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Systematic Review of Hyperbaric Oxygen Therapy in Burn Management: A Comprehensive Analysis from Past to Present

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Abstract: ***Background: Burn injury historically carried a poor prognosis, affecting several organ beyond the skin. Amongst various interventions for burns, hyperbaric oxygen therapy (HBOT) was proposed as a game changer since the spearhead in 1965, a lot of well-experimental studies, clinical work has been done and been extensively integrated as an adjunctive treatment for its therapeutic properties in reducing hypoxia, inflammation, reperfusion injury and promotes neovascularization. Improved and accelerate wound healing as well as a reduction of morbidity and mortality after burn injury are expected. However, in spite of numerous undisputedly positive results regarding the effectiveness of adjunctive HBOT for burn injury, the method has not yet been established in clinical routine. This review aims to identify the efficacy of HBOT as an adjunctive therapy in burns. Materials and Methods: PRISMA guidelines were followed to identify studies. Sources for this review were collected by searching PubMed, Embase, Google Scholar, Cochrane Library, and Garuda in any time frame. The information was compared and bandied to generate an up to date conclusion. Results: 55 publications (38 animal experiments, 4 trials in human volunteers and 13 clinical studies) were included in this review. All were able to show a profound effects of HBOT, most of them describing reduced edema, increased microvascularity, improved epithelialization, significant reduction of bacterial growth. Secondary burn wound progression was prevented, as microvascular perfusion could be preserved, and cells were kept viable on stasis zone. Conclusion: HBOT presents a promising adjunctive treatment for burn injuries, with potential to enhance healing, reduce complications, and improve patient outcomes. Continued research that focus on outcome measures, wound healing time, complications, mortality rates, and scar quality is necessary to establish standardized treatment protocols and confirm long-term benefits. As the field evolves, HBOT may become an integral part of burn care in specialized centers.***

Keywords: hyperbaric oxygen therapy, hyperbaric oxygen, burns, review

1. Introduction

1.1. History of Hyperbaric Therapy

Hyperbaric medicine's history spans nearly 350 years, beginning with Nathaniel Henshaw, an English physician, in 1662.[1] He created a "domicilium, " a sealed room with organ bellows to alter atmospheric pressure, inspired by the health effects of climate change. Henshaw used compressed air for acute conditions and decompressed air for chronic diseases. He suggested it could aid digestion and lung health even in healthy individuals.[1]

Oxygen was discovered by Carl Wilhelm Scheele in 1772 and independently by Joseph Priestley in 1775, with Priestley often credited for the discovery.[2, 3] Initial therapeutic uses of oxygen were hindered by concerns over toxicity, as described by Lavoisier and Seguin in 1789.[4] Interest revived with Paul Bert's studies in 1878, leading to the first hyperbaric chambers in North America.

In 1917, Bernhard and Heinrich Dräger used pressurized air to treat decompression sickness, confirmed by Shaw and Behnke in 1937.[5] In 1956, Dutch surgeon Boerema demonstrated the benefits of pressurized oxygen in heart surgery, and in 1961, Willem Brummelkamp noted its effectiveness against anaerobic infections.[6, 7] Boerema introduced the concept of "life without blood"[8], highlighting the clinical value of Hyperbaric Oxygen Therapy (HBOT).

1.2. Principle and Mechanisms of Hyperbaric Oxygenation

Hyperbaric oxygen therapy is the treatment of a disease or medical condition by the inhalation of near-100% (at least 95%) medical grade oxygen* at pressures greater than 1 atmosphere absolute (ATA) (101.3 kilopascals (kPa)) in a pressure vessel constructed for that purpose. However, in certain instances at chamber treatment pressures above 3.0 ATA, oxygen levels are reduced below 100% to achieve a partial pressure of oxygen of at least 1.2 ATA and lower than 3.0 ATA, to avoid oxygen toxicity. Medical grade oxygen should meet USP (US Pharmacopeia) or national equivalent standard for purity. In a word, the main mechanism of hyperbaric oxygenation is to increase the amount of dissolved oxygen and re-oxygenize the tissues in which circulation is disturbed and oxygen supply is decreased.[9]

Hyperbaric Oxygen Therapy (HBO) increases dissolved oxygen, supporting life without hemoglobin and enhancing

tissue metabolism. Blood oxygen includes two components: one binds with hemoglobin for transport, and the other dissolves in plasma for tissue diffusion. With hemoglobin binding 1.39 mL of oxygen per gram and a blood level of 15 g/dL, the arterial oxygen bound to hemoglobin at 98% saturation can be calculated as follows:
1.39 mL/g × 15 g/dL × 0.98 = 20.43 mL/dL (= 20.43 vol%)

Similarly, Hb-O2 in the venous blood (provided oxygen saturation is 70%) is estimated as follows:
1.39 mL/g × 15 g/dL × 0.70 = 14.60 vol%

Next, dissolved oxygen in the arterial blood at regular condition is calculated as follows when oxygen solubility coefficient to the plasma is assumed as 0.0031 vol%/ mmHg and oxygen partial pressure in the alveolus is postulated to be 100 mmHg:
0.0031 vol%/mmHg × 100 mmHg = 0.31 vol%

Similarly, partial pressure of oxygen in the venous blood is assumed as 40 mmHg, so dissolved oxygen in the vein becomes as follows:
0.0031 vol%/mmHg × 40 mmHg = 0.12 vol%

Accordingly, total amount of oxygen in the artery or vein is calculated, respectively, as follows:
Artery: 20.43 vol% + 0.31 vol% = 20.74 vol%
Vein: 14.60 vol% + 0.12 vol% = 14.72 vol%

Oxygen consumption at rest is calculated as a result of subtracting the value of total oxygen in the venous blood from that in the arterial blood:
20.74 vol% − 14.72 vol% = 6.02 vol%

Therefore, 6.02 vol% is considered to be the minimally required blood oxygen level in order to sustain basic metabolism of the body. Once Hb is 100% saturated with oxygen, the increase of Hb-O2 cannot be expected anymore because an upper limit of oxygen binding capacity for Hb is 1.39 mL/g. However, HBO therapy can increase the oxygen supply according to Henry's law in which the amount of dissolved oxygen increases in proportion to the increased level of partial pressure of oxygen. If pure oxygen is breathed at 3 ATA (≈ 2280 mmHg), dissolved oxygen reaches 6.02 vol% thereby providing theoretically sufficient oxygen.[10]

Physiological effects of HBO are roughly divided into three categories: (1) increase of oxygen partial pressure, (2) direct effect on blood vessels, i.e., vasoconstriction, and (3) increase of physical pressure. HBOT increases oxygen diffusion from the alveolar space to capillaries that surround alveoli, thereby increasing the amount of dissolved oxygen in the pulmonary veins and ultimately in the peripheral arteries after cardiac output. Increased oxygen tension / dissolved oxygen in the blood results in tissue oxygenation and provides improved oxygen supply to damaged tissues, which leads to various subsequent actions including washout of toxic gases[11], neovascularization[12], stimulation of fibroblast proliferation[13], enhancement of bacterial killing by increasing reactive oxygen species[14], suppression of inflammation by inhibiting adhesion of leukocytes on to the endothelium[15], and so on. Increased blood oxygen content recovers the tissues from hypoxic conditions or circular disturbances, and enhances wound healing, regeneration of damaged tissues, and improves the remodeling of fibrotic scars.

1.3. HBO in Burn Injury

Burn are a complex and evolving injury with both local and systemic consequences.[16] An estimated 180 000 deaths every year are caused by burns, the vast majority occur in low-and middle-income countries.[17] The characteristic of a burn is described as a zone of coagulation, surrounded by an area of stasis, and bordered by the hyperemic zone.[16] The destruction and obstruction of microvascularization impede cellular and humoral immunity and alters macrophage function. The systemic pathophysiologic changes following thermal injuries affect multiple organs and body systems leading to clinical manifestations. Major burn injury is associated with extreme hypermetabolism and catabolism.[18] The ultimate goal of treating burns are minimizing the edema, keeping tissue viable in the stasis zone, protecting the microvasculature, and enhancing host defenses to stave off infection.[16, 19] The first report of successful use of HBOT in burn victims was introduced by the well-known thoracic surgeon Juro Wada in 1965, who observed improved healing tendency in burn wounds after the application of HBOT for survivors of a coal mine fire with CO poisoning[20, 21] and was repeatedly expected to be a game changer in burn wound treatment because of its beneficial effects on wound healing and recovery through revascularization, pathological edema reduction, and immune response. Since then, beneficial effects for burn injury treatment have been demonstrated in numerous experimental and clinical trials.

We established a synopsis of both animal and human experimental or clinical studies on HBOT in burns published since 1965.[20-21, 23 – 76]

2. Materials and Methods

Literature Search and Evaluation
The sources for this review were proceeded according to PRISMA guideliness.[22] For terms "hyperbaric oxygen" and "burn" for randomized controlled trials, systematic evidence-base reviews and metaanalysis on HBOT in any time frame. Since 1965, there were 88 articles were identified in PubMed, 19 in Embase, 2 in Cochrane, and 2 in Garuda. We included only the full text publications which was available and excluded papers that not providing sufficient information and redundant work. The information was compared and discussed to generate an up to date conclusion regarding the current standpoint of offering HBOT for patients suffering from burn injury. Down below is PRISMA 2020 selection process.

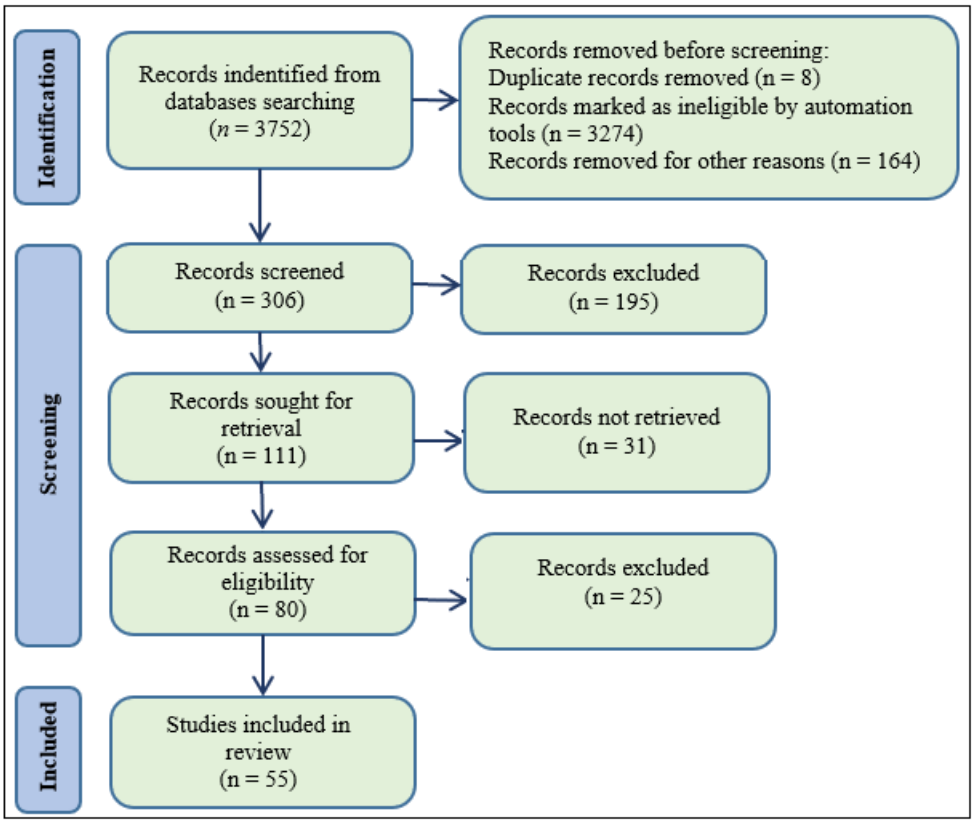

Figure 1: PRISMA selection process

Species, number of individuals, percentage of total body surface area (%TBSA), depth of burn, pressure applied during HBOT sessions, and outcome results were evaluated.

3. Results

Fifty- five publications (38 animal experiments, 4 trials in human volunteers and 13 clinical studies) were included in this review. The total number of animals amounted is more than 3237, while there were 58 human volunteers and clinical studies in 2280 patients. For the details of both experimental and clinical studies see Tables 1.

Table 1: Depth of burns: PT: partial thickness, FT: full thickness, S: superficial; HBO: hyperbaric oxygenation; AB: Antibiotic

Author/Year	Species	Number Individuals	%TBSA	Depth of Burn	Pressure applied (ATA)	Outcome
Ikeda/1967	Human	43	>50	PT, FT	3	Reduced edema, increased epithelization
Marchal/1966	Rats	187	20 75	FT PT	3	Better granulation. faster healing, less infection, mortality higher in HBOT than in controls
Nelson/1966	Dogs	24	75	PT	2	
Ketchum/1967	Rats	26	5	PT, FT	2	Healing time reduced, infection reduced
Benichoux/1968	Rats	160 200	75 30	PT PT	3 3	Positive effect on mortality
Bornside/1968	Rats					unknown
Ikeda/1968	Rabbits					Reduced edema with HBO
Spinadel/1969	Guinea Pigs Hamsters	99 75	25 25	PT PT	2 3	HBOT and AB best results concerning healing, untreated controls do markedly worse
Ketchum/1970	Rats	30	20	FT	3	Increased microvascularity
Lamy/1970	Human	27	20 to >50	PT, FT	3	Fewer infections, better granulation and healing
Gruber/1970	Rats	24	10	FT	3	return of pathologically low oxygen tensions to normal achieved by HBO in flaps, grafts or burns; oxygen levels returning to pretreatment values soon after discontinuing HBO
Perrins/1969	Scalded Pigs	8 4	12 8	FT PT	2 2	No benefit
Bleser/1971	Rats	520	32	PT	3	Rapid restoration of total body water; hematocrit, blood volume, plasma volumein HBO; accelerated recovery in HBO
Bleser/1973	Rats	100	5	FT	3	First no effect, but soon better granulation, more

						rapid healing and less infection with HBO.
Härtwig/1974	Rats	100	2	FT	2, 5	Increased microvascularity, reduced inflammation and healing time
Hart/1974	Human	191	10 to 50	PT, FT	2	Mean healing time reduced
Wells/1977	Dogs	24	40	FT	2 3	Reduced fluid extravasation with HBO
Korn/1977	Guinea Pigs	117 54 40	5 5 5	PT PT PT	2 2 2	Improved epethelialization
Niccole/1977	Rats	80	20	40 PT 40 FT	2, 5	No advantage of HBO over SSD
Arzinger Jonasch/1978	Guinea Pigs	120	15	PT, FT	2	Time until healing of partial or full-thickness burn shortened by 5 days in HBO. Quick reduction of edema, hardly any thromboses, collateral perfusion in HBO. Take of full-thickness skin graft shortened by 2 days in HBO. Positive effect unrelated to time of exposition
Grossmann/1978	Human	821	>20 <80	PT, FT	2	Fluid requirements, healing time 2nd degree, eschar separation time, donor graft harvesting time, length of hospital stay, complications, mortality all reduced compared to non-HBO group; no paralytic ileus in severe burns and HBO, reduction in cost
Waisbern/1982	Human	72	50	PT, FT		Better healing, 75% fewer grafts in HBO
Nylander/1984	Mice	54	6	PT	2, 5	Reduction of edema
Kaiser/1985	Guinea Pigs	102	5	FT	3	noninfected wounds in controls healed quicker than noninfected HBO treated wound; infected wounds treated with primary HBO healed quicker than infected controls; infected wounds treated with secondary HBO healed somewhat slower
Niu/1987	Human	835	Severe Burns; any	PT, FT	2, 5	Fluid loss reduced, earlier re-epithelization,
Kaiser/1988	Guinea Pigs	75	5	PT	3	Extent of burn increased in controls, not in HBO-group; Rapid reduction of wound surface and less edema only in HBO-group
Stewart/1989	Rats	90	5	PT	2, 5	36h post injury, with 2 HBO/day more than tenfold increase tissue ATP compared to 36 h. controls, improved dermal elements
Saunders/1989	Guinea Pigs	30		PT	2	Improved microcirculation, dermal elements, and collagen quality
Cianci/1989	Human	20	18-39	PT, FT	2	Duration of hospitalization and number of surgeries reduced in HBO
Cianci/1990	Human	21	19-50	PT, FT	2	Duration of hospitalization, cost of burn care and number of surgeries reduced in HBO
Hammarlund/1991	Human Volunteers	8	<1	PT	2, 8	Less exsudation, less hyperemia, wound size reduced
Tenenhaus/1994	Mice	125 139	32	FT	2, 4	Reduction in bacterial colonies but increased mortality with HBO
Espinosa/1995	Guinea Pigs	20	10	PT	2, 8	significant reduction of edema in HBO with or without antibiotic
Germonpré/1996	Rats	46	5	PT	2	Improved preservation of basement mebrane and reduced leucocyte infiltration with HBO
Hussmann/1996	Rats	74	10	FT	2, 5	only regimen to downregulate cytotoxic (OX8) T-cells to normal values on days 5 and 15
Brannen/1997	Human	125	20-50	PT, FT	2	No difference in number of surgeries, duration of hospitalization or mortality
Niezgoda/1997	Human Volunteers	12	<1	PT	2, 4	Exsudation, hyperemia, wound surface reduced
Shoshani/1998	Guinea Pigs	54	5	PT	2	Worse re-epithelialization with HBO
Akin/2002	Rats	54	30	PT	2, 5	Reduced bacterial counts and translocation through intestinal wall with HBO
Bilic/2005	Rats	70	20	PT	2, 5	Improved edema, neoangiogenesis, preserved dermal follicles, and epithelialization
Dinar/2008	Rats	80	10	FT	2, 5	Biointegration of porous polyethylene in hypoxic burn scar area were enhanced, collagen synthesis and neovascularization were improved
Türkaslan/2010	Rats	20	5	PT	2, 5	no differences in the 24h-groups; 5 day group HBO: Vital zones preserved; more cells in proliferative phase, more vital cells; prevents

						progression from stasis zone to necrosis, less edema
Chong/2013	Human	17	<35	PT, FT	2, 4	Significantly lower rate of positive bacterial cultures (staph aureus, pseudomonas).
Selçuk/2013	Rats	32	12	PT, FT	2, 5	After 21 days no difference concerning microbiology; yet best epithlization, lowermost inflammatory cell response, fewest fifibrosis in non-nicotine/HBO
Rasmussen/2015	Human Volunteers	17	1	S	2, 4	HBO attenuates central sensitation by thermal injury
Setiadi/2016	Rabbits	36	1	PT	2, 4	Reduction in bacteria
Chiang/2017	Human	53	20-≥60	PT, FT	2, 5	Procalcitonin serum returned to normal significantly faster, no limb amputation
Susilo/2017	Rabbits	34	1	PT	2, 4	Reduced edema, increased epithelization, no difference in angiogenesis
Chen/2018	Human	35	<60	PT, FT	2, 5	Postburn pain score lower
Wu/2018	Rats	36	1	FT	2, 5	early HBO inhibits Gal – 3 dependent TLR-4 pathway; decreases proinflammatory cytokines and proteins in hind horn and paw; suppresses microglia/macrophage activation following burn injury; decreases mechanical withdrawal threshold; promotes wound healing
Wu/2019	Rats	30	1	FT	2, 5	more HBO sessions reduce burn—induced mechanical allodynia (upregulation: melatonin, opioid-receptors, downregulation: brain derived neurotropic factor, substance P, calcitonin gene related peptide)
Wahl/2019	Human Volunteers	21	1	S	2, 4	Long-lasting reduction of pain sensitivity surrounding injured area; immediate mitigating effect, long lasting preconditioning effect on hyperalgesia
Hatibie/2019	Rabbits	36	1	PT	2, 4	fewer inflammatory cells and more epithelium in HBO; no difference in angiogenesis
Hatibie/2020	Human	20	20-60	PT, FT		Wound complication significantly reduced, length of stay in hospital reduced, ICAM-1 mRNA gene expression and serum level reduced
Hatibie/2022	Rabbits	38	1	PT		Significant reduction of bacterial growth in the HBO group

4. Discussion

In a comprehensive review of hyperbaric oxygen therapy (HBOT) outcomes across various species and burn severities, numerous studies converge on its efficacy in promoting healing and minimizing complications associated with severe burns. One of the earliest studies by Ikeda in 1967 involving 43 patients with severe burns demonstrated significant reductions in edema and enhanced epithelialization when treated with HBOT.[20, 21] This finding set the stage for further investigations into the benefits of this therapy.

Marchal (1966) conducted a pivotal study on rats, revealing that those treated with HBOT not only healed faster but also exhibited fewer infections compared to control groups.[23] This was echoed by Ketchum (1967), whose research indicated that HBOT significantly shortened healing times and reduced infection rates in rats with partial and full-thickness burns.[25] The positive outcomes observed in animal models prompted further exploration in human subjects, leading to more extensive evaluations of HBOT's clinical effectiveness.

In human studies, Grossmann (1978) showed that patients treated with HBOT had reduced fluid requirements and experienced fewer complications, which translated into shorter hospital stays.[42] This was particularly important for severe burn cases, where prolonged hospitalization can lead to increased risk of infection and other complications. Waisbern (1982) found that HBOT not only improved healing times but also reduced the number of skin grafts needed, highlighting its role in enhancing recovery outcomes.[43]

However, the body of research is not without its complexities. For example, Brannen's 1997 investigation found no significant differences in the number of surgeries or mortality rates among treated patients, [57] suggesting that while HBOT may offer benefits, its effectiveness can vary based on individual circumstances and the nature of the injuries.

More recent research has continued to support the benefits of HBOT. For instance, Hatibie (2020) reported significant reductions in wound complications and a decrease in the length of hospital stays among patients receiving HBOT, demonstrating its lasting impact on recovery.[75] Similarly, studies by Wu (2018) and Wu (2019) revealed that early intervention with HBOT could inhibit pro-inflammatory pathways and reduce pain sensitivity, further enhancing the healing process.[71, 72]

Collectively, these studies underscore the profound benefits of HBOT in managing burn injuries, showcasing its potential to improve patient outcomes across various animal models and human cases. The consistent evidence supporting HBOT's effectiveness not only emphasizes its role as a critical therapeutic option but also invites further research into optimizing treatment protocols and understanding the underlying mechanisms that contribute to its success in promoting wound healing and recovery. As the field continues to evolve, the insights gathered from these studies will undoubtedly guide future applications of HBOT in clinical practice, offering hope for improved recovery in patients suffering from the devastating effects of severe burns.

5. Conclusion

In conclusion based on the data presented, the evidence suggests that adjunctive HBOT can be an effective modality for enhancing the healing of burn wounds, improving clinical outcomes, and reducing complications, although further research is warranted to define the most effective treatment parameters and to understand the mechanisms involved. A comprehensive experimental investigation into the timeline of patho-molecular events related to burn injuries and their interactions with HBO treatment is essential. To accurately evaluate the clinical efficacy of HBO as an adjunctive treatment—an area still under debate—there is a pressing need for rigorously designed clinical studies that focus on outcome measures, wound healing time, complications, mortality rates, and scar quality. Additionally, establishing the optimal dosage and timing of HBO therapy is crucial for maximizing its benefits. Advancements in this field could significantly improve patient outcomes and enhance the understanding of HBO therapy in burn treatment.

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