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REVIEW ARTICLE

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The efficacy of topical oxygen therapy for wound healing: A meta-analysis of randomized controlled trials and observational studies

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Abstract

In preclinical studies, topical oxygen treatment (TOT) was shown to enhance wound healing by applying supplemental oxygen topically to the surface of a moist wound at normobaric conditions. The objective of this systematic review and meta-analysis is to provide a thorough evaluation of published RCTs and observational studies that compare supplemental TOT with standard wound care. A total of 1077 studies were obtained from a variety of databases, including PubMed, ScienceDirect, Web of Science, ProQuest, Scopus, ClinicalTrials.gov, EU Clinical Trial Registers, and Preprints.org. The Jadad scale was employed to assess the reliability of RCT studies, while the Newcastle-Ottawa Scale (NOS) was employed to assess the quality of observational studies. Seven RCT studies ($n = 692$) and two controlled observational studies ($n = 111$) were analysed. The rate of healed wounds was 25.8% in the control group and 43.25% in the adjuvant TOT group, which shows the use of TOT significantly increased the number of healed wounds (RR = 1.77; 95% CI 1.18–2.64; $p = 0.005$). A significant decrease in the percentage of wound area was found in the TOT group in RCT studies (mean difference = 15.64; 95% CI 5.22–26.06; $p = 0.003$). In observational studies, the rate of healed wounds was 37.5% in the standard care group and 80.95% in the adjuvant TOT group, which shows a significant increase in the number of healed wounds in the adjuvant TOT group (RR = 2.15; 95% CI 1.46–3.15; $p < 0.00001$). Topical oxygen therapy is considered a great adjuvant therapy for chronic wound healing, particularly

wounds with vascular compromise such as diabetic ulcers and pressure ulcers. Further studies on this topic are still needed as there are a lot of potential uses for this technology in various types of wounds.

KEYWORDS

chronic wound, medical care, topical oxygen therapy, wound healing

Key messages

- The use of topical oxygen therapy is established as a great adjuvant therapy for chronic nonhealing wounds, particularly wounds with vascular compromise such as diabetic ulcers and pressure ulcers.
- The use of TOT as the main and sole treatment still needs to be researched further as more recent TOT technologies could allow for a more efficient and simplified wound care treatment.
- As TOT technology becomes more available worldwide, we are looking forward to more extensive studies on this topic.

1 | INTRODUCTION

Chronic wounds are characterized by extended inflammation, persistent infections, and the formation of drug-resistant biofilms, which prevent timely healing.[1,2] Chronic wounds are often categorized as vascular ulcers, diabetic ulcers, and pressure ulcers.[3] Chronic wounds are sometimes referred to as hypoxic because the wound's oxygen levels are often below the necessary threshold to support the enzyme activity needed for tissue repair.[4] Although acute hypoxia can promote angiogenesis, chronic hypoxia hinders the production of reactive oxygen species (ROS) that are necessary for the upregulation of growth factors, cell signalling, and bacteriostatic characteristics.[5,6]

Chronic wounds remain a challenge for healthcare professionals. For example, diabetic foot ulcers (DFU) significantly contribute to preventable morbidity in diabetic adults, with a lifetime risk of 19%–34% and high recurrence rates of up to 65%.[7,8] It is predicted that between 1% and 6% of people in developed nations will suffer from a chronic wound at some point in their lives.[4,5,9–11] In this setting, wound care is estimated to cost approximately 2%–5.5% of the healthcare budget.[7,11,12] A more recent study in Singapore showed an average annual cost of US $3.368 (SG $4776) for ulcer-only patients, and up to US $30.131 (SG $42730) for major amputation patients.[13]

Poor wound healing has been strongly associated with transcutaneous partial oxygen of less than 40 mmHg, indicating that the partial pressure of oxygen (pO_2) is a major determinant in wound healing.[14] Topical oxygen therapy (TOT) utilizes pure oxygen administered topically at normobaric pressures to a moist wound bed and has been demonstrated in preclinical studies to rapidly and dramatically boost the pO_2 of the superficial wound tissue,[15] increasing angiogenesis, collagen production, fibroblast growth, and suppression of bacterial multiplication, which subsequently aids tissue regeneration.[16–19] Currently, available TOT devices are mainly classified into two types: intermittent (with constant or cyclical pressure) and continuous, as summarized in Figure 1.

This systematic review and meta-analysis attempt to provide a thorough evaluation of known randomized controlled trials (RCTs) and observational studies which compare the use of supplementary TOT with standard wound care. Prior reviews and meta-analyses exclusively focused on the group with diabetic foot ulcers (DFU), revealing encouraging findings that support the use of TOT. In order to gain a more thorough understanding of the impact of TOT on the healing process of different types of wounds, we have included all forms of chronic wounds in our study as the population. The data from studies on continuously and cyclically pressured systems were consolidated and integrated due to a lack of adequate studies for performing separate meta-analyses.

2 | MATERIALS AND METHODS

2.1 | Study protocol

The study was conducted using the meta-analysis procedures outlined in the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA)[20] (Figure 2). Prior to commencing the investigation, the study protocol was officially registered in PROSPERO for

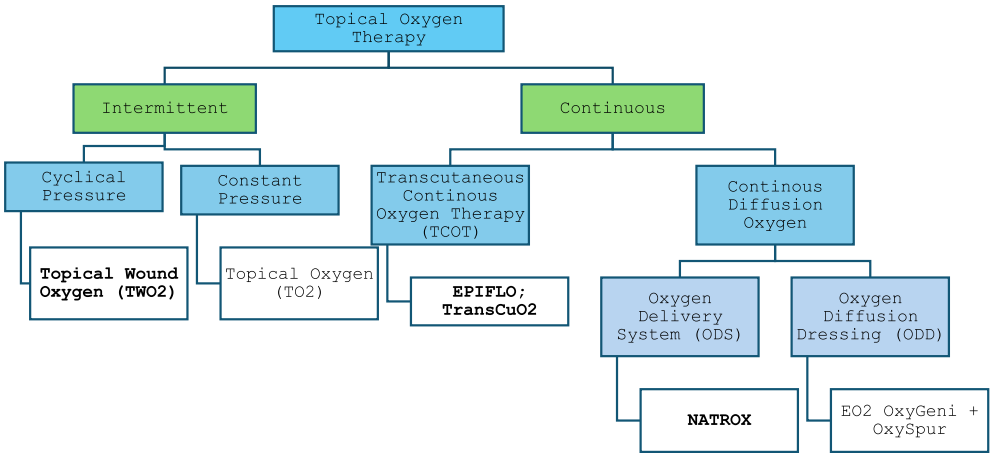

FIGURE 1 Classification of topical oxygen therapy and currently available types in the market (the ones in bold are included in this meta-analysis).

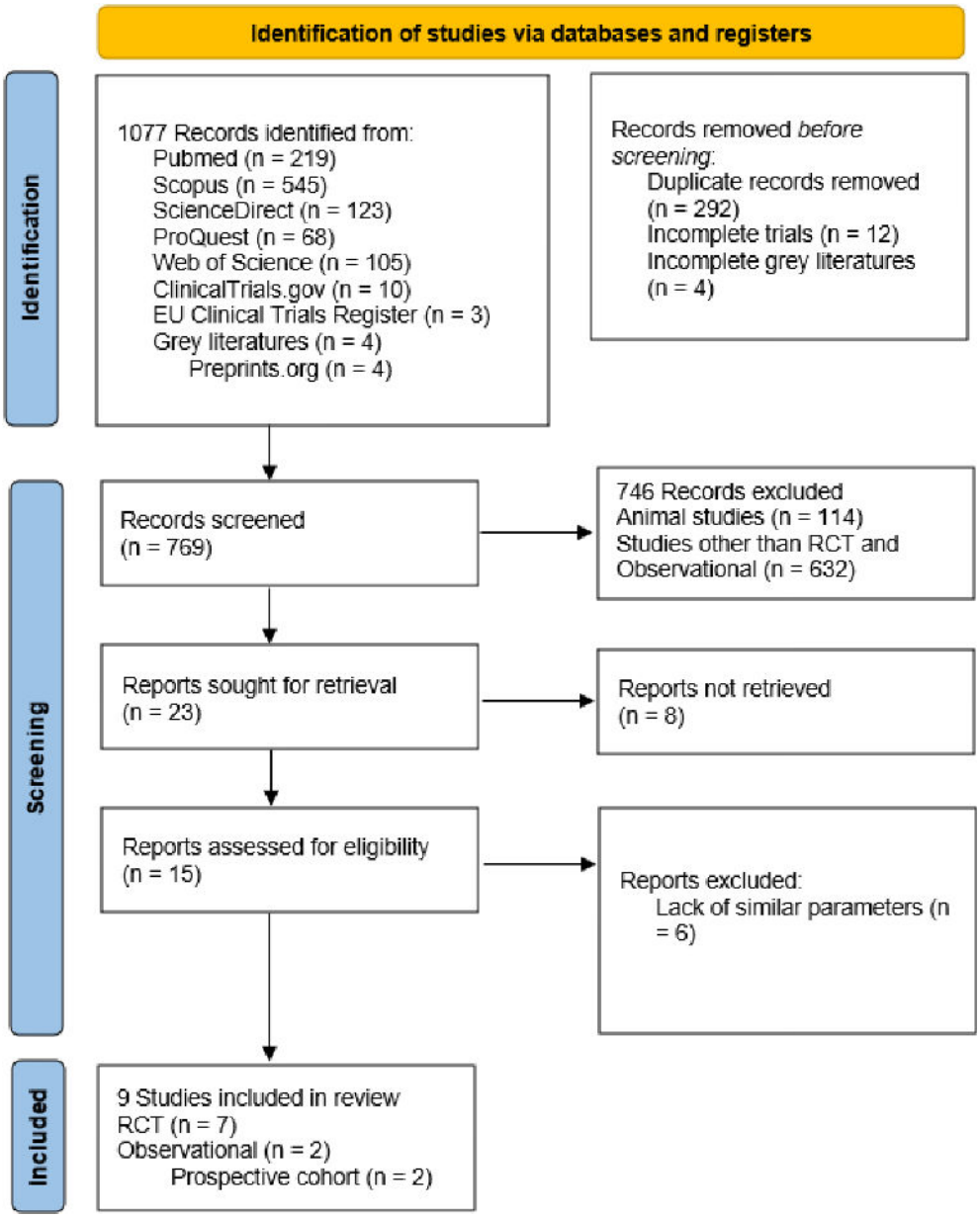

FIGURE 2 PRISMA flow chart.

Systematic Review and Meta-Analysis, with a specific identification number of CRD42023434231.

2.2 | Study selection

Three reviewers (I. L. Putri, A. Alyssa, and R. Pramanasari) conducted a search for observational studies with a control group and RCTs that compared TOT with standard wound care. The purpose was to examine the effects of these interventions on the rate of wound healing. Only English-language human studies that were fully accessible in full text were considered. The original draft writing, editing, and reviewing process was overseen by two authors, I. F. Aisyah and A. Alyssa. Any discrepancies were resolved through a consensus meeting with the senior authors (A. A. I. Y. Permatasari and C. D. K. Wungu). The main outcome was the number of healed wounds at the end of respective studies. The secondary outcome was the percentage of wound area decrease, the time needed for the wound to heal, and the pain level.

2.3 | Literature search

The search was conducted using the keywords topical oxygen therapy, topical wound oxygen, topical hyperbaric oxygen, wound, ulcer, and relevant MeSH terms when applicable. The search terms utilized were (wound* OR ulcer* OR "wound healing") AND ("topical oxygen therapy*" OR "topical wound oxygen" OR "hyperbaric topical oxygen" OR "topical hyperbaric oxygen"). These terms were modified to meet the specific search criteria of each respective database.

The three researchers conducted a comprehensive search for relevant papers in several databases including PubMed, ScienceDirect, Web of Science, ProQuest, Scopus, ClinicalTrials.gov, EU Clinical trials, and the grey literature resource Preprints.org. All relevant studies conducted prior to 1 June 2023, were included and transferred to Mendeley software for organization. Subsequently, any duplicates, animal studies, and research that were not relevant were eliminated.

2.4 | Data extraction

The reviewers separately chose and compiled data into a spreadsheet, including information on "authors", "publication year", "country", "study design", "population", "mean age", "follow-up duration", "kind of wound", "mean wound area", "type of intervention", "type of control", "length of intervention", and "TOT technology utilized". The data was subsequently cross verified to prevent any inconsistencies.

2.5 | Risk of bias and quality assessment

We used the Jadad scale to assess the calibre of randomized controlled trials (RCTs),[21] and the Newcastle-Ottawa Scale (NOS) to assess the calibre of observational research.[22] A study is considered to be of excellent quality if it achieves a NOS score of 7 or above, and a Jadad score of 3 or above.

2.6 | Statistical analysis

Studies will be grouped based on the outcome scale used in the studies and Microsoft Excel software will be used to group studies. We will also do separate analyses for RCT studies and observational studies. To assess heterogeneity, inconsistency index statistic (I^2) will be used. If I^2 was higher than 50% with a significant p value, the random-effects method will be used, otherwise fixed-effect method will be utilized in this meta-analysis.

It is expected that there may be a high degree of heterogeneity among studies. Therefore, a minimum of two similar studies with the same data parameter will be included in this meta-analysis. For RCT studies, we will analyse the number of healed wounds and the duration of wound healing. For observational studies, we will analyse the incidence of healed wounds. Values for these studies will be combined using RevMan 5.4 statistical software.

3 | RESULTS

3.1 | Study selection and characteristics

A total of 1077 studies were retrieved from various databases: 219 studies from PubMed; 545 studies from Scopus; 123 studies from ScienceDirect; 68 studies from ProQuest; 105 studies from Web of Science; 10 studies from ClinicalTrials.gov; 3 studies from EU Clinical Trial Registers; and 4 studies from Preprints.org. Duplicate records ($n = 292$) and incomplete studies ($n = 16$) were removed and a total of 769 studies were then screened for English language, human study, RCT, and observational studies, of which 746 studies—animal studies ($n = 114$) and studies that are neither RCT nor observational ($n = 632$)—were excluded. After evaluation of the remaining 23 studies, we were unable to retrieve data

TABLE 1 Baseline data of RCT studies.

Author, year, country, design	Population (male)	Patient setting; wound type	Baseline HbA1c (%); mean ABI	Baseline wound area (cm^2)	Mean age, years (SD)	Duration	Follow-up	Control (type of dressings)	Intervention (device name); oxygen flow
Frykberg, 2019, Multinational, RCT (23)	C: 37 (31) N: 36 (32)	Outpatient; DFU	C: 8.14; 1.00 N: 8.43; 1.07	C: 3.22 N: 3.02	C: 69.1 N: 64.6	12w	12 months	SC (foam and hydrogel) + Sham	TWO_2 (Hyperbox by AOTI, Ltd.); cyclical, 10 L/min, 10–50 mbar
Azimian, 2016, Iran, RCT (24)	C: 50 (26) N: 50 (26)	Intensive Care & Neurology unit; pressure ulcer, sacral or ischial	n/a	C: 28.74 N: 31.81	C: 69.56 N: 70.48	12d	n/a	SC (saline-soaked)	TWOT (n/a); interval, 10 L/min, 3×/day, @20 mins
Serena, 2021, USA, RCT (25)	C: 64 (53) N: 81 (54)	Outpatient; DFU	n/a	C: 3.47 N: 2.86	C: 62.69 N: 64.20	12w	n/a	SC (hydrofiber or alginate)	CDO (Natrox by Inotec AMD Ltd.); constant, 15 mL/h
He, 2021, China, RCT (26)	C: 40 (24) N: 40 (23)	Outpatient; DFU	n/a	C: 42.07 N: 35.35	C: 63.1 N: 63.5	8w	12 months	SC (alginate)	CDO (Greens O-4-3 by Institute of Fuel Cells, Shanghai Jiao Tong University); constant, n/a
Niederauer, 2018, USA, RCT (27)	C: 72 (11) N: 74 (10)	Outpatient; DFU	C: 8.3; 1.02 N: 8.4; 1.05	C: 3.89 N: 3.54	C: 56.6 N: 56.1	12w	n/a	SC (foam & thin film, optional alginate) + Sham	CDO (TransCu O_2 by EO_2 Concepts); constant, 3 mL/h
Yu, 2016, Canada, RCT (28)	C: 10 (9) N: 10 (9)	Outpatient; DFU	C: 7.3; 0.96 N: 8.6; 1.10	n/a	C: 58 N: 57	8w	n/a	SC (foam)	CDO (Natrox by Inotec AMD Ltd.); constant, n/a
Driver, 2017, USA, RCT (29)	C: 63 N: 65	Outpatient; DFU	C: 7.9 N: 8.0	C: 2.3 N: 2.0	59	12w	2w and 10w	SC (hydrocolloid/ alginate and foam) + Sham	TCOT (Epiflo by Neogenix); constant; 3 mL/h

Abbreviations: C, control group; CDO: continuous diffusion oxygen; DFU, diabetic foot ulcer; N, intervention group; SC, standard care; TWO_2, topical wound oxygen; TWOT: topical wound oxygen therapy.

TABLE 2 Baseline data for observational studies.

Author, year, country, design	Population (male)	Patient setting; wound type	Baseline HbAlc (%); mean ABI	Baseline wound area (cm^2)	Mean age, years (SD)	Duration	Follow-up, months	Control (type of dressings)	Intervention (device name); oxygen flow
Blackman, 2010, Canada, Cohort (30)	C: 11 (8) N: 17 (12)	Outpatient; DFU	C: 7.4; 1.0 N: 7.3; 0.9	C: 1.4 N: 4.1	C: 63.4 N: 62.4	90d	24	SC (silvercel by Johnson and Johnson Inc.)	TWO_2 (Hyperbox by AOTI, Ltd.); cyclical, 10 L/min, 5–50 mbar, 5×/week, @60 min
Tawfick, 2009, Ireland, Cohort (31)	C: 37 (24) N: 46 (29)	Inpatient; Refractory venous leg ulcer	n/a	n/a	C: 65 N: 66	12w	12	CCD (Profore by Smith & Nephew Ltd.)	TWO2 (Hyperbox by AOTI, Ltd.); interval, 10 L/min, 50 mbar, 2×/day, @180 min

Abbreviation: CCD, conventional compression dressing.

from eight studies, and six studies did not include the parameters required to conduct a meta-analysis. Finally, nine eligible studies (seven RCTs and two cohorts) were then reviewed qualitatively. The 2020 PRISMA flow chart of the data selection process can be seen in Figure 1.

3.2 | RCT studies

Seven RCT studies ranging from 2015 to 2021 with a total of 692 participants were analysed, with 336 control patients treated with standard care (SC) consisting of various types of moist wound dressing, and 356 patients treated with standard care and adjuvant TOT. Of note, we excluded a group of 40 participants from the study by He et al.[23] which was treated with only TOT without standard wound care. The mean age of those studies ranges from 57 to 70.48 years. Four studies were conducted for 12 weeks, two were 8 weeks, and one study was conducted for only 12 days. Only two[23,24] out of the RCT studies mentioned a 12-month follow-up, while one study[25] had two follow-ups, on week 2 and week 10 after completing wound closure. The TOT technology used varies among these studies, with one study using topical wound oxygen (TWO_2), two studies using transcutaneous oxygen therapy (TCOT), one study using TCOT and the rest using continuous diffusion oxygen (CDO). More details can be seen in Table 1.

3.3 | Observational studies

Two controlled cohort studies, which were from the years 2009 and 2010 respectively, included 111 participants with 48 patients treated with standard wound care and 63 patients treated with standard wound care with adjuvant TWO_2. The mean age ranged from 62.4 to 66 years, and the duration of treatment was 90 days and 12 weeks respectively. Both studies mentioned follow-up, one with a 12-month follow-up period and the other with a 24-month follow-up period. Details can be seen in Table 2.

4 | QUALITY ASSESSMENT

The quality assessment of seven RCT articles was conducted using the Jadad score. Among them, the studies by Frykberg,[24] Niederauer,[26] and Driver[25] received the highest score of 5, indicating robustness in randomization (score of 2), double blinding (score of 2), and detailed reports of withdrawals and dropouts (score of 1). Azimian and Serena's studies both obtained a Jadad score of

TABLE 3 JADAD scale for RCT studies quality assessment.

Author, year, country, design	Randomization	Double-blind	Withdrawals	Total
Frykberg, 2019, USA, RCT	2	2	1	5
Azimian, 2016, Iran, RCT	2	1	0	3
Serena, 2021, USA, RCT	2	0	1	3
He, 2021, China, RCT	1	0	1	2
Yu, 2016, Canada, RCT	2	0	1	3
Niederauer, 2017, Multinational (USA, UK, France, Germany & Luxembourg), RCT	2	1	1	5
Driver, 2017, USA, RCT	2	2	1	5

3, indicating satisfactory randomization. He's study scored 2, with minimal double-blinding and randomization, while Yu's study also received a score of 3, with proper randomization but lacking double-blinding. Overall, Frykberg's, Niederauer's and Driver's studies demonstrate superior methodological quality, while He's study shows comparatively lower rigour in design and execution (Table 3).

In the quality assessment utilizing the Newcastle-Ottawa Scale for two observational studies, both attained a commendable score of 7 out of 9, indicating robust methodological quality. Both studies demonstrated adequate comparability (score of 1), suggesting that the groups being compared were similar in key characteristics, enhancing the internal validity of the findings. However, both studies scored lower in ascertainment of exposure (score of 0), indicating limitations in the methods used to ascertain or measure the exposure variable of interest. Despite this, the overall high score suggests that both studies possess strong methodological rigour and provide valuable insights into their respective research questions (Table 4).

All studies were considered representative, which included reports of the number of healed wounds during of study. Several studies included the percentage of wound area decrease and time needed for wounds to heal, therefore we included those as the secondary outcome.

5 | PRE-INTERVENTION PROCEDURES

5.1 | Run-in period

Three of the RCTs incorporated a run-in period in the studied publications to identify actual cases of failure in routine care. Frykberg et al.[1] conducted a study that excluded wounds with a recovered area of 30% or more. Serena et al., on the other hand, excluded wounds with a healed area of more than 20% in the first 2 weeks. Both studies implemented a 2-week run-in period. The study done by Niederauer et al. examined the run-in outcomes by analysing the percentage of wound area reduction (PWAR) in active TOT and sham treatments. The findings showed that TOT was more effective in healing chronic wounds compared to sham treatment. The trial conducted by Driver et al.[25] implemented a brief run-in period lasting only 1 week, during which patients with more than 30% of wound area healed were eliminated.

5.2 | Debridement and off-loading

Throughout our comprehensive review, it was consistently observed in eight out of nine studies that debridement was conducted either before and/or during the TOT intervention as a component of regular wound care, with the sole exclusion being the randomized controlled trial conducted by Azimian.[27] In all seven investigations that particularly examined diabetic foot ulcers, the therapeutic regimen included the use of offloading methods.

6 | PRIMARY OUTCOMES (NUMBER OF HEALED WOUNDS)

6.1 | RCT studies

Seven studies reported the number of healed wounds during the study with and without adjuvant TOT, three of which also included the use of a sham TOT machine in the standard care group. The rate of healed wounds was 25.8% in the control group and 43.25% in the adjuvant TOT group, which shows the use of TOT significantly increased the number of healed wounds

TABLE 4 Newcastle-Ottawa scale for observational studies quality assessment.

Study	Selection				Comparability	Exposure			Total
	Case definition adequate (1)	Representative of the cases (1)	Selection of controls (1)	Definition of controls (1)	Comparability based on design or analysis (2)	Ascertainment of exposure (1)	Same method of ascertainment for cases and control (1)	Non-response rate (1)	
Blackman, 2010	1	1	1	1	1	0	1	1	7
Tawfick, 2009	1	1	1	1	1	0	1	1	7

(RR = 1.77; 95% CI 1.18–2.64; $p = 0.005$). Random effect model was applied due to the statistical heterogeneity found in the evaluated studies ($I^2 = 65\%$; $p = 0.009$) (Figure 3).

6.2 | Observational studies

Two controlled cohort studies documented the quantity of healed wounds both with and without the addition of adjuvant TOT. The standard treatment group had a healing rate of 37.5%, whereas the adjuvant TOT group had a healing rate of 80.95%. This indicates a substantial increase in the number of healed wounds in the adjuvant TOT group (relative risk = 2.15; 95% CI 1.46–3.15; $p < 0.00001$). The reviewed studies did not show any significant statistical heterogeneity ($I^2 = 0\%$; $p = 0.58$) (Figure 4).

7 | SECONDARY OUTCOMES

7.1 | Wound area decrease

7.1.1 | RCT studies

Two RCTs documented the reduction in the percentage of wound area at the conclusion of the investigation. The adjuvant TOT group experienced a substantial reduction in the percentage of wound area (mean difference = 15.64; 95% CI 5.22–26.06; $p = 0.003$). No substantial statistical heterogeneity was detected in the evaluated studies ($I^2 = 0\%$; $p = 0.43$) (Figure 5).

All of the RCT investigations, except for one, reported a decrease in wound area as the average size. Therefore, the data cannot be examined separately and must be compared to the initial wound area in each respective study. Frykberg et al.[24] saw a notable decrease in wound area in the active TOT group compared to the sham group by week 12, with statistical significance ($p = 0.041$). A study conducted by Yu et al.[28] demonstrated a substantial reduction in wound area by the conclusion of the eighth week ($p < 0.001$). Azimian et al.[27] saw a reduction in wound area on alternate days throughout the 12-day duration of the trial. There was a significant difference in the decrease of the wound area between the usual care group and the adjuvant TOT group on day 6 ($p = 0.003$), day 8 ($p = 0.0011$), and day 12 ($p = 0.0011$). In a separate study conducted by Tawfick and Sultan,[29] it was found that at week 12, the adjuvant TOT group experienced a significant decrease in surface area, with a reduction of 96%. In comparison, the standard care group only had a drop of 61%.

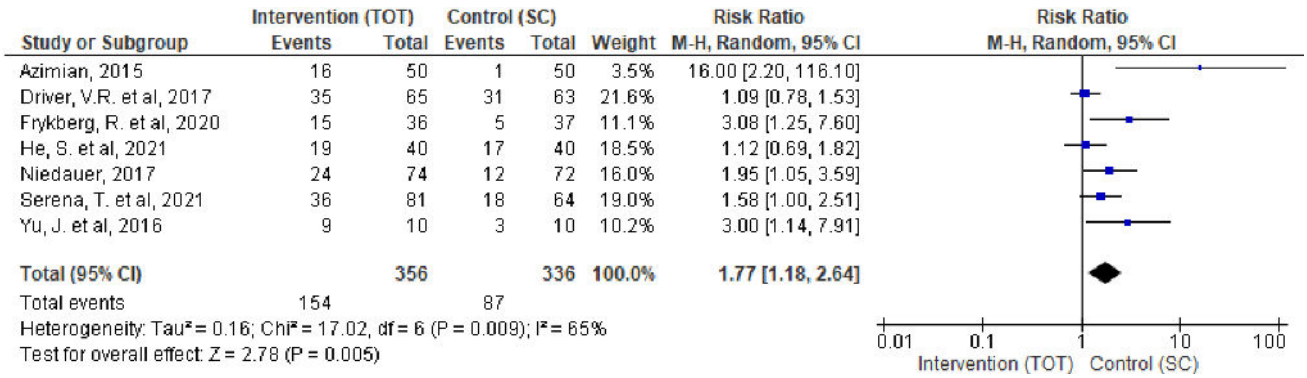

FIGURE 3 Analysis of RCT studies with the number of healed wounds as the primary outcome.

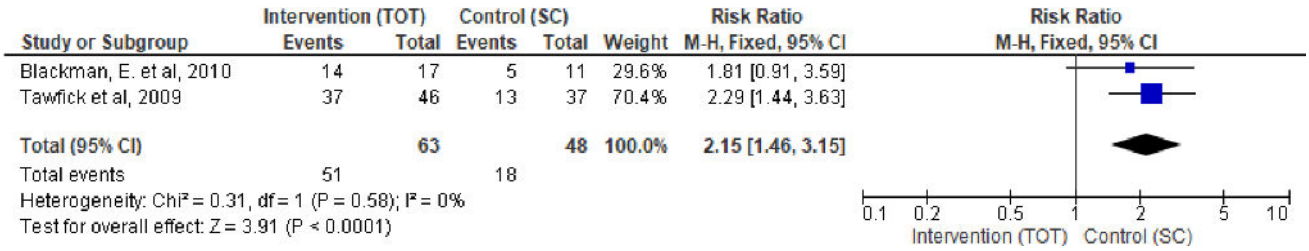

FIGURE 4 Analysis of observational studies with the number of healed wounds as the primary outcome.

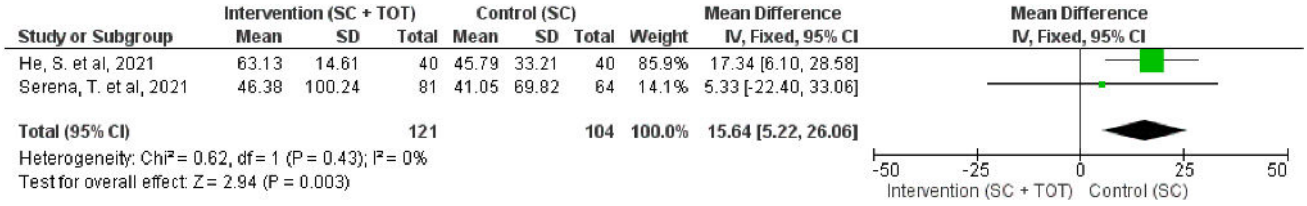

FIGURE 5 Analysis of RCT studies with wound decrease area as a secondary outcome.

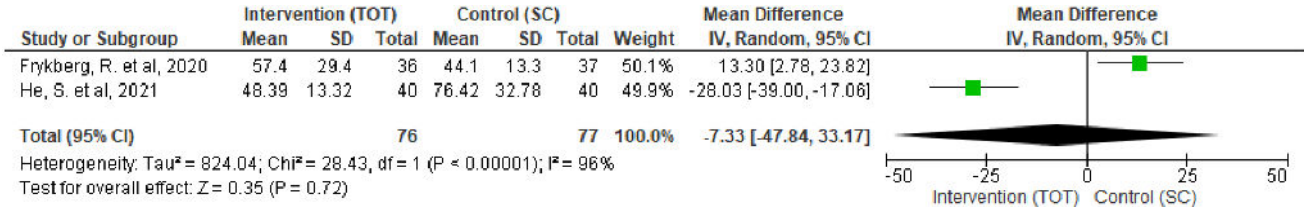

FIGURE 6 Analysis of RCT studies with wound healing time as a secondary outcome.

7.2 | Wound healing time

7.2.1 | RCT studies

Two RCTs provided data on the mean time it took for wounds to completely heal in both the standard care group and the adjuvant TOT group. There was no statistically significant disparity in the time it took for wounds to heal between the two groups (mean difference = −7.33; 95% CI −47.84 to 15.78; $p = 0.07$). The analysed studies exhibited a substantial quantity of statistical heterogeneity ($I^2 = 96\%$; $p = 0.000001$) (Figure 6).

7.2.2 | Observational studies

In a cohort study conducted by Blackman et al.,[30] it was shown that the adjuvant TOT group had a median healing time of 56 days (with an interquartile range [IQR] of

39–81 days), while the usual care group had a median healing time of 93 days (with an IQR of 62–127 days).

7.3 | Pain level

7.3.1 | RCT study

A single study[31] was the only one to provide a comparison of pain level evaluation at the beginning and end of the study (week 12) using a Visual Analogue Scale (VAS). There were no statistically significant variations in pain level between the standard care group and the adjuvant TOT group ($p = 0.278$).

8 | DISCUSSION

8.1 | Number of healed wounds

The number of healed wounds in both RCT and observational studies was consistently and significantly higher in the adjuvant TOT group. This result is in line with previous meta-analyses showing more DFU wounds healed in the adjuvant TOT group.[32–34] However, the study by Driver et al.[25] was the only one to find no statistically significant results. In a previous meta-analysis, Carter suggested that this outcome might be attributed to flaws in the older Epiflo device, which lacked an indicator for adequate oxygen flow and only indicated whether the device was on or off.[34] Additionally, our review revealed that the study was unable to assess patient compliance with offloading protocols, which could lead to a non-significant result.

Our meta-analysis examined wounds beyond DFUs, specifically including one trial on pressure ulcers and another on refractory venous ulcers. These studies similarly shown a rise in the number of cured wounds in the adjuvant TOT group. These findings provide further evidence for the generally known hypothesis that oxygen is crucial for the healing of different types of wounds. The application of topical oxygen on wounds was shown to increase tissue oxygen concentration from 21% ($pO_2 = 159$ mmHg) to 100% ($pO_2 = 760$ mmHg), which is considered optimal for various important biochemical pathways involved in the wound healing process in experimental studies.[35] A high level of oxygen pressure is necessary during the inflammatory phase of wound healing to enhance the process of bacterial elimination through phagocytosis. The neutrophil's membrane engulfs the pathogen and creates superoxide, which combine with oxygen molecules to create ROS. These ROS are essential for the bactericidal process.[36,37] Interestingly, both hypoxia and ROS have the paradoxical effect of promoting angiogenesis. The presence of low oxygen levels in wounds will trigger the activation of the transcription factor known as hypoxia-inducible factor (HIF)-1a. This, in turn, will increase the production of vascular endothelial growth factor (VEGF), initiating the process of angiogenesis.[38,39] The production of the extracellular matrix (ECM) and the process of angiogenesis are closely linked, leading to the expansion of new capillaries that invade and occupy the surrounding matrix. Fibroblasts subsequently synthesize and secrete fresh ECM to substitute the aged matrix.[40,41]

8.2 | Wound area

All RCT studies showed substantial reductions in wound area. This finding was similarly illustrated in a prior meta-analysis that specifically focused on the population with DFU.[32] A separate investigation conducted by Aniruddh et al.[42] demonstrated a noteworthy decrease in the size of ulcers in the group that received the intervention, as compared to the control group. At the conclusion of the 6th week, there was a significant reduction in the average size of ulcers in the intervention group. The measurement, done on a logarithmic scale, decreased from 2.72 (baseline) to 1.54 ($p = 0.019$). This indicates that TOT is beneficial in encouraging the healing of ulcers compared to standard care. Unfortunately, we had to omit this study from our calculations since the measurement units used (log area vs. % of wound area decrease) were not consistent.[42]

The reduction in wound area is dependent upon the complex and delicate equilibrium of the hypoxic gradient extending from the edge to the core of the wound. The initial lack of oxygen in the centre of the wound stimulates the formation of new blood vessels (angiogenesis). The level of oxygen is essential for the proliferation of tissue fibroblasts and the production of collagen. Chronic hypoxia, as seen in a wound with compromised blood flow, hinders the necessary processes for the development of new tissues. This inhibition prevents the formation of new blood vessels and reduces collagen content by excessively increasing the production of collagenase-1 (MMP-1) in fibroblasts. Consequently, wound healing is further delayed.[43–45] MMP-1 is often expressed exclusively in the early stages of keratinocyte re-epithelialization. This expression aids in the movement of keratinocytes through collagen by breaking it down into gelatine.[45]

8.2.1 | Wound healing time

There was no significant difference in the average time required for complete healing of the wounds. One study[23] found substantial disparities in healing time ($p < 0.001$), with the TOT group showing better results. However, another study[24] did not see any significant difference in the time it took for wounds to close ($p = 0.350$). The observed outcome may be attributed to significant variation within the dataset, potentially impacted by the initial size of the wound. While the absolute area healed per day may overstate bigger wound healing rates, the wound healing rate presented as a percentage of the initial area repaired per day may overstate smaller wound healing rates. To summarize, the rate at which a wound heals, which refers to the movement of the wound edge into the centre of the wound, is not affected by the initial size of the wound.[46]

8.2.2 | Pain level

The pain level analysis conducted in our study, which assessed 145 individuals with DFU, revealed no statistically significant decrease compared to the initial measurements. Our hypothesis was that factors such as phantom limb pain (PLP) and preexisting neuropathy play a role in this study. Tang et al.[47] conducted an uncontrolled study with 20 participants and observed a significant decrease in VAS scores. The scores went from 2.4 (±1.8) at the beginning to 0.5 (±1.0) after 3 months of TOT treatment ($p = 0.008$). A significant distinction is in Tang's research population, where 60% of the individuals had non-healing minor amputation surgery wounds.[47] Research has indicated that around 80% of those who have undergone amputation of the lower leg will have PLP, which refers to the sensation of pain coming from a body part that is no longer present. Phantom limb pain often reaches its highest intensity at two distinct periods following amputation: 1 month and 1 year after the procedure. Subsequently, the pain gradually diminishes over time. Importantly, the presence of preexisting neuropathy does not influence the form of PLP. However, it is worth noting that neuropathy is expected to occur in 26% of diabetics after 5 years and in 41% after 10 years. In our study, the average duration of diabetes was 18.33 years for the conventional care group and 18.35 years for the TOT group. However, this difference did not lead to a substantial reduction in pain levels.[37,48–53]

Recent studies have demonstrated that topical oxygen therapy is a beneficial addition to routine wound care. Out of the eight studies included in this review, one study conducted by He et al.[23] focused on the use of CDO as the primary treatment without combining it with moist wound dressing. However, we did not include this study in our data analysis. The outcome following 8 weeks of TOT alone exhibited greater resemblance to the SC group rather than the TOT combo group.[23] The suggested hypothesis was that the layer of exudate covering the wound could hinder the supply of oxygen to the wound bed. This is because topical oxygen can only permeate via a maximum distance of 50–100 μm.[54] The latest CDO, oxygen diffusion dressing (ODD), allows for the use of TOT as the primary and only treatment, since it eliminates the need for separate dressing changes by connecting an oxygen tube to the absorbent wound dressing.[35] As a point of consideration, it is worth contemplating the concept of a TOT device that utilizes intermittent negative pressure to remove exudate. Similarly, TOT should be approached with the same level of care as moist wound therapy. Research has shown that better results are achieved when the wound is free from non-viable tissues, which obstruct the direct entry of oxygen into the wound site.[54] When applying TOT, it is important to avoid using occlusive dressings, such as petrolatum-based salves.[35]

8.2.3 | Strengths and limitations

The main strength of our study is the inclusion of a more recent study by He et al.[23] which has not been analysed in previous reviews and meta-analysis. Furthermore, despite the small number, we included two observational studies in our analysis. We are aware that the relatively small number of total samples ($n = 803$) could lead to the lack of generality of our results.

Our investigation further found variations in the definition of the control (standard care, SC) across studies, ranging from conventional approaches such as saline-soaked gauze to contemporary approaches involving hydro fibre or hydrogel dressings. Nevertheless, given their adherence to the overarching principle of moist wound care, we contend that these various modalities do not pose a substantive issue.

Furthermore, there is also a lack of similar parameters measured and various lengths of the study, which might affect the accuracy of our analysis as different study implements different parameters and those parameters do not equally represent the intended endpoints. Therefore, we can only analyse one primary outcome (number of healed wounds), the main parameter found across all studies. Other parameters such as wound area decrease and wound healing time are found only in

several studies, therefore we included those as the secondary outcome.

We also encountered an issue regarding the diversity in TOT devices, encompassing variations in device types, such as cyclical or constant models, as well as discrepancies in oxygen flow rates and the pressurization status. It is certainly preferable if we can obtain data on how different types of devices affect wound healing. However, with current conditions, there is still not enough data to conduct a meta-analysis for each type of TOT device.

Moreover, we found a lack of RCT research regarding TOT for various types of wounds such as acute or burn wounds, and whether it is effective in aiding those types of wounds. The application of TOT for cancer wounds also warrants further research as previously contraindicated treatment such as negative pressure wound therapy (NPWT) has been shifting in favour due to its benefits.[55] For this study, we have inquired about the pricing of each TOT device, but alas there is either no response from the respective company or there is still no established price as policies and government subsidies differ from each region or country.

9 | CONCLUSION

The use of TOT is established as a great adjuvant therapy for chronic nonhealing wounds, particularly wounds with vascular compromise such as diabetic ulcers and pressure ulcers. The lack of standard protocol regarding parameters like duration, oxygen flow, and pressure in TOT devices presents a significant challenge in its widespread adoption and effectiveness. Moving forward, it is crucial for the medical community to collaborate on establishing evidence-based protocols to optimize TOT efficacy while ensuring safety. This involves conducting rigorous research to determine optimal settings tailored to different conditions and patient needs, ultimately paving the way for more consistent and reliable application of TOT in clinical practice.

AUTHOR CONTRIBUTIONS

Indri Lakhsmi Putri: Conceptualization; formal analysis; methodology; supervision; validation; writing – review and editing. **Agnesia Alyssa:** Data curation; investigation; software; writing – original draft. **Imaniar Fitri Aisyah:** Project administration; resources; visualization; writing – original draft. **Rachmaniar Pramanasari:** Formal analysis; investigation; supervision; writing – review and editing. **Citrawati Dyah Kencono Wungu:** Formal analysis; methodology; software; supervision; writing – review and editing.

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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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