



Dear Readers,

Hyperbaric oxygen therapy (HBOT) delivers 100% inspired oxygen to individuals at 2.0 to 2.5 absolute atmospheres (ATA) of pressure for a typical total duration of 60-120 minutes during 1-2 daily sessions

inside a hyperbaric chamber. During a course of up to 30 treatments, adequately perfused wounds with delayed healing associated with limited local tissue oxygenation are expected to improve in healing parameters based on the assumption that local hypoxia is contributing to their delayed healing. A wound must have sufficient circulation for the 100% inspired oxygen to increase local oxygen levels in its hypoxic periwound tissue to respond to HBOT. The wide variety of chronic wound etiologies, not all involving local hypoxia, coupled with wide variability in parameters for administering HBOT have contributed to uncertainty about HBOT efficacy in treating chronic wounds. Instead of asking, "Does chronic wound healing improve in response to HBOT?" perhaps the question should be, "How can one recognize which chronic wound(s) are likely to improve their healing in response to HBOT as an adjunct to recognized standard(s) of care?" This *Evidence Corner* describes 2 publications designed to clarify the question of HBOT efficacy. The first is a Cochrane review of HBOT effects on chronic wounds.¹ The second is the only randomized clinical trial (RCT) of HBOT effects on venous insufficiency ulcers² found by searching the MEDLINE, Google Scholar, and ClinicalTrials.gov databases from inception to November 8, 2015, for combined terms "hyperbaric oxygen and venous ulcer" while seeking evidence supporting the multinational intersociety collaboration updating the former Association for the Advancement of Wound Care Venous Ulcer Guideline, now called the International Consolidated Venous Ulcer Guideline.

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Hyperbaric Oxygen Therapy Effects on Chronic Wounds

Reference: Kranke P, Bennett MH, Martyn-St James M, Schnabel A, Debus SE, Weibel S. Hyperbaric oxygen therapy for chronic wounds. *Cochrane Database Syst Rev.* 2015;24(6):CD004123. doi: 10.1002/14651858.CD004123.pub4.

Rationale: Hyperbaric oxygen therapy (HBOT) has been proposed to improve oxygen supply to hypoxic chronic wounds.

Objective: Conduct a systematic review of randomized clinical trials (RCTs) comparing HBOT effects on chronic wounds to those of another therapeutic regimen.

Methods: Cochrane Library, MEDLINE, CINAHL, and EMBASE databases were searched from inception to February 2015 for RCTs comparing effects of HBOT to at least 1 other non-HBOT therapeutic regimen on chronic wound healing. Qualifying RCTs were reviewed independently by 3 authors reaching consensus on risk of RCT bias. Healing outcomes data were extracted, summarized, and, where appropriate, meta-analyzed.

Results: Five RCTs on 205 participants with a diabetic foot ulcer (DFU) revealed a transient increase ($P = 0.01$) in the percent of patients healed during 6 weeks of treatment with standard care plus adjunctive HBOT compared to the same standard of care alone, or with control subjects breathing ambient air at the same absolute atmospheres (ATA) (sham), or compared to a standardized protocol including debridement plus topical antiseptic agents. One RCT³ reported increased 30-day percent wound area reduction ($P < 0.00001$) and higher periwound transcutaneous oxygen tensions after HBOT treatment ($P < 0.0002$). No significant effects of HBOT were reported on risk of minor amputations. A possible HBOT effect reducing major amputations required "cautious interpretation" due to diverse ulcer characteristics and "trial reporting and methodological discrepancies."

Authors' Conclusions: Some evidence supports significant DFU healing improvement during 6 weeks of HBOT, but this benefit is not evident at later follow up. Hyperbaric oxygen therapy does not appear to significantly improve related minor amputation rates. Further research is needed to explore HBOT effects on other chronic wounds or on major amputations for individuals with a DFU.

DO NOT DUPLICATE

Adjunctive Hyperbaric Oxygen Therapy May Initiate Venous Ulcer Repair

Reference: Hammarlund C, Sundberg T. Hyperbaric oxygen reduced size of chronic leg ulcers: a randomized double-blind study. *Plast Reconstr Surg.* 1994;93(4):829-833. doi: 10.1097/00006534-199404000-00027.

Rationale: Hyperbaric oxygen therapy improves healing of devascularized tissue, but no blind evaluated RCT has explored its effects on nondiabetic chronic leg ulcers without large vessel disease.

Objective: Conduct a double-blind RCT to evaluate HBOT effects on leg ulcers of patients without large vessel disease or diabetes.

Methods: Patients with leg ulcers of at least 1 year duration, not resulting from large vessel disease or diabetes were stratified by age, then randomized to breathe either air (sham group, n = 8) or 100% oxygen (n = 8) at 2.5 ATA during five 90-minute sessions per week for a total of 30 sessions. Each age-matched patient had 1 leg ulcer area monitored by tracing at baseline and study weeks 2, 4 and 6. Patients and those measuring outcomes were blinded to treatment group. The primary healing outcome was percent area reduction, calculated as (baseline area - area at time of measurement) / baseline area. The Mann-Whitney U Test was used to test for significant treatment effects between sham and HBOT-treated subjects' percent wound area reduction at each area measurement, with $P < 0.05$ being significant. Percent of target ulcers completely healed was compared at follow-up 18 weeks after the initial treatment, ie, 12 weeks after the last treatment.

Results: Participants receiving HBOT experienced progressively greater improvement in percent area reduction compared to those receiving sham treatment at weeks 4 ($P < 0.05$) and 6 ($P < 0.001$). At week 18, two HBOT subjects (25%) healed as compared to no sham subjects and mean percent area reduction was 56% for HBOT or 26% for the sham group. Numbers of subjects were too small for these differences to be statistically significant.

Authors' Conclusions: Hyperbaric oxygen therapy may be used as a valuable adjunct to good standard practice for nondiabetic leg ulcers that do not heal.

Clinical Perspective

Evidence summarized by Kranke and colleagues¹ confirm the healing advantage of HBOT for DFUs while highlighting the scarcity of adequately powered RCTs on chronic ulcers of venous, pressure, or mixed etiology on individuals without diabetes. Kranke et al¹ reported results from only 2 RCTs

that included any venous ulcers. One was the study by Hammarlund and Sundberg² summarized above. The other,³ a study of 30 participants, included 20 with chronic leg ulcers of nondiabetic etiology and an unspecified number associated with venous insufficiency. This study randomized 15 subjects in each of 2 groups to receive 30 days of HBOT plus conventional treatment or conventional treatment alone, and reported wound improvement on a standardized 0-4 scale based on wound area (length x width), exudate, and granulation tissue at baseline and after 10, 20 or 30 days of treatment. Participants receiving HBOT experienced more wound score improvement at days 10, 20, and 30 than conventionally treated controls and more area reduction (all P values < 0.01). The consistency of early results from these 2 studies^{2,3} suggest the merit of larger double blind RCTs exploring the effects of HBOT on ulcers resulting from venous insufficiency and other nondiabetic etiologies. They also raise the question of how long the effects of HBOT may last. Hammarlund and Sundberg² applied HBOT 5 days per week for 6 weeks in their small, blind-evaluated RCT, then evaluated the percent healed 12 weeks after the last treatment.

What is the effective interval between HBOT treatments that suffices to sustain significant reductions in venous ulcer area? How long does the effect of a 30-day regimen of HBOT treatment last? Do we know the answers to these questions for DFUs? What about pressure ulcers or ulcers of mixed etiology? While the systematic review¹ results support HBOT efficacy on DFUs, we still have much to learn about optimal frequency, duration, and perhaps other parameters of HBOT treatment, as well as about which recipients may benefit from it.

References

1. Kranke P, Bennett MH, Martyn-St James M, Schnabel A, Debus SE, Weibel S. Hyperbaric oxygen therapy for chronic wounds. *Cochrane Database Rev Syst.* 2015;24(6):CD004123. doi: 10.1002/14651858.CD004123.pub4
2. Hammarlund C, Sundberg T. Hyperbaric oxygen reduced size of chronic leg ulcers: a randomized double-blind study. *Plast Reconstr Surg.* 1994;93(4):829-833. doi: 10.1097/00006534-199404000-00027.
3. Kaur S, Pawar M, Banerjee N, Garg R. Evaluation of the efficacy of hyperbaric oxygen therapy in the management of chronic nonhealing ulcer and role of periwound transcutaneous oximetry as a predictor of wound healing response: a randomized prospective controlled trial. *J Anaesthbesiol Clin Pharmacol.* 2012;28(1):70-75.

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