Chapter 13

Topical Wound Oxygen Versus Conventional Compression Dressings in the Management of Refractory Venous Ulcers

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/63566

Abstract

Topical wound oxygen (TWO_2) proposes an innovative therapy option in the management of refractory non-healing venous ulcers (RVU) that aims to accelerate wound healing. TWO_2 accelerates epithelialisation. This leads to the development of a higher tensile strength collagen, which lessens scarring and the risk of recurrence. Sixty-seven limbs with 67 ulcers were managed using TWO_2 therapy, and 65 limbs with 65 ulcers were managed using conventional compression dressings (CCD). The proportion of ulcers completely healed by 12 weeks was 76% in patients managed with TWO_2, compared to 46% in patients managed with CCD ($p < 0.0001$). The mean reduction in ulcer surface area at 12 weeks was 96% in the TWO_2 therapy group, compared to 61% in patients managed with CCD. The median time to full ulcer healing was 57 days in the TWO_2 group, in contrast to 107 days in patients managed with CCD ($p < 0.0001$). TWO_2 patients had a significantly improved Quality-Adjusted Time Spent Without Symptoms of disease and Toxicity of treatment (Q-TWiST) compared to CCD patients, denoting an improved outcome ($p < 0.0001$). TWO_2 reduces the time needed for RVU healing and is successful in pain alleviation and MRSA elimination. TWO_2 therapy radically degrades recurrence rates. Utilising diffused oxygen raises the capillary partial pressure of oxygen (Po_2) levels at the wound site, stimulating epithelialisation, and granulation of new healthy tissue. Taking the social and individual aspects of chronic venous ulceration into account, the use of TWO_2 can provide an overwhelmingly improved quality of life for long-time sufferers of this debilitating disease.

Keywords: topical wound oxygen, conventional compression dressings, refractory venous ulcers, MRSA, epithelialisation

1. Introduction

Chronic venous ulceration is a common disease. Its prevalence is 1% of the total population, with 20% of venous ulcers presented in octogenarians [1–5]. Refractory venous leg ulceration is a common basis of morbidity [6, 7] and leads to a reduced quality of life [8], especially in the elderly population [4, 5]. It causes a considerable amount of work incapacity, social exclusion and lack of self-esteem [4]. There is a probable underestimation of the true extent of venous leg ulceration in the general population due to its underreporting [7]. Venous ulcers are characterised by a recurring pattern of healing and subsequent 70% recurrence rate at one year [9–14]. Venous ulceration places a huge monetary burden on the healthcare system [15]. The cost of managing venous ulcers accrues to £400 million sterling per year in the UK [16].

Ambulatory venous hypertension is one of the leading causes of chronic reperfusion injury. This in turn provokes venous ulceration with its habitual history of chronicity and recurrence [1]. Over the past 40 years, compression bandaging has been the gold standard form of therapy for treatment of venous ulceration. We have learned that compression will both improve perfusion and enhance healing [2, 17, 18]. Nevertheless, active healthy tissue granulation can take upwards to 3 weeks to cultivate [19]. Therefore, the following question is posed: How can we speed up epithelial coverage in a granulating wound?

1.1. Topical wound oxygen

Topical wound oxygen (TWO_2) proposes an innovative therapy option in the management of refractory non-healing venous ulcers (RVU) that aims to accelerate wound healing. The application of positive pressure oxygen to manage open wounds has been studied extensively and has demonstrated promising clinical results [20–28]. The systemic complications associated with the use of a full-body hyperbaric chamber have been overcome by the application of topical wound pure oxygen at an appropriate cycled pressure to only the specific wound site. This maximizes the beneficial wound healing effects and minimizes the negative systemic side effects [29].

Delivered through a targeted delivery system, a Hyper-Box, TWO_2 accelerates epithelialisation and eliminates MRSA within 72 h. This leads to the development of a higher tensile strength collagen, which lessens scarring and the risk of recurrence [29–32]. Hyperbaric oxygen promotes angiogenesis and increases the expression of angiogenesis-related growth factors [33, 34]. It promotes leukocyte function with enhanced bactericidal activity [35–40]. The intermittent cycled pressure, under which TWO_2 is delivered, stimulates circulation, reduces oedema and provides a sealed humidified environment essential for healing [41].

http://dx.doi.org/10.5772/63566

2. Materials and methods

The aim of this study is to scrutinise the use of TWO_2 when compared to conventional compression dressings (CCD) for managing RVU, with reference to technical and clinical outcomes from our tertiary referral leg ulcer clinic.

A 5-year study of TWO_2 versus CCD for chronic RVU was carried out at our tertiary referral leg ulcer clinic [42, 43]. This parallel group observational comparative study aimed at examining the safety and efficacy of TWO_2 in managing RVU in the short-term (12 weeks), and the mid-term (36 months).

Ethical approval was obtained from the local research ethics committee. Patients with chronic RVU, with an ulcer of more than two years duration, were recruited from the vascular unit. All patients must show no sign of improvement of the ulcer over the past 12 months, despite acceptable compliance with a suitable treatment, provided by community-based leg ulcer clinics. All patients were managed on an intention to treat basis and were given the choice of receiving CCD or TWO_2 therapy. Patients were informed on both CCD and TWO_2 therapies, and the treatment choice was discussed with their primary care physician and local tissue viability nurse. Treatment allocation was based on each patient's choice. All patients signed an informed consent form prior to beginning therapy.

2.1. Technical and clinical endpoints

The end points of this study were the proportion of ulcers healed at 12 weeks and recurrence rates at 36 months. Secondary end-points were time taken for full healing, percentage of reduction in the ulcer size at 12 weeks, methicillin-resistant *Staphylococcus aureus* (MRSA) elimination, pain reduction, recurrence rates and Quality-Adjusted Time Spent Without Symptoms of disease and Toxicity of treatment (Q-TWiST).

2.2. Inclusion criteria

Informed written consent was required from patient's aged ≥ 18 years.

The patients must be treated at a dedicated veins unit with $C_{6,s}$ in the Clinical, Etiological, Anatomical, and Pathophysiological (CEAP) classification [44, 45]. The venous ulcer must have been present for more than 2 years, with no improvement over the past 12 months despite adequate treatment at the veins unit. The patients must also have a normal ankle-brachial index (ABI) with a normal digital pressure.

2.3. Exclusion criteria

Patients who are bedridden, have ischemic or malignant ulcers, or osteomyelitis in the treated limb were primarily excluded. Patients with ischemic diabetic ulcers were excluded; however, it should be noted that diabetes in isolation was not considered an exclusion criterion. A prior study has shown that the AOTI Hyper-Box (AOTI Ltd., Galway, Ireland) is not sufficient in

ischemic diabetic ulcers. It may induce iatrogenic deterioration of the affected diabetic limb due to the cyclic pressure of the Hyper-Box [46, 47].

2.4. Statistical analysis

Data was collected and analysed using SPSS 18 software (SPSS Inc., Chicago, IL). An independent sample *t*-test was used for continuous variables, while the Mann-Whitney *U* test was used to compare unpaired, non-parametric data. Categorical proportions were examined using the chi-squared test. Time for healing was examined using Kaplan-Meier with log-rank comparison.

2.5. Quality-Adjusted Time Spent Without Symptoms of disease and Toxicity of treatment (Q-TWiST)

The survival time for patients was divided into three separate phases: the time spent with toxicity of the disease or severe adverse events prior to disease progression known as Toxicity (TOX); the time spent without any symptoms of disease progression or toxicity of treatment known as TWiST; and finally the time spent with progression of the disease known as Progression (PROG). Ulcer recurrence in fully healed ulcers or an increase of size in ulcers that had not fully healed was defined as progression of disease. The Kaplan Meier method was used to determine the mean time spent in each of the TOX, TWiST and PROG periods for each treatment group. Mean Q-TWiST was calculated for each treatment.

2.6. Techniques

The anatomical location and duration of the ulcer, signs of infection, slough, and cellulitis, as well as any other vascular risk factors were observed in each patient. The leg ulcers were swabbed for culture as well as for level of sensitivity. Prior to therapy, a numerical rating scale in regards to pain was used. This was then repeated every three days. To record surface area, maximum length and maximum width of the ulcer, the ulcers were cleaned, debrided and digitally photographed using a Visitrak system (Smith & Nephew Ltd., Hull, United Kingdom). For all patients, ABI with big toe digital pressure measurement and punch biopsy were performed, as well as venous duplex ultrasound scan for full CEAP assessment [44, 45]. Venous Clinical Severity Score was recorded for each patient [48, 49].

2.6.1. TWO_2 therapy

Sixty-seven ulcers were treated with TWO_2 therapy. The limb was placed in the Hyper-Box for twice daily for a duration of 180 min and under pressure of 50 mbar. Oxygen supplied at 10 L/min with continuous humidification. Between each session, wounds were washed and left exposed with no dressings or compression. Wounds were cleaned, debrided and re-measured twice weekly [42, 46, 47].

http://dx.doi.org/10.5772/63566

2.6.2. Compression therapy

Sixty-five ulcers were treated with compression therapy. Full compression was performed using Profore ◊ multilayer compression bandage system with underlying non-adherent Profore◊ wound contact layer dressings (Profore◊, Smith & Nephew plc., London, United Kingdom). Dressings were applied by a wound care specialist nurse and changed as required, one to three times per week, depending on the amount of exudates.

Treatment was continued for 12 weeks or until complete healing of the ulcer or whichever can be first. As soon as the ulcer is healed, the leg was fitted with a class 3, closed toe, below knee elastic stocking during the day [50]. Patients were advised to revitalise the skin by soaking the leg with tap water, baby oil or olive oil to prevent itching and dry cracked skin. Patients were followed up at 3 monthly intervals following the end of the therapy. Patients without full healing of their ulcer by 12 weeks were considered failures of treatment. They were managed with CCD and continued to be seen on a weekly basis.

3. Results

Over the course of 5 years at our tertiary referral leg ulcer clinic, 1460 patients were diagnosed of chronic venous ulcers (**Figure 1**). Following application of the inclusion and exclusion criteria, 431 patients were enrolled in this study, but only 148 patients were eligible. One hundred and thirty-two patients consented to join the study, of which 67 limbs with 67 ulcers were treated using TWO_2 therapy, and 65 limbs with 65 ulcers were treated with CCD. Fifty-seven percent of the patients treated with TWO_2 were males (n = 38), and 54% of the patients treated with CCD were males (n = 35). Risk factors, such as age, gender, the presence of diabetes mellitus, smoking, hypertension and MRSA, were similar, with no statistical significance between each group. There was no significant difference between both the groups in the anatomical distribution of ulcers, size of the ulcers or the duration of the ulcer.

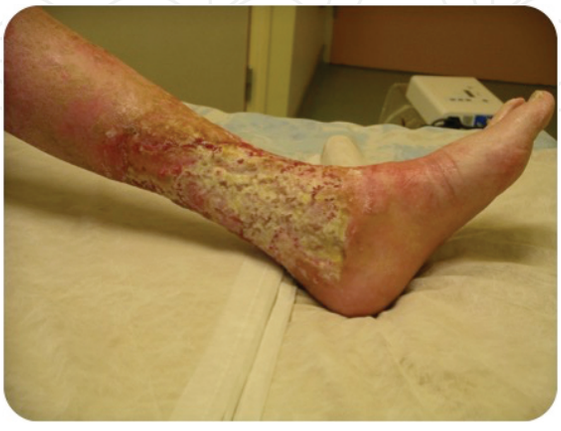

Figure 1. Patient with a chronic venous leg ulcer prior to therapy.

Twenty-four patients (36%) in the TWO_2 group and 19 patients (28%) in the CCD group were MRSA positive. Following treatment, MRSA was eliminated in 11 patients (46%), while zero cases of MRSA were eliminated in the CCD group.

The proportion of ulcers completely healed by 12 weeks was 76% (n = 51/67) in patients managed with TWO_2 compared to 46% (n = 30/65) in patients managed with CCD ($P < 0.0001$). The mean reduction in ulcer surface area at 12 weeks was 96% in the TWO_2 therapy group (**Figure 2**) compared to 61% in patients managed with CCD. The median time to full ulcer healing was 57 days in the TWO_2 group in contrast to 107 days in patients managed with CCD ($P < 0.0001$). Healing time for patients managed with TWO_2 was not affected by the extent of time of the ulcer and its size. In fact, ulcers managed with TWO_2 had a considerably shorter healing time, when compared to CCD ulcers, regardless of duration ($P < 0.0001$) or ulcer size ($P < 0.0001$). TWO_2 patients had a significantly improved Q-TWiST compared to CCD patients, denoting an improved outcome ($p < 0.0001$).

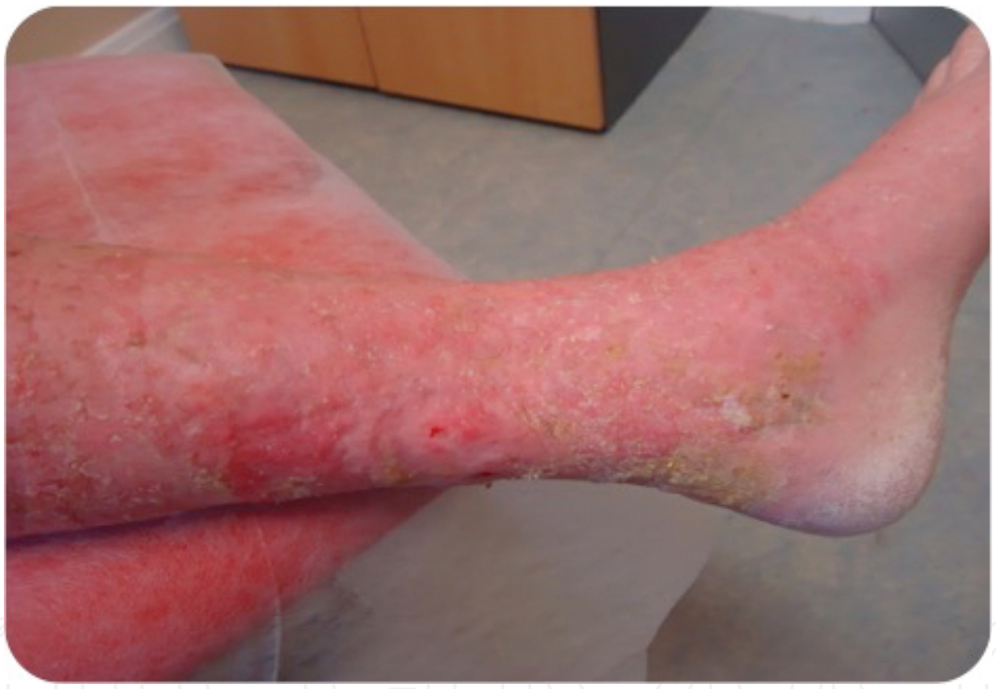

Figure 2. Significant healing and decrease in ulcer surface area post 9 weeks of TWO_2 therapy.

In all, three of the patients managed with TWO_2 were referred to our facility for primary amputation following the failure of other treatment modalities, including skin grafting. These three ulcers fully healed with no need for amputation in any case. After 36 months of follow-up, 14 of the 30 healed CCD ulcers showed recurrence compared to three of the 51 TWO_2-healed ulcers. Two CCD-managed ulcers that had not completely healed showed signs of deterioration and increase in surface area ($P < 0.0001$). All the cases that healed with TWO_2 showed reversed gradient healing phenomena where the ulcer healed from the centre to the periphery. This might be the reason for the absence of scarring and recurrence.

http://dx.doi.org/10.5772/63566

4. Discussion

The socio-economic consequences of management of RVU, merged with high recurrence rates, have encouraged the development of a disruptive technology innovative therapy, such as TWO_2 therapy. Compression therapy within the setup of a leg ulcer clinic is widely recognised as the main modality for managing venous leg ulcers [17, 18, 51, 52]. A previous study mentioned that contemporary dressing materials do not stimulate healing, and expenses are not clinically justified as they have no proven efficacy [19]. After 30 years of research, there is no data to defend using anything other than a simple, inexpensive, low-adherence dressing under multilayer compression [19].

The first publication on the use of TWO_2 was by Fischer in 1969 [20]. Fischer noted that lesions became aseptic and enhanced granulation was witnessed two days after TWO_2. In a prospective randomised study by Heng et al. red granulation tissue was present one week after TWO_2 [27]. Heng noted an absence of clinical scarring and most ulcers healed within 2–16 weeks. Gordillo et al. conducted a study on full-body hyperbaric oxygen (HBO) therapy versus TWO_2. Topical oxygen treatment showed a significant reduction in wound size and was associated with higher vascular endothelial growth factor (VEGF)165 expression in healing wounds [53].

Blackman et al. explored the efficacy of topical oxygen therapy as an adjunctive modality in repairing diabetic ulcers that failed to heal by best practice standard wound care. The healing rate after 12 weeks of topical wound oxygen therapy was 82.4%, and the mean time to complete healing was reduced. Patients also showed very low recurrence rates after 18 months [54].

Results from the Venous ULcer Cost-effectiveness of Antimicrobial dressings (VULCAN) trial showed that it took 101 days to heal 3-cm ulcers, while there was a 1-year recurrence rate of 14% in 86% of small ulcers [55], using silver dressings. These types of dressings are now rarely seen in a standard tertiary vein unit. In our unit, we have abandoned the use of silver dressing in any form as it showed a higher incidence of contacting eczema and an increase in the chronicity of the wounds.

Oxygen plays a major role in the promotion of vascular endothelial cell proliferation, collagen synthesis [56, 57] and infection control [58] by providing a direct microbial growth inhibitory effect [59] and also by activating neutrophils [60]. TWO_2 therapy evades the consequences of a full-body hyperbaric chamber [61], such as grand mal seizures and pulmonary oxygen toxicity [61, 62]. There is also the high associated cost of acquiring and maintaining a chamber to consider.

Utilising diffused oxygen raises the capillary partial pressure of oxygen (Po_2) levels at the wound site, stimulating epithelialisation and granulation of new healthy tissue [29, 32]. Oxygen generates reactive oxygen species at the wound site, acting as signalling substances, which increase the production of VEGF [63, 64]. Repeated treatment therefore accelerates wound closure.

TWO_2 therapy enhances both polymorph nuclear function and bacterial clearance and is fatal to anaerobic bacteria [35–37]. It reduces neutrophil adherence based on hindering the β-2

integrin function [38]. Eleven patients (46%) with MRSA were negative at the end of treatment with TWO_2. This informs us of its effectiveness against MRSA infection in comparison to CCD. TWO_2 therapy supports and strengthens antibiotic distribution for aminoglycosides, cephalosporins, quinilones and amphotericin [39, 40].

While TWO_2 therapy has been available for many years, there is paucity in clinical evidence for its safety and efficacy. Experience from our clinic shows that TWO_2 therapy is effective and valuable in managing RVU. Our course of therapy accomplished enhanced wound healing time, without complications, in a relatively large number of patients. TWO_2 therapy drastically reduced the time required for RVU healing and recurrence rates when compared to CCD. Quality of time spent without symptoms or toxicity of the disease was significantly improved in TWO_2 managed patients compared to CCD patients ($p < 0.0001$).

5. Conclusion

TWO_2 therapy is practical, effective and valuable in managing RVU without the risks associated with full-body hyperbaric chambers. TWO_2 therapy requires no further specialist skills by the primary care physician or local tissue viability nurse. It is therefore readily available for application under most circumstances, even for domiciliary use. The treatment has an extremely low risk of systemic complications when compared to HBO, and single-use devices greatly reduce the possibility of secondary infections.

TWO_2 slashes the time needed for RVU healing and is successful in pain alleviation, MRSA elimination and management. Utilising diffused oxygen raises the capillary partial Po_2 levels at the wound site, stimulating epithelialisation and granulation of new healthy tissue. TWO_2 therapy radically degrades recurrence rates. Taking the social and individual aspects of chronic venous ulceration into account, the use of TWO_2 can provide an overwhelmingly improved quality of life for long-time sufferers of this debilitating disease.

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http://dx.doi.org/10.5772/63566

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