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Systematic review of the effects of topical oxygen therapy on wound healing

Khanjan Nagarsheth, MD[a], **Aman Kankaria, BS**[a], **Justin Marsella, BA**[a], **Eleanor Dunlap, CRNP**[a], **Shannon Hawkins, RN**[a], **Areck Ucuzian, MD, PhD**[a,b], **Brajesh K. Lal, MD**[a,b]

[a]Division of Vascular Surgery, University of Maryland School of Medicine

[b]Vascular Service, VA Maryland Health Care System

Abstract

Background: Various adjunct therapies are available for wound healing in addition to standard care. Topical oxygen therapy (TCOT) is one such novel therapy. We conducted a systematic review and meta-analysis to evaluate the role of TCOT in the healing of cutaneous wounds of any etiology.

Methods: The review was conducted on articles related to wounds treated with TCOT identified through PubMed, MEDLINE/OVID, Cochrane, and Google Scholar. We included randomized controlled trials, double-arm prospective studies, single-arm prospective studies, case-control series, and case reports published on or after 2012. Only articles addressing TCOT were included; other forms of oxygen delivery were excluded. We aimed to evaluate the proportion of wounds completely healed, the percent decrease in wound area of those not completely healed, the recurrence of wounds after treatment, and effects on pain and ulcer rating scales.

Results: A total of 22 articles were included in this review. The results showed that TCOT has a significant salutary effect on complete wound healing in case-control studies (odds ratio, 4.48; 95% confidence interval, 2.05-9.77; $P < .001$; $I^2 = 76.34\%$) and in single-arm studies (pooled prevalence, 0.48 [48.0%]; 95% confidence interval, 0.34-0.62; $P < .001$; $I^2 = 86.58$). However, no significant effect was observed for percent wound reduction, the difference in ulcer grade scores,

Correspondence: Brajesh K. Lal, MD, University of Maryland School of Medicine, Vascular Surgery, 22 South Greene St, S10-B00, Baltimore, MD 21201 (blal@som.umaryland.edu).

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or the difference in pain scores. Most of the included studies had a high risk of bias because they were not blinded, were single-arm studies, or were case reports.

Conclusions: Our findings indicate that TCOT can have a positive effect on wound healing when compared with standard care. However, owing to the lack of randomized, controlled trials or studies with comparable end points, a definitive conclusion on the full impact of TCOT on wound healing cannot be reached. More high-quality data are needed to definitively determine the effects of TCOT on wound healing, preferably from a comprehensive, randomized controlled trial.

Keywords

Transcutaneous oxygen therapy; Topical oxygen therapy; Wound healing; Chronic wounds

Patients can suffer delayed or impaired wound healing owing to the location of a wound, local tissue ischemia, infection, or systemic comorbidities. The process of wound healing requires many biological systems working in conjunction.[1] Several cell types must be activated and mobilized to initiate angiogenesis, smooth muscle cell and keratinocyte migration, and the creation of tissue extracellular matrix. Cytokines and growth factors must be generated to orchestrate this process. The metabolic activities of the cells responsible for wound healing require an abundance of oxygen. Although a certain degree of hypoxia can serve to initiate wound repair, chronic ischemia of wound beds inhibits wound healing.[2] In addition, underlying systemic comorbidities that often accompany arterial occlusive disease can increase the risk of developing a surgical site infection, which further worsens wound healing.[2]

Currently, standard wound care includes ensuring the wound is dressed, cleaned regularly, and debrided if needed.[3] Multiple adjunct treatments have been coupled with the standard of care to aid wound healing. One such approach involves the delivery of supplemental oxygen to the wound. The original means of oxygen delivery involved hyperbaric oxygen therapy (HBOT) and ozone therapy.[4] However, in response to logistical challenges, economic concerns, and potential systemic adverse effects associated with HBOT or ozone therapy, an alternative approach has been proposed that involves delivering oxygen directly to the wound site such as topical oxygen therapy (TCOT).[5,6] Recent studies have reported on the topical delivery of oxygen as a means of improving wound healing as an adjunct therapy for chronic wounds. These studies have addressed diabetic foot ulcers, pressure ulcers, and ulcers secondary to vascular disease.

We conducted a systematic review and meta-analysis of literature pertaining to TCOT to assess its effects on healing cutaneous wounds secondary to any etiology. We aimed to look at the proportion of wounds healed completely, the percent reduction in area of wounds, not healed completely, the recurrence of wounds after treatment, and effects on pain and ulcer rating scales.

METHODS

This systematic review and meta-analysis was performed using the PRISMA methodology.[7]

Eligibility criteria.

All articles pertaining to cutaneous wounds that were treated with TCOT were searched for. The oxygen therapy could have been applied intermittently over limited time periods or continuously. Only studies on humans were included. Randomized controlled trials, double-arm prospective studies, single-arm prospective studies, and case reports were included. Articles without full text, opinion pieces, editorials, systematic reviews, and meta-analyses were excluded. Articles published before 2012 were also excluded, because they pertained to HBOT only. Finally, articles related to animal experiments, HBOT, or ozone therapy were excluded. There are multiple devices that provide TCOT delivery, and studies related to all available devices were included. These devices include EPIFLO Transdermal Continuous Oxygen Therapy (Ogenix, Beachwood, OHH), Topical Wound Oxygen (TWO2) Therapy (Advanced Oxygen Therapy Inc., Oceanside, CA), NATROX Oxygen Wound Therapy (Inotec AMD Inc., Hickory, NC), OxyGeni (EO2, San Antonio, TX), REZair (RashEndZ Inc., St. Petersburg, FL), and O2Boot, O2Sacral, and O2Sleeve (GWR Medical Inc., Chadds Ford, PA). Each of these devices extracts oxygen from room air and topically delivers oxygen-enriched air to the wound. The key differentiator among these devices was their varying flow rates. Notably, studies on these TCOT devices consistently reported that a flow rate of 3 mL/h proved as effective in oxygen delivery as a higher rate of 15 mL/h.

Information sources, search strategy, and selection process.

The search was performed using PubMed, MEDLINE/OVID, Cochrane, and Google Scholar search engines. The following MESH terms were used: Transcutaneous Oxygen Therapy AND Wounds, Transdermal Oxygen Therapy AND Wounds or Cutaneous Wounds, Topical Oxygen Therapy AND Wounds, and Oxygen Therapy AND Wounds. Fig 1 summarizes the screening processes used to assess the eligibility of articles and to arrive at a collection of articles included for review.[8–30] Two reviewers independently searched for articles and pooled their findings. Both reviewers evaluated each article included in the study. The reviewers concluded that 22 articles were eligible for the study.

Data collection and extraction.

The following information was collected on patients: gender, average age, wound classification, and types of wounds assessed. Information on the oxygen delivery device and study sponsor information was collected where available. Study design, oxygen treatment regimen, and any adverse events were also recorded. The following post-treatment outcomes were extracted and recorded: proportion of wounds completely healed, mean and standard deviation (SD) of percentage of wound area reduction, changes in the pressure ulcer scale for healing (PUSH) score,[31] changes in the visual analog pain scale (VAPS),[32] and recurrence rate of ulcers after treatment. After thoroughly discussing the key outcomes to prioritize, one reviewer manually collected data from all 22 articles. A second reviewer then assessed the first reviewer's efforts and grouped the data into comparable groups for analysis.

Data risk bias analysis.

Risk analysis was conducted for all eligible articles. If the study was a randomized clinical trial, the Cochrane Risk of Bias tool for randomized trials was used to assess bias. Five domains were assessed with this tool. The domains include the risk of bias arising from the randomization process, deviations from the intended interventions, missing outcome data, measurement of outcomes, and selection of the reported results.[33] When analyzing a nonrandomized study (eg, case-control, case series, or case report), the Cochrane Risk of Bias in Non-Randomized Studies of Interventions tool was used to assess risk in seven domains. The domains assessed included biases regarding confounding variables, selections of participants, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, and selection of reported results.[34] To ensure consistency, one reviewer independently assessed the risk bias for all articles.

Meta-analytical methods.

Twenty-two articles were deemed eligible and were used to perform a meta-analysis to assess the efficacy of TCOT on wound healing. A continuous random-effects model (DerSimonian-Laird) was used for all analyses.[35] After analysis, heterogenicity was assessed as the I^2 statistic (percentage of variation across studies that is due to heterogeneity rather than chance). The random effects model was deemed to be significant if the I^2 was >25%. If the heterogeneity was <25%, a binary fixed-effect inverse variance model was used.[36] Regarding end point analyses for single-arm studies, proportion analysis, and treatment mean were calculated. The end point analysis reported for double-arm studies were odds ratios (OR) and standardized mean difference (SMD). If a SD was not listed in the double-arm studies results, Hedge's g statistics were used to calculate SMDs between the control and treatment groups. The software OpenMeta [analyst] was used to conduct the data analysis (Brown University, Providence RI).[37]

RESULTS

Ten randomized controlled trials and 12 nonrandomized studies (prospective double-arm and single-arm studies, and case reports) were included in the analysis (Supplementary Table, online only). The wounds that were treated in these articles ranged from diabetic foot ulcers, pressure ulcers, ulcers secondary to vascular etiology, ulcers secondary to sickle cell disease, and ulcers secondary to infected surgical wounds. The study duration of the included articles ranged from 10 days to 3 months. A variety of methods were used to classify the wounds. The most common scales used were the Wagner grade or the University of Texas classification. Our co-primary end points were (1) the proportion of wounds completely healed after TCOT in double- and single-arm studies, and (2) the SMD of wound reduction after TCOT in double- and single-arm studies. Our secondary end points were the effect of TCOT on PUSH scores, VAPS scores, and ulcer recurrence after treatment.

Primary outcomes

The proportion of wounds completely healed in double-arm studies.—Seven double-arm studies reported proportions of wounds completely healed. A total of 725 participants were included in this analysis (control n = 356 and treatment n = 369).

Complete healing was significantly different after treatment with TCOT vs control (standard of care) therapy (OR, 4.48; 95% confidence interval [CI], 2.05-9.77; $P < .001$; $I^2 = 76.34\%$) (Fig 2, A).

The proportion of wounds completely healed in single-arm studies.—Nine single-arm studies were included in the analysis of wounds completely healed. A total of 4273 participants were included in this analysis, with 1195 participants reported to have completely healed their wounds after TCOT. A significantly higher proportion of wounds were completely healed after TCOT vs standard of care (pooled prevalence, 0.48 [48.0%]; 95% CI, 0.34-0.62; $P < .001$; $I^2 = 84.11\%$). In addition, several studies reported that ulcers were on the trajectory to healing, but did not fully heal when the end points were being assessed (Fig 2, B). Because the measurement of the trajectory was not consistent across articles, we did not perform a quantitative analysis of this observation. A secondary analysis was performed to assess the quality of the data. Removal of both case series did not change the results regarding the proportion of wounds healed for the single-arm studies (the proportion of wounds healed was significantly higher in those treated with TCOT; $P < .0001$). The heterogenicity remained the same for the forest plot and the CI did not change substantially either.

Mean and SD of wound reduction in double-arm studies.—Six studies reported the mean and SD for wound reduction after treatment with TCOT. The SMD between the treatment (n = 226) and control arms (n = 236) was calculated. The SMD was not significantly different between treatment and control groups regarding wound reduction (SMD, −0.85; 95% CI, −1.88 to 0.18; $P = .12$; $I^2 = 95.93\%$). (Fig 2, C).

Mean and SD of wound reduction in single-arm studies.—Two single-arm studies reported mean and SD for wound reduction after TCOT. A total of 29 participants were included in this analysis. The results suggested wound reduction after TCOT (treatment mean, 1.54; 95% CI, 0.71-2.38). However, heterogeneity was <25% ($I^2 = 0$) and, therefore, of no statistical significance, even when a continuous fixed effect model was used to perform the analysis ($P = .33$) (Fig 2, D).

Secondary outcomes

SMD of PUSH scores in double-arm studies.—Two studies reported results for total PUSH score to assess wound healing after treatment. There was no significant difference in the SMD between treatment (n = 79) and control (n = 74) arms (SMD, 0.65; 95% CI, −0.56 to 1.86; $P = .29$; $I^2 = 92.38\%$) (Fig 3, A).

SMD in the VAPS in double-arm studies.—Three articles used the VAPS to assess their pain rating in controls vs TCOT. There was no significant difference in the SMD of VAPS scores between treatment (n = 163) and control (n = 151) arms (SMD, −0.17; 95% CI, −0.92 to 0.59; $P = .67$; $I^2 = 90.88\%$). Additional articles reported pain using metrics other than the standardized VAPS. These studies were not included in this analysis because they were not comparable with VAPS (Fig 3, B).

OR for ulcer recurrence in double-arm studies.—Two double-arm studies reported data on ulcer recurrence after complete wound healing had occurred. A total of 101 patients were included in this analysis (treatment n = 66, control n = 35). There was a significant reduction in ulcer recurrence rates in patients receiving TCOT treatment vs controls (OR, 0.08; 95% CI, 0.02-0.26; $P < .001$; $I^2 = 45.99\%$) (Fig 3, C).

Risk bias assessment

An assessment of the 10 randomized trials included in our analysis found that five showed a low risk of bias, four showed some risk, and one showed a high risk of bias (Table I). An evaluation of the 12 nonrandomized trials included in the analysis found that nine studies had some risk of bias, and three had a high risk of bias (Table II). Overall, 17 articles displayed some degree of risk of bias. This result can be attributed to the fact that more articles published on this topic were either case-control series or observational studies compared with randomized trials.

Adverse effects

Most of the studies did not report adverse effects or serious adverse effects of oxygen delivery devices. Studies that did list adverse effects were focused primarily on complications associated with a chronic wound (eg, infection, fever, cellulitis) rather than complications related specifically to TCOT. Our analysis, therefore, could not include an objective assessment of the presence, or rate, of TCOT-related adverse events. A search of the Manufacturer and User Facility Device Experience[40] database did not identify any reported device malfunctions or adverse events. There are few currently reported serious or adverse events associated with TCOT. Although the studies did not collect this information systematically, it still suggests that TCOT might be a safer alternative to systemic oxygen therapy for localized wounds.

Ongoing studies

We searched clinicaltrials.gov to identify ongoing studies to determine the quality, quantity, and timeline of additional data that may be available in the future to help improve the reliability with which the effect of TCOT on wound healing could be determined. We found ongoing randomized controlled trials assessing the impact of TCOT on vascular incisional wound healing (NCT03746132), prevention of tissue necrosis after breast reconstruction (NCT04307355), prevention of breakdown of general surgical incisions (NCT03960463), and healing of diabetic foot ulcers (NCT04709419). The studies anticipate reporting results in the coming years.

DISCUSSION

TCOT is a relatively novel approach to delivering oxygen to local tissues in need of healing. Currently, it is being used and studied in a clinical setting to assess whether TCOT, coupled with traditional wound therapy, provides any improvement in healing chronic wounds. Our systematic review and meta-analysis identified only 10 randomized trials, 4 nonrandomized double-armed studies, and 8 single-armed observational studies evaluating this approach. The studies included in the review enrolled patients with wounds

involving the superficial and subcutaneous tissues from a variety of causes such as venous hypertension, diabetes, pressure, sickle cell disease, and after surgery. Our analysis of both randomized and nonrandomized double-armed studies found that TCOT was associated with a significantly higher rate of complete wound healing compared with standard wound care approaches. Although nonrandomized double-armed studies found a higher percentage of wounds covered with TCOT compared with standard wound care, single-arm studies did not confirm this finding. With respect to our secondary outcomes, non-randomized double-armed studies found that ulcer recurrence was decreased after TCOT, although we did not find a difference in VAPS or PUSH. These findings are encouraging and consistent with our current understanding of the high oxygen demand during the process of wound healing. However, collectively, the studies do not provide definitive and reliable proof of efficacy. TCOT was introduced relatively recently, and we found that there are insufficient high-quality, unbiased data on which to base reliable conclusions. There is a need for well-controlled prospective randomized trials to confirm the safety and efficacy of TCOT.

Our primary outcome assessed two measures—complete wound healing and percent wound reduction—with the use of TCOT. We found that TCOT resulted in a higher odds of complete wound healing compared with standard care. Our analysis included studies of venous ulcers, diabetic foot ulcers, and pressure ulcers. Six of the studies were randomized trials, and one was a nonrandomized double-armed study. A meta-analysis conducted previously had studied the effects of TCOT on diabetic foot ulcers alone.[41] This study included four randomized trials. The outcome evaluated was complete wound healing over a 12-week period. In that report, three of the four studies showed improved healing with TCOT compared with controls.[41] Our analysis included these four studies in addition to three more RCTs related to pressure ulcers and venous ulcers.[9,14,18] The follow-up in our studies ranged from 12 days through 12 weeks. We found that, regardless of the type of ulcer being treated, there was an improvement in complete wound healing rates with TCOT. With respect to percent wound reduction, our results were similar to findings published in another systematic review studying the effects of TCOT on diabetic foot ulcers, which reported that TCOT improved the percent wound reduction achieved compared with standard of care.[42] For this end point, Sun et al.[42] included three randomized controlled trials, whereas our analysis included six randomized controlled trials. They did not restrict their analysis based on treatment duration; each article they included had a different follow-up time period.

Regarding our secondary outcomes of the assessment of PUSH scores, VAPS scores, and ulcer recurrence, there were few data published in previous meta-analyses conducted on TCOT. Ulcer recurrence has not been reported in most (n = 2) studies evaluating TCOT. Sun et al.[42] indicated that the TCOT group had a lower incidence of wound recurrence compared with controls in the seven studies they reviewed. With respect to PUSH and VAPS scores, many of the reported articles in the included analysis failed to use these assessments as end points or used different nonstandardized scoring systems.

We found that the risk of bias in the available studies was higher compared with previously published meta-analyses. Our approach was to include all available studies that have covered our target therapeutic approach (TCOT) and reported on our target outcomes (primary and secondary), using all possible study designs (double armed [randomized

and nonrandomized], as well as single-armed studies). We believe that this offers a more comprehensive and impartial impression of the type and level of evidence available. Other meta-analyses only included randomized controlled trials or double-arm studies, thereby falsely reducing their report on the risk of bias of published studies, and excluded single-arm studies or case reports that may have suggested a different outcome.[41–43] We took this broad approach to produce a comprehensive systematic review and meta-analysis on TCOT, assessing its effects on wounds secondary to any etiology.

Other oxygen delivery approaches are being used coupled with standard-of-care treatments to promote wound healing. These include HBOT and ozone therapy. HBOT is another method that has been implemented to treat chronic, nonhealing wounds. This approach aims to enhance tissue oxygenation by increasing the partial pressure of oxygen. By meeting the body's energy demands, it contributes to wound healing, reduces infections, and enhances the overall success of the healing process.[42] Multiple meta-analyses have been conducted regarding HBOT. One meta-analysis reported that the effects of HBOT have shown improved healing rates and decreased healing times for wounds.[44] Another meta-analysis found that this treatment method was significantly effective in completely healing DFUs and reducing major amputation rates. However, it did not show effectiveness in minor amputations. It is noteworthy that the standard treatment group experienced fewer adverse events.[45] Although HBOT has the potential to benefit wound healing, it is associated with higher equipment and delivery costs, a lack of portability, and known systemic complications.[6] One meta-analysis specifically analyzed the adverse effects of HBOT when administered. The results indicated that the incidence of adverse effects was significantly higher in the HBOT group compared with the control group. Subgroup analyses revealed that the significant effects were ear discomfort and ocular issues. Sinus pain, claustrophobia, chest pain, headaches, and fatigue were also mentioned, but they were not considered significant. These results leads to the conclusion that most effects were mild and self-limiting.[46]

In comparison, TCOT is less expensive and is a smaller, portable device that patients can carry on their person without impacting their daily activities. If proven to be effective therapeutically, these features will make it a promising alternative for wound therapy in the future. Ozone therapy is another alternative for oxygen delivery that has been studied for wound healing. The methodology behind this treatment is that eliciting mild oxidative stress or disinfection can help to treat patients suffering from chronic wounds.[47] It can be administered through various delivery methods, including gaseous exposure within a hyperbaric chamber, application of ozonated oils, or immersing wounds in ozonated water.[47] In a systematic review, Fitzpatrick et al.[47] evaluated various databases for randomized human trials using ozone therapy in the topical treatment of chronic wounds. A total of nine studies were included in this meta-analysis and revealed a significant improvement in wound closure for patients who underwent ozone therapy. However, owing to the significant limitations of the study, the authors could not definitively state that ozone therapy is superior to the normal standard of care procedures, suggesting that ozone therapy may improve the proportion of chronic wounds healed quickly, but further research is required.[47]

To the best of our knowledge, this systematic review and meta-analysis is the most up-to-date to examine the effects of TCOT on wound healing. We have compiled information from investigations using a broad variety of study designs, including randomized controlled trials, case-control studies, case reports, and case series. We provide a comprehensive assessment of TCOT by evaluating its impact on a broad variety of wounds. Our analysis, therefore, tests the hypothesis that TCOT has a beneficial effect on cellular metabolism which improves all underlying wound-healing pathways. Despite these strengths, several limitations should be considered. Currently, there are not enough studies focused on specific subtypes of wounds. Therefore, if TCOT has differential effects on specific subtypes of wounds, we do not have a sufficient quantity or quality of studies to discern those differences. Despite this constraint, it is important to recognize that the ultimate biological pathway to wound healing remains consistent. Existing studies have used a variety of study designs and recorded a large variety of outcomes; therefore, finding comparable end points throughout the included articles was challenging. Our analysis could not establish a standard healing time window; the available published studies have used different time ranges to end their study. They have, thus, reported total healing times ranging from a 10-day to a 3-month timeline. Finally, few studies reported secondary outcomes such as pain reduction, ulcer recurrence, and infection rates. Those that did report those secondary outcomes, did not commonly use standardized means of scoring them. This prevented us from objectively analyzing such qualitative data. PUSH and VAP scores were only available in two and three studies, respectively. This factor limits the reliability of any conclusions and highlights the need for standardization of assessment and reporting of these important outcome measures. Currently, several randomized trials are testing the impact of TCOT. One such trial is underway to assess the effect of TCOT on vascular incisional wound healing (NCT03746132). The hypothesis is that the TCOT to the surgical site for up to 28 days will decrease the rate of incisional breakdown and infection when compared with standard of care.

CONCLUSIONS

This meta-analysis shows that TCOT may improve rates of complete wound healing and percent wound reduction across a broad variety of wounds. Complete wound healing was improved significantly with TCOT in both double-arm and single-arm studies. Multiple study designs with a high level of bias and limited information on individual wound subtypes preclude reliable and conclusive therapeutic evidence for any one specific wound type. The studies provide limited reliable evidence on the impact of TCOT on secondary outcomes, such as infection rates, pain after treatment, and ulcer recurrence, although the few studies that report on these outcomes suggest a beneficial effect of TCOT. Therefore, TCOT should continue to be studied, preferably with randomized control trials, and be considered for integration into daily practice for therapy in recalcitrant wounds that have failed standard care.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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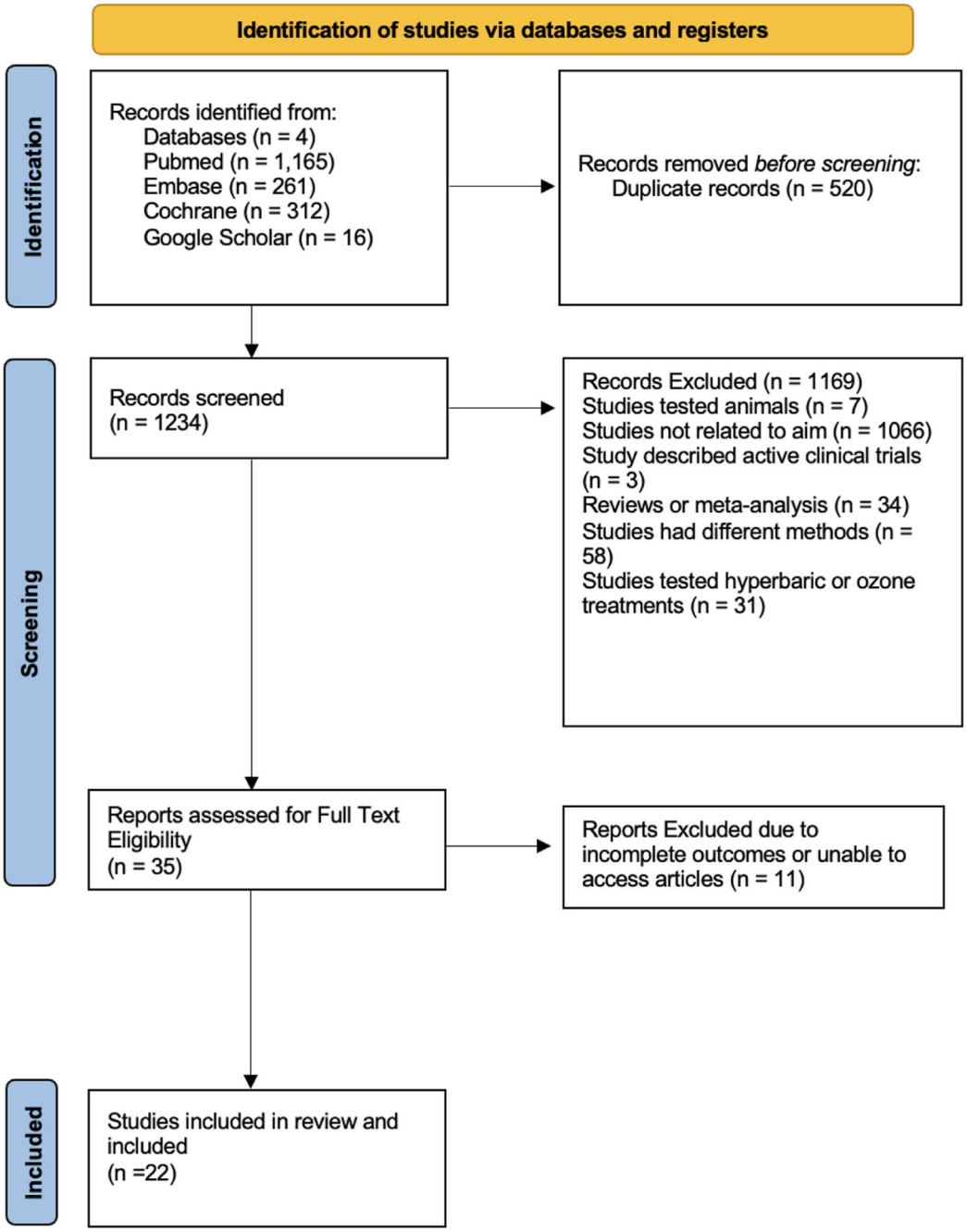

Fig 1.

PRISMA flow diagram for assessment of eligible articles regarding transcutaneous oxygen therapy for wound healing.

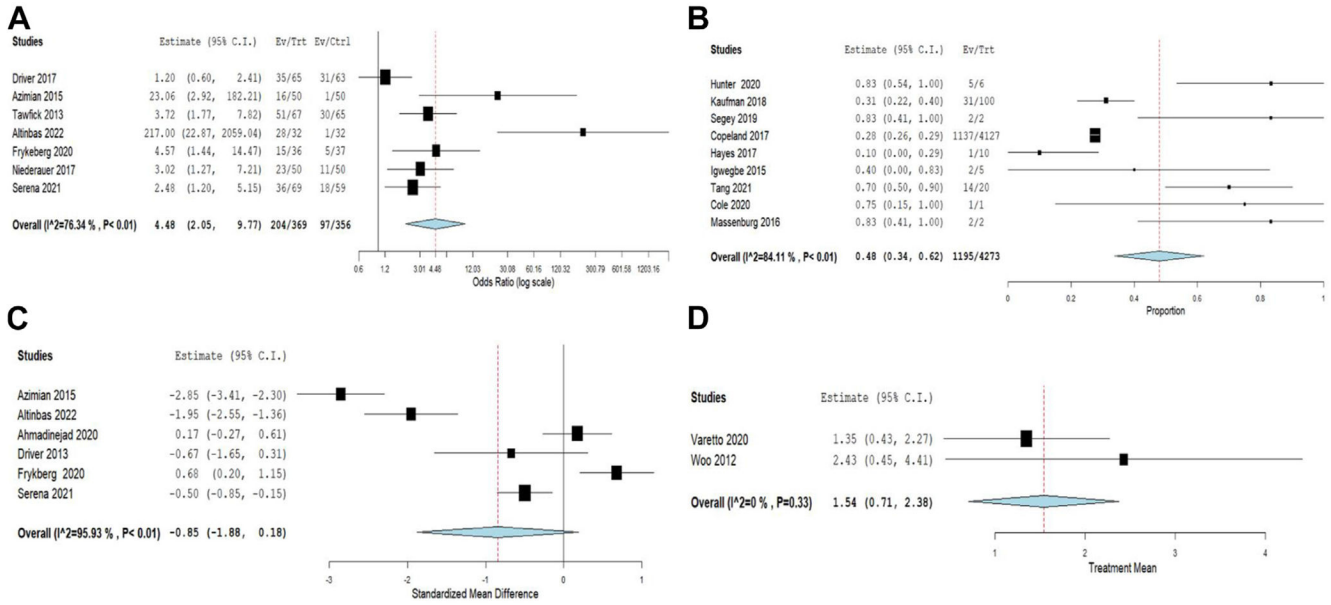

Fig 2.

Forest plots for studies related to wound healing with transcutaneous oxygen therapy (*TCOT*). (**A**) Proportion of wounds completely healed in double-arm studies.). (**B**) Proportion of wounds completely healed in single-arm studies. The *x* axis in both graphs shows the odds of having a wound healing completely. (**C**) The standardized mean difference (SMD) of wound reduction in double-arm studies. The *x* axis in this graph shows the SMD of wound reduction. (**D**) The treatment means in wound reduction in single-arm studies. The *x* axis in this graph shows the mean reduction of wounds after TCOT. *CI*, confidence interval; *Ctrl*, control group; *Ev*, events or completely healed wounds; I^2, percentage of variation across studies that is due to heterogeneity rather than chance; *Trt*, treatment group.

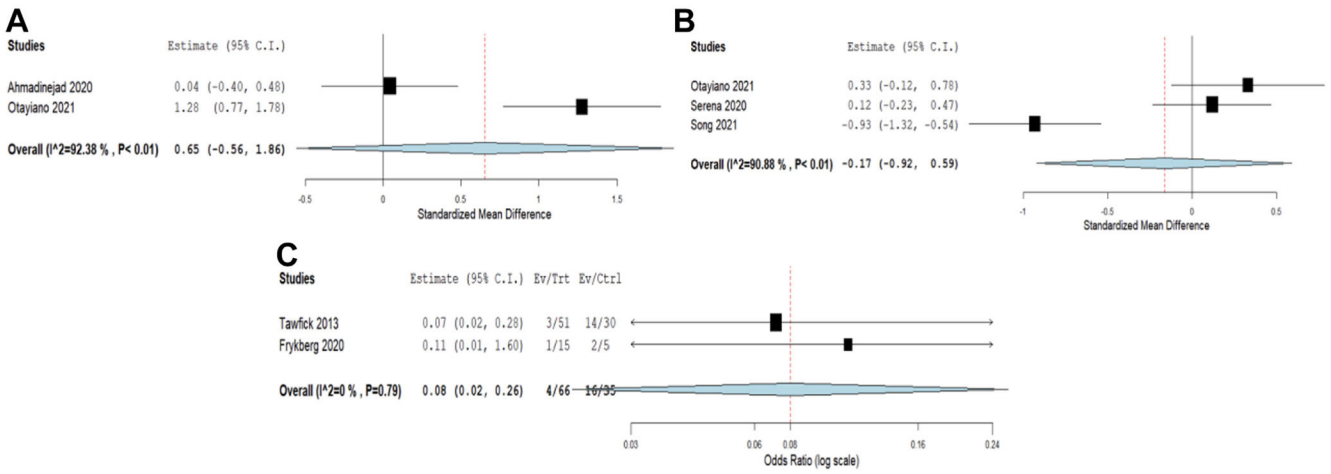

Fig 3.

Forest plots for the studies related to secondary outcomes associated with transcutaneous oxygen therapy (*TCOT*). (**A**) Standardized mean difference (*SMD*) between pressure ulcer scale for healing (*PUSH*) scores in double-arm studies. (**B**) SMD between the visual analog pain scale (*VAPS*) in double-arm studies. The *x* axis in both graphs shows the difference of means for their respective assessments. (**C**) The proportion of recurrence of ulcers in double-arm studies. The *x* axis shows the odds of a recurrence ulcer between treatment and control groups. *CI*, confidence interval; *Ctrl*, control group; *Ev*, events or completely healed wounds; I^2, percentage of variation across studies that is due to heterogeneity rather than chance; *Trt*, treatment group.

Table I.

Risk assessment for randomized control trials using the Cochrane risk-of-bias tool for randomized trials (RoB 2)

	Domains evaluated				
Article	**Randomization process**	**Deviation from intended intervention**	**Deviations from missing outcome data**	**Data measurement techniques**	**Selection of reported results**
Driver et al[8]	Low	Low	Low	Low	Low
Azimian et al[9]	Low	Low	Low	Low	Low
Driver et al[11]	Low	Some	Low	Low	Low
Altinbas et al[18]	Low	Low	Low	Low	Low
Ahmadinejad et al[19]	Some	Some	Low	Low	Low
Song et al[21]	Low	Some	Low	Low	Low
Otaviano et al[22]	Low	Some	Low	Low	Low
Serena et al[23]	Low	Some	Low	Low	Low
Frykaberg et al[25]	Low	Low	Low	Low	Low
Niederauer et al[38]	Some	Low	Low	Low	Low

Table II.

Risk assessment for nonrandomized trials using the Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-I)

	Domains evaluated						
Article	**Confounding variables**	**Selection of included participants**	**Classification of interventions**	**Deviation from intended interventions**	**Potential missing data**	**Measurement of outcomes**	**Selection of reported results**
Varetto et al[10]	Moderate	Low	Low	Low	Low	Low	Low
Massenburg et al[12]	Moderate	Low	Low	Low	Low	Low	Low
Hunter et al[13]	Moderate	Low	Low	Low	Low	Low	Low
Tawfick et al[14]	Moderate	Low	Low	Low	Low	Low	Low
Kaufman et al[15]	Moderate	Moderate	Low	Low	Low	Low	Low
Hayes et al[39]	Moderate	Moderate	Low	Low	Low	Low	Low
Woo et al[16]	Moderate	Moderate	Low	Low	Low	Low	Low
Igwegbe et al[17]	Serious	Serious	Moderate	Low	Low	Moderate	Moderate
Tang et al[20]	Moderate	Moderate	Low	Low	Low	Low	Low
Segev et al[24]	Serious	Serious	Moderate	Low	Low	Low	Moderate
Copeland et al[27]	Moderate	Low	Low	Low	Low	Low	Low
Cole et al[30]	Moderate	Serious	Low	Low	Low	N/A	Low

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