The role of continuous topical oxygen therapy as an adjunctive treatment in non-healing chronic wounds: a South African perspective

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Background: This study aims to investigate the impact of continuous topical oxygen therapy (cTOT) as an adjunct to routine standard of care (SoC) in several patients with chronic, hard-to-heal wounds at the Wound Management Centre in Pretoria, South Africa.

Patients and methods: Patients with non-healing wounds lasting more than 30 days without active, untreated infection or osteomyelitis were included in this study. Following review and informed consent, patient, wound, and pain assessments (numeric rating scale, NRS) were performed. The cTOT system (cTOT, NATROX® O_2 wound therapy) was applied to the wound and covered with an appropriate secondary dressing. Wound assessments and dressing changes were performed weekly until healing was achieved.

Results: A total of 14 patients received cTOT. Two patients were lost to follow-up, and one failed to return to the clinic after eight weeks of treatment; however, data from that point were included. Six wounds healed within a mean duration of 11.7 weeks. The diabetic foot ulcer (DFU, Texas grade 2B, patient 4) took the longest time to heal (17 weeks), whereas the fastest healing was seen in a venous ulcer (VU) reported to heal in just six weeks, despite a duration of seven months before cTOT. The mean area reduction across the 12 wounds was 78.6%. The NRS pain score was shown to reduce in 5/6 wounds by 3.2 points on average (2–4 range).

Conclusion: cTOT proved to be a valuable adjunct to help improve wound healing and reduce pain in these challenging wounds in South Africa, highlighting the possible benefit of access to this therapy for patients with chronic, non-healing wounds in the region.

Keywords: non-healing wounds, topical oxygen therapy

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Introduction

There is a paucity of data on the burden of wounds across South Africa. However, a recent study reported a wound burden of 34.6% in patients admitted to hospital.[1] Several factors drive the increased need for efficient wound care in South Africa, including a demand for faster recovery of patients with wounds, the need for shortened hospital stay, the rising incidence of chronic diseases that can result in wounds (diabetes, cancer, autoimmune diseases), and the expected increase in the number of surgical procedures.[2] Therefore, more effective treatment pathways will be required to support a growing number of non-healing wounds.

Evidence-based care algorithms can be further optimised with the addition of advanced wound interventions, such as topical oxygen therapy (TOT), that can be easily used and adapted to a patient's lifestyle. TOT is advocated as adjunctive to good standard of care (SoC) when a hard-to-heal wound has not reduced size by more than 40–50% within one month.[3-5] Oxygen supports multiple essential wound-healing functions. Oxygen demand is high in a wound, initially due to the inflammatory processes, as the production of reactive oxidative species (ROS) by phagocytes is oxygen-dependent. Adequate oxygen is also needed for cellular activity throughout the many tissue repair processes, such as the maturation of collagen fibres and appropriate fibroblast proliferation in wounds.[6-10]

Following injury, poor blood circulation, oedema, injured microcirculation, and contraction of vessels in traumatised tissue all limit oxygen distribution to a wound.[8] These issues are common across all chronic, non-healing wounds. Whilst the pathologies that lead to chronic wounds differ on a macro scale, such as diabetes vessel damage, venous skin damage, oedema vascular constriction, and vascular insufficiency, the impact of these states on the actual wound environment in any non-healing wound provides similar challenges.[11,12] This environment results in reduced wound perfusion and oxygen in the localised wound, thereby reducing the wound's capacity to heal.[11,12] Thus, reversing hypoxic conditions in any chronic non-healing wound should support faster healing by supporting the increased demand for oxygen required by the immune response, cell migration, and tissue repair processes.

This case series examined the impact of incorporating continuous topical oxygen therapy (cTOT) as an adjunct to routine SoC in patients with hard-to-heal wounds at the Eloquent Advanced Wound

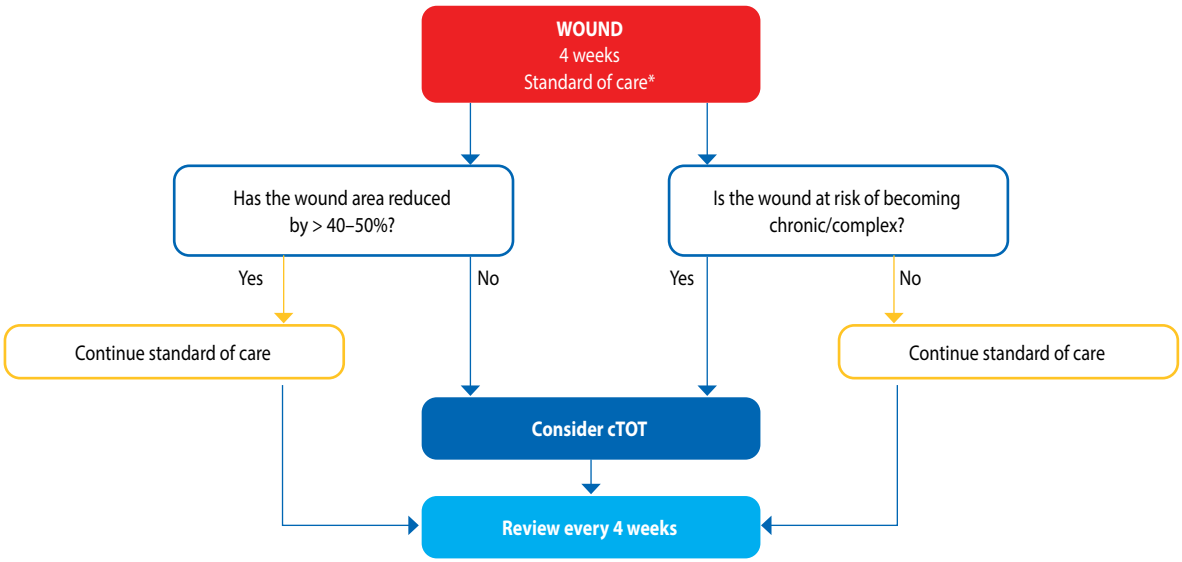


Figure 1: Recommended treatment pathway for the use of cTOT[3,13]
cTOT – continuous topical oxygen therapy
* Standard of care appropriate to wound and patient

Table I: Patient demographics and wound information

Patient				Comorbidities	Wound			
#	Age	Sex	Fitzpatrick scale		Type	Location	Duration (months)	Previous treatments
1	62	M	6	Diabetes (type 1), hypertension, neuropathy	DFU (Texas 3B)	Left forefoot	3	Cadexomer iodine with foam, Hydrofiber Ag dressing, silver foam dressings, PHMB foam, silicone foam
2	53	M	3	Hypertension, PAD, previous MI, DVT, heart failure	AU	Left lower leg lateral	3	Medical-grade honey with silicone foam and light compression
3	83	F	2	Hypertension, PAD, oedema, heart failure	VU	Right leg anterior	4	Silicone foam dressing with medical-grade honey ointment to deslough
4	62	M	3	Diabetes (type 2), hypertension, neuropathy (both feet), Charcot	DFU (Texas 2B)	Left plantar midfoot	12	PHMB foam, honey, silver, PHMB and betaine gel, NPWT, cadexomer iodine
5	73	F	6	Hypertension	VU	Left leg medial	30	Variety of treatments
6	41	F	5	Vitiligo, Lupus	Burn (using IR heat lamp)	Left thigh	3	Petroleum-impregnated tulle, various dressings, antibiotics and analgesia, medical-grade honey with foam dressings, blister graft
7	69	F	2	Venous hypertension	VU	Left lower leg	7	Silicone foam dressing, cadexomer iodine, silver foam dressings
8	25	M	2	Quadriplegia C4–C5	PI (stage 3)	Sacrum	2	Medical-grade honey ointment
9	80	M	2	Hypertension, PAD, venous hypertension, revascularisation	Mixed vascular ulcer	Left leg posterior medial	3	Icing sugar, medical-grade honey, fusidic acid cream
10	25	M	2	None	Surgical (postoperative dehiscence)	Left leg lateral	2	Impregnated povidone-iodine tulle, foam dressing
11	62	M	6	TB, lung removed, extensive thorax surgery	Surgical	Thorax left lateral side	14	Povidone-iodine ointment and gauze, ceramic granules, whole blood clot therapy
12	60	F	6	Hypertension, venous insufficiency, venous hypertension, limb deformity	VU	Right leg anterior	23	Medical-grade honey, petroleum-impregnated gauze tulle, PHMB, SSD cream
13	67	F	2	Hypertension, renal failure, venous insufficiency	VU	Bilateral lower legs	> 144	Various, including compression
14	70	M	2	Paraplegic, colostomy, venous hypertension, venous insufficiency, dependent oedema partly resulting from paraplegia	VU, the wound started as spider bite 12 years ago	Left leg lateral	144	Variety of treatments, including compression

AU – arterial ulcer, DFU – diabetic foot ulcer, DVT – deep vein thrombosis, F – female, IR – infrared, M – male, MI – myocardial infarction, N/A – not applicable, ND – no data/lost to follow-up, NPWT – negative pressure wound therapy, PAD – peripheral artery disease, PHMB – polyhexamethylene biguanide, PI – pressure injury, TB – tuberculosis, SSD – silver sulfadiazine, VU – venous ulcer

Management Centre in Pretoria, South Africa, between 2022 and 2023.

Patients and methods

Patients with a history of hard-to-heal wounds of any aetiology for longer than 30 days were included in this case series. Patients were excluded if any active, untreated infection or osteomyelitis was reported. Patients were eligible for adjunctive therapy if they had less than 40–50% reduction in the wound area in alignment with recommendations, detailed in Figure 1.[3,13]

Wound assessment

Following informed, written consent from the patients, standard patient and wound assessments were performed, capturing the previous management regime, wound aetiology, and wound details (tissue description, size, duration, and location). Pain was assessed using a numeric rating scale (NRS) scored 0–10, where 0 is no pain and 10 is the worst pain possible.

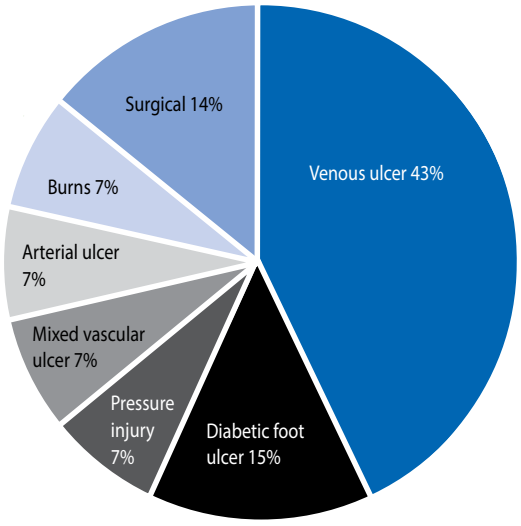


Figure 2: Breakdown of assessed wound aetiologies (*n* = 14)

Table II: Wound assessment information from 14 patients treated with NATROX® O_2 cTOT

#	Wound	Week 1			End of treatment					Time to healing* (weeks)
		Wound area (cm^2)	Wound appearance	Pain score (NRS 0–10)	Wound area (cm^2)	Wound appearance	Pain score (NRS 0–10)	Week	Wound area reduction (%)	
1	DFU (Texas 3B)	24	Granulation, epithelial tissue	0	0	Healed	0	14	100	14
2	AU	13	Sloughy, some granulation, epithelial tissue	5	ND	ND	ND	ND	ND	ND
3	VU	17.5	Sloughy, some granulation, epithelial tissue	3	2.5	Granulation, epithelial tissue	0	7	85.7	N/A
4	DFU (Texas 2B)	1.5	Slough, granulation, epithelial tissue	0	0	Healed	0	17	100	17
5	VU	6.3	Slough, granulation tissue	3	3.2	Some slough, granulation tissue	0	12	49.2	N/A
6	Burn	28	Granulation, epithelial tissue	0	0	Healed	0	12	100	12
7	VU	29.3	Slough, granulation tissue	4	0	Healed	0	6	100	6
8	PI (stage 3)	7.5	Sloughy, some granulation, epithelial tissue	0	0	Healed	0	12	100	12
9	Mixed vascular ulcer	11.3	Slough, necrotic, some granulation	3	0.5	Nearly healed, patient self-care	3	14	95.6	N/A
10	Surgical	2.1	Granulation, epithelial tissue	2	0	Healed	0	9	100	9
11	Surgical	4.5	Granulation, epithelial tissue, exposed muscle/ bone	0	2.7	Granulation, epithelial tissue	0	20	40	N/A
12	VU	32	Some slough, granulation, epithelial tissue	4	25	Granulation, epithelial tissue	0	8	21.9	N/A
13	VU	60	Some slough, granulation, epithelial tissue	0	ND	ND	ND	ND	ND	ND
14	VU	40	Slough, granulation tissue	0	19.6	Some slough, granulation, epithelial tissue	0	7	51	N/A

AU – arterial ulcer, DFU – diabetic foot ulcer, N/A – not applicable, ND – no data/lost to follow-up, NRS – numeric rating scale, PI – pressure injury, VU – venous ulcer
* If applicable
Wound area (cm^2) was calculated by multiplying the maximum wound length (cm) by the maximum wound width (cm). Patients 2 and 13 were lost to follow-up (no data past week 0) and were not included in the analysis. Patient 12 had eight weeks of treatment but failed to return to the clinic.

Treatment regime

The wound was initially cleaned with cleansing solutions containing either hypochlorous acid or polyhexamethylene biguanide (PHMB), and betaine. If required, either sharp debridement or mechanical debridement pads were used. A baseline wound image was then captured using a tablet or mobile phone device (Samsung, Korea). The cTOT system (NATROX® O_2, NATROX Wound Care, Cambridge, United Kingdom) was applied directly to the wound bed and covered with a semipermeable, secondary dressing appropriate for exudate management based on wound assessment and needs.

Wound assessments were performed weekly to monitor progress and change dressings for up to six visits or until healing was achieved. Patients were followed up a month after wound closure.

Results

A total of 14 patients were eligible for adjunctive treatment with wound aetiologies, shown in Figure 2, and additional patient demographics and wound information are in Table I. Two patients were lost to follow-up, and one failed to return to the clinic after eight weeks of treatment; however, data from that point were included. The remaining 11 patients showed either complete healing (n = 6) or ongoing progression to healing (n = 5).

The wound area, pain score (NRS 0–10), and appearance at baseline and the end of cTOT treatment are shown in Table II. Six wounds healed within a mean duration of 11.7 weeks. The DFU Texas grade 2B (patient 4) took the longest time to heal (17 weeks), whereas the fastest healing was seen in a venous ulce (VU) reported to heal in just six weeks despite a duration of seven months before cTOT. The mean area reduction across the 12 wounds was 78.6% during the treatment period (64.3% excluding the six healed patients). Of the six patients that identified initial wound pain, the score from 0 to 10 was reduced by the end of treatment in five wounds by 3.2 points on average (2–4 range). Clinician feedback reported that the ease of application of the device also made it user-friendly for the patients, who, in some cases, could apply the cTOT device by themselves at home.

Below is a summary of four cases as examples within the different types of wounds in the study (Figure 3). The cTOT was well tolerated by the patients with rapid wound healing progression despite the previously long non-healing duration, as demonstrated in Figure 3. Two complicated diabetic foot ulcers (DFUs) (patients 1 and 4) briefly used TOT for 12 and 14 weeks, respectively. Healing was demonstrated by week 14 for patient 1 and week 17 for patient 4. Similar results were shown in patient 6 (burn), which healed in 12 weeks with softer quality scarring reported anecdotally by the clinical team following six weeks of cTOT treatment and good SoC. Finally, patient 8 highlights the management of a stage 3 pressure ulcer; cTOT was applied under a semi-occlusive foam dressing along with SoC for nine weeks, with complete healing recorded at this time, which remained healed at follow-up.

Discussion

The burden of non-healing wounds is growing globally, and South Africa is no exception.[14,15] Whilst acute traumatic wounds tend to predominate in terms of prevalence in South Africa, more complex and severe chronic wounds are increasingly reported in ageing demographics and those with comorbidities.[1,16,17] Furthermore, the financial burden of wounds in South Africa was reported with an estimated spend on wound care of $1.1630 billion in 2019, quoted as purchasing power parity in billions of international dollars, (PPP international $ billion).[18] In addition, patients with non-healing wounds will often have a lower quality of life score compared with other chronic conditions.[19,20]

Non-healing wounds require timely interventions in addition to good SoC to progress healing. The availability and access to advanced therapies have been shown to directly impact on reducing morbidities in chronic wounds, with a recent United States study highlighting a 33% reduction in amputation rates in diabetes patients with access to Medicaid healthcare.[21] TOT is advocated as adjunctive to good SoC when a hard-to-heal wound has not reduced size by more than 40–50% within one month.[3,22] Moreover, TOT use is endorsed and recommended by international expert guidance, including the International Working Group on the Diabetic Foot (IWGDF), the Wound Healing Society (WHS), and the American Diabetes Association (ADA), with potential benefits highlighted across any non-healing wound.[3-7,10,22,23]

This guidance is supported by a growing body of high-level evidence that advocates using cTOT as a beneficial adjunct to wound healing in these hypoxic wounds. The substantive meta-analysis and randomised controlled trial (RCT)-level evidence in DFU is supported by broader real-world evidence in DFU and other chronic wound aetiologies, including leg ulcers (venous and arterial) and other traumatic or surgical non-healing, chronic wounds.[11,24-39]

cTOT delivers a continuous low flow of low-pressure oxygen to the wound, 24 hours a day, seven days a week. The oxygen is generated from the surrounding air using a small electrochemical oxygen generator unit, powered by rechargeable batteries and is wearable and silent. The oxygen is delivered to the wound through a thin, flexible tube using an oxygen delivery system (ODS) and is covered by a semi-occlusive dressing. Once positioned, the ODS is covered with an appropriate secondary semi-occlusive dressing to manage the wound exudate. cTOT is compatible as an adjunctive therapy alongside the gold SoC for the specific wound (i.e. compression for VUs and offloading for DFU). The device is portable, discreet, and silent, enabling the patient to continue their daily activities with minimal disruption.[3]

In this case series, cTOT, along with SoC as appropriate for the wound and the patient, was successfully employed across challenging wounds of different aetiologies with a previous long duration of non-healing. During treatment, rapid progress was observed in wound size reduction (almost 80%). The wounds that healed completely (42.8%) did so, on average, within less than 12 weeks. This concurs with published data, demonstrating a 44.4% healing rate compared to standard care alone (28.1% healed), and a 70.1% reduction in wound area compared to only a 40% reduction in the standard care group in a recent RCT in DFU in a 12-week study.[29] Similar outcomes were reported in other chronic wounds, particularly VUs. In a recent case series of 20 patients with non-healing VUs, 40% of wounds demonstrated complete healing.[37]

Findings were further corroborated in two large observational studies from Kaufman et al.[36] in which cTOT was effective in healing DFUs, pressure ulcers, and "other" chronic wounds. However, it was most

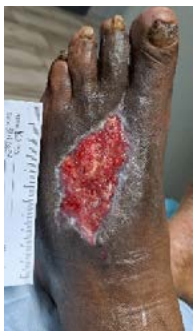
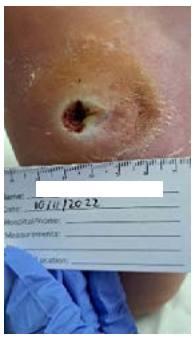
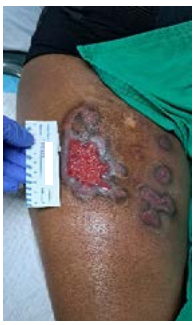
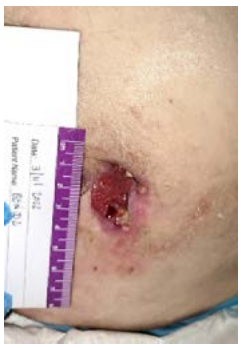
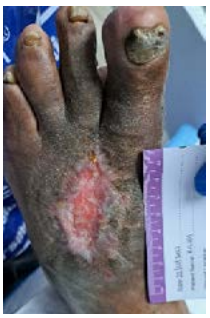
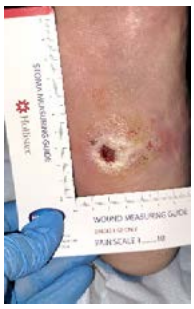
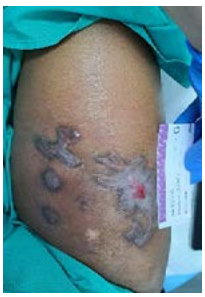
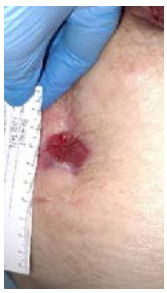
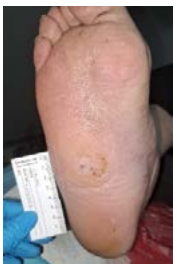
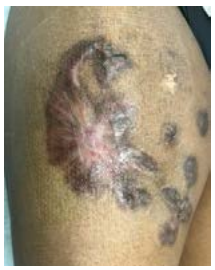
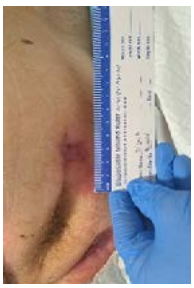
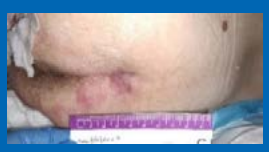
Patient 1: Complicated DFU on forefoot with history of underlying osteomyelitis and amputation of the second toe. Duration: 3 months	**Patient 4: Complicated Charcot DFU plantar. No underlying osteomyelitis present.** Duration: 12 months	**Patient 6: Complicated full-thickness burn on right thigh. NATROX® applied to the main ulcer.** Duration: 3 months	**Patient 8: Quadriplegic patient; multiple pressure ulcers due to defective equipment during loadshedding in SA. Sacral pressure ulcer stage 3.** Duration: 2 months
			
Week 1	**Week 1**	**Week 1**	**Week 1**
			
Week 6	**Week 6**	**Week 6** cTOT therapy discontinued	**Week 4**
			
Week 12 cTOT therapy discontinued at week 9*	**Week 17** cTOT therapy discontinued at week 14*	**Week 12** Wound healed	**Week 8** cTOT therapy discontinued at week 9*
Patient continued home care with silicone-bordered dressing; healed at 14 weeks. 	Wound healed at week 17 and is still intact at home. 	Follow-up to monitor scaring and overall healing. Hypertrophic scarring improved. The TOT site had better, softer quality scarring present.	Patient continued with pressure care; healed at 12 weeks. 

Figure 3: Four case examples of different non-healing wound aetiologies from the study highlighting the progress of cTOT treatmentcTOT – continuous topical oxygen therapy, DFU – diabetic foot ulcer, SA – South Africa
* Therapy discontinued before complete healing due to clinic access issues

effective in healing chronic venous leg ulcers (60% VUs in the healed/healing group vs. 18% in the non-responder group).[36] An overall reduction in VU wound area of 52% was achieved following the cTOT intervention.[11,36] This remarkable effect was also reflected in this case series with the fastest healing observed in a VU in just six weeks, despite a duration of seven months before cTOT. This promising data highlights the beneficial healing outcomes across multiple types of chronic wounds and warrants further exploration in controlled studies.

In this study, a marked reduction in pain in five patients during and following treatment highlights the additional benefits of cTOT use,

which may aid patient well-being and engagement with care. This finding is congruent with the published data of cTOT use in DFU, showing a significant reduction in mean pain scores from 2.4 (± 1.8) at baseline to 0.5 (± 1.0) at three months ($p = 0.008$).[31] Furthermore, recent data from Sweden highlighted that 76% of patients whose wounds were treated with cTOT reported a substantial relief of pain during the therapy, and 53% had complete resolution of all pain symptoms, resulting in a concurrent cessation of opioid medication in 69% of patients.[37]

Injury-associated pain, combined with inflammation, oedema, ischaemic nerve damage, and infection, can lead to a vicious cycle of pain in chronic wounds.[40,41] This is compounded by the fact that opioid medications used for chronic wound pain can delay wound healing, and the literature reports that some wounds are refractory to analgesic treatments.[42,43] Patients with chronic wounds find the pain particularly distressing, with one recent qualitative meta-synthesis of studies highlighting pain as one of the most common symptoms of venous leg ulcer (VLU), which significantly affects the patient's life.[44,45] Therefore, adequate pain management is an essential part of the patient journey and may help improve patient compliance with treatment plans.[41] Hence, as demonstrated in this report, alternative technology interventions, such as cTOT, that can support pain reduction in addition to the multiple benefits of wound progression and healing, should be considered to help patients regain their lives.

In this series, an improvement in the quality of granulation tissue and scarring was reported, an area that wider controlled trials should further substantiate. Furthermore, none of the cases with healed wounds had any further breakdown at the one-month follow-up visit, frequently observed with previous treatment strategies in those patients. This enhanced durability concurs with a post hoc analysis in a follow-up to a recent RCT, which demonstrated that 85% of wounds healed with cTOT remained healed at one year following treatment compared to only 60% with good SoC.[46]

Conclusion

The role of oxygen is critical to the wound environment and progression of wound healing, irrespective of aetiology, and has been substantiated in this case series using cTOT as an advanced intervention that positively influences wound healing. cTOT was found to be a beneficial adjunctive therapy to progress wound healing in these previously recalcitrant, challenging wounds. The ease of application of the device and pain reduction in the wounds supported a user-friendly, patient-centred approach to care, allowing patients to regain control of their wounds.

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Conflict of interest

L Naude created and led the case series. L Naude, E Woodmansey, and W Cole contributed to data analysis and interpretation, literature review, and manuscript preparation. E Woodmansey and W Cole are employees of NATROX® Wound Care (Inotec AMD Ltd., United Kingdom).

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L Naude received cTOT devices from Vertice MedTech for this study.

Ethical approval

This observational study followed routine practice and measures, so no additional ethical approval was required. All patients provided written consent to participate in this case series.

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References

1. Lotz M. The burden of wounds in a resource constrained tertiary hospital a cross-sectional-study. WHSA [Internet]. 2019;12(1):29-33. Available from: https://hdl.handle.net/10520/EJC-17b0876853. Accessed 29 October 2023.
2. Giaquinto-Cilliers MGC, Nair A, von Pressentin KB, Coetzee F, Saeed H. A 'game of dressings': strategies for wound management in primary health care. S Afr Fam Pract. 2022;64(1):5462. https://doi.org/10.4102/safp.v64i1.5462.
3. Frykberg R, Andersen C, Chadwick P, et al. Use of topical oxygen therapy in wound healing. J Wound Care. 2023;32(Sup8b):S1-32. https://doi.org/10.12968/jowc.2023.32.Sup8b.S1.
4. Chen P, Vilorio NC, Dhatariya K, et al. Guidelines on interventions to enhance healing of foot ulcers in people with diabetes (IWGDF 2023 update). Diabetes Metab Res Rev. 2024;40(3):e3644. https://doi.org/10.1002/dmrr.3644.
5. El Sayed NA, Aleppo G, Aroda VR, et al. 12. Retinopathy, neuropathy, and foot care: standards of care in diabetes-2023. Diabetes Care. 2023;46(Suppl 1):S203-15. https://doi.org/10.2337/dc23-S012.
6. Frykberg RG. Topical wound oxygen therapy in the treatment of chronic diabetic foot ulcers. Medicina (Kaunas). 2021;57(9):917. https://doi.org/10.3390/medicina57090917.
7. Serena TE, Andersen C, Cole W, et al. Guidelines for the use of topical oxygen therapy in the treatment of hard-to-heal wounds based on a Delphi consensus. J Wound Care. 2021;31(Sup3):S20-4. https://doi.org/10.12968/jowc.2022.31.Sup3.S20.
8. Gottrup F. Physiology and measurement of tissue perfusion. Ann Chir Gynaecol. 1994;83(3):183-9.
9. Boulton AJM, Armstrong DG, Löndahl M, et al. New evidence-based therapies for complex diabetic foot wounds. Am Diabetes Assoc. 2022;2022(2):1-23. https://doi.org/10.2337/db2022-02.
10. Gottrup F, Dissemond J, Baines C, et al. Use of oxygen therapies in wound healing. J Wound Care. 2017;26(Sup5):S1-43. https://doi.org/10.12968/jowc.2017.26.Sup5.S1.
11. Kaufman H, Gurevich M, Tamir E, et al. Topical oxygen therapy stimulates healing in difficult, chronic wounds: a tertiary centre experience. J Wound Care. 2018;27(7):426-33. https://doi.org/10.12968/jowc.2018.27.7.426.
12. Kaufman H, McCardle J, Jones NJ. Challenging wounds, improving outcomes: treatment of complex diabetic foot wounds using topical oxygen therapy [Internet]. London: Wounds International; 2018. p. 1-12. Available from: https://www.natroxwoundcare.com/wp-content/uploads/diabetic-foot-ulcers-booklet.oifxq_.pdf. Accessed 29 October 2023.
13. Cullen B, Al Eisa AA, Kaufman H, et al. Consensus round table meeting: topical oxygen therapy for healing complex wounds [Internet]. London: Wounds International; 2018. p. 1-20. Available from: https://woundsinternational.com/wp-content/uploads/sites/8/2023/02/92c7b47255eee2a1511106a60516e7ed.pdf. Accessed 29 October 2023.
14. Carter MJ, DaVanzo J, Haught R, et al. Chronic wound prevalence and the associated cost of treatment in Medicare beneficiaries: changes between 2014 and 2019. J Med Econ. 2023;26(1):894-901. https://doi.org/10.1080/13696998.2023.2232256.
15. Guest JF, Fuller GW, Vowden P. Cohort study evaluating the burden of wounds to the UK's National Health Service in 2017/2018: update from 2012/2013. BMJ Open. 2020;10(12):e045253. https://doi.org/10.1136/bmjopen-2020-045253.
16. Norman R, Matzopoulos R, Groenewald P, Bradshaw D. The high burden of injuries in South Africa. Bull World Health Organ. 2007;85(9):695-702. https://doi.org/10.2471/BLT.06.037184.
17. Mokgethi MJT. Wound assessment and patients' knowledge of wound care at a rural community health centre in the Bojanala district, Rustenburg [Master of Science in Nursing]. Johannesburg: University of the Witwatersrand; 2019. Available from: https://wiredspace.wits.ac.za/server/api/core/bitstreams/7b65446b-2e03-4d66-8cab-498edf8e3cf6/content. Accessed 29 October 2023.
18. Queen D, Harding K. What's the true costs of wounds faced by different healthcare systems around the world? Int Wound J. 2023;20(10):3935-8. https://doi.org/10.1111/iwj.14491.

19. Zhu X, Olsson MM, Bajpai R, et al. Health-related quality of life and chronic wound characteristics among patients with chronic wounds treated in primary care: a cross-sectional study in Singapore. Int Wound J. 2022;19(5):1121-32. https://doi.org/10.1111/iwj.13708.
20. Finlayson K, Miaskowski C, Alexander K, et al. Distinct wound healing and quality-of-life outcomes in subgroups of patients with venous leg ulcers with different symptom cluster experiences. J Pain Symptom Manage. 2017;53(5):871-9. https://doi.org/10.1016/j.jpainsymman.2016.12.336.
21. Tan T-W, Crocker RM, Palmer KNB, et al. A qualitative study of barriers to care-seeking for diabetic foot ulceration across multiple levels of the healthcare system. J Foot Ankle Res. 2022;15(1):56. https://doi.org/10.1186/s13047-022-00561-4.
22. Lavery LA, Suludere MA, Attinger CE, et al. WHS (Wound Healing Society) guidelines update: diabetic foot ulcer treatment guidelines. Wound Repair Regen. 2024;32(1):34-46. https://doi.org/10.1111/wrr.13133.
23. Atkin L, Bućko Z, Montero EC, et al. Implementing TIMERS: the race against hard-to-heal wounds. J Wound Care. 2019;28(Sup3a):S1-50. https://doi.org/10.12968/jowc.2019.28.Sup3a.S1.
24. Carter MJ, Frykberg RG, Oropallo A, et al. Efficacy of topical wound oxygen therapy in healing chronic diabetic foot ulcers: systematic review and meta-analysis. Adv Wound Care (New Rochelle). 2023;12(4):177-86. https://doi.org/10.1089/wound.2022.0041.
25. Sun X-K, Li R, Yang X-L, Yuan L. Efficacy and safety of topical oxygen therapy for diabetic foot ulcers: an updated systematic review and meta-analysis. Int Wound J. 2022;19(8):2200-9. https://doi.org/10.1111/iwj.13830.
26. Sethi A, Khambhayta Y, Vas P. Topical oxygen therapy for healing diabetic foot ulcers: a systematic review and meta-analysis of randomised control trials. Health Sci Rev. 2022;3:100028. https://doi.org/10.1016/j.hsr.2022.100028.
27. Connaghan F, Avsar P, Patton D, O'Connor T, Moore Z. Impact of topical oxygen therapy on diabetic foot ulcer healing rates: a systematic review. J Wound Care. 2021;30(10):823-9. https://doi.org/10.12968/jowc.2021.30.10.823.
28. Thanigaimani S, Singh T, Golledge J. Topical oxygen therapy for diabetes-related foot ulcers: a systematic review and meta-analysis. Diabet Med. 2021;38(8):e14585. https://doi.org/10.1111/dme.14585.
29. Serena TE, Bullock NM, Cole W, et al. Topical oxygen therapy in the treatment of diabetic foot ulcers: a multicentre, open, randomised controlled clinical trial. J Wound Care. 2021;30(Sup5):S7-14. https://doi.org/10.12968/jowc.2021.30.Sup5.S7.
30. Yu J, Lu S, McLaren A-M, Perry JA, Cross KM. Topical oxygen therapy results in complete wound healing in diabetic foot ulcers. Wound Repair Regen. 2016;24(6):1066-72. https://doi.org/10.1111/wrr.12490.
31. Tang TY, Mak MYQ, Yap CJQ, et al. An observational clinical trial examining the effect of topical oxygen therapy (NatroxTM) on the rates of healing of chronic diabetic foot ulcers (OTONAL trial). Int J Low Extrem Wounds. 2021;23(2):326-37. https://doi.org/10.1177/15347346211053694.
32. Hunter P, Greco E, Cross K, Perry J. Topical oxygen therapy shifts microbiome dynamics in chronic diabetic foot ulcers. Wounds. 2020;32(3):81-5.
33. Wilson D, McIntyre K, Goodfellow P, et al. Case series: using NATROX® oxygen wound therapy in the management of diabetic foot ulcers [Internet]. London: Wounds UK; 2019. p. 1-13. Available from: https://wounds-uk.com/wp-content/uploads/sites/2/2023/02/c1bd5fefe7fb58272a6daa249065f72a.pdf. Accessed 29 October 2023.
34. Jones NJ, Curran G, Ivins NM, Harding KG, Hayes PD. The role of topical oxygen therapy in the treatment of diabetic foot ulceration. Harrogate: Wounds UK; 2017. Available from: https://www.natroxwoundcare.com/resource/the-role-of-topical-oxygen-therapy-in-the-treatment-of-diabetic-foot-ulceration/. Accessed 29 October 2023.
35. Hayes PD, Alzuhir N, Curran G, Loftus IM. Topical oxygen therapy promotes the healing of chronic diabetic foot ulcers: a pilot study. J Wound Care. 2017;26(11):652-60. https://doi.org/10.12968/jowc.2017.26.11.652.
36. Kaufman H, Gurevich M, Tamir E, et al. Topical oxygen therapy used to improve wound healing in a large retrospective study of wounds of mixed aetiology. Wounds International [Internet]. 2021;12(2):63-8. Available from: https://woundsinternational.com/wp-content/uploads/sites/8/2023/02/2efb079ef38d8971ce34f0c5e13c6467.pdf. Accessed 29 October 2023.
37. Jebril W, Nowak M, Palin L, et al. Topical oxygen treatment relieves pain from hard-to-heal leg ulcers and improves healing: a case series. J Wound Care. 2022;31(1):4-11. https://doi.org/10.12968/jowc.2022.31.1.4.
38. Silvestrini S. Supplementary oxygen and wound healing. Wounds International [Internet]. 2019;10(4):50-6. Available from: https://woundsinternational.com/wp-content/uploads/sites/8/2023/02/c54fb6116a946e978df21618d7023eeb.pdf. Accessed 29 October 2023.
39. Mani R. Topical oxygen therapy for chronic wounds: a report on the potential of InotecTM a new device for delivering enriched oxygen to chronic wounds. J Wound Technology. 2010;9(3):28-30.
40. Bechert K, Abraham SE. Pain management and wound care. J Am Col Certif Wound Spec. 2009;1(2):65-71. https://doi.org/10.1016/j.jcws.2008.12.001.
41. Cole W, Woodmansey E. Supporting the patient journey: there are alternative methods of pain management in wound care [Internet]. Podiatry Management; 2023. p. 77-84. Available from: https://www.natroxwoundcare.com/wp-content/uploads/NWC.PodiatryMgmt_Nov23_SupportingThePatientJourney.pdf. Accessed 29 October 2023.
42. Shanmugam VK, Couch KS, McNish S, Amdur RL. Relationship between opioid treatment and rate of healing in chronic wounds. Wound Repair Regen. 2017;25(1):120-30. https://doi.org/10.1111/wrr.12496.
43. Kogure T, Sumitani M, Abe H, et al. Ischemic ulcer pain is both nociceptive and neuropathic pain based on a discriminant function analysis using the McGill pain questionnaire. J Pain Palliat Care Pharmacother. 2017;31(2):98-104. https://doi.org/10.1080/15360288.2017.1304495.
44. Price P, Fogh K, Glynn C, et al. Managing painful chronic wounds: the Wound Pain Management Model. Int Wound J. 2007;4 Suppl 1(Suppl 1):4-15. https://doi.org/10.1111/j.1742-481X.2007.00311.x.
45. Guo X, Gao Y, Ye X, Zhang Z, Zhang Z. Experiences of patients living with venous leg ulcers: a qualitative meta-synthesis. J Tissue Viability. 2024;33(1):67-74. https://doi.org/10.1016/j.jtv.2023.11.012.
46. Al-Jalodi O, Kupcella M, Breisinger K, Serena TE. A multicenter clinical trial evaluating the durability of diabetic foot ulcer healing in ulcers treated with topical oxygen and standard of care versus standard of care alone 1 year post healing. Int Wound J. 2022;19(7):1838-42. https://doi.org/10.1111/iwj.13789.