Supplemental Oxygen Therapy in Wound Healing

When used together or sequentially, HBOt and cTOT are a winning combination for treating DFUs.

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Introduction

When a wound forms, there is disruption in the protective barrier function of the skin. Subsequently, the processes of wound repair and regeneration are orchestrated by an innate homeostatic mechanism known as the healing cascade. This dynamic series of events involves the coordinated interaction of blood cells, proteins, proteases, growth factors, and extracellular matrix components to support tissue repair and regeneration.[1]

When the healing cascade is interrupted, chronic, non-healing wounds develop. These wounds commonly present with deficient oxygen gradients, inadequate blood and nutrient supply, low levels of growth substance, and senescent cellular activity.[2–4] When wounds fail to heal in a timely manner, there is an increased risk of infection and amputation.[5–7]

Adequate oxygen is required for a multitude of processes in the wound healing cascade, including angiogenesis, phagocytosis of bacteria, collagen deposition, and epithelialization.[8] Unfortunately, patients with hard-to-heal wounds often exhibit paltry levels of oxygen within wounded tissues, resulting in a delay in healing. There exists in these wounds a substantial imbalance between the supply of oxygen and the high energy demand of the healing tissue.[8–10]

A wealth of studies from both clinical and pre-clinical perspectives support the use of oxygen delivery to the wounded tissues to aid in wound healing.[8,9,11–15] Hyperbaric Oxygen Therapy (HBOt) and Topical Oxygen Therapy (TOT) are established means of delivering supplemental oxygen to the wound milieu in order to improve the wound healing environment and trajectory.[14]

Figure 1: Typical hyperbaric oxygen chamber

This article will examine two readily utilized supplemental oxygen therapies, HBOt and continuous Topical Oxygen Therapy (cTOT), highlighting the synergies in use when applied sequentially as part of a clinical pathway. Improvements in tissue oxygenation and wound healing through sustained and continuous complementary oxygen therapy will be explored.

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Hyperbaric Oxygen Therapy

Hyperbaric Oxygen Therapy (HBOt) involves delivering systemic oxygen to a patient by placing them into a pressurized container (typically between 2.0-2.5 atmosphere absolute (ATA)) and administering 100% respiratory oxygen for a duration of 90-120 minutes once daily, five times per week (Figure 1).[16] Most patients receive between 10 and 40 treatments.

The super-physiologic oxygen tension of HBOt increases the partial pressure of oxygen (pO2) to over 1800 mmHg at 2-3 ATA.[16] A high level of oxygen at high pressure is forced into the tissues and lungs. By increasing the atmospheric pressure in the chamber, more oxygen can be dissolved into the plasma than would be seen at surface pressure. During treatment, the arterial O2 tension often exceeds 2000 mmHg and levels of 200 to 400 mmHg occur in tissues, thus impacting oxygen systemically and locally (Figure 1).[17]

Untreated pneumothorax is an absolute contraindication to HBOt while relative contraindications include history of seizures, fever/untreated infection, upper respiratory tract infections (URTI), eustachian tube conditions/Tympanic membrane trauma, sinus issues, pacemakers or epidural pain pump, pregnancy, congenital spherocytosis, claustrophobia, asthma, latent tuberculosis, and patients taking certain medications such

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as Doxorubicin, Bleomycin, Disulfiram, Cisplatin.[18]

Hyperbaric oxygen therapy has been established as a therapy for serious conditions such as decompression syndrome, carbon monoxide poisoning, and gas emboli.[19] However, since the 1960s, HBOt has also been used as a treatment for chronic, hard-to-heal wounds, particularly where wounds are more severe or larger in size.[16,20] Current wound care indications include chronic refractory osteomyelitis, refractory diabetic lower extremity wounds, radiation injuries to soft tissue, compromised grafts and flaps, acute thermal burn injury, clostridial myonecrosis, gas gangrene, and necrotizing wounds.[16]

Heterogeneous results have been reported across four recent meta-analyses in the treatment of diabetic foot ulcers (DFUs). In DFUs with arterial insufficiency, Brouwer, et al. (2020) reported significantly fewer major amputations in the HBOt group (10.7% vs. 26.0% p = 0.002). No difference was found for minor amputations (p = 0.46). Three studies reporting on complete wound healing showed contrasting results. No significant difference was found for mortality or amputation-free survival.[21]

In contrast, Tao, et al. 2023) reported HBOt was found to significantly improve the complete healing rates of DFUs (p < 0.001). However, HBOt's impact on both major and minor amputation rates did not yield statistically significant results.(220 HBOt was significantly effective in complete healing of diabetic foot ulcers and reduction of major amputations,although it was not effective for minor amputations.[23]

Most recently, Chen and colleagues reported HBOt significantly increased the complete healing rate of DFUs compared to conventional care (46.76% vs. 24.46%, p < 0.00001) and decreased the amputation rate (26.03% vs. 45.00%, p = 0.04).[24] A 2020 Cochrane review of HBOT use in chronic wounds reported that in DFUs, HBOt significantly improved the ulcers, healing in the short-term but not the long-term. However, the trials had various flaws in design and/or reporting, reducing confidence in the results.[25]

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Continuous Topical Oxygen Therapy

Continuous Topical Oxygen Therapy (cTOT, NATROX® O2, Inotec AMD Ltd. Cambridge, UK) is a battery-powered device that generates oxygen from electrolysis of water vapor (H2O) in the air, splitting it into hydrogen and oxygen. Oxygen is passed directly to the wound from the cell phone-sized generator at a rate of 11ml/hr via a sterile tube and wheel-like oxygen delivery system (Figure 2 a-c).

The cTOT device is wearable, therefore allowing oxygen delivery 24 hours a day, 7 days a week, supporting patient ambulation and the ability to continue to perform uninterrupted activities of daily living.[26] cTOT is intended for use in open wounds including diabetic foot ulcers, leg ulcers (venous, arterial and mixed), pressure injuries, and surgical and traumatic wounds.[27] It can also be used under compression therapy and with offloading devices.[28]

Contraindications for cTOT include known hypersensitivities to any of the components of the system, as well as malignant or potentially malignant wounds, wounds being treated with topical ointments or creams, deep sinus wounds or tracts, necrotic wounds, and wounds with untreated osteomyelitis.[28]

Figure 2: cTOT wound therapy system: (a) Oxygen generator (OG), (b) Rechargeable batteries, (c) Oxygen delivery system (ODS)

cTOT has been the focus of five meta-analyses supporting significantly faster healing and increased likelihood of healing in DFUs since 2021. Carter, et al. (2023) reported that TOT improved wound healing at 12 weeks over standard of care (SoC) alone (p = 0.021)—supporting the use of TOT for the treatment of chronic Wagner 1 or 2 DFUs in the absence of infection and ischemia.[15] Sethi and colleagues (2022) showed a higher rate of complete healing with TOT by approximately 60% at 12 weeks in DFUs compared to SoC alone (p = 0.021).[29]

Sun, et al.(2022) reported that the TOT group had a higher healing rate with no effect on adverse events vs. SoC, (p = 0.096).[30] Thanigaimani, et al. (2021) reported TOT significantly increased the likelihood of ulcer healing compared to controls (p = 0.040).31 Connaghan and colleagues (2021) showed that DFUs are > 2 times more likely to heal with TOT than with SoC alone (p < 0.0001).[32]

Additionally, high level RCTs for DFUs[33,34] are supported by wider real-world evidence[35–39] and across other chronic wound etiologies including leg ulcers (venous and arterial) and other traumatic or surgical non-healing chronic wounds.[40–42]

This increasing level of evidence now available for TOT has led to its inclusion and recommendation in multiple diabetic foot treatment guidelines recently, including the American Diabetes Association (ADA), International Working Group of the Diabetic Foot (IWGDF), and the Wound Healing Society (WHS).[43–46]

Case Examples

Case 1: HBOt and cTOT sequential therapy

This is a 57-year-old insulin-dependent diabetes mellitus (IDDM) male

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patient admitted to the hospital with a necrotic diabetic foot ulcer to the right heel with underlying osteomyelitis of the calcaneus (Figure 3a). Vascular evaluation showed good arterial flow into the foot. The patient underwent surgical intervention consisting of debridement of the devitalized tissue and partial calcanectomy as shown in Figure 3b. Bone cultures obtained intra-operatively confirmed the diagnosis of osteomyelitis. Tailored IV antibiotic therapy continued for 6 weeks.

Additionally, the wound was treated with negative pressure wound therapy (NPWT) immediately post-op (Figure 3c). Upon discharge from the hospital, the patient was followed in the outpatient wound care setting where NPWT was discontinued, and he subsequently received 40 treatments of HBOt. At the conclusion of HBOt, the wound was not completely healed, so cTOT was applied directly to the wound and covered with a semi-occlusive dressing (Figure 3d).

The patient was monitored weekly at the wound care center until complete wound healing was obtained 4 months after the original surgery (Figure 3e). While this case example illustrates the use of cTOT upon the completion of HBOt, the success observed was the genesis of the idea for cTOT and HBOt combination therapy.

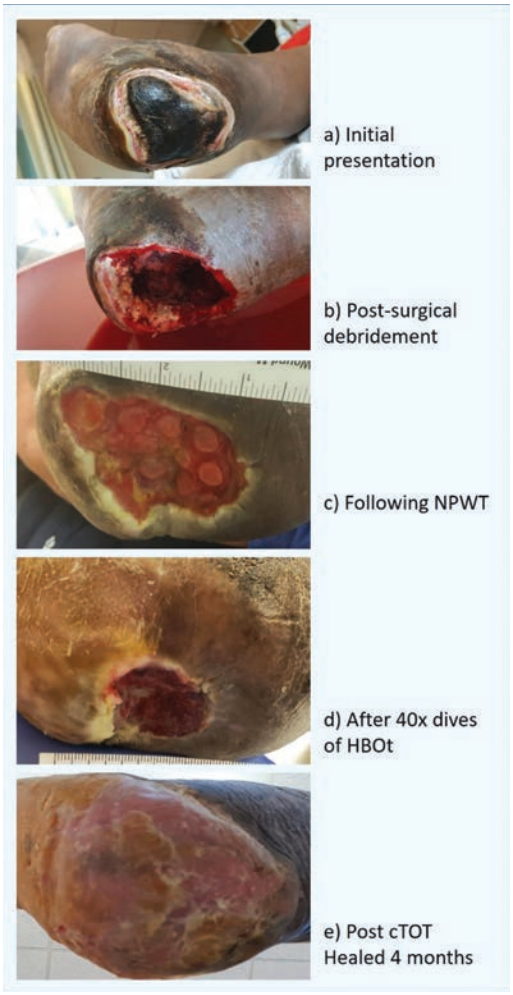

Figure 3: Case 1—Progression of a necrotic DFU to the right heel: (a) on initial presentation, (b) following surgical intervention, (c) NPWT, (d) HBOt, (e) subsequent cTOT treatment and healing four months following presentation

Case 2: HBOt and cTOT complementary therapy

A 51-year-old IDDM male presents with a Wagner Grade 3 ulcer of the left lateral forefoot (Figure 4a). Patient had previously undergone a trans-metatarsal amputation on this extremity. The patient was started on appropriate standard of care including systemic antibiotics, wound debridement, and offloading, and was seen weekly at the wound care center. After four weeks of treatment, the wound had not reached a percentage area reduction (PAR) of 50% and HBOt was recommended. At this visit, cTOT was initiated while HBOt was authorized (Figure 4b). Once HBOt was started, cTOT was continued in between dives and on the weekends. The patient's wound made significant progress with the cTOT and HBOt combined therapy as demonstrated in Figure 4c. At the time of publication, the patient has completed HBOt and is still being treated with cTOT to progress the wound to complete closure.

Figure 4: Case 2—DFU Wagner Grade 3 ulcer of the left lateral forefoot following previous trans-metatarsal amputation: (a) on initial presentation, (b) minimal progression after four weeks aggressive wound treatment; HBOt and cTOT interventions initiated (*cTOT used alone initially during HBOt authorization period), (c) Marked progress towards wound healing following complementary HBOt and cTOT.

Both cases highlight the importance of a multi-modal toolkit for clinicians when managing chronic, non-healing wounds, considering holistically when complementary interventions can work as part of a clinical pathway to improve healing outcomes and provide flexibility for the patient. Following these initial cases, the authors propose the following clinical pathway as shown in Figure 5.

Conclusion

HBOt and TOT are not competing therapeutic methods. They are complementary to each other and could be used together or sequentially.[14] It is feasible that a patient with a non-healing wound may receive HBOt, and in-between sessions use cTOT. cTOT may also be used following completion of HBOt sessions to progress the wound to healing. cTOT can be used in conjunction with other wound interventions such as absorbent dressings, compression, or offloading,

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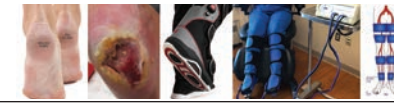

DFU cTOT/HBOt Wound Management Algorithm

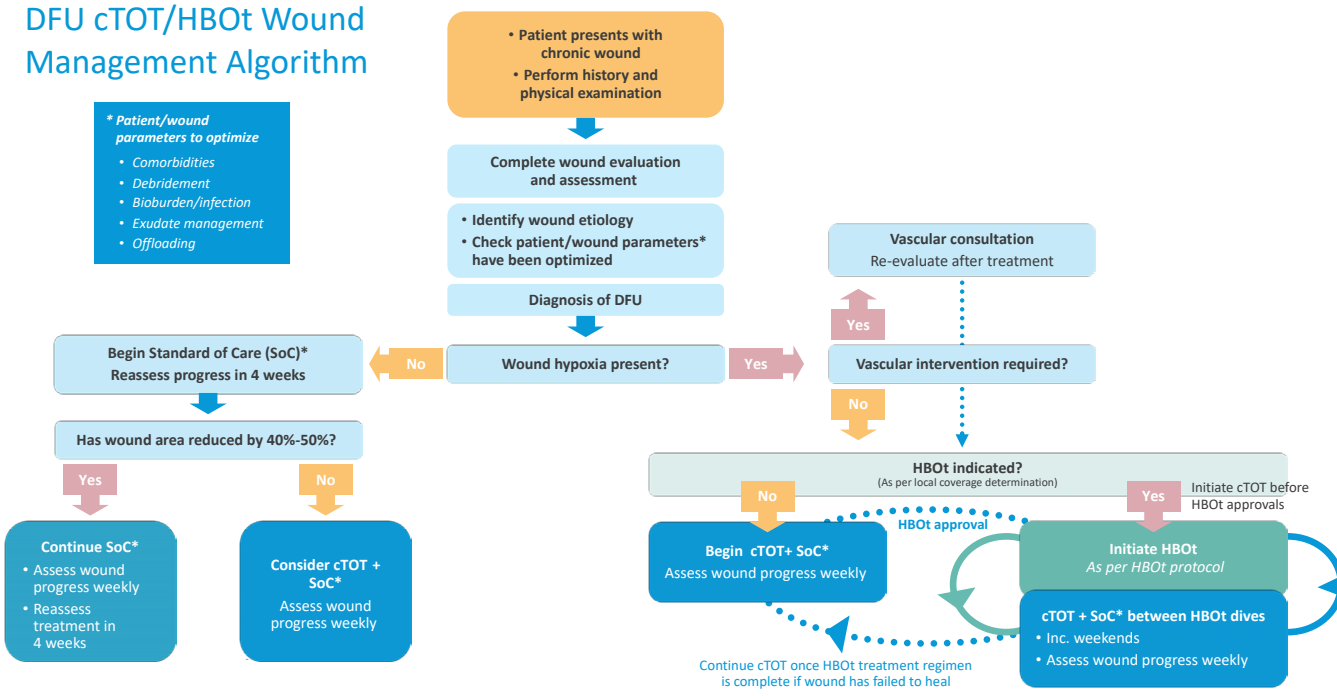

Figure 5: Clinical pathway highlighting the complementary use of HBOt and cTOT in non-healing DFUs.

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allowing patients to continue with their usual daily activities. The device doesn't have any alarms or settings. cTOT can also help reduce wound-related pain, allowing patients to regain their quality of life.[47] Future scientific studies targeting the oxygen response signaling pathways in hard-to-heal wounds will enhance our understanding of the biological and chemical pathways involved in tissue repair and regeneration. **PM**

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