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Topical oxygen therapy stimulates healing in difficult, chronic wounds: a tertiary centre experience

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Topical oxygen therapy stimulates healing in difficult, chronic wounds: a tertiary centre experience

Objective: Oxygen plays a central role in wound healing. Recent technological advances have miniaturised oxygen delivery systems, with novel topical oxygen therapy allowing patients to receive oxygen therapy 24 hours a day while remaining completely mobile. Here we aim to examine the efficacy and safety of continuous topical oxygen diffusion in a 'real-world' setting.
Methods: Topical oxygen therapy (TOT) was evaluated in patients with chronic, non-healing wounds in a tertiary referral specialist clinic.
Results: The mean wound duration before TOT was 15 months. Regardless of treatment duration, in this previously non-healing group complete wound closure was observed in 32% of the total patients treated with the TOT device. However, optimal wound healing occurred when the device was used for >25 days, with an 83% wound area reduction and 47% wound closure rate seen in venous leg ulcers (VLUs) and a 74% reduction and a 57% wound closure rate in arterial foot ulcers.
Conclusion: Use of TOT in chronic wounds stimulates a healing state. In our study, almost half of the previously non-healing wounds closed.
Declaration of interest: Paul Hayes acts as Medical Director for Inotec AMD and has a share-holding in the company

chronic wound • new technology • tertiary centre • topical oxygen • wound healing

Wound prevalence is increasing every year due to an aging population with increasing rates of diabetes and obesity.[1] Wounds impact at a personal level[2] and increasing numbers of chronic wounds also have a detrimental impact on health-care systems as they consume resources. Innovation has led to novel approaches to wound care which offer the promise of closing previously unhealed wounds, along with improving the patients' quality of life (QoL).

Topical oxygen therapy (TOT) is one such innovation. Oxygen-dependent energy production is required for the cellular processes of fighting infection, cell division, angiogenesis and collagen production, all of which are essential for wound healing.[3] Local metabolic needs increase 5-fold in skin with a wound.[4] Hypoxia (low oxygen) inhibits crucial cellular mechanisms that promote and underlie tissue healing such as collagen synthesis and cross linking, sustained angiogenesis, bacteria-targeted cellular release of reactive oxygen species (phagocytosis) and epithelialisation.[4,5] It is therefore unsurprising that low transcutaneous oxygen pressure is associated with inferior wound healing outcomes.[6,7] When oxygen levels in a wound are low, one molecule of glucose generates just 2 molecules of adenosine triphosphate (ATP), the molecular unit used for the generation of energy. However, with plentiful local oxygen at the wound site, the process is 18 times more efficient, with each glucose molecule generating 36 molecules of ATP. As such, by creating an oxygen-rich environment, cellular resources are increased and wound healing is improved.[8–10] Some of the roles of oxygen in wound healing is summarised in Fig 1.

To date, most efforts to improve wound healing by increasing available oxygen have involved chambers for hyperbaric oxygen delivery either systemic or via local hyperbaric boots. Systemic hyperbaric oxygen therapy (HBOT), in which patients are confined to a full-body chamber for the duration of the treatment, has shown limited success in wound healing primarily because its use is restricted to only a fraction of the week. Assuming a patient can access HBOT for 1.5 hours over 5 days of the week, this adds up to 7.5 hours out of 168 hours in the week, or around 5% of the week. This limits its efficacy in raising oxygen levels in wounds for a prolonged period. Current guidelines are inconclusive with respect to incorporating HBOT into standard treatment on grounds of insufficient evidence.[11,12] Adverse effects arising from barotrauma and oxygen toxicity have also impacted on its widespread applicability, along with practical limitations such as accessibility and cost of treatment.[13]

The use of local chambers or inflatable boots employs a different route of delivery that circumvents systemic

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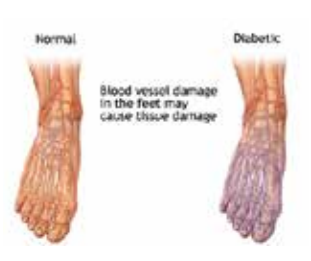
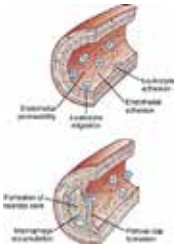
Fig 1. Most wounds exhibit a degree of hypoxia, low oxygen levels lead to reduced rates of wound healing

Possible causes of low oxygen levels

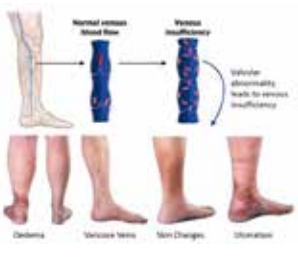
Diabetes



Atherosclerosis



Venous Disease

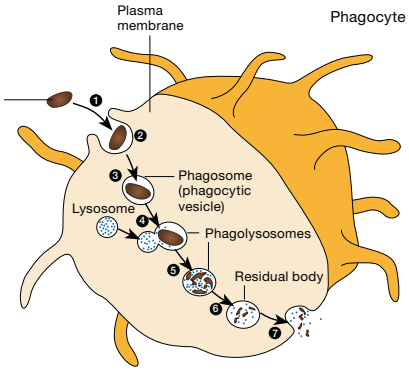


Biofilm and Neutrophil activity

LOW WOUND OXYGEN CAN LEAD TO

1

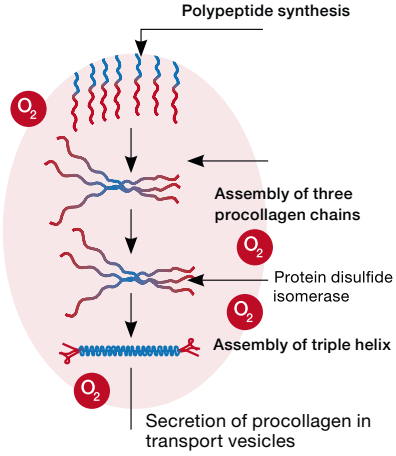
Failure to fight infection leading to wound deterioration



Neutrophils and macrophages are key for clearing infection from wounds. During this process their oxygen demands increase 50-fold. The oxygen is used to generate potent antibacterial superoxide molecules

2

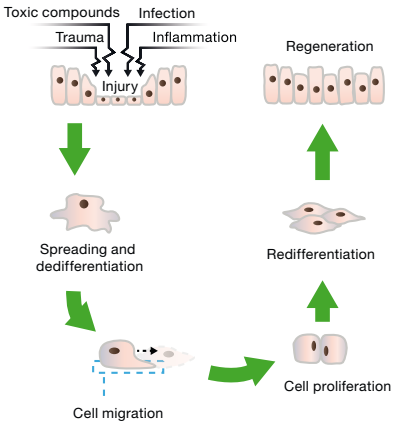
Poor quality tissue with high wound recurrence rates



Oxygen is key to the assembly of a strong collagen matrix. When wound oxygen levels are low, the collagen formed is only one-third of its usual strength. The oxygen is used to bind the strands of collagen together

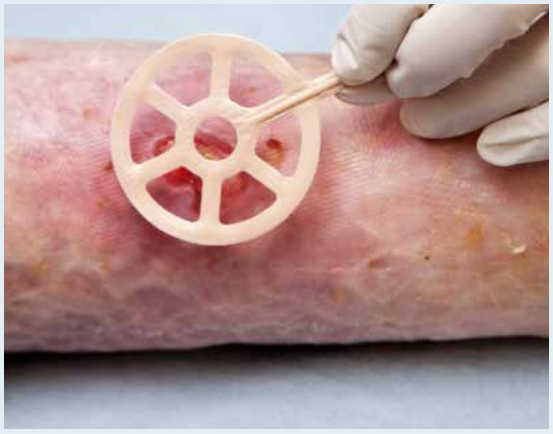
3

Inability to produce new skin cells that spread and cover the wound



Epithelial migration is very energy dependent as a large number of processes need to occur. Energy production in the presence of adequate oxygen is 18-times more efficient than in a hypoxic wound

Fig 2. Topical oxygen therapy (TOT) device *in situ*



exposure to supra-atmospheric air pressures and supra-physiologic oxygen levels. Acceleration in healing with local HBOT has been demonstrated,[14] although again level 1 or 2 evidence is lacking to support its routine use. A common difficulty with both treatments is that the administration of oxygen is intermittent due to the restrictive nature of the chamber or device by which it is provided. Given the potentially long period required to heal chronic wounds, reliable patient adherence throughout this period is often difficult. In contrast, the local TOT evaluated in this study increases wound oxygen levels above physiological normal levels for the vast majority of the day, while allowing the patient to undertake most of their normal activities.[15]

The concept of delivering oxygen topically to the wound surface is not new. In the past, clinicians have used oxygen direct from wall supplies or tanks, but this has obvious practical constraints. Modern delivery of gaseous oxygen can be administered by a device consisting of a small battery-powered electrochemical oxygen generator that electrolyses atmospheric water vapour to produces pure humidified oxygen. The oxygen is transported down a fine bore tube and delivered directly onto the surface of the wound, creating a high concentration of oxygen under the dressing and allowing for oxygen to be diffused down the concentration gradient into the wound. The compact nature of the device allows the patient to be completely ambulatory and therefore undergo continuous 24/7 treatment while the device is *in situ* (Fig 2). From a practical standpoint, this method's simplicity of use creates the potential for it to be a widely available treatment adjunct in hospital and community settings, if evidence supports its efficacy in healing chronic wounds and reducing associated morbidity and mortality. The effectiveness of topical oxygen in chronic wounds remains largely unverified due to the relatively recent development of the therapy, but has been reviewed in a larger study of generalised oxygen therapy.[16] Recent papers have evaluated use of this particular device in chronic diabetic foot ulcers (DFUs) in a controlled trial setting.[15,17]

Aims

This study aims to examine the efficacy and safety of topical continuous diffusion of oxygen in a 'real-world', tertiary mixed wound care centre.

Methods

The study represents a consecutive case series of patients treated with the TOT delivery system (Natrox, Inotec AMD). All patients going into the study had been managed with standard of care and best local practice previously and had failed to heal. Access to the device was not limited by any criteria such as chronicity of wound, wound size or level of ankle-brachial pressure index (ABPI) and as such this represents a real-world, uncontrolled cohort of patients. The wounds were imaged using a digital camera and an analogue scale to allow assessment of size. The patient data was collected in a prospective manner on a structured database. The study was conducted as an audit of a CE-marked and 510K approved product and as such did not require institutional review board (IRB) approval. Written permission for the use of patient data and photos was obtained for all patients. Only adult patients with mental capacity were included. The first patient was treated in November 2014 and the final patient finished their treatment in November 2017.

The ambulatory TOT delivery device[15] used in this study delivers continuous oxygen to the wound bed through an oxygen distribution system, or diffuser that sits directly on the wound surface and is connected to the generator by a fine bore tube. The generator employs a small battery-powered electrochemical 'oxygen generator' that produces oxygen from water molecules in the atmosphere at a concentration of around 98% and a rate of approximately 13ml per hour (as per the Natrox manufacturer's instructions for use). The oxygen concentration ultimately generated under the dressing will vary depending on wound area, permeability of the dressing and rate of leakage of oxygen from around the dressing edges. The oxygen distribution system is held in place overlying the wound bed by a conventional dressing and the oxygen generator is worn by the patient in a holster on the waist or above the calf, or can be placed in a trouser pocket.

There were limited inclusion and exclusion criteria for the use of the device. Patients with evidence of acute, invasive infection were excluded, but chronic osteomyelitis being treated with oral antibiotics was allowable. Patients needed to be able to change and charge the battery in the device themselves. The device was used in conjunction with standard good wound care practices, including debridement to healthy wound edges and the removal of excess necrotic material in the wound bed. In each patient, the disposable oxygen delivery system dressing was placed

directly on to the wound bed and the wound was then dressed with what was felt to be standard of care for each particular wound. Secondary overlying dressings were chosen from each hospital's wound care formulary. The TOT was not used when there were ointments or creams applied to the wound surface that would act as a barrier to oxygen delivery. Use of the oxygen delivery system under compression bandaging was allowed and care was taken to place padding under the oxygen delivery tubing. Changes of dressing types were allowable through the study period according to the nature of each individual's wound at any time.

Statistical analysis

Data was tested for normality of distribution. For normally distributed data, repeated measures were assessed with independent t-tests. Data with a skewed variation were examined with a Mann Whitney U-test. Discrete variables were analysed using Fisher's exact test. Statistical analysis was performed with SPSS Statistics (IBM, v22, 2013,. Armonk, NY:IBM Corp.) with $p<0.05$ was deemed significant.

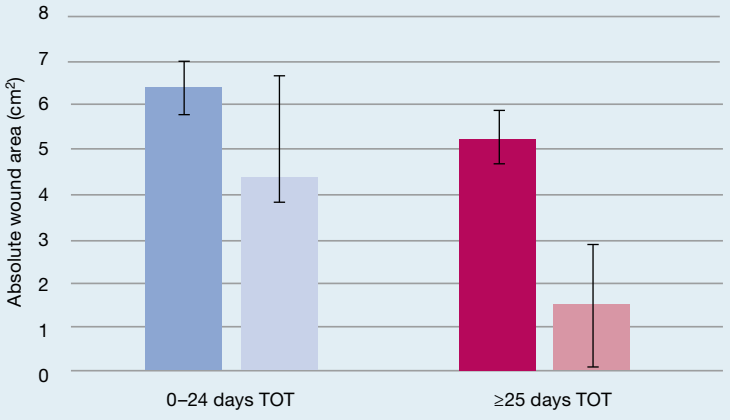
Results

Between November 2014 and April 2017, 100 patients were treated with TOT in the clinic. The patients had chronic wounds with a mean duration of 15.2 months before the initiation of TOT (range: 1–192 months). The mean patient age was 66.9 years of age and 62% of patients were male. There were 18% of the total cohort reported themselves as active smokers at the time of treatment, this did not influence healing rates.

There were a number of pathologies represented: 48 venous leg ulcers (VLU); 27 arterial ulcers; 13 diabetic foot ulcers (DFUs); four post-trauma; three pressure ulcers (PUs); two burns and three postoperative wounds. In order to undertake meaningful analysis of the data, the 27 arterial ulcers and 13 DFUs were grouped together based on their similar anatomical and pathological characteristics and in the remainder of the document these will be referred to as the foot group. In addition, all the wounds types with four or less data points were grouped into a miscellaneous category.

The device was very well tolerated by the patients; complete adherence with TOT during the study was achieved in 88% of patients. The mean duration of treatment was 40.3 days. Across the whole cohort, the median weekly wound reduction was 7.0%/week. In this chronic wound cohort complete wound closure with TOT was achieved in 32.2% of patients.

Fig 3. Larger median wound area reduction with and treatment length. Patients with a longer duration of exposure to the topical oxygen therapy (TOT) healed more effectively (0–24 days, n=30; 25+ days n=70). The short duration group reduced by 39% compared with a 76% reduction with longer treatment (p=0.0002; Z=3.70 on 2-tailed Mann-Whitney U-test)



Study results demonstrate that TOT durations >25 days was optimal for wound healing. During initial inspection of data, it was apparent that a subset of

Fig 4. Complete wound closure rates. Rates of complete wound closure for different pathologies in patients completing 25 days of topical oxygen therapy (TOT). Venous wounds n=36; arterial wounds n=24 and miscellaneous n=10

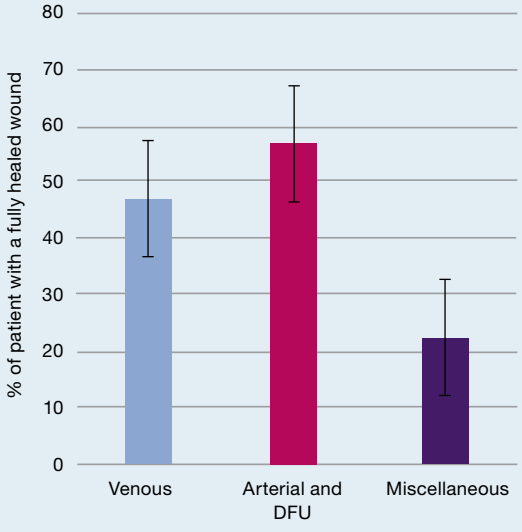
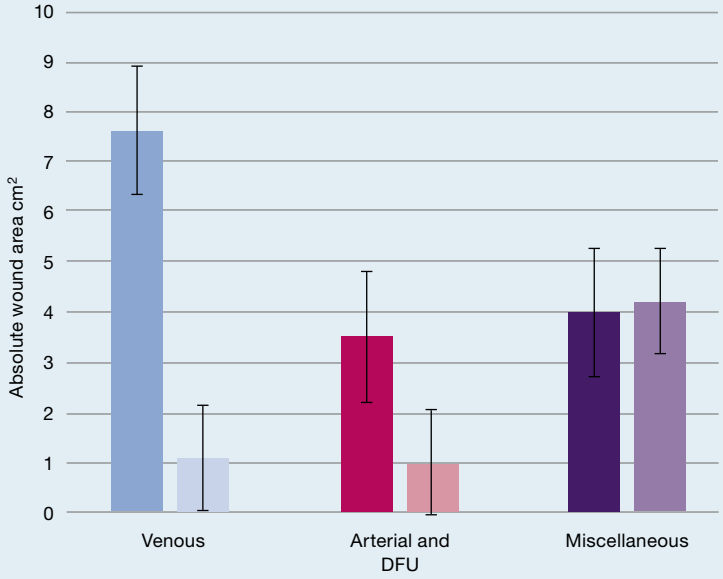


Table 1. Data comparing those with fully healed wounds against those without complete closure in the group treated for ≥25 days and were adherent with treatment

	n	Age	Male	Active smokers	Wound duration	Start area	Treatment time
Wounds not fully closed	34	68.1	70.6%	26.5%	17.4 months	13.20 cm^2	57.4 days
Completely healed wounds	31	65.8	61.3%	25.8%	14.1 months	5.36 cm^2	46.8 days
p-vaule		0.574	0.437	0.952	0.602	0.054	0.157

Fig 5. Median wound area reduction between groups. The wound area reduction between the size and the end of treatment for those patients for those patients receiving topical oxygen therapy (TOT) for more than 25 days. Venous patients' wound area reduced by 84% (p=0.001, Z=3.86, 2-tailed Mann-Whitney U-test) and arterial cases by 71% (p=0.007; Z=2.72; 2-tailed Mann Whitney U-test)



patients (n=30) had been treated for a shorter period of time, <25 days, a treatment decision resulting from limited experience with the therapy. In order to address this discrepancy, the data were split into those patients treated for a minimum of 25 days (mean duration: 52 days) and compared with those treated for shorter time periods (Table 1). In total, 70 patients were treated with the TOT for >25 days and in this group the complete healing rate was 46%, as opposed to 0% in those receiving a shorter treatment regime. The longer duration treatment group reduced their wound size by 76%, from a mean of 5.2cm^2 to 1.75cm^2), compared with only a 39% wound area reduction in the shorter timeframe, from a mean of 6.4cm^2 to 4.3cm^2 (Fig 3).

Further analysis of the data will concentrate on those cases treated for >25 days with TOT. There were four patients felt by the team to be inadequately adherent, as they were using the device less than 50% of the time; these patients were also excluded.

The wound closure rate for the chronic VLUs with >25 days treatment was 47% and for the foot group this was higher, at 57% (Fig 4). The wound area reduction was greatest in the VLUs (p<0.001), 83% over the course of the study, with an average closure rate of 9.5% per week. Foot ulcers (for the arterial and diabetic groups combined) had an overall wound reduction of 74% (p<0.01) Fig 5.

An analysis was undertaken to compare those patients with complete healing, relative to those whose wounds failed to close completely, trying to identify factors that may predict a positive response to TOT. The main difference between the healed and non-healed wounds was the initial size of the wound, with non-healing wounds having a higher initial area. The healed wounds were still 'hard-to-heal wounds' as they had been present for over 14 months before the TOT. The results are summarised in Table 1.

Discussion

The data presented here demonstrate that the technology underpinning TOT works in a 'real world' setting, when used on a variety of patients in our specialist wound care centre. Many of the patients had been treated with a large variety of therapies previously and failed to heal. The patients included in our study were a hard-to-heal group, with average ulcer duration of over 15 months. The use of TOT on chronic wounds that had previously failed to heal led to complete closure in 57% of chronic foot wounds and in 47% of VLUs, wound closures achieved after 52 days on average of TOT. In contrast, the UK national average chronic wounds closure rate is 43% after a full year of treatment,[18] 7-fold longer closure rates than observed in this study.

Hypoxia in chronic wounds

There are number of reasons why TOT can aide wound closure in foot wounds. Wound hypoxia is well recognised to occur in diabetes and peripheral arterial disease (PAD) primarily due to macrovascular and microvascular disease, and local oedema. Even in patients with diabetes and foot pulses, there can be a failure of oxygen delivery to the capillary bed, and therefore the tissues, due to arterio-venous shunting. Tissue oxygenation in the central area of a wound in a patient with diabetes can be as low as 0 to 10mmHg,[8] well below that required to heal wounds, especially given the higher metabolic demands of wounds in diabetic patients.[9]

The 47% wound closure rate observed in VLUs treated with TOT may be surprising to some, as the relative levels of hypoxia which occur in VLU patients are poorly recognised. However, tissue oxygen levels are reduced via a number of mechanisms in venous disease such as lower limb oedema; with a relatively fixed amount of oxygen being delivered to the lower limb, the increased limb volume caused by the oedema effectively dilutes the oxygen concentration available to the cells.[19] Lipodermatosclerosis causes the deposition of dense scar-like tissue around the microvessels, which both compresses them and restricts the rate at which oxygen will diffuse down its concentration gradient from the capillaries into the tissues.[20] The ultimate expression of lipodermatosclerosis is atrophe blance, where the skin is essentially infarcted through lack of oxygen. Finally, venous reflux leads to venous hypertension, and the impaired outflow flow through the capillary bed which limits the rate at which new oxygen-laden haemoglobin molecules arrive and can deliver their oxygen to the neighbouring tissues.[21] Given all of these factors, along

with the fact that standard of care covers the VLUs in multiple layers of bandages, thus excluding atmospheric oxygen, it is likely that topical oxygen to VLUs should improve healing.

Topical oxygen therapy: mechanisms of action

Oxygen is known to stimulate activity of neutrophils and macrophages,[10] phagocytes which are essentially the cell's cleaning crew. Neutrophils and macrophages clear wound colonising bacteria and associated materials through the generation of powerful reactive oxygen species. The production of reactive oxygen species (ROS) requires large amounts of both energy and oxygen, leading to a significant increase in local cellular oxygen consumption.[22] Therefore, without adequate amounts of oxygen present, clearance of the bacteria will not be effective. Furthermore, there is evidence that increasing the levels of oxygen around neutrophils and macrophages above the physiological 21% level will increase their activity into supra-physiological levels,[23] suggesting an antibacterial benefit of oxygen therapy even for patients with normal blood supply, whose tissue oxygen levels we assume to be optimal.

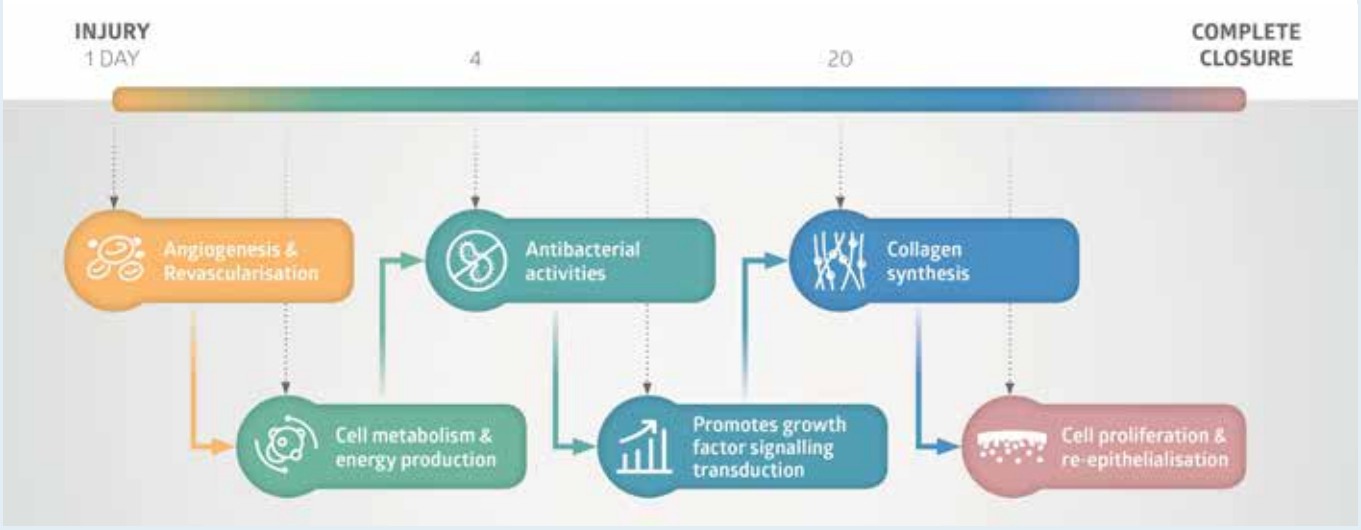
Topical oxygen stimulated bacterial clearance may also benefit collagen production. Chronic bacterial presence inhibits the production of good quality collagen and increases its rate of breakdown through inflammation and the subsequent rise in matrix-metalloprotease activity.[3] Additionally, collagen production is itself dependent on adequate concentrations of oxygen for a number of stages of its assembly, such as oxygen-dependent cross linking to form stable bonds between collagen strands,[24] strengthening this essential structural protein. Hypoxic conditions in chronic wounds results in collagen produced at approximately 1/3 of the strength of collagen produced in normal levels of oxygen.[24] In addition, raising the oxygen level above its normal 21% can accelerate collagen production, suggesting that even patients with relatively normal oxygen tensions would benefit from TOT.[25]

The final major area where oxygen has an impact on wound healing is epithelial migration. Only once the wound has been thoroughly debrided and there is a solid foundation of collagen will the epithelial cells migrate across the surface to close the wound. Epithelial cells will not cross an infected wound bed. The rate of epithelial migration is related to the oxygen tension at the wound surface,[26] and again raising the levels of oxygen to supra-physiological levels, as can be achieved with TOT, will accelerate wound closure above normal levels.[26] As topical oxygen is being applied directly to this cell layer, high concentrations of oxygen are achieved thus stimulating migration. Therefore, topical oxygen benefits numerous cellular mechanisms required for wound healing (e.g. antibacterial-mechanisms, collagen production and epithelial migration). Chronic wounds must progress through all of these stages before wound closure is obtained (Fig 6). Short term use of oxygen can help with a single stage, but in order to move these difficult wounds towards healing, longer term application is required.

Conclusions

In this study, best results were seen with >25 days of TOT, with complete closure in 57% of foot wounds and in 47% of VLUs that had previously been deemed hard-to-heal. Chronic wounds are a complex environment, often with dysfunction in many of the diverse systems needed to function optimally in order to heal. The unique power of topical oxygen, its ability act on many different facets of wound healing, making it more likely to close a chronic wound than therapies directed against only one or two pathophysiological processes. **JWC**

Fig 6. The role of oxygen in wound healing



References:
1 Nussbaum SR, Carter MJ, Fife CE et al. An economic evaluation of the impact, cost, and medicare policy implications of chronic nonhealing wounds. Value Health 2018; 21(1):27–32. https://doi.org/10.1016/j.jval.2017.07.007
2 Fejfarová V, Jirkovská A, Dragomirecká E et al. Does the diabetic foot have a significant impact on selected psychological or social characteristics of patients with diabetes mellitus? J Diabetes Res 2014; 2014:371938 https://doi.org/10.1155/2014/371938
3 Schreml S, Szeimies RM, Prantl L et al. Oxygen in acute and chronic wound healing. Br J Dermatol 2010; 163(2):257–268. https://doi.org/10.1111/j.1365-2133.2010.09804.x
4 Jonsson K, Jensen JA, Goodson WH Iii et al. Tissue oxygenation, anemia, and perfusion in relation to wound healing in surgical patients. Ann Surg 1991; 214(5):605–613. https://doi.org/10.1097/00000658-199111000-00011
5 Wu L, Xia YP, Roth SI et al. Transforming growth factor-beta1 fails to stimulate wound healing and impairs its signal transduction in an aged ischemic ulcer model: importance of oxygen and age. Am J Pathol 1999; 154(1):301–309. https://doi.org/10.1016/S0002-9440(10)65276-5
6 Wang Z, Hasan R, Firwana B et al. A systematic review and meta-analysis of tests to predict wound healing in diabetic foot. J Vasc Surg 2016; 63(2 Suppl):29S–36S.e1-2. https://doi.org/10.1016/j.jvs.2015.10.004
7 Wyss CR, Harrington RM, Burgess EM, Matsen III FA. Transcutaneous oxygen tension as a predictor of success after an amputation. J Bone Joint Surg Am 1988; 70(2):203–207
8 Silver IA. Tissue PO2 changes in acute inflammation. Adv Exp Med Biol 1977; 94:769–774
9 Ruangsetakit C, Chinsakchai K, Mahawongkajit P et al. Transcutaneous oxygen tension: a useful predictor of ulcer healing in critical limb ischaemia. J Wound Care 2010; 19(5):202–206. https://doi.org/10.12968/jowc.2010.19.5.48048
10 Sen CK. Wound healing essentials: Let there be oxygen. Wound Repair Regen 2009; 17(1):1–18. https://doi.org/10.1111/j.1524-475X.2008.00436.x
11 Kranke P, Bennett MH, Martyn-St James M et al. Hyperbaric oxygen therapy for chronic wounds. Cochrane Database Syst Rev 2012; 4(4):CD004123. https://doi.org/10.1002/14651858.CD004123.pub3
12 Gottrup F, Apelqvist J. Present and new techniques and devices in the treatment of DFU: a critical review of evidence. Diabetes Metab Res Rev 2012; 28(Suppl. 1):64–71. https://doi.org/10.1002/dmrr.2242
13 Thom SR. Hyperbaric oxygen: Its mechanisms and efficacy. Plast Reconstr Surg 2011; 127(Suppl 1): 131S–141S. https://doi.org/10.1097/PRS.0b013e3181fbe2bf
14 Blackman E, Moore C, Hyatt J et al. Topical wound oxygen therapy in the treatment of severe diabetic foot ulcers: a prospective controlled study. Ostomy Wound Manage 2010; 56(6):24–31
15 Hayes PD, Alzuhir N, Curran G, Loftus IM. Topical oxygen therapy promotes the healing of chronic diabetic foot ulcers: a pilot study [Internet]. J Wound Care 2017; 26(11):652–660. https://doi.org/10.12968/jowc.2017.26.11.652
16 Gottrup F, Dissemond J, Baines C et al. Use of oxygen therapies in wound healing. J Wound Care, 2017; 26(Sup5):S1–S43. https://doi.org/10.12968/jowc.2017.26.Sup5.S1
17 Yu J, Lu S, McLaren AM et al. Topical oxygen therapy results in complete wound healing in diabetic foot ulcers. Wound Repair Regen 2016; 24(6):1066–1072. https://doi.org/10.1111/wrr.12490
18 Guest JF, Ayoub N, McIlwraith T et al. Health economic burden that wounds impose on the National Health Service in the UK. BMJ Open 2015; 5(12):e009283. https://doi.org/10.1136/bmjopen-2015-009283
19 Edwards S. Physiological insult/injury: pathophysiology and consequences. Br J Nurs 2002; 11(4):263–274. https://doi.org/10.12968/bjon.2002.11.4.10079
20 Jünger M, Steins A, Hahn M, Häfner HM. Microcirculatory dysfunction in chronic venous insufficiency (CVI). Microcirculation 2000; 7(6 Pt 2):S3–12
21 Wollina U, Abdel-Naser MB, Mani R. A review of the microcirculation in skin in patients with chronic venous insufficiency: the problem and the evidence available for therapeutic options. Int J Low Extrem Wounds 2006; 5(3):169–180
22 Dunnill C, Patton T, Brennan J et al. Reactive oxygen species (ROS) and wound healing: the functional role of ROS and emerging ROS-modulating technologies for augmentation of the healing process. Int Wound J 2017; 14(1):89–96. https://doi.org/10.1111/iwj.12557
23 Chandra PK, Ross CL, Smith LC et al. Peroxide-based oxygen generating topical wound dressing for enhancing healing of dermal wounds. Wound Repair Regen 2015; 23(6):830–841. https://doi.org/10.1111/wrr.12324
24 Kimmel HM, Grant A, Ditata J. The presence of oxygen in wound healing. Wounds 2016; 28(8):264–270
25 Brem H, Tomic-Canic M. Cellular and molecular basis of wound healing in diabetes. J Clin Invest 2007; 117(5):1219–1222. https://doi.org/10.1172/JCI32169
26 Kalliainen LK, Gordillo GM, Schlanger R, Sen CK. Topical oxygen as an adjunct to wound healing: a clinical case series. Pathophysiology 2003; 9(2):81–87. https://doi.org/10.1016/S0928-4680(02)00079-2

Reflective questions

- When you consider your patients with hard-to-heal wounds, do you regularly think about the supply of oxygen to the tissues?
- What are the number of different factors influencing wound healing that are improved when oxygen levels are restored to normal?
- Are there patients under your care who might benefit from a trial of topical oxygen therapy and if so, what are the benefits to them?