Chronic Diabetic Foot Ulcers

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While hyperbaric oxygen therapy has been well studied in this regard, comparative clinical studies have fallen short of providing clear evidence in support of this modality for healing chronic diabetic foot ulcers (DFU). Topical oxygen therapy (TOT) has been in clinical use for over 50 years with encouraging pre-clinical and clinical studies that have shown improved healing rates when compared to standard care. Nonetheless, TOT has heretofore been discounted as an unproven wound healing modality without theoretical or clinical evidence to support its use.

Keywords: oxygen ; topical oxygen therapy ; diabetic foot ulcers ; wound healing

1. Introduction

While many clinicians might consider topical oxygen therapy (TOT) to be an unproven or controversial wound healing modality, it has been in clinical use for over fifty years. In his 1969 publication, Fischer described his novel topical “hyperbaric” oxygen system used to treat a variety of chronic wounds in an in-patient environment [1]. Using humidified oxygen under a constant pressure of 22 mmHg for 4–12 h per day, he was able to achieve success in 88% of his cases including diabetic foot ulcers (DFU), venous leg ulcers (VLU), and various decubitus pressure ulcers. In a subset of six patients with bilateral lesions using one side as a control, only the six “hyperbaric oxygen” treated wounds healed within 3 to 17 days. When the unhealed control wounds were subsequently switched to topical oxygen therapy, they all healed within 6 weeks. While this rudimentary case series was not up to the scientific standards of present-day clinical investigations, it was certainly compelling enough to lead to further applications for topically applied oxygen therapies.

Recognizing that Oxygen (O 2) is required for almost every step of the response to the injury and wound healing cascade, several recent reviews have focused not only on the role of molecular oxygen in this regard but also on cellular and biochemical mechanisms for O 2 generation [2][3][4][5][6]. Chronic wounds are typically characterized as being hypoxic in that the partial pressure of oxygen (pO 2) in the center of the wound is often below a critical threshold necessary to fully support those enzymatic processes necessary to regenerate tissue [6]. Disrupted vascular supply, chronic inflammation, bacterial overload, and exhausted local metabolic oxygen production all contribute to chronic hypoxia. While acute, short-term hypoxia can indeed be a stimulus for angiogenesis, chronic hypoxia impedes not only angiogenesis but also the associated generation of reactive oxygen species (ROS) necessary for the upregulation of growth factors, cell signaling, and bacterial killing [2]. Oxygen is the rate limiting substrate for numerous biochemical reactions and plays a crucial role in energy production and cellular metabolism. Molecular oxygen is, of course, also necessary for the synthesis of nitric oxide (NO) that regulates vasodilatation. Oxygen-dependent processes, so relevant in wound healing, include mitochondrial-driven adenosine triphosphate (ATP) production for chemical/cellular energy and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase for the production of ROS (“respiratory burst”) involved in signal transduction of growth factors, cellular recruitment, and bacterial killing [4][5][6][7]. The two most prevalent ROS, superoxide and hydrogen peroxide (H 2O 2), both serve to upregulate the release of vascular endothelial growth factor (VEGF) and platelet derived growth factor (PDGF) that stimulate endothelial cell division and migration to initiate angiogenesis, lymphocyte/leukocyte migration, and fibroblast division and migration to synthesize new extracellular matrix (ECM). ROS driven phagocytosis and bacterial killing by bacteriostatic H 2O 2 release by platelets and neutrophils also play an important role in the initial clearing of bacterial pathogens [5] (**Table 1**).

Table 1. Role of Oxygen in Wound Healing.

Oxygen-Dependent Product	Enzyme or Substrate	Function	Cytokine, Cell Mediators; or Cellular/Tissue Effect
ATP	**ATP synthase, Cytochrome C, Electronic Transport Chain**	**Chemical Energy for metabolism**	

Oxygen-Dependent Product	Enzyme or Substrate	Function	Cytokine, Cell Mediators; or Cellular/Tissue Effect
Reactive Oxygen Species (ROS) "respiratory burst" (Superoxide, Hydrogen peroxide (H_2O_2))	NADPH oxidase	Cellular Signaling/transduction Bacterial defenses Angiogenesis	Cell division and migration. Upregulation of Growth Factors (VEGF, PDGF, etc.) (leukocyte migration and phagocytosis, bacteriostatic H_2O_2) VEGF, PDGF, NO, etc.
Collagen synthesis	Prolyl hydroxylase, lysyl hydroxylase	Collagen deposition and crosslinking	Fibroblasts
Nitric oxide (NO)	Nitric oxide synthase	Vasodilatation, angiogenesis	Endothelium

NADPH: nicotinamide adenine dinucleotide phosphate; VEGF: vascular endothelial growth factor; PDGF: platelet derived growth factor.

2. Topical Oxygen Devices

Topical oxygen therapy (TOT) can be defined as the administration of oxygen applied topically over injured tissue by either continuous diffusion or pressurized systems. Although there are dressings, gels, and hemoglobin sprays that can provide for oxygen release when applied to wounds, for the purposes of this discussion only mechanical devices specifically indicated for topical oxygen therapy will be discussed herein [2].

CDO devices apply topical continuous diffusion of non-pressurized (normobaric) pure oxygen through small cannulas or thin tubes to semi-occlusive or proprietary wound dressings. Small portable, battery powered, electrochemical oxygen generators supply a continuous flow of pure oxygen over the wounds 24 h per day at a flow rate of up to 15 mL/h [8][9][10]. An oxygen gradient then develops between the overlying dressing and the wound bed, thereby facilitating oxygen diffusion. The wound dressings are typically changed weekly, and the oxygen generators (or batteries) are generally replaced after 1 to 2 weeks of continuous use. These light-weight devices can be held in a small pouch affixed to the patient's leg or hip and allow for unrestricted ambulation within the prescribed offloading devices. There have been several recently published randomized controlled trials (RCT) that attest to their ease of use and positive effect on DFU wound healing [10][11][12][13].

The lower constant pressure devices provide oxygen delivery in a simple plastic boot that is placed over the extremity with the ulcer. One hundred percent oxygen is delivered for 90 min for 4 consecutive days per week. Constant pressure is then maintained within the chamber up to 22 mmHg (1.03 atm). Although less widely used than the other modalities, numerous studies have been conducted on these types of devices over the last four decades that have shown good clinical efficacy. However, the majority of these studies have consisted of case series or uncontrolled trials, including one animal study [14] [15][16]. The one very poorly conducted RCT that used a similar device has been previously discussed [17]. A more recent retrospective chart review of a variety of non-healing wounds in patients from the manufacturer's database reported that >50% of wounds less than 1 year in duration experienced healing [18].

The Topical Wound Oxygen (TWO 2) system differs from other devices in that it applies cyclically pressurized (10–50 mb) pure oxygen within a disposable extremity chamber connected to a stationary oxygen concentrator. Humidity can be added to the system if required. The benefit of this approach is that the higher pressure gradient (pO 2) results in oxygen molecules diffusing deeper into the hypoxic wound tissue to enhance multiple molecular and enzymatic functions [15][19]. Within the extremity chamber containing pure O 2 at sea level (760 mmHg), the pO 2 can be cyclically pressurized up to nearly 800 mmHg that optimizes enzymatic activity as previously discussed [4]. The cyclical pressure applied with TWO 2 of between 8 mmHg and 38 mmHg creates sequential non-contact compression of the limb that also helps to reduce peripheral edema, and thereby, stimulate wound site perfusion further [20][21]. Several prospective clinical studies have been successfully conducted using this device on both VLUs as well as DFUs [21][22][23].

3. Topical Oxygen Effect on Wound Healing—The Evidence

An increasing number of prospective (as well as retrospective) , comparative clinical studies have provided the translational evidence necessary to support the efficacy of TOT in conjunction with the standard of care for healing chronic wounds [3]. Although most clinical research has focused on DFUs, several prospective, comparative cohort studies have also shown significantly improved healing of VLUs using cyclical pressurized TWO 2. One non-randomized study of 83

VLU patients measured the effect of TWO 2 compared to conventional compression dressings (CCD) [20]. At 12 weeks, 80% of TWO 2 managed ulcers were completely healed compared to 35% of the CCD managed ulcers. These same authors later conducted another VLU non-randomized comparative study that similarly investigated the efficacy of TWO 2 vs. CCD in the management of refractory non-healing venous ulcers (RVU) with a duration of at least two years [21]. At 12 weeks, 76% of the TWO 2 managed ulcers had completely healed, compared to 46% of the CCD-managed ulcers with a median time to full healing of 57 days and 107 days, respectively. No other formal VLU studies using TOT have been published to date.

In 2010, a small, prospective, non-blinded, non-randomized study was conducted to examine the clinical efficacy of topical wound oxygen therapy in healing ambulatory DFU patients [22]. Patients were simply allocated to the topical oxygen if a unit (TWO 2) was available or were otherwise treated with advanced moist wound therapy. At 12 weeks 82.4% of the ulcers in the active therapy arm and 45.5% in the control standard of care arm had healed completely ($p = 0.04$). The median time to complete healing was 56 days in the TWO 2 therapy arm and 93 days in the control standard of care arm ($p = 0.0013$).

This same device has subsequently been investigated to examine the real-world impact of TWO 2 on hospitalizations and amputations in patients with diabetic foot ulcers (DFU) compared to patients who had not used TWO 2. An, as of yet, unpublished retrospective, comparative cohort study of 202 DFU patients found that 6.6% and 12.1% of TWO 2 patients had hospitalizations and amputations at one year, respectively, compared to 54.1% and 41.4% of patients who had not used adjunctive TWO 2 ($p < 0.0001$, $p < 0.0001$), representing 88% and 71% reductions [24]. Although this data is still subject to peer review, it infers that treating DFU patients with TWO 2 can lead to significant reductions in hospitalizations and amputations in the real-world setting.

4. Conclusions

From the foregoing, it is evident that topical oxygen therapy can no longer be considered an experimental or unproven therapy for the healing of chronic wounds, especially diabetic foot ulcers. The data clearly have demonstrated a significant improvement in the healing of chronic DFUs treated with either CDO devices or pressurized devices (TWO 2) as compared to standard of care alone. That being said, it is also critical to emphasize that TOT (as for any advanced wound therapy) must be administered in conjunction with optimal wound care. Without addressing the basic tenets of wound care (debridement, offloading, treatment of infection, treatment of ischemia, etc.), no therapy can be expected to miraculously heal a chronic wound. Furthermore, not all wounds are suitable for TOT and not all wounds thus treated will heal; this therapy is certainly not a panacea. However, when used adjunctively with optimal wound care, the aforementioned studies provide the clinical evidence necessary to support the use of topical oxygen in the management of chronic DFUs.

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