Effectiveness of Hyperbaric Oxygen Therapy for Wound Healing in Patient with Diabetic Foot Ulcer: A Mini Review

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ABSTRACT

Diabetes mellitus (DM) is a metabolic disease in which the body has difficulty producing insulin which leads to high blood glucose levels. Consequently, people suffering from DM can have damage organs, blood vessels, and nerves which resulting in getting diabetic foot ulcer (DFU). Other therapeutic interventions are offered if the DFU does not heal with normal standard wound care. One of which is hyperbaric oxygen therapy (HBOT) that will increase the oxygen supply to wounds. However, the effectiveness of this therapy is not clearly known till present. Thus, the review of this paper aimed to report on the results of analysis of research that focuses on the effect HBOT on diabetic foot ulcer healing. Relevant literature was searched in Google Scholar and PubMed used keywords “hyperbaric oxygen therapy" "diabetic foot ulcer" "wound healing", and “chronic ulcer”. Five articles that met the inclusion criteria based on the results of the analysis. Although there was some indication of a beneficial effect of wound healing process, it is currently unknown which patients are likely to benefit from HBOT and which patients are not.

KEYWORD: hyperbaric oxygen therapy, diabetic foot ulcer, wound healing

INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic syndrome (1), and a complex problem throughout the world (2), with around 422 million adults suffer from diabetes mellitus (3), and 15% of people with DM will experience diabetic foot ulcer (DFU) in their lifetime (4). DFU is one of the most common complications of diabetes mellitus (5). The DFU can be defined as chronic wound that is infected by bacteria with tissue injuries that do not heal within 12 weeks (6), and end with amputation (7). Chronic wounds are characterized by the appearance of aerobic and anaerobic bacteria (8).
Prevention of these impacts can be done by arranging interventions in the form of managing diet, taking medication, controlling blood sugar, vascular control, foot care, education, and control of infected wound (9). Wound control can be done by treating diabetic ulcer wound. Patients with DFU are treated with standard wound care (10). It may be that many patients end up being referred to hyperbaric oxygen therapy (HBOT) clinics when healing is not achieved with standard wound care alone (11).

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The HBOT is a treatment designed to increase oxygen supply to wounds (12), with a concentration of 100% oxygen (13). The HBOT is a modality therapy which is effectively used in chronic wounds, necrotic tissue, patients with diabetes, and accelerates the healing process of DFU wounds (14-16). The wound healing phases are consisting of inflammation, proliferation, and remodeling (16, 17).

Increased method of wound care with hyperbaric oxygen therapy with a 100% oxygen concentration will accelerate the process of wound healing. The review of this paper aims to report on the results of analysis of research that focuses on the effect of hyperbaric oxygen therapy on diabetic foot ulcer healing.

METHODS

The main focus of the review of this paper was on the effectiveness of the HBOT on the wound healing process of DFU. In optimizing the interpretation of the review of this paper, first clarification of the research findings was carried out to do a review of literature. This review paper focuses on five journals for analysis.
The literature search was done by searching for relevant literature through the Google Scholar search engine and PubMed database. The keywords used in the search review of this paper are "hyperbaric oxygen therapy" "diabetic foot ulcer" "wound healing", and “chronic ulcer”. The inclusion criteria in this review paper were published between 2014 and 2018, in English, HBOT was the main topic, using RCT or Meta-analysis study design. The included journals were the original article so that the data can be presented completely and facilitate the review of the research.

RESULT

The search strategy at the beginning identified 800 articles from databases and search engines. Eight hundred articles for title review and 755 articles were excluded because they were irrelevant based on title ratings. Finally, 5 articles were included in this review since they met the inclusion criteria based on the results of the analysis. The details of review process can be referred to the figure 1.

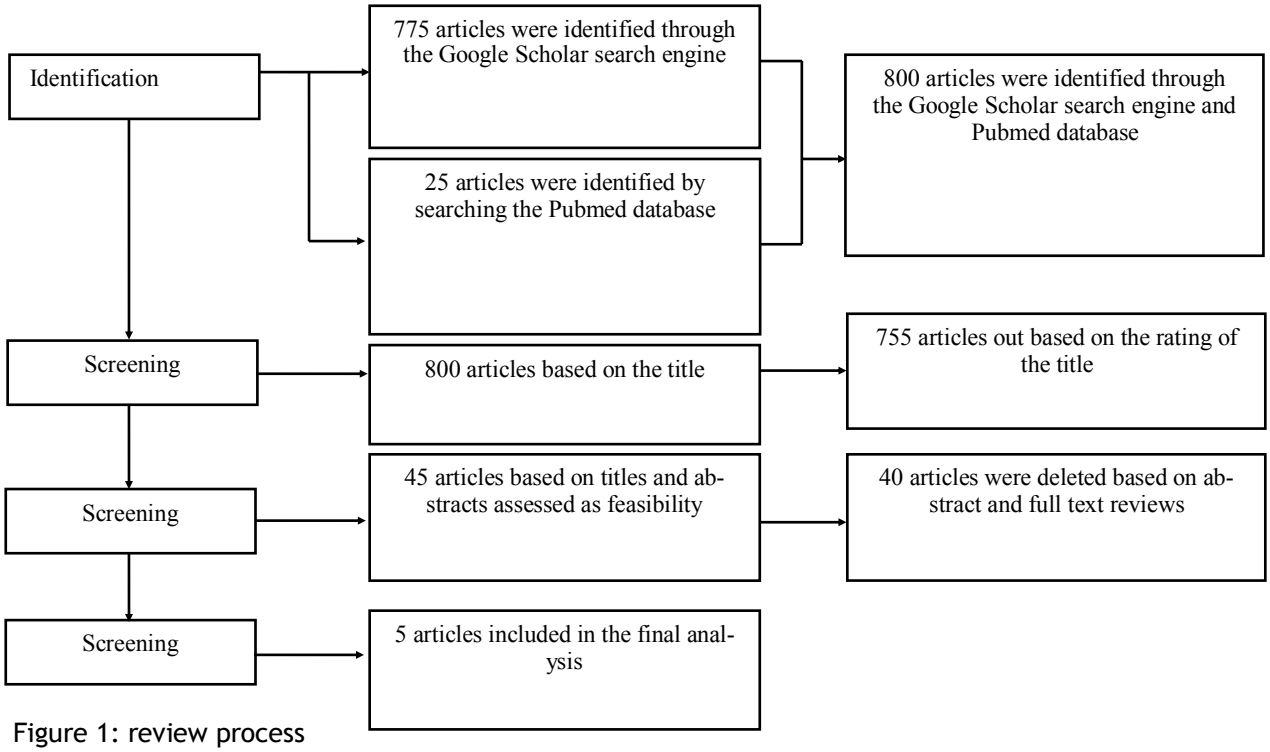

Figure 1: review process

Out of five articles, there are four studies that using research design randomized trial (RCT) and one study using meta-analysis approach. Sample size range from 38 – 528 patient and follow-up between 2 weeks and 12 months during studies. Most patient had DFU and some patient had venous leg ulcer. Study population were heterogeneous, partially as to the wound characteristic and present of severe ulcers. Table 1 summarizes the HBOT characteristic and outcome in each trial. To aid better understanding of the effectiveness of HBOT in wound healing process for this review, a few themes synthesized from the literature are presented as follows;

WOUND HEALING AND WOUND SIZE REDUCTION

In one trial and one meta-analysis that included patient with DFU, the HBOT resulted in improved rates of wound healing at the final follow-up compare with control patient, with an p value P = .038 (Mann-Whitney U test) and P = 0.091. No significant differences have been shown in another trail study in the reduction in manual width surface area. The reduction in manual width was slightly greater in the sham group, with a mean difference of 0.12 cm (95% CI 20.46, 0.22, P = 0.491). The Bates-Jensen wound assessment score was similar for ulcers at baseline in both groups (mean difference 0.6 points [95% CI 22.58, 3.64], P = 0.735). Wagner Classification also did not show a significantly result, P = 0.823.

Amputation

A reduction in amputation rates was reported in one trial study with patient with DFU. In the trial of Chen HBOT result the reduction of amputation rate was 5% for the HBOT group and 11% for the routine care group (x 2 = 15.204, *P* = .010). In three trials studies, it showed that there was no effect of HBOT in amputation rate reduction. Santema et al, who reported at the end of follow-up, 41 patients (68%) were alive and free from major amputation on the index limb in the standard care group vs. 49 (82%) in SC+HBOT group (RD13% [95% CI22 to 28]).

Pressure Ulcer Scale

A study showed that the HBOT group had a significantly greater ulcer percent area reduction, with mean of 95 (SD 6.53) compared to the placebo group mean 54 (SD 67.4), with p value 0.045. A two-way ANOVA of pressure ulcer scale for healing (PUSH) cores found the interaction effect for group over time, with the HBOT group recording a greater improvement in the PUSH scores over time than the placebo group, was not significant (F=4.27, p=0·051); while both groups improved significantly over time (F=29.42, p<0.001). On a scale from 0 – 17, where 0= completely healed, and 17 = worst possible score; the placebo group went from a mean of 12.46 (SD 2.22) to 7.62 (SD 5.53) at the end of the study, and the HBOT group from a mean of 12.17 (SD 2.02) to 3.38 (SD 4.09).

Table 1: The studies included in this review

Author	Source	Aim	Design and sampling	HBOT Procedure	Measure	Findings
Thistlethwaite et. al (2018) (17)	PubMed	To determine the effectiveness of HBOT for patients with non-healing venous leg ulcers on	Randomised, double-blind, placebo-controlled trial. This research only use participant that have venous leg ulcers which is failed to reach 50 % area of reduction after 4 weeks 1st group : 43 participants received HBOT 2nd group : 31 participants received placebo	1. For participants randomized to the HBOT intervention, following compression over six to eight minutes, 100% oxygen was administered for two 40 minutes with a five-minutes break on air after the first period and a 30 minute decompression period on 100% oxygen back to sea level, for a total treatment time each session of 120 minutes 2. Participants randomized to the placebo group received air initially pressurized for 8 minutes 3.Intervention phase: 4 weeks (weeks 5-10) 5 days every week. Follow up phase (week 11-16)	Pressure Ulcer Scale for Healing (PUSH) Score Follow up : 12 month after last intervention	The HBOT group has a significantly compare to the placebo group, p value = 0.045
Santema et. al (2018) (18)	PubMed	To investigate whether additional HBOT would benefit patients with diabetes and ischemic leg ulcers	Randomized Clinical trial 1st group: HBOT + standard care 57 participant 2nd group: standard care only 58 participant	HBOT included sessions of 90min in a multiplied chamber, pressurized at 2.4 or 2.5 atmospheres absolute during which patients were breathing 100% FiO2 except for three blocks of 5 min during which ambient air was administered to prevent oxygen intoxication. HBOT was scheduled for 5 days per week until a maximum of 40 sessions was reached or until complete wound healing was achieved.	1. Limb Salvage 2. Amputation Freedom Survival 3. Additional revascularization Follow up : 3, 6, 12 after the last intervention	1. Limb salvage was achieved in 47 patients in the SC group vs. 53 patients in the SC+HBOT group (risk difference [RD] 10% [95% CI24 to23]). 2.41 patients (68%) were alive and free from major amputation on the index limb in the SC group vs. 49 (82%) in SC+HBOT group (RD13%[95% CI22 to 28]). 3.24 (40%) patients underwent planned revascularization vs. 25 (42%) in the SC+HBOT group

Author	Source	Aim	Design and sampling	HBOT Procedure	Measure	Findings
Fedorko et. al (2016) (19)	Google Scholar	To assess the efficacy of HBOT in reducing the need of major amputation and improving wound healing in patients with diabetes and chronic DFUs	Double-blind, Randomized Controlled Trial 1st group : allocated to HBOT, 39participants 2nd group : allocated to sham, 48 participant	1. HBOT Procedure : 5 days per week for 6 weeks (30 sessions). HBOT consisted of breathing oxygen for 90min at 244 kPa of pressure, with 5-min intervals of breathing air for every 30 min of oxygen. 2.Sham : sessions consisted of breathing air at ;125 kPa of pressure (equivalent to breathing 27% O2 by face mask) on the same schedule.	1. Primary Outcome: Indication for Amputation (ITT) 2. Secondary Outcomes : • Wound Measurements (LAWE, The Wound Areas consultant Group) • Bates-Jensen Wound Assessment Tool • Wagner Classification Score Follow up : 6 weeks after last intervention	1. Non significant difference was found for HBOT, with 11 (22.5%) HBOT group participants band 13 (24.1%) sham group participants meeting the criteria for major amputation (odds ratio [OR] 0.91 [95% CI 0.37, 2.28], P = 0.846) 2. No significant difference was found at 12 weeks in the reduction in manual width or digital surface area after controlling for baseline wound size. The reduction in manual width was slightly greater in the sham group, with a mean difference of 0.12 cm (95% CI 20.46, 0.22, P = 0.491) 3. The Bates-Jensen wound assessment score was similar for ulcers at baseline in both groups (mean difference 0.6 points [95% CI 22.58, 3.64], P = 0.735) 4. At 12 weeks, the percentage of participants whose wounds were healed was 20% and 22% in the HBOT and sham groups, respectively (OR 0.90 [95% CI 0.35, 2.31], P = 0.823)
Chen et. al (2017) (20)	Research Gate	To compare the effect of standard wound care with HBOT to Standard wound care alone on wound healing, markers of inflammation, glycemic control, amputation rate, survival rate of tissue, and health- related quality of life in Diabetic Foot Ulcers	Randomized Controlled Trial 1st group : Standard Care + HBOT = 20 participant 2nd group : Standard Care = 18 participant	Hyperbaric oxygen therapy was administered in a hyperbaric chamber under 2.5 absolute atmospheric pressure for 120 minutes; subjects were treated 5 days a week for 4 consecutive weeks. Both groups received standard wound care including debridement of necrotic tissue, topical therapy for Wagner grade 2 DFUs, dietary control and pharmacotherapy to maintain optimal blood glucose levels.	1.Wagner Classification 2.Amputation Rate Follow up : 2 weeks after last intervention	1.Complete DFU closure was achieved in 5 patients (25%) in the HBOT group (n = 20) versus 1 participant (5.5%) in the routine care group (n = 18) (P = .001). 2.The amputation rate was 5% for the HBOT group and 11% for the routine care group (χ_2 = 15.204, P = .010).

Author	Source	Aim	Procedure	Study Selection	Findings	Result
Zhao et. al (2017) (21)	Google Scholar	To evaluate the efficacy and safety profile of HBOT in patient with diabetic foot ulcer	Meta-analysis of RCT research. Using 4 database PubMed, Cochrane Library, EMBASE, and Clinical Trials.gov	Studies of literature will be search and screened by 2 investigators, and third investigators was consulted if there were disagreements. From searching and screening procedure, there was 9 studies that with 526 participants that met the inclusion criteria.	No difference was found in the incidence of healed ulcers (risk ratio [RR] ¼ 2.22; 95%CI,0.87–5.62; P ¼ 0.32; I2 ¼ 81%), minor amputations (RR ¼ 0.95; 95%CI, 0.39–2.29; P ¼ 0.91; I2 ¼ 74%), major amputations (RR ¼ 0.47;95%CI,0.17–1.28; P ¼ 0.14; I2 ¼ 61%), and adverse events(RR ¼ 1.00;95%CI,0.64–1.56; P ¼ 0.99; I2 ¼ 26%) between the HBOT and standard therapy (ST) groups. HBOT was associated with a greater reduction in the ulcer wound area versus ST (standard mean difference ¼ 1.12; 95%CI, 0.20–2.04; P ¼ 0.04; I2 ¼ 70%).	No differences existed between HBOT and ST with respect to the incidence of healed ulcers, risk of minor or major amputations, and adverse events. HBOT was associated with a greater reduction in the ulcer wound area than ST. HBOT is a clinically meaningful adjuvant therapy for patients with diabetic foot ulcer.

DISCUSSION

Management of DFUs begins with debridement, off-loading and infection control. When DFUs do not heal despite adequate conservative management or progress to Wagner Grade 3 or 4, HBOT can be considered as an adjuvant therapy. However, its efficacy is not universally accepted (22). The available evidence on the effectiveness of HBOT for DFU is still not solid, and it could be due to methodological or the outcome measurement. The HBOT can generally be considered a safe treatment modality, which is reflected by the low frequency of adverse events in several trials (23). It has been postulated that the addition of the HBOT to standard care in chronic DFU is an effective way of decreasing of the overall costs of diabetic wounds (20) Patient should be strictly administered the standard therapy formed through multidisciplinary approach for the wounds to heal. Additionally, the HBOT is recommended over conventional therapies for several indications; including delayed radiation injury, necrotizing soft tissue infections and chronic wound in DFU (24).

While this work brought a doubt to the effectiveness of HBOT, a 2015 Cochrane report of HBOT for chronic wounds found that HBOT has strong clinical evidence for improved short-term healing (early wound healing response), limited clinical evidence for improved long-term healing, and limited evidence for decreasing the rate of lower limb amputation (25). Wound healing is a normal process following injury that comprises four phases: hemostasis, inflammation, proliferation, and tissue remodeling. Oxygen availability is critical in wound healing primarily for facilitating oxidative phosphorylation for normal cellular function. However, during the initial phases of wound healing, the wound is hypoxic (26). Erdogan et al recently, performed a prospectively study, that involving 100 participants with DFU reported significant healing process in the hyperbaric oxygen group, and were more likely to undergo amputation distal to the metatarsophalangeal joint compared with those patients receiving standard therapy without hyperbaric oxygen(24).

At normal atmospheric conditions, almost 100% of oxygen is transported by binding to hemoglobin. Poorly perfused tissues create steeper gradients that induce a larger cumulative demand(22). Patient with DM with microvascular diseases such as diabetes have fewer capillaries to provide oxygenation to the tissues. HBOT combats this state of hypoxia by increasing the amount of oxygen dissolved in plasma as well as the partial pressure of oxygen in tissue fluid (27). Recently, a clinical trial of 55 patients with diabetic ulcers had shown that Capillary venous oxygen saturation had significant increase in the HBOT group on day 24; however, this increase was significant at this time point only. Also blood flow in the micro circulation showed a significant increase on days 17, 21 and 31 but a significant decrease on days 24 and 28. Inflammation scoring showed significantly decreased CD68 counts in the HBOT group on day 42, but not in the early stages of wound healing (28).

CONCLUSION

Considering the differences between the results of trials, there is several trials that indicated beneficial effects of HBOT particularly in diabetic patients with foot ulcer. Although there is some indication of a beneficial effect of wound healing process, it is currently unknown which patients are likely to benefit from HBOT and which patients are not. Before the large-scale implementation of the HBOT in routine practice can be justified, its effectiveness needs to be confirmed in trials with proper methodical research using uniform measure to enable comparison of outcomes. Moreover, future trials should identify the subgroup of patients who are most likely to benefit from HBOT, establish the optimal HBOT regimen, and should be adequately powered to identify a possible effect on another outcomes. The results of these trials will contribute to evidence-based decision making on the use of the HBOT as an adjunctive therapy in patients with a diabetic foot ulcer.

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