Mechanistic insights and international use cases of continuous topical oxygen therapy in wound management

Introduction: Chronic wounds are a growing global health concern, often complicated by tissue hypoxia and impaired healing. Continuous topical oxygen therapy (cTOT) has emerged as a promising adjunctive treatment that delivers sustained oxygen directly to the wound bed, supporting cellular metabolism, immune modulation, angiogenesis and tissue regeneration.

Methods: This article reviews the mechanistic basis of cTOT, including its effects on hypoxia-inducible factors, mitochondrial ATP production, immune cell function and extracellular matrix remodelling. Eight international case studies were collected from six countries, each documenting the use of cTOT in managing complex, non-healing wounds. Cases included diabetic foot ulcers, vasculitis, burns, surgical dehiscence, calciphylaxis and osteoradionecrosis.

Results: All cases demonstrated significant clinical improvement following cTOT, with complete wound closure achieved in each instance. Healing timelines ranged from 4 to 29 weeks, depending on wound type and severity. The therapy was well-tolerated, easily integrated into standard care protocols, and effective across diverse healthcare settings and patient populations.

Conclusions: cTOT is a mechanistically sound, globally adaptable adjunct for managing hard-to-heal wounds. Its demonstrated efficacy across a range of wound types supports its broader integration into comprehensive wound care strategies. Further research is warranted to optimise treatment protocols and expand clinical indications.

Windy Cole
Director of Wound Care Research, Kent State University College of Podiatric Medicine, Independence, Ohio, USA
Harikrishna KR Nair
Head and Consultant of Wound Care Unit, Dept of Internal Medicine, Hospital Kuala Lumpur, Kuala Lumpur, Malaysia
Sagar U Nigwekar
Co-director of the Kidney Research Center, Massachusetts General Brigham, Massachusetts, USA
Viviana Gonçalves
Tissue Viability Nurse Cardiothoracic Surgery, Unidade Local de Saúde de São João, Porto, Portugal
Liezl Naude
Director, Eloquent Health & Wellness, Pretoria, South Africa
Wolmark Xiques Molina
Head of Research & Development Unit, Cure Latam Health Technologies, Colombia, South America
Noel B Natoli
Plastic surgeon, New York Plastic Surgical Group, New York, USA
Andrew Camilleri
Consultant Oral and Maxillofacial Surgeon, Luton and Dunstable University Hospital NHS Foundation Trust, Luton, UK

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- cTOT
- Use cases
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- Complex wounds

Oxygen is a fundamental element for sustaining life; however, the intricate molecular mechanisms by which cells perceive and adapt to variations in oxygen availability were not unraveled until the latter part of the 20th century. The seminal discoveries made by Gregg Semenza, Sir Peter Ratcliffe and William Kaelin, which were recognised with the 2019 Nobel Prize in physiology or medicine, elucidated the critical role of hypoxia-inducible factors (HIFs) in the cellular sensing of oxygen levels (Lee et al, 2020). Their pioneering research clarified the complex signalling pathways that govern gene expression in response to hypoxic conditions, thereby establishing a foundation for a transformative epoch in biomedical research and therapeutic innovation (Lee et al, 2020). These findings expanded the understanding of the pathophysiological processes underlying hard-to-heal wounds, allowing clinicians to more effectively employ therapies aimed at overcoming barriers to healing.

This article reviews the historical development of topical oxygen therapy in the management of hard-to-heal wounds and emphasises its utility through a wide variety of international use cases, building on the global clinical significance of the therapy.

The evolution of topical oxygen therapy

The therapeutic application of oxygen has undergone significant evolution since its initial identification in the late 18th century. Originally considered a panacea for various respiratory conditions, oxygen therapy gained momentum through the pioneering contributions of Thomas Beddoes and James Watt, who founded the study of pneumatic medicine, to address respiratory ailments such as asthma and heart failure (Miller and Levere, 2008). However, it was not until the 20th century that oxygen therapy began to be subjected to systematic investigation and refinement. The endeavour to comprehend how organisms adapt to fluctuating oxygen levels is steeped in the history of physiology and medicine. For centuries, the essential role of oxygen in sustaining life has been acknowledged; nevertheless, the cellular mechanisms responsible for detecting and responding to hypoxia remained poorly understood. Initial

physiological investigations during the 20th century identified systemic responses to low-oxygen environments, such as heightened ventilation and increased production of erythropoietin, yet the molecular mechanisms underpinning these adaptations were largely obscure (Goldberg and Schneider, 1994).

Topical oxygen therapy (TOT), a specialised modality of oxygen application, emerged as a consequence of broader advancements in respiratory care. Distinct from systemic oxygen delivery via inhalation, TOT entails the direct application of oxygen to wounds or localised tissues, with the objective of enhancing healing through improved cellular oxygenation. This approach garnered attention in the mid-20th century, particularly in relation to chronic wounds, diabetic ulcers, and ischaemic injuries, where compromised oxygen delivery significantly impedes tissue regeneration (Dawi et al, 2025). The introduction of portable oxygen systems in the 1950s, spearheaded by innovators such as Dr Alvan Barach, facilitated more flexible and targeted oxygen delivery modalities (Heffner, 2012). These technological advances laid the groundwork for the implementation of TOT, which became increasingly feasible with the evolution of wound care techniques and oxygen diffusion systems. By the 1970s, the invention of the pulse oximeter by Takuo Aoyagi revolutionised the monitoring of oxygen levels, thereby further promoting the clinical integration of oxygen-based therapies (Miyasaka et al, 2021).

The foundational discoveries and innovations in pneumatic medicine have propelled advancements in the field and facilitated new therapeutic interventions for diseases characterised by disrupted cellular oxygen gradients, particularly in the context of chronic, non-healing wounds. The historical evolution of oxygen as a medical intervention has been the catalyst for the broader advancement of TOT, transitioning from a generalised therapeutic approach to a precise and targeted tool in contemporary wound care practices.

Mechanisms of action of TOT

Effective wound management is paramount within the medical field, necessitating a comprehensive evaluation and treatment process that incorporates systematic assessment and tailored intervention strategies. This process entails the identification of potential aetiological factors contributing to delayed healing, necessitating adjustments to the treatment plan as appropriate. A thorough evaluation serves as the cornerstone for formulating a personalised care strategy that integrates various medical management approaches, including vascular assessments, metabolic and nutritional evaluations, the reduction of pressure sources, and robust infection control measures (Handelsman et al, 2023). Despite the implementation of these strategies, a significant proportion of chronic wounds fail to achieve the expected healing outcomes through conventional care practices alone (Monika et al, 2022). In these instances, timely and proactive interventions, which extend beyond traditional methodologies, are often requisite to mitigate physiological barriers to tissue repair and regeneration, thus promoting complete wound closure.

Wound healing as a multifaceted process

Wound healing constitutes a complex, multi-phase biological process that necessitates the precise coordination of cellular activities, which include inflammation, proliferation and tissue remodelling (Rodrigues et al, 2018). Oxygen plays a critical role in each of these phases, serving not only as a substrate for energy production, but also as a crucial signalling molecule that modulates gene expression and affects cellular behaviour. Hypoxia, frequently observed in wounded tissue as a result of disrupted vasculature or ischaemic pathologies, initiates a cascade of molecular responses predominantly influenced by HIFs (Boersema et al, 2021).

Therapeutic strategies designed to modulate oxygen availability have shown promise in enhancing the wound healing process, particularly in chronic wounds characterised by persistent hypoxia. A profound understanding of the molecular mechanisms through which oxygen regulates wound healing offers insights into fundamental biological processes and has significant implications for the development of targeted interventions aimed at improving clinical outcomes (Boersema et al, 2021).

Cellular requirements for energy

Oxygen is indispensable for mitochondrial oxidative phosphorylation, which is recognised as the primary source of adenosine triphosphate (ATP) in most eukaryotic cells (Sen, 2009). During the wound healing process, energy demands escalate substantially to sustain various cellular functions, including proliferation, migration, and the synthesis of extracellular matrix components (Sen, 2009). Under hypoxic conditions, cells often resort to anaerobic glycolysis, a less efficient metabolic pathway, potentially compromising the healing process unless counterbalanced by adaptive physiological responses (Sen, 2009).

Immune cell function and oxygen dynamics

Oxygen availability is pivotal in augmenting the bactericidal efficacy of immune cells, such as neutrophils and macrophages, through the production of reactive oxygen species (Frykberg et al, 2023). These molecules are essential for pathogen clearance and the modulation of inflammation. Conversely, hypoxic conditions can impair immune cell functionality, facilitating persistent infections and chronic inflammatory states.

Oxygen levels also influence the phenotypic expression of macrophages during the wound healing process. Initially, hypoxia induces a pro-inflammatory M1 phenotype, which later transitions to a reparative M2 phenotype as tissue oxygenation improves (Al Sadoun, 2022). This phenotype shift is fundamental for the resolution of inflammation and the initiation of tissue repair. Furthermore, the availability of oxygen in the cellular milieu critically determines the activation and operational capacity of neutrophils, vital components of the innate immune response (Allen et al, 1997).

Optimal oxygen concentrations enable neutrophils to produce superoxide, a reactive species integral to the oxidative burst mechanism that facilitates bacterial destruction (Allen et al, 1997). Superoxide also plays a role in orchestrating inflammation and recruiting additional immune cells to sites of infection, underscoring the necessity of maintaining adequate oxygen levels for effective neutrophil activity and overall immune function (Fraisl et al, 2009).

Angiogenesis and wound healing

Oxygen exerts regulatory effects on the expression of angiogenic factors, particularly vascular endothelial growth factor, which is crucial for neovascularisation – the formation of new blood vessels (Fraisl et al, 2009). This process is essential for restoring perfusion to the wound site and ensuring an adequate supply of nutrients and immune cells. Clinical observations have demonstrated the beneficial effects of oxygen therapy on neovascularisation, improved microcirculation, and enhanced oxygenated hemoglobin levels in wounded tissues (Cole and Woodmansey, 2025).

Collagen synthesis and extracellular matrix remodeling

Oxygen is vital for promoting fibroblast migration and proliferation, as well as enhancing collagen synthesis and the tensile strength of collagen fibers. Fibroblasts necessitate oxygen for the hydroxylation of proline and lysine residues during collagen biosynthesis. Sufficient oxygenation is therefore critical for the appropriate cross-linking and tensile integrity of the extracellular matrix, which is essential for effective wound closure and scar formation (Sen, 2009). Moreover, fibroblasts and keratinocytes exhibit adaptive responses to oxygen gradients, modulating collagen synthesis, cellular proliferation, and re-epithelialisation processes (Knighton et al, 1981). This oxygen-dependent regulation ensures that healing progresses efficiently and that tissue integrity is reinstated.

Keratinocyte behaviour and oxygen availability

The influence of oxygen on wound healing, particularly regarding keratinocyte behaviour, is significant, as it facilitates both proliferation and migration, which are vital for successful re-epithelialisation. Oxygen levels markedly affect the expression of critical growth factors, most notably transforming growth factor-beta (TGF-β) (Ramirez et al, 2014). TGF-β is instrumental in coordinating interactions between epithelial cells and the stromal environment during the healing cascade. It promotes granulation tissue formation by enhancing the synthesis of extracellular matrix components, including collagen, by fibroblasts. Furthermore, TGF-β stimulates the differentiation of fibroblasts into myofibroblasts, which are integral to wound contraction (Ramirez et al, 2014). Additionally, TGF-β acts as a critical inducer for the migration of mesenchymal cells, thus significantly contributing to the processes of wound re-epithelialisation and closure (Asmis et al, 2010). This comprehensive role underscores the importance of oxygen in the terminal phases of the wound healing cascade.

A nuanced understanding of the multifaceted role of oxygen in wound healing paves the way for the use of innovative therapeutic strategies aimed at reversing hypoxia in the tissues to enhance healing outcomes, particularly in challenging hard-to-heal wound cases.

Continuous topical oxygen therapy

Currently, TOT is acknowledged as a significant adjunctive treatment in hard-to-heal wound management, especially for patients presenting with compromised vascular supply due to various comorbid conditions. The term topical oxygen therapy encompasses a range of modalities aimed at the localised delivery of oxygen to wounds or ulcers to facilitate tissue repair and promote healing (Frykberg et al, 2023).

A notable technique within this framework is continuous topical oxygen therapy (cTOT), specifically utilising the NATROX O_2 device (NATROX O_2, NATROX Wound Care, Cambridge

UK), which administers a continuous flow of low-pressure oxygen to the affected area, functioning ceaselessly for 24 hours a day, seven days a week. This cTOT device generates oxygen from ambient air through a compact electrochemical oxygen generator (Oxygen Generator, OG), which operates on rechargeable batteries **[Figure 1]**.

The cTOT system is characterised by its portability, wearability, and operational silence, which allows patients to engage in daily activities without significant disturbance. Oxygen is delivered at a controlled flow rate of 11 ml per hour via a thin, flexible tube, integrated within an oxygen delivery system (ODS), and is subsequently covered with a semi-occlusive dressing to maintain a suitable environment for wound healing. Upon application, the ODS is often secured with a semi-occlusive secondary dressing to effectively manage wound exudate. Importantly, cTOT is designed to act as an adjunctive therapy, complementing standard care protocols for specific wound types, such as compression therapy for venous ulcers and offloading techniques for diabetic foot ulcers (DFU). The discreet and silent nature of this device affords patients the ability to adhere to their treatment regimen while minimising disruption to their daily lives. For patients with painful wounds that limit ambulation and transportation to receive treatment, cTOT offers an opportunity to receive an effective and portable oxygen therapy and may mitigate the risk of pain evocation.

Clinical applications

Chronic wounds present a significant and increasingly prevalent global health issue, with current estimates indicating prevalence rates of 1.51–2.21 per 1000 individuals, equating to over 13 million patients affected worldwide (Martinengo et al, 2019). The burden of chronic wounds is expected to escalate, largely due to the demographic shift towards aging populations, as older adults are at greater risk of developing conditions such as diabetes and vascular insufficiencies that predispose them to non-healing wounds (Martinengo et al, 2019).

This anticipated rise in incidence underscores the urgent need for enhanced management strategies, evidence based practices, and allocation of healthcare resources to effectively address the complex needs of this growing patient demographic. A comprehensive understanding of the epidemiological trends surrounding chronic wounds is imperative for healthcare professionals and policymakers to develop targeted preventive and therapeutic interventions.

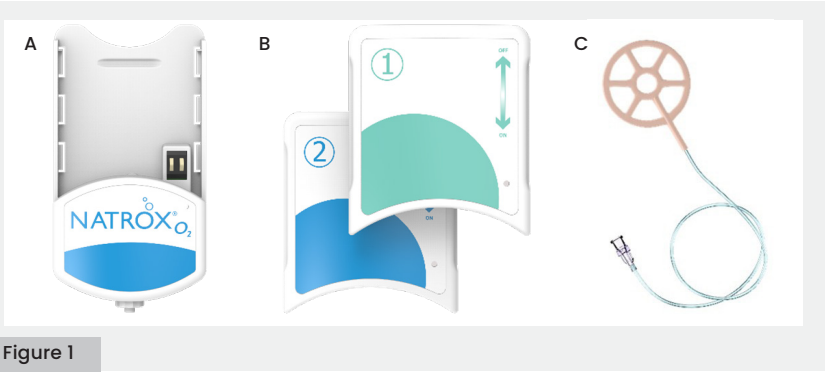

Figure 1

Figure 1. The NATROX O_2 system. Oxygen Generator (A); rechargeable batteries (B); oxygen delivery system (C).

There is a growing body of literature supporting the efficacy of TOT, providing a robust evidence base that underscores its potential as a valuable adjunct in contemporary wound management strategies. It has been shown to be particularly effective in the treatment of chronic wounds that have failed to respond to standard of care interventions, thereby addressing a critical gap in the management of these challenging conditions. The synthesis of findings from peer-reviewed randomised controlled trials provides robust evidence for use of TOT in the management of DFUs, which are notoriously complex and challenging to heal (Yu et al, 2016; Frykberg et al, 2020; Serena et al, 2021; Al-Jalodi et al, 2022).

Moreover, the utilisation of topical oxygen therapy has been demonstrated to facilitate enhanced wound healing rates in multiple systematic reviews and meta-analyses (Connaghan et al, 2021; Carter et al, 2022; Sun et al, 2022; Du et al, 2024; OuYang et al, 2024). This accumulating evidence has resulted in the incorporation of topical oxygen therapy within various expert guidelines, recommending its application for non-healing wounds that exhibit resistance to conventional treatment modalities (Chen et al, 2023; ElSayed et al, 2023; ElSayed et al, 2024; Lavery et al, 2024).

Continuous topical oxygen therapy is increasingly being integrated into comprehensive wound care protocols on a global scale, owing to its demonstrated efficacy in the management of diverse hard-to-heal wounds. In this context, the authors present eight brief clinical case studies of cTOT from six countries, highlighting its application across a spectrum of challenging wound types with global representation.

International use cases

All patients provided informed consent for the de-identified use of these images for publication purposes. Continuous topical oxygen therapy was initiated per manufacturer IFU and secondary semi-occlusive moisture managing dressings were used and changed

Figure 2. Case 1 DFU. Wound appearance at baseline (A); wound appearance after 7 weeks of cTOT (B); wound appearance after 29 weeks of cTOT (C).

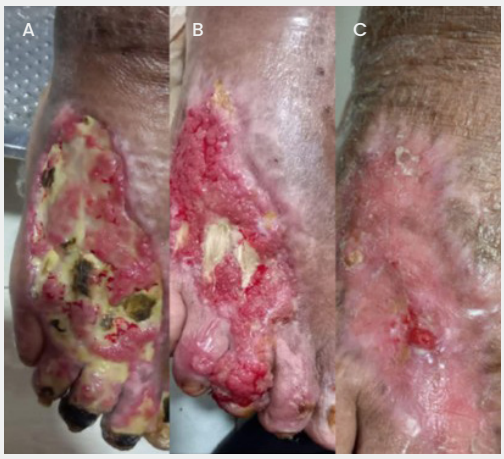

Figure 2

at least every 7 days or with more frequency based on exudate levels.

Case 1: Diabetic foot ulcer
This case was submitted by Wolmark Xiques Molina (Bogotá, Colombia). The patient was a 53-year-old man with a past medical history (PMH) of type 2 diabetes mellitus. He presented with a Wagner grade 2 DFU on the right foot, with a baseline measurement of 13.0 cm × 5.0 cm **[Figure 2]**.

Clinical course
The patient had with a non-healing DFU resistant to standard care for over 2 months. Continuous topical oxygen therapy was initiated. After 7 weeks, the wound showed marked granulation and reduction in size. By week 29, near-complete wound closure was achieved, demonstrating the long-term efficacy of cTOT in managing complex diabetic wounds.

Case 2: Leukocytoclastic vasculitis wound
This case was submitted by Windy Cole (Cleveland, Ohio, USA). The patient, a 59-year-old woman, was an active smoker, had a PMH of depression and anxiety, a recent initiation of NSAID for osteoarthritis, and no prior vasculitis. Histopathology confirmed leukocytoclastic vasculitis with neutrophilic infiltration and fibrinoid necrosis of small dermal vessels. The patient presented with a leukocytoclastic vasculitis wound with a baseline measurement of 3.7 cm × 3.2 cm **[Figure 3]**.

Figure 3. Case 2 leukocytoclastic vasculitis wound. Wound appearance at baseline (A); wound appearance after 30 days of cTOT (B); complete wound closure after 77 days cTOT (C).

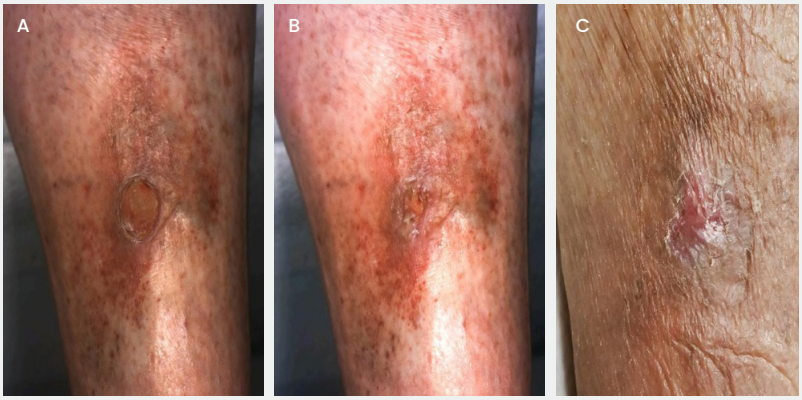

Figure 3

Clinical course
The patient developed a drug-induced leukocytoclastic vasculitis wound that was treated with cTOT. After 30 days the wound area had decreased by 60%. Complete wound closure was obtained by day 77 of cTOT. This case shows the utility of cTOT to reverse delayed healing in vasculitis wounds by decreasing persistent inflammation and tissue hypoxia.

Case 3: Burn wound
This case was submitted by Liezl Naude (Pretoria, South Africa). A 41-year-old woman presented with a complicated full-thickness burn on her right thigh **[Figure 4]** with a duration of 3 months. The wound had a baseline area of 28 cm^2.

Clinical course
The chronic burn wound was treated with cTOT. After 6 weeks, the wound showed significant epithelialisation and reduction in size. By week 12, continued wound contraction and healing was observed, indicating cTOT's effectiveness in managing burn injuries.

Case 4: Open amputation site
This case was submitted by Harikrishna KR Nair (Kuala Lumpur, Malaysia). A 51-year-old male with a PMH of type 2 diabetes presented with an open amputation site. The wound had a baseline measurement of 7cm × 5 cm **[Figure 5]**.

Clinical course
The wound of 1 month duration status post ray amputation of the fourth toe due to infection, was treated with cTOT. At baseline the wound extended to bone and tendon. By day 49, significant granulation tissue was noted at the wound base covering the previously exposed bone and tendon structures, with significant new epithelium noted on wound periphery. Complete wound closure was achieved with cTOT by day 111 illustrating cTOT's effectiveness on complex wounds with exposed deep tissue structures.

Case 5: Calciphylaxis
This case was submitted by Sagar Nigwekar (Boston, MA, USA). The patient was a 59-year-old woman with a PMH of type 2 diabetes, obesity, and Roux-en-Y gastric bypass surgery.

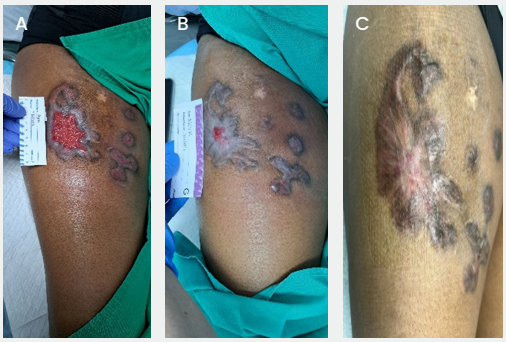

Figure 4

Figure 4. Case 3 burn wound. Wound appearance at baseline (A); wound appearance after 6 weeks of cTOT (B); complete wound closure after 12 weeks of cTOT (C).

A diagnosis of calciphylaxis was confirmed via clinicopathological assessment. The wound had a baseline measurement of 15 cm × 5 cm covered by necrotic tissue [Figure 6].

Clinical course

This complex painful wound was treated with cTOT. After 4 weeks, the necrotic tissue was resolved, and new areas of granulation tissue were evident. Complete wound closure and substantial improvement in pain severity was achieved by week 9, underscoring cTOT's potential in rare and severe wound types like calciphylaxis.

Case 6: Sternotomy wound dehiscence

This case was submitted by Viviana Gonçalves (Porto, Portugal). A 72-year-old man presented with a sternotomy surgical wound dehiscence that had a duration of 2 months, and a baseline measurement of 15 cm × 4 cm [Figure 7].

Clinical course

The patient's wound responded rapidly to cTOT. After 2 weeks, granulation tissue was present, and by week 4, complete wound closure was achieved. This case illustrates cTOT's rapid action in post-surgical wound healing.

Case 7: Mastectomy wound dehiscence

This case was submitted by Noel B Natoli (New York, USA). The patient was a 25-year-old transgender man with a PMH of gender reassignment surgery (female to male). He presented with surgical wound dehiscence post-mastectomy, with dermal pedicle exhibiting ischaemia on the right dermal pedicle [Figure 8].

Clinical course

The wound was treated with cTOT. After 4 weeks, significant healing was observed, and by week 7, the wound had closed. This case highlights cTOT's role in managing post-operative complications in gender-affirming surgeries.

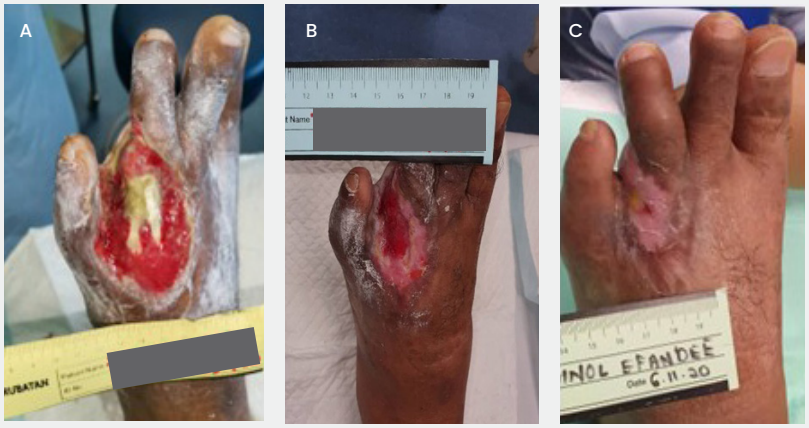

Figure 5

Figure 5. Case 4 open amputation site. Wound appearance at baseline (A); wound appearance after 49 days of cTOT (B); complete wound closure after 111 days of cTOT (C).

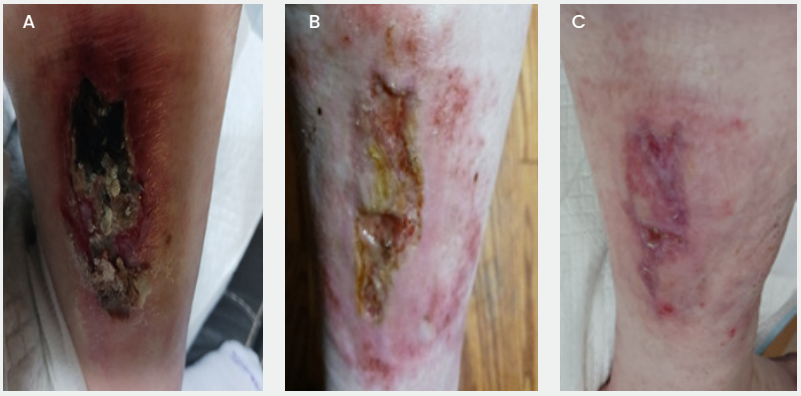

Figure 6

Figure 6. Case 5 calciphylaxis wound. Wound appearance at baseline (A); wound appearance after 4 weeks of cTOT (B); complete wound closure after 9 weeks of cTOT (C).

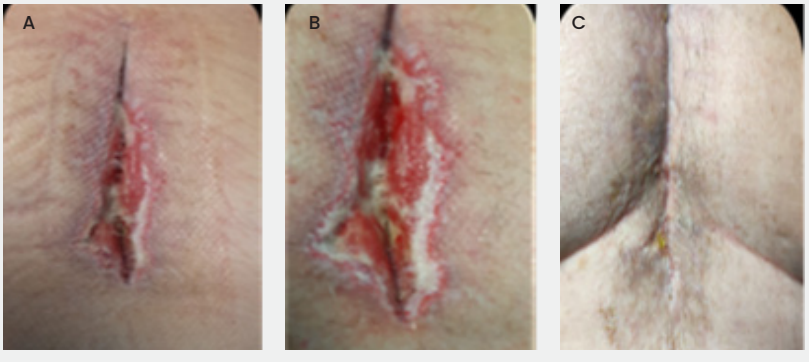

Figure 7

Figure 7. Case 6 sternotomy wound. Wound appearance at baseline (A); wound appearance after 2 weeks of cTOT (B); complete wound closure after 4 weeks of cTOT (C).

Case 8: Maxillofacial osteoradionecrosis

This case was submitted by Andrew Camilleri (Luton, UK). The patient was a 65-year-old man with a PMH of osteoradionecrosis following radical radiotherapy for squamous cell

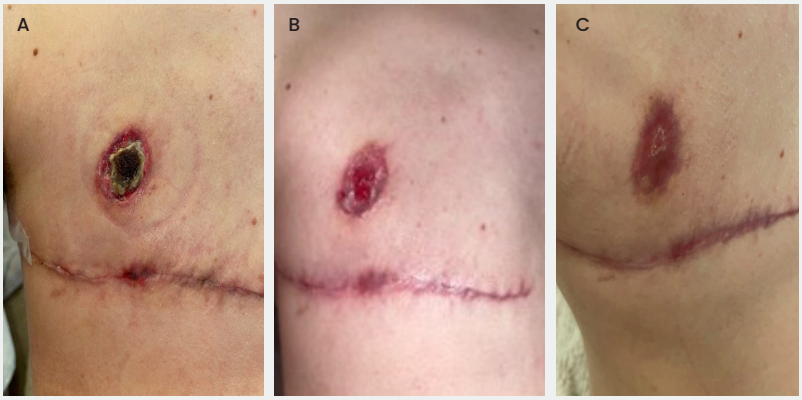

Figure 8

Figure 8. Case 7 mastectomy surgical wound tissue necrosis. Wound appearance at baseline (A); wound appearance after 4 weeks of cTOT (B); wound obtained complete closure after 9 weeks of cTOT (C).

carcinoma. He presented with a non-healing surgical reconstruction wound, with a duration of 4.5 months and a baseline measurement of 3.5 cm × 1.5 cm [Figure 9].

Clinical course

The wound showed improvement after 3 weeks of cTOT, with complete closure achieved by week 5. This case demonstrates cTOT's effectiveness in irradiated tissue and complex maxillofacial wounds.

Discussion

Continuous topical oxygen therapy has emerged as an adaptable adjunct in the management of hard-to-heal wounds. The mechanistic underpinnings of cTOT are rooted in its ability to reverse tissue hypoxia, modulate immune responses, and stimulate angiogenesis and extracellular matrix remodelling – increasingly supported by a growing body of clinical evidence. The international case studies presented here underscore the versatility and efficacy of cTOT across a diverse array of wound types, patient populations and healthcare settings.

While the published evidence on cTOT is largely confined to DFUs, its role in enhancing tissue oxygenation and promoting wound closure has been demonstrated in a wide variety of wound types. The cases described here – from vasculitis wounds in the USA to burn injuries in South Africa and maxillofacial dehiscence in the UK – emphasise that the therapeutic benefits of cTOT extend far beyond DFUs. These examples illustrate cTOT's capacity to address complex wound etiologies, including inflammatory, ischemic, post-surgical, and rare conditions such as calciphylaxis and osteoradionecrosis.

Mechanistically, cTOT supports wound healing by enhancing mitochondrial ATP production, promoting fibroblast and keratinocyte function, and facilitating the transition of macrophages from pro-inflammatory (M1) to reparative (M2) phenotypes (Knighton et al, 1981; Allen et al, 1997; Fraisl et al, 2009; Sen, 2009; Al Sadoun, 2022; Frykberg et al, 2023; Cole and Woodmansey, 2025). These cellular effects are critical in overcoming the physiological barriers that impede healing in chronic wounds. Moreover, the continuous delivery of oxygen via wearable devices like the NATROX O_2 system ensures sustained therapeutic exposure, which is particularly beneficial in outpatient and resource-limited settings.

The global applicability of cTOT is further reinforced by its integration into standard hard-to-heal wound care protocols for a variety of wound aetiologies, as illustrated by the cases discussed. However, despite these promising outcomes, further research is warranted to delineate optimal treatment parameters, identify the patient subgroups most likely to benefit, and evaluate long-term outcomes. Randomised controlled trials and real-world studies across diverse healthcare systems will be essential to validate these findings and inform evidence-based guidelines.

Conclusion

Continuous topical oxygen therapy represents a clinically validated, mechanistically sound, and globally adaptable adjunct in the management of chronic and complex wounds. Its ability to enhance tissue oxygenation and accelerate healing has been demonstrated across diverse wound types and international settings. As evidence continues to accumulate, cTOT is poised to become an integral component of comprehensive wound care strategies, offering improved outcomes for patients worldwide.

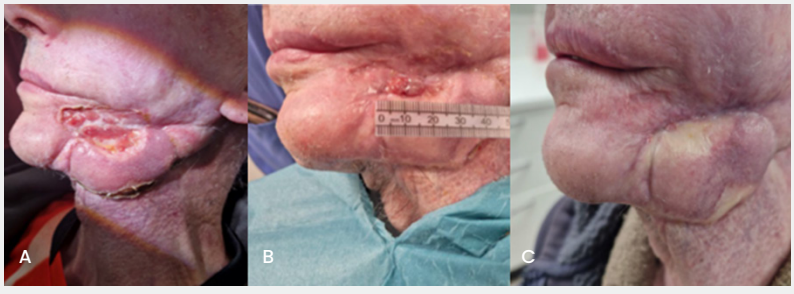

Figure 9

Figure 9. Case 8 maxillofacial wound dehiscence. Wound appearance at baseline (A); wound appearance after 3 weeks cTOT (B); complete wound closure after 5 weeks cTOT (C).

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