

# Technical and Clinical Outcome of Topical Wound Oxygen in Comparison to Conventional Compression Dressings in the Management of Refractory Nonhealing Venous Ulcers

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## Abstract

Topical wound oxygen (TWO<sub>2</sub>) proposes an option in the management of refractory nonhealing venous ulcers (RVUs). End points are proportion of ulcers healed at 12 weeks, recurrence rates, reduction in ulcer size, and time to full healing. A total of 67 patients with RVU were managed using TWO<sub>2</sub> and 65 patients with conventional compression dressings (CCDs) for 12 weeks or till full healing. Mean reduction in ulcer surface area at 12 weeks was 96% in patients managed with TWO<sub>2</sub> and 61% in patients managed with CCD. At 12 weeks, 76% of the TWO<sub>2</sub>-managed ulcers had completely healed, compared to 46% of the CCD-managed ulcers ( $P < .0001$ ). Median time to full healing was 57 days in patients managed with TWO<sub>2</sub> and 107 days in patients managed with CCD ( $P < .0001$ ). After 36 months follow-up, 14 of the 30 healed CCD ulcers showed recurrence compared to 3 of the 51 TWO<sub>2</sub>-healed ulcers. The TWO<sub>2</sub> is effective and valuable in managing RVU. The TWO<sub>2</sub> slashes the time required for RVU healing and radically decreases the recurrence rates.

## Keywords

topical wound oxygen, venous ulcer, compression dressing

## Introduction

Chronic venous ulceration is a common disease. The prevalence is 1% of the total population,<sup>1-4</sup> with 20% of venous ulcers portrayed in octogenarians.<sup>4,5</sup> Ambulatory venous hypertension is the trigger of chronic reperfusion injury. This provokes venous ulceration<sup>1</sup> with its saga of chronicity and recurrence.<sup>1</sup>

Management of venous ulcers costs upward of 1 billion dollars annually in the United States,<sup>6</sup> and around 600 million Euros per year, in a population of 60 million.<sup>7,8</sup> Despite this, recurrence rates have been reported up to 70% in most published series.<sup>9,10</sup>

Over the past 40 years, we learnt that compression will improve the perfusion and ameliorate healing.<sup>2,11,12</sup> Nevertheless, active healthy granulation takes up to 3 weeks to cultivate.<sup>13</sup> The crucial step is how can we speed up the epithelial coverage of a granulating wound?

One therapy that aims at expediting wound healing is topical wound oxygen (TWO<sub>2</sub>). Delivered through a Hyper-Box, it promotes angiogenesis and expedites epithelialization. This leads to a higher tensile strength collagen which diminishes scarring and the risk of recurrence.<sup>14-17</sup> It increases the expression of angiogenesis-related growth factors<sup>18,19</sup> and promotes leukocyte function with enhanced bactericidal activity.<sup>20-25</sup>

## Aim and Objectives

We aim to assess the technical and clinical outcome of using TWO<sub>2</sub> and conventional compression dressings (CCDs) in chronic refractory venous ulceration (RVU).

We previously published our experience in the use of TWO<sub>2</sub> in chronic RVU.<sup>26</sup> In this current study, we aimed to examine the mid-term efficacy of TWO<sub>2</sub> in managing RVUs and the recurrence rates, after a 5-year follow-up.

Primary end points were proportion of ulcers healed at 12 weeks and recurrence rates at 36 months. Secondary end points were reduction in the ulcer size at 12 weeks, time taken for full

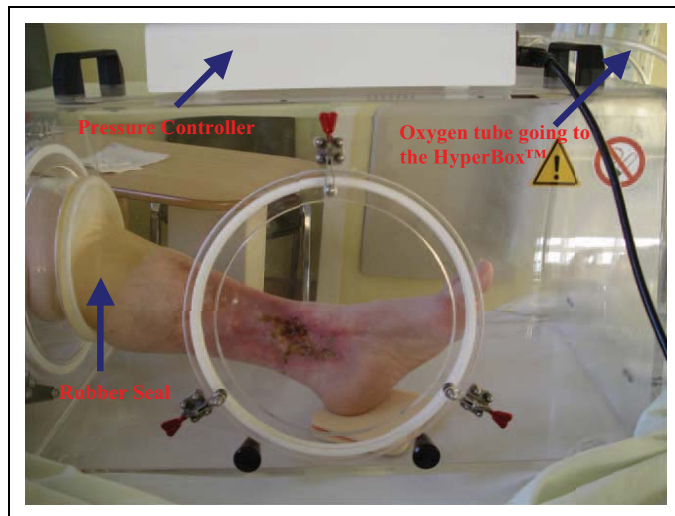
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**Figure 1.** Limb in AOTI-HyperBox. Patient with a medial malleolus ulcer during a  $TWO_2$  treatment session, with the limb placed inside the AOTI-HyperBox. Oxygen and pressure seal is maintained by the rubber cuff, placed below the knee.  $TWO_2$  indicates topical wound oxygen.

healing, and methicillin-resistant *Staphylococcus aureus* (MRSA) elimination.

### Inclusion Criteria

A written informed consent was obtained from men/women of age  $\geq 18$  years.

The duration of the venous ulcer must be more than 2 years with no improvement over the past 1 year in a dedicated veins unit with  $C_{6,s}$  in the Clinical, Etiological, Anatomical, and Pathophysiological (CEAP) classification.<sup>27,28</sup> The patient must have a normal ankle-brachial index (ABI) with normal digital pressure.

### Exclusion Criteria

Bedridden patients and patients with ischemic ulcers or osteomyelitis in the treated limb were primarily excluded. Patients diagnosed with malignant ulcers were excluded. Diabetes was not considered an exclusion criterion; however, patients with ischemic diabetic ulcers were excluded. A prior pivotal study in our center had proved that the AOTI Hyper-Box (AOTI Ltd, Galway, Ireland) does not work in ischemic diabetic ulcers and might induce iatrogenic deterioration of the affected diabetic limb because of the cyclic pressure.<sup>29,30</sup>

## Methods

### Study Design

From October 2006 to December 2011, ethical endorsement was attained from patients with chronic RVUs of more than 2 years duration. All patients had to have experienced no sign of progress of the ulcer over the past year, despite ample compliance with

appropriate treatment, provided by community-based leg ulcer clinics.

All patients were managed in an intention to treat basis, with the option to be managed either using CCD or using  $TWO_2$ . Patients were fully instructed on both the therapies and treatment was conversed with their primary care physician and local tissue viability nurse. Allotment to treatment was centered on the patient's preference.

### Techniques

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

The leg ulcer was swabbed for culture and sensitivity. The pain numerical rating scale was used prior to therapy and repeated every 3 days.

Ulcers were cleaned, debrided, digitally photographed, and measured using a Visitrak system (Smith & Nephew Ltd, Hull, United Kingdom), to ascertain the surface area and maximum length and width of the ulcer. Venous duplex ultrasound scan was performed for full CEAP assessment.<sup>27,28</sup> The ABI with big toe digital pressure measurement and punch biopsy were performed for all patients. Patients were assessed regarding their Venous Clinical Severity Score.<sup>31,32</sup>

**$TWO_2$  therapy: 67 ulcers.** The limb was placed in the AOTI Hyper-Box for 180 minutes twice daily under pressure of 50 mbars, with oxygen supplied at 10 L/min with continuous humidification (Figure 1). Wounds were washed and left exposed between sessions with no dressings and no compression. Wounds were cleaned, debrided, and remeasured twice per week.<sup>26,29,30</sup>

**Compression therapy: 65 ulcers.** Full compression was performed, using Profore<sup>◊</sup> multilayer compression bandage system with underlying nonadherent Profore<sup>◊</sup> wound contact layer dressings (Profore<sup>◊</sup> by Smith & Nephew Ltd). Dressings were applied by a wound care specialist nurse and changed as required, 1 to 3 times per week, depending on the amount of exudates.

### Protocol Post "Venous Ulcer Healing" or "Failure to Heal"

Treatment was sustained until complete ulcer healing or for 12 weeks, whichever sooner. In either arm of the study, as soon as the ulcer heals the leg is fitted with class 3, closed toe, below knee elastic stockings during the day<sup>33</sup> and advised to rejuvenate the skin of their legs with tap water soaking, baby oil, or olive oil to prevent itching and dry cracked skin with subsequent scratching.

Patients who did not reach complete ulcer healing by 12 weeks, in either treatment arm, were deemed failures of treatment. They were managed with CCD and continued to be seen on a weekly basis. Patients were followed up at 3 monthly intervals following cessation of the therapy.

**Table 1.** Demographics<sup>a</sup>

Demographics	TWO <sub>2</sub>	CCD	P Value
Number of ulcers	67	65	
Age (mean/range)	69.34 years (range = 46-85 years)	67.78 years (range = 44-88 years)	.693 <sup>b</sup>
Gender, M: F	38: 29	35: 30	.447 <sup>c</sup>
Diabetes mellitus	n = 21	n = 18	.425 <sup>c</sup>
Smoking	n = 5	n = 2	.628 <sup>c</sup>
Hypertension	n = 30	n = 31	.554 <sup>c</sup>
MRSA positive	n = 24	n = 19	.291 <sup>c</sup>
Patient referred for primary amputation	n = 3	n = 0	.386 <sup>c</sup>

Abbreviations: CCD, conventional compression dressings; F, female; M, male; MRSA, methicillin-resistant *Staphylococcus aureus*; TWO<sub>2</sub>, topical wound oxygen.

<sup>a</sup> There was no significant difference between both the groups in the demographics or vascular-related risk factors.

<sup>b</sup> P value is analyzed using t test

<sup>c</sup> P values are analyzed using chi-squared test.

**Table 2.** Characteristics of the Leg Ulcers<sup>a</sup>

Anatomical Distribution	TWO <sub>2</sub> , n	CCD, n	P Value
Medial maleolus	32	30	.406 <sup>b</sup>
Lateral maleolus	16	17	.574 <sup>b</sup>
Calf	9	9	.840 <sup>b</sup>
Shin	10	9	.801 <sup>b</sup>
Ulcer surface area			
≤5 cm <sup>2</sup>	9	8	.459 <sup>b</sup>
6 to 10 cm <sup>2</sup>	10	9	.801 <sup>b</sup>
11 to 20 cm <sup>2</sup>	25	28	.538 <sup>b</sup>
21 to 40 cm <sup>2</sup>	12	11	.794 <sup>b</sup>
≥41 cm <sup>2</sup>	11	9	.715 <sup>b</sup>
Duration of the ulcer			
2 to 3 years	12	11	.794 <sup>b</sup>
4 to 5 years	23	18	.407 <sup>b</sup>
6 to 10 years	19	22	.446 <sup>b</sup>
11 to 20 years	9	11	.726 <sup>b</sup>
Over 20 years	4	3	.874 <sup>b</sup>

Abbreviations: CCD, conventional compression dressings; TWO<sub>2</sub>, topical wound oxygen.

<sup>a</sup> 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.

<sup>b</sup> P values are analyzed using chi-squared test.

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 quality-adjusted time without symptoms of disease or toxicity of treatment were assessed throughout the treatment and follow-up period.

### Statistical Analysis

Data were accumulated and analyzed using SPSS 18 software (SPSS Inc, Chicago, Illinois). Continuous variables were balanced with the independent sample *t* test. Categorical proportions were judged using the chi-squared test. Mann Whitney *U* test was used to compare unpaired, nonparametric data. Time to healing was gauged using Kaplan-Meier with log-rank comparison.

**Table 3.** The CEAP Classification<sup>a</sup>

CEAP Class <sup>b</sup>	TWO <sub>2</sub> , n	CCD, n	P Value
C <sub>6,s</sub>	67	65	
E <sub>p</sub>	47	51	.186 <sup>c</sup>
E <sub>s</sub>	20	14	.589 <sup>c</sup>
A <sub>s</sub>	15	20	.531 <sup>c</sup>
A <sub>p</sub>	11	7	.769 <sup>c</sup>
A <sub>s, p</sub>	41	38	.259 <sup>c</sup>
P <sub>r</sub>	46	42	.217 <sup>c</sup>
P <sub>o</sub>	4	3	.862 <sup>c</sup>
P <sub>r,o</sub>	17	20	.618 <sup>c</sup>

Abbreviations: CCD, conventional compression dressings; CEAP class, Clinical, Etiological, Anatomical, and Pathophysiological classification; TWO<sub>2</sub>, topical wound oxygen.

<sup>a</sup> There was no significant difference between both the groups in the CEAP classification.

<sup>b</sup> Basic CEAP Classification.<sup>26</sup>

<sup>c</sup> P values are analyzed using chi-squared test.

## Results

### Patients

Over a period of 5 years, from October 2006 to December 2011, 1460 patients were reviewed with a diagnosis of chronic venous ulcers, at our tertiary referral leg ulcer clinic. Of these patients, 431 met the inclusion criteria to be enrolled in this study. After application of the exclusion criteria, only 148 patients were eligible. Out of these, 132 patients consented to join the study.

Totally, 67 limbs with 67 ulcers were managed using the TWO<sub>2</sub> therapy; 65 limbs with 65 ulcers were managed using CCD. In all, 57% of the patients managed with TWO<sub>2</sub> were males (n = 38) and 54% of the patients managed with CCD were males (n = 35; *P* = .447; Table 1).

Risk factors were similar in both the treatment groups (Table 1). 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 (Table 2).

Of the 67 ulcers, 24 ulcers were MRSA positive in the TWO<sub>2</sub> group, while 19 of 65 were MRSA positive in the CCD

**Table 4.** Previous Ulcer Treatment<sup>a</sup>

Previous Treatment	TWO <sub>2</sub> , n	CCD, n	P Value
SFJ ligation and division ( $\pm$ perforator avulsion)	7	5	.596 <sup>b</sup>
SFJ ligation, division, and LSV stripping ( $\pm$ perforator avulsion)	26	23	.213 <sup>b</sup>
SPJ ligation and division ( $\pm$ perforator avulsion)	9	10	.472 <sup>b</sup>
Multilayer compression dressings	45	37	.175 <sup>b</sup>
Local dressing + elastic stocking	13	18	.286 <sup>b</sup>
Local dressing + no compression	9	10	.472 <sup>b</sup>

Abbreviations: SFJ, sapheno-femoral junction; LSV, long saphenous vein; SPJ, sapheno-popliteal junction; CCD, conventional compression dressings; TWO<sub>2</sub>, topical wound oxygen.

<sup>a</sup> There was no significant difference between both groups regarding the surgical or local treatment the patients had received prior to the study.

<sup>b</sup> P values are analyzed using chi-squared test.

group ( $P = .386$ ; Table 1). Using the CEAP classification all patients were classified as C<sub>6,s</sub><sup>27,28</sup> (Table 3). Using the Venous Clinical Severity Score,<sup>31,32</sup> mean score in patients managed with TWO<sub>2</sub> was 25 and was 23 in patients managed with CCD.

There was no significant difference in the previous surgical or local management the patient had received to the ulcers, prior to the study (Table 4).

### End points

In all, 86% of the TWO<sub>2</sub>-managed ulcers showed a reduction in surface area by 3 weeks of treatment ( $n = 58/67$ ), compared to 72% of the CCD ulcers ( $n = 47/65$ ;  $P = .021$ ; Table 5).

The proportion of ulcers completely healed by 12 weeks was 76% in the TWO<sub>2</sub> group ( $n = 51/67$ ) in contrast to 46% of the CCD group ( $n = 30/65$ ;  $P < .0001$ ; Table 5).

The mean reduction in ulcer surface area at 12 weeks was 96% in the TWO<sub>2</sub> therapy group, compared to 61% in the CCD group (Figure 2).

The median time to full ulcer healing was 57 days in the TWO<sub>2</sub> group, in contrast to 107 days in the Profore<sup>o</sup> group ( $P < .0001$ ; Table 5; Figure 3).

Within the TWO<sub>2</sub> group, the duration the patient had the ulcer and the size of the ulcer did not affect the healing time. The TWO<sub>2</sub>-managed ulcers had a substantially shorter healing time, compared to CCD ulcers, no matter what was the duration of ulcer ( $P < .0001$ ) or the size of the ulcer ( $P < .0001$ ; Table 6). Figures 4 and 5 show an ulcer with a large surface area that healed completely over 8 weeks using TWO<sub>2</sub>.

In all, 3 of the patients managed with TWO<sub>2</sub> were referred to our facility for primary amputation following the failure of other treatment modalities, including skin grafting. These 3 ulcers fully healed and none of these patients compelled to have an amputation.

Of the 67 ulcers, 51 of the TWO<sub>2</sub>-treated ulcers showed a reverse gradient of healing, where healing commenced from the core of the ulcer and expanded toward the margin (Figure 6).

**Table 5.** Results<sup>a</sup>

Results	TWO <sub>2</sub>	CCD	P Value
Ulcers showing signs of healing in 3 weeks	86% ( $n = 58/67$ )	72% ( $n = 47/65$ )	.021 <sup>b</sup>
Ulcers completely healed by 3 months	76% ( $n = 51/67$ )	46% ( $n = 30/65$ )	<.0001 <sup>b</sup>
Median time to full healing	57 days	107 days	<.0001 <sup>c</sup>
MRSA elimination	11/24	0/19	<.001 <sup>b</sup>

Abbreviations: CCD, conventional compression dressings; MRSA, methicillin-resistant *Staphylococcus aureus*; TWO<sub>2</sub>, topical wound oxygen.

<sup>a</sup> Topical wound oxygen ulcers had a significantly shorter healing rate and healing time, as well as improved methicillin-resistant *Staphylococcus aureus* elimination, compared to conventional compression dressings managed ulcers.

<sup>b</sup> P values are analyzed using chi-squared test.

<sup>c</sup> P value is log rank.

This is conflicting to the conventional healing process that initiates from the outward edges of the ulcer inwardly.

Using the pain numerical ranking scale, the pain score threshold in the TWO<sub>2</sub>-managed patients recuperated from 8 to 3 by 13 days.

A total of 11 of the 24 MRSA-positive ulcers in the TWO<sub>2</sub> therapy group were MRSA negative after 5 weeks of treatment regardless of the closure of the ulcer. None of the 19 MRSA-positive ulcers in the CCD group were MRSA negative by 5 weeks of treatment ( $P < .001$ ; Table 5). No local or systemic complications were encountered in either treatment group.

Patients were followed up for a median of 36 months. During that period, 4 TWO<sub>2</sub>-managed patients underwent primary varicose vein surgery, while 7 patients (2 TWO<sub>2</sub> and 5 CCD) underwent redo-varicose vein surgery.

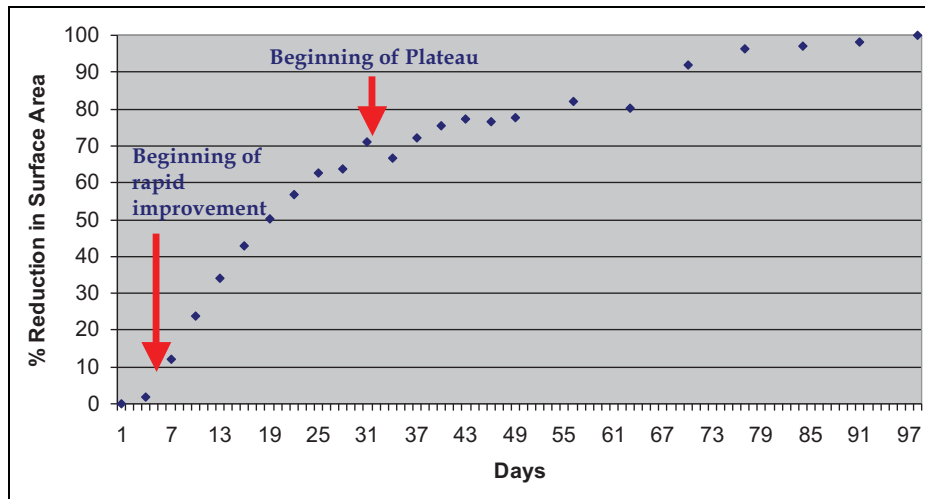
During the follow-up, 3 of the 51 fully healed TWO<sub>2</sub>-managed ulcers showed signs of recurrence. In comparison, 14 of the 30 fully healed CCD-managed ulcers showed signs of recurrence. Furthermore, 2 CCD-managed ulcers that had not completely healed showed signs of deterioration and increase in surface area ( $P < .0001$ ).

### Discussion

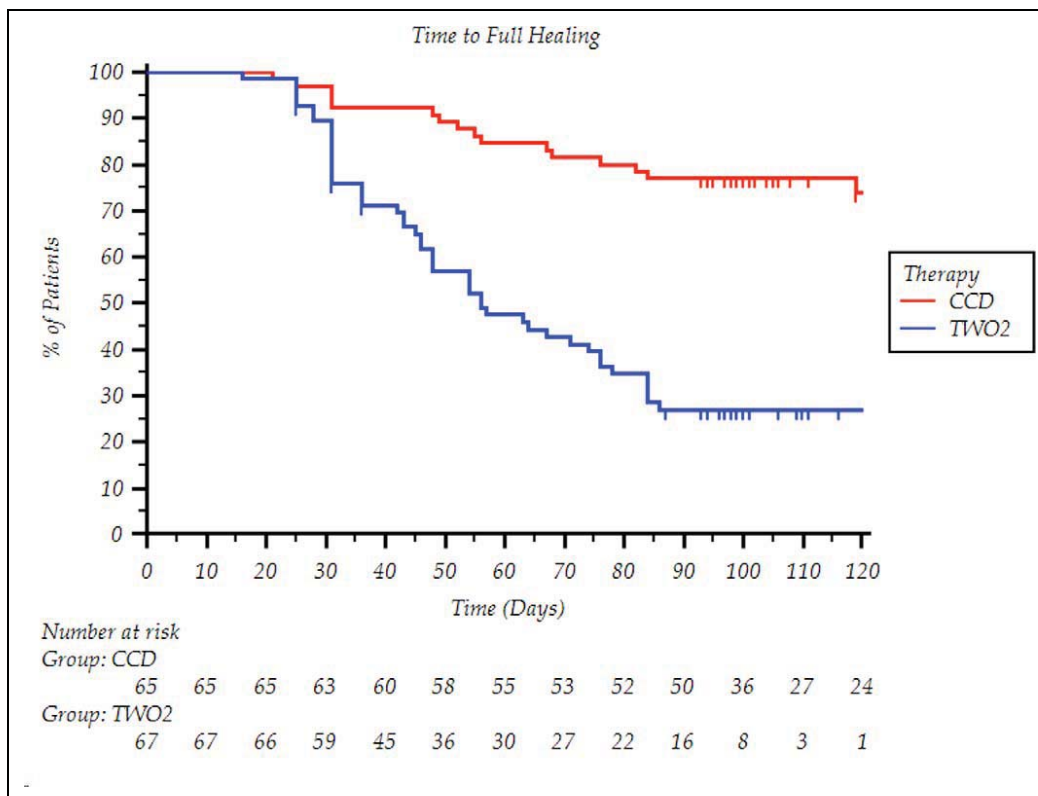
The socioeconomic consequences of management of RVU, merged with high recurrence rates, have encouraged the development of a disruptive technology innovative therapy, as TWO<sub>2</sub> therapy.

The McCollum group from Manchester mentioned that contemporary dressing materials do not sway the healing development and that expenses on these products cannot be vindicated on a clinical ground, as they have no proven efficacy. Moreover, they regret that after 30 years of research there is no data to defend using anything other than a simple, inexpensive, low-adherence dressing under multilayer compression in the management of venous leg ulcers.<sup>13</sup>

In the Venous Ulcer Cost-effectiveness of ANtimicrobial dressings (VULCAN) trial, it took 101 days to heal 3 cm ulcers. Moreover, only 86% of the small ulcers that had healed at 1 year had a recurrence rate of 14%.<sup>34</sup> This is by using silver dressings on small ulcers that we rarely witness in a typical tertiary vein unit practice.



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



**Figure 3.** Time to full healing. Kaplan Meier curve showing time to full ulcer healing. The TWO<sub>2</sub>-managed ulcers had a significantly shorter median time to full healing (57days) compared to 107 days in CCD-managed ulcers ( $P<.0001$ ). TWO<sub>2</sub> indicates topical wound oxygen; CCD, conventional compression dressings.

The TWO<sub>2</sub> circumvents the consequence of a total body hyperbaric chamber, with its drawbacks on eyes, lungs, and ears.<sup>35</sup> Moreover, it eradicates the skyrocket price tag to set up and maintain a total body chamber in a downturn economy, where every Euro and space matters.

The work by Paul Bert verified the toxic consequences of systemic oxygen by yielding grand mal seizures as well as the effort of J. Lorrain-Smith, who confirmed the pulmonary oxygen toxicity, both after systemic administration of oxygen.<sup>35,36</sup> This led to the concept of hyperbaric oxygen

**Table 6.** Effect of the Size of the Ulcer and the Duration the Patient Had the Ulcer on the Median Duration Required for Healing<sup>a</sup>

Ulcer Surface Area	TWO <sub>2</sub> Median Time to Full Healing	CCD Median Time to Full Healing	P Value
≤5 cm <sup>2</sup>	54 days	87 days	<.0001 <sup>b</sup>
6 to 10 cm <sup>2</sup>	60 days	118 days	<.0001 <sup>b</sup>
11 to 20 cm <sup>2</sup>	53 days	109 days	<.0001 <sup>b</sup>
21 to 40 cm <sup>2</sup>	59 days	113 days	<.0001 <sup>b</sup>
≥41 cm <sup>2</sup>	61 days	119 days	<.0001 <sup>b</sup>
Duration of the ulcer			
2 to 3 years	58 days	111 days	<.0001 <sup>b</sup>
4 to 5 years	63 days	99 days	<.0001 <sup>b</sup>
6 to 10 years	52 days	102 days	<.0001 <sup>b</sup>
11 to 20 years	57 days	115 days	<.0001 <sup>b</sup>
Over 20 years	59 days	n = 0	<.0001 <sup>b</sup>

Abbreviations: CCD, conventional compression dressings; TWO<sub>2</sub>, topical wound oxygen.

<sup>a</sup> Topical wound oxygen-managed ulcers had a significantly shorter healing time in comparison to conventional compression dressings, regardless of the size of the ulcer or the length of time the patient had the ulcer.

<sup>b</sup> P values are analyzed using Mann Whitney U test.



**Figure 4.** Case 1, Pre-treatment. Large ulcer (98cm<sup>2</sup> surface area) with thick eschar on medial aspect of the leg.

delivery to the site of tissue loss without the side effects of systemic oxygen toxicity.

Conversely, TWO<sub>2</sub> is established on the hypothesis that oxygen diffuses through tissue at a depth of 30 to 50 μm.<sup>36</sup> By calculating all these variables, we established our protocol of cyclic pressure of 50 mbars for 180 minutes twice daily, with oxygen supplied at 10 L/min with continuous humidification.<sup>26,29,30</sup>

The cycling of the pressure in the AOTI Hyper-Box permits the delivery of oxygen under a much higher pressure, allowing improved topical penetration, rather than the limitation of a constant pressure.



**Figure 5.** Case 1 after 8 weeks of TWO<sub>2</sub> therapy. Ulcer less than 3cm<sup>2</sup> in the surface area.



**Figure 6.** Reverse gradient of healing. Healing starts at the center of the ulcer and then spreads outward.

The TWO<sub>2</sub> promotes capillary neoangiogenesis<sup>18,19</sup> through transdermal sustained delivery of oxygen. This leads to higher tensile strength collagen being formed during wound healing, which eliminates scarring and the risk of recurrence.<sup>14,15</sup>

Diffused oxygen raises the capillary  $P_{O_2}$  levels at the wound site, stimulates epithelization, and granulation of new healthy tissue.<sup>16,17</sup> Repeated treatment accelerates wound closure.

Moreover, oxygen generates reactive oxygen species at the wound site, acting as signaling substances, which increase the production of vascular endothelial growth factor (VEGF).<sup>37,38</sup>

Of the 24 MRSA-positive ulcers in the  $TWO_2$  group, 11 were rendered MRSA negative at the end of their treatment protocol in comparison to none in the CCD group, which outlines the topical bactericidal effect on one of the most feared bacterial infection in the patient's mentality.

The  $TWO_2$  is lethal to anaerobic bacteria and enhances polymorph nuclear function and bacterial clearance.<sup>20-22</sup> It diminishes neutrophil adherence based on inhibition of  $\beta$ -2 integrin function.<sup>23</sup> This enlightens us of its potency against MRSA infection. The  $TWO_2$  assists antibiotic dispersion for aminoglycosides, cephalosporins, quinilones, and amphotericin.<sup>24,25</sup>

Although  $TWO_2$  has been employed over a protracted period of time, the clinical evidence for efficacy and safety are sparse. In our study, we exploited the AOTI Hyper-Box cycled pressure from atmospheric to 50 mbars and back to atmospheric pressure in 1-minute cycles. This permitted the extended treatment administration time while plummeting the risk of endothelial cell toxicity. Our course of therapy accomplished enhanced wound healing time, without complications, in a relatively large number of patients.

During  $TWO_2$  therapy sessions, patients endured limb elevation. These patients had their ulcers for a minimum of 2 years and up to 43 years, and had already revealed no signs of healing over the past year, regardless of ample compliance with the therapy. Although we acknowledge that this may have aided in ulcer healing, it would be futile to accredit the superior outcome to limb elevation alone.

In our study, only 46% of the ulcers managed with CCD fully healed. Although acknowledging that this is a lesser figure than some published studies on such treatment, nevertheless the refractory nature of these ulcers has to be taken into consideration.

In our study 76% (51 of 67) of the  $TWO_2$ -treated ulcers exhibited reverse gradient of healing. All these ulcers further continued to fully heal with no scarring and zero recurrence. This is accredited to topical absorption of oxygen which leads to the establishment of privileged tensile strength collagen.<sup>14-17</sup>

Notwithstanding that the mean Venous Clinical Severity Score<sup>31,32</sup> was elevated in patients managed with  $TWO_2$ , yet a superior outcome was observed, in contrast to patients managed with CCD, in all facets of clinical and technical outcome.

We believe this to be the principal study in the English literature that embodies venous ulcer management through a portable hyperbaric oxygen chamber and judges against the habitual long-established traditional best medical management in the form of CCD.

The numbers recruited are trivial; however, our foremost ambition was to display the null hypotheses of a disruptive innovative technology with mid-term efficacy and safety. A

randomized controlled trial is currently underway to further assess the benefits of  $TWO_2$  therapy.

## Conclusion

The  $TWO_2$  is prudent, effective, and valuable in managing RVUs without the risks of full body hyperbaric chambers. The  $TWO_2$  slashes the time needed for RVU healing and is successful in pain alleviation, MRSA elimination, and management.

The  $TWO_2$  radically degrades recurrence rates, thus providing an improved quality of life.

## Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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