Continuous Topical Oxygen Therapy made easy

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Introduction

It has been shown that 97% of chronic, non-healing wounds have low oxygen levels (Hauser, 1987) and additional associated comorbidities will only compromise oxygen supply further. Oxygen is essential for wound healing and plays a vital role in key processes such as angiogenesis, collagen deposition, and epithelialisation [Figure 1]. In addition, oxygen is required to create energy for cells to function and is essential for immune cells to attack bacteria, thus is pivotal in the host response to tackling infection (Chen et al, 2023; Frykberg et al, 2023).

Patients with a chronic wound may experience lack of oxygen (hypoxia) due to a variety of systemic disease states contributing to poor circulation (Cole and Woodmansey, 2023). Chronic hypoxia leads to inactivation of growth factors and cellular senescence, with eventual wound deterioration (Frykberg et al, 2023). Early intervention with supplemental oxygen, such as topical oxygen therapy (TOT), can help to correct this. TOT involves the administration of topical oxygen directly to injured tissue by either continuous delivery or pressurised systems (Connaghan et al, 2021; Chen et al, 2023).

INTRODUCING NATROX® O_2

NATROX® O_2 is a wearable medical device designed to deliver continuous topical oxygen directly to a wound to promote and enhance the healing process [Figure 2]. Battery-powered, portable, and completely silent, the discreet device is easy to manage, and practical for everyday use, allowing patients to continue with their usual daily activities. NATROX® O_2 has also been shown to help relieve pain in hard-to-heal leg ulcers while improving healing rates (Jebril et al, 2022). In a recent study, 76% of patients reported substantial pain relief, which led to 69% discontinuing opioids (Jebril et al, 2022).

How can NATROX® O_2 help non-healing wounds?

NATROX® O_2 is a low-flow (11ml/hour) tissue oxygenation system intended to provide topical oxygen to non-healing wounds, including diabetic foot ulcers (DFUs), leg ulcers, pressure injuries and open surgical wounds stalled in any phase of wound healing. See Box 1 for when to consider NATROX® O_2 therapy*.

**Always refer to the Instructions For Use (IFU) for the country of use as indications can vary from CE countries to the US.*

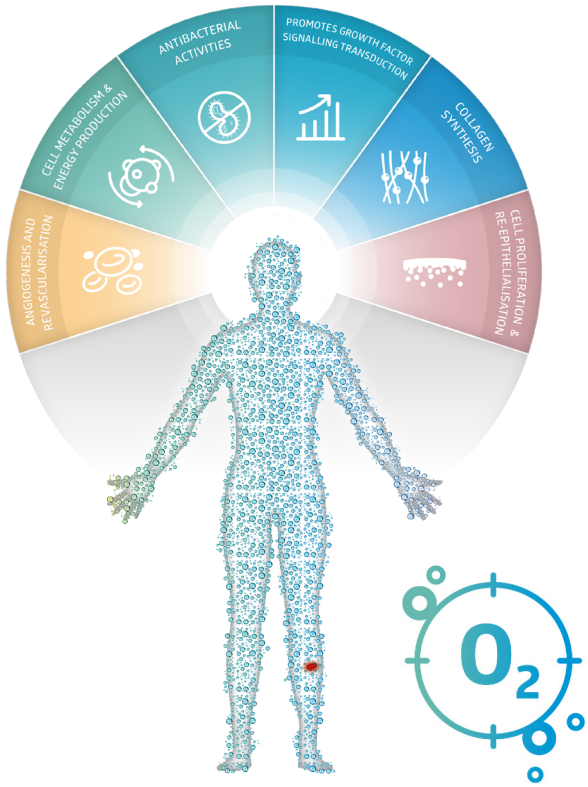

Figure 1: Summary of essential roles of oxygen in wound

Box 1: When to consider NATROX® O_2 therapy

- If the wound has failed to respond to standard of care (SoC) within 4 weeks
- If there are clinical signs that the wound is hypoxic
- If the patient has underlying conditions or risk factors that make them more susceptible to wound complications.

How does NATROX® O_2 work?

Through a process of water electrolysis, the NATROX® O_2 Oxygen Generator (OG) takes atmospheric air and creates a flow of highly concentrated oxygen, which is delivered to the wound using the NATROX® O_2 Oxygen Delivery System (ODS). The sterile, single-use ODS has a soft, pliable "wheel" shape that allows optimal oxygen flow and conformability to the wound bed. This ensures comfort for the patient whilst allowing free passage of wound exudate into the secondary dressing. The OG is powered by one of two rechargeable batteries that are interchanged every 24 hours.

EVIDENCE-BASED PRACTICE

Recent evidence-based guidelines call out the use of TOT and recognise the high-level of evidence supporting the technology. The Wound Healing Society (WHS) Guidelines update increased TOT to 'Level 1' Evidence in its updated DFU treatment guidelines;

Figure 2: The NATROX® O_2 system consists of three proprietary components: a) NATROX® O_2 Oxygen Generator (OG); b) two interchangeable batteries; c) NATROX® O_2 Oxygen Delivery System (ODS)

the guideline states that "topical oxygen has been shown to increase the incidence of healing and decrease the time to heal" (Lavery et al, 2023). The new International Working Group on the Diabetic Foot (IWGDF) Guidelines also gives TOT recognition as an accepted intervention when treating non-healing DFUs where standard of care (SoC) alone has failed (Chen et al, 2023). Similarly, the American Diabetes Association (ADA) gave TOT an "A Grade" evidence rating; panel findings state "multiple reasonably robust randomised controlled trials (RCTs), systematic reviews and meta-analyses provide supportive evidence for the more established TOTs" (ElSayed et al, 2023). The same rating was given in 2024 for this advanced wound care option (ElSayed et al, 2024).

A multicentre, open, RCT was carried out to investigate the effect of continuous topical oxygen therapy (cTOT) on healing rates in patients with hard-to-heal DFUs (i.e. non-responsive over four weeks; Serena et al, 2021). After a 4-week run-in period to exclude any wounds healing with SoC, this study demonstrated that cTOT could lead to a statistically significant improvement in healing rates in patients with DFUs that are resistant to healing with SoC alone. The patient group receiving NATROX® O_2 in conjunction with SoC had a 71% greater healing rate and a 73% greater average reduction in wound size than those receiving SoC alone (Serena et al, 2021).

It was also noted that interventions, such as cTOT, that can support faster healing and maintain care in the community rather than the hospital setting may lead to more cost-effective care in the longer term (Serena et al, 2021). The high-quality RCT level evidence in DFUs is substantiated by the consistent positive outcomes recognised in many real-world case series for both DFUs and other chronic wounds (e.g. leg ulcers, pressure injuries, and other non-healing wounds), highlighting the extent of use and practical impact in real-world wound care settings. An extensive list of key evidence for all methods of topical oxygen can be found in Table 1.

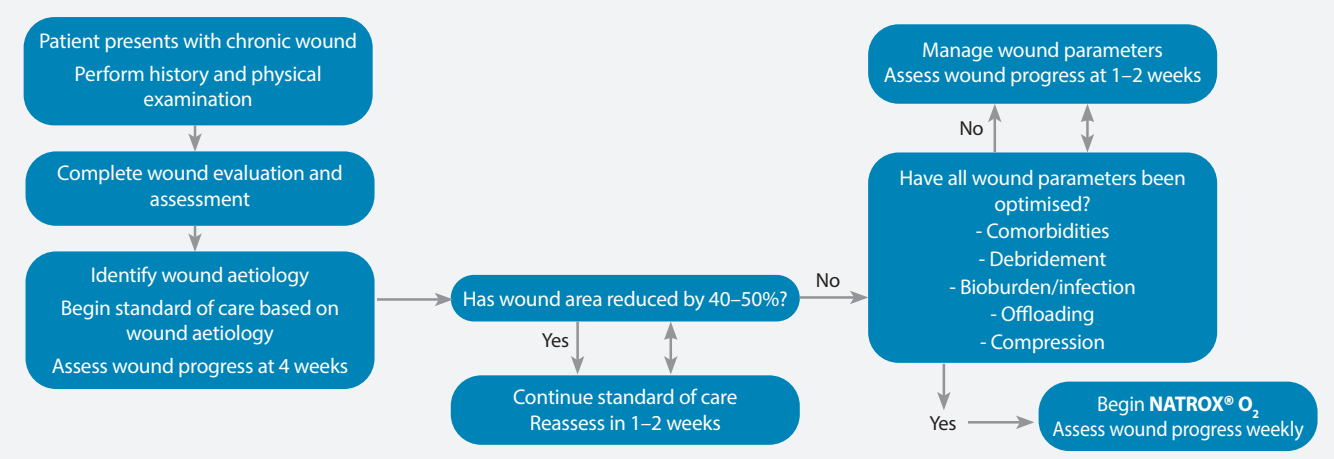

Figure 3: Chronic wound management algorithm

Table 1. Key evidence for the use of TOT	
Systematic Reviews and Meta-Analyses of RCTs	**Key outcomes**
Carter et al, 2023	A random-effects meta-analysis of four RCTs demonstrated that TOT improved wound healing at 12 weeks vs. SoC alone, supporting the use of TOT for the treatment of chronic Wagner 1 or 2 DFUs in the absence of infection and ischemia. The overall GRADE level of evidence for TOT was moderate. RR: 1.59; 95% CI: 1.07–2.37; *p*=0.021
Sethi et al, 2022	Meta-analysis of four RCTs demonstrated that use of adjuvant TOT significantly increased complete wound healing by approximately 60% at 12 weeks of wound healing in DFUs vs. SoC alone. RR: 1.59; 95% CI: 1.07, 2.37; *p*=0.02; NNT: 6.3
Sun et al, 2022	Meta-analysis of seven trials demonstrated that the TOT group had a higher healing rate with no effect on adverse events. RR: 1.63; 95% CI: 1.33, 2.00; *p*=0.096
Thanigaimani et al, 2021	Meta-analysis of six RCTs demonstrated that TOT significantly increased the likelihood of ulcer healing vs. controls. RR: 1.94; 95% CI: 1.19, 3.17; I^2: 57%; NNT: 5.33
Connaghan et al, 2021	Meta-analysis of five RCTs demonstrated that DFUs are >2 times more likely to heal with TOT vs. SoC alone. OR: 2.49; 95% CI: 1.59–3.90; *p*=0.00001
RCTs	**Key outcomes**
Serena et al, 2021 Multi-centre RCT, *n*=145 DFU	**Complete healing:** significantly more patients in the cTOT group healed by 12 weeks vs. the SoC group (36/81 [44.4%] vs. 18/64 [28.1%] respectively [*p*=0.044]) **Wound reduction:** significantly higher wound reduction reported in the cTOT group vs. the SoC group, achieving a mean reduction of 70.1% vs. 40% respectively (*p*=0.005) **Pain:** measured using the Visual Analogue Scale — majority of patients reported no pain in either group initially. Therefore, no significance was seen between the groups
Yu et al, 2016, RCT, *n*=20 DFU	**Complete healing:** Grade II ulcers: 100% cTOT-treated wounds healed vs. zero in the control group, Grade III ulcers: 50% cTOT-treated vs. zero in the control group **Wound reduction:** significant decrease in mean wound area size from baseline over 8 weeks (*p*<0.001) in the cTOT group and with the exception of week 1, significant reduction at every week (W2-8). Wound exudate increased significantly (in the first two weeks); treatment significantly increased rate of wound closure
RCT follow-up	**Key outcomes**
Al-Jalodi et al, 2022 Follow-up to Serena et al (2021) RCT	**Recurrence:** 85% of the cTOT patients remained healed at 1 year vs. 60% of the SoC patients **Amputation:** 1 major amputation in a SoC patient
Case Series	**Key outcomes**
Lee et al, 2024 Case series, *n*=8 non-healing wounds, cTOT and shared care	**Complete healing:** 2/8 wounds completely epithelialised (12 weeks) **Wound reduction:** mean percentage area reduction 92% in 12 weeks **Resource:** remote telehealth resulted in operational efficiencies — 54% increase in clinical interactions, whereas clinical time reduced by 25.8% **Patient satisfaction:** 8/8 patients had improved Health Status Scores
Cole et al, 2023 Case series, *n*=3 post-radiation wounds	**Complete healing:** cTOT resulted in complete wound healing in all 3 patient cases **Pain:** marked reduction in wound pain during the course of treatment
Jebril et al, 2022 Retrospective case series, *n*=20	**Complete healing:** 8/20 (40%) of the wounds completely healed with cTOT — time taken varied from <1 month–12 months **Pain:** measured using the Numeric Pain Rating Scale (mean value reduced from 8 to 2 following treatment) — 13 (76%) patients had substantial pain relief; 9 (53%) patients had complete pain regression (p<0.00001); 11/16 patients (69%) stopped taking opioids completely following cTOT intervention

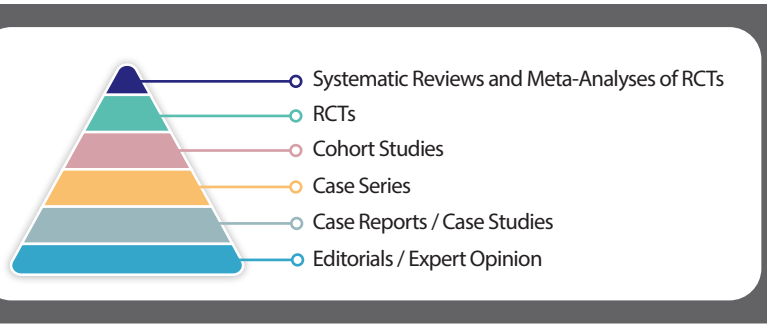

Table 1. Key evidence for the use of TOT *(Continued)*

Case Series	Key outcomes
Kaufman et al, 2021 Retrospective study, *n*=200 chronic non-healing wounds	**Complete healing:** 56/200 wounds healed in the study — variable dependant on wound type: Arterial = 16%; DFU = 26%; PI = 31%; VLU = 34%; Other = 20% **Wound reduction:** significant wound area reduction in 108/200 wounds
Tang et al, 2021 Longitudinal, open prospective registry study, *n*=20 DFU	**Complete healing:** wound closure of >75% was observed in 14/20 (70%) patients Mean time for 100% closure was 77.6 ± 32.5 days No ulcer recurrence reported in follow-up period **Wound reduction:** significant wound area reduction compared to baseline 91.3% (±14.9%) by 3 months (*p*=0.001) **Pain:** mean pain scores reduced from 2.4 (±1.8) at baseline to 0.5 (±1.0) at 3 months (*p*=0.008) **Quality of life:** assessed every 4 weeks using the Diabetic Foot Ulcer Scale — significant improvements in "leisure" and whether "bothered by the ulcer care" between baseline and 3 months. Negative emotions reduced between baseline to 2 months. All patients were very satisfied using the ambulatory device
Hunter et al, 2020 Case series, wound and microbiome assessment, *n*=6 DFU	**Complete healing:** 5/6 healed over 8 weeks **Microbiome swab genome analysis:** no obvious pattern between presence of a specific pathogen and duration/severity of ulcer; however, the wound microbiome shifted toward a diverse flora dominated by aerobes and facultative anaerobes with oxygen therapy in 5 healed wounds (no change in population in the non-healing ulcer)
Expert Opinion	**Consensus/guideline title**
Lavery et al, 2023	WHS DFU Treatment Guidelines
Frykberg et al, 2023	Use of TOT in Wound Healing Consensus
Chen et al, 2023	IWGDF DFU Intervention Guidelines
ElSayed et al, 2023; 2024	ADA Standards of Care in Diabetes Guidelines
Pachecho et al, 2023	LATAM cTOT Consensus
Health Technology Wales, 2022	Evidence Appraisal Report

RR = risk ratio; CI = confidence interval; NNT = number needed to treat; I^2 = measure of heterogeneity; OR = odds ratio

Scan the QR code to view all NATROX® O_2 resources.

WHEN TO USE?

The chronic wound management algorithm [Figure 3] may help to guide clinicians using NATROX® O_2 on non-healing wounds (i.e. wounds not reducing in size >50% in 4 weeks by SoC alone).

How to apply?

1. It is important to practice good wound hygiene/wound bed preparation prior to NATROX® O_2 application. Firstly, cleanse the wound with normal saline or any preferred wound cleansing product and pat dry. Any necrotic/thick sloughy tissue should also be removed through the appropriate debridement method.
2. Remove the ODS from the sterile packaging and place the white side of the wheel directly onto the wound bed (with the beige shiny side facing upwards). A second kit can be ordered if the wound is larger than 10 x 10 cm/4 x 4 inches, or the location of the ODS wheel can be rotated to a new location on the wound bed at each dressing change.
3. Secure the tubing to the skin with tape that can be easily removed on fragile skin and position the tubing so that it runs towards the waist. Consider cushioning the tubing to prevent pressure damage to the skin. If using with compression, tubing can be fed out when wrapping.
4. For wounds with heavy exudate or wounds that require a filler, place these products over the ODS.
5. Apply an appropriate semi-occlusive dressing over the ODS — dressing choice is indicated by the amount of drainage and wound characteristics.
6. Change the ODS with each dressing change, and at least once a week. No product (e.g. cream, ointment or gel) should be applied to the wound bed under the ODS. Frequency of dressing changes should be based on the amount of exudate and the dressing manufacturer's guidance, in accordance with clinical best practice.
7. Slide a fully charged battery into the OG, check the green light is blinking and connect the ODS tubing via the leur lock connector.
8. Place the OG in an appropriate place so the tubing does not kink and, if using a holster, make sure the green light is visible.

Scan the QR code to watch the NATROX® O_2 therapy application video series.

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WHAT TO EXPECT?

NATROX® O_2 can be administered by clinicians and patients/carers in clinical settings or at home and is compatible with most standard secondary dressings, including compression. Treatment is typically 8–12 weeks to complete healing, but this can vary from patient to patient. Generally, there are stages of healing that help to indicate the wound is on a healing trajectory, see **Figure 4.** Exudate levels usually increase for the first two weeks of cTOT treatment. Periwound protection via a tissue protectant or barrier product should be considered to prevent maceration. The ODS should be replaced with each dressing change (a minimum of once every 7 days). It may also be useful to consider continuing treatment for a short duration following closure to ensure that the skin has fully healed and to reduce risk of recurrence (Wounds International, 2018).

TIPS AND TRICKS FOR PATIENTS

- Always have the spare battery on charge
- Batteries need to be changed every 24 hours
- Check the blinking green light is visible on the OG
- Initially, an increase in exudate and wound size may be noticeable due to NATROX® O_2 kickstarting cellular processes involved in removal of non-viable tissue and healing in the first two weeks of therapy — this will decrease as healing progresses
- Adjust the tubing so that it is comfortable — tubing that is pulling too tight may disconnect and tubing that has a kink or is bent may restrict the flow of oxygen
- Disconnect the OG before taking a shower or bath and avoid direct exposure of the dressing and the ODS to water.

Figure 4: What may be expected during treatment with NATROX® O_2

Authors

Viviana Gonçalves,
Tissue Viability Nurse, Cardiothoracic Surgery Department, Centro Hospitalar e Universitário de São João, Porto, Portugal

Alison Schofield,
Head of Education/Tissue Viability Nurse Consultant, NHS Pioneer Wound Healing and Lymphoedema Centres, Eastbourne, UK

CASE STUDY

The following case study represents everyday use of NATROX® O_2 in promoting wound healing and relieving pain and, ultimately, helping to improve patient quality of life.

Patient presentation and history

A 55-year-old male with diabetes mellitus and high blood pressure was admitted for a heart transplant following a 2-month stay in intensive care. The patient developed a category/grade IV pressure injury 30 days after the transplant was carried out.

Management and outcomes

Previous treatment included hydromechanical debridement and commencement of negative pressure wound therapy (NPWT; -125mmHg, every 96 hours) and a white foam dressing. After 45 days of treatment, there was increased exudate and delayed wound healing with suspected biofilm. The wound was covered with devitalised and senescent tissue and the wound edges were macerated [Figure 5]. Dressings were becoming saturated prior to planned dressing changes and the wound was very painful (9 out of 10 on a Numerical Pain Rating Scale, where 10 is the worst pain imaginable). Due to the lack of wound progress, pain and periwound complications, the decision was made to discontinue NPWT.

The wound was cleansed with hypochlorous acid and mechanical debridement was performed. The NATROX® O_2 ODS was applied to the wound bed along with a polyabsorbent fibre dressing (based on ammonium polyacrylate polymer around an acrylic core) and polyurethane foam with silicone. During follow-up (+4 days), exudate and inflammatory signs had reduced [Figure 6]. The patient reported a significant reduction in pain and improved sleep and mobility, allowing him to continue with his usual daily activities. The decision was made to continue with the current treatment regimen. Dressing changes were planned for every 3–4 days.

After the fourth dressing change (+14 days), the wound showed no inflammatory signs and exudate had decreased significantly. Granulation tissue was present in the wound bed and the wound edges were contracting [Figure 7]. The wound was cleansed as before; the treatment plan was changed to: ODS application covered with a sucrose octasulfate (TLC-NOSF) dressing and polyurethane foam with silicone. After five days, the wound showed signs of epithelialisation and the patient had no wound pain. Treatment continued with ODS application, a sucrose octasulfate (TLC-NOSF) dressing and simple secondary dressing. The wound closed 5 days later [Figure 8].

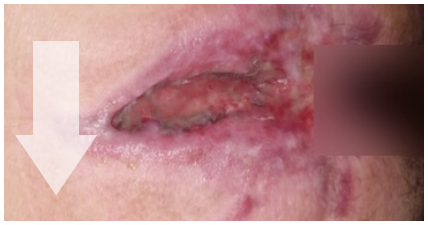

Figure 5: Macerated wound edges following 45 days of NPWT; cTOT commenced

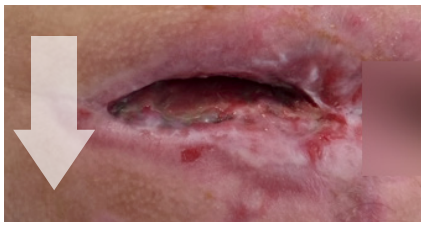

Figure 6: Reduced pain, exudate and inflammatory signs (+4 days)

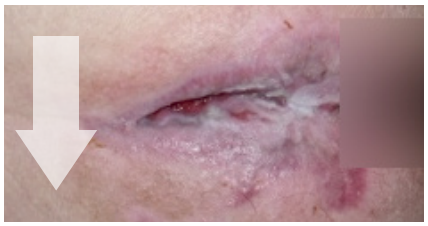

Figure 7: Reduced wound size and inflammation with increased granulation tissue (+14 days)

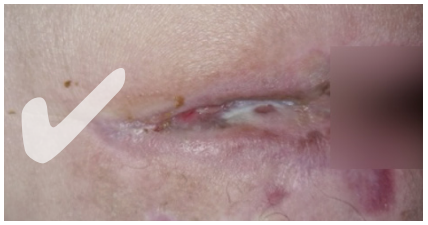

Figure 8: Wound closure (+42 days)

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NATROX® Wound Care

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