

**Comparaç o da efic cia da bota de Unna e da terapia com oz nio nas  lceras venosas
cr nicas das pernas: uma s rie de casos**

**Comparison of Efficacy of Unna's boot and Ozone therapy on Chronic Venous Leg
Ulcers: a series of case**

**Comparaci n de la efectividad de la bota Unna y la terapia de ozono en las  lceras
venosas cr nicas de las piernas: una serie de casos**

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Resumo

O objetivo do presente estudo foi analisar e comparar a eficácia das terapias por Bota de Unna e Ozônio em úlceras venosas crônicas (UVs) de perna. Sete pacientes randomizados em dois grupos: Bota de Unna (UB) como tratamento; Grupo Ozônio como tratamento (OZ). Realizou-se as terapias semanalmente até fechamento da completo ferida. Os resultados morfológicos descritivos evidenciaram que durante os presença de bordas semi-planas, redução de edema, tecido de granulação, pouco exsudato e fibrina e ausência de odor. As características morfológicas foram mais evidenciadas no grupo OZ comparado ao grupo BU. Ainda, foi possível observar que ambos os tratamentos tiveram o mesmo tempo de cicatrização da ferida, entretanto, a terapia utilizando ozônio produziu uma porcentagem de redução semanal de ferida menor quando comparada com a terapia por Bota de Unna. Desta forma, as terapias utilizando a Bota de Unna e o Ozônio desempenharam impactos positivos sobre curso da cicatrização de feridas crônicas de origem vascular, no entanto, ozonioterapia demonstrou melhores resultados na cicatrização de UVs crônicas devido apresentar uma porcentagem de cicatrização semanal mais elevada.

Palavras-chave: Úlcera venosa crônica; Bota de unna; Ozonioterapia.

Abstract

The aim of this study was to evaluate and compare the effectiveness of Unna's boot and ozone therapy on chronic venous leg ulcers. Seven patients with chronic venous leg ulcers were taken into the study and were randomly divided into two groups: Unna's boot treatment group (BU); Ozone treatment group (OZ). The therapies were performed weekly until wound closure. The morphological descriptive results demonstrated that during the treatments, it was possible to observe the presence of semi-planar borders, granulation tissue, reduction of edema, fibrin and exudate and absence of odor. These morphological modifications were more pronounced in the OZ when compared to the BU. Furthermore, both treatments promoted the same wound healing time, never the less the ozone therapy produced a higher percentage of weekly wound reduction compared to Unna's boot. Unna's boot and ozone therapy treatments appeared to positively impact the course of wound healing in chronic

wounds, however the ozone therapy may improve the healing of chronic venous leg ulcers in a higher weekly percentage.

Keywords: Venous leg ulcers; Unna's boot; Ozone therapy.

Resumen

El objetivo de este estudio fue evaluar y comparar la efectividad de la bota y el ozono de Unna en las úlceras venosas crónicas de las piernas. Siete pacientes con úlceras venosas crónicas en las piernas fueron incluidos en el estudio y se dividieron aleatoriamente en dos grupos: el grupo de arranque de Unna (UB); Grupo de ozono (OZ). Las terapias se realizaron semanalmente hasta el cierre de la herida. Los resultados descriptivos morfológicos demostraron que durante los tratamientos, fue posible observar la presencia de bordes semi-planos, tejido de granulación, reducción de edema, fibrina y exudado y ausencia de olor. Estas modificaciones morfológicas fueron más pronunciadas en el OZ en comparación con el UB. Además, ambos tratamientos promovieron el mismo tiempo de curación de heridas, sin embargo, la terapia de ozono produjo un mayor porcentaje de reducción semanal de heridas en comparación con la bota de Unna. Los tratamientos de terapia de ozono y de arranque de Unna parecieron impactar positivamente el curso de la curación de heridas en heridas crónicas, sin embargo, la terapia de ozono puede mejorar la curación de las úlceras venosas crónicas de las piernas en un porcentaje semanal más alto.

Palabras clave: Úlceras venosas de la pierna; La bota de unna; Ozonoterapia.

1. Introduction

Venous leg ulcers (VLUs) are a chronic and often debilitating condition and its high prevalence represent a public health problem (Souza et al., 2013). VLUs are caused by dysfunction of the deep venous system and sustained venous hypertension, which results from valvar insufficiency and/or an impaired calf muscle (Kelechi et al., 2015; Eberhardt & Raffetto, 2015). The venous ulcers represent 75 % of cases of the all types of ulcers in the lower limbs (Souza et al., 2013; Scotton et al., 2014). Epidemiological studies suggest that prevalence is correlated with female sex and the population aging (O'Meara et al., 2013). The chronicity and a long and difficult treatment are major issues. Most of the VLs taking approximately two years for heal and the reoccurrence is common, with rates around 45 % (Harrison et al., 2001; Borges et al., 2016). Clinically, VLUs are manifested by exudate, odor,

skin irritation, and sleep disturbances, causing a negative effect on health-related quality of life (Botelho et al., 2020; Phillips et al., 2008).

Furthermore, treatments for reducing these complications are based mainly to leg compression and elevation, topical steroids, aspirin and surgery (O'Meara et al., 2013). However, these therapies often do not lead sufficient healing of these ulcers. Recently, more innovative therapeutic approaches have been developed aiming to attenuate these chronic leg ulcers caused by vascular alterations. Among the innumerable range of interventions, the positive effects of Unna's boot on vascular ulcers have been highlighted (Mosti, 2016).

Unna's boot is the most known inelastic compression therapy used in clinical practice to promote healing and to prevent recurrences of venous ulcers (Silva et al., 2017). Clinical trials have demonstrated that Unna's boot has the ability to improve the function of venous pumping and reduce of the venous hypertension reducing pain, increase healing rates, functional capacity and self-esteem improvement in chronic venous ulcers patients (Silva et al., 2017; Abreu et al., 2013).

Another promising therapeutic intervention that has been showing stimulatory effects on chronic wound healing is the ozone therapy, mainly due to its antioxidant functions and antimicrobial property. Ozone (O₃) react instantaneously with polyunsaturated fatty acids to form reactive oxygen species (ROS), which can accelerate the cell cycle and induce the synthesis of important cytokines and growth factors relevant to wound healing (Patel et al., 2011; Sagai & Bocci, 2011; Kim et al., 2009). The beneficial effects have been found of treating vascular ulcer with ozone therapy (Izadi et al., 2019; Zhang et al., 2014; Rosul & Patskan, 2016).

Although all the positive effects of both therapies for treatment of ulcers healing, the comparison of both therapies are not known yet. Based on the need of determining a more appropriate therapeutic intervention, the present study aimed to evaluate and compare the efficacy of Unna's boot and ozone therapy in patients with chronic venous leg ulcers. We intend to establish an optimal treatment for chronic venous ulcers and allowing, with confidence, the use of these therapies in the clinical setting.

2. Materials and Methods

This study was designed a series of case study with qualitative and quantitative approach. All procedures were conducted at the Basic Health Unit of Marabaixo (Macapá, AP, Brazil), approved by the Ethics in Human Research Committee of SEAMA (Amazon

Education Society) College (approval CAAE no. 54563216.2.0000.5021). Volunteers were informed of the purpose and the procedures of the study and signed a Term of Free Informed Consent (TFIC) before their participation in the study.

2.1 Subjects

For the present study, patients with chronic venous ulcers were recruited through newspaper and radio ads in Macapá, Amapá, Brazil.

Patients included in this study were both sexes, aged ≥ 18 years, with a medical diagnosis of Chronic Venous Insufficiency of the lower extremity for more than 6 months, not diabetic, presenting palpable dorsalis pedis and posterior tibial pulses, not been previously treated with Unna's boot or ozone therapy were inclusion criteria.

Exclusion criteria were pregnant women; skin lesions other than venous leg ulcers; patients with signs of allergy; patients with arterial, diabetic, neuropathic or pressure ulcers; vasculitis.

2.2 Randomization

The randomization procedure was performed through a computer program, and allocation secrecy was kept by numbered, sealed, opaque envelopes. The patients were randomized into two groups: (1) Unna's boot group (UB; $n = 3$): patients who were submitted to Unna's boot treatment; (2) Ozone group (OZ; $n = 4$): patients who were submitted to ozone therapy.

2.3 Study protocol

The study consisted of two stages. In the first stage, there was the initial approach and signing of the TFIC and authorization for making photographic records of the lesion. The second stage, the weekly consultations were held with a medical history, clinical evaluation of the patient and of the wound, changing of dressings, Unna's foot or ozone therapy treatment and digital photographs

2.4 Treatments

The therapies were performed weekly until the total closure of the wound.

2.4.1 Unna's Boot

The application of the Curatec® brand Unna boot was used as the primary dressing, starting from the extremity of the foot and proceeding up to the knee with a pressure of approximately 35 mmHg. After that, a secondary dressing gauze was applied and bandage used to give support and tape-type fixative. This procedure was performed every 7 days until the time of its total wound repair.

2.4.2 Ozone Therapy

The O₃ was administered topically by involving a plastic bag around the lesion area and insufflating an O₂-O₃ (Oxygen-Ozone) mixture at a concentration of 52 µg/ml. The insufflated bag was sealed just above the lesion to avoid gas leakage. The bag was positioned to let the gas mixture be in contact with the ulcer wound for around 20 min.

2.5 Procedures

2.5.1 Morphological descriptive analysis

Morphological analysis of wounds was performed weekly using the following criteria: ulcers border, granulation tissue, the quantity of exudate, edema and odor.

2.5.2 Quantitative Ulcers evaluation

The ulcers evolution was evaluated by photographs taken from a digital camera (Sony Cyber-Shot DSC-W190 brand) at a distance of 10 cm from the camera lens to the injured region. The photographs were taken weekly until the wound was completely heals. The lesion area of ulcers was measured using the Image J® software and expressed in square centimeters (cm²). The time required for the wound healing, the weekly percentual reduction of the ulcer and the ulcer area reduction rate was computed using the acquired lesion area.

Time required for the wound healing was established as the week number were the patient no longer presented ulcer lesion. The weekly percentual reduction of the ulcer was calculated from the percentage variation of the area in relation to the previous week.

Ulcer area reduction rate was obtained by a linear fit over the lesion area data for each patient. The slope of the linear fit is equal to the reduction rate.

2.6 Statistical Analysis

Data were reported as mean \pm standard deviation. The normality of distribution for all variables was verified using the Kolmogorov-Smirnov test. When variables were compared between groups, the unpaired Student's t test and Mann-Whitney test were used as appropriate. Statistical analyses were performed using Minitab[®] Statistical Software (Minitab, Inc, State College, PA). The significance level was set at $p < 0.05$.

3. Results

3.1 Sociodemographic evaluation

The study was performed with 7 patients of both sexes being 4 males and 3 females and aged 55 to 72 years. Table 1 summarizes the clinical cases studied in this work. The BU group consisted of 1 woman and 2 men with a mean age of 60 years. In the OZ group it was composed of 2 women and 2 men with mean age of 63 years. The time of the ulcers, prior to this treatment, were 3 years and 8 months for BU and 3 years and 3 months for OZ group.

Table 1. Summary of clinical description of the cases.

Cases	Gender	Age (years)	Time of ulcers	Initial Area (cm ²)	Treatment	Treatment period (weeks)
#1	F	57	4 years	211.04	Unna's boot	12
#2	M	69	7 years	90.30	Unna's boot	12
#3	M	55	6 months	91.28	Unna's boot	6
#4	F	58	4 years	277.15	Ozone therapy	9
#5	F	64	3 months	99.22	Ozone Therapy	8
#6	M	58	4 years	340.20	Ozone Therapy	9
#7	M	72	3 months	188.31	Ozone Therapy	6

M male, *F* female. Source: Author.

Table 1 summarizes the clinical cases studied in this work. BU group: 1 woman and 2 men; mean age: 60 years; mean period to treatment: 10 weeks. OZ group: 2 women and 2 men; mean age: 63 years. mean period to treatment: 8 weeks.

3.2 Morphological descriptive analysis

Representative images of the venous leg ulcers are shown in Figure 1A and 1B. Morphological analysis revealed that at the beginning of treatments, BU and OZ groups demonstrated severe morphological modifications, characterized by high and irregular borders, intense edema, exudate and fibrin and week odor. During the treatments, it was possible to observe the presence of semi-planar borders, granulation tissue, reduction of edema, fibrin and exudate and absence of odor. These morphological modifications were more pronounced in the OZ (figure 1B) when compared to the BU (figure 1A). At the end of treatment the ulcers of both groups had total closure.

Figure 1. Representative photomicrographs of morphological descriptive analysis of VLUs. A) Unna's boot group (BU); B) Ozone group (OZ).



Source: Author.

Figure 1 demonstrate representative images of the venous leg ulcers used to morphological descriptive analysis of VLUs. During the first weeks: it is observed high and irregular borders, intense edema, exudate and fibrin in both groups. During treatments: it is observed semi-planar borders, granulation tissue, reduction of edema, fibrin and exudate more pronounced in OZ group (B). At the end: total closure.

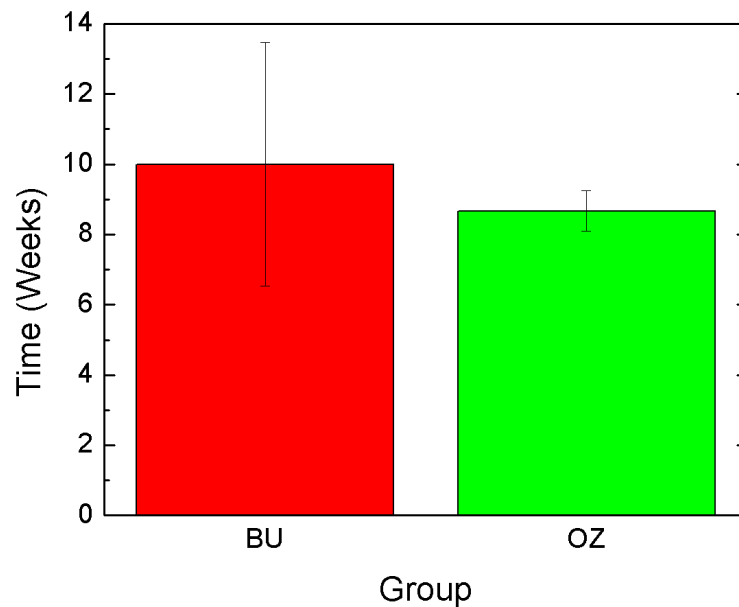
3.3 Quantitative Ulcers evaluation

For the time required for the wound to heal, both BU and OZ presented normal distribution (despite the low group size). Figure 2 presents the mean value and the standard deviation of the time, in weeks, required for the ulcer to completely close after the BU and OZ treatment, respectively.

The average time for ulcer healing is smaller for OZ group, however it was not observed significant statistical difference (p -value = 0.44) between BU and OZ treatments. The standard deviation for the wound healing time is smaller for the OZ group, indicating a

higher uniformity on the healing time. It could indicate a more predictable healing process and advantageous for clinical practices.

Figure 2. Time for the Ulcers completely heals. Unna's boot group (BU); Ozone group (OZ).



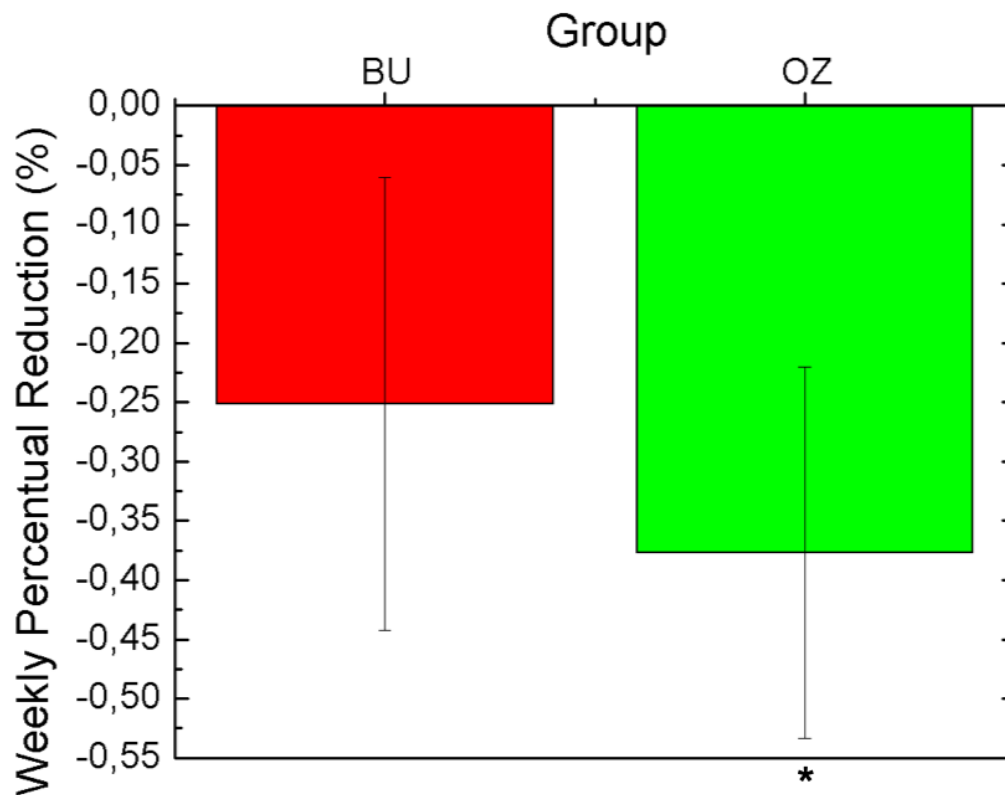
Source: Author

Figure 2 represents the average value and standard deviation of the time for the Ulcers completely heals (weeks) after BU and OZ treatments. The average time for ulcer healing revealed a lower values in OZ group compared to BU group (however it was not observed significative statistical difference [$p = 0.04$]).

3.4 Weekly percentual reduction of the ulcer

The initial area of the ulcer for BU and OZ groups do not presented statistical difference (p -value = 0.22) in our study. Computing the percentual reduction of the ulcer area for each week, in relation to the previous one, it was observed a statistical difference between OZ and BU groups (p -value = 0.007). The OZ group presented a higher value of percentual reduction, in modulus, compared to the BU group. Figure 3 presents the weekly percentual reduction for the BU and OZ group.

Figure 3. Weekly percentual reduction of the ulcer. Unna's boot group (BU); Ozone group (OZ). (indicated as * p-value = 0.007).



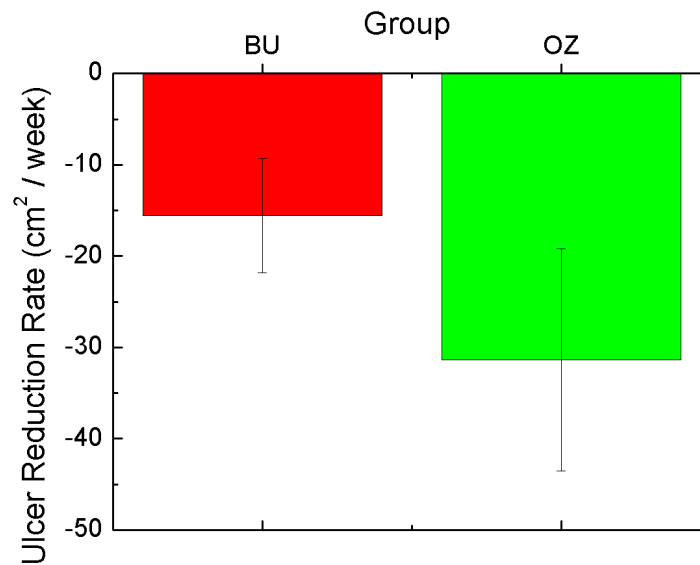
Source: Author.

Figure 3 represents the average value and standard deviation of the weekly percentual reduction for the ulcer after BU and OZ treatments. The values of percentual reduction was higher in OZ group compared to BU group (*p= 0.007).

3.5 Ulcer area reduction rate

Figure 4 presents the average and standard deviation of the ulcer reduction rate obtained by the linear fit over the lesion area data. The negative values reflects the ulcer reduction in size. OZ groups presented a higher value (in module), however it was not observed a significant statistical difference (p-value = 0.09) using the significance level of 0.05.

Figure 4. Ulcer area reduction rate. Unna's boot group (BU); Ozone group (OZ).



Source: Author.

Figure 4 represents the average and standard deviation of the ulcer reduction rate. The values of the ulcer reduction in size was higher in OZ groups compared to BU group (however it was not observed significant statistical difference [$p = 0.09$]).

4. Discussion

This study aimed to evaluate and compare the effectiveness of Unna's boot and ozone therapy on chronic venous leg ulcers. The morphological descriptive findings demonstrated that both treatments produced stimulatory effects on healing, however these modifications were more pronounced in the ozone therapy. Furthermore, both treatments promoted the same time required for the wound to heal never the less the ozone therapy produced a higher percentage of weekly wound reduction compared to Unna's boot.

It is of common knowledge that chronic venous ulcers are associated with reduced blood flow, impaired skin healing and often reoccurs (Boateng & Catanzano, 2015). These changes are correlated with a reduced quality of life, particularly due to pain and physical function (Lal, 2015). Also, the high cost to the healthcare system and the ineffectiveness of current treatments, underscores the need for research related to chronic venous legs ulcers.

In this context, the Unna's boot and ozone therapy have been considered promising alternatives to treat venous ulcers due its positive effects on the repair process (Silva et al.,

2017; Izadi et al., 2019). The morphological descriptive findings of the present study showed that both treatment seems to have directly stimulated the good evolution of these wounds. Also, the morphological modifications were more pronounced in the ozone therapy when compared to the Unna's boot. Soares et al. (2019) also observed that ozone therapy increased the granulation tissue, dermal cellularity, intense collagen deposition and reduced the number of inflammatory cells during wound healing in rats. It may be suggested that the ozone offered to the skin tissue was able of inducing an appropriate tissue-response, modulating the inflammatory process and improving the quality of wound healing.

It is well known that venous ulcers are a major cause of morbidity and their care is expensive. Studies have shown that chronic nature of the wounds and the difficult to heal result in long term costs and the frequent recurrences further multiply the expenses (Lal, 2015). The main goal of venous leg ulcers treatment is the use of therapeutic strategies that optimize ulcer healing and prevention of recurrence. In the present study, both therapies promoted total wound closure. Abreu et al. (2013) analyzed the process of tissue repair in patients with venous ulcers using Unna boot (inelastic compression therapy), in comparison with the use of the elastic bandage. The authors found a shorter ulcer healing time in the Unna's boot group when compared to inelastic compression therapy. Zhang et al. (2014) demonstrated that ozone therapy optimized the healing process of diabetic ulcers when compared to control.

Interestingly, there was no difference in time required for the wound to heal from the therapies used in this study. The average wound healing time was 10 weeks for Unna's boot treatment and 8 weeks for ozone treatment. It is important to highlight that the standard deviation for the wound healing time is notably smaller for the Ozone group, which may indicate more effective and predictable treatment over time.

Additionally, the weekly percentual reduction of the ulcer was higher in the ozone group compared to Unna's boot treatment. Similar findings were observed by Izadi et al (2019) who observed a significant reduction in size of the diabetic ulcers, explaining the beneficial effect of ozone therapy in the treatment of vascular ulcers. Possibly, the positive effects of ozone therapy on weekly percentual reduction of the ulcers may be related to the its antioxidant functions and antimicrobial property that favor ulcer healing.

Furthermore, in the present study the ulcers area reduction rate was 16 cm²/week in the Unna's boot group and 31 cm²/week on ozone therapy group. Although there was no statistical difference between the groups, the ulcer area reduction rate was higher in patients

treated with ozone therapy. Increasing the sample size could improve in the future these analyses.

Some limitations and difficulties were encountered during the research. Among these, it can be highlighted factors including the ulcer size and severity and the low number of patients available for evaluated. Moreover, one crucial point that needs to be determined in the field of ozone therapy is the importance of studies exploring the effect of different doses and application technique, in order to try to establish the effective and safe treatment parameters of ozone therapy for an optimal stimulation in tissue repair strategies within the clinical setting.

5. Final considerations

Unna's boot and ozone therapy treatments appeared to positively impact the course of wound healing in chronic wounds, however the ozone therapy may improve the healing of chronic venous leg ulcers in a higher weekly percentage.

Consequently, these data highlight the potential of the use of the ozone therapy to optimize the skin wound healing process. Further additional randomized placebo-controlled trial studies should be performed to investigate the effectiveness of this therapy including larger and more homogeneous samples, which will provide evidences to support the use of the approach as an efficient treatment in the clinical setting.

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