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ORIGINAL ARTICLE

Effect of hyperbaric oxygen treatment on diabetic foot ulcers: A meta-analysis

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Abstract

The meta-analysis aimed to assess the effect of hyperbaric oxygen treatment on diabetic foot ulcers. Using dichotomous or contentious random or fixed effect models, the outcomes of this meta-analysis were examined and the odds ratio (OR) and the mean difference (MD) with 95% confidence intervals (CIs) were computed. 17 examinations from 1992 to 2022 were enrolled for the present meta-analysis, including 7219 people with diabetic foot ulcers. Hyperbaric oxygen treatment had a significantly higher healed ulcer (OR, 14.39; 95% CI, 4.02–51.52, $p < 0.001$), higher adverse event (OR, 2.14; 95% CI, 1.11–4.11, $p = 0.02$), lower mortality (OR, 0.22; 95% CI, 0.07–0.71, $p = 0.01$) and higher ulcer area reduction (MD, 23.39; 95% CI, 11.79–34.99, $p < 0.001$) compared to standard treatment in patients with diabetic foot ulcers. However, hyperbaric oxygen treatment and standard treatment had no significant difference in amputation (OR, 0.62; 95% CI, 0.22–1.75, $p = 0.37$), major amputation (OR, 0.59; 95% CI, 0.18–1.92, $p = 0.38$), minor amputation (OR, 0.64; 95% CI, 0.15–2.66, $p = 0.54$) and healing time (MD, −0.001; 95% CI, −0.76 to 0.75, $p = 0.99$) in patients with diabetic foot ulcers. The examined data revealed that hyperbaric oxygen treatment had a significantly higher healed ulcer, adverse event, and ulcer area reduction and lower mortality, however, there was no significant difference in amputation and healing time compared to standard treatment in patients with diabetic foot ulcers. Yet, attention should be paid to its values since most of the selected examinations had a low sample size and some of the comparisons had a low number of selected studies.

KEYWORDS

amputation, diabetic foot ulcer, healed ulcer, hyperbaric oxygen treatment

Key Messages

- The meta-analysis aimed to assess the effect of hyperbaric oxygen treatment on diabetic foot ulcers.

- The examined data revealed that hyperbaric oxygen treatment had a significantly higher healed ulcer, adverse event, and ulcer area reduction and lower mortality, however, there was no significant difference in amputation and healing time compared to standard treatment in patients with diabetic foot ulcers.
- Yet, attention should be paid to its values since most of the selected examinations had a low sample size and some of the comparisons had a low number of selected studies.

1 | INTRODUCTION

Several million people worldwide have diabetes mellitus; of these, three-quarters live in middle-income countries and the remaining handful reside in low-income nations. By 2050, the International Diabetes Federation projects that there will be more than 700 million people worldwide who have diabetes mellitus. Surprisingly, nearly half of type-2 diabetic patients in adults are not aware that they have the condition. In addition, Almost 200 million people with undiagnosed diabetes mellitus live in middle-income nations.[1] The majority of the time, type-2 diabetes mellitus goes unnoticed for a very long time before complications including neuropathy, retinopathy, metabolic disorders and diabetic foot ulcers appear. These complications are very challenging to treat. The occurrence of an ulcer in the lower leg in a diabetic patient that is linked to neuropathy and/or peripheral artery disease is known as a diabetic foot ulcer.[2] Particularly in poor nations,[3] diabetic foot ulcers that are infected and multi-drug resistant eventually stop healing and significantly contribute to amputations and mortality. A prominent consequence of diabetes is the loss of a lower limb, which occurs globally every 30 s. Diabetes patients have a 2% incidence rate of diabetic foot ulcers, and their risk rises by 17%–60% if they have had one in the previous 3 years[4]; additionally, 50% of these patients have lower limb amputations at some point in their lives.[1] Additionally, patients with diabetic foot ulcers who have already undergone one amputation are more likely to need a second one within 5 years.[5] Additionally, diabetic individuals have been shown to have a higher mortality rate between 90 days and 5 years following amputation,[6] as well as a drop in survival rate at 5 years after minor and major amputations, respectively, in diabetic patients with diabetic foot ulcers.[7] It is clear that diabetic foot ulcers and the resulting need for amputations increase the risk of premature death, lower life expectancy and financial strain on families and the healthcare system.[8] For patients and the medical community, diabetic foot ulcers continue to be a major concern. This could be because of uneven healthcare facilities, a lack of awareness, a delay in referral, or a shortage of trained medical personnel.[9] Different modalities are available in the usual line of treatment for diabetic foot ulcers and among them are pressure relief, surgical debridement, antibiotics for the infection and blood sugar control.[10] The majority of the time, polymicrobial agents,[11] a compromised immune system,[12] and a high rate of antibiotic resistance are developed,[3] resulting in non-healing ulcers, in diabetes patients' foot ulcers. Importantly, every patient with diabetic foot ulcers cannot be treated with surgical debridement, which may require different treatment modalities.[13] Additionally, chronic non-healing ulcers may not respond to the standard treatment. One adjunct therapy that has been utilised for years to treat complicated diabetic foot ulcers is hyperbaric oxygen treatment.[10] Since hypoxic tissues in chronic wounds prevent ulcer repair, oxygen plays a significant role in the healing of these wounds. For a better therapeutic outcome in hyperbaric oxygen treatment, the patient is kept in a chamber with 100% oxygen breathing and an atmospheric pressure higher than sea level.[14] Patients receiving hyperbaric oxygen treatment have reported several positive physiological improvements, including increased angiogenesis, enhanced collagen deposition, increased leukocyte activity and decreased edema.[15] To speed up the healing of ulcers and further prevent amputations, hyperbaric oxygen treatment helps to increase the oxygen level in tissues.[16] Despite these advantages and their possible use in treating diabetic foot ulcers that are not healing, hyperbaric oxygen treatment is still a dubious therapy and is only used as a last resort. Kranke et al.'s Cochrane study from 2015 found that patients who received hyperbaric oxygen treatment experienced a considerable improvement in their ability to repair wounds.[17] While a recent meta-analysis by Brouwer et al.[18] found that hyperbaric oxygen treatment reduces major amputation rates but is ineffective in wound healing, this study omitted five randomised controlled trials, meaning that any conclusions drawn from these reviews may not be supported by all of the available evidence. Additionally, these evaluations incorrectly evaluated the quality of the data, which means the

conclusions drawn concerning the effectiveness of hyperbaric oxygen treatment in the treatment of diabetic foot ulcers that refuse to heal may not be complete. To provide the most reliable evidence about the effectiveness of hyperbaric oxygen treatment as an adjunctive therapy for the treatment of diabetic foot ulcers, the current meta-analysis was conducted to assess the effect of hyperbaric oxygen treatment on diabetic foot ulcers.

2 | METHOD

2.1 | Design of the examination

The meta-analyses were incorporated into the epidemiological declaration and evaluated according to a predetermined process. For data collection and analysis, many databases were accessed, including OVID, PubMed, the Cochrane Library, the Cochrane Central Register of Controlled Trials, Embase and Google Scholar. These datasets were utilised to compile examinations that compared and evaluated the effect of hyperbaric oxygen treatment for personnel with diabetic foot ulcers.[19,20]

2.2 | Data pooling

Several clinical outcomes were obtained when hyperbaric oxygen treatment was compared to standard care for the management of diabetic foot ulcers. The main inclusion parameter outcome in these findings was diabetic foot ulcer healing parameters. When selecting which study to include and screening candidates, language restrictions were not taken into account. There was no restriction on the number of recruited subjects for the studies. Reviews, editorials and letters do not contain an intervention, hence, we did not include them in our synthesis. The entire examination identification process is shown in full in Figure 1.

2.3 | Eligibility of included studies

It is being looked at whether hyperbaric oxygen treatment has a positive or negative impact on the clinical outcomes of diabetic foot ulcers. Only articles that addressed how interventions affected the frequency of diabetic foot ulcers evaluated parameters were included in the sensitivity analysis. Sensitivity and subclass analyses were conducted using comparisons between the interventional groups and a variety of subtypes.

2.4 | Inclusion and exclusion criteria

2.4.1 | Inclusion criteria

The following criteria had to be completed for a study to be eligible for inclusion in the meta-analysis: a comparison of hyperbaric oxygen treatment's effects on diabetic foot ulcers to standard medical care. For statistical analysis to be used, the output must contain the outcome's expression.

2.4.2 | Exclusion criteria

We excluded studies with a non-comparative design. In addition, no letters, books, reviews, or book chapters were included in the current assessment.

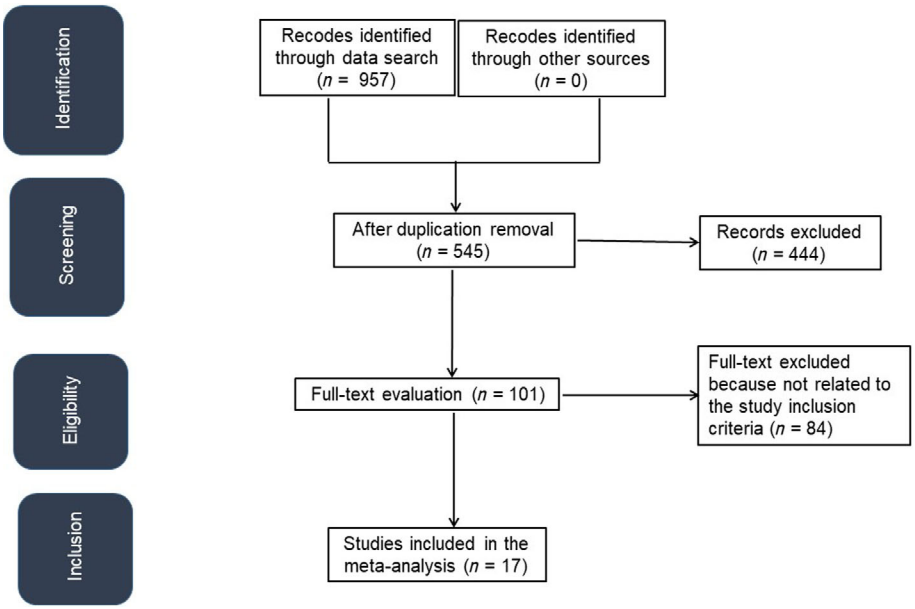

FIGURE 1 Schematic diagram of the examination procedure.

2.5 | Identification of studies

A protocol of search strategies was devised and specified as follows by the PICOS principle, which states: P (population) individuals with diabetic foot ulcers; hyperbaric oxygen treatment was the 'intervention' or 'exposure'; C (comparison): the comparative effectiveness of hyperbaric oxygen treatment compared with standard treatment. O (outcome): diabetic foot ulcer healing parameters; S (design of the examination): the planned examination had no boundaries.

We carried out a thorough search of the relevant databases up to August 2023 using the keywords and associated terms provided in Table 1. All publications included in a reference management program, including titles and abstracts, as well as any studies that did not relate the type of treatment to clinical results, were reviewed. Two authors also serve as reviewers to find relevant tests.

2.6 | Screening of studies

The amount of data was condensed using the following criteria: examination and personal features presented in a standard format; first author's last name; time and year of examination; nation in which examination was conducted; gender; population type that was recruited for examination; total number of individuals; qualitative and quantitative evaluation methods; demographic information; clinical and treatment characteristics. Two anonymous reviewers looked at the potential of bias in each test as well as the standard of the procedures used in the tests that were chosen for further investigation. Two reviewers independently evaluated each examination's methodology.

TABLE 1 Database search strategy for inclusion of examinations.

Database	Search strategy
Google Scholar	#1 'diabetic foot ulcer' OR 'amputation' #2 'hyperbaric oxygen treatment' OR 'healed ulcer' #3 #1 AND #2
Embase	#1 'diabetic foot ulcer'/exp OR 'amputation' #2 'hyperbaric oxygen treatment'/exp OR 'healed ulcer'/ #3 #1 AND #2
Cochrane library	#1 (diabetic foot ulcer):ti,ab,kw (amputation): ti,ab,kw (Word variations have been searched) #2 (hyperbaric oxygen treatment):ti,ab,kw OR (healed ulcer):ti,ab,kw (Word variations have been searched) #3 #1 AND #2
Pubmed	#1 'diabetic foot ulcer' [MeSH] OR 'amputation' [All Fields] #2 'hyperbaric oxygen treatment' [MeSH Terms] OR 'healed ulcer' [All Fields] #3 #1 AND #2
OVID	#1 'diabetic foot ulcer' [All Fields] OR 'amputation' [All Fields] #2 'hyperbaric oxygen treatment' [All fields] OR 'healed ulcer' [All Fields] #3 #1 AND #2

2.7 | Statistical analysis

In the current meta-analysis, the odds ratio (OR) and mean difference (MD) with a 95% confidence interval (CI) were estimated using dichotomous or continuous random- or fixed-effect models. The I^2 index was determined (in percent), and it has a range of 0 to 100. Higher I^2 values indicate increased heterogeneity, while $I^2 = 0$ indicates a lack of heterogeneity. The random effect was chosen when I^2 was 50% or higher; if I^2 was lower than 50%, the choice to choose the fixed effect was raised.[21] As was already mentioned, the results of the initial investigation were categorised as part of the subcategory analysis. Publication bias was assessed using Begg's and Egger's tests for quantitative analysis, and it was found to be present if $p > 0.05$. The p-values were computed using a two-tail analysis. Using Jamovi 2.3, graphs and statistical analysis were produced.

3 | RESULTS

17 tests that were published between 1992 and 2022 were included in the meta-analysis after an evaluation of 957 applicable exams since they fit the inclusion criteria.[16,22–37] Table 2 summarises the findings of these investigations. 7219 people with diabetic foot ulcers were in the used studies' starting point, 1328 of them were using hyperbaric oxygen treatment, and 5891 were using standard treatments. The sample size was 18 to 5466 people.

Hyperbaric oxygen treatment had a significantly higher healed ulcer (OR, 14.39; 95% CI, 4.02–51.52, $p < 0.001$) with high heterogeneity ($I^2 = 80\%$), higher adverse event (OR, 2.14; 95% CI, 1.11–4.11, $p = 0.02$) with no heterogeneity ($I^2 = 0\%$), lower mortality (OR, 0.22; 95% CI, 0.07–0.71, $p = 0.01$) with low heterogeneity ($I^2 = 34\%$) and higher ulcer area reduction (MD, 23.39; 95% CI, 11.79–34.99, $p < 0.001$) with high heterogeneity ($I^2 = 76\%$) compared to standard treatment in patients

TABLE 2 Characteristics of studies.

Study	Country	Total	Hyperbaric oxygen treatment	Control
Doctor, 1992[22]	India	30	15	15
Faglia, 1996[23]	Italy	30	15	15
Kalani, 2002[16]	Sweden	38	17	21
Kessler, 2003[24]	France	27	14	13
Abidia, 2003[25]	UK	18	9	9
Duzgun, 2008[26]	Turkey	100	50	50
Löndahl, 2010[27]	Sweden	94	49	45
Ma, 2013[28]	China	36	18	18
Margolis, 2013[29]	USA	6259	793	5466
Khandelwal, 2013[30]	India	40	20	20
Fedorko, 2016[31]	Canada	103	49	54
Chen, 2017[32]	Taiwan	38	20	18
Santema, 2018[33]	Netherlands	120	60	60
Erdoğan, 2018[34]	Turkey	130	71	59
Perren, 2018[35]	Greece	26	13	13
Salama, 2019[36]	Egypt	30	15	15
Pasek, 2022[37]	Poland	100	100	0
	Total	7219	1328	5891

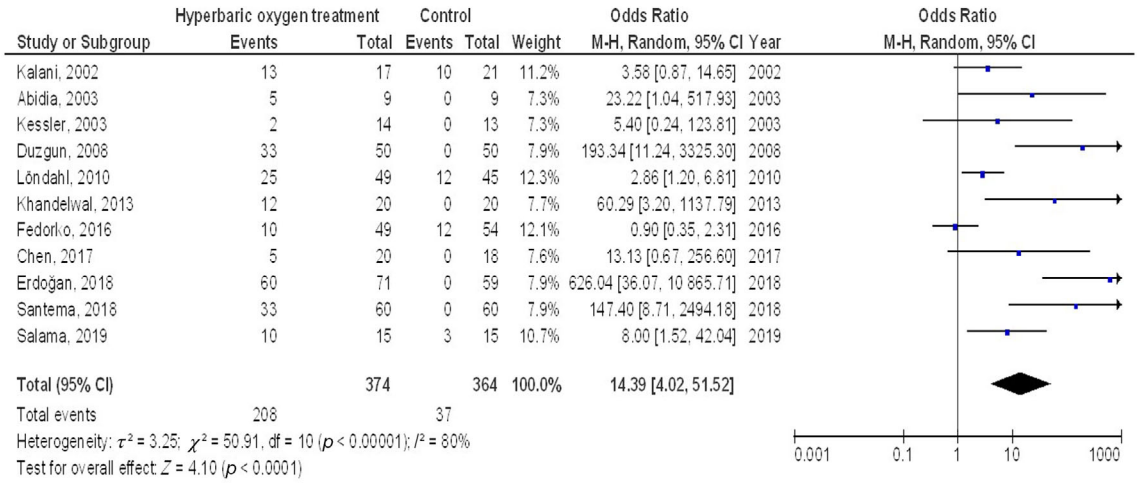

FIGURE 2 The overall effect's forest plot of the hyperbaric oxygen treatment compared to standard treatment on healed ulcer in personals with diabetic foot ulcers.

with diabetic foot ulcers, as revealed in Figures 2–5. However, hyperbaric oxygen treatment and standard treatment had no significant difference in amputation (OR, 0.62; 95% CI, 0.22–1.75, $p = 0.37$) with high heterogeneity ($I^2 = 90\%$), major amputation (OR, 0.59; 95% CI, 0.18–1.92, $p = 0.38$) with high heterogeneity ($I^2 = 79\%$), minor amputation (OR, 0.64; 95% CI, 0.15–2.66, $p = 0.54$) with high heterogeneity ($I^2 = 85\%$) and healing time (MD, −0.001; 95% CI, −0.76 to 0.75, $p = 0.99$) with no heterogeneity ($I^2 = 0\%$) in patients with diabetic foot ulcers, as revealed in Figures 6–9.

The quantitative Egger regression test and the visual interpretation of the funnel plot did not reveal any evidence of examination bias ($p = 0.89$). The bulk of pertinent exams, it was found, had poor practical quality and no bias in selective reporting.

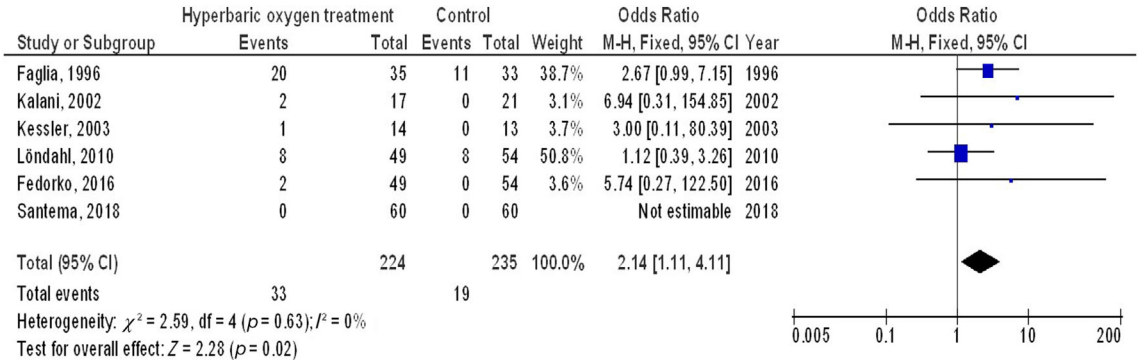

FIGURE 3 The effect's forest plot of the hyperbaric oxygen treatment alone compared to standard treatment on adverse events in personals with diabetic foot ulcers.

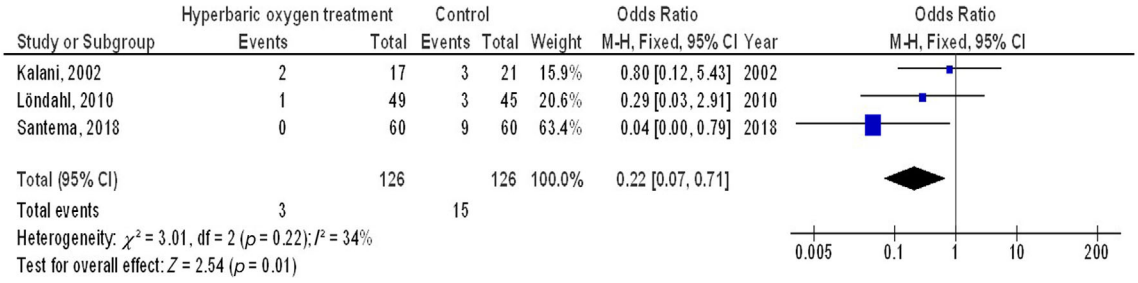

FIGURE 4 The effect's forest plot of the hyperbaric oxygen treatment and healed ulcer compared to standard treatment on ulcer area reduction in personals with diabetic foot ulcers.

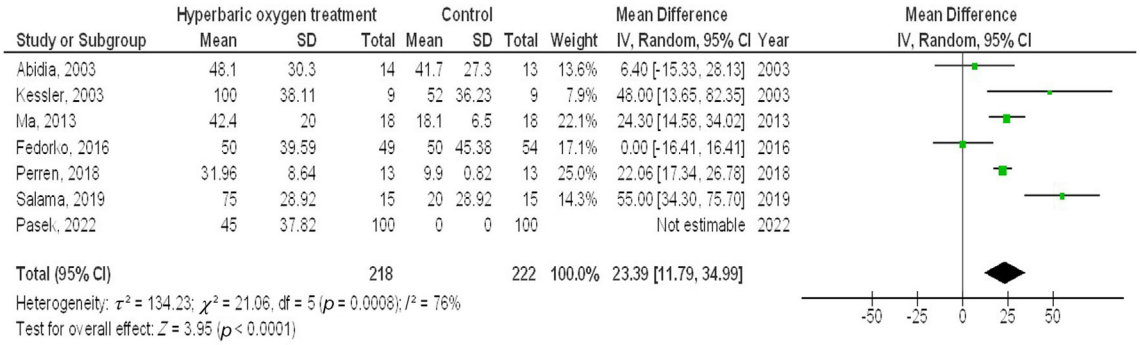

FIGURE 5 The effect's forest plot of the overall hyperbaric oxygen treatment compared to standard treatment on mortality in personals with diabetic foot ulcers.

4 | DISCUSSION

17 examinations from 1992 to 2022 were enrolled for the present meta-analysis, comprising 7219 people with diabetic foot ulcers at the used studies' starting point, 1328 of them were using hyperbaric oxygen treatment and 5891 were using standard treatments. The sample size ranged from 18 to 5466 people.[16,22–37] The examined data revealed that hyperbaric oxygen treatment had significantly higher healed ulcers, higher adverse events, lower mortality and higher ulcer area reduction compared to standard treatment in patients with diabetic foot ulcers. However, hyperbaric oxygen treatment and standard treatment had no significant difference in amputation, major amputation, minor amputation and healing time in patients with diabetic foot ulcers. Yet, attention should be paid to its values since most of the selected examinations had a low sample size (11 out of 17 examinations were ≥100) and some of the comparisons had a low number of selected studies.

Oxygen is crucial to the complicated process of wound healing. Increased oxygen levels in wound tissues

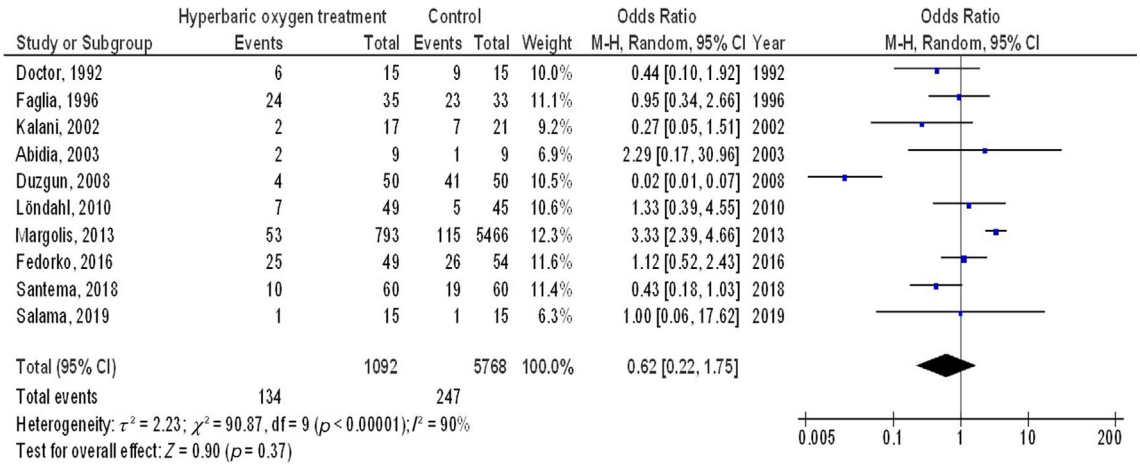

FIGURE 6 The effect's forest plot of the hyperbaric oxygen treatment alone compared to standard treatment on amputation in the personals with diabetic foot ulcers.

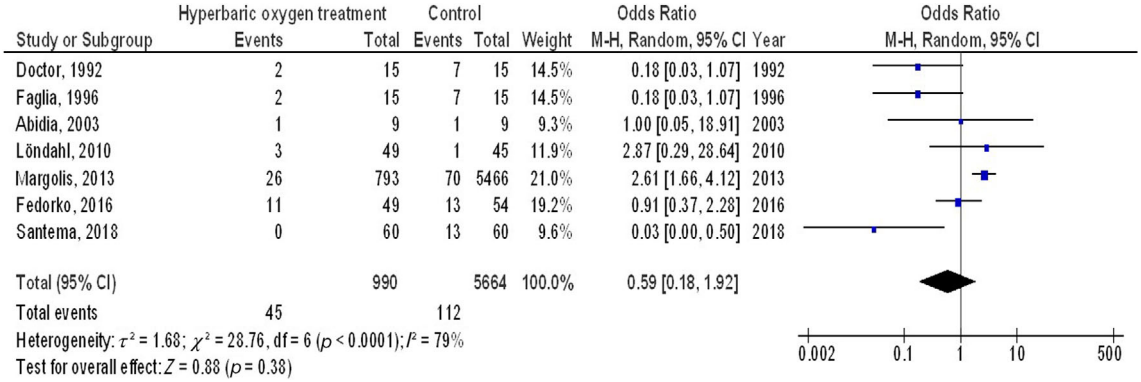

FIGURE 7 The effect's forest plot of the hyperbaric oxygen treatment and healed ulcer compared to standard treatment on major amputation in the personals with diabetic foot ulcers.

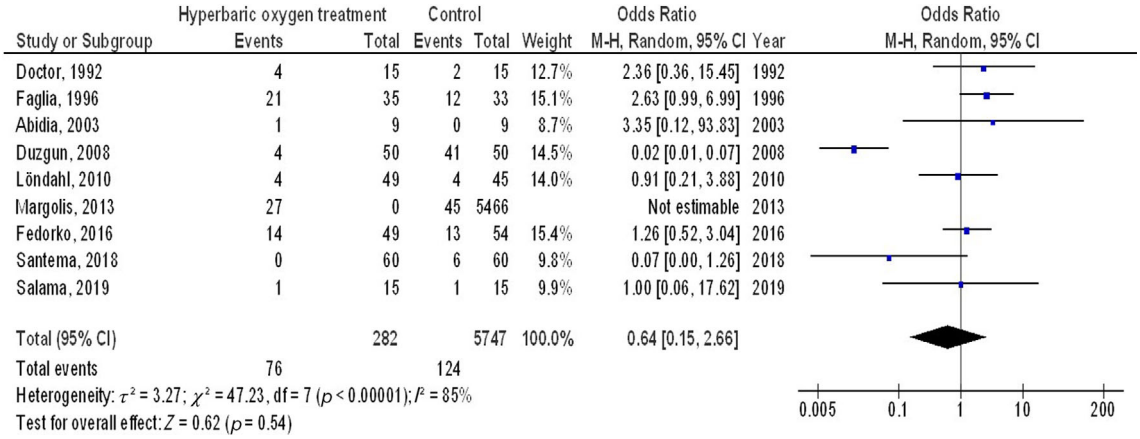

FIGURE 8 The effect's forest plot of the hyperbaric oxygen treatment alone compared to standard treatment on minor amputation in the personals with diabetic foot ulcers.

have been found to improve wound healing and reduce bacterial colonization in chronic wounds.[38] The human body receives 100% oxygen while at higher atmospheric pressure than usual during hyperbaric oxygen treatment, which increases the amount of oxygen in human cells and speeds up the healing process of wounds.[16] Although

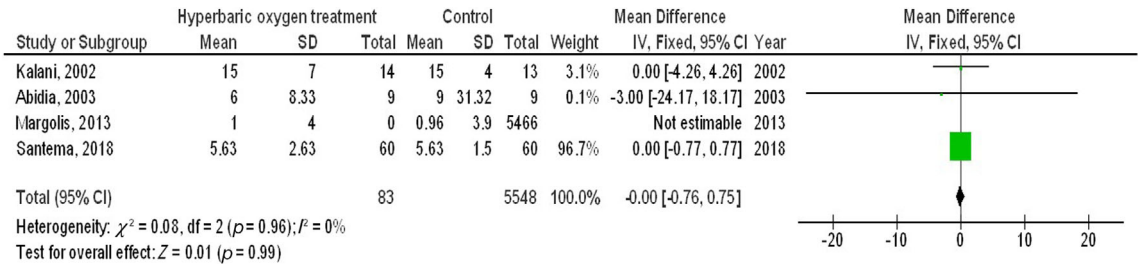

FIGURE 9 The effect's forest plot of the hyperbaric oxygen treatment and healed ulcer compared to standard treatment on healing time in the personals with diabetic foot ulcers.

the effect is contradictory, it may be explicable by variations in the clinical profiles of the patients, comorbidities, variations in the method and duration of hyperbaric oxygen treatment, oxygen pressure and other potential confounding factors.[39] The findings of our study are similar to those of other studies by O'Reilly et al.,[40] Rui et al.[41] and Kranke et al.[17] in terms of favourable outcomes that favour hyperbaric oxygen treatment. The overall time and number of sessions, not only the hyperbaric oxygen treatment itself, are what will ultimately determine if expected results materialise, particularly in terms of lowering the amputation risk among diabetic patients with diabetic foot ulcers. Patients with non-healing diabetic foot ulcers frequently experience the following well-established risk factors for amputations: chronic arterial insufficiency,[42] neuro ischemic foot,[43] inadequate glycemic control[44] and infection.[45] By reducing ischemia at both local and regional tissues, hyperbaric oxygen treatment aids in the achievement of physiological effects. As a result, hyperbaric oxygen treatment helps to stimulate oxygen-dependent mechanisms to boost host antimicrobial responses, bone marrow stem cell generation and wound repair.[16] The effectiveness of any treatment is also based on any negative effects it may have on a patient. Our results oppose a systematic review[41] that found no distinction between the hyperbaric oxygen treatment and standard treatment groups in terms of side effects. Studies that were included had documented negative effects, including oxygen toxicity, oxygen-induced seizure,[27] ocular effects, barotraumatic lesions, harm to the ear,[23,24,27,31,33] hypoglycemia[27,31] and cataracts.[16,27] Barotrauma which affects air-filled cavities in the human body, particularly the middle ear, lungs and sinuses, is the most frequent adverse impact linked to hyperbaric oxygen treatment. It happens as a result of compression.[31] Barotrauma is typically simply treatable and recoverable without the need for therapeutic intervention. The most uncommon conditions to occur are pulmonary barotrauma, injuries, or fire in the chamber; these are the main side effects.[46] The causes of mortality were multi-organ failure,[16,27] progressive heart failure,[16] and gallbladder perforation followed by sepsis,[33] although none of these conditions were associated with hyperbaric oxygen treatment. The results of a recent meta-analysis by Brouwer et al.,[18] which examined the impact of hyperbaric oxygen treatment on mortality, are congruent with those of the present investigation.

After hyperbaric oxygen treatment, cellular and biochemical changes in the tissues of diabetic wounds support wound healing,[47] which further leads to an increase in growth factors and fibronectin[48] to hasten cellular proliferation, migration and the production of extracellular matrix molecules. Additionally, a variation in the methodology used to measure ulcer size and the length of the evaluation could be a factor in the results being non-significant.[25,30,35] To use the usefulness of hyperbaric oxygen treatment in reducing ulcer size in patients with diabetic foot ulcers, more studies or robust randomised controlled trials with a high sample size are needed.

The following were the limitations of the meta-analysis: Because some of the studies that were selected for the meta-analysis were excluded, there may have been an assortment bias. However, the deleted study did not satisfy the criteria for inclusion in the meta-analysis. Additionally, we needed the data to determine whether variables like age, gender and ethnicity had an impact on the results. The purpose of the meta-analysis was to study the typical treatment for people with diabetic foot ulcers using hyperbaric oxygen treatment. It's possible that bias was worsened by using erroneous or incomplete data from an earlier investigation. The core causes of discrimination were likely the person's nutritional status, along with their ethnicity, gender and age. Values could unintentionally change as a result of inadequate data and some unpublished studies.

5 | CONCLUSIONS

The examined data showed that hyperbaric oxygen treatment revealed significantly higher healed ulcers, higher adverse events, lower mortality and higher ulcer area

reduction compared to standard treatment in patients with diabetic foot ulcers. However, hyperbaric oxygen treatment and standard treatment had no significant difference in amputation and healing time in patients with diabetic foot ulcers. Yet, attention should be paid to its values since most of the selected examinations had a low sample size (11 out of 17 examinations were ≥100) and some of the comparisons had a low number of selected studies.

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CONFLICT OF INTEREST STATEMENT

Nothing to declare.

DATA AVAILABILITY STATEMENT

On request, the corresponding author is required to provide access to the meta-analysis database.

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