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Does Topical Wound Oxygen (TWO_2) Offer an Improved Outcome Over Conventional Compression Dressings (CCD) in the Management of Refractory Venous Ulcers (RVU)? A Parallel Observational Comparative Study

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KEYWORDS
Topical wound oxygen;
TWO_2;
Compression dressings;
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Q-TWiST

Abstract *Objectives:* Topical wound oxygen (TWO_2) may help wound healing in the management of refractory venous ulcers (RVU). The aim of this study was to measure the effect of TWO_2 on wound healing using the primary end-point of the proportion of ulcers healed at 12 weeks. Secondary end-points were time to full healing, percentage of reduction in ulcer size, pain reduction, recurrence rates and Quality-Adjusted Time Spent Without Symptoms of disease and Toxicity of Treatment (Q-TWiST).
Design: A parallel observational comparative study.
Methods: Patients with CEAP $C_{6,s}$ RVU, assessed by duplex ultrasonography, were managed with either TWO_2 ($n = 46$) or conventional compression dressings (CCD) ($n = 37$) for 12 weeks or till full healing. Patients were followed up at 3 monthly intervals.
Results: At 12 weeks, 80% of TWO_2 managed ulcers were completely healed, compared to 35% of CCD ulcers ($p < 0.0001$). Median time to full healing was 45 days in TWO_2 patients and 182 days in CCD patients ($p < 0.0001$). The pain score threshold in TWO_2 managed patients improved from 8 to 3 by 13 days. After 12-month follow-up, 5 of the 13 healed CCD ulcers

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showed signs of recurrence compared to none of the 37 TWO_2 healed ulcers. TWO_2 patients experienced a significantly improved Q-TWiST.
Conclusion: TWO_2 reduces recurrence rates, alleviates pain and improves the Q-TWiST. We believe it is a valuable tool in the armamentarium of management of RVU.

Introduction

Refractory venous leg ulceration is a common source of morbidity[1,2] and reduced quality of life,[3] especially in the elderly population.[4,5] The prevalence of venous ulcers has been estimated at 0.3% within the UK population,[6,7] with comparable rates in other countries.[5,8–10] There is a probable underestimation of the true extent due to under-reporting.[2]

Venous ulcers are characterized by a cyclical pattern of healing and recurrence,[11] with recurrence rates up to 70% at one year.[12–16]

Venous ulceration places a huge burden on the health-care system.[17] The cost of managing venous ulcers amasses to £400 million sterling per year in the UK.[18] It causes a considerable amount of morbidity amongst patients, with work incapacity, social exclusion and lack of self esteem.[3]

Conventional compression dressings (CCD) are now widely recognised as the main treatment for venous leg ulcers,[19–22] with the addition of surgical correction of superficial venous reflux to reduce recurrence rates.[23,24] However, the socio-economic implications of management of RVU, combined with high recurrence rates have stimulated the development of innovative therapies, as Topical Wound Oxygen (TWO_2) therapy.

The application of positive pressure oxygen to manage open wounds has been studied extensively for decades, demonstrating promising clinical results.[25–33] The traditional limitations of a full body hyperbaric chamber have been overcome by an approach that allows 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.[34]

The intermittent cycled pressure, under which the TWO_2 is delivered, stimulates circulation, reduces oedema and provides a sealed humidified environment essential for healing.[35] TWO_2 promotes epithelialisation and capillary neoangiogenesis.[34,35] This leads to higher tensile strength collagen being formed during wound healing, which reduces scarring and the risk of recurrence.[36–39]

Objectives

This parallel group observational comparative study was aimed at examining the safety and efficacy of TWO_2 in managing refractory venous ulcers (RVU). We aim to compare the outcome of using TWO_2 to that of CCD in chronic RVU.

Primary end-points

The primary end-point study is the proportion of ulcers healed at 12 weeks.

Secondary end-points

Secondary end-points are time taken for full healing, percentage of reduction in the ulcer size at 12 weeks, MRSA elimination, pain reduction, recurrence rates and Quality-Adjusted Time Spent Without Symptoms of disease and Toxicity of treatment (Q-TWiST).

Methods

Ethical approval was obtained from the local research ethics committee. Patients with chronic refractory non-healing venous ulcers, with an ulcer of more than two years duration, were recruited from the vascular unit in a tertiary referral centre. All patients had to have shown no sign of improvement of the ulcer over the past year, despite adequate compliance with appropriate treatment, provided by community based leg ulcer clinics (Table 1).

All patients were managed on an intention to treat basis. They were given the choice to either be managed using CCD or TWO_2. Patients were fully briefed on both therapies and treatment was discussed with their primary care physician and local tissue viability nurse. Allocation to treatment was based on patient's choice. All patients signed an informed consent prior to commencement of therapy.

Inclusion criteria:
- Written informed consent
- $\geq$18 years of age
- Venous ulcer, with normal ankle—brachial index (ABI) $\geq$0.9 and digital pressures $\geq$0.7
- Duration of ulcer of more than two years
- No improvement over the past year.

Exclusion criteria:
- Bed ridden patients
- Ischaemic ulcers
- Diabetic ulcers
- Osteomyelitis
- Presence of gangrene
- Deep venous thrombosis

Patients underwent a venous duplex scan and a full CEAP[40,41] assessment (Table 1). ABIs and big toe digital pressures were measured. Punch biopsies were taken from all patients.

Patients were assessed regarding the anatomical location of the ulcer, duration of presence of the ulcer, signs of infection, slough and cellulitis. All vascular risk factors were noted.

The leg ulcer was swabbed and a sample taken for culture and sensitivity.

Table 1 Demographics. There was no significant difference between both groups in vascular related risk factors, the CEAP class of the patient, or the treatment patients had received prior to the study.

Demographics	TWO_2	CCD	*p* value
Number of ulcers	46	37	
Age (mean/range)	66 yrs (range = 49—83 yrs)	65 yrs (range = 44—87 yrs)	$p = 0.860$
Gender (M:F)	29:17	24:13	$p = 0.524$[a]
Diabetes mellitus	$n = 15$	$n = 11$	$p = 0.484$[a]
Smoking	$n = 4$	$n = 1$	$p = 0.255$[a]
Hypertension	$n = 22$	$n = 15$	$p = 0.330$[a]
MRSA positive	$n = 19$	$n = 17$	$p = 0.251$[a]
Patient referred for primary amputation	$n = 3$	$n = 0$	$p = 0.165$[a]
CEAP class[b]			
$C_{6,s}$	$n = 46$	$n = 37$	
E_p	$n = 33$	$n = 27$	$p = 0.423$[a]
E_s	$n = 13$	$n = 10$	$p = 0.396$[a]
A_s	$n = 10$	$n = 10$	$p = 0.531$[a]
A_p	$n = 7$	$n = 4$	$p = 0.347$[a]
$A_{s,p}$	$n = 29$	$n = 23$	$p = 0.520$[a]
P_r	$n = 33$	$n = 27$	p = 0.423[a]
P_o	$n = 2$	$n = 2$	$p = 0.325$[a]
$P_{r,o}$	$n = 11$	$n = 8$	$p = 0.372$[a]
Previous treatment			
SFJ ligation & division (±perforator avulsion)	$n = 5$	$n = 3$	$p = 0.275$[a]
SFJ ligation, division & LSV stripping (±perforator avulsion)	$n = 19$	$n = 17$	$p = 0.251$[a]
SPJ ligation & division (±perforator avulsion)	$n = 7$	$n = 7$	$p = 0.433$[a]
Multilayer compression dressings	$n = 34$	$n = 21$	$p = 0.214$[a]
Local dressing + Elastic stocking	$n = 8$	$n = 14$	$p = 0.564$[a]
Local dressing + no compression	$n = 4$	$n = 2$	$p = 0.207$[a]

(SFJ = Sapheno-Femoral junction, LSV = Long Saphenous Vein, SPJ = Sapheno-Popliteal junction).
[a] *p* values are Chi-Square.
[b] Basic CEAP classification.[40]

Patients were asked to assess the severity of their pain, on a scale from 1 to 10 using the pain numerical rating scale, prior to therapy and repeated every 3 days.

Ulcers were cleaned, debrided, digitally photographed and measured using a Visitrak system (Smith & Nephew Ltd, Hull, UK), to determine the surface area and maximum length and width of the ulcer.

Patients receiving CCD were managed in an outpatient leg ulcer clinic, using Profore◇ multilayer compression bandage system with underlying non-adherent Profore◇ Wound Contact Layer (WCL) dressings (Profore◇ by Smith & Nephew Ltd, Hull, UK). Dressings were applied by a tissue viability nurse, supervised by the treating physician. Dressings were changed, depending on the amount of exudate, from one to three times per week, after cleaning, debriding and re-measuring the wound.

TWO_2 patients were managed in an inpatient setup, as oxygen was delivered from piped oxygen wall outlets. During treatment sessions, patients were seated, with the affected limb extended and placed in the AOTI Hyper-Box™ (AOTI Ltd, Galway, Ireland) for 180 min twice daily under pressure of 50 mbar (Fig. 1). Oxygen was supplied at 10 l/min with continuous humidification. Between sessions, the limb was left exposed, with no dressings. Patients were allowed to leave the ward or hospital between treatment sessions, if they desired, during which the ulcer was temporarily covered with a non-adherent WCL dressing and gauze bandage, until they returned. No compression was applied. Wounds were cleaned, debrided and re-measured twice per week.[42,43]

Treatment was continued until full ulcer healing or for 12 weeks, whichever sooner. When full healing was achieved, patients from both treatment arms were commenced on class II elastic stockings. Patients who did not achieve full ulcer healing by 12 weeks, in either treatment arm, were considered failures of treatment. They were managed with CCD and continued to be seen on a weekly basis. Patients were followed up at three monthly intervals following cessation of therapy.

End-points were assessed at 12 weeks, apart from the time to full ulcer healing which continued to be assessed beyond the 12-week point. Recurrence rates and Q-TWiST were assessed throughout the treatment and follow-up period.

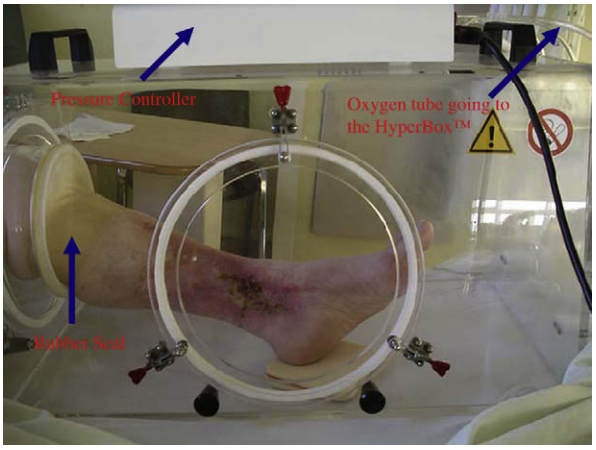

Figure 1 Limb in AOTI Hyper-Box™. Patient with a medial maleolar ulcer during a TWO_2 treatment session, with the limb placed inside the AOTI Hyper-Box™. Oxygen and pressure seal are maintained by the rubber cuff, placed below the knee.

Survival time was divided into three periods;

Toxicity (TOX): time spent with toxicity of disease or severe adverse events prior to disease progression.
TWiST: time spent without symptoms of disease progression or toxicity of treatment.
Progression (PROG): Time spent with progression of disease. Progression of disease was defined as ulcer recurrence in fully healed ulcers, or increase in ulcer size in ulcers that had not fully healed.

The mean time spent in each of the three periods was determined separately for each treatment group, using the Kaplan–Meier method.

Mean Q-TWiST for each treatment arm was calculated as[44–46]:

$$\text{Q-TWiST} = (\mu_{TOX} \times \text{TOX}) + \text{TWiST} + (\mu_{PROG} \times \text{PROG})$$

TOX, TWiST and PROG represented the mean health state duration from Kaplan–Meier analysis; μ_{TOX} and μ_{PROG} signify the utility coefficients for TOX and PROG, respectively. TWiST was considered to have utility of 1, indicating the best possible quality of life for a patient with RVU.

μ_{TOX} and μ_{PROG} were weighted using a range of utility scores, to reflect quality of time in each health state, relative to TWiST. Sensitivity analyses were conducted by varying the assigned utilities for TOX and PROG in 0.25 increments across the full range of possible utility weights from 0 (representing poorest health) to 1.

Statistical analysis

Data were collected and analysed using SPSS 14 software (SPSS Inc, Chicago, Illinois). Continuous variables were compared with the independent sample *t* test. Categoric proportions were compared using the Chi-Square test. Mann–Whitney *U* test was performed to compare unpaired, non-parametric data. Time to healing & Q-TWiST were assessed using Kaplan–Meier with Log-rank comparison.

Results

46 limbs with 46 ulcers were managed using TWO_2 therapy. 37 limbs with 37 ulcers were managed using CCD. 63% of the TWO_2 patients were men ($n = 29$). 65% of the CCD patients were men ($n = 24$, $p = 0.524$, Table 1).

Risk factors were similar in both treatment groups (Table 1). There was no significant difference between both groups in the anatomical distribution of ulcers, size of the ulcers or the duration the patient had the ulcer (Table 2).

19/46 ulcers were MRSA positive in the TWO_2 group, while 17/37 were MRSA positive in the CCD group ($p = 0.251$) (Table 1).

Using the CEAP classification all patients were classified as $C_{6,s}$.[40,41]

Using the Venous Clinical Severity Score,[47–49] the mean score in TWO_2 patients was 25, and was 23 in CCD patients.

Following commencement of TWO_2 therapy, there was an initial latent phase up to five days, where no reduction in surface area was seen. This was followed by a period of rapid improvement, where ulcers reached 70% reduction in surface area. This was followed by a plateau where healing slowed down until either near healing or full healing (Fig. 2).

89% of the TWO_2 managed ulcers showed a reduction in surface area by 3weeks of treatment ($n = 41/46$), compared to 68% of CCD ulcers ($n = 25/37$, $p = 0.016$).

The proportion of ulcers completely healed by 12 weeks was 80% in the TWO_2 group ($n = 37/46$) in contrast to 35% of the CCD group ($n = 13/37$, $p < 0.0001$).

The mean reduction in ulcer surface area at 12 weeks was 96% in the TWO_2 therapy group, compared to 61% in the CCD group.

Table 2 Characteristics of the leg ulcers. There was no statistically significant difference between both treatment groups, regarding the anatomical location of the ulcer, the size of the ulcer, or the duration the patient had the ulcer.

Anatomical distribution	TWO_2	CCD	*p* value
Medial maleolus	$n = 18$	$n = 14$	$p = 0.543$[a]
Lateral maleolus	$n = 12$	$n = 11$	$p = 0.450$[a]
Calf	$n = 8$	$n = 6$	$p = 0.563$[a]
Shin	$n = 8$	$n = 6$	$p = 0.563$[a]
Ulcer surface area			
≤ 5 cm^2	$n = 6$	$n = 6$	$p = 0.459$[b]
6–10 cm^2	$n = 7$	$n = 5$	$p = 0.541$[b]
11–20 cm^2	$n = 17$	$n = 12$	$p = 0.423$[b]
21–40 cm^2	$n = 7$	$n = 7$	$p = 0.437$[b]
≥ 41 cm^2	$n = 9$	$n = 7$	$p = 0.584$[b]
Duration of the ulcer			
2–3 years	$n = 10$	$n = 9$	$p = 0.492$[b]
4–5 years	$n = 16$	$n = 10$	$p = 0.303$[b]
6–10 years	$n = 12$	$n = 12$	$p = 0.347$[b]
11–20 years	$n = 6$	$n = 5$	$p = 0.600$[b]
Over 20 years	$n = 2$	$n = 1$	$p = 0.582$[b]

[a] *p* values are Chi-Square.
[b] *p* values are Mann–Whitney *U*.

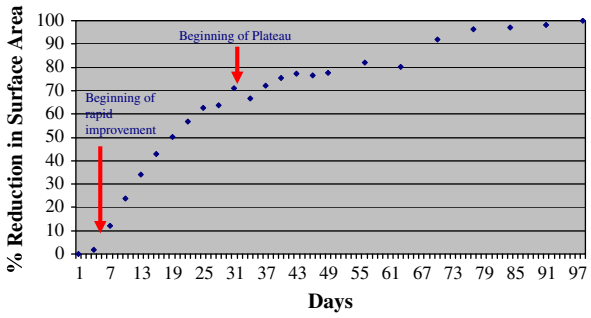

Figure 2 Mean reduction in surface area. There was an initial latent phase up to 5 days, followed by rapid improvement, where ulcers reached 70% reduction in surface area. This was followed by a plateau of slow improvement.

The median time to full ulcer closure was 45 days in the TWO_2 group (95% CI: 39—51), compared to 182 days in the Profore$^{\diamond}$ group (95% CI: 162—203, $p < 0.0001$) (Fig. 3).

Within the TWO_2 group, the duration the patient had the ulcer and the size of the ulcer, did not affect the healing time. TWO_2 managed ulcers had a significantly shorter healing time, compared to CCD ulcers, regardless of the duration of ulcer ($p < 0.0001$) or the size of the ulcer ($p < 0.0001$).

Three of the TWO_2 patients were referred to our service for primary amputation following failure of other treatment modalities, including skin grafting. These three ulcers healed completely and none of these patients required amputation.

Three of the TWO_2 ulcers showed no signs of healing at 4 weeks. One patient had an ulcer exposing tendons and bone. Histology proved that the other two patients have underlying basal cell carcinoma ($n = 1$) and squamous cell carcinoma ($n = 1$).

32/46 of the TWO_2 treated ulcers showed a reverse gradient of healing, where healing commenced from the centre of the ulcer and expanded towards the periphery (Fig. 4). Using the pain numerical rating scale, the pain score threshold in the TWO_2 managed patients improved from 8 to 3 by 13 days.

9 of the 19 MRSA positive ulcers in the TWO_2 therapy group were MRSA negative after 5 weeks of treatment regardless of closure of the ulcer, compared to none of the 17 MRSA positive ulcers in the CCD group ($p = 0.007$).

No local or systemic complications were encountered in either treatment group.

Patients were followed up for a mean of 12 months. During that period, 2 TWO_2 patients underwent varicose vein surgery, while 5 patients (2 TWO_2 and 3 CCD) underwent redo-varicose vein surgery.

During follow-up, none of the 37 fully healed TWO_2 managed ulcers showed signs of recurrence. In comparison, 5 of the 13 fully healed CCD managed ulcers showed signs of recurrence. Furthermore, 2 CCD managed ulcers that had not completely healed, showed signs of deterioration and increase in surface area.

TWO_2 patients had a significantly shorter mean TOX (1.5 months), in comparison to CCD patients (6 months, $p < 0.001$). TWO_2 patients had a significantly longer mean TWiST (12.5 months), opposed to 4.5 months in CCD patients ($p < 0.001$).

TWO_2 patients had no PROG, in contrast to a mean PROG of 3 months for CCD patients ($p < 0.0001$).

TWO_2 patients experienced an overall improved Q-TWiST when assigned any utility coefficient, across the full range of possible utility weights. When the utility coefficient assigned was 0.5 the Q-TWiST for TWO_2 patients was 13.625 compared to 27 in the CCD group ($p < 0.0001$, Table 3).

Discussion

Compression therapy within the setup of a leg ulcer clinic is widely recognised as the main modality for managing venous leg ulcers.[19—22] High recurrence rates and the socio-economic burden of RVU, have motivated the development of alternative therapies as TWO_2 therapy.

The first publication on the use of TWO_2 was by Fischer in 1969.[25] Fischer noted that lesions became aseptic and enhanced granulation was witnessed two days after TWO_2. These findings are similar to our own results. In our study,

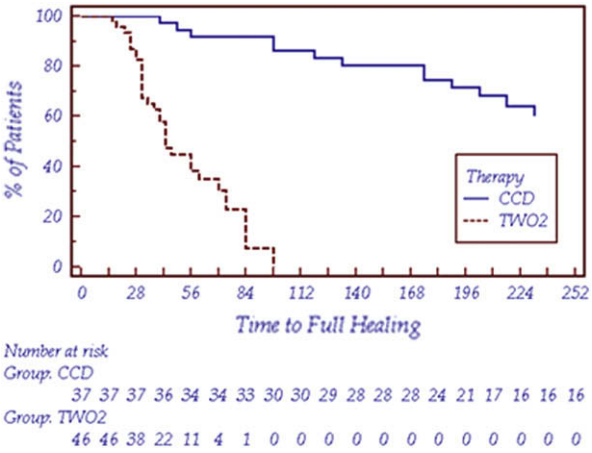

Figure 3 Time to full healing. Kaplan—Meier curve showing time to full ulcer healing. TWO_2 managed ulcers had a significantly shorter median time to full healing (45 days) compared to 182 days in CCD managed ulcers ($p < 0.0001$).

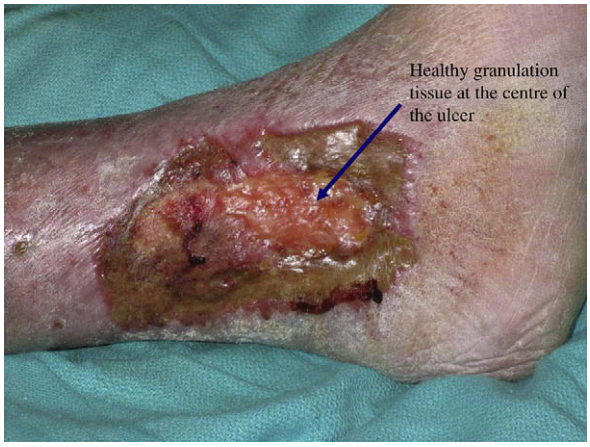

Figure 4 Reverse gradient of healing. Healing starts at the centre of the ulcer & then spreads outwards.

Table 3 Quality Time Spent Without Symptoms of Disease and Toxicity of Treatment (Q-TWiST) was significantly improved in TWO_2 patients.

Time period	TWO_2	CCD	*p* value
TOX	1.5 months	6 months	$p < 0.0001$
TWiST	12.5 months	4.5 months	$p < 0.0001$
PROG	0	3 months	$p < 0.0001$
Q-TWiST	13.625	27	$p < 0.0001$

however, no improvement was witnessed within the first four to five days of TWO_2. This discrepancy in timing of clinical improvement could be attributed to the difference in treatment regimes. While Fischer used a constant pressure of 22 mmHg, the AOTI Hyper-Box™ used in our study cycled the pressure between atmospheric pressure and 50 mbar.

A series of feasibility studies and randomised controlled studies, assessed a mixed aetiology of ulcers and none were dedicated to assess the effect of TWO_2 on RVU.[25–33] We believe our study to be the first study on the use of TWO_2 in RVU.[42,43]

In a prospective randomised study by Heng et al, red granulation tissue was present one week after TWO_2.[32] Heng noted absence of clinical scarring and most ulcers healed within 2–16 weeks. This mimics our findings where healthy granulation tissue was witnessed in the ulcers following four to five days of TWO_2.

In both our own study and the Heng study,[32] positive effects could be found, whereas in a study by Leslie et al. no significant effects could be detected.[33] The treatment schedule in the Leslie study was short, which could have had an impact on the overall results. Two daily 90-min sessions were applied for 7–14 days, compared to 4-h a day, 4 days a week over 4 weeks in the ''positive'' Heng study[32] and 3-h bi-daily, 7 days a week in our study.

In our study, treatment was commenced at 90-min sessions once daily, in the first 5 cases where TWO_2 was used. These patients were excluded from this study analysis and are not a subset of the 46 patients managed with TWO_2. We noted minimal response within the first 10 days of treatment. Through close monitoring and adjusting our protocol, treatment sessions were increased gradually until reaching 180-min sessions bi-daily, where an adequate response was witnessed and no safety concerns were observed.[42,43]

During TWO_2 therapy sessions, patients endured limb elevation. These patients had their ulcers for a minimum of 2 years(up to 43years), and had already shown no signs of improvement over the past year, despite adequate compliance with treatment. While accepting that this may have assisted in ulcer healing, it would be futile to attribute the improved outcome to limb elevation alone.

In our study, only 35% of ulcers managed with CCD fully healed. Whilst accepting that this is a lower rate than most published studies on this treatment, yet the refractory nature of these ulcers, has to be taken into consideration.

Fischer et al.,[28] showed reduced rates of infection with TWO_2. This depicts our findings, where 9 of the 19 MRSA positive ulcers in the TWO_2 group were rendered MRSA negative after 5 weeks of treatment.

Cronje stated that if topical oxygen could increase wound oxygen levels, it would create a reverse gradient, with higher values in the wound than in the periphery.[50] In our study 69.5% ($n = 32/46$) of the TWO_2 treated ulcers showed reverse gradient of healing. All these ulcers further continued to fully heal with minimal scarring and no recurrence. This could be attributed to topical absorption of oxygen, leading to formation of higher tensile strength collagen.[36–38]

Despite the fact that the mean Venous Clinical Severity Score[47–49] was higher in TWO_2 patients, yet an improved outcome was witnessed compared to CCD patients.

Ulcers that showed no signs of healing in the TWO_2 group, proved to have an underlying cause. One patient had an ulcer exposing tendons and bone. The other two ulcers had underlying malignancy. Since this finding, evidence of mitotic activity was added as an exclusion criterion.

TWO_2 patients had a significantly improved Q-TWiST compared to CCD patients, denoting an improved outcome ($p < 0.0001$). TWO_2 patients had a significantly shorter mean period of time with TOX ($p < 0.0001$). This is attributed to the significantly shorter time to full ulcer closure and higher percentage of ulcers that achieved full healing.

TWO_2 patients had a significantly longer mean TWiST ($p < 0.0001$). TWO_2 managed patients did not experience any complications from their therapy. There was no recurrence of the ulcers or pain witnessed in the TWO_2 patients.

TWO_2 patients had no time with PROG, compared to a mean period of 3 months of PROG in CCD patients ($p < 0.0001$). In the TWO_2 group, once healing of the ulcer was achieved, these patients continued to maintain an ulcer free course over a mean period of 12 months of follow-up, with no recurrence of symptoms or progress of disease.

Conclusion

TWO_2 is safe and effective in RVU management. It has a superior outcome to CCD, through achieving a shorter healing time, alleviating pain, reducing recurrence rates and improving the Q-TWiST. We believe that TWO_2 is a valuable tool in the armamentarium of management of patients with RVU, without the risks of full body hyperbaric chambers.

Following these initial observational findings, a randomised controlled trial is currently underway to further assess the benefits of TWO_2 therapy.

Conflict of Interest/Funding

None.

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