

ORIGINAL ARTICLE

Efficacy and safety of topical oxygen therapy for diabetic foot ulcers: An updated systematic review and meta-analysis

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Funding information

Popularization and application project of Sichuan Provincial Health Commission, Grant/Award Number: 20PJ023; West China Nursing Discipline Development Special Fund project of Sichuan University, Grant/Award Number: HXHL19005

Abstract

To evaluate the efficacy and safety of topical oxygen therapy (TOT) in diabetic foot ulcers (DFUs), researchers systematically retrieved relevant studies from PubMed, EMBASE, Web of Science, CENTRAL and [ClinicalTrials.gov](https://www.clinicaltrials.gov). Relevant studies were searched from database inception to January 2022. Two researchers independently screened the literature, extracted data and assessed the quality of the included studies. Statistical analysis was performed in Stata 16.0. A total of seven RCTs involving 614 participants were included. Compared with the control group, the TOT group had a higher healing rate (RR = 1.63, 95% CI [1.33, 2.00]). According to descriptive analysis, TOT reduced the ulcer area and improved healing durability and quality of life. Furthermore, it had no effect on the occurrence of adverse events. However, it was unclear whether it would be able to reduce the healing time. The existing evidence suggests that TOT is effective and safe for chronic DFUs. Further studies are warranted to validate our findings.

KEYWORDS

diabetic foot ulcer, meta-analysis, systematic review, topical oxygen therapy

Key Messages

- oxygen is a crucial element in the wound healing process, and topical oxygen therapy (TOT) can ameliorate oxygen deficiency
- to evaluate the efficacy and safety of TOT in diabetic foot ulcers, researchers systematically retrieved four databases and [ClinicalTrials.gov](https://www.clinicaltrials.gov)
- the existing evidence suggests that TOT is effective and safe in DFUs. Further studies are warranted to validate our findings

1 | INTRODUCTION

Diabetic foot ulcers (DFUs) are the most frequently recognised and notorious diabetic complication.¹ Between 19% and 34% of diabetic patients are likely to be affected by a DFU in their lifetime.¹ DFUs are a major cause of amputation in diabetic patients, and 85% of amputations are related to DFUs.² They have the potential to not only

diminish patients' quality of life³ but also their life expectancy. DFU patients have a 2.5-fold higher risk of death at 5 years than diabetes patients without foot ulcers.⁴ Frequent medical visits and hospital admissions result from a high recurrence rate.

Oxygen is a crucial element in the wound healing process.⁵ It has been shown that wounds and tissue injuries cause the injured area to become hypoxic, presumably due

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to the disruption of the vasculature and increased oxygen consumption.⁶ Acute hypoxia initiates wound healing, whereas chronic hypoxia impairs neovascularisation.⁷ Increasing amounts of evidence have suggested that increased hypoxic conditions and impaired cellular responses to hypoxia are essential pathogenic factors of delayed wound healing in DFU.⁸ To increase oxygenation, the rationale for applying exogenous oxygen to a wound can trigger healing responses that have been hindered by hypoxia.⁹ At present, different technologies for supplying oxygen to wounds have been developed. Topical oxygen therapy (TOT) can ameliorate oxygen deficiency by directly delivering oxygen to the wound bed without relying on an (impaired) vascular system or respiratory system.^{5,10,11} Studies have shown that TOT is beneficial for numerous cellular mechanisms required for wound healing (eg, antibacterial mechanisms, collagen production and epithelial migration).¹²

To date, a number of systematic reviews also found that TOT could promote DFU healing.¹³⁻¹⁵ Among them, two reviews included non-randomised trials, and another review only searched two databases. Furthermore, recently three further RCTs were published that were not included in the previous systematic reviews.¹⁶⁻¹⁸ Therefore, this study aimed to perform an updated meta-analysis and impact clinical decision-making.

2 | MATERIALS AND METHODS

The study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.¹⁹ The corresponding protocol was registered in PROSPERO (CRD42020152750).

2.1 | Data sources and searches

To identify relevant RCTs, two researchers systematically retrieved studies from PubMed, CENTRAL, EMBASE (via OVID), Web of Science (core) and ClinicalTrials.gov. After reading some relevant literatures, medical subject heading (MeSH) terms, entry terms and keywords were used to build filters. Taking PubMed as an example, the retrieval strategy is as follows: (((("Diabetic Foot"[Mesh]) OR "Foot Ulcer"[Mesh])) OR ((diabet*[Title/Abstract]) AND (((((((ulcer*[Title/Abstract]) OR foot[Title/Abstract]) OR feet[Title/Abstract]) OR wound*[Title/Abstract]) OR amputat*[Title/Abstract]) OR defect*[Title/Abstract]) OR gangrene[Title/Abstract]))) AND (((((((((((topical[Title/Abstract]) OR local*[Title/Abstract]) OR partial[Title/Abstract]) OR regional[Title/Abstract]) OR percutaneous [Title/Abstract]) OR transcutaneous[Title/Abstract]) OR

transdermal[Title/Abstract]) OR skin[Title/Abstract]) OR ulcer*[Title/Abstract]) OR wound*[Title/Abstract]) OR continuous diffusion[Title/Abstract]))) AND (((((oxygen therap*[Title/Abstract]) OR oxygen treatment[Title/Abstract]) OR oxygen supply[Title/Abstract]) OR oxygen delivery[Title/Abstract]) OR oxygen[Title])). Retrieval strategies were adjusted according to different databases. The references of the included studies were manually searched. The retrieval period was from database inception to January 2022.

2.2 | Study selection

Inclusion criteria: (a) Participant: patients with DFUs and corresponding podiatric grading; (b) intervention: TOT alone or combined with standard of care (SOC); (c) control: SOC; (d) outcome: number of complete ulcer healing, ulcer area, healing time, adverse event, follow-up and quality of life (QOL); (e) study design: clinical RCT. Exclusion criteria: (a) lack of key data; (b) abstract; (c) as for interim reports or bilingual publications, the most comprehensive was retained; (d) clinical trial protocol.

2.3 | Data extraction

Two researchers independently accomplished the same tasks. First, duplicated literature was removed. After reading the titles and abstracts, studies that obviously did not meet the aforementioned criteria were removed. Then, the researchers identified relevant studies by perusing the full text. Finally, two researchers checked each other's work. Discrepancies were resolved through discussion.

Two researchers independently extracted data from the included studies, and the principle of intention-to-treat (ITT) analysis was followed. The following data were collected: characteristics of the included study (first author, publication year, sample size, details of TOT, therapeutic regimens of the control group, curative time), baseline characteristics (country, sex, age, HbA1c, podiatric grade, duration of DFU, ulcer area, ankle-brachial index) and outcomes (as shown in inclusion criteria).

2.4 | Assessment of risk of bias

Applying the Cochrane risk of bias assessment tool, the quality of each included study was evaluated based on the following items: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome

data, selective reporting and other biases.²⁰ Two researchers independently assessed each item and checked each other's work. If there were any disagreements, the researchers discussed and resolved them.

2.5 | Statistical analysis

Extracted data were imported into Stata 16.0 (Stata Corp, College Station, TX, USA) for meta-analysis, and heterogeneity tests were performed by Q -tests and the I^2 index. If the heterogeneity test results were $P \geq .1$ and $I^2 \leq 50\%$, a fixed-effects model was used; otherwise, a random-effects model was used. In the absence of key data, descriptive analysis was performed. Relative risk (RR) and 95% confidence interval (CI) were used for dichotomous data. Mean difference and 95% CI were presented for continuous data, but the measurement units were inconsistent, so standardised mean difference and 95% CI were used. Sensitivity analysis was performed by excluding individual studies one at a time and recalculating pooled estimates. Harbord's modified linear regression test and funnel plot were used to analyse potential publication bias.²¹ All analyses were conducted with Stata 16.0, and a P -value less than .05 was considered significant.

3 | RESULTS

3.1 | Study selection

A total of 2681 potential studies were obtained. First, 983 duplicate studies were removed. After reading the titles and abstracts, 1654 studies that did not meet the inclusion criteria were also removed. Eligible studies were retained after perusing the full-text of the remaining 44 studies. Finally, seven studies^{16-18,22-25} were qualitatively analysed and quantitatively analysed, as shown in Figure 1.

3.2 | Study characteristics

A total of seven studies^{16-18,22-25} were included, including 614 DFU patients. Among them, four studies^{17,22-24} were conducted in America, and the other three studies^{16,18,25} came from China, India and Canada. The sample sizes ranged from 20 to 146. The publication years ranged from 2016 to 2021. There were 451 males and 153 females in the included studies, with a sex ratio of 2.95:1. Five studies^{16,17,22,24,25} reported continuous diffusion of oxygen therapy and the remaining studies used intermittent TOT. Four studies²²⁻²⁵ adopted the Texas grade, from I A

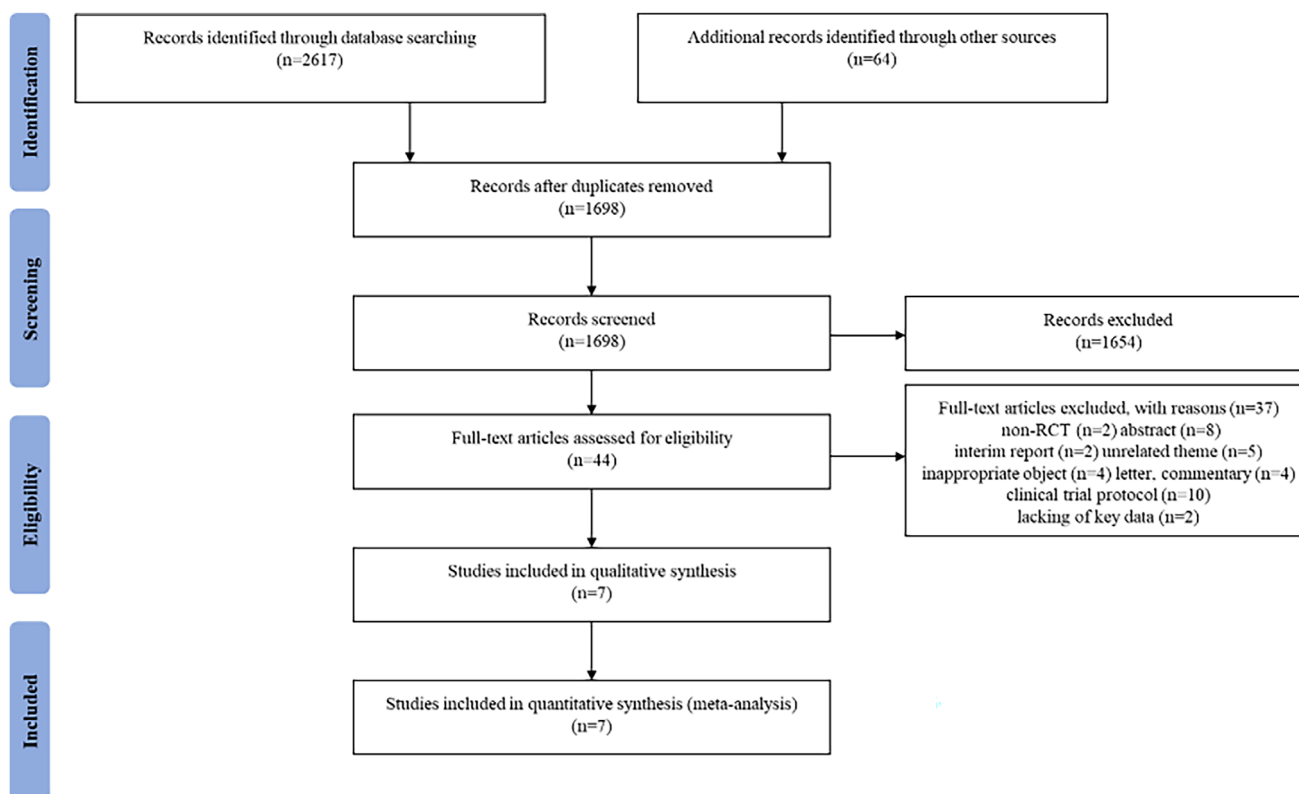


FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow chart

to III D, and the others¹⁶⁻¹⁸ adopted the Wagner grade, from 1 to 3. The curative time ranged from 6 to 12 weeks, with an average of 10 weeks. Six studies^{17,18,22-25} were registered on clinical trial platforms, and four studies^{17,22-24} were multicentre RCTs. Other characteristics of the included studies are shown in Tables 1 and 2.

3.3 | Assessment of risk of bias

The risk of bias is shown in Figure 2. The main bias comes from selective reporting and other biases. Two studies^{16,25} had a high risk of selective reporting. This was because adverse events were not routinely reported. Other bias was at high risk. The main reason was that two studies^{24,25} accepted the funding of companies. One study²⁵ had a high risk of attrition bias. Moreover, all studies provided details about random sequence generation. Six studies^{17,18,22-25} reported allocation concealment. Three studies²²⁻²⁴ described their blinded methods and placebo-controlled.

3.4 | Data analysis

3.4.1 | Number of complete ulcer healing

Six studies^{16,17,22-25} reported the effect of TOT on the number of complete ulcer healing of DFUs after 8-week or 12-week treatment. Therefore, we conducted a subgroup analysis at 8 weeks and 12 weeks. And, He et al provided that clinical outcomes of DFU wound between the two groups after 8 and 12 weeks of treatment.¹⁶ There was heterogeneity ($P = .096$, $I^2 = 46.5\%$) among these studies. A fixed-effects model was used. Meta-analysis showed that TOT could improve the number of ulcer that completely healed compared with the control group (RR = 1.63, 95% CI [1.33, 2.00], $P < .00001$) (Figure 3).

3.4.2 | Ulcer area

Five studies^{16-18,23,25} reported on ulcer area. Two studies^{18,25} found that TOT significantly decreased the mean ulcer area from baseline values. Another study²³ indicated that the mean absolute reduction in ulcer area from baseline was 1.97 cm² for the TOT arm compared with 0.40 cm² for the sham arm ($t(df) = 2.12$, $P = .041$). Although the other two studies^{16,17} showed that the TOT group had a higher ulcer reduction rate than the control group, their intervention durations were inconsistent, so meta-analysis was not conducted. Hence, TOT helped reduce the ulcer area.

3.4.3 | Healing time

Due to the inconsistent units and reporting, we conducted descriptive analysis on healing time. Four studies^{16,22-24} reported ulcer healing time. One trial²³ found that TOT did not shorten the healing time compared with the control group (TOT 8.2 ± 4.2 vs control 6.3 ± 1.9 weeks, $P = .35$). Similarly, one study²² also reported that the median time to complete closure in the per-protocol population group was 63 days for the TOT and 77 days for the control group ($P > .05$); however, for the ≥ 65 -year-old subgroup, the median time to closure was 35 days for the TOT and 70 days for the control group ($P < .05$). In contrast, the time to 50% DFU closure was significantly shorter in patients who received TOT (mean 18.4 vs 28.9 days, $P = .001$) in one trial.²⁴ Another study¹⁶ also found that the average wound healing times were 48.39 ± 13.32 days in the TOT group and 76.42 ± 32.78 days in the control group ($P < .05$). Whether TOT could shorten ulcer healing time was unclear.

3.4.4 | Adverse events

Five studies^{17,18,22-24} reported on adverse events. One study¹⁸ reported no adverse events in the intervention group compared to three adverse events in the control group. The other four studies^{17,22-24} showed that the adverse events were similar between the two groups. Only one included study²² described three cases of adverse events that might have been caused by TOT device. The remaining studies did not report any adverse events related to TOT. Thus, there are reasons to believe TOT has no clinical risk.

3.4.5 | Follow-up

Four studies^{16,18,23,24} were followed up. During the 1-year follow-up, one study¹⁶ reported that six patients and no patients in the control and TOT groups, respectively, underwent amputation. During the 12-week follow-up, one trial¹⁸ reported no amputation in the TOT group compared to two amputations in the control participants. Frykberg's study²³ showed that only 1 of 15 healed ulcers (6.7%) in the TOT group recurred, compared with 2 of 5 healed ulcers (40%) in the control group ($P = .07$) after 1 year. Another study²⁴ indicated that there were no significant differences between the treatment arms ($P = .83$) at the 12-week follow-up. Although there were different follow-up periods and indicators in the above studies, we concluded that TOT might contribute to ulcer durability.

TABLE 1 Baseline characteristics of the included studies

Author	Sex	Age	HbA1c	DFU	DFU	DFU	DFU	Sample size
Year	M/F	Mean ± SD (year)	Mean ± SD (%)	Grading	Duration	Ulcer area (cm ²)	ABI	T/C
Yu et al 2016 ²⁵	17/3	[T] 57 ± (9.5) [C] 58 ± (9.5)	[T] 8.6 ± (2.3) [C] 7.3 ± (0.5)	Texas (I A~III D)	[T] 47.4 ± (23.4) wk [C] 46.2 ± (17.9) wk	[T] 1.37 ± (0.95) [C] 1.68 ± (1.31)	[T] 1.10 ± (0.19) [C] 0.96 ± (0.20)	10/10
Driver et al 2017 ²²	[T] 43/18 ^a [C] 47/14	[T] 58.6 ± (12.31) [C] 58.8 ± (9.4)	[T] 8.0 ± (1.7) [C] 7.9 ± (1.7)	Texas (I A)	[T] 17.7 ± (12.8) wk [C] 14.9 ± (12.5) wk	[T] 2.0 ± (1.7) [C] 2.3 ± (1.7)	[T] 1.0 ± (0.2) [C] 1.0 ± (0.2)	65/63
Niederauer et al 2018 ²⁴	[T] 59/15 [C] 54/18	[T] 56.1 ± (10.1) [C] 56.6 ± (14.4)	[T] 8.4 ± (1.6) [C] 8.3 ± (2.0)	Texas (I A)	[T] 131.6 ± (89.2) d [C] 143.8 ± (97.7) d	[T] 3.54 ± (1.68) [C] 3.89 ± (2.02)	[T] 1.05 ± (0.14) [C] 1.02 ± (0.15)	74/72
Frykberg et al 2020 ²³	[T] 32/4 [C] 31/6	[T] 64.6 ± (10.3) [C] 61.9 ± (9.5)	[T] 8.43 ± (1.75) [C] 8.14 ± (1.49)	Texas (I A~II C)	[T] 160.3 ± (96) d [C] 174.6 ± (94) d	[T] 3.02 ± (2.66) [C] 3.22 ± (2.54)	[T] 1.07 ± (0.23) [C] 1.00 ± (0.23)	36/37
He et al 2021 ¹⁶	[T] 24/16 ^a [C] 23/17	[T] 63.5 ± (10.1) [C] 63.1 ± (9.3)	[T] 7.91 ± (1.17) [C] 7.85 ± (1.23)	Wagner (2, 3)	[T] 3.03~4.68 mo [C] 2.00~5.80 mo	[T] 35.35 ± (20.83) [C] 42.07 ± (38.55)	NR	40/42
Serena et al 2021 ¹⁷	[T] 54/26 ^a [C] 53/11	[T] 64.20 ± (14.15) [C] 62.29 ± (12.56)	NR	Wagner (1-3)	[T] 24.46 ± (22.62) wk [C] 23.77 ± (17.85) wk	[T] 2.86 ± (2.93) [C] 3.47 ± (4.12)	NR	81/64
Anirudh et al 2021 ¹⁸	[T] 7/3 ^a [C] 7/2	[T] 58.7 ± (5.7) [C] 57.1 ± (9.9)	[T] 8.7 ± (0.8) [C] 8.0 ± (1.6)	Wagner (2, 3)	NR	[T] 11.7~31.50 ^b [C] 10.4~27.50	[T] 0.77 ± (0.09) [C] 0.79 ± (0.09)	10/10

Abbreviations: ABI, ankle brachial index; C, control group; d, day; DFU, diabetic foot ulcer; mo, month; NR, not reported; SD, standard deviation; T, TOT group; TOT, topical oxygen therapy; wk, week; y, year.

^aThe gender of lost subjects were not described.

^bInter quartile range.

TABLE 2 Intervention protocols of the included studies

Author	Trial group	Control group	Detail of TOT	Therapeutic regimens of the control group	Curative time (week)	Outcomes
Yu et al 2016 ²⁵	TOT	SOC	The Oxygen Delivery System was placed directly on the wound surface and attached to the active Natrox Oxygen Generator using the tubing provided.	Sharp debridement and antimicrobial dressings, offloading standard practice.	8	①②
Driver et al 2017 ²²	TOT + SOC	SOC + Placebo	Continuous administration of oxygen (>98%) to the wound site using a 15-d device changed every 15 d.	Removal of necrotic or infected tissue, wound cleaning, establishment of adequate blood circulation, maintenance of a moist wound environment, offloading, management of wound infection, nutritional support and glycaemic control.	12	①③④
Niederauer et al 2018 ²⁴	TOT + SOC	SOC + Placebo	TransCu O ₂ System continuously generate pure (>99.9%), humidified oxygen at flow rates of 3~15 mL/h and delivers it directly to the wound bed environment within the MWT dressing system by tubing.	Wound cleaning, MWT, offloading, aggressive debridement.	12	①③④⑤
Frykberg et al 2020 ²³	TOT + SOC	SOC + Placebo	The affected limb was put into the air chamber, humidified oxygen was cycled between 10 and 50 mb within the chamber. A 10 L/min oxygen concentrator was used. Patients treated themselves at home for 90 min daily five times per week.	Debridement, offloading, MWT.	12	①②③④⑤⑥
He et al 2021 ¹⁶	TOT + SOC	SOC	A micro-oxygen supply device (Greens O-4-3, China) was used to generate high purity oxygen, which was continuously delivered to the center surface of the wound at a constant flow rate through oxygen connection tubing.	Control of blood pressure, blood glucose and lipid levels, treatment of peripheral neuropathy, nutritional support and correction of hypoproteinaemia and electrolyte imbalance, offloading, antibiotic treatments, debridement, moist wound dressing.	8	①②③⑤
Serena et al 2021 ¹⁷	TOT + SOC	SOC	The Natrox Oxygen Generator delivers a pure oxygen flow rate of 15 mL/h. The oxygen delivery system allows wound exudate to pass through to the secondary dressing while allowing the diffusion of oxygen across the wound bed.	Wound cleaning, sharp debridement, offloading, moisture balance.	12	①②④

(Continues)

TABLE 2 (Continued)

Author	Trial group	Control group	Detail of TOT	Therapeutic regimens of the control group	Curative time (week)	Outcomes
Anirudh et al 2021 ¹⁸	TOT + SOC	SOC	The device is designed to deliver topical oxygen at a controlled temperature of 42°C, a concentration of 93% (±3%), and a flow rate of 1 L/min. This protocol was repeated alternate day of every week for 6 wk (18 sessions).	Wound cleaning, debridement, glycaemic control, antimicrobials.	6	⊕⊕⊕⊕⊕⊕

Note: ⊕, number of complete ulcer healing; ⊕, ulcer area; ⊕, healing time; ⊕, adverse event; ⊕, follow-up; ⊕, quality of life. Abbreviations: MWT, moist wound therapy; SOC, standard of care; TOT, topical oxygen therapy.

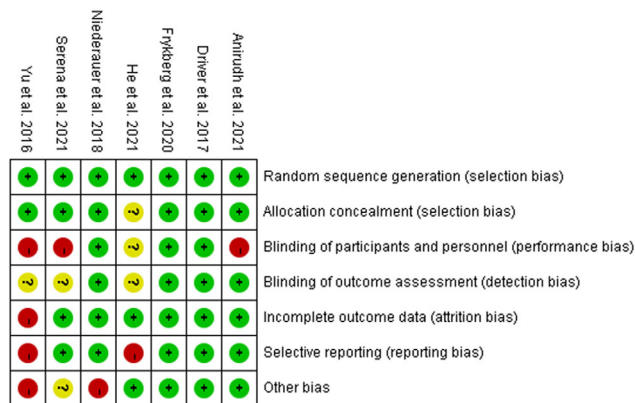


FIGURE 2 Risk of bias summary

3.4.6 | Quality of life

Two studies^{18,23} reported on quality of life. One study¹⁸ showed that patients in the TOT group had a better quality of life using the IVDP-QOL questionnaire after 6-week treatment. The IVDP-QOL score decreased from 7.5 to 4.44. Another study²³ also showed that the greatest improvement was seen for the well-being component using the CWIS QOL index, with mean score difference between baseline and the end of 12 weeks of treatment in the TOT arm of 9.1 compared with 20.1 in the sham arm ($t(df) = 2.18, P = .033$). Although they used different questionnaires to investigate the participants' quality of life, we still found that TOT helped to improve their quality of life.

3.5 | Sensitivity and heterogeneity analysis

In the sensitivity analysis of the number of complete ulcer healings, individual studies were excluded one by one, and the heterogeneity was mainly related to Driver's study.²² After excluding that study, the heterogeneity was $I^2 = 0%$ (RR = 1.93, 95% CI [1.49, 2.49]) (Figure 4). This may be related to the fact that the patients in that study had a relatively mild condition. Two recent studies^{23,24} showed that chronic or larger DFUs were more suitable for TOT. In summary, the above result was robust.

3.6 | Publication bias analysis

Publication bias is that the publication or non-publication of research findings, depending on the nature and direction of the results.²⁶ Generally, statistically significant results were more likely to be published. The funnel plot of ulcer-complete healing number displayed

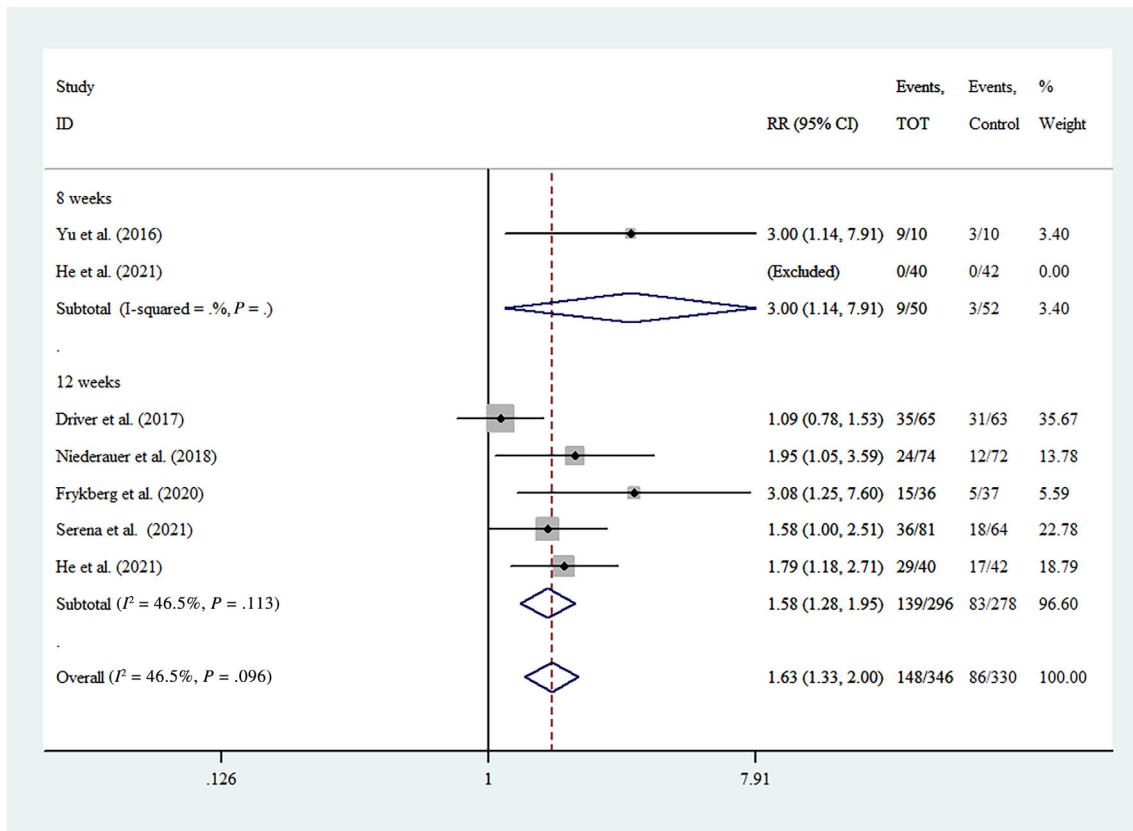


FIGURE 3 Forest plot of number of complete ulcer healing

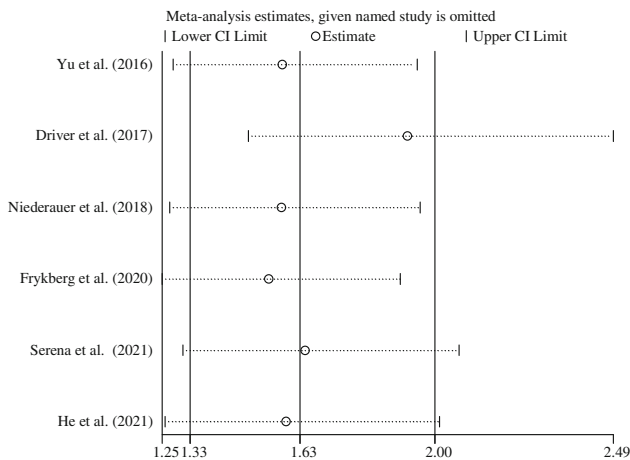


FIGURE 4 Sensitivity analysis of number of complete ulcer healing

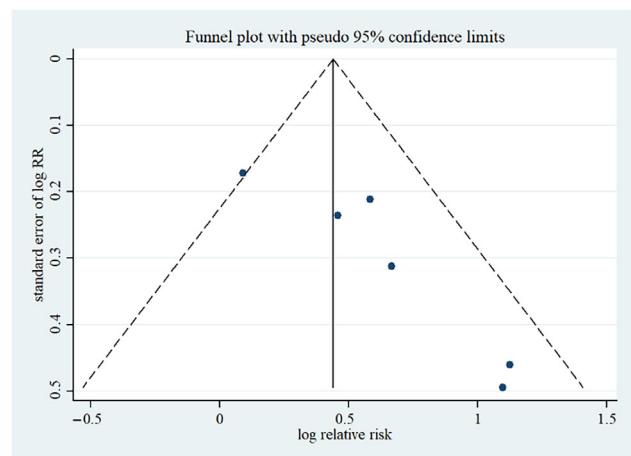


FIGURE 5 Funnel plot of number of complete ulcer healing

an apparent asymmetry that suggested the presence of a potential publication bias (Figure 5). Moreover, Harbord's modified linear regression test also indicated that there was a risk of publication bias ($P = .02$). Hence, there is reason to believe that some studies with negative results may not have been published. To reduce the risk of publication bias, more databases and grey literatures needed to be searched.

4 | DISCUSSION

Currently, SOC alone may not be sufficient to prevent and treat DFUs, and novel adjunctive therapies are urgently needed.²⁷ For all this, it is also critical to emphasise that TOT (as for adjunctive therapy) must be administered in conjunction with optimal wound care.²⁸ In other words, DFU patients still need to receive SOC

combined with other adjunctive therapies. This combination therapy can not only achieve better therapeutic effects but also complies with ethical principles. In this review, seven RCTs with 614 patients were analysed in our meta-analysis. All studies have been published since 2016. Six included studies used combination therapy in the trial arm. There were nearly three times as many men as women in the included studies. More studies believe that a 12-week course is more reasonable. The findings of this review provide a detailed summary of the present evidence of TOT for the treatment of DFUs. This result indicated that compared with SOC, TOT was beneficial for promoting ulcer healing without increasing the incidence of adverse events.

Unfortunately, there were four predefined outcomes that were qualitatively analysed. Although these studies indicated TOT helped to reduce the ulcer area, Serena et al reported that for the ITT analysis, there was no statistical difference in percentage reduction in ulcer area (TOT 46.38 ± 100.24 vs control 41.50 ± 69.82 , $P = .72$).¹⁷ With respect to healing time, two included studies^{22,23} displayed that TOT did not shorten the healing time, but two other studies^{16,24} showed opposite results. It is worth noting that SOC, run-in period, definition of ulcer healing time were different in these studies. Therefore, we were not certain whether TOT could reduce the time to ulcer healing. This indicator will need to be given more consideration in future studies. We also summarised durability of the included studies. Four included studies^{16,18,23,24} found that TOT helped to increase healing durability during the 12-week or 12-month follow-up period. In fact, healing durability may lower the rate of readmission. Only two studies^{18,23} offered significant data on quality of life. They employed various questionnaires and presented the results in various ways. As a result, a meta-analysis was ruled out. Furthermore, future studies should take into account the subjective results of patients, such as psychological states and patient satisfaction. This was due to the fact that patient compliance required a better treatment experience.

Previous reviews were consistent with our results, but there were some distinctions. Nataraj et al¹³ included two RCTs, two non-RCTs and one case report, without meta-analysis. Likewise, Connaghan et al¹⁴ performed a meta-analysis, but four included studies were non-RCTs. Meanwhile, Thanigaimani et al¹⁵ also conducted a similar meta-analysis, but only two databases were retrieved. Moreover, two included studies^{24,29} were from the same study protocol and research team. Hence, there is a risk of duplication data. Unlike previous studies, our review only included RCTs. Apart from healing rate and adverse events, our review showed more outcomes. Because

podiatric grading can reflect illness severity, all included studies reported on paediatric grading. These factors can improve the credibility of our study.

Although all included studies were RCTs, there were also some weaknesses. First, inclusion and exclusion criteria were not identical for all included studies, yet baselines between the two groups were similar in each study, or the wounds in the TOT group were more serious, implying that TOT had an effect. However, three included studies^{16,18,25} did not have a run-in period for chronic wound screening. This might reduce the homogeneity of participants. Second, inconsistent intervention lead to clinical heterogeneity. Offloading, for example, is an important element DFU treatment. However, two included studies^{16,18} did not use an offloading device. Third, different intervention durations (eg, 6 weeks, 8 weeks, 12 weeks) also resulted in clinical heterogeneity. Future studies should be registered on a clinical trial platform and give intermediate indicators in order to investigate the appropriate period of intervention. Fourth, some studies relied on in-home care, while others relied on outpatient treatment. Patients' compliance with home care should be evaluated and reported in order to follow treatment regimens. Fifth, due to small number of studies included, no subgroup analysis of continuous diffusion oxygen therapy and intermittent TOT was undertaken. Furthermore, additional randomised double-blind placebo-controlled trials should be considered to strengthen the credibility of research results by reducing the influence of patients' and researchers' subjective elements on study results. Therefore, the findings should be interpreted cautiously.

5 | CONCLUSION

The existing evidence suggests that TOT is effective and safe for DFU patients. TOT may be an alternative for some chronic DFUs. In the future, more high-quality studies are needed to support or refute the findings. Additionally, the mechanism, optimal treatment and economic evaluation still need to be further explored.

ACKNOWLEDGEMENT

This work was supported by West China Nursing Discipline Development Special Fund project of Sichuan University, Grant Number: HXHL19005; Popularization and application project of Sichuan Provincial Health Commission, Grant Number: 20PJ023.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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How to cite this article: Sun X-K, Li R, Yang X-L, Yuan L. Efficacy and safety of topical oxygen therapy for diabetic foot ulcers: An updated systematic review and meta-analysis. *Int Wound J*. 2022;19(8):2200-2209. doi:10.1111/iwj.13830