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A Deep Dive into the Role of Hyperbaric Oxygen Therapy in Enhancing Burn Wound Healing

Nabila Fairuz Sari[1], **Ahmad Fawzy**[2]

[1]Faculty of Medicine, University of Jenderal Soedirman, Indonesia

[2]Department of Surgery, Faculty of Medicine, University of Jenderal Soedirman, Prof. Dr. Margono Soekarjo Hospital, Indonesia

ABSTRACT

Burn injuries are a significant cause of admissions to burn and plastic surgery units. One treatment modality for burn injury patients is hyperbaric oxygen therapy (HBOT). HBOT exposes patients to high concentrations of oxygen at increased atmospheric pressure levels. It can enhance burn wound healing by promoting cellular response, inflammatory cytokines, neovascularization, and collagen formation.

This review explores the role of HBOT in enhancing burn wound healing, particularly in plastic surgery. We gathered and analyzed information from various web databases, using specific keywords related to burn wound injuries and HBOT. Inclusion criteria encompassed open-access journals and articles relevant to the subject matter.

This review revealed that despite some controversial findings and the absence of treatment guidelines for burn patients, HBOT can complement other modalities. Side effects may include neurological and ophthalmic toxicity, as well as mild effects such as nausea and gastrointestinal disturbance.

In conclusion, HBOT serves as an adjunctive therapy for promoting wound healing, including in burn patients. Evidence suggests its effectiveness in plastic surgery, potentially reducing hospital stays, costs, and recovery times. Further prospective randomized controlled trials with larger sample sizes and blinding are necessary to address remaining controversies and evaluate the full benefits of HBOT.

KEYWORDS: hyperbaric oxygen, HBOT, burn, wound healing

ARTICLE DETAILS

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INTRODUCTION[1-5]

Burns occur when skin contacts heat sources such as high temperatures, electricity, friction, radiation, or chemicals, impacting wound healing and survival. Location, temperature, and exposure duration significantly influence injury severity and outcomes. Burns allow entry of harmful microorganisms, risking infection and sepsis, and often result in functional and aesthetic damage. This has made burns a leading cause of admissions to burn and plastic surgery units globally.

Hyperbaric oxygen therapy (HBOT), introduced in 1965 for thermal injuries, involves treating patients with high oxygen levels under increased pressure. The Undersea and Hyperbaric Medical Society specifies this pressure at a minimum of 2 ATA (atmosphere absolute). HBOT is recognized for 14 conditions, including air embolism and severe anemia, and is proven effective in primary and complementary treatments for conditions like carbon monoxide poisoning and diabetic foot. While HBOT promotes healing by boosting revascularization and immune responses, skepticism about its efficacy persists due to limited evidence-based studies.

METHODS

We compiled this literature review and analyzing information from numerous web databases. Our inclusion criteria included: (1) the journal were open accessible and (2) the articles which were matched and relevant to the subject matter covered in this literature review. We were using “Burn Injury”, “Hyperbaric Oxygen Therapy”, and “Hyberbaric Oxygen Therapy in Burn Injuries” keywords in the literature search on PubMed, Google Scholar, and Elsevier. Data were

collected, organized, and summarized into this literature review.

PHYSIOLOGY OF BURN WOUND HEALING

Pathophysiology of Burn Injuries[6-13]

Burn injuries cause coagulative necrosis across skin layers. The skin, acting as a barrier, usually limits deeper damage, but the severity depends on factors like temperature and exposure duration. Burned skin can be divided into three zones:

- Zone of coagulation: shows irreversible necrosis right after injury.
- Zone of stasis: surrounds the coagulation zone, may recover or worsen to necrosis due to vascular and inflammatory damage.
- Zone of hyperaemia: features inflamed, dilated vessels with increased blood flow and minimal necrosis risk unless complications like sepsis occur.

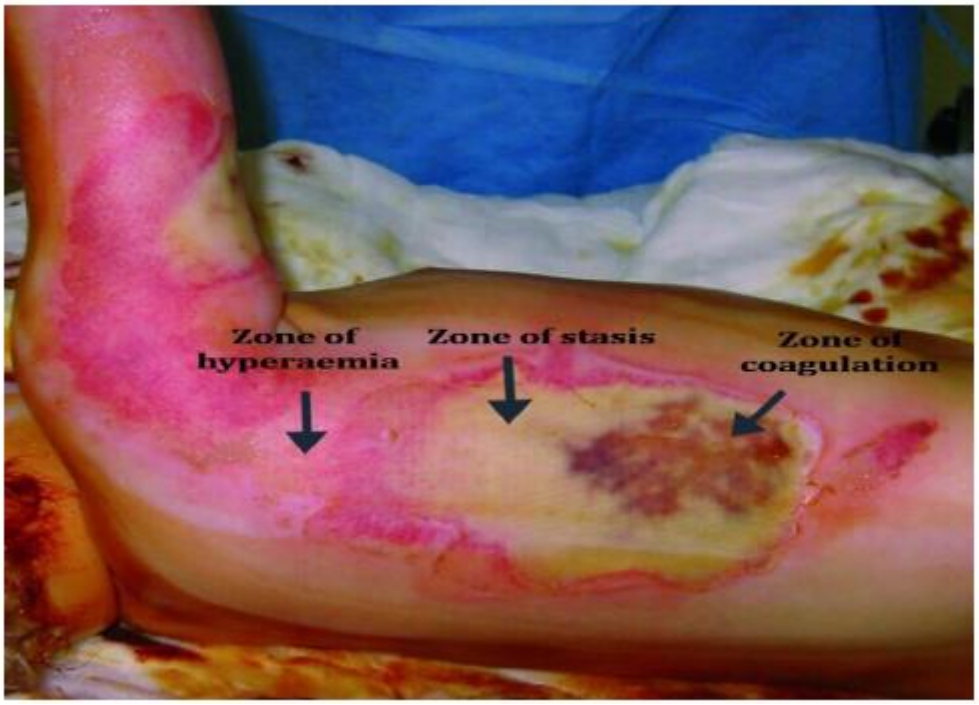

Figure 1. Clinical images of burn zones.[6]

Burns over 30% of total body surface area (TBSA) cause significant hypovolemia and a systemic inflammatory response, leading to burn shock and potential multiple organ failure due to cardiovascular and microcirculatory dysfunction. Plasma leaks and systemic vascular resistance (SVR) increase, altering hemodynamics and decreasing cardiac output.

Burns also trigger a rapid initial increase in tissue water content, followed by progressive fluid accumulation, doubling water content within the first hour. These changes extend to distant skeletal muscles, causing membrane depolarization and ionic shifts, documented in cells like cardiac and hepatic. Reduced adenosine triphosphate (ATP) levels and increased adenosine triphosphatase (ATPase) activity further exacerbate cellular dysfunction.

Moreover, burns induce a hypermetabolic state increasing energy expenditure. This response involves hormonal and inflammatory mediators like catecholamines, cortisol, and interleukins-1 and -6 (IL-1, IL-6). The "ebb" phase following injury lowers oxygen consumption and elevates glucose levels, while the "flow" phase increases thermogenesis via mitochondrial activity.

Nutritional support is critical post-burn to meet increased metabolic demands, although burns impair digestion and nutrient absorption, complicating recovery. Thermal trauma affects liver function and alters immune responses,

Increasing infection risks due to compromised skin barriers and weakened immune systems.

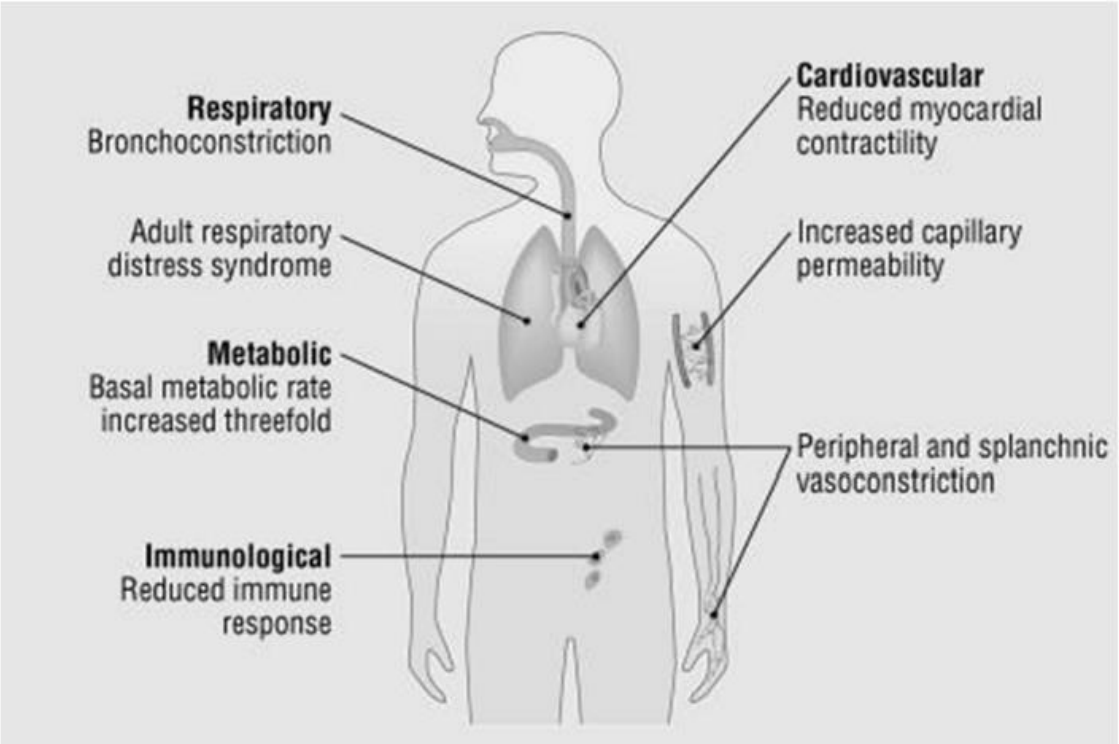

Figure 2. Systemic changes in burn injuries.[6]

Phases of Burn Wound Healing[14-16]

Wound healing involves cytokines, growth factors, blood cells, the extracellular matrix, and parenchymal cells across four phases: hemostasis, inflammation, tissue proliferation, and maturation.

In the hemostasis phase, skin injury triggers vasoconstriction to stop bleeding, followed by platelet aggregation releasing clotting factors to activate the coagulation cascades. These processes convert prothrombin into thrombin and fibrinogen into fibrin. Platelets also release cytokines and growth factors, including platelet-derived growth factor (PDGF), epidermal growth factor (EGF), and transforming growth factor beta (TGF-β), facilitating healing.

The inflammation phase starts within 24 hours of injury, lasting days to weeks, with platelets and inflammatory cells initiating healing. Enzymes from cell membranes promote prostaglandins and leukotrienes synthesis, while capillary endothelial cells secrete histamines increasing capillary permeability and causing edema.

In the second inflammation stage, fluid and cytokines move through capillaries, enhancing the immune response. White blood cells, including macrophages and neutrophils, migrate to the wound, removing dead cells. Activated macrophages and endothelial cells produce angiogenesis factors like platelet-derived growth factor (PDGF) and transforming growth factor beta (TGF-β), stimulating fibroblast migration and proliferation.

During the proliferation phase (3 days to 2-4 weeks post-injury), fibroblasts produce collagen and initiate neovascularization under hypoxia-induced conditions. Macrophages release vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF), while re-epithelialization by epidermal growth factor (EGF) and transforming growth factor beta (TGF-β) occurs, leading to wound closure by keratinocytes.

The maturation phase involves protein degradation and collagen reorganization, potentially extending up to 2 years. Chronic wounds, impacted by factors like ischemia or diabetes, can impede these processes, affecting white cell function and fibroblast activity.

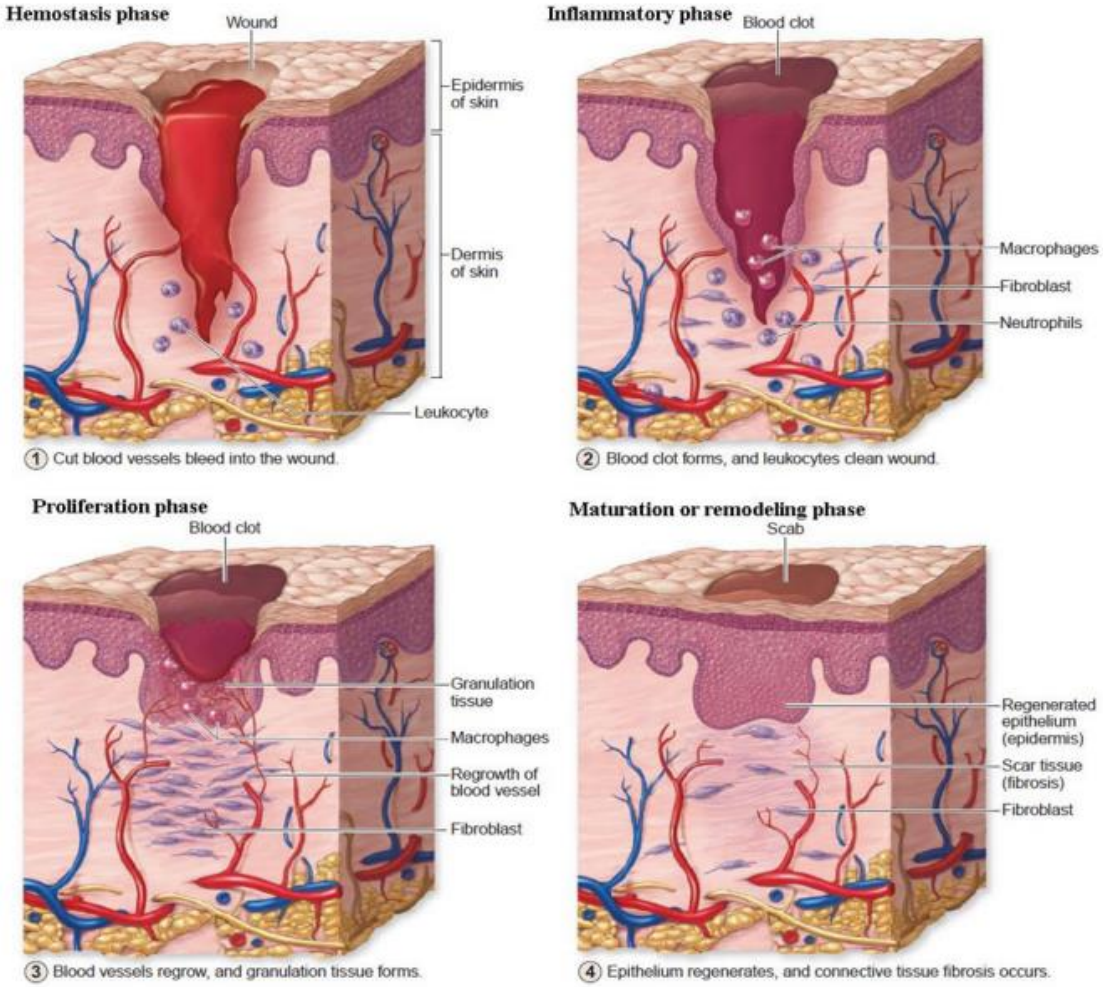

Figure 3. Wound healing process.[14]

Factors Influencing Burn Wound Healing[17,18]

Burn wound recovery is impacted by various factors such as those specific to the injury site, the overall effects of the burn trauma on the body, and factors associated with the patient clinical condition and any accompanying health issues. These factors are detailed and their impacts are elucidated in Table 1 and Table 2.

Table 1. Local and systemic factors influencing burn wound healing.

Factors in burn wound	Description
Necrosis	devitalized tissues delay wound healing
Desiccation	epithelization is faster if the local environment is moist and hydrated
Maceration	a rapid removal of urine or fecals (proper hygiene) keep skin integrity
Infection	invasion into deeper tissues, destruction of granulation tissues – proper topical and systemic antibiotic should be used
Trauma/edema	the local blood supply is affected + limitation of the local nutrients exchange + obstruction of the venous and lymphatic return, and the healing cannot begi
Local pressure	the the blood supply (capillary) is disrupted – delayed healing
Anemia	a low hemoglobin level decrease oxygen-carrying capacity
Hypotension	low tissular perfusion pressure – delayed healing
Ischemia	malnourishment of the adjacent tissues, cell death – impairs and delays wound healing

Table 2. Patient-related factors influencing burn wound healing18

Patient condition	Description
Age	in older patients (compromised immune system, ineffective inflammatory response, hormonal imbalances, low cellular turnover, poor nutritional status, and hydration) the healing process is slower – prolonged hospitalization
Gender	higher mortality in women (different hormonal and inflammatory responses in men and women)
Body type	obese patients (poor blood supply in the adipose tissue, protein malnutrition) have a delayed wound healing
Stress	reduced levels of pro-inflammatory cytokine, hormonal imbalances – delayed wound healing
Nutritional status	albumin, prealbumin, transferrin, lymphocyte – markers of malnutrition – monitored regularly
Chronic disease	various chronic diseases delay the healing process: coronary artery disease, diabetes mellitus, cancer, peripheral vascular disease, chronic obstructive pulmonary disease, chronic kidney disease, cirrhosis
Chronic medication	glucocorticoids and non-steroidal anti-inflammatory drugs – decrease collagen production, suppress the immune system aspirin inhibit platelet action and cell destruction
Immunosuppression	due to medication or cancer – impaired wound healing
Radiation therapy	through skin ulcers and hypertrophy impairs the healing
Vascular insufficiency	chronic wounds and ulcers decrease the local blood supply and tissues integrity
Smoking	vasoconstriction + hypoxia – delays wound healing
Alcoholism	reduced resistance to infections – delayed wound healing

Role of Oxygen in Wound Healing Process[19-24]

Blood and oxygen circulation to wounds is critical for inflammation and healing. Disrupted blood flow, increased body oxygen demand, and health conditions can impair circulation. Low tissue oxygen (below 30mmHg) impacts all healing stages. Oxygen within cells aids oxidative phosphorylation in mitochondria, essential for ATP production and maintaining cellular functions. Studies show that ROS like hydrogen peroxide (H_2O_2) play significant roles in healing and antibacterial activities.

A study in 1984 by Knighton and colleagues found that higher inhaled oxygen reduced infections in animal skin models. Oxygen enables neutrophils to generate ROS, crucial during the early inflammatory stage and later in angiogenesis by triggering vascular endothelial growth factor (VEGF) production through hypoxia. Studies from the early 1980s to recent findings suggest that while low oxygen levels promote new blood vessels via HIF-1 and vascular endothelial growth factor (VEGF), adequate oxygen levels are beneficial throughout all healing phases.

Neutrophils, crucial in initial inflammation, produce ROS influencing oxygen consumption and their antibacterial effectiveness, which can be enhanced by high inhaled oxygen levels. HIF-1α activates under hypoxia, enhancing gene expression for various functions, crucial for maintaining oxygen balance and influencing neutrophil activation and angiogenesis.

For collagen synthesis in wound healing, oxygen is vital for proline and lysine hydroxylation, necessary for collagen stability and release. Oxygen-dependent enzymes like prolyl hydroxylase and lysyl oxidase are crucial for collagen synthesis and cross-linking, influencing fibroblast to myofibroblast differentiation in wound contraction.

Table 3. Role of oxygen in each steps of wound healing process[25]

Phase	Role of oxygen
Inflammation	Prevention of infection via: • Increased ROS activity in oxidative killing of bacteria • ROS role in inducing neutrophil chemotaxis • Optimal production of ROS by NADPH-linked oxygenase • Synergism with antibiotics
Proliferation	• Increased reepithelialization via ROS role in the function of growth factors, such as epidermal growth factor (EGF)

	• Increased keratinocyte differentiation and keratinocyte migration • Increased production of fibroblasts and endothelial cells
Collagen synthesis	• Induction of basic fibroblast growth factor via ROS production • Optimal function of enzymes for proper posttranslational hydroxylation and cross-linking of collagen • Enhanced wound contraction by triggering myofibroblast differentiation
Angiogenesis	• Induction of vascular endothelial growth factor (VEGF) via destabilization of normoxia

MECHANISM OF ACTION OF HYPERBARIC OXYGEN THERAPY (HBOT)

Overview of Hyperbaric Oxygen Therapy (HBOT)[3,4,25-28]

Hyperbaric oxygen therapy (HBOT) uses pure oxygen in a pressurized chamber set to at least 2 atmospheres absolute (ATA) to treat various medical conditions. The Undersea and Hyperbaric Medical Society (UHMS) recommends pressures of 1.4 ATA or higher. Initially developed in 1662 by British physician Henshaw, HBOT evolved despite early challenges with oxygen toxicity, highlighted by Lavoisier in 1789 and later defined by Paul Bert in 1872 as the neurotoxic effects of oxygen (Paul Bert effect). Today, HBOT has 14 approved applications including treatment for air embolism and severe anemia, and roles in managing conditions like carbon monoxide poisoning and diabetic foot, as noted by the recent European Consensus Conference on Hyperbaric Medicine.

HBOT works by increasing blood oxygen levels as per Henry's Law, shrinking blood gas bubbles through Boyle's Law, and enhancing oxygen diffusion from lungs to tissues, efficiently treating hypoxia and aiding wound healing and tissue repair.

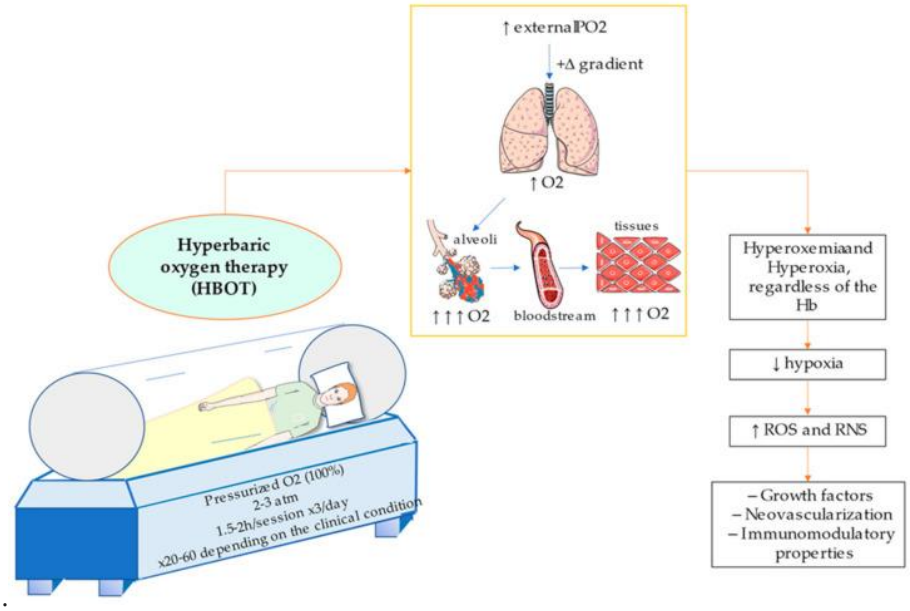

Figure 4. An illustration of a monoplace hyperbaric chamber and the impact of hyperbaric oxygen therapy. Typically, pressurized oxygen at 2-3 atmospheres and 100% concentration is administered for 1.5-2 hours per session, repeated thrice daily. The number of sessions, ranging from 20 to 60, varies based on the patient's condition. Inhaling air from an externally increased oxygen pressure results in a positive gradient, facilitating higher oxygen intake. This increased oxygen diffusion reaches the alveoli, bloodstream, and subsequently enhances oxygen delivery to tissues. This "hyperoxemia" and "hyperoxia" effect is not reliant on hemoglobin and reduces tissue hypoxia. Consequently, it leads to a greater production of reactive oxygen species (ROS) and reactive nitrogen species (RNS), triggering increased growth factor expression, promoting neovascularization, and enhancing immunomodulatory properties.[28]

Effects of Hyperbaric Oxygen in Cellular Processes[29-32]

Under normal oxygen and pressure conditions, humans regulate oxygen to support metabolism and minimize harmful reactive oxygen and nitrogen species (RONS) production. In high-pressure oxygen environments like hyperbaric oxygen therapy (HBOT), the body employs mechanisms such as vasoconstriction and enhancing antioxidant defenses to manage increased oxygen levels and oxidative stress. HBOT increases both reactive nitrogen species (RNS), notably nitric oxide (NO) from inducible nitric oxide synthase (iNOS), and reactive oxygen species (ROS), primarily hydrogen peroxide (H_2O_2). While high RNS and ROS levels can threaten cell survival, controlled HBOT doses (2.4 ATA) positively affect

wound healing by elevating tissue oxygen and hydrogen peroxide (H_2O_2) levels. This hydrogen peroxide (H_2O_2) acts as a secondary messenger activating Nuclear Factor Kappa Beta (NF-kβ), which drives rapid gene transcription and regulates inflammatory responses and gene expression for cell adhesion molecules.

RONS mainly arise from cellular respiration, enzyme reactions with oxidase enzymes, or direct biomolecule oxidation occurring in mitochondria, endoplasmic reticulum, and other cellular locations. Significant sources include the mitochondrial electron transport chain and enzymes like xanthine oxidase and NADPH oxidase. The enzyme superoxide dismutase (SOD) converts superoxide anion (O2−·) into less harmful hydrogen peroxide (H_2O_2), which crosses cell membranes to signal cellular functions. Neutrophils use hydrogen peroxide (H_2O_2) to produce hypochlorous acid (HClO) during immune responses, while in HBOT, NO synthase (NOS) activation increases NO production.

The stability and membrane diffusibility of hydrogen peroxide (H_2O_2) make it a key signaling molecule in RONS, predominantly generated by NADPH oxidase enzymes (NOXs) and converted to H2O or water by scavenging enzymes like peroxiredoxin (PRX), glutathione peroxidase (GPx), and catalase (CAT). It modifies proteins to regulate metabolic and growth processes and can form highly reactive hydroxyl radicals (OH·) via Fenton reactions. Controlling hydrogen peroxide (H_2O_2) levels is crucial for maintaining normal cellular signaling and preventing toxicity, which is a focus in influence of HBOT on cellular growth, inflammation, and stress response regulation through redox signaling

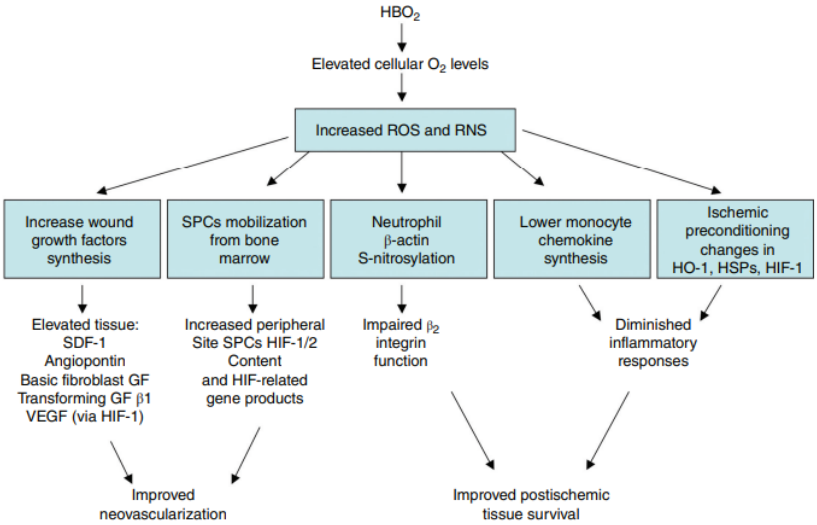

Figure 5. Overview on therapeutic mechanisms of HBOT related to elevations of tissue oxygen tensions. The figure outlines initial effects (denoted by boxes) that occur due to increased production of ROS and RNS and their consequences. Other abbreviations: growth factor (GH), vascular endothelial growth factor (vascular endothelial growth factor (VEGF)), hypoxia inducible factor (HIF), stem/progenitor cells (SPCs), heme oxygenase (HO)-1, heat-shock proteins (HSP).[32]

Impact of Hyperbaric Oxygen on Angiogenesis and Neovascularization[32,33]

Hyperbaric oxygen therapy (HBOT) enhances wound healing by promoting neovascularization, which includes angiogenesis and vasculogenesis. HBOT facilitates the growth of new blood vessels and the recruitment of stem/progenitor cells (SPCs), which are capable of creating blood vessels from scratch. While radiation therapy can restrict SPC mobilization, worsening radiation-induced wounds, HBOT effectively mobilizes SPCs in healthy, diabetic, and radiated individuals. This process, revealed in animal studies, is driven by redox processes and involves SPC migration to wounds.

HBOT also activates Hypoxia Inducible Factor (HIF) transcription factors, notably HIF-1, which along with HIF-2 and HIF-3, boosts SPC mobilization and vascularization. The therapy increases Vascular Endothelial Growth Factor (vascular endothelial growth factor (VEGF)) expression, a critical enhancer of neovascularization driven by HIF-1, to improve wound healing. Additionally, controlled reactive oxygen species (ROS) production during HBOT therapy stimulates vascular endothelial growth factor (VEGF) release, enhancing angiogenesis and thus healing outcomes.

Modulation of Inflammation and Immune Response by Hyperbaric Oxygen[32]

Phagocytes, vital components of the immune defense, actively produce substantial amounts of superoxide via nicotinamide adenine dinucleotide phosphate (NADPH) oxidase. Superoxide and its derivatives profoundly impact cellular elements, crucially regulating the immune system and inflammation. The primary function of immune system is to protect against microbial invaders and cancer. Macrophages, neutrophils, and eosinophils rapidly release

reactive oxygen and nitrogen species upon encountering pathogens, utilizing NADPH oxidase anchored in their membranes. These species, like hydrogen peroxide and singlet oxygen, react with microbial components, damaging pathogens and activating inflammatory pathways. Hyperbaric oxygen therapy (HBOT) enhances immune cells' antimicrobial capabilities by boosting respiratory burst activity and increasing bacterial phagocytosis. HBOT elevates reactive oxygen and nitrogen species production, eliminating anaerobic microorganisms and enhancing antibiotic effectiveness. HBOT modulates inflammation, both amplifying and diminishing proinflammatory cytokine levels. Additionally, HBOT accelerates wound healing by mitigating inflammation, potentially through hypoxia-inducible factor (HIF) pathways. Elevated oxygen levels trigger the generation of reactive oxygen and nitrogen species, which regulate signaling pathways crucial for immune function. Nitric oxide influences cytokine expression, showcasing the complex interplay between reactive species and immune cells. Reactive species play a significant role in hyperbaric oxygen therapy, influencing immune function and mitigating abnormal immune responses in various conditions. HBOT also reduces neutrophil adherence, decreasing reperfusion injuries in multiple organs.

Clinical Evidence Supporting the Efficacy of HBOT in Burn Wound Healing

Previous Clinical Studies Investigating HBOT in Burn Patients[34-41]

In 1979, Lamy and colleagues studied 27 patients with burns covering 50% of their total body surface area (TBSA). They received hyperbaric oxygen therapy (HBOT) at 3 atmospheres absolute (ATA). Lamy and colleagues observed improved healing and fewer infections, though mortality rates remained unchanged. Hart conducted a randomized trial in 1974, treating 138 patients with burns covering an average of 35% TBSA with 2 ATA HBOT therapy. Time to healing, morbidity, and mortality decreased significantly compared to historical controls. Grossmann provided routine care along with 2 ATA HBOT therapy to 419 patients with burns covering an average of 40% TBSA. The HBOT group experienced reduced fluid requirements, shorter healing times, and decreased complications compared to the non-HBOT group. In 1982, Waisbren and colleagues compared standard treatment to 2.5 ATA HBOT therapy in cases of 50% TBSA burns. They noted poorer renal function and higher bacteremia incidence in the HBOT group but confirmed enhanced healing and reduced need for skin grafts. Cianci and colleagues integrated 2 ATA HBOT therapy into standard burn care for 20 patients with 30% TBSA burns in 1989. They observed reduced hospital stay and surgical procedures. A subsequent study reaffirmed these findings in 21 patients in 1990. Another randomized trial investigated HBOT therapy on 125 burn patients admitted within 24 hours of injury. No statistically significant differences were found in outcomes between the treatment and control groups. Chong and colleagues studied HBOT in adult burn patients with less than 40% TBSA affected. HBOT did not significantly impact burn depth, white blood cell count, or plasma cytokine levels. Notably, positive bacterial cultures were found in some patients. Chen and colleagues compared historical controls to patients receiving HBOT therapy for 25% TBSA burns. While the HBOT group showed improved pain scores, no significant impact was observed on infection rates or scarring quality.

Analysis of Randomized Controlled Trials Evaluating HBOT Efficacy[42]

Over five decades, research in experimental and clinical settings proved the benefits of hyperbaric oxygen therapy (HBOT). Initial studies used basic techniques; later ones employed advanced methods as understanding of the molecular mechanisms of HBOT improved. Healing in burns involved faster epithelialization, preserving microvasculature, enhancing skin appendages, and increasing intracellular ATP. Some studies failed to validate positive effects of HBOT. Post-burn swelling and fluid requirements decreased significantly. HBOT hindered bacterial growth on burn wounds and intestines, reducing sepsis cases and ileus. Recent studies noted decreased post-burn pain sensitization after HBOT treatment. Results on effects of HBOT in burns varied. Grossmann and Hart reported decreased mortality and complications, shorter hospital stays, and reduced costs. However, there were discrepancies in findings, likely due to varied HBOT dosage factors. Adverse effects of high pressure levels were observed in animals. HBOT therapy within a specific timeframe potentially reduces mediator cascades in acute injuries like strokes and carbon monoxide poisoning. Yet, there is no universally accepted HBOT treatment protocol for burn management.

Meta-analyses and Systematic Reviews on HBOT in Burn Wound Healing[43-46]

A review by Eskas and colleagues suggests limited evidence from well-designed studies on efficacy of hyperbaric oxygen therapy (HBOT) in acute wound treatment. Despite scarce trials with methodological flaws, HBOT shows potential benefits, particularly in crush injuries and burns, accelerating healing and improving graft success. Adverse events were noted in one trial but lacked biological explanation. Another review by Radzikowska-Buchner and colleagues supports effectiveness of HBOT in enhancing tissue oxygen levels and reducing inflammation across various conditions, including burns. Integration into burn treatment may control sepsis, yet more extensive trials are needed to confirm efficacy. Lindenmann and colleagues identified four clinical trials confirming positive impacts of HBOT on wound recovery, primarily through angiogenesis and anti-inflammatory effects. Most research on HBOT effect on tissue regeneration is animal-based, with significant molecular pathway modulation observed, depending on injury characteristics. A

review of 11 papers since 1965 by Smolle and colleagues highlighted varied HBOT protocols for burns, recommending prompt initiation post-injury for optimal results. Conflicting findings on efficacy of HBOT in burns indicate a need for further research.

Case Series and Observational Studies on HBOT Outcomes[47-49]

Oley and colleagues in 2021 conducted a case-control study on twenty patients with thermal burns, dividing them into HBOT and control groups. They assessed ICAM-1 mRNA gene and serum levels, as well as wound epithelialization, before and after treatment. Comparing the groups, HBOT significantly reduced thermal wound complications ($p = .006$) and hospital stay ($p = .001$). ICAM-1 serum levels strongly correlated with mRNA expression ($R2 = 0.909$, $p < .001$). The expression of ICAM-1 mRNA and serum levels in patients with ≥50% burn area exceeded those with smaller areas. HBOT significantly decreased ICAM-1 mRNA gene expression ($p < .05$) and serum levels ($p = .004$). The number of HBOT sessions strongly correlated with serum levels ($p = .043$) but poorly with mRNA expression ($p = .22$). In conclusion, HBOT reduces thermal wound complications, hospital stay, ICAM-1 mRNA gene expression, and serum levels.

Fouda and colleagues in 2023 conducted a case-control study on facelift patients, comparing HBOT recipients with controls. The HBOT group ($n = 9$) had an average of 7.22 sessions lasting 78 ± 5 min each. Wound healing duration was significantly shorter in the HBOT group (mean = 13.3 days) than the control (mean = 36.9 days), ($P < .001$).

HBOT improves postoperative quality of life after cosmetic procedures. Its therapeutic benefits arise from gas concentration, volume, and pressure dynamics. Besides aesthetics, HBOT offers diverse advantages, promoting neovascularization, fibroblast stimulation, immune enhancement, inflammation reduction, growth factor production, antibiotic action, antioxidant defense, and ischemia-reperfusion damage alleviation.

Oley and colleagues (2022) presented a case series of lower extremity trauma cases treated with HBOT. Positive wound granulation was observed in patients with soft tissue loss and gas gangrene. HBOT may enhance neovascularization, benefiting patients with gas gangrene alongside antibiotics and necrotic tissue removal. HBOT effectively reduces mortality in soft tissue infections.

HBOT for burns reduces edema, supports microcirculation and angiogenesis, and enhances wound healing. It mitigates burn injury complications and postoperative pain. Analgesics were administered for only two days post-surgery due to potential of HBOT in reducing wound pain via hyperoxia-induced vasoconstriction. During follow-up, patients treated with HBOT generally displayed enhanced wound healing, especially those with burn injuries, and supported skin graft survival.

Challenges and Limitations of HBOT in Burn Wound Healing

Patient Selection Criteria for HBOT[50]

In hyperbaric medicine, healthcare providers must note that awareness of approved uses of HBOT may be limited outside the specialty. Even professionals at facilities with chambers may lack knowledge about conditions warranting referral. When assessing patients, providers should confirm if their condition aligns with recommended indications. Practitioners must inform patients about treatment processes, safety protocols, and care plans during consultations. There are currently 15 approved indications by the Undersea and Hyperbaric Medical Society, both urgent and non-urgent, as described in Table 4.

Table 4. Indications for HBOT.50

Urgent
• Air or gas embolism (can be the iatrogenic or diving related type of injury) • Carbon monoxide poisoning • Central retinal artery occlusion • Clostridial myonecrosis (gas gangrene) • Compromised surgical grafts and flaps • Crush injuries/skeletal muscle compartment syndrome/acute arterial insufficiency • Decompression sickness • Intracranial abscess • Necrotizing soft tissue infections • Exceptional blood loss anemia • Specific acute thermal burns • Idiopathic sudden sensorineural hearing loss (urgent)
Non-urgent
• Delayed radiation injuries for soft tissue or bony necrosis/osteoradionecrosis • Chronic refractory osteomyelitis • Enhancement of healing in a problematic wound (diabetic foot ulcers Wagner grade 3, 4, or 5)

The sole definitive contraindication is untreated pneumothorax. Prior to treatment, all patients need lung imaging. If a patient had pneumothorax treatment, a risk-benefit assessment is necessary before chamber placement. For managing pneumothorax, using a chest tube with an open Heimlich valve before treatment could be appropriate in urgent scenarios. Healthcare providers should assess relative contraindications before treatment. Healthcare providers should also assess various relative contraindications, including but not limited to the following:

- Hypertension can worsen during treatment.
- Diabetes with glucose levels beyond 300 or below 100.
- Congestive heart failure with ejection fraction under 35%.
- Claustrophobia is more prevalent in monoplace chambers.
- Congenital spherocytosis may lead to severe hemolysis.
- Upper respiratory infection raises concerns for barotrauma.
- Fever can decrease seizure threshold during treatment.
- Chronic sinus condition raises barotrauma risks.
- Pacemaker/implantable device may malfunction under pressure.
- Recent eye/retinal/cataract surgery requires waiting period.
- Recent thoracic surgery necessitates imaging for pneumothorax.
- Obstructive lung disease/COPD/asthma risk air trapping.
- Seizures need control before treatment initiation.
- Untreated cancer, its effect on hyperbarics is still controversial.
- Gas permeable contact lenses are required.

Practical Considerations in Administering HBOT to Burn Patients[5,51]

Hyperbaric oxygen therapy (HBOT) has shown benefits in treating thermal injuries across various research settings. Studies examined impact of HBOT on blood vessel and connective tissue growth in burn scar tissue with normal and compromised blood flow. Enhanced collagen production and new blood vessel formation improved porous polyethylene integration in oxygen-deprived burn scar tissues, contrasting with slower integration in healthy tissue. HBOT also prevented the progression of second-degree burns to third-degree burns by halting the advancement of the zone of stasis within 24 hours post-burn. A pressure exceeding 300 mmHg indicated normal arterial flow and wound healing capability, with HBOT recommended for patients below 300 mmHg but above 100 mmHg. The European Committee for Hyperbaric Medicine (ECCHM) recommended HBOT for managing second-degree burns covering over 20% of the body surface area. However, uniform patient selection criteria, oxygen dosage, and potential adverse effects like pulmonary barotrauma and drug reactions require consideration. Despite some medical centers advocating for HBOT in thermal burns, comparative studies supporting its efficacy are scarce. Given the significant costs involved, routine HBOT for thermal burns warrants further evaluation beyond this review.

Adverse Effects and Risks Associated with HBOT[52,53]

Hyperbaric oxygen therapy (HBOT) can induce various adverse effects, categorized into pressure-related and oxygen-related groups. Barotrauma affects enclosed air-filled spaces like ears, sinuses, and lungs, causing discomfort and potential complications. Middle ear barotrauma (MEB) is common, leading to ear pressure challenges and potential hearing loss. Barosinusitis affects sinuses, causing congestion and facial discomfort. Dental discomfort may arise due to pressure changes, leading to tooth fractures. Pulmonary barotrauma (PBT) risks increase for individuals with lung conditions, potentially causing serious complications. Arterial gas embolism (AGE) may result from PBT, leading to severe symptoms like unconsciousness and cardiac arrest. HBOT may elevate left ventricular afterload and oxidative stress, necessitating caution in heart failure patients. CNS oxygen toxicity can cause seizures, with risk factors including treatment pressure and medical conditions. Prolonged exposure to high oxygen levels can induce pulmonary toxicity, leading to breathing difficulties. Elevated oxygen levels may harm the eyes, potentially causing oxygen toxicity-related issues. HBOT can lower blood sugar in diabetic patients, necessitating careful glucose monitoring before treatment.

Cost-effectiveness and Resource Implications of HBOT in Burn Care[54-56]

Hyperbaric oxygen therapy (HBOT) costs encompass capital and operating expenses, the latter involving staff, maintenance, and overheads. Session and treatment costs hinge on duration and frequency. In our primary analyses, we base HBOT treatment costs on 30 sessions per patient, acknowledging variation across indications. To address this uncertainty, we calculate incremental cost-effectiveness ratios using estimates of 15 and 40 sessions per patient. The average cost per treatment course is approximately $6,941.54. Research by Struzyna and colleagues found no significant difference in length of stay (LOS) for HBOT-treated patients compared to non-treated ones. Two independent reviews by Cianci and Struzyna concluded that HBOT reduces therapy costs for burn patients, with potential savings of $107,000 (36%) per patient in the former study. Dressing changes during HBOT sessions occur under medical supervision, potentially reducing healthcare provider interactions. However, self-administered changes may compromise

patient monitoring. The requirement for 40 to 45 sessions, each lasting 90 minutes, could hinder treatment accessibility, with associated costs such as travel and caregiver assistance not factored into economic evaluations.

Future Directions and Potential Innovations in HBOT for Burn Wound Healing

Novel Approaches to Enhance HBOT Efficacy in Burn Patients[57]

The primary aims of treating burns are to reduce swelling, preserve tissue viability, maintain microvascular circulation, and boost the immune system. Success in burn healing hinges on the coordination of treatment strategies, patient variables, and the characteristics of the burn injury. Imbalance may lead to significant scarring.

Burn wounds typically harbor aerobic bacteria, potentially indicating antibiotic resistance. Severe burn infections trigger hypermetabolic reactions, causing body-wide catabolism, muscle breakdown, growth impairment, insulin resistance, and multiorgan dysfunction. A study confirmed the beneficial interaction between hyperbaric oxygen therapy (HBOT) and burn recovery.

Innovative treatments target inflammatory mediators and signaling pathways. Tumor necrosis factor alpha (TNF-α), notably elevated in burn wounds, can be addressed with HBOT. HBOT enhances tissue oxygenation, boosting aerobic metabolism and activating reactive oxygen species (ROS), crucial for myofibroblast formation and collagen synthesis.

HBOT as adjunctive therapy improves burn injury outcomes by modulating cytokines and bactericidal effects. Its application should be considered for second to third-degree burns based on case studies. HBOT sessions can be tailored to individual conditions, with doses typically around 2.4 ATA. However, medical practitioners must be vigilant regarding side effects and prevent oxygen toxicity when using higher doses.

Integration of HBOT with Other Modalities in Burn Wound Management[44]

Hyperbaric oxygen therapy (HBOT) improves tissue oxygenation, neovascularization, and reduces inflammation in burns. It may speed wound healing and reduce morbidity and mortality in thermal burns and carbon monoxide poisoning. Yet, evidence doesn't firmly support routine HBOT in burn care. Large-scale trials are needed to assess effectiveness and cost of HBOT despite burn variability. The U.S. Food and Drug Administration (FDA) has approved HBOT as supportive treatment for burns. Using HBOT alongside other therapies merits consideration for burn management.

HBOT can accelerate wound healing in advanced treatment. Combined with systemic antibiotics, HBOT prevents sepsis in severe burns due to its bactericidal effect. Surgery, followed by HBOT, benefits severe burns. Many studies have suggested HBOT improves post-surgery healing.

Emerging Advanced Technologies in Hyperbaric Oxygen Delivery Systems[58]

Excessive oxygen levels, known as hyperoxia, aid wound healing and tissue regeneration by elevating cellular oxygen levels, triggering a temporary rise in intracellular reactive oxygen species (ROS) and reactive nitrogen species (RNS), which promote cell proliferation and wound restructuring. Therapeutic approaches like hyperbaric oxygen therapy (HBOT), oxygen carriers, and peroxide materials serve as oxygen delivery systems for treating wounds, vascular disorders, and tissue regeneration. HBOT, though used clinically, faces constraints like limited oxygen diffusion and potential lung damage. Oxygen carriers and peroxides, extensively employed, mitigate some limitations such as toxicity and rapid oxygen release. However, developing advanced oxygen delivery carriers to overcome these challenges remains a significant hurdle despite progress in creating oxygen-generating biomaterials.

A novel biomaterial, hyperbaric oxygen-generating (HOG) hydrogels, acts as a bioactive acellular matrix producing hyperbaric oxygen levels. Studies indicate that HOG hydrogels rapidly generate oxygen within their matrices at hyperbaric concentrations and release oxygen continuously. In vitro experiments show that HOG hydrogels promote the growth of human dermal fibroblasts (HDFs) and endothelial cells (ECs), while in vivo studies demonstrate their effectiveness in enhancing wound healing and tissue repair by facilitating tissue ingrowth and neovascularization from host tissues.

Areas for Further Research and Clinical Investigation[59]

Since the 1960s, HBOT has been used to treat a wide variety of conditions, either as a standard regimen in the management plan or as an adjunctive treatment. Nevertheless, the use of HBOT as an adjunct to treating thermal burns remains controversial due to limited and conflicting evidence. The urge for a higher quality and quantity of randomized controlled trials (RCTs) of the use of HBOT in treating burns is essential to further understand and assess the harms and benefits, and determine whether to instill HBOT as an adjunct to the standard course of management in such patients or not. In the meantime, if a clinician opts to use HBOT in addition to the standard burn care, it should be used with extreme caution to minimize any possible harm to the patient.[59]

CONCLUSION

Hyperbaric oxygen therapy (HBOT) aids wound healing as an adjunctive therapy. This literature review suggests HBOT enhances wound healing outcomes, especially in burn patients. HBOT mechanisms include increasing reactive nitrogen species (RNS) and reactive oxygen species (ROS), activating Nuclear Factor Kappa Beta (NF-kβ), regulating inflammation, promoting neovascularization, and enhancing the body's defense mechanisms via nicotinamide adenine dinucleotide phosphate (NADPH) oxidase. However, research shows conflicting results on HBOT's efficacy for

wound healing, necessitating its use alongside other modalities in burn care. Consideration of indications, costs, and resources is crucial due to lack of guidelines. Oxygen toxicity poses a severe side effect. Further research, particularly on HBOT dosage and sessions' cutoff points, is warranted, with emphasis on prospective randomized controlled trials with larger sample sizes and blinding. HBOT, in combination with other modalities, has shown effectiveness in plastic surgery, reducing hospital stays, costs, and recovery time. Its impact on each phase of burn wound healing enhances aesthetic outcomes by promoting epithelization and collagen formation.

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