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Photodynamic Therapy, Laser Therapy and Cellulose Membrane for the Healing of Venous Ulcers: Results of a Pilot Study

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Abstract

Background: Venous ulcers, characterized as discontinuous areas of epidermis, are caused by venous hypertension and insufficiency of the muscle pump. They can affect the patient's life quality and cause aesthetic deformity, complications and serious sequelae.

Objective: This study investigates the combined effects of photodynamic therapy, laser therapy and cellulose membrane on the healing of venous wounds.

Methods: Seven patients at an average of 70 years old and with ulcer history for more than one year were selected. The patients received 3 times per week the application of photodynamic therapy and cellulose membrane; and 2 times per week was applied laser therapy.

Results: The results show the reduction of area of ulcer in 7 session ($p<0.04$) and 8 session ($p<0.02$).

Conclusion: The ulcers treatment proposes can decrease the healing time of venous ulcers and promote higher life quality for patients.

Keywords: Curcumin; Laser; Terapia fotodinamica; wound

Introduction

Venous ulcer, also known as varicose ulcer and characterized as a discontinuous area of epidermis, is caused by venous hypertension and insufficiency of the muscle pump [1]. It is commonly found in the adult population and exerts major social and economic impacts [2] on the society, as it is a public health problem due to its high incidence, recurrence and long treatment periods. It also represents 70% to 90% of lower limbs ulcers [1,3].

The costs of treatment of chronic ulcers in lower limbs in the USA represent 1% of the health budget. They lead to a loss of 6 million of useful days of work [4] and affect over 2.5 million patients per year [5]. Most studies have indicated higher prevalence of ulcers (approximately 4%) in individuals over 65 years old [6].

A study conducted in Brazil [7] showed the prevalence of venous veins in 47% of 1755 patients and presence of ulcers or ulcer scars in 3.6%.

According to Hess [8], another aggravating factor is the long-time of treatment, which exceeds 9 months in 50% of the cases and over 2 years in 20% of patients. Moreover, the lesions may reappear after complete healing in over 60% of patients, because of the non-follow-up of the recommendations and care proposed in cases with vascular alterations [8].

Due to the significant psychosocial and economic impacts and complexity of the disease, we analyzed the combination of three tools for its treatment, namely photodynamic therapy, laser therapy and cellulose membrane, for a better microbiological control of the lesion and acceleration in the healing process and injury reparation. The clinical protocol involves the application of photodynamic therapy (PDT) characterized as an association between light and a photosensitive substance for the decontamination of the injury. PDT involves three basic elements, namely a photosensitive substance that absorbs light for the initiation of a series of chemical reactions, light, for the activation of the substance, and the oxygen present in the target cell, which reacts with the active substance and generates reactive oxygen species responsible for the destruction of microorganisms [9,10]. The photosensitizer used was curcumin, a natural compound extracted from saffron (*Curcuma longa*).

In the PDT process as an alternative antibiotic treatment, the photosensitizer acts on the located superficial infections [11]. The method has been employed for the treatment of various dermatological conditions, as it promotes the microbiological control of the injury and, in a low dosage, interferes in several stages of the healing process, accelerating the tissue repair [12,13].

The use of cellulose membrane was incorporated for enhancing the cell adhesion and protection of the injury. It is produced by a gram-negative bacterium (*Gluconacetobacter xylinus*) and contains a biopolymer that blocks the entry of microorganisms in the injury, prevents the loss of exudate and promotes cell adhesion.

The association of this process with laser therapy enables the biostimulation of the healing process and tissue repair and involves the application of light in a known wavelength [14,15]. It has been used in the treatment of various types of injury and ulceration and has yielded positive results, especially in chronic cases [16].

Since 1971, the laser therapy has been reported as a non-invasive alternative for the treatment of ulcers [17], due to its bio modulator effect for tissue repair and increases in local circulation, stimulation and proliferation of cells and synthesis of collagen [18]. The mechanisms by which the method accelerates the healing process comprehend the local liberation of growth factors [17] and mitochondrial increase of ATP production [19,20].

We have evaluated a new clinical protocol for the treatment of venous ulcers through the combination of three techniques, namely laser therapy, cellulose membrane application and PDT.

Methods

Patients

This study was approved by the ethics committee under research protocol number 667752, CAAE: 30625714.2.0000.5380 of May 29, 2014.

Patients were selected through the confirmatory diagnosis of venous ulcer by dermatologists and complied with the inclusion criteria.

Inclusion criteria: venous ulcer diagnosis and ulcer located in the lower limbs; patients with venous insufficiency and edema, varicosities, lipodermatoesclerosis and ezcema.

Exclusion criteria: Patients allergic to any medicament used in the study; pregnant women; evidence of diseases, such as cellulitis, osteomyelitis and gangrene in the affected place; patients that used antibiotics for 15 days prior to the treatment; patients with arterial impairments, diabetes or other systemic diseases; patients that use corticosteroid or immunosuppressive and cancer patient.

Seven patients at an average of 70 years old were treated during our study.

Clinical protocol

The venous ulcers were washed only with a 0.9% physiological saline solution. The photosensitizer, i.e., curcumin gel 1.5% (supplied by Pharma PDT) was applied across the ulcer, which was immediately occluded with plastic film, aluminum paper and gauze. 30 minutes after the application of curcumin, both curative and excess gel was removed with a physiological saline solution and gauze.

Photodynamic therapy (PDT) with light emission diode (LED) of 450 nm wavelength and 75 mW/cm^2 intensity was applied for 12 min and a total energy dose of 54 J/cm^2 was delivered to the tissue. The cellulose membrane (Nanoskin® provided by Innovative technology-Innovatecs) was then placed across the area of the ulcer and a curative was applied. A nurse changed the cellulose membrane every 3 days. Twice a week, the laser therapy (660 nm laser) was applied on the full extension of the ulcer and under the cellulose membrane for 30 s at 10 J/cm^2 fluence. The patients underwent weekly sessions that followed the same protocol for 4 weeks or until the complete healing of the ulcer. The procedure is shown in Figure 1.

Figure 1: Conjugated therapies of venous ulcer treatment. A) PDT; B) Laser therapy; C) Cellulose membrane.

Follow-up treatment

During all process, a sterilized steel ruler measured the length and width of the ulcer for analysis of the reductions in the lesion size and photographic records were made. The ulcer area was calculated in cm^2 through the multiplication of the longest length by the largest width in each session. The session was considered each wound dressing.

Results

Figure 2 shows the evolution of the venous ulcer reduction. Significant differences were observed between the measurements taken along the treatment. The mean area of the injuries showed statistical differences in comparison with the injuries in the initial session versus session 7 ($p<0.04$) and initial session versus session 8 ($p<0.02$). The mean dimension of the initial area was 51 cm^2, whereas in sessions 7 and 8, they were 13,6 cm^2 and 7,44 cm^2, respectively.

The evolution in the venous ulcer (12 years of injury) treatment is shown in Figure 3. Our results are promising, especially regarding the microbiological control of the injury by PDT with curcumin as a photosensitizer. The acceleration of the tissue repair through the association of laser therapy methods and cellulose biomembrane in 7 patients, after 8 sessions, is shown in Figure 2.

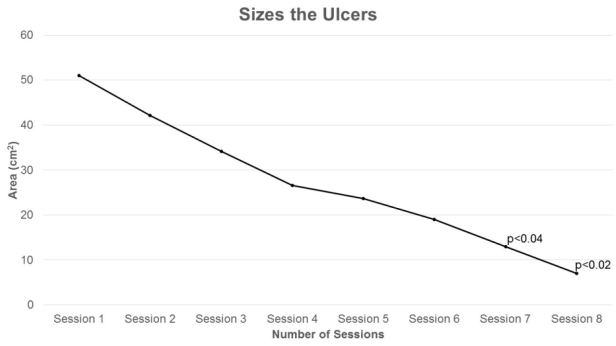

Figure 2: Representative graphic of the Area evolution (cm^2) of the venous ulcer healing along 8 sessions in the 7 patients treated. Significant statistical differences between Sessions 1 and 7 (<0.04) and between Sessions 1 and 8 ($p<0.02$).

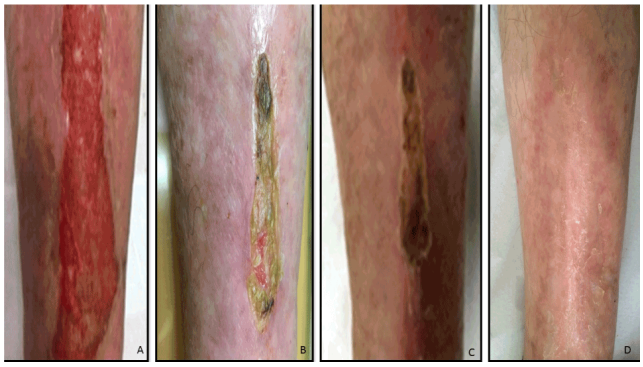

Figure 3: Evolution of a venous ulcer during 8 sessions of the treatment (patient with 12 year old injuries), WITH PDT, laser therapy and cellulose membrane. A) Initial injury; B) After session 1; C) After session 6; D) After session 8 end-healing process.

Discussion

The results showed acceleration in the venous ulcer healing after the eighth session, on average. The combination of laser therapy, cellulose membrane application and PDT improved the wound healing.

Such results can be attributed to the effectiveness of each technique in the wound healing, i.e., laser therapy alone has proven effective in both local and systemic responses, showing an anti-inflammatory effect, reducing pain, accelerating the cell proliferation and optimizing the healing process [21].

In the study realized by Caetano et al. [22] 20 patients and 32 chronic ulcers were used, divided in three groups. In group 1, sulfadiazine cream was used and treated with placebo phototherapy (<0.03 J/cm^3), group 2 phototherapy was used and group 3 was a control group, only with sulfadiazine cream without phototherapy. The results from this research were that phototherapy promotes healing of chronic venous ulcers, due to treatment with phototherapy healed significantly faster than controls when compared at day 30 (p 0.01), day 60 (p 0.05), and day 90 (p 0.001) and similarly healed faster than the placebo-treated ulcers at days 30 and 90 (p 0.01), but not at day 60.

The cellulose membrane exhibits a distinctive nanofibrillar structure that is a highly nanoporous material that enables the transfer of medicines and is an efficient physical barrier against any external infection. It is a perfect matrix with optimal properties for wound healing [23].

According to Farah [24], a membrane applied under a wound acts as a new skin that can eliminate pain through the isolation of nerve endings, although it may enhance the absorption of exudates in the wound.

In the study realized by Basmaji et al. [25] Nanoskin® was applied in patients with burns and wound naturopathic (Hansen), the results show that Nanoskin® is very effective in promoting autolytic debridement, reducing pain, and accelerating granulation, all of which are important for wound healing.

The PDT process, on the other hand, kills the bacteria through the combination of a photosensitizer and a source of light in an appropriate wavelength, which results in the wound decontamination.

Hamblin et al. [26,27] were the first authors to report on the PDT process in relation to wounds infected in the mouse model. They evaluated the wounds measuring 100 mm^2 (8 mm × 12.5 mm), which were made on the backs of mice. The wounds were infected with *E. coli* and *P. aeruginosa* and observed that 90% of the mice infected with *P. aeruginosa* and treated with PDT survived, which demonstrated PDT is a non-invasive technique for the treatment of infected wounds.

Although treatments that use each technique alone (laser therapy, cellulose membrane application and PDT) have shown promising results, the combination of techniques used in this new clinical protocol was more effective regarding reductions in the treatment time due to improvements in the wounds healing.

Conclusion

The new integrated method can decrease the healing time of venous ulcers, promote higher life quality for patients and generate positive social and economic impacts.

Author Disclosure Statement

No competing financial interests exist.

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