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Lou Ann Hall-Matos, DPM, MSa; Ivan Vela, DPMb; Christopher Japour, DPM, MSb

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Cyclical Topical Oxygen Therapy of Trauma-Induced Venous Leg Wounds in Patients With Diabetes

Lou Ann Hall-Matos, DPM, MS^a; Ivan Vela, DPM^b; Christopher Japour, DPM, MS^c

Background: Traumatic wounds are common in the emergency department (ED). Intermittent cyclical compression topical applied oxygen therapy (cTOT) has been efficacious for healing foot wounds, especially chronic wounds.

Methods: When topically applied oxygen is pressurized to mimic physiologic conditions, pneumatic compression pushes third-space fluid into the venous system, removing metabolic toxins and enhancing the environment for tissue repair. Together, these induce localized expression of tissue growth factors, encouraging angiogenesis through

upregulation of enzymatic reactions and providing a reparative environment.

Results: Between May 1, 2016, and July 31, 2021, 69 patients underwent cTOT, and 8 patients with 10 wounds met the inclusion criteria. All wounds healed following cTOT. Patients had a mean 11.3 weeks of failed healing attempts at baseline compared with a mean 8.1 weeks time to healing with cTOT.

Conclusions: This case series demonstrates the efficacy of cTOT in treating chronic traumatic lower-extremity wounds complicated by venous insufficiency and diabetes mellitus.

Author affiliations can be found at the end of this article.

Correspondence:

Christopher Japour
(christopher.japour@va.gov)

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Lower extremity venous ulcerations impact the health, well-being, and associated costs of patient care. These ulcerations are associated with comorbidities such as diabetes mellitus and chronic venous insufficiency or may be related to trauma. Often, the standard of care fails to effectively and completely heal ulcers, causing them to become stalled, chronic, and require ≥ 1 month of treatment.

Healthy skin partial pressure of oxygen (PO_2) approximates 100 mm Hg, but prolonged periods of poor blood perfusion from vascular damage can cause the PO_2 within a wound bed to become as low as 10 mm Hg.¹ Deprivation of oxygen impairs biological processes essential for bacterial control and growth factor activity, contributing to wound chronicity.²⁻⁵ Exposure to oxygen not only upregulates growth factors essential for maintaining a well-vascularized wound core, but also aids enzymatic reactions responsible for healing the skin that are sensitive to PO_2 levels.^{3,6,7} These physiologic processes can be maximized by raising oxygen level concentrations by means of oxygen therapy.⁸

Hyperbaric oxygen therapy (HBOT) uses a pressurized system to deliver concentrated oxygen that is diffused in the lungs, resulting in increased blood oxygen levels for delivery to bodily tissues. Full chamber HBOT can accelerate the wound healing process. Some disadvantages of HBOT include its high cost, the possibility of oxygen toxicity, and travel time to facilities for daily therapy sessions that last

an average of 1.5 hours and may continue for ≤ 60 sessions.^{7,9} Thus, alternatives to HBOT have been developed, including topical oxygen therapy (TOT), which uses portable bags or chambers that deliver concentrated oxygen applied directly over ulcers, allowing oxygen to diffuse directly into the injured tissue. Combined with the standard of care and regular debridement, TOT saturates the wound base and surrounding tissues with oxygen, thereby inducing growth factors that promote angiogenesis as well as upregulation of enzymatic reactions that create a reparative environment.⁶

In a study conducted in pigs, Fries et al induced full-thickness wounds that were allowed to heal by secondary intention. They demonstrated that wounds treated with TOT not only healed in fewer days but also revealed a higher presence of vascular endothelial growth factor, greater density of vascular structures, and more histologically mature healing tissues when compared with control wounds exposed to room air.²

The effectiveness of TOT in ulcer healing has been previously reported. Frykberg et al performed a multicenter randomized controlled trial (RCT) comparing TOT with sham therapy to determine the efficacy of TOT in diabetic foot ulcers (DFUs) that had previously failed treatment with the standard of care. The RCT demonstrated that wounds treated with TOT had a 4.5-fold greater likelihood of complete epithelialization within 12 weeks compared with the sham group.³ In a multicenter RCT,

TABLE. Delayed Wound Healing After Failing Standard of Care

Patient	Wound type	Failed healing, wk	Wound volume after failed healing, cm ³	Healing time with topical oxygen therapy, wk
1	Iatrogenic	8	0.45	7
2	Accident	14	1.25	8
3	Accident	4	0.62	12
4 ^a	Thermal	8	7.20	6
		8	1.50	6
5	Accident	47	1.10	21
6	Accident	12	0.26	12
7 ^a	Accident	4	0.38	4
		4	1.93	4
8	Accident	4	0.18	1

^aPatient 4 had 1 wound on each lower leg; patient 7 had 2 distinct wounds on 1 lower leg.

Al-Jalodi et al found that 56% of DFUs treated with TOT remained epithelialized at 12 months compared with 27% of ulcers treated with the standard of care alone. Al Jalodi et al argued that TOT may increase the durability of DFU closure.⁸ In addition, a small prospective cohort study biopsied 23 DFUs treated with TOT and noted increased cytokines and growth factors, as well as increased transcutaneous oxygen measurement perfusion after only 1 week of treatment compared with wounds treated with the standard of care.⁹

Yellin et al reported that patients with DFU treated with TOT had reduced hospital lengths of stay and a lower amputation rate compared with patients who did not receive TOT modality.¹⁰ Another study compared conventional compression dressings with TOT in managing 132 recalcitrant venous ulcers. In that study, Nataraj et al found that 76% of ulcers treated with TOT had completely healed at 12 weeks compared with 46% of those treated with compression only.¹¹ Furthermore, numerous systematic reviews and meta-analyses have analyzed the efficacy of TOT, concluding that this modality not only improves healing among ulcers of varying severity when compared with the standard of care but also contributes to the durability of healed ulcers and thus helps improve patient quality of life by preventing recurrence.^{2,12-18}

Intermittent cyclical compression topical oxygen therapy (cTOT) is a modality that provides concentrated oxygen at a rate of 10 L/min. cTOT cycles twice a minute and applies noncontact compression directly to ulcerations between 10 and 50 millibars (7.5-37.5 mm Hg). In a study of 8 patients with leg ulcers, transcutaneous oxygen tension was higher after treatment with intermittent pneumatic compression (42.7 mm Hg) when compared with baseline values. The authors postulated that intermittent compression decreased interstitial fluid volume and venous stasis, both of which lead to increased cutaneous oxygenation. The data suggested that removal of carbon dioxide from tissues and enhancement of cutaneous cyclical oxygenation promoted ulcer healing.¹⁹

To the best of our knowledge, there are no published studies that have evaluated the efficacy of cTOT for traumatic injuries while also considering existing comorbidities such as diabetes mellitus and venous insufficiency in veterans. The aim of this study was to demonstrate the efficacy of cTOT in the setting of traumatic wounds that failed the standard of care and were complicated by venous insufficiency and diabetes mellitus. We hypothesized that cTOT enhances healing of trauma-induced venous leg wounds in patients with diabetes mellitus, achieving full epithelialization within 12 weeks after failing the standard of care.

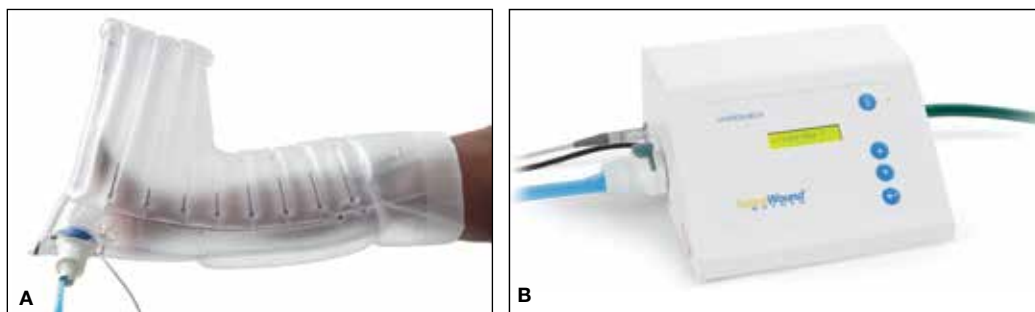


FIGURE. Topical oxygen therapy device. A, Topical Wound Oxygen extremity chamber; B, controller. Source: Advanced Oxygen Therapy Inc. Reprinted with permission.

METHODS

Institutional review board approval was granted prior to commencement of this single-center retrospective review at the Veterans Affairs Illiana Healthcare System (VAIHS) in Danville, Illinois. Electronic health records between May 1, 2016, and July 31, 2021, were examined to find patients treated with cTOT using the Advanced Oxygen Therapy Inc. Topical Wound Oxygen (TWO₂) system (Figure). Data collected included demographics, follow-up, and outcomes.

Inclusion criteria included patients who failed standard wound care for ≥ 4 weeks with venous insufficiency, trauma to the lower legs by means of iatrogenic injury, accidental injury, thermal injury/burn, or diabetes mellitus determined to be an active problem and a hemoglobin A_{1c} (HbA_{1c}) obtained within 3 months of wound treatment. The VAIHS standard of care was weekly visits to a wound care physician, physician assistant, or a nurse practitioner who performed sharp wound debridement and applied multilayer compression therapy. Patients with confirmed history of intermittent claudication, stroke, absent pedal pulses, abnormal blood pressure, deep vein thrombosis, pulmonary embolism, revascularization of the lower extremity, trauma fractures of the affected leg, phlebitis, pregnancy, coagulopathy, infection, or history of malignancy were excluded.

Patients who failed the standard of care for ≥ 4 weeks were enrolled in the cTOT program, after which they began weekly visits to an outpatient wound healing center where visits consisted of sharp wound debridement, wound measurement, and application of compressive dressing

to the affected lower extremity. Following wound-healing center visits, the subjects received cTOT at home according to the manufacturer's protocol, which consisted of ≤ 90 -minute sessions, 5 to 7 times weekly. The wounds were measured from initial presentation to complete epithelialization, and the patients were followed for ≤ 27 months.

RESULTS

Sixty-nine patients underwent cTOT between May 1, 2016, and July 31, 2021, and 8 patients with 10 wounds met the inclusion criteria. The patients had a mean age of 76 years, BMI of 27, and HbA_{1c} of 8.0%. All wounds completely healed following cTOT. Prior to the use of cTOT, the included patients had a mean 11.3 weeks of failed healing attempts when receiving standard of care therapy. Following cTOT implementation, the mean time to healing was 8.1 weeks (Table). One wound recurred after 10 weeks in a patient with uncontrolled diabetes mellitus. One patient died of causes unrelated to the wound and was excluded from follow-up. All other wounds remained closed and healed after a mean end follow-up period of 110 weeks through June 2023.

DISCUSSION

Traumatic wounds are commonly seen in the emergency department (ED), accounting for 5.4% of all ED visits.²⁰⁻²² According to the National Hospital Ambulatory Medical Care Survey, 14.6% of 117 million ED visits in 2007 involved lower-extremity wounds, costing the health care system $> \$25$ billion annually.²³ Kulkarni et al reported that 44% of patients experienced

leg ulcerations secondary to trauma.²⁴ Traumatic wounds that lack epithelialization > 4 weeks are categorized as chronic, placing a large social and financial impact on patient health and well-being.

This case series supports the benefits of cTOT and demonstrates improved wound-closure rates with sustained healing compared with standard care alone, corroborating findings reported by the American Diabetes Association (ADA).²³ The ADA cited high-quality RCTs and systematic reviews supporting the healing benefits of cTOT for chronic DFUs through the upregulation of essential growth factors.²⁴

The current literature offers many examples of the healing benefits of TOT for arterial ulcerations. Benefits include faster healing with longer lasting reparative ulcer tissue, prevention of amputation and improved quality of life. However, there is a lack of literature on the use of cTOT for venous stasis traumatic wounds, which prompted this study. Our case series presents evidence that cTOT enhances healing of trauma-induced venous leg wounds in male veterans with diabetes mellitus within 12 weeks after failure of the standard of care. Other risk factors that were recorded but not included in our analysis included tobacco use, chronic kidney disease, chronic obstructive pulmonary disease, use of cellular-based tissue/collagen products, and neuropathy.

This case series provides evidence that cTOT can be a beneficial and cost-effective treatment. Economic considerations are derived from retrospective cohort analyses and a published decision-analytic Markov model representing modeled estimates and need to be interpreted in that context rather than as findings from prospective comparative cost analyses healing.^{25,26}

The authors did not conduct an independent health economic evaluation as part of this review. Wound recurrence, hospitalizations and lower extremity amputations represent major cost drivers in chronic wound care. In addition, repeat ED admissions, surgical intervention, rehabilitation, prosthetics, and long-term disability contribute to economic burden and negative psychosocial and quality of life impacts on patients and caregivers. The reductions in hospitalization ($\leq 88\%$) and amputation ($\leq 73\%$) observed

in real-world TWO₂ cohorts suggest significant potential downstream cost savings. A recent Markov model analysis suggested that TWO₂ may be cost-favorable compared with standard care, with modeled estimates indicating lower total 2-year costs and improved quality-adjusted life years. These projections are based on modeling assumptions and require confirmation through prospective economic evaluations comparing TWO₂ directly with negative pressure wound therapy, HBOT, and skin substitutes across longer time horizons.

Limitations

The findings of this case series were small and lacked statistical power with only 8 male patients. Literature gaps also exist regarding the specific effects of TOT on traumatic wounds. This review was limited by its single-center location.

CONCLUSIONS

This case series suggests that cTOT may be an effective adjuvant therapy in managing trauma-induced venous leg wounds and supports consideration of early implementation for expedited epithelialization. However, further studies with larger sample sizes are required.

Author affiliations

^aSaint Joseph Health System, Mishawaka, Indiana

^bVeterans Affairs Illiana Healthcare System, Danville, Illinois

Author disclosures

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Disclaimer

The opinions expressed herein are those of the authors and do not necessarily reflect those of *Federal Practitioner*, Frontline Medical Communications Inc., the US Government, or any of its agencies.

Ethics and consent

This retrospective chart review was determined to be exempted by facility policy and Director of Education from institutional review board review and adhered to ethical principles for medical research as mentioned above. Informed consent was not obtained as a retrospective chart review.

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