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

Emily Haesler, PhD, P Grad Dip Adv Nurs (Gerontics), BN, FWA
Adjunct Professor, Curtin Health Innovation Research Institute, Wound Healing and Management (WHAM) Collaborative, Curtin University, Bentley WA, Australia
Email emily.haesler@curtin.edu.au


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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-analyses on the effectiveness of mechanically delivered topical oxygen therapy demonstrated that the treatment is associated with statistically significant improvements in complete healing at 12 weeks, and in the number of DFUs healed at 8—12 weeks. These findings are supported by a narrative systematic review, although a seventh, narrative review 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%, which may be clinically significant for some people with DFUs. Two Level 1 reviews 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 Institute. 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. Peripheral arterial disease, which is a complicating factor for

<table>
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<th>Level 1 evidence</th>
<th>Studies reported in included 1.a and 1.b systematic reviews</th>
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<tr>
<td>Experimental designs</td>
<td>Level 1 studies</td>
</tr>
<tr>
<td>1.a Systematic review of randomised controlled trials (RCTs)</td>
<td>13-22</td>
</tr>
<tr>
<td>1.b Systematic review of RCTs and studies of other designs</td>
<td>26-28</td>
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the majority of DFUs, can lead to reduced perfusion of the wound and therefore decreased wound bed oxygenation. 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. 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). This intervention is designed to increase oxygen supply to the wound bed through the application of a topical, aqueous, haemoglobin-containing spray. 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. In the laboratory, the spray has been demonstrated to increase angiogenesis, cell proliferation and collagen deposition. 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.

### CLINICAL EVIDENCE

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

The literature search identified seven recently published systematic reviews exploring the use of topical oxygen therapy, all focused on DFUs. There was substantial crossover in the studies included in the different reviews. The reviews variously limited inclusion eligibility to studies with randomised designs, and/or based on the number of participants, outcome measures reported, or comparator interventions. Across the reviews, 11 RCTs were reported, most of which were appraised as being at moderate or high risk of bias. An additional four studies providing Level 2 or Level 3 evidence were reported in these reviews.

The most methodologically robust review 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 RCTs, the difference in wound healing rates versus the comparator ranged from 5% to 27% (Level 1).

A second review included a meta-analysis of the same four RCTs, reporting the same results for complete DFU healing at 12 weeks as in the above review. Pooled results

### Table 2: Types of mechanically delivered topical oxygen therapy

<table>
<thead>
<tr>
<th>Continuous oxygen delivery system</th>
<th>Battery-powered unit delivers oxygen through small cannulas to semi-occlusive, sealed wound dressing system</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Light-weight device, attaches to patient to enable mobilisation</td>
</tr>
<tr>
<td></td>
<td>Wound dressings changed weekly</td>
</tr>
<tr>
<td></td>
<td>Oxygen generator/battery replaced after 1-2 weeks</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Low constant pressure oxygen delivery system</th>
<th>Oxygen is delivered through a plastic chamber/boot system (usually single use)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant low flow oxygen</td>
<td>Patient immobile while therapy is delivered</td>
</tr>
<tr>
<td>Constant pressure maintained (up to 22 mmHg)</td>
<td>Wound dressings are removed for therapy and a new wound dressing is applied when therapy is completed</td>
</tr>
<tr>
<td>100% pure oxygen</td>
<td></td>
</tr>
<tr>
<td>Oxygen delivered on a specific regimen (e.g., 60-90 minutes for 3-7 days per week)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cyclical pressurised and humidified oxygen delivery system</th>
<th>Oxygen delivered within an extremity chamber connected to an oxygen concentrator</th>
</tr>
</thead>
<tbody>
<tr>
<td>High flow, pressurised oxygen</td>
<td>Patient immobile while therapy is delivered</td>
</tr>
<tr>
<td>Cyclical, sequential, non-contact pressure (5-50mmHg)</td>
<td>Cyclical pressure can reduce wound oedema</td>
</tr>
<tr>
<td>100% pure oxygen</td>
<td>Gas permeable wound dressings and compression dressings can remain in place during therapy if this is consistent with the manufacturer’s instructions</td>
</tr>
<tr>
<td>Humidity can be added</td>
<td></td>
</tr>
<tr>
<td>Oxygen delivered on a specific regimen (e.g., 60-90 minutes for 3-7 days per week)</td>
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from three of the RCTs\textsuperscript{14-16} 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, \( p = 0.16 \))\textsuperscript{9} (Level 1).

A third review\textsuperscript{1} included a meta-analysis of six RCTs\textsuperscript{13-17}, \textsuperscript{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\textsuperscript{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\textsuperscript{14-16, 19} reported healing time, with the majority showing no significant difference compared to control (Level 1).

A fourth review\textsuperscript{2} included a meta-analysis of six RCTs\textsuperscript{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; \( p = 0.04 \))\textsuperscript{9} (Level 1).

The next review\textsuperscript{4} reported eight studies\textsuperscript{14, 15, 17, 20, 21, 23, 24, 26} of various designs. A meta-analysis of five of the studies\textsuperscript{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 review\textsuperscript{4} reported that DFUs generally healed faster when treated with topical oxygen therapy but had no impact on recurrence rates (Level 1).

A sixth review\textsuperscript{5} included five studies\textsuperscript{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 review\textsuperscript{7}, which underpinned recommendations from International Working Group of the Diabetic Foot (IWGDF) working group, included six studies that explored topical oxygen therapy\textsuperscript{14, 16, 22, 23, 27}. This review\textsuperscript{7}, 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-analyses\textsuperscript{1-5} demonstrate statistically significant outcomes achieved with mechanically delivered topical oxygen therapy; however, the clinical significance is unclear. Four of the reviews\textsuperscript{1-3, 5} included sensitivity analyses, three of which identified one RCT\textsuperscript{14} as significantly contributing to heterogeneity of the evidence. This study used an older oxygen delivery system that may have been less reliable\textsuperscript{2}, but also included participants with less severe DFUs\textsuperscript{1}. Analysis showed that the body of evidence is at risk of publication bias\textsuperscript{1, 2, 5}.

**TOPICAL HAEMOGLOBIN THERAPY FOR TREATING DIABETIC FOOT ULCERS**

Two systematic reviews\textsuperscript{8, 9} reported on the effectiveness of topical haemoglobin spray. Both reviews\textsuperscript{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 reviews\textsuperscript{8} included 15 studies\textsuperscript{25, 28, 30-33, 38-47}, most of which provided low level evidence covering the use of topical haemoglobin spray for DFUs, VLUs, PIs and mixed aetiology wounds. The second systematic review\textsuperscript{9} reported 14 studies conducted in chronic wounds\textsuperscript{25, 30-33, 38-41, 43, 44, 46, 47}, all of which were reported in the review by Tayyib et al. (2022)\textsuperscript{8} (Level 1).

Focusing on the evidence for DFUs, five of the studies were relevant\textsuperscript{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 study\textsuperscript{25}, 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\textsuperscript{1-5, 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\textsuperscript{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)\textsuperscript{9}. The literature search was not designed to identify economic studies and the reviews did not report cost-effectiveness\textsuperscript{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 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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REFERENCES


