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SYSTEMATIC REVIEW OR META-ANALYSIS

Topical oxygen therapy for diabetes-related foot ulcers: A systematic review and meta-analysis

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Abstract

Introduction: Topical oxygen therapy (TOT) has been suggested as a treatment for diabetes-related foot ulcer (DFU) but no prior meta-analyses of randomised clinical trials (RCT) have been reported. This systematic review and meta-analysis examined the randomised evidence for the benefit of TOT in healing DFU.

Methods: Publicly available databases were searched for RCTs investigating the effect of TOT on wound healing in participants with a DFU. The primary outcome was ulcer healing defined as full epithelialisation. Meta-analyses were performed using random effect models and reported as risk ratios (RR) and 95% confidence intervals (CI). Study quality and publication bias were assessed using a modified version of the Cochrane Collaboration's tool and funnel plots, respectively.

Results: Six RCTs involving 530 participants with a DFU testing TOT were included. Meta-analysis suggested that TOT significantly increased the likelihood of ulcer healing compared to controls (Risk ratio [RR] 1.94; 95% CI 1.19, 3.17; $I^2 = 57\%$; NNT = 5.33) and findings were robust in sensitivity analyses. Risk of bias was high, moderate and low in two, one and three studies, respectively. Analysis of the three trials judged to be at low risk of bias suggested that TOT increased the likelihood of ulcer healing compared to controls (RR 2.37; 95% CI 1.52, 3.68; $I^2 = 0\%$). Funnel plots suggested the possibility of publication bias. Data on amputation were too limited for meta-analysis.

Conclusion: This meta-analysis suggests that TOT improves the likelihood of DFU healing; however, its effect on amputation and cost-effectiveness are unclear.

KEYWORDS
diabetic foot ulcer, peripheral artery disease, topical oxygen therapy, wound healings

1 | INTRODUCTION

Diabetes-related foot ulceration (DFU) is one of the top 10 causes of global disability.[1] About 6.3% of the global population (approximately 440 million people) are estimated to be affected by DFU.[2] In the United States, it has been estimated that managing DFU costs between US$28 and 97 billion per year.[3] The 5-year mortality of patients with a DFU has been reported to be 31% which is comparable with a group or patients with a range of different cancers.[4] DFUs re-occur in more than 50% within 3 years and many remain unhealed with conventional therapies for extended periods.[5,6] Topical oxygen therapy has been proposed as a treatment for DFU by improving tissue oxygenation and collagen synthesis, promoting angiogenesis, enhancing the function of fibroblast and leukocytes, and inhibiting microbial growth.[7,8] These proposed beneficial effects of topical oxygen therapy would be expected to improve wound healing. The clinical efficacy of this treatment in healing DFUs is however controversial.[9] A position statement from the Undersea and Hyperbaric

Medical Society (UHMS) stated that topical oxygen therapy is emerging as a potential treatment for chronic wounds, but that the therapeutic efficacy is not adequately supported by scientific evidence for guideline recommendation.[10,11] Since then, a number of randomised controlled trials have, however, reported beneficial effects of topical oxygen therapy.[12-17]

A number of prior systematic reviews have examined the evidence on topical oxygen therapy in treating DFU. These have included both randomised and non-randomised trials and not performed meta-analyses.[18,19] This has made it difficult to draw firm conclusions on the evidence for this treatment. Furthermore, recently two further randomised trials had been reported that were not included in the previous systematic reviews.[14,16] The aim of this systematic review was to perform an up to date assessment of the evidence for topical oxygen therapy in treating DFU through a pooled analysis of findings from randomised control trials.

2 | METHODS

2.1 | *Search strategy*

This systematic review was performed according to the 2015 Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) statement.[20] The study protocol was registered with PROSPERO (CRD42021214994). The literature search was conducted by two authors (ST and TS) to identify randomised controlled trials that evaluated the effect of topical oxygen therapy in people with a DFU. The PubMed and Cochrane databases were searched to include all relevant publications until the 14th October 2020. The search strategy used terms similar or synonymous to 'Topical oxygen therapy' and 'DFU' as given in the supplementary material. References from the included studies were also searched for potential studies to be included. No language restrictions were applied.

2.2 | *Inclusion and exclusion criteria*

Inclusion required the studies to be randomised controlled trials that tested the efficacy of topical oxygen therapy as a treatment for DFU and compared against placebo or no active/sham treatment. Non-randomised or cohort studies, reviews and case reports were excluded. Included studies were identified by two authors (ST and TS) and reviewed by a third author (JG) to confirm the eligibility for inclusion. Discrepancies were resolved through discussion.

2.3 | *Data extraction*

The full texts of included studies were independently assessed by two investigators (ST and TS) to extract study design, number of people who were screened, randomised and completed follow-up, intervention method and duration, primary outcome, and qualitative and quantitative methods of assessing the DFU. Age, sex, current smoking, ankle–brachial index (ABI), toe pressure, transcutaneous oxygen pressure, HbA_{1c} levels, duration of wound, prior history of revascularisation procedures, lower extremity amputation, hypertension, cardiovascular disease, metformin prescription and safety data were also extracted. Extracted data were discussed in a meeting with another researcher (JG) and finally agreed through consensus.

2.4 | *Quality assessment*

Two authors (ST and TS) independently assessed the risk of bias of all included studies. A modified version of the Cochrane Collaboration's tool was used which assessed reporting of concealment of random allocation of participants, random sequence generation method, sample size calculations, reporting of statistical analysis methods, percentage of participants lost to follow-up and intent-to-treat analysis.[21] The modifications included the addition of assessments of how DFU was defined and wound size measured. Any discrepancies were resolved through discussion between the authors. Assessment scores with <50%, 50%–75% and >75% were considered to have high, moderate and low risk of bias, respectively.

2.5 | *Outcomes and data analysis*

The primary outcome was complete ulcer healing, defined as complete epithelialisation, following topical oxygen therapy compared to control or sham treatment at the end of the follow-up period. The secondary outcome was any amputation including toe, trans-metatarsal and below, through or above knee amputations. To consistently take account of missing data due to loss to follow-up, two types of outcome analyses were planned as previously described.[22] In the main analysis, patients who were lost during follow-up were considered to have achieved full ulcer healing (best-case scenario). In a sensitivity analysis, all participants lost to follow-up were considered to have not achieved full ulcer healing (worst-case scenario). A minimum of three studies

were required to be eligible for meta-analysis of the primary or secondary outcomes. Due to anticipated statistical heterogeneity, random-effects models using Mantel–Haenszel's method were used. Data were expressed as risk ratio (RR) with 95% confidence intervals (CI). Leave-one-out sensitivity analyses, by removing studies individually, were performed for the main analysis to assess the contribution of any single study towards the overall outcomes. A separate sensitivity analyses of studies deemed to be at low risk of bias were also planned if enough eligible studies were identified. The I^2 index was used to assess the degree of statistical heterogeneity between studies, with $I^2 \geq 75\%$ accepted to denote high heterogeneity. Funnel plots of the effect size versus the standard error of mean (SEM) of the log-transformed effect were plotted as scatterplot to assess potential publication bias. In addition, the rank correlation test was used to estimate the effects of smaller studies. Number needed to treat (NNT) was calculated using the formula [1/(Experimental event rate)-(Control event rate)] to report the number of patients needed to be treated with the intervention to achieve one additional positive outcome. All analyses were conducted using the 'meta' and 'metafor' packages of R software version 3.4.4. A p value of <0.05 was considered as statistically significant.

3 | RESULTS

3.1 | *Study selection*

The literature search identified 719 studies, of which 665 unique records were assessed. In all, 96 studies that investigated any form of oxygen therapy were selected for full-text assessment (* MERGEFORMAT Figure 1). Finally, six trials were deemed eligible based on the inclusion criteria.[12-17]

3.2 | *Study characteristics*

The characteristics of the included studies are summarised in Table S1. Among the six RCTs, four were conducted in the United States,[12,13,15,16] one in Canada[17] and one was a multi-centre trial that were conducted in the United States, Germany, the United Kingdom and France.[14] Eligibility for inclusion typically required a diagnosis of type 1 or 2 diabetes mellitus and a non-healing, full thickness wound that could be categorised as class 1A or above of the University of Texas classification of DFUs and a duration of at least 4 weeks and <52 weeks or wound sizes ranging from 1.5 cm^2 to 10 cm^2 (see Table S1). Studies provided a variable duration

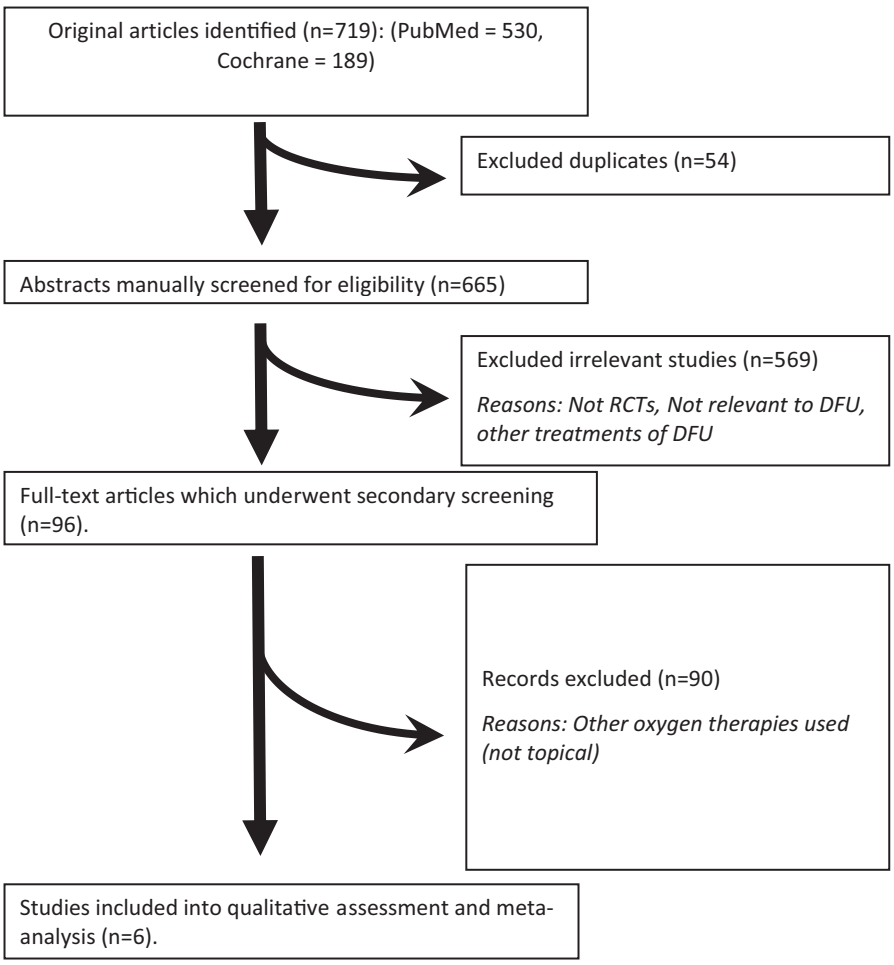

FIGURE 1 Preferred Reporting Items of Systematic Review and Meta-analyses (PRISMA) flow diagram. A total of 719 studies were screened and 6 trials were included. DFU – Diabetes-related foot ulcer; RCT – Randomized controlled trials

of usual standard of care of 1,[12,13] 2[15,16] or 4 weeks[14] before considering the DFU non-healing as part of the eligibility criteria. In one trial, potential participants were excluded if the DFU was considered only neuropathic in aetiology with no contribution of ischaemia unless the ulcer had failed to heal with 12 weeks of optimum management.[17] Patients were followed up while the topical oxygen therapy was delivered in all included studies for between 4 and 12 weeks. In one study, patients were also followed for 12 months after the topical oxygen therapy concluded.[14]

3.3 | Interventions tested and controls

Topical oxygen therapy was delivered using a variety of different Food and Drug Administration approved devices

TABLE 1 Baseline patient characteristics in the included studies

Study ID	Groups	Male gender, %	Age, mean±S.D	BMI, kg/m2	Current smoking, %	HbA_{1c}, mean±S.D	Duration of diabetes, months	Duration of ulcer, mean±S.D	Prior revascularisation procedures, %
Driver 2013	TOT	70.6	58.6±7.1	NA	NA	NA	NA	20 months	NA
	Control		59.9±12.6	NA	NA	NA	NA	14 months	NA
Driver 2017	TOT	68.2	59.2±13.1	NA	NA	8.0±1.7	NA	NR	NA
	Control	76.6	58.5±9.5	NA	NA	7.9±1.7	NA	NR	NA
Yu 2016	TOT	85	57.0±9.5	NR*	NR*	8.6±2.3	NR	47.4±23.4 wks	NR
	Control		58.0±9.5	NR*	NR*	7.3±0.5	NR	46.2±17.9 wks	NR
Niederauer 2017	TOT	78	57.5±10.9	NR	NR	8.1±1.7	NR	NR	NR
	Control	80	59.1±13.3	NR	NR	8.3±1.9	NR	NR	NR
Niederauer 2018	TOT	79.7	56.1±10.1	NR	NR	8.4 ± 1.6	NR	131.6±89.2 days	NR
	Control	75	56.6±14.4	NR	NR	8.3 ± 2.0	NR	143.8±97.7 days	NR
Frykberg 2019	TOT	89	64.6±10.3	30.8±5.9	36	8.4±1.7	NR	160.3±96.0 days	NR
	Control	84	61.9±9.5	31.2±7.6	27	8.1±1.5	NR	174.6±94.0 days	NR

Abbreviations: %, Percentage; *, Measured but not reported; BMI, Body mass index; CVD, Cardiovascular disease; HTN, Hypertension; mmHg: Millimetres of mercury; NR, Not reported; NRC, Not reported correctly; sABI, Ankle Brachial Index; SD, Standard deviation; TcPo2, Transcutaneous oxygen pressure; TOT, Topical oxygen therapy.

To convert percentage HbA_{1c} values to mmol HbA_{1c} per mol Hb, use the following equation $10.93 \times \%\ HbA_{1c} - 23.5$ mmol/mol.

TABLE 2 Quality assessment of all included studies

Author	Patient subset definition	Mentioned the number of patients who completed the study	Random sequence generation	Allocation of random sequence concealed	Sample size estimate not reached
Driver 2013	1	1	0.5	0.5	0
Driver 2017	1	1	0.5	1	0
Yu 2016	1	1	0.5	1	0
Niederauer 2017	1	1	0.5	0.5	1
Niederauer 2018	1	1	0.5	0.5	0
Frykberg 2019	1	1	1	1	1

Abbreviations: %, Percentage; 0.5 = Unclear; 0 = No; 1 = Yes; ITT, Intent to treat.

which supplied ≥98% transdermal continuous oxygen at flow rate of 3–15 ml/hr, including the TransCu O2® System,[15,16] Natrox Oxygen Delivery System (ODS)[17] and continuous tissue oxygen insufflation with Epiflo® oxygen generators provided by Neogenix, LLC.[1312] One study tested variable oxygen flow using the cyclical Topical Wound Oxygen therapy device.[14] Most studies delivered oxygen at atmospheric pressure using a single-use system, but in one study, oxygen was delivered intermittently using a multi-use system at variable pressure and flow rate[14] (Table S2). Three studies provided standard of care without any sham device for control participants[12,13,17] and three studies used sham devices along with standard of care in control participants.[14-16] This affected investigator, participant and assessor blinding that was reflected in the quality assessment of these studies.

History of lower extremity amputation, %	HTN, %	CVD, %	Metformin prescription	ABI, mean±S.D	Toe pressure, mmHg	$TcPo_2$, mmHg	Neuropathy	Follow-up period (weeks)	Ulcer site (%)
NA	NA	NA	NA	NA	NR	NR	NR	4	NR
NA	NA	NA	NA	NA	NR	NR	NR		NR
NA	NA	NA	NA	NA	NR	NR	NR	12	At or below the malleoli (100)
NA	NA	NA	NA	NA	NR	NR	NR		At or below the malleoli (100)
NR	20	20	NR	1.1±0.2	NR	NR	NR	8	NR
NR	20	0	NR	1.0±0.2	NR	NR	NR		NR
NR	NR	NR	NR	NRC	NR	NR	NR	12	NR
NR	NR	NR	NR	NRC	NR	NR	NR		NR
NR	NR	NR	NR	1.0±0.1	NR	NR	NR	12	Weight bearing (79.7)
NR	NR	NR	NR	1.0±0.2	NR	NR	NR		Weight bearing (73.6)
47.2	78	36	NR	1.1±0.2	84.5±30.5	NR	78%	52	Dorsal foot (22.2), Leg below malleoli (2.8), Pedal foot (50), Toe (25)
21.6	81	24	NR	1.0±0.2	83.0±32.7	NR	78%		Dorsal foot (13.5), Leg below malleoli (10.8), Pedal foot (59.5), Toe (16.2)

Blinding of participants	Blinding of assessors	Blinding of outcome assessment	HbA_{1c} values reported	Baseline wound size reported	Verified wound measurement method	ITT	Total	Quality (%)
0	0	0	0	1	1	0	5	41.7
0	0	1	1	1	1	1	8.5	70.8
0	0	0	1	1	0	0	5.5	45.8
1	1	1	1	1	1	0	10	83.3
1	1	1	1	1	1	1	10	83.3
1	1	1	1	1	1	1	12	100

3.4 | *Patient characteristics*

The baseline participant characteristics are shown in * MERGEFORMAT Table 1. The wound duration, HbA_{1c} levels, ABI, smoking status, prior history of amputation and revascularisation procedures, toe pressure, transcutaneous pressure, neuropathy and ulcer site are illustrated in * MERGEFORMAT Table 1. Reporting of ulcer aetiology was limited in the included studies and those that reported ABI or toe pressure suggested that majority of the included participants had non-ischaemic ulcers. Only one study reported body mass index, prior history of lower extremity amputations and toe pressure.[14] Four studies reported the duration of ulcers in the included participants.[13,14,16,17] Only one study reported smoking history and prevalence of neuropathy[14] and none of the trials reported prior history of revascularisation procedures, transcutaneous oxygen pressures, duration of diabetes and prescription of metformin and cost-effectiveness of topical oxygen therapy compared to other contemporary treatments.

3.5 | *Risk of bias of included studies*

Three studies were assessed as at low risk of bias,[14-16] one study was assessed at moderate risk of bias[12] and two assessed as at high risk of bias[13,17] (* MERGEFORMAT Table 2). All studies reported the population included, the number of participants who completed the study and the baseline wound size.[12-17] Five studies reported the HbA_{1c} levels of the participants.[12,14-17] Two trials determined the wound size by measuring the length, width and depth with a ruler.[12,13] One trial measured wound size using automated CE-marked wound measurement software,[14] one trial measured maximum perpendicular length and width of the wound[17] and two trials measured wound size using planimetric analysis.[15,16] Three trials blinded both the participants and assessors.[14-16] Three trials used intent-to-treat analyses.[12,14,16] Two trials recruited the required population size based on a sample size estimate.[14,15] Only one trial clearly reported the random sequence generation.[14]

3.6 | *Effect of topical oxygen therapy on complete ulcer healing*

Overall, five [13-17] of the six trials reported that topical oxygen therapy significantly increased the proportion of participants that achieved ulcer healing by comparison to controls. The main meta-analysis of all six trials, including 267 participants undergoing topical oxygen therapy and 263 controls, suggested that topical oxygen therapy resulted in greater likelihood of ulcer healing compared to controls (RR 1.94; 95% CI 1.19, 3.17). The included trials had moderate statistical heterogeneity (I^2 = 57%; * MERGEFORMAT Figure 2). The worst-case scenario sensitivity analysis suggested, similar to the main analysis, that topical oxygen therapy resulted in greater likelihood of ulcer healing compared to controls but with a lower RR (RR 1.57; 95% CI 1.07, 2.30) (Figure S1). The funnel plots were asymmetrical suggesting a risk of publication bias (* MERGEFORMAT Figure 3). The correlation rank test suggested the possibility of small study effects ($p = 0.05$). Leave-one-out sensitivity analyses showed that removal of any single study did not affect the significance of the findings (* MERGEFORMAT Table 3). Meta-analysis of three studies that were assessed as low risk of bias with 183 intervention participants and 182 controls suggested that topical oxygen therapy resulted in greater likelihood of ulcer healing compared to controls (RR 2.37; 95% CI 1.52, 3.68) (Figure S2). Meta-regression suggested no significant relationship between the benefit achieved with topical oxygen therapy and the length of follow-up in the included studies ($R^2 = 26.6\%$, $p = 0.16$, * MERGEFORMAT Figure 4). The number needed to treat to achieve one additional positive outcome was 5.33.

3.7 | *Effect of topical oxygen therapy on amputation*

Only two studies reported the requirement for amputation.[12,14] One trial reported no amputations in the intervention group as compared to one amputation in the control participants

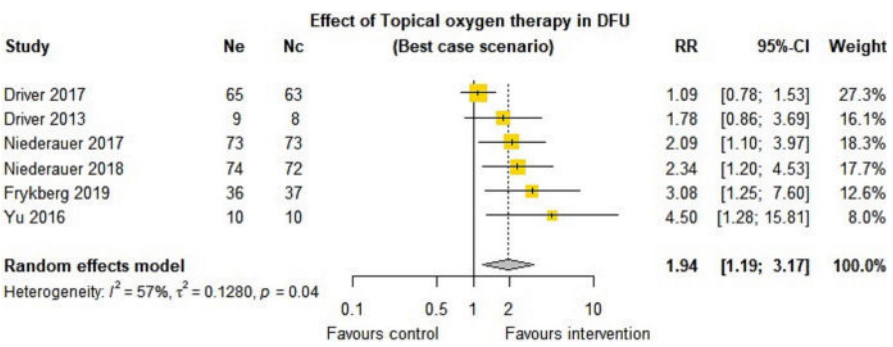

FIGURE 2 Forest plot suggesting a significant benefit of topical oxygen therapy in healing of diabetes-related foot ulcers. RR: Risk ratio; CI: Confidence interval; Ne: Number of experimental events; Nc: Number of control events

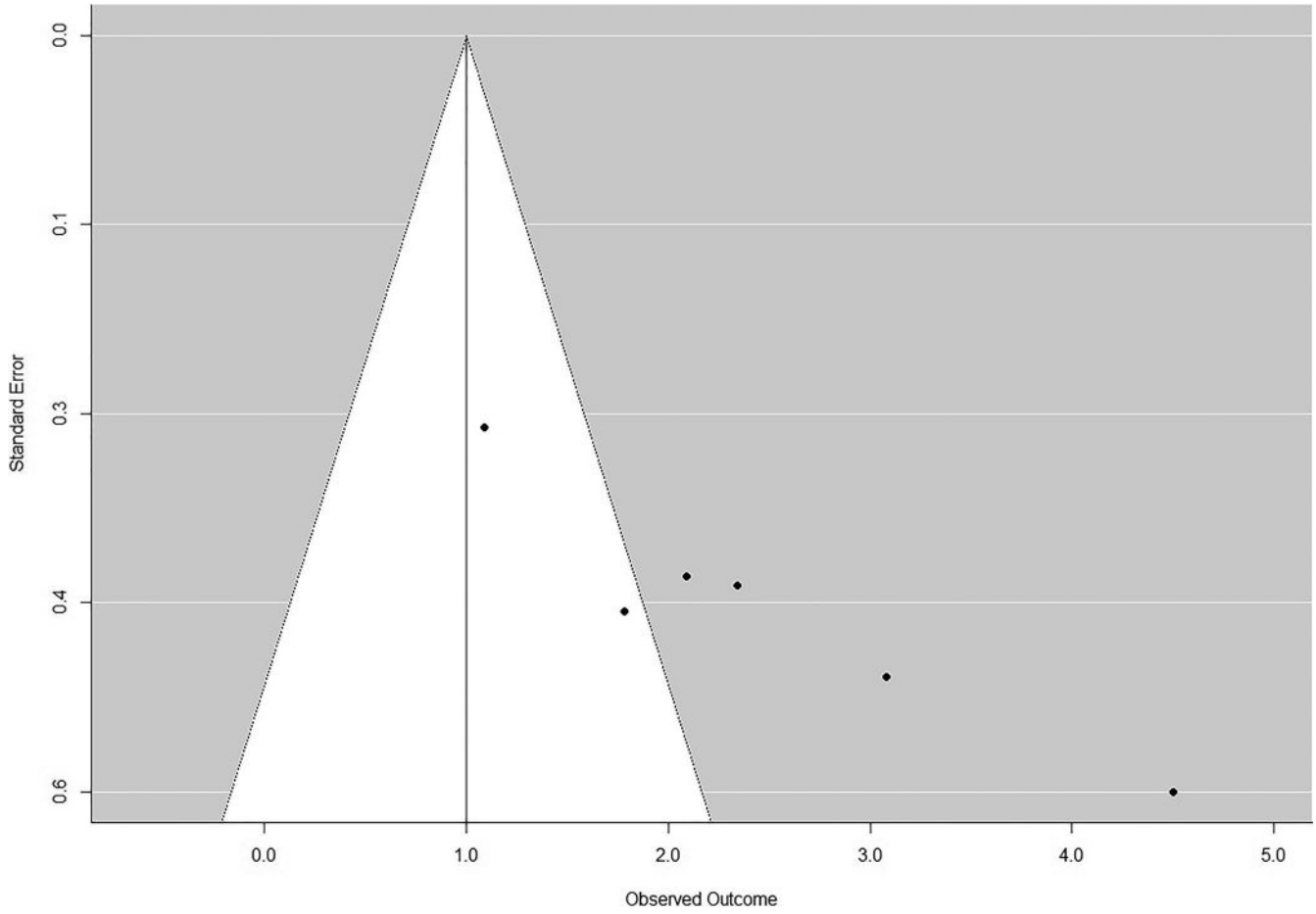

FIGURE 3 Funnel plot using Egger's test suggesting a potential publication bias due to asymmetry in the observed outcomes

TABLE 3 Leave-one-out sensitivity analysis of the main analysis (best-case scenario approach)

Author	*Effect size*	*Lower CI*	*Upper CI*	I^2
Driver 2013	2.02	1.06	3.83	0.65
Driver 2017	2.35	1.64	3.38	0.0
Yu 2016	1.77	1.07	2.94	0.55
Niederauer 2017	1.96	1.02	3.77	0.62
Niederauer 2018	1.91	1.01	3.62	0.60
Frykberg 2019	1.83	1.03	3.25	0.57

Abbreviations: CI, Confidence interval; I^2, Heterogeneity index.

during 12-week follow-up.[12] Another trial reported two amputations in the intervention group compared to three amputations in the control participants. In this study, although the intervention was undertaken for 12 weeks, the patients were followed up for up to 12 months.[14] Meta-analysis was not eligible due the absence of sufficient studies reporting this outcome.

3.8 | *Serious adverse events with topical oxygen therapy*

Three studies reported safety data and noted a similar number of serious adverse events in both intervention and control participants.[12,14,16] Two studies reported mortality rates.[14,16] One trial reported no deaths in the intervention group as compared to two deaths in control participants after 12 weeks.[16] Another trial reported two deaths each in intervention and control groups after 12-month follow-up.[14] Although none of the included studies perform economic analyses, three studies stated that it would be cost-effective compared to hyperbaric oxygen therapy.[15-17]

4 | DISCUSSION

This systematic review and meta-analysis suggested that topical oxygen therapy improved the healing of DFUs, as evidenced by an approximate twofold increased likelihood of ulcer healing. Sensitivity analyses suggested that the findings

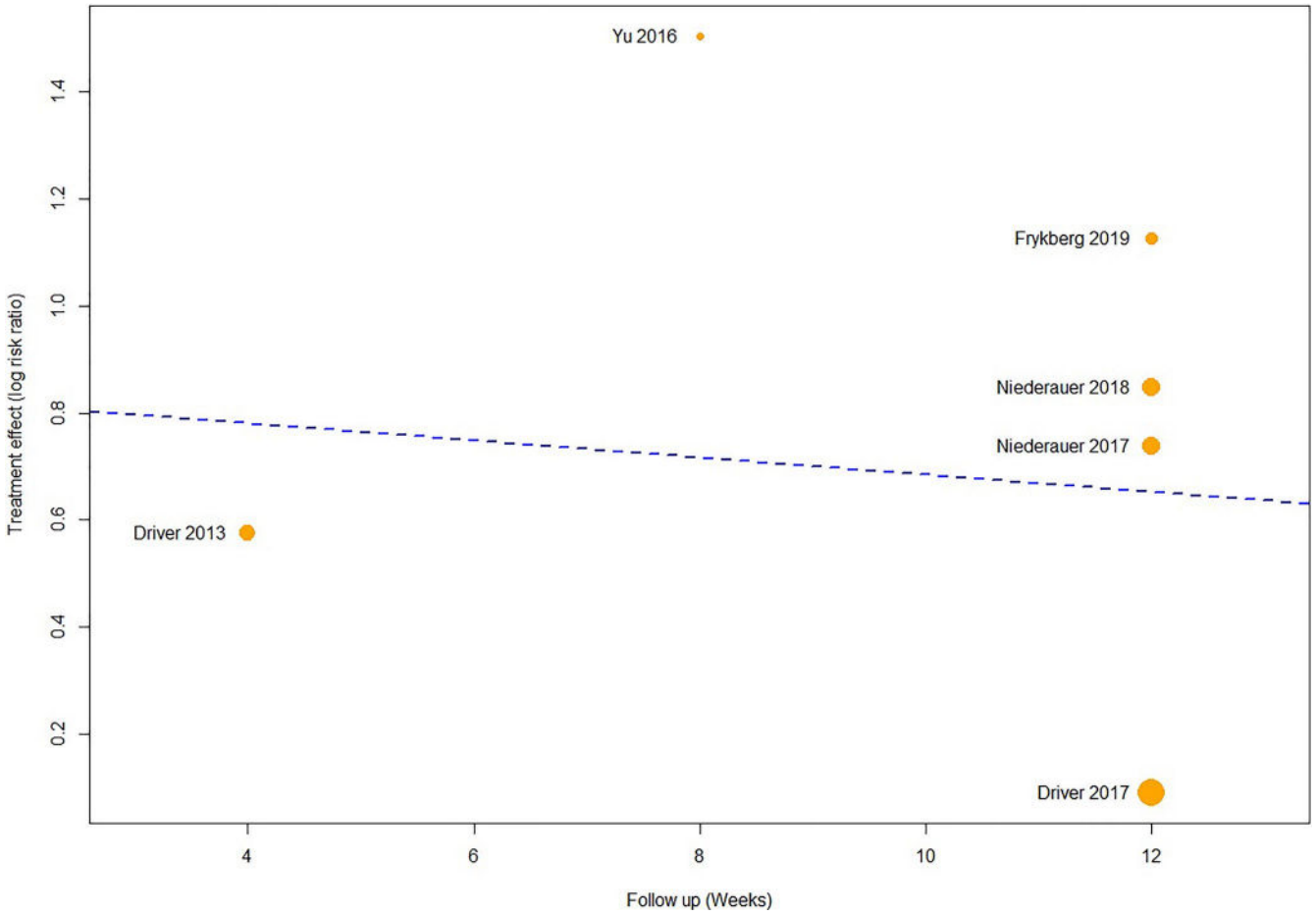

FIGURE 4 Meta-regression suggesting no significant effect of varying follow-up period on treatment outcomes (R2 = 26.6%, $p = 0.16$)

were robust. Analysis of secondary outcomes of amputations was not possible due to limited number of studies; however, two studies that reported amputations showed no significant differences.[12,14] Serious adverse events were reported to be similar between intervention and control groups. The included DFUs appeared to be non-healing neuropathic ulcers based on the ABI reported in the studies. Overall, the findings of this meta-analysis suggest that topical oxygen therapy could be considered for the treatment of non-healing neuropathic DFUs, although due to the heterogeneity between studies and small sample sizes of included trials the findings should be interpreted cautiously.

The cost of treating a DFU has been reported to be between £3,339 [23] and £20,351 per patient depending on the interventions used and ulcer chronicity.[24] A simulation model using inputs from peer-reviewed journal publications and publicly available documents reported that 5-year cost per person treated with continuous delivery of topical oxygen was £2,770 less than negative pressure wound therapy.[25] Furthermore, topical oxygen therapy can be provided at the patient's home, rather than a hospital setting, unlike hyperbaric oxygen therapy. Hyperbaric oxygen therapy, an established treatment for non-healing DFU in some countries, is normally delivered for 1 to 2 months three to four times per week at a central facility. The cost of a course of hyperbaric oxygen therapy has been estimated as £3000 per patient.[26] In contrast, the included trials showed that the topical oxygen therapy enables the patients to be home based for most of the treatment period by providing equipment that can deliver continuous oxygen therapy for a few weeks before being replaced (Table S2). Therefore, topical oxygen therapy has the potential to provide an easy-to-use and more cost-effective means of delivery oxygen to treat DFUs.

Hyperbaric oxygen therapy has been reported to have some complications such as those related to barotrauma, such as pneumothorax and ear drum rupture. Safety data were only available from three of the trials included in this systematic review which reported no excess of serious adverse events[12,14,16] (Table S3). None of the trials reported cost-effectiveness analyses and this information will likely have an important impact on implementation of this treatment. Future trials are needed to provide cost-effectiveness and further safety analyses.

This meta-analysis and the included trials had a number of limitations and potential biases that should be acknowledged. First, all the included trials were relatively small making it difficult to draw any reliable conclusions. Reporting of participant risk factors, prior treatment and adverse events was generally limited making it difficult to draw conclusions on the generalisability of findings.[14] None of the studies reported economic analyses which has important implications for implementation. Furthermore, there was significant clinical heterogeneity due to differences in duration of treatment and follow-up, and poor reporting of the presence of peripheral ischaemia. Funnel plots suggested the possibility of publication bias. There was heterogeneity in the characteristics of the included patients and design of the studies. This should be taken into account in applying the results of this systematic review. Furthermore, ischaemic DFUs do not appear to have been included and requirement for amputation was poorly reported. Finally, both Driver et al[12,13] and Niederauer and colleagues[15,16] reported two studies included in this meta-analysis. We were unable to clarify whether there was an overlap in the participants reported in these trials. The leave-one-out sensitivity analysis suggested that the findings that topic oxygen therapy significantly increased the likelihood of ulcer healing remained following removal of individual trials. In view of the small number of trials, however, further assessment of the effectiveness of topical oxygen therapy in larger populations of patients is advisable before widespread use.

In conclusion, this systematic review suggested that topical oxygen therapy improved the likelihood of DFU healing; however; its effect on requirement for amputation is unclear. Further clinical trials adequately powered to test the effect of this treatment on amputation, its value in treating ischaemic ulcers and its cost-effectiveness are needed. A large clinical trial including heterogeneous DFUs would also help provide confidence that the findings are repeatable and can be widely applied.

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None.

CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

Dr. Shivshankar Thanigaimani was involved in the study conceptualisation, keyword search, full-text screening, data extraction, data analysis and manuscript preparation and editing. Dr. Tejas Singh was involved in data extraction, validation and manuscript preparation and editing. Prof. Jonathan Golledge was involved in the study conceptualisation, data validation, supervision, manuscript preparation and editing, critical assessment of the manuscript and funding acquisition.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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