



TITLE: Topical Oxygen Treatment for Wound Healing: A Review of Clinical and Cost-Effectiveness

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CONTEXT AND POLICY ISSUES

Chronic wounds are often associated with diabetes or vascular disease and have a high impact on the quality of life of those affected.¹ Hypoxemia, caused by disrupted or compromised vasculature, is a key factor limiting wound healing, especially because of its high prevalence in lower extremities.² In ischemic wounds, limited oxygen supply and increased oxygen demands used to fight infection and repair tissue lead to extreme hypoxia. Oxygen (O₂) is essential for collagen synthesis and cross-linking, fibroblast and leukocyte activation, and angiogenesis associated with tissue repair.³

Clinical use of O₂ to promote wound healing began in the 1960s with the administration of systemic full body hyperbaric oxygen therapy (HBOT) to treat wounds. HBO is administered in single- or multiplace chambers using pressures of 2,500 millibar (mb) or higher.⁴ A Cochrane review by Kranke et al. demonstrated that HBO significantly reduced the risk of major amputation and may improve the chance of healing within one year in patients with diabetic foot ulcers (DFU).⁵ The availability of HBO facilities, contraindications to their use, patient transfer requirements and risk of undesired systemic side effects limit widespread HBO use. In the late 1960s, pressurized topical wound oxygen (TWO₂) was introduced in an effort to address these limitations. In contrast to HBO, topically oxygenating the wound does not involve high pressures and is portable so it can be administered in a variety of settings.⁴ Conventional wound care often involves dressing the wound to create a moist environment for epithelialization and collagen synthesis.³

This report will review the clinical and cost-effectiveness of TWO₂ versus HBOT or conventional wound healing in order to inform decision-making regarding its place in wound care.

RESEARCH QUESTIONS

1. What is the clinical effectiveness of topical wound oxygen (TWO₂) for wound healing compared with hyperbaric oxygen treatment (HBOT) or conventional wound care?

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2. What is the cost-effectiveness of topical wound oxygen for wound healing compared with hyperbaric oxygen treatment or conventional wound care?

KEY MESSAGE

While TWO₂ heals 80% of diabetic foot ulcers (DFU), refractory venous ulcers (RVU) and chronic wounds without recurrence, its place in therapy can not be fully determined as the absence of randomization and blinding prevent direct comparison between groups. No evidence was found regarding the cost-effectiveness of TWO₂ compared with HBOT or conventional wound care.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including Ovid MEDLINE, PubMed, The Cochrane Library (2011, Issue 12), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and abbreviated list of major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, and economic studies. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2006 and December 19, 2011.

Selection Criteria and Methods

One reviewer screened citations to identify clinical and cost-effectiveness evidence regarding TWO₂. Potentially relevant articles were ordered based on titles and abstracts, where available. Full-text articles were considered for inclusion based on the selection criteria listed below.

Table 1: Selection Criteria

Population	Patients with wounds Subgroups: diabetic patients, hospitalized patients
Intervention	TWO ₂
Comparator	HBOT or conventional wound care (for example, traditional dressing)
Outcomes	Clinical effectiveness, time to wound healing, need for surgical closure or debridement, infection rate, pain control, quality of life, cost-effectiveness
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, and economic evaluations

Exclusion Criteria

Articles that did not satisfy the selection criteria in Table 1 or were case studies were excluded.

Critical Appraisal of Individual Studies

Critical appraisal of the included studies was based on study design. Randomized and non-randomized studies were assessed for quality using the Down's and Black instrument.⁶ Instead of calculating numeric scores, the strengths and limitations of each study were described. No health technology assessments, systematic reviews, meta-analyses, or economic evaluations were identified for critical appraisal.

SUMMARY OF EVIDENCE:

Quantity of Research Available

The literature search yielded 336 citations. Upon screening titles and abstracts, 13 potentially relevant articles were retrieved for full-text review. Three additional potentially relevant reports were retrieved from grey literature or hand searching. Of the 16 potentially relevant reports, 13 did not meet the selection criteria. No articles were identified regarding the cost-effectiveness of topical oxygen treatment for wound healing compared with HBOT or conventional care. Three articles reported on the clinical effectiveness of TWO_2 compared with HBOT or conventional care.^{4,7,8} The process of study selection is outlined in the PRISMA flowchart (Appendix 1).

Summary of Study Characteristics

Study design

One prospective controlled single centre study⁴ and two parallel observational comparison studies^{7,8} were selected for review. The articles, ranging in date from 2008⁸ to 2010⁴, originated from Canada,⁴ Ireland⁷ and the United States.⁸

Population

The prospective controlled study reported on the healing of diabetic foot ulcers (DFU) in 28 outpatients attending a wound clinic in St. Catharines, Canada.⁴ Baseline wound duration and area were longer and larger in the TWO_2 group than in the advanced moist wound therapy (AMWT) group (6.2 months, 4.1 cm^2 versus 3.2 months, 1.4 cm^2 , p =not significant and $p=0.02$, respectively).⁴ An Irish parallel observational comparison study evaluated the healing of 83 refractory venous ulcers (RVU) at 12 weeks.⁷ Approximately 31 percent of patients were diabetic and 45 percent were hypertensive. Patients in the TWO_2 group were managed as inpatients and had a higher venous clinical severity score (VCSS) than patients in the conventional compression dressing (CCD) outpatient group.⁷ The observation comparison study conducted in the United States reported on the healing of chronic wounds at 14 weeks in 57 patients treated in an outpatient setting.⁸ The proportion of known diabetics in the TWO_2 and HBOT groups was 31 percent and 52 percent, respectively. Median wound volumes for TWO_2 and HBOT patient groups were 3.3 cm^3 and 9.4 cm^3 , respectively.⁸ Overall, 70 percent of subjects in these studies were male with a mean age of 61 years.^{4,7,8}

Interventions

The Canadian prospective controlled study compared healing rates of chronic DFUs with TWO_2 versus AMDT.⁴ TWO_2 devices were provided by AOTI Ltd (Galway, Ireland). In this study, the TWO_2 device delivered humidified medical grade O_2 into an extremity chamber in a cyclical manner. The cycle consisted of pressurizing the chamber to 50 mb and allowed pressure to fall towards ambient pressure before re-pressurizing. Sixty-minute treatments were given five days per week. If all devices were occupied, the participant was offered AMWT using a silver-based

dressings (Silvercel,™ Johnson and Johnson, Somerville, NJ).⁴ The Irish study compared healing rates of RVU with TWO₂ versus conventional compression dressing (CCD).⁷ TWO₂ was managed in an inpatient setting where O₂ was piped from wall outlets. Patients were seated with the affected limb in the AOTI Hyper-Box™ (AOTI Ltd, Galway, Ireland) for 180 minutes twice daily under 50 mb pressure. O₂ was supplied at 10 l/min. Patients receiving CCD were managed in an outpatient clinic using multilayer compression bandages with underlying non-adherent Profore Wound Contact Layer dressings changed up to three times per week.⁷ The study conducted in the United States evaluated healing of chronic wounds with TWO₂ versus HBOT.⁸ The TWO₂ device (GWR Medical, PA, USA) is a single-use disposable device was connected to a portable O₂ source used in an outpatient setting. TWO₂ was administered for 90 minutes/day for four consecutive days, followed by three days without supplemental O₂. The cycle was repeated for 14 weeks or until the wound healed. HBOT was administered at outpatient clinics.⁸

Outcomes

The Canadian prospective controlled study compared healing and recurrence rates of chronic DFUs treated with TWO₂ versus AMWT.⁴ The Irish parallel observational study compared healing, recurrence rates and Quality-Adjusted Time Spent Without Symptoms (Q-TWiST) of RVU treated with TWO₂ versus CCD.⁷ The observational comparison study from the United States compared changes in wound closure and expression of O₂-sensitive genes in patients with chronic wounds treated with TWO₂ versus HBOT.⁸

Summary of Critical Appraisal

The research questions, inclusion and exclusion criteria, patient characteristics, outcomes, and study findings were explicit in all three studies.^{4,7,8} Participants were representative of the entire population from which they were recruited and those lost to follow-up were reported.⁴ Compliance with the intervention was reliable in the Irish study as TWO₂ patients were managed as inpatients.⁷ Ulcer duration and area were greater in the TWO₂ group in the Canadian study, perhaps due to selection bias.⁴ CCD patients in the Irish study had less severe ulcers and were managed as outpatients, while TWO₂ patients were managed as inpatients. The added inpatient care may have influenced outcomes.⁷ Treatment allocation was unconcealed and based on device availability,⁴ patient choice⁷ or physician discretion.⁸ All three studies lacked randomization and blinding, therefore, it is not possible to directly compare findings between treatment and intervention groups.^{4,7,8}

Summary of Findings

A prospective controlled single-centre study⁴ and two parallel observational comparison studies^{7,8} provided evidence on the clinical effectiveness of TWO₂ for wound healing compared to HBOT or conventional care.

A Canadian prospective controlled study reported that the proportion of DFU with complete healing was significantly greater in the TWO₂ patients than AMWT patients ($p=0.013$).⁴ Fourteen of 17 (82%) of DFU treated with TWO₂ and five of 11 (46%) ulcers treated with AMWT showed complete epithelialization of the wound ($p=0.04$). Median time to closure was 56 days in the TWO₂ group and 93 days in the AMWT group. No adverse events were reported and no recurrences were noted in either group at 24 month follow-up.⁴

The Irish parallel observational comparison study reported that the proportion of RVU with complete healing was significantly greater in TWO₂ patients than CCD patients.⁷ Eighty percent (37/46) of RVU treated with TWO₂ and 35% (13/37) of ulcers treated with CCD were completely healed by 12 weeks ($p < 0.0001$).⁷ At three weeks of treatment, 89% (41/46) of TWO₂ managed ulcers showed a reduction in surface area compared with 68% (25/37) of CCD ulcers ($p = 0.016$).⁷ The mean reduction in ulcer surface area at 12 weeks was 96% in the TWO₂ group compared to 61% in the CCD group. The median time to full ulcer closure was 45 days in the TWO₂ group (95% CI: 39 to 51), compared with 182 days in the CCD group (95% CI: 162 to 203, $p < 0.0001$).⁷ TWO₂ managed ulcers had a significantly shorter healing time compared to CCD ulcers regardless of the duration ($p < 0.0001$) or size ($p < 0.0001$) of the ulcer.⁷ Of the three TWO₂ patients that showed no signs of healing at four weeks, one had an ulcer exposing tendons and bone and the other two patients had carcinomas. Most TWO₂ treated ulcers (32/46) showed a reverse gradient healing where healing started from the centre of the ulcer and expanded towards the periphery.⁷ The pain score in TWO₂ patients improved from eight to three by 13 days, according to the pain numerical rating scale.⁷ During a 12-month follow-up, five of 13 fully healed CCD ulcers showed signs of recurrence, while 37 fully healed TWO₂ ulcers remained healed. TWO₂ patients experienced a significantly longer mean TWiST compared to CCD patients (12.5 months versus 4.5 months, $p < 0.001$).⁷

A parallel observational comparison study conducted in the United States reported that TWO₂ induces *VEGF* expression and significantly improves chronic wound size compared to HBOT.⁸ TWO₂ significantly improved wound closure by decreasing wound volume ($p = 0.001$; $R^2 = 0.414$), while HBOT did not ($p = 0.150$, $R^2 = 0.068$). TWO₂ significantly increased *VEGF* expression, known to stimulate angiogenesis, while neither *TGF-β* nor *COL1A1* responded.⁸ Differences in gene expression of healing versus non-healing wound outcomes HBOT patients was not statistically significant for any of the O₂-sensitive genes examined (*VEGF*, $p = 0.995$, *TGF-β*, $p = 0.190$, *COL1A1*, $p = 0.415$).⁸

No evidence was found regarding the cost-effectiveness of TWO₂ for wound healing compared versus HBOT or conventional wound care.

Table 2. Summary of the Clinical Effectiveness of TWO₂ Compared to HBOT or Conventional Care for Wound Healing

Intervention	Evidence	Results
TWO ₂	Prospective controlled single-centre study, ⁴ two parallel observational comparison studies ^{7,8}	<ul style="list-style-type: none"> 82% of TWO₂ managed DFU healed after a median of 56 days with no adverse events or recurrences at 24 months.⁴ 80% of TWO₂ managed RVU were healed at 12 weeks with a median time to full healing of 45 days and no recurrence at 12 months.⁷ TWO₂ significantly improved chronic wound closure by decreasing wound volume and increasing <i>VEGF</i> expression.⁸
AMWT	Parallel observational comparison ⁴	<ul style="list-style-type: none"> 46% of AMWT managed DFU healed after a median of 93 days with no adverse events or recurrences at 24 months.
CCD	Parallel observational comparison ⁷	<ul style="list-style-type: none"> 35% of CCD managed RVU healed after a median of 182 days, however, 5 of 13 healed CCD ulcers showed recurrence at 12 months.⁷

Intervention	Evidence	Results
HBOT	Parallel observational comparison ⁸	<ul style="list-style-type: none"> • HBOT did not significantly improve wound closure or increase VEGF expression.⁸

AWMT: advanced moist wound therapy; CCD: conventional compression dressings; HBOT: hyperbaric oxygen treatment; RVU: refractory venous ulcers; TWO₂: pressurized topical wound oxygen therapy; VEGF: vascular endothelial growth factor

Limitations

The quantity of evidence on the clinical effectiveness of TWO₂ for wound healing is limited to a prospective single centre study and two parallel observational studies involving small numbers of DFU,⁴ RVU,⁷ and chronic wound patients.⁸ Ulcer duration, area and severity differed between groups in two studies, perhaps due to selection bias.^{4,7} The management of TWO₂ patients as inpatients in the Irish study may have resulted in improved outcomes due to increased care.⁷ Allocation to treatment was based on device availability, patient choice or physician discretion.^{4,7,8} The absence of randomization and blinding in all trials may under- or overestimate the treatment effect of either group and prevent direct comparison between groups.^{4,7,8} No evidence was found regarding the cost-effectiveness of TWO₂ compared to HBOT for healing wounds.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING:

All three observational comparison studies reviewed in this report suggest that TWO₂ heals about 80 percent of DRU, RVU and chronic wounds completely in a median of approximately 56 days without recurrence.^{4,7,8} In contrast, 35 percent of DRU and 45 percent of RVU managed with AMWT and CCD healed after 93 days and 182 days, respectively. Thirty-eight percent of CCD managed ulcers showed signs of recurrence within 12 months.⁷ While HBOT was of benefit for some chronic wounds, it did not result in statistically significant improvements in most patients.⁸ While TWO₂ improves the healing of DFU, RVU and chronic wounds, its place in therapy cannot be fully determined as the absence of randomization and blinding prevent direct comparison between groups. Economic evaluations comparing the cost-effectiveness of TWO₂ versus HBOT or conventional wound care were not identified, so a conclusion cannot be provided.

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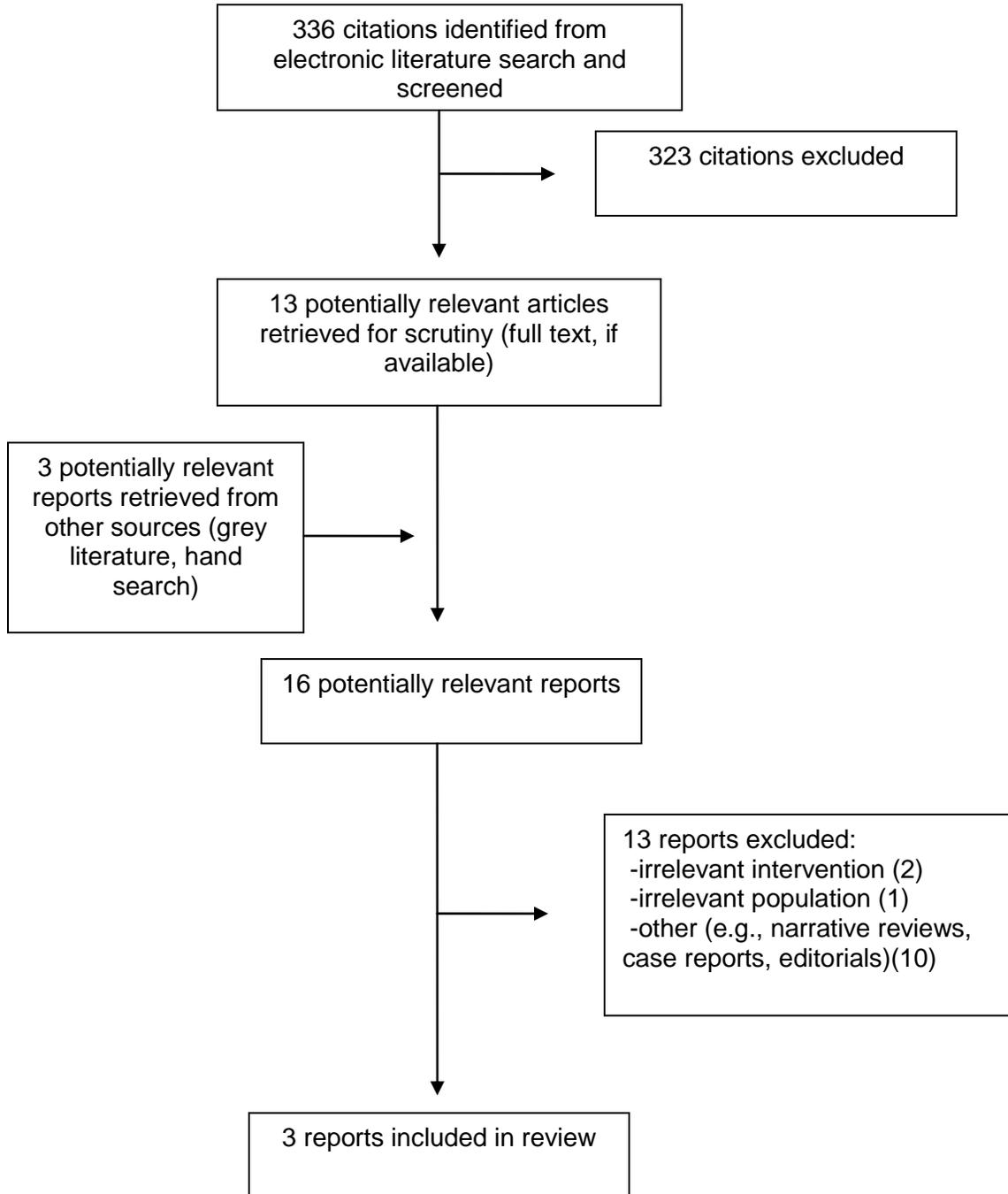
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APPENDIX 1: Selection of Included Studies



APPENDIX 2: Summary of Study Characteristics

First Author, Publication Year, Country	Study Design	Patient Characteristics	Intervention	Comparator	Clinical Outcomes Measured
Blackman ⁴ 2010 Canada	Prospective controlled single centre	DFU outpatients Duration and area: 6.1 mo, 4.1 cm ² (TWO ₂); 3.2 mo, 1.4 cm ² (CCD) p=0.02 (n=28; 71% M; 63 yr)	TWO ₂ 5x/wk, 60 min treatment, pressure cycles between 5-50 mb (n=17)	AMWT using silver-containing dressings changed 2x/wk (n=11)	Clinical efficacy, ulcer recurrence rates after 24 months
Tawfick ⁷ 2009 Ireland	Parallel observational comparison	Patients with RVU in inpatient setting Diabetic, hypertensive, VCSS: 33%, 48%, 25 (TWO ₂); 30%, 40%, 23 (CCD) (n=83; 64% M; 66 yr)	TWO ₂ managed in inpatient setting as O ₂ was piped from wall outlets (180 min 2x/d under 50 mb at 10 l/min until healed or for 12 wk) (n=46)	CCD using multilayer compression bandage with non-adherent dressings changed 1-3x/wk in outpatient setting (n=37)	Proportion of ulcers healed at 12 wks, time to full healing, % reduction in ulcer size, pain reduction, recurrence rates and Q-TWiST
Gordillo ⁸ 2008 United States	Parallel observational comparison	Outpatients with chronic wounds (>4 wk) Diabetic and median wound volume: 52%, 3.3 cm ³ (TWO ₂), 31%, 9.4 cm ³ (HBOT) (n=57; 71% M; 54 yr)	TWO ₂ single-use device (90 min/d, 4 consecutive d/wk, followed by 3 d without O ₂ supplementation; cycle repeated until healed or for 14 wk) (n=25)	HBOT (n=32)	Changes in wound closure outcomes and expression of oxygen-sensitive genes (TGF-β, COL1A1, VEGF)

AMWT: advanced moist wound therapy; CCD: conventional compression dressings; COL1A1: collagen, type 1, alpha 1; d: day; DFU: diabetic foot ulcers, HBOT: hyperbaric oxygen therapy; M: males; mb: millibars; mo: month; O₂: oxygen; TWO₂: pressurized topical wound oxygen therapy; Q-TWiST: Quality-Adjusted Time Spent Without Symptoms of disease and Toxicity of Treatment; RVU: refractory venous ulcers; TGF-β: transforming growth factor beta; VCSS: venous clinical severity score; VEGF: vascular endothelial growth factor; wk: week; yr: year

APPENDIX 3: Summary of Critical Appraisal

First Author, Publication Year	Strengths	Limitations
Blackman ⁴ 2010	<ul style="list-style-type: none"> • The research question inclusion/exclusion criteria, patient characteristics, interventions and study findings were explicit. • The participants were representative of the entire population from which they were recruited and patients lost to follow-up were reported. 	<ul style="list-style-type: none"> • Ulcer duration and area were greater in the treatment group perhaps due to selection bias. • Allocation to treatment was based on device availability. Absence of randomization and blinding may under- or overestimate the treatment effect of either group.
Tawfik ⁷ 2009	<ul style="list-style-type: none"> • The objective, inclusion/exclusion criteria, patient characteristic, main outcomes and findings were explicit. • Compliance with intervention was reliable as TWO₂ patients were managed as inpatients. 	<ul style="list-style-type: none"> • Allocation to treatment was based on patient choice. Absence of randomization and blinding may under- or overestimate the treatment effect of either group. • CCD patients with less severe ulcers were managed as outpatients while more severe TWO₂ patients were managed as inpatients. This difference may have influenced outcomes.
Gordillo ⁸ 2008	<ul style="list-style-type: none"> • The objective, patient characteristics, interventions, outcomes, and main findings were explicit. 	<ul style="list-style-type: none"> • Allocation treatment was made at physician discretion. Patients who did not qualify for HBOT were offered TWO₂. Enrolment to treatment groups was not randomized, thus directly comparing findings between TWO₂ and HBOT is not possible.

CCD: conventional compression dressings; HBOT: hyperbaric oxygen therapy; TWO₂: pressurized topical wound oxygen therapy

APPENDIX 4: Summary of Findings

First Author, Publication Year	Main Study Findings	Authors' Conclusions
Blackman ⁴ 2010	Fourteen of 17 (82%) ulcers in TWO ₂ patients and five of 11 (46%) ulcers in AMWT patients healed after a median of 56 and 93 d, respectively (p=0.04). No adverse events or recurrences were noted after 24 mo of follow-up. ⁴	“Although the absence of randomization and blinding may have under- or overestimated the treatment effect of either group, the significant differences in treatment outcomes confirm the potential benefits of TWO ₂ in the management of difficult-to-heal DFUs.” ⁴
Tawfik ⁷ 2009	Eighty percent of TWO ₂ managed ulcers and 35% of CCD ulcers (p<0.0001) were completely healed at 12 wks. Median time to full healing was 45 d and 182 d in TWO ₂ and CCD patients (p<0.001), respectively. The pain score threshold in TWO ₂ patients improved from 8 to 3 by 13 d. Five of 13 healed CCD ulcers showed signs of recurrence compared to none of the 37 TWO ₂ patients. TWO ₂ patients experienced significant improvements in Q-TWiST. ⁷	“TWO ₂ reduces recurrence rates, alleviates pain and improves Q-TWiST. We believe it is a valuable tool in the armamentarium of management of RVU.” ⁷
Gordillo ⁸ 2008	Overall, HBOT treatment did not significantly improve wound closure (p=0.15, R ² =0.068) or increase VEGF expression (p=0.995). TWO ₂ significantly improved wound closure by decreasing wound volume (p=0.001; R ² =0.414) and increasing VEGF expression (p=0.031). Neither TGF-β nor COL1A1 exhibited statistically meaningful response to TWO ₂ treatment (p=0.34 and 0.52, respectively). ⁸	“HBOT did not result in statistically significant improvements in wound size in the given population. TWO ₂ treatment induces VEGF expression in wound edge tissue and improves wound size. TWO ₂ benefits wound healing in patients with chronic wounds.” ⁸

AMWT: advanced moist wound therapy; CCD: conventional compression dressings; d: day; COL1A1: collagen, type 1, alpha 1, d: day; DFU: diabetic foot ulcers, HBOT: hyperbaric oxygen therapy; mo: month; TGF-β: transforming growth factor beta; TWO₂: pressurized topical wound oxygen therapy; Q-TWiST: Quality-Adjusted Time Spent Without Symptoms of disease and Toxicity of Treatment; RVU: refractory venous ulcers; VEGF: vascular endothelial growth factor.