The efficiency of transdermal oxygen wound therapy in lower extremity venous ulcers

Transdermal wound oxygen therapy

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Abstract

Aim: Despite improved healthcare quality and technological facilities, chronic venous ulcer is still an important health challenge all over the world. Although different treatment modalities are being used, the results are not satisfactory in many patients. The purpose of this study is to evaluate the efficiency of transdermal oxygen wound therapy in patients with lower extremity chronic venous ulcer due to deep venous insufficiency.

Material and Methods: Sixty-four patients with chronic venous ulcer related to deep venous insufficiency were enrolled in the study between 2017 and 2019. The patients were divided into two groups. Group 1 was the control group and received routine wound therapy, and Group 2 was the experimental group and received transdermal oxygen therapy additional to routine therapy. The status of the wound was evaluated between the groups.

Results: The number of patients with complete wound healing in the experimental group was statistically significantly higher than in the control group. In addition, the total mean area of the wound in the experimental group was significantly lower than in the control group.

Discussion: Transdermal wound oxygen therapy is an efficient treatment modality for patients with lower extremity chronic venous ulcers related to venous insufficiency.

Keywords

Transdermal Oxygen Therapy, Venous Insufficiency, Venous Ulcer, Wound

DOI: 10.4328/ACAM.20835    Received: 2021-08-29   Accepted: 2021-09-28   Published Online: 2021-10-05

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Introduction
Venous ulcer is a serious clinical condition due to chronic venous insufficiency (CVI). It is the main reason of approximately 70% of chronic ulcers of the lower limbs [1]. Diabetes mellitus, sickle cell disease, rheumatoid arthritis, chronic osteomyelitis, peripheral vascular disease, skin tumor and vasculitis are other common reasons of chronic ulcers. Whereas some cases with venous ulcer may be idiopathic and some can be multifactorial [2]. Despite technological improvements in the field of medicine, it is still a big challenge to deal with venous ulcers worldwide [3].

Different advanced treatment modalities include supplemental systemic oxygen, hyperbaric oxygen treatments (HBOT), and locally performed transdermal wound oxygen therapy (TWOT) has been reported in the literature to treat chronic or ischemic wounds. TWOT has become popular among them recently due to increased patient comfort, decreased risk of oxygen toxicity, portability and efficiency [4].

In this study, we aimed to evaluate TWOT for the healing of chronic venous ulcers due to deep venous insufficiency.

Material and Methods
Between 2017-2019, sixty-four patients with lower extremity venous ulcer due to deep venous insufficiency were included in the study. Written informed consent was obtained from all participants and the clinical council of the related department approved this randomized controlled study protocol. The study was designed according to the Declaration of Helsinki.

Patients were divided into two groups. Group 1 was the control group and Group 2 was the experimental group. The coin tossing method and the block randomization technique were used to determine the group of patients. The inclusion criteria were age over 18 years and the presence of grade 4 deep venous insufficiency and venous ulcer in one of the lower extremities, according to venous Doppler ultrasound results and physical examination. The exclusion criteria were any kind of cancer, pregnancy, peripheral vascular disease like diabetes mellitus, which can induce vascular complications, acute thrombophlebitis, wounds completely covered with eschar, ulcer due to Raynaud disease, wound with fistulae or deep sinus tracts where the end cannot be probed and deep venous thrombus. Thus, all patients underwent venous and arterial Doppler ultrasound of the lower extremities to determine venous insufficiency and the absence of venous thrombus and peripheral arterial disease. Demographic data of the patients were also recorded.

Group 1 consisted of 32 patients (males: 24, females: 8), and routine wound and venous insufficiency therapy included debridement and antibiotherapy, if necessary, venotonic drugs, lower extremity elevation and compression socks. The sample was taken from the patients who had suppurrative and malodorous wounds, and the decision to prescribe antibiotherapy was made according to any bacterial growth. Group 2 consisted of 32 patients (males: 25, females: 7). TWOT was performed in addition to routine therapy, except for compression socks in this group. Compression socks could not be used in this group because of the location of the device (Figure 1). TWOT was applied to the area with ulcer to maintain continuous delivery of oxygen for 15 days. Initially, the site of the ulcer was debrided to remove impurities from the wound, area if necessary, then a disposable catheter was inserted into the wound site, thereafter wound dressing was applied using saline-soaked gauze and the device was started for the treatment. This process was repeated three times and the total treatment lasted 45 days. The area of the wound was measured in square millimeters using a standard sterile graded clipper. The wound status was assessed before and every fifteen days after the beginning of the intervention. Accordingly, the wound status was evaluated four times: before the intervention, and fifteen days, thirty days, and forty-five days after the intervention.

Statistical Analysis
All values were shown as mean ± SD or percentage. The distribution of all variables was checked using the Kolmogorov–Smirnov test. The Mann-Whitney U test was used for data with abnormal distribution. Otherwise, the differences between the mean values of the two groups were analyzed using the unpaired Student’s t-test. The gender of the two groups was analyzed using the chi-square test. Pearson’s test was used to assess the correlations, but Spearman’s correlation analysis was performed in the correlation analysis of data with abnormal distribution. GraphPad Instat (version 3.05, GraphPad Software Inc., San Diego, CA, USA) statistical software was employed. Statistical significance was accepted at the level of 0.05.

Results
Between 2017 and 2019, a total of 64 patients were included in the study. The TWOT group consisted of 32 patients (males: 25 and females: 7) and the control group consisted of 32 patients (males: 24 and females: 8). The number of male patients was predominant in both groups, with a percentage of 75% in the control group and 78% in the TWOT group. There were no statistically significant differences in age, gender and wound area between the groups (Table 1).

Table 1. Patient’s Demographic Data and Wound Area

<table>
<thead>
<tr>
<th></th>
<th>Control group</th>
<th>TWOT group</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>49.46±8.25</td>
<td>50.48±8.36</td>
<td>0.17</td>
</tr>
<tr>
<td>Gender, male/female, n</td>
<td>24/8</td>
<td>25/7</td>
<td>0.00</td>
</tr>
<tr>
<td>Wound area, cm²</td>
<td>27.7±14.87</td>
<td>30.82±11.93</td>
<td>0.15</td>
</tr>
</tbody>
</table>

*Data are presented as mean ±SD, TWOT: Transdermal Wound Oxygen Therapy
Five patients in both groups required antibiotic therapy for sensitive microorganisms detected in the wound sample for two weeks. There was no growth in control samples.

The number of completely healed ulcer, defined as complete epithelialization of the wound without drainage, was 28 in the TWOT group and only 1 in the control group. This difference was statistically significant according to the binomial test results (p<0.001).

The results of repeated wound area measurements on the fifteenth, thirtieth and forty-fifth days showed a statistically significant decrease in the TWOT group, however, the wound area did not differ significantly in the control group. Moreover, the total mean of wound area in the TWOT group was statistically significantly lower than the control group (Table 2).

**Discussion**

Venous ulcers are common disorders worldwide and various risk factors were defined for the development of this clinical condition, including a family history of chronic venous insufficiency, age 55 years and older, a history of thrombophlebitis or venous thrombus, physical inactivity, increased body mass index, skeletal or joint disease of lower extremities, a high number of pregnancies and venous reflux in the deep veins. The quality of life of patients with venous ulcer is generally affected negatively due to prolonged and unsatisfactory treatments. Severe complications like infection and malignant change can be observed [5].

The most common type of chronic lower extremity ulcers is venous ulcers, with 1% overall prevalence and up to 3% in the age of 65 years and over [6]. Venous ulcers of lower extremities are usually localized in the malleolar region, both in the lateral and medial sites of the ankle. However, they also occur in the infra and supra-malleolar regions of the foot and leg [7]. Venous hypertension due to venous reflux, varicose veins, postthrombotic syndrome and venous insufficiency are the most frequent causes of the lower extremity ulcers. The underlying mechanism of venous ulcer is tissue ischemia as a result of damage and destruction of capillaries that maintain nutrients and oxygen to the skin and subcutaneous tissues [8]. Coherent with the literature, all participants in our study had grade 4 deep venous insufficiency and ulcers on the lower extremities.

For lower extremity ulcers related to venous insufficiency, a variety of treatment regimens are used, including local dressings, topical and systemic agents, exercise, tissue products, compression therapy and ablation or surgery of the superficial venous incompetence [9]. None of the participants in our study had superficial venous insufficiency, thus ablation and surgery were not performed.

To understand the role of oxygen in wound healing, several modalities using oxygen have been explored in recent years, including supplemental oxygen therapy, HBOT and TWOT, as alternative methods in the treatment of chronic venous ulcers. Supplemental oxygen therapy is a kind of inhalation therapy performed using a nasal cannula or ventral mask to improve tissue oxygen concentration [10]. It is a cost-effective, easy and useful way to provide supplementary systemic oxygen, which has been shown to decrease the infection rate and be beneficial in the healing of wounds [11]. HBOT is another kind of systemic oxygen therapy that was initially used in the treatment of decompression sickness and CO2 poisoning. Subsequently, it began to be used in clinical situations such as burn, chronic wound and acute crush [12]. HBOT maintains increased oxygen dissolved in the circulating blood plasma, which results in an elevated oxygen concentration in tissues [13]. Besides the evidence of benefits in wound healing, HBOT has several disadvantages. The most serious side effect of the HBOT is tension pneumothorax, which can be life-threatening if unrecognized or untreated. Reversible myopia due to lens deformation, ear and sinus barotraumas, exacerbation of congestive heart failure, pulmonary edema, seizure and retinal damage are the other side effects of HBOT [14]. In addition, it is expensive, limits mobility and has an impact on the quality of life [15]. Other disadvantages of this therapy are access difficulties for the patients due to the limited number of healthcare centers that have HBOT units, and the intolerance to the therapy for medical reasons [14].

Thanks to developments in the area of wound care and research on more effective treatment methods for skin ulcers, TWOT was introduced in the literature as an alternative therapy using oxygen directly to the wound site. It concentrates oxygen to nearly 100% and continuously delivers it to the wound at a rate of 3 mL/h [16]. Direct application of oxygen to the wound bypasses the oxygen transport system, so an oxygen-rich wound bed environment can be achieved, which promotes healing [17]. All stages of wound healing include hemostasis, inflammation, proliferation, maturation, and remodeling, facilitated by oxygen through the release of several mediators and cytokines, which initiate angiogenesis, thrombosis, granulation tissue formation, and re-epithelialization [18]. In a study designed by Howard et al [14], the oxygen level under the normal skin surface area was 45-65 mmHg. Schreml et al [19] declared this level under

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### Table 2. Wound Area (cm²) in the Study groups*  

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Day Fifteen</th>
<th>Day Thirty</th>
<th>Day Forty five</th>
<th>Mean</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>TWOT Group</td>
<td>30.82±11.93</td>
<td>21.45±4.24</td>
<td>13.21±2.64</td>
<td>4.41±2.21</td>
<td>6.72±3.35</td>
<td>0.001</td>
</tr>
<tr>
<td>Control Group</td>
<td>27.73±14.87</td>
<td>27.75±13.42</td>
<td>26.84±13.74</td>
<td>27.41±13.42</td>
<td>27.72±14.66</td>
<td>0.17</td>
</tr>
<tr>
<td>p value</td>
<td>0.15</td>
<td>0.005</td>
<td>0.003</td>
<td>0.001</td>
<td>0.001</td>
<td></td>
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</table>

*Data are presented as mean ±SD, p value by the repeated measure test, The result of the independent sample t-test.
chronic wound conditions as 5-20 mmHg, moreover 0-5 mmHg in the center of the wound, where the vascular supply is absent. Thus, an increased risk of infection and delayed wound healing may occur due to the anaerobic process. Directly applied oxygen to the ulcerative area helps prevent this unfortunate situation by increasing the oxygen to the desired level.

Several studies were conducted in the literature on the use of TWOT. According to a study, which designed a controlled wound model in rabbits, significantly greater epithelial coverage was detected in the TWOT group when compared to the control group [20]. Tawfick et al [21] compared the efficiency of TWOT and conventional compression dressing therapy in patients with lower extremity venous ulcers. According to their study, the rate of completely healed ulcers was 80% in the TWOT group and 35% in the other group. Similarly, the proportion of completely healed ulcers was 87.5% in the TWOT group in our study. The efficiency of TWOT in recurrence of the completely healed venous ulcers was studied, and 3 of the 51 healed ulcers managed with TWOT showed recurrence signs, besides, the recurrence of completely healed ulcers managed by a compression dressing therapy was significantly higher with the rate of nearly 50% [22]. According to the study designed by Kaufmann et al [23] in patients with venous and arterial ulcers with the mean wound duration of 15 months, the reduction in wound area was 83%, and total closure of the wound was 47% in venous leg ulcers and 74% and 57% in arterial foot ulcers, respectively when using TWOT.

TWOT can be applied not only in chronic venous ulcer therapy, but also in chronic diabetic foot ulcers. Driver et al [24] declared in their study on 16 patients with chronic diabetic foot ulcers that wound site reduction was 87% in the TWOT group (n=9), and 46% (n=7) in the control group. Similarly, Hayes et al [25] emphasized that topical oxygen therapy promotes the healing of chronic foot ulcers due to diabetes mellitus.

In conclusion, TWOT is easy to use, safe, cost-effective method and promotes the healing of chronic wounds. In addition, TWOT provides therapy at home and hospital stay is not needed. Further studies are necessary to evaluate more of the effects of the TWOT.

Acknowledgment
The authors thanked Prof. Dr. Abdullah Tuncay Demiryurek for assessing the article in terms of the language grammar.

Scientific Responsibility Statement
The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement
All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

Funding: None

Conflict of interest
None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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How to cite this article: Ozgur Altinbas, Mehmet Orkun Sahsivar. The efficiency of transdermal oxygen wound therapy in lower extremity venous ulcers. Ann Clin Anal Med 2021; DOI 10.4328/ACAM.20835