacy [1,16,17]. Furthermore, despite growing interest in the biological rationale for HBOT, integration of mechanistic evidence with clinical outcomes remains limited.

The aim of this narrative review was to critically evaluate the current evidence regarding the use of hyperbaric oxygen therapy in acute traumatic ischemic injuries of the extremities, with particular emphasis on the pathophysiology of ischemia-reperfusion injury, the biological mechanisms of HBOT, the importance of treatment timing, and currently available clinical evidence concerning tissue salvage and limb-related outcomes.

2. Methods

A narrative literature review was conducted to identify and synthesize available experimental and clinical evidence regarding hyperbaric oxygen therapy (HBOT) in acute traumatic ischemic injuries of the extremities.

A literature search was performed using the PubMed/MEDLINE and Google Scholar databases, supplemented by manual reference screening of relevant articles. Articles published through April 2026 were considered eligible for review. The search strategy included combinations of the following keywords and Medical Subject Headings (MeSH) terms: “hyperbaric oxygen therapy”, “HBOT”, “traumatic ischemia”, “acute limb ischemia”, “crush injury”, “crush syndrome”, “compartment syndrome”, “ischemia-reperfusion injury”, “mangled extremity”, “soft tissue injury”, and “limb salvage”.

Eligible publications included randomized controlled trials, observational studies, retrospective cohorts, case series, systematic reviews, and relevant experimental or mechanistic studies addressing HBOT in traumatic ischemic injuries of the extremities. Preference was given to studies reporting objective clinical outcomes related to tissue viability, wound healing, limb salvage, ischemic progression, or functional recovery. Studies focused exclusively on chronic wound conditions unrelated to acute trauma, non-traumatic ischemic conditions, or publications lacking sufficient methodological or clinical relevance were excluded from detailed analysis.

Because of substantial heterogeneity in study design, injury patterns, HBOT protocols, and reported outcome measures, a quantitative meta-analysis was not performed. Instead, findings were synthesized narratively with emphasis on biological plausibility, consistency of clinical observations, and integration of mechanistic and clinical evidence.

3. Pathophysiology of Acute Traumatic Ischemic Injuries of the Extremities

Acute traumatic ischemic injuries of the extremities are characterized by a complex interaction between primary mechanical tissue destruction, impaired perfusion, microvascular dysfunction, inflammatory activation, and secondary ischemia-reperfusion injury. In severe limb trauma, tissue damage is frequently not limited to the initial insult itself but continues to progress during the subsequent hours as a result of evolving hypoxia, endothelial injury, edema formation, and inflammatory cascade activation [1,3,4,11]. Importantly, progressive impairment of tissue oxygen delivery may ultimately result in irreversible cellular injury and coagulative necrosis of skeletal muscle, vascular endothelium, and peripheral nerves, substantially increasing the risk of permanent functional loss and limb amputation [7,10,11]. Consequently, the final extent of tissue necrosis often exceeds the damage caused directly by the original trauma.

The severity of tissue injury in crush trauma, compartment syndrome, and traumatic vascular injury is closely related to impaired oxygen delivery at the microcirculatory level [7,10,11]. Skeletal muscle tissue is particularly vulnerable to ischemia because of its high metabolic demand and dependence on continuous aerobic metabolism for adenosine triphosphate (ATP) production [10]. During ischemia, depletion of intracellular ATP disrupts ion transport mechanisms, resulting in sodium and water influx into the cell, intracellular calcium accumulation, mitochondrial dysfunction, and progressive loss of membrane integrity [8]. Elevated intracellular calcium activates phospholipases, proteases, and endonucleases, leading to degradation of structural proteins, lipid membranes, and intracellular organelles [8,10]. These processes ultimately contribute to myocyte necrosis and rhabdomyolysis [3,10].

Crush syndrome represents the systemic manifestation of severe skeletal muscle destruction caused by prolonged compression or traumatic tissue disruption [3,11]. Damage to the sarcolemma results in the release of intracellular contents, including myoglobin, potassium, phosphate, urate, and creatine kinase, into the systemic circulation [2,3]. Clinically, this may lead to hyperkalemia, metabolic acidosis, acute kidney injury, and systemic inflammatory response syndrome [2,3]. In addition to direct cellular destruction, injured muscle tissue undergoes progressive interstitial edema formation, which further compromises capillary blood flow and exacerbates local hypoxia [7,11].

A similar self-perpetuating cycle is observed in acute compartment syndrome. Compartment syndrome develops when elevated pressure within a closed fascial compartment reduces capillary perfusion below the level required for tissue viability [4,7,11]. Increased intracompartmental pressure impairs venous outflow, leading to progressive accumulation of interstitial fluid, worsening tissue edema, and further elevation of compartment pressure [7,11]. This vicious cycle of ischemia, edema, and microvascular collapse may rapidly progress toward irreversible muscle and nerve injury if decompression is delayed [4,7,11]. Previous experimental and clinical observations suggest that prolonged ischemia may lead to progressive skeletal muscle necrosis, endothelial injury, and deterioration of tissue oxygenation even in the presence of restored macroscopic arterial inflow [7,9]. Importantly, once critical microvascular failure develops, restoration of arterial circulation alone may become insufficient to prevent ongoing tissue necrosis because capillary-level perfusion remains severely impaired [7,9,10].

In traumatic vascular injuries, restoration of large-vessel blood flow does not necessarily result in normalization of tissue perfusion. Increasing evidence suggests that ischemia-reperfusion injury plays a central role in secondary tissue damage following revascularization [1,9,10]. Reperfusion of previously ischemic tissue triggers excessive production of reactive oxygen species (ROS), including superoxide anion, hydrogen peroxide, hydroxyl radicals, and peroxynitrite [9,10]. One of the principal sources of ROS generation is xanthine oxidase activation during reperfusion following ATP depletion and hypoxanthine accumulation in ischemic tissue [10]. In parallel, activated neutrophils adhere to damaged endothelium and produce additional oxidative mediators through nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and myeloperoxidase-dependent pathways [9,10].

Oxidative stress contributes to lipid peroxidation, mitochondrial dysfunction, endothelial injury, and activation of pro-inflammatory signaling pathways [9,10,14]. At the microvascular level, ischemia-reperfusion injury is associated with increased endothelial permeability, leukocyte-endothelial adhesion, capillary plugging, and impaired tissue perfusion [9,10]. Adhesion molecules such as intracellular adhesion molecule-1 (ICAM-1), selectins, and CD18-dependent neutrophil interactions are believed to play an important role in this process [9]. The resulting impairment of capillary blood flow may persist despite successful restoration of arterial circulation, leading to the development of the no-reflow phenomenon and continued tissue hypoxia [9,10].

Inflammatory activation further amplifies tissue injury following reperfusion. Experimental and preclinical studies have demonstrated increased production of pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6), following severe ischemic skeletal muscle injury [10,14]. Activation of the complement cascade and recruitment of neutrophils contribute to endothelial dysfunction and propagation of local and systemic inflammation [10]. In severe cases, these processes may extend beyond the injured extremity and contribute to acute respiratory distress syndrome, systemic inflammatory response syndrome, and multiple organ dysfunction [10,11].

An important determinant of tissue survival in acute traumatic ischemia is the duration of impaired perfusion. Experimental observations suggest that skeletal muscle demonstrates limited tolerance to prolonged ischemia, with irreversible injury potentially developing within several hours depending on the severity of perfusion compromise [7,9,10]. Nerve tissue is also highly susceptible to prolonged hypoxia, whereas skin and bone generally exhibit greater ischemic tolerance [10]. Progressive edema, endothelial swelling, and microvascular obstruction may significantly reduce the therapeutic window during which tissue salvage remains possible [7,9]. Once prolonged ischemia results in widespread myonecrosis and severe destruction of capillary architecture, the probability of successful tissue salvage decreases substantially [7,9,10]. Consequently, early restoration of tissue oxygenation and preservation of microcirculatory integrity are considered critical factors influencing limb viability and functional recovery after severe extremity trauma.

4. Biological Effects and Rationale for HBOT

Given the central role of tissue hypoxia, microvascular dysfunction, edema formation, and ischemia-reperfusion injury in the progression of traumatic extremity damage, hyperbaric oxygen therapy (HBOT) has emerged as a potential adjunctive strategy aimed at preserving tissue viability and limiting secondary ischemic injury [7,9,11,12,14]. Unlike conventional oxygen delivery, HBOT markedly increases the amount of oxygen physically dissolved in plasma, thereby facilitating oxygen diffusion into hypoperfused tissues even in the presence of impaired capillary blood flow [9,11,12]. This effect is particularly relevant in severe traumatic ischemia, where endothelial swelling, interstitial edema, leukocyte adhesion, and capillary obstruction may significantly impair oxygen delivery despite restoration of macroscopic arterial circulation [7,14].

Under hyperbaric conditions, arterial oxygen tension may increase several-fold above physiological levels, substantially enhancing the diffusion gradient between plasma and ischemic tissue [9,12]. Because dissolved oxygen is capable of diffusing independently of hemoglobin-bound oxygen transport, HBOT may temporarily support aerobic cellular metabolism in critically hypoxic tissue located within partially perfused ischemic zones [12]. This concept appears especially important in traumatic skeletal muscle injury, where progression from reversible ischemia toward irreversible necrosis is strongly time-dependent [7,11]. Experimental observations suggest that preservation of tissue oxygenation during this potentially reversible phase may contribute to maintenance of cellular viability and limitation of secondary tissue loss [7].

In addition to improving oxygen delivery, HBOT appears to influence several mechanisms responsible for progressive microvascular deterioration after traumatic ischemia. One of the most clinically relevant effects is reduction of tissue edema [9,11,12]. Hyperoxia-induced vasoconstriction reduces blood flow in non-ischemic vascular beds without compromising tissue oxygen availability because of the markedly increased plasma oxygen content [12]. As a consequence, capillary hydrostatic pressure and transcapillary fluid extravasation may decrease, leading to attenuation of interstitial edema [11,12]. In crush injury and compartment syndrome, where elevated tissue pressure contributes directly to worsening perfusion and capillary collapse, edema reduction may partially interrupt the vicious cycle of ischemia, swelling, and further microvascular compromise, thereby potentially limiting progression of secondary tissue necrosis [9,11].

Beyond its hemodynamic effects, HBOT has been increasingly recognized as a modulator of ischemia-reperfusion injury [7,8,14]. Reperfusion-associated tissue damage is characterized by excessive production of reactive oxygen species (ROS), endothelial dysfunction, neutrophil activation, and progressive impairment of capillary perfusion [7,14]. Although hyperoxia might theoretically augment oxidative stress, experimental and preclinical studies suggest that HBOT may paradoxically attenuate several pathways involved in reperfusion-mediated injury [7,8,14].

One of the most extensively described mechanisms involves reduction of leukocyte-endothelial adhesion [7,14]. Experimental studies demonstrated that HBOT may inhibit β2 integrin (CD18)-dependent neutrophil adhesion and reduce expression of adhesion molecules involved in endothelial-leukocyte interactions, including intracellular adhesion molecule-1 (ICAM-1) and selectins [7,14]. Limitation of neutrophil adhesion may reduce endothelial injury, capillary plugging, and microvascular obstruction, thereby

improving tissue perfusion at the level of the microcirculation and potentially preserving viability of partially ischemic tissue [7,14]. This mechanism may be particularly important in potentially limiting progression of the no-reflow phenomenon, in which persistent capillary dysfunction continues despite restoration of large-vessel blood flow [7].

HBOT also appears to modulate oxidative stress through activation of endogenous antioxidant defense systems [8,14]. Experimental studies have reported increased activity of superoxide dismutase (SOD), catalase, glutathione-dependent antioxidant pathways, and heme oxygenase-1 following hyperbaric oxygen exposure [14]. Hyperbaric oxygen has additionally been associated with activation of nuclear factor erythroid 2-related factor 2 (NRF2), an important transcription factor involved in cellular resistance to oxidative injury [14]. Through these mechanisms, HBOT may reduce lipid peroxidation, mitochondrial dysfunction, endothelial damage, and ROS-mediated cellular injury observed after reperfusion [7,14].

Several studies have additionally demonstrated anti-inflammatory effects of HBOT at both cellular and molecular levels [7,8,14]. Hyperbaric oxygen exposure has been associated with reduced activity of pro-inflammatory signaling pathways involving nuclear factor kappa B (NF-κB), tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6) [14]. Experimental observations also suggest that HBOT may stabilize endothelial barrier integrity and reduce vascular permeability, potentially limiting secondary edema formation and preservation of microvascular architecture within injured tissue [7,14].

The biological effects of HBOT extend beyond acute modulation of inflammation and perfusion. Experimental and mechanistic studies suggest that hyperbaric oxygen may also influence pathways involved in tissue repair and regeneration [9,14]. HBOT has been associated with increased fibroblast proliferation, collagen synthesis, angiogenesis, and vascular endothelial growth factor (VEGF)-related signaling [9,14]. Improved transcutaneous oxygen tension and favorable changes in tissue perfusion parameters observed during HBOT additionally support the concept that maintenance of oxygen availability may facilitate survival of ischemic but potentially salvageable tissue during the early stages of traumatic injury [15].

Importantly, currently available evidence suggests that the potential effectiveness of HBOT is strongly dependent on timing of intervention [7,11]. The biological rationale for HBOT appears most relevant during the phase of reversible ischemic injury, before development of irreversible tissue damage, severe endothelial destruction, and complete microvascular collapse [7,11]. Similar timing-dependent mechanisms associated with potentially reversible hypoxic cellular injury have also been described in other acute conditions treated with HBOT, including acute acoustic trauma and sudden sensorineural hearing loss [19]. Consequently, HBOT should not be considered a replacement for definitive surgical treatment such as fasciotomy, debridement, or vascular reconstruction, but rather a supportive strategy aimed at limiting progression of secondary ischemic necrosis and improving conditions for preservation of potentially salvageable tissue [9,11]. Taken together, the available mechanistic evidence suggests that HBOT may exert its therapeutic effects through simultaneous modulation of tissue oxygenation, edema formation, inflammatory activation, oxidative stress, endothelial dysfunction, and microvascular perfusion — processes that collectively play a central role in the progression of acute traumatic ischemic injury.

5. Results

Table 1. Summary of included clinical studies evaluating adjunctive hyperbaric oxygen therapy (HBOT) in acute traumatic ischemic injuries of the extremities.

Study	Design/ population	Injury type	HBOT protocol	Main findings	Key limitations
Bouachour et al. (1996) [20]	Randomized double-blind placebo-controlled trial; 36 patients	Severe crush injuries	2.5 ATA, 90 min, twice daily for 6 days	Reduced tissue necrosis and repeated surgical procedures; no amputations in HBOT group	Small sample size
HOLLT Trial (2022) [5]	Multicentre randomized clinical trial; 120 patients	Severe lower limb trauma	2.4 ATA, 90 min, 12 HBOT sessions	Reduced major soft tissue necrosis and late complications; despite a non-significant primary composite endpoint	Heterogeneous trauma patterns

Study	Design/ population	Injury type	HBOT protocol	Main findings	Key limitations
Roje et al. (2008) [21]	Retrospective cohort; 388 war injury reconstructions	Upper and lower extremity war injuries	Adjunctive perioperative HBOT	Reduced reconstructive complications including infection, graft loss and flap necrosis	Retrospective design
Yamada et al. (2014) [22]	Observational cohort; 29 patients	Crush injuries	Early adjunctive HBOT	Reduced infectious complications and need for drainage procedures	Small cohort; non-randomized
Jirangkul et al. (2021) [6]	Retrospective cohort; 18 patients	Severe mangled extremities	Adjunctive HBOT following limb reconstruction	Reported limb salvage in 94% of patients	No control group
Shupak et al. (1987) [23]	Case series; 13 patients	Acute peripheral post-traumatic ischemia	HBOT after revascularization	Limb salvage or reduction of ischemia in most patients	Small uncontrolled study
Monies-Chass et al. (1977) [24]	Case series; 7 patients	Persistent ischemia after vascular repair	2.8 ATA HBOT	Reported preservation of ischemic tissue and limitation of gangrene progression	Very small historical cohort
Oley et al. (2021) [25]	Randomized biomarker study	Crush injury	Adjunctive HBOT	Increased VEGF serum levels and VEGF mRNA expression	Biomarker endpoints without clinical outcome assessment

Clinical Evidence Overview

The currently available evidence regarding hyperbaric oxygen therapy (HBOT) in acute traumatic ischemic injuries of the extremities remains limited and heterogeneous. Published studies include randomized controlled trials, retrospective cohort studies, observational cohorts, case series, and case reports involving crush injuries, compartment syndrome, post-traumatic peripheral ischemia, mangled extremities, and severe lower limb soft tissue trauma [1,2,5,6,16–18,20–24]. Considerable variability exists with respect to injury severity, timing of HBOT initiation, concomitant surgical interventions, treatment protocols, and reported outcome measures. The main characteristics and findings of the included clinical studies are summarized in Table 1.

The systematic review by Kwee et al. identified seven eligible studies involving a total of 229 patients with severe lower limb soft tissue injuries, including two randomized clinical trials, one retrospective cohort study, three case series, and one case report [1]. Similarly, the Cochrane review by Eskes et al. concluded that the currently available evidence remains limited by small sample sizes, methodological heterogeneity, and variable risk of bias across published studies [16]. Earlier systematic reviews likewise emphasized the limited number of adequately powered randomized studies evaluating HBOT in traumatic wounds and limb-threatening ischemic injuries [17,18].

Tissue Necrosis, Wound Healing, and Soft Tissue Preservation

Across both randomized and observational studies, adjunctive HBOT was most consistently associated with lower rates of tissue necrosis, wound-related complications, and repeated surgical interventions in patients with severe traumatic extremity injuries [5,20,21,22].

The strongest randomized evidence was provided by Bouachour et al. in a double-blind placebo-controlled trial involving 36 patients with severe crush injuries of the extremities [20]. Complete wound healing without tissue necrosis requiring surgical excision was achieved in 17 of 18 HBOT-treated patients (94%) compared with 10 of 18 control patients (56%; $p < 0.01$) [20]. Additional surgical procedures were required in one HBOT-treated patient versus six control patients ($p < 0.05$), while no amputations occurred in the HBOT group compared with two amputations in the control group [20].

In the HOLLT randomized clinical trial evaluating patients with severe lower limb trauma requiring orthopedic fixation or reconstructive procedures, the composite primary endpoint of significant soft tissue necrosis and/or infection occurred in 43% of HBOT-treated patients compared with 58% of controls, although this difference did not reach statistical significance (OR 0.55; 95% CI 0.25–1.18; $p = 0.12$) [5]. However, major soft tissue necrosis occurred less frequently in the HBOT group (29% vs 53%; OR 0.35; 95% CI 0.16–0.78; $p = 0.01$), while serious late complications were also reduced (12% vs 35%; OR 0.24; 95% CI 0.08–0.68;

p = 0.007) [5]. Delayed fracture union occurred less frequently among HBOT-treated patients (10% vs 25%; OR 0.31; 95% CI 0.10–0.95; p = 0.04) [5].

Similar findings were observed in retrospective cohorts evaluating reconstructive extremity trauma. Roje et al. demonstrated lower rates of skin graft lysis/loss (23% vs 52%; p < 0.001), flap necrosis (15% vs 51%; p < 0.001), deep soft-tissue infection (35% vs 68%; p < 0.001), and osteomyelitis (63% vs 74%; p = 0.030) among HBOT-treated patients undergoing reconstruction of upper and lower extremity war injuries [21]. These associations remained significant after adjustment for differences in surgical management strategies [21].

Observational studies evaluating traumatic vascular compromise and crush injuries likewise reported improved preservation of ischemic but viable tissue following adjunctive HBOT administration [22,24]. Monies-Chass et al. described persistent ischemia despite technically successful vascular reconstruction in several trauma patients, with reported avoidance of progression to gangrene following adjunctive HBOT treatment [24].

Yamada et al. reported no infections in HBOT-treated crush injury patients compared with six infections in controls (0/16 vs 6/13; p = 0.003), while additional drainage procedures were required in five control patients and none of the HBOT-treated patients (0/16 vs 5/13; p = 0.013) [22].

Infection, Edema, and Postoperative Complications

Reduction of postoperative infectious and reconstructive complications was a recurrent finding across both retrospective cohorts and prospective trauma studies evaluating adjunctive HBOT in severe extremity injuries [5,21,22]. Lower rates of deep infection, graft loss, wound dehiscence, and flap necrosis were reported among HBOT-treated patients undergoing reconstructive or limb salvage procedures [5,21].

In the HOLLT trial, fewer infectious complications were observed in HBOT-treated patients, although some infection-related endpoints did not reach statistical significance [5]. Similarly, Roje et al. demonstrated significantly lower rates of wound infection and graft-related complications in HBOT-treated patients undergoing extremity reconstruction [21].

Across observational studies, reductions in tissue edema, improved wound stability, and preservation of marginally viable tissue were recurrent findings associated with HBOT administration [6,21,22,24]. In the randomized trial by Bouachour et al., persistent skin cyanosis during treatment was significantly less frequent in HBOT-treated patients, while transcutaneous oxygen tension progressively increased in patients with successful healing outcomes [20].

Limb Salvage and Amputation-Related Outcomes

Evidence regarding limb salvage and amputation prevention remains less definitive because most available studies were underpowered for amputation-specific endpoints.

Nevertheless, multiple studies suggested improved preservation of threatened extremities and reduced progression of irreversible tissue injury following adjunctive HBOT administration [5,6,20,23]. In the Bouachour trial, no amputations occurred in the HBOT group compared with two amputations in control patients [20]. Jirangkul et al. reported limb salvage in 17 of 18 patients (94%) with severe mangled extremities treated with adjunctive HBOT [6].

In a case series involving patients with acute peripheral post-traumatic ischemia, Shupak et al. reported complete limb salvage in 8 of 13 patients (62%), distal reduction of ischemia in 4 patients (31%), and no clinical improvement in one patient (8%) following adjunctive HBOT [23].

Despite these findings, systematic reviews consistently concluded that currently available evidence remains insufficient to establish definitive conclusions regarding amputation prevention because of limited sample sizes and substantial study heterogeneity [1,16–18].

Biological and Mechanistic Findings

Limited clinical studies have evaluated biological markers associated with HBOT in traumatic ischemic injuries.

In a randomized controlled biomarker study, Oley et al. demonstrated that HBOT increased vascular endothelial growth factor (VEGF) serum levels from 6181 ng/mL to more than 11,000 ng/mL, while VEGF messenger RNA expression increased from 9.5-fold to 13.1-fold following treatment. These within-group changes were statistically significant (p < 0.001). However, comparisons of treatment-related changes between the HBOT and control groups did not reach statistical significance [25].

Lindstrom et al. evaluated perfusion parameters and transcutaneous oxygen measurements in trauma patients with tibial fractures undergoing HBOT [15]. HBOT administration resulted in increased

transcutaneous oxygen tension and improved tissue perfusion parameters during treatment sessions, supporting the physiological rationale for enhanced oxygen delivery to injured tissues [15].

Experimental and mechanistic studies summarized in multiple reviews additionally suggested that HBOT may attenuate ischemia-reperfusion injury, reduce tissue edema, improve microvascular perfusion, and preserve marginally viable tissue following severe traumatic ischemia [2,4,7–14].

Timing of HBOT and Treatment Protocols

Substantial heterogeneity was observed among HBOT protocols used in traumatic ischemic injuries.

Most studies utilized treatment pressures between 2.0 and 2.5 atmospheres absolute (ATA), with treatment durations ranging from approximately 90 to 120 minutes per session [2,5,11,20,26]. In severe crush injuries and compartment syndromes, treatment schedules frequently involved two or three sessions daily during the initial 24–48 hours following injury [2,11].

Bouachour et al. initiated HBOT within 24 hours after initial surgical management and utilized 90-minute sessions at 2.5 ATA twice daily for six days [20]. Strauss and Garcia-Covarrubias et al. emphasized that early treatment initiation may be important for limiting secondary ischemic injury and preserving marginally perfused tissue [2,11]. The European Consensus Conference on Hyperbaric Medicine recognized acute traumatic ischemia as an accepted indication for HBOT when used as an adjunct to standard surgical and critical care management [26].

Overall Synthesis of Available Clinical Evidence

Overall, the currently available evidence suggests that adjunctive HBOT may reduce tissue necrosis, wound-related complications, and the need for repeated surgical procedures in selected patients with severe traumatic ischemic injuries of the extremities [1,5,16–18,20]. Across both randomized and observational studies, the most consistent findings involved reduced soft tissue necrosis, improved wound-related outcomes, and improved preservation of marginally viable tissue [5,20,21,22].

Evidence supporting reductions in tissue necrosis and wound complications appears stronger than evidence regarding definitive amputation prevention or long-term functional recovery. However, the current evidence base remains limited by small study populations, heterogeneous injury patterns, variability in HBOT protocols, and the relatively low number of high-quality randomized clinical trials [1,16–18]. Consequently, although the available literature supports the biological and clinical rationale for adjunctive HBOT in acute traumatic ischemic injuries, definitive conclusions regarding optimal treatment protocols, patient selection, and long-term limb salvage outcomes remain limited.

6. Discussion

The available evidence suggests that hyperbaric oxygen therapy (HBOT) may primarily influence the progression of secondary ischemic injury rather than reverse the consequences of the initial traumatic insult itself. Across both randomized and observational studies, the most consistent clinical findings involved reductions in tissue necrosis, wound-related complications, and deterioration of marginally viable tissue rather than definitive prevention of amputation or restoration of severely destroyed tissue [1,5,16–18,20]. This distinction is particularly important in traumatic ischemia, where final tissue viability is often determined not only by the severity of the initial mechanical injury, but also by the subsequent evolution of edema formation, endothelial dysfunction, inflammatory activation, impaired capillary perfusion, and ischemia-reperfusion injury [7–10].

The biological rationale supporting HBOT in traumatic ischemia aligns closely with the mechanisms responsible for secondary tissue injury progression after severe extremity trauma. Experimental and mechanistic studies have demonstrated that ischemia-reperfusion injury contributes substantially to endothelial dysfunction, leukocyte-endothelial adhesion, oxidative stress, capillary obstruction, and progressive impairment of local oxygen delivery even after restoration of macroscopic arterial circulation [7–10]. Consequently, tissue surrounding the primary zone of injury may remain metabolically compromised despite technically successful surgical management. The clinical findings observed in studies such as HOLLT, Bouachour et al., and Roje et al. are therefore biologically coherent with the proposed effects of HBOT on tissue oxygenation, edema reduction, inflammatory modulation, and preservation of tissue perfusion [5,20,21].

Importantly, published evidence suggests that HBOT is unlikely to substantially alter outcomes in tissue that has already undergone irreversible ischemic necrosis at the time of treatment initiation. Instead, the observed clinical benefits may primarily result from attenuation of secondary ischemic progression occurring within partially perfused or metabolically compromised tissue surrounding the primary injury zone. This concept may explain why the strongest clinical findings across published studies involved reduced progression

of tissue necrosis, lower rates of wound-related complications, and preservation of threatened soft tissue rather than dramatic improvements in major amputation endpoints [5,20,21,22].

Several biological mechanisms may contribute to these effects. Hyperbaric oxygen therapy significantly increases dissolved oxygen content in plasma, thereby improving oxygen diffusion into hypoxic tissue even under conditions of impaired regional circulation [9,12]. Experimental evidence additionally suggests that HBOT may attenuate leukocyte-endothelial interactions, reduce oxidative endothelial injury, decrease tissue edema, and improve capillary perfusion following ischemia-reperfusion injury [7–10,13,14]. These mechanisms are particularly relevant in crush injuries and compartment syndrome, where progressive edema and elevated compartment pressures may further impair local oxygen delivery and perpetuate a vicious cycle of tissue hypoxia and secondary necrosis [2–4,11].

The relationship between HBOT and treatment timing appears especially important. Both experimental and clinical observations suggest that HBOT is most likely to provide benefit before irreversible microvascular collapse and coagulative necrosis become fully established [2,11]. This interpretation is consistent with the pathophysiology of traumatic ischemia itself. Once prolonged hypoxia results in endothelial swelling, capillary obstruction, mitochondrial dysfunction, and extensive cellular membrane disruption, restoration of oxygen delivery alone may no longer be sufficient to prevent progression toward irreversible necrosis [7–10]. Consequently, HBOT may be most valuable during the dynamic phase of evolving ischemia, when tissue remains threatened but potentially salvageable. The relatively favorable outcomes observed in studies utilizing early HBOT initiation support this interpretation [2,5,11,20].

This concept additionally has important implications for patient selection. The existing literature suggests that patients with evolving ischemia, incomplete microvascular collapse, reperfusion-associated injury, or marginally viable soft tissue may represent the subgroup most likely to benefit from adjunctive HBOT. In contrast, patients with extensive devascularization, prolonged complete ischemia, or irreversible skeletal muscle destruction may derive substantially less benefit because the biological substrate required for tissue recovery is already absent. This distinction may partially explain the heterogeneity of outcomes observed across published studies and may also contribute to inconsistent findings regarding limb salvage endpoints [1,5,16–18].

Importantly, heterogeneity within the available literature likely reflects not only methodological limitations, but also substantial biological variability between injury patterns themselves. Crush syndrome, compartment syndrome, post-traumatic peripheral ischemia, and complex mangled extremities represent fundamentally different pathophysiological states with varying degrees of vascular disruption, tissue viability, inflammatory activation, reperfusion injury, and reconstructive potential [2–4,7–10]. Similarly, reperfused ischemic tissue differs biologically from prolonged complete ischemia associated with extensive skeletal muscle necrosis. Variability in HBOT outcomes may therefore partly represent expected differences in underlying tissue physiology rather than solely inconsistencies in study design.

Methodological limitations nevertheless remain substantial. Most published studies involve relatively small patient populations and heterogeneous injury classification systems [1,16–18]. Many cohorts additionally combine different trauma phenotypes, ranging from compartment syndrome and crush injury to reconstructive vascular trauma and war-related extremity injuries [1,5,21]. Variability in surgical management, debridement strategies, fasciotomy timing, vascular reconstruction, negative-pressure wound therapy, and reconstructive techniques further complicates direct comparison between studies. Selection bias also remains an important concern, particularly in retrospective cohorts where HBOT may have been preferentially administered to patients considered more salvageable or physiologically stable. Furthermore, HBOT protocols themselves vary substantially with respect to treatment pressure, number of sessions, treatment duration, and timing of initiation [1,11,26].

Interpretation of amputation-related outcomes remains particularly complex. Major amputation is not purely a biological endpoint determined exclusively by tissue oxygenation or wound healing. Decisions regarding limb salvage are influenced by multiple surgical, reconstructive, neurological, infectious, and patient-related factors, including the extent of vascular disruption, nerve injury, skeletal destruction, contamination, rehabilitation potential, and overall patient condition. In addition, thresholds for amputation may differ substantially between institutions, trauma systems, military and civilian settings, and individual reconstructive teams. Therefore, the absence of definitive evidence demonstrating reduced amputation rates should not necessarily be interpreted as evidence that HBOT lacks clinically meaningful effects on tissue preservation [1,16–18].

Another important limitation of the current evidence base is the relative scarcity of long-term functional outcome data. Although several studies demonstrated reductions in tissue necrosis, wound complications, and repeated surgical procedures, relatively few investigations evaluated long-term neurological recovery, chronic pain, functional mobility, return to activity, or patient-reported quality of life [1,16–18]. This distinction is clinically important because successful limb salvage does not necessarily correspond to satisfactory long-term functional recovery.

Despite these limitations, the overall consistency between the biological rationale of HBOT and the observed clinical findings remains notable. Experimental evidence demonstrating improved tissue oxygenation, attenuation of ischemia-reperfusion injury, modulation of inflammatory pathways, and preservation of tissue perfusion corresponds closely with the reduced rates of tissue necrosis and wound-related complications reported in clinical studies [5,7–10,13,14]. Importantly, HBOT should not be viewed as a replacement for surgical intervention, but rather as a potential adjunctive therapy integrated within comprehensive trauma management including revascularization, fasciotomy, debridement, fracture stabilization, and reconstructive surgery [2,11,26].

Collectively, the available evidence supports the concept that HBOT may serve primarily as a tissue-preserving adjunct during the potentially reversible phase of traumatic ischemic progression. Although evidence supporting reductions in tissue necrosis and wound-related complications appears increasingly consistent, definitive conclusions regarding long-term limb salvage and functional recovery remain limited by the quality, heterogeneity, and scale of existing clinical studies.

7. Conclusions

Hyperbaric oxygen therapy (HBOT) represents a biologically plausible adjunctive treatment strategy in acute traumatic ischemic injuries of the extremities. The available evidence suggests that HBOT may contribute to reductions in tissue necrosis, wound-related complications, and progression of secondary ischemic injury, particularly in patients with threatened but potentially salvageable tissue. Across both randomized and observational studies, the most consistent findings involved preservation of viable soft tissue and reduction of wound-related complications rather than definitive evidence of improved long-term limb salvage or functional recovery.

The proposed therapeutic effects of HBOT appear closely aligned with the pathophysiology of traumatic ischemia and ischemia-reperfusion injury. Experimental and mechanistic evidence suggests that HBOT may improve oxygen delivery, attenuate inflammatory and oxidative injury, reduce edema formation, and support preservation of regional perfusion during the potentially reversible phase of ischemia. These mechanisms may be particularly relevant before irreversible microvascular failure and coagulative necrosis become fully established.

However, the current evidence base remains limited by substantial heterogeneity in injury patterns, treatment protocols, study design, and outcome reporting. Most available studies involve relatively small patient populations, while high-quality randomized clinical trials remain scarce. In addition, long-term functional outcomes and standardized patient selection criteria remain insufficiently studied.

Overall, the currently available literature supports the role of HBOT as a tissue-preserving adjunct integrated within comprehensive surgical and critical care management of severe extremity trauma. Future multicenter studies using standardized injury classification systems, clearly defined HBOT protocols, and long-term functional outcome assessment will be essential to better define the optimal role of HBOT in acute traumatic ischemic injuries of the extremities.

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