

Topical oxygen therapy for treating diabetic foot ulcers: a WHAM evidence summary

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CLINICAL QUESTION

What is the best available evidence for topical oxygen therapy for treating diabetic foot ulcers (DFUs)?

SUMMARY

Topical oxygen therapy is an adjunctive therapy that seeks to improve cell proliferation in chronic wounds by delivering high concentration oxygen directly to the wound bed. Oxygen application can be via a mechanical system that delivers gaseous oxygen to the wound bed (carrier systems) or can be via topical applications (e.g., oxygen generating/releasing dressings or haemoglobin spray) that directly or indirectly increase oxygen in the wound bed. *Level 1* evidence consisting of five meta-analyses¹⁻⁵ on the effectiveness of mechanically delivered topical oxygen therapy demonstrated that the treatment is associated with statistically significant improvements in complete healing at 12 weeks²⁻⁵, and in the number of DFUs healed at 8–12 weeks¹. These findings are supported by a narrative systematic review⁶, although a seventh, narrative review⁷ concluded that the evidence was inadequate to make recommendations. There is evidence that topical oxygen therapy delivered via mechanical systems is associated with improvement in wound healing at 12 weeks with differences over standard care of between 5% and 27%², which may be clinically significant for some people with DFUs. Two *Level 1* reviews^{8,9} reported narrative results from *Levels 2, 3 and 4* studies on effectiveness of haemoglobin spray for treating DFUs, but this body of evidence is currently inadequate to recommend this method of topical oxygen delivery.

CLINICAL PRACTICE RECOMMENDATIONS

All recommendations should be applied with consideration to the wound, the person, the health professional and the context.

Topical oxygen therapy delivered via a mechanical system could be considered as an adjunctive therapy for diabetic foot ulcers that have failed to respond to standard care (Grade B).

There is no strong evidence to support the use of a haemoglobin spray for treatment of diabetic foot ulcers.

SOURCES OF EVIDENCE

This summary, including the making of recommendations, was conducted using methods published by the Joanna Briggs Institute¹⁰⁻¹². The summary is based on a systematic literature search combining search terms related to chronic wounds/DFUs and topical oxygen therapy/topical haemoglobin. Searches were conducted in Embase, AMED, Medline, the Cochrane Library and Google Scholar for evidence published up to 30 June 2022 in English. Due to the volume of recent systematic reviews identified on this topic, inclusion was limited to *Level 1* evidence.

BACKGROUND

Topical oxygen therapy is an advanced wound healing intervention that seeks to improve wound healing by increasing the oxygen supply within the wound bed.³⁴⁻³⁶ Peripheral arterial disease, which is a complicating factor for

Table 1: Levels of evidence for intervention studies

Level 1 evidence	Studies reported in included 1.a and 1.b systematic reviews
Experimental designs	
1.a Systematic review of randomised controlled trials (RCTs) ^{1-3, 5}	Level 1 studies ¹³⁻²² Level 2 studies ²³⁻²⁵
1.b Systematic review of RCTs and studies of other designs ^{4, 6-9}	Level 3 studies ²⁶⁻²⁸ Level 4 studies ²⁹⁻³³

the majority of DFUs, can lead to reduced perfusion of the wound and therefore decreased wound bed oxygenation.³⁴ Topical oxygen delivery interventions seek to address this complication and improve healing outcomes. Oxygen is delivered locally, directly to the wound bed using either mechanical systems that deliver sustained high concentration oxygen or via oxygen-releasing/generating wound dressings or topical sprays.³⁴⁻³⁶ For mechanical systems, oxygen is delivered in a gaseous form to the wound bed using a specific system (see Table 2) that enables an oxygen gradient to develop around the wound, facilitating diffusion of oxygen into the wound bed.

Haemoglobin spray is another form of topical oxygen treatment (sometimes referred to as facilitated delivery or oxygen carrier system).³⁴ This intervention is designed to increase oxygen supply to the wound bed through the application of a topical, aqueous, haemoglobin-containing spray.^{8, 9} Because haemoglobin is capable of transporting oxygen within the body, the spray is designed to promote oxygen-binding in the wound bed from the surrounding air for transport deeper into the wound bed and diffusion into cells to promote healing.⁹ In the laboratory, the spray has been demonstrated to increase angiogenesis, cell proliferation and collagen deposition.³⁷ Oxygen can also be delivered via wound dressings that contain embedded pure oxygen that is released into the wound bed when the oxygen-containing dressing is in contact with moisture.³⁵ The literature search did not identify any *Level 1* evidence for these products.

CLINICAL EVIDENCE

Topical oxygen therapy delivered via mechanical systems for treating diabetic foot ulcers

The literature search identified seven recently published systematic reviews¹⁻⁷ exploring the use of topical oxygen therapy, all focused on DFUs. There was substantial cross-over in the studies included in the different reviews. The reviews variously limited inclusion eligibility to studies with randomised designs^{1-3, 5}, and/or based on the number of participants², outcome measures reported^{1, 2, 4, 5} or comparator interventions^{3, 4, 6}. Across the reviews¹⁻⁷, 11 RCTs^{13-22, 29} were reported, most of which were appraised as being at moderate or high risk of bias. An additional four studies^{23, 24, 26, 27} providing *Level 2* or *Level 3* evidence were reported in these reviews.

The most methodologically robust review² included a meta-analysis that showed statistically significant results favouring use of topical oxygen therapy over sham therapy or standard care (risk ratio [RR] = 1.59 (95% confidence interval [CI] 1.07 to 2.37; $p = 0.021$) for complete wound healing at 12 weeks. Across the four included RCTs¹³⁻¹⁶, the difference in wound healing rates versus the comparator ranged from 5% to 27%² (*Level 1*).

A second review⁵ included a meta-analysis of the same four RCTs¹³⁻¹⁶, reporting the same results for complete DFU healing at 12 weeks as in the above review². Pooled results

Table 2: Types of mechanically delivered topical oxygen therapy³⁴⁻³⁶

Continuous oxygen delivery system	<ul style="list-style-type: none"> • Constant flow, normobaric oxygen (atmospheric pressure) • 100% pure oxygen • Oxygen delivered constantly 	<ul style="list-style-type: none"> • Battery-powered unit delivers oxygen through small cannulas to semi-occlusive, sealed wound dressing system • Light-weight device, attaches to patient to enable mobilisation • Wound dressings changed weekly • Oxygen generator/battery replaced after 1-2 weeks
Low constant pressure oxygen delivery system	<ul style="list-style-type: none"> • Constant low flow oxygen • Constant pressure maintained (up to 22 mmHg) • 100% pure oxygen • Oxygen delivered on a specific regimen (e.g., 60-90 minutes for 3-7 days per week) 	<ul style="list-style-type: none"> • Oxygen is delivered through a plastic chamber/boot system (usually single use) • Patient immobile while therapy is delivered • Wound dressings are removed for therapy and a new wound dressing is applied when therapy is completed
Cyclical pressurised and humidified oxygen delivery system	<ul style="list-style-type: none"> • High flow, pressurised oxygen • Cyclical, sequential, non-contact pressure (5-50mmHg) • 100% pure oxygen • Humidity can be added • Oxygen delivered on a specific regimen (e.g., 60-90 minutes for 3-7 days per week) 	<ul style="list-style-type: none"> • Oxygen delivered within an extremity chamber connected to an oxygen concentrator • Patient immobile while therapy is delivered • Cyclical pressure can reduce wound oedema • Gas permeable wound dressings and compression dressings can remain in place during therapy if this is consistent with the manufacturer's instructions

from three of the RCTs¹⁴⁻¹⁶ showed faster healing with topical oxygen therapy versus standard care, but this was not statistically significant (hazard ratio [HR] = 1.45, 95% CI 0.87 to 2.42, $p = 0.16$)⁵ (*Level 1*).

A third review¹ included a meta-analysis of six RCTs^{13-17, 19} that showed statistically significant results favouring use of topical oxygen therapy over control for number of DFUs healed at 8–12 weeks (RR = 1.63 (95% CI 1.33 to 2.00; $p < 0.00001$)). Five RCTs^{13, 15, 17-19} that reported reduction in ulcer size favoured topical oxygen therapy over control, but duration of therapy was of different lengths across the trials, so no pooled analysis was conducted. Four RCTs^{14-16, 19} reported healing time, with the majority showing no significant difference compared to control (*Level 1*).

A fourth review³ included a meta-analysis of six RCTs^{14-17, 20, 21} that showed statistically significant results favouring use of topical oxygen therapy over control for complete DFU healing (RR = 1.94, 95% CI 1.19 to 3.17; $p = 0.04$)³ (*Level 1*).

The next review⁴ reported eight studies^{14, 15, 17, 20, 21, 23, 24, 26} of various designs. A meta-analysis of five of the studies^{14, 15, 17, 20, 23} favoured topical oxygen therapy over standard care for complete healing of DFUs (odds ratio [OR] = 2.49, 95% CI 1.59 to 3.90, $p = 0.04$). This review⁴ reported that DFUs generally healed faster when treated with topical oxygen therapy but had no impact on recurrence rates (*Level 1*).

A sixth review⁶ included five studies^{17, 21, 23, 24, 29} of various designs. This review, which did not include a meta-analysis, concluded that topical oxygen therapy was associated with better healing outcomes for people with Wagner Grade 1 DFUs than for those with more severe DFUs (*Level 1*).

Finally, the seventh systematic review⁷, which underpinned recommendations from International Working Group of the Diabetic Foot (IWGDF) working group, included six studies that explored topical oxygen therapy^{14, 16, 17, 22, 23, 27}. This review⁷, which did not include a meta-analysis or GRADE evaluation of the evidence, concluded there was inadequate evidence from published studies to support a recommendation to use topical oxygen therapy (*Level 1*).

Overall, the evidence for topical oxygen therapy has increased in recent years but remains small and subject to moderate to high risk of bias. Multiple meta-analyses¹⁻⁵ demonstrate statistically significant outcomes achieved with mechanically delivered topical oxygen therapy; however, the clinical significance is unclear. Four of the reviews^{1-3, 5} included sensitivity analyses, three of which identified one RCT¹⁴ as significantly contributing to heterogeneity of the evidence. This study used an older oxygen delivery system that may have been less reliable², but also included participants with less severe DFUs¹. Analysis showed that the body of evidence is at risk of publication bias^{1, 2, 5}.

TOPICAL HAEMOGLOBIN THERAPY FOR TREATING DIABETIC FOOT ULCERS

Two systematic reviews^{8, 9} reported on the effectiveness of topical haemoglobin spray. Both reviews^{8, 9} included studies conducted in participants with any type of chronic wound that used randomised, comparative or non-comparative designs and identified the same body of evidence. The first of these systematic reviews⁸ included 15 studies^{25, 28, 30-33, 38-47}, most of which provided low level evidence covering the use of topical haemoglobin spray for DFUs, VLU, PIs and mixed aetiology wounds. The second systematic review⁹ reported 14 studies conducted in chronic wounds^{25, 30-33, 38-41, 43, 44, 46, 47}, all of which were reported in the review by Tayyib et al. (2022)⁸ (*Level 1*).

Focusing on the evidence for DFUs, five of the studies were relevant^{25, 28, 30, 32, 33}. These were low level studies (generally with no comparator group) and only reported outcomes for approximately 80 wounds, treated for between 4 and 28 weeks. All these studies showed reduction in wound size for DFUs treated with topical haemoglobin spray. In one comparative study²⁵, the DFUs receiving haemoglobin spray displayed superior reductions in both slough and wound pain compared to an historical control group (*Levels 2, 3 and 4*).

CONSIDERATIONS FOR USE

In research studies the adverse events experienced by group treated with topical oxygen were similar in type and frequency to those experienced by groups receiving standard wound care^{1-3, 6-9}. These included serious adverse events such as death that were deemed to be not related to the wound treatment.

Topical oxygen therapy should be considered as an adjunctive therapy for chronic wounds, used in conjunction with standard care including offloading and moist wound healing, and for people who are able to follow their wound management regimen^{1, 2}.

Consider the balance between potential benefits from topical oxygen therapy and the potential increased burden of treatment (e.g., cost of equipment, clinician time and the resources required to access treatment more often for some types of topical oxygen therapy)⁶. The literature search was not designed to identify economic studies and the reviews did not report cost-effectiveness^{1-3, 6-9}.

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CONFLICTS OF INTEREST

The author declares no conflicts of interest in accordance with International Committee of Medical Journal Editors (ICMJE) standards.

ABOUT WHAM COLLABORATIVE EVIDENCE SUMMARIES

The WHAM Collaborative evidence summaries are consistent with methodology published in Munn Z, Lockwood C, Moola S. The development and use of evidence summaries for point of care information systems: A streamlined rapid review approach, *Worldviews Evid Based Nurs*. 2015;12(3):131-8. Methods are provided in detail in resources published by the Joanna Briggs Institute as cited in this evidence summary. WHAM evidence summaries undergo peer review by a 20-member international multidisciplinary Expert Reference Group. More information about WHAM Collaborative methodology and the peer review process are available at: <http://WHAMwounds.com>

The WHAM Collaborative evidence summaries provide a summary of the best available evidence on specific topics and make suggestions that can be used to inform clinical practice. Evidence contained within this summary should be evaluated by appropriately trained professionals with expertise in wound prevention and management, and the evidence should be considered in the context of the individual, the professional, the clinical setting and other relevant clinical information.

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