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A REVIEW ON THE EFFECTIVE MANAGEMENT OF DIABETIC FOOT ULCERS USING HYPERBARIC OXYGEN THERAPY

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ABSTRACT

Diabetes-related foot ulcers are common and disabling, and they frequently result in leg amputation. The death rate is high, and ulcers that have previously healed often recur. Foot ulcers have a complex aetiology and a wide spectrum of clinical manifestations, necessitating early expert evaluation. Despite treatment, ulcers can readily evolve into chronic sores. HBOT (hyperbaric oxygen therapy) is a sort of treatment that helps DFU's (Diabetic foot ulcer) repair serious wounds faster and prevent recurrence of ulcers. Which is due to increased oxygen availability in the tissues by breathing 100% oxygen under higher atmospheric pressure. HBOT-mediated increase in tissue oxygen availability have been shown to promote angiogenesis and granulation tissue development through improved fibroblast function, as well as infection control in wounds through improved leukocyte function. This review supports the idea that HBO enhances healing in DFU patients and reduces severe amputation. Careful implementation of HBO treatment could improve the long-term quality of life of patients treated with it.

KEYWORDS: DFU's (Diabetic foot ulcer), HBOT (hyperbaric oxygen therapy), Oxygen availability, Amputation, recurrence.

INTRODUCTION

The global diabetes epidemic has heightened awareness of some of the disease's most common complications, such as foot ulcers, secondary infections, and limb amputations.[9,10] Lower limb ulcers are a substantial source of morbidity and lost income for diabetics, accounting for 20% of diabetes-related hospital admissions.[11,12] Diabetic foot ulcer is an open wound that affects many of the diabetic individuals and typically found on the bottom of the foot. Patients with DFU are at risk of significant consequences because treatment is typically inadequate and ineffective. HBO has been proposed as a treatment option for diabetic foot ulcers.[13,14,15], and it has been shown to decrease the need for severe amputations.[16]

Under typical climatic and physiological settings, haemoglobin transports the majority of oxygen in the blood, with only a minor fraction dissolved in blood plasma. An increase in barometric pressure or an ambient oxygen concentration of 100% will not boost haemoglobin-mediated oxygen transport to a clinically meaningful degree in patients with normal cardiac and pulmonary function. While inhaling pure oxygen at 2.5 Atmosphere Absolute, increased barometric pressure promotes oxygen dissolution in blood plasma, resulting in close to 60 mL of oxygen per litre of blood plasma (ATA). Even without the addition of haemoglobin, such conditions are sufficient to meet tissue oxygen demand during rest. The oxygen diffusion distance from capillary to tissue is increased by HBOT from 64 to 247 metres. As a result, oxygen dissolved in blood plasma can more easily reach bodily tissues in these conditions.

HBOT-mediated increase in tissue oxygen availability have been shown to promote angiogenesis and granulation tissue development through improved fibroblast function, as well as infection control in wounds through improved leukocyte function. In the treatment of diabetic foot ulcers, it is generally given as daily treatments at 2.0–2.5 ATA for 90–120 minutes. Compression and decompression take an additional 5–10 minutes for each session. To lessen the risk of oxygen poisoning, several centres provide one or two 5-minute "air breaks" during which pure oxygen is replaced with air.

HBOT is not recommended if you have an untreated pneumothorax or are taking certain chemotherapeutics at the same time. Relative contraindications include upper respiratory infections, chronic sinusitis, severe emphysema, high fever, and pregnancy.

The most prevalent HBOT adverse effect is middle-ear barotrauma. When HBOT is used to equalise middle-ear pressure, up to 20% of patients report feeling ear pain or discomfort. The oxygen toxicity of the lens causes reversible myopia. Prolonged HBOT increases the likelihood of cataract formation, according to animal studies and clinical trials. Rare complications include oxygen seizures, pulmonary barotrauma, pneumothorax, and gas embolism chamber fire.

STUDY 1 M. Londahl *et al*., 2010 conducted a study on Hyperbaric oxygen therapy improves health-related quality of life in patients with diabetes and chronic foot ulcer.

The purpose of this study is to see if hyperbaric oxygen therapy improves these individuals' health-related quality of life.

The study is a single-centre prospective randomised double-blind placebo-controlled trial that compares the effects of hyperbaric oxygen therapy to treatment with hyperbaric air (placebo) in diabetic individuals with persistent foot ulcers. Treatment sessions were held in a multiplace hyperbaric chamber for eight weeks, ideally five days a week (40 treatment sessions). The treatment time might be prolonged to ten weeks, but no more than forty treatments were authorized. A 5-minute interval of compression in air was followed by an 85-minute treatment period at 2.5 atmospheres absolute (ATA), followed by a 5-minute decompression period. Study gases were delivered via masks, and air or 100 percent oxygen entered the chamber through separate double-blinded pipes, allowing patients from both groups to be treated in the same session. During the therapy phase (the first 8–10 weeks), outcomes were monitored every week and then every three months. The Wagner classification system was used to grade ulcers, and Visitrak Digital was used to measure ulcer regions. The current study included all HODFU patients who completed the predetermined criterion of receiving at least 36 out of 40 scheduled therapy sessions. Before and after hyperbaric oxygen therapy, all patients completed a self-reported (Please explain SF 36 in full here – use abbreviation later) health measurement questionnaire to assess their physical and mental function, as well as their HRQL.

The trial included 75 patients, 38 of whom were assigned to the hyperbaric oxygen group and 37 to the placebo group (hyperbaric air). During the first year of follow-up, two patients in the placebo group died. Due to their worsening medical state, two patients in the hyperbaric oxygen group did not complete the SF-36 at the 12-month follow-up. The comparison

analysis does not include these four cases. The baseline features of patients in the hyperbaric oxygen and placebo groups were not significantly different. The median ulcer duration at the time of inclusion was 11.8 and 10.3 months, respectively (hyperbaric oxygen vs. placebo, NS.). At the 12-month follow-up, ulcer healing rates in the hyperbaric oxygen group were 61 percent versus 27 percent in the placebo group (P = 0.009). Patients with Type 1 and Type 2 diabetes had similar outcomes. When patients who healed their ulcers (healers) were compared to those who did not (non-healers), healers had considerably greater post-treatment levels of social functioning and role restrictions owing to physical and emotional health. Non-healers showed no differences in any SF-36 dimension.

Hyperbaric oxygen therapy enhances the long-term health-related quality of life in diabetic foot ulcer patients, potentially due to improved ulcer healing.

STUDY 2 Anders Nilsson *et al.*, 2010 conducted a study on Hyperbaric Oxygen Therapy Facilitates Healing of Chronic Foot Ulcers in Patients with Diabetes.

The purpose of this study was to see how well hyperbaric oxygen treatment (HBOT) worked in treating persistent diabetic foot ulcers.

The HODFU research was a randomised, single-centre, double-blind, placebo-controlled clinical experiment that looked at how HBOT affected ulcer healing in diabetic patients with chronic foot ulcers. The outcomes of those who received HBOT were compared to those who received hyperbaric oxygen treatment. Treatment sessions took held five days a week for eight weeks (40 treatment sessions) in a multi-place hyperbaric chamber. The treatment term might be prolonged to 10 weeks, but no more than 40 treatments were authorised. A 5-minute interval of compression in air was followed by an 85-minute treatment period at 2.5 atmospheres absolute (ATA), followed by a 5-minute decompression period. Study gases were delivered via masks, and air or 100 percent oxygen entered the chamber through separate double-blinded pipes, allowing patients from both groups to be treated in the same session. During the therapy phase (the first 8–10 weeks), outcomes were monitored every week and then every three months. The Wagner classification system was used to grade ulcers, and Visitrak Digital was used to measure ulcer regions.

The healing of the index ulcer was the primary outcome. When an ulcer was entirely covered by epithelial regeneration and remained that way until the next study visit, it was declared

healed. When the gangrene had split and the ulcer below was entirely covered by epithelial regeneration, Wagner grade 4 ulcers were declared healed. Major amputations and death are recorded as secondary end points in this study. Major amputations and death are recorded as secondary end points in this study.

Fifty-seven patients (57%) finished all 40 treatment sessions, whereas 75 (80%) completed 35 sessions. Nine individuals finished ten treatment sessions, while the other ten received between 14 and 28 sessions. Complete healing of the index ulcer was achieved in 37 patients at one year of follow-up in the intention-to-treat analysis: 25/48 (52%) in the HBOT group and 12/42 (29%) in the placebo group (P = 0.03). Healing of the index ulcer occurred in 23/38 (61%) of HBOT patients and 10/37 (27%) of placebo patients in a sub-analysis of those who completed 35 HBOT sessions (P = 0.009). Adverse occurrences occurred infrequently. During the first year of the research, four participants—one in the HBOT group and three was in the placebo group—died.

The current research backs up the theory that HBOT can help diabetic people heal their foot ulcers faster. As a result, as compared to supplementary treatment with hyperbaric air used as a placebo, HBOT doubled the number of cured ulcers in our patients with long-standing chronic ulcers after a 1-year follow-up.

STUDY 3 Bishop AJ *et al.*, 2012 conducted a review on Diabetic foot ulcers treated with hyperbaric oxygen therapy: a review of the literature.

The aim of the study is to find clinical studies and evaluate the available evidence, a literature search on Hyperbaric oxygen therapy (HBO) used as an adjunct for healing diabetic foot ulcers (DFUs).

This review includes relevant clinical trials and systematic reviews, literature searches using PubMed and Cinahl using the search terms 'hyperbaric', 'diabetes', 'foot ulcers', 'retrospective', and 'systematic review' in various combinations. The systematic reviews were then combed through for additional relevant references.

There were ten prospective trials and seven retrospective studies that evaluated HBO for DFUs. Only five of the ten prospective studies discovered were published during the last decade. The majority of prospective trials also had small treatment groups. Because all of the retrospective investigations were done within the past 14 years, they are significantly more

relevant to contemporary clinical practise. The outcomes were discussed after they were reviewed. In one study, patients who received hyperbaric oxygen had the same outcomes as those who did not. Patients in this study received hyperbaric oxygen twice daily rather than once, which set them apart from all other research. The most common outcomes found were reduced amputation rates and improved healing.

The study supports the idea that HBO helps patients with DFUs heal faster and reduces the need for major amputations. Only a handful of the trials looked at long-term results, but they found that wounds treated with HBO were more likely to heal properly in the future.

STUDY 4 Rui Liu *et al.*, 2013 conducted a Systematic Review of the Effectiveness of Hyperbaric Oxygenation Therapy in the Management of Chronic Diabetic Foot Ulcers.

This study involves a comprehensive evaluation and meta-analysis of the literature to determine the efficacy and safety of hyperbaric oxygenation (HBO) therapy as an additional treatment for diabetic foot ulcers.

All randomised controlled trials that compared adjunctive HBO therapy to no HBO therapy for persistent diabetic foot ulcers were included. A meta-analysis was conducted to determine the effectiveness and safety of hyperbaric oxygen in the treatment of foot ulcers. Thirteen trials (a total of 624 participants) were recognised as appropriate for inclusion in the investigation, including 2 case control studies, 7 prospective randomised and 4 prospective nonrandomized trials. HBO therapy expenses vary depending on the region, setup costs, ongoing costs, and the number of patients treated.

According to the study Adjunctive HBO treatment resulted in a considerably larger proportion of cured diabetic ulcers when compared to treatment without HBO (relative risk, 2.33; 95 percent CI, 1.51-3.60). Treatment with HBO was also linked to a lower incidence of major amputations (relative risk, 0.29; 95 percent confidence interval, 0.19-0.44).

This meta-analysis shows that treating diabetic foot ulcers with HBO increases the likelihood of healing and minimises the need for severe amputations. Furthermore, adverse effects are few and tolerable. As a result, we believe that careful implementation of HBO treatment could improve the long-term quality of life of patients treated with it.

STUDY 5 Robert P. Wunderlich *et al.*,2000 conducted a review on systemic hyperbaric oxygen therapy.

The objective of the study was to compile a list of peer-reviewed medical papers that have discussed hyperbaric oxygen (HBO) therapy as an adjuvant to standard lower extremity wound care, with an emphasis on diabetic foot publications**.** PubMed, the National Library of Medicine's MEDLINE search engine on the World Wide Web, was used to perform a review of the medical literature**.** "Wound healing," "diabetes foot," "gas gangrene," "chronic osteomyelitis," "necrotizing fasciitis," and "thermal burns" were key phrases used in the search engine to find related articles. In addition, the references cited in the articles found through the MEDLINE search were examined to find further publications that were relevant. Articles that met the inclusion and exclusion criteria were categorised into three groups: reviews and case reports, experimental animal or in vitro investigations, and human studies.
There was a total of 76 articles that met the inclusion and exclusion criteria. There were 21 human individuals in 21 studies (2–22). 28 reviews and/or case reports (50–77) and 27 animal or in vitro research (23–49). A control group was included in 62 percent of the research involving human participants (13 of 21 papers). Seven of the human investigations that were published included diabetes-related foot pathology. Five of the trials included a control group that did not receive HBO treatment, two of which were randomised. There was an average of 28 patients in the HBO therapy group (range 10–62) and 16.2 subjects in the non-HBO control group (range 5–33) in the controlled diabetic foot investigations. Between 1987 and 1996, the same group of researchers at the University of Milan published four of the seven papers regarding the diabetic foot.

More randomised placebo-controlled clinical trials in large diabetic populations would add to the body of evidence that HBO therapy improves clinical outcomes. Given the relatively high cost of this treatment method, a better understanding of the medical literature may help to alleviate the financial burden that HBO therapy places on financially strapped healthcare providers.

CONCLUSION

All of these trials support the idea that HBO enhances healing in DFU patients and can reduce severe amputation. Some studies also support that HBO is used as an adjunctive therapy in chronic foot ulcer Furthermore, adverse effects are few and tolerable. As a result, we believe that careful implementation of HBO treatment could improve the long-term

quality of life of patients treated with it. HBO was likely to survive in the future. DFUs have a substantial impact on society, financially and socially, in addition to impacting a patient's quality of life; consequently, therapies can reduce ulcer recurrence and amputation rates.

REFERENCES

1. Hammarlund C, Sundberg T, Hyperbaric oxygen reduced size of chronic leg ulcers: a randomized double-blind study. Plastic and Reconstructive Surgery, 1994; 93.
2. Wagner FW Jr. The dysvascular foot: a system for diagnosis and treatment. Foot and Ankle International, 1981; 2.
3. McHorney CA, Ware JE Jr, Raczek AE, The MOS 36-Item Short Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. Medical Care, 1993; 31.
4. Sullivan M, Karlsson J. The Swedish SF-36 Health Survey III, Evaluation of criterion-based validity: results from normative population. Journal of Clinical Epidemiology, 1998; 51.
5. Faglia E, Favales F, Aldeghi A, Calia P, Quarantiello A, Oriani G, Michael M, Campagnoli P, Morabito A, Adjunctive systemic hyperbaric oxygen therapy in treatment of severe prevalently ischemic diabetic foot ulcer. Diabetes Care, 1996; 19.
6. Baroni G, Porro T, Faglia E, Pizzi G, Mastropasqua A, Oriani G, Pedesini G, Favales F, Hyperbaric oxygen in diabetic gangrene treatment. Diabetes Care, 1987; 10.
7. Oriani G, Meazza D, Favales F, Pizzi GL, Aldeghi A, Faglia E, Hyperbaric oxygen therapy in diabetic gangrene. Journal of Hyperbaric Medicine, 1990; 5.
8. Oriani G, Michael M, Meazza D, Sacchi C, Ronzio A, Montino O, Sala G, Campagnoli P, Diabetic foot and hyperbaric oxygen therapy: a ten-year experience. Journal of Hyperbaric Medicine, 1992; 7.
9. Boulton AJ, Vileikyte L, Ragnarson-Tennvall G, Apelqvist J, The global burden of diabetic foot disease. Lancet, 2005; 12.
10. Pecoraro RE, Reiber GE, Burgess EM, Pathways to diabetic limb amputation: basis for prevention. Diabetes Care, 1990; 13.
11. Humphrey AR, R, Dowse GK, Thoma K, Zimmet PZ, Diabetes and nontraumatic lower extremity amputations: incidence, risk factors, and prevention a 12-year follow-up study in Nauru. Diabetes Care, 1996; 19.
12. Lehto S, Ronnemaa T, Pyorala K, Laakso M Risk factors predicting lower extremity amputations in patients with NIDDM. Diabetes Care, 1996; 19.

13. Singer AJ, Clarck RA, Cutaneous wound healing. The New England Journal of Medicine, 1999; 341.
14. Meltzer T, Myers B, The effect of hyperbaric oxygen on the bursting strength and the rate of vascularization of skin wounds in the rat. The American Surgeon, 1986; 52.
15. Roberts GP, Harding KG, Stimulation of glycosaminoglycan synthesis in cultured fibroblasts by hyperbaric oxygen. British Journal of Dermatology, 1994; 131.
16. Faglia E, Favales F, Aldeghi A, Adjunctive systemic hyperbaric oxygen therapy in treatment of severe prevalently ischemic diabetic foot ulcer: a randomized study. Diabetes Care, 1996; 19.
17. Rui Liu, Ling Li, Mengliu Yang, Guenther Boden, and Gangyi Yang, Systematic Review of the Effectiveness of Hyperbaric Oxygenation Therapy in the Management of Chronic Diabetic Foot Ulcers, Mayo Foundation for Medical Education and Research, 2013; 88(2).
18. Magnus Löndahl, Per Katzman, Anders Nilsson, Christer Hammarlund, Hyperbaric oxygen therapy for chronic diabetic foot ulceration, The Diabetic Foot Journal, 2011; 14(1).
19. Alexandra J Bishop, Elizabeth Mudge, Diabetic foot ulcers treated with hyperbaric oxygen therapy: a review of the literature, International Wound Journal, 2012.
20. M. Londahl, M. Landin-Olsson and P. Katzman, Hyperbaric oxygen therapy improves health-related quality of life in patients with diabetes and chronic foot ulcer, Diabetic Medicine, 29 October 2010.
21. Robert P, Edgar J.G. Peters, Md Lawrence A. Lavery, Wunderlich, Systemic Hyperbaric Oxygen Therapy, Diabetes Care, October 2000; 23(10).