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EFFECT OF PHOTOBIOMODULATION ON HEALING OF POST-MINOR AMPUTATION ULCERS IN PATIENTS WITH DIABETES MELLITUS

EFEITO DA FOTOBIOMODULAÇÃO NA CICATRIZAÇÃO DE ÚLCERAS PÓS-AMPUTAÇÃO MENOR EM PACIENTES COM DIABETES MELLITUS

EFECTO DE LA FOTOBIOMODULACIÓN EN LA CICATRIZACIÓN DE ÚLCERAS POSTERIORES A AMPUTACIÓN MENOR EN PACIENTES CON DIABETES MELLITUS

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ABSTRACT

Aims: To evaluate the effect of laser photobiomodulation on the closure of ulcers after minor amputations in patients with DM.

Method: 16 patients undergoing outpatient treatment in a public tertiary hospital were randomly divided into two groups. The conventional group was treated by cleaning the lesion

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with saline solution and using primary dressing; the photobiomodulation group received the conventional treatment+laser with λ=660nm, I=2.7W/cm2, H=108J/cm2, t=40s, E=4.32J. Each week the lesions were evaluated by measuring the area, perimeter, temperature, pH and glycemia levels. Statistical analysis was performed and the significance of all tests was □=0.05.

Results: After 5 weeks there was no significant difference between groups, but 100% of the patients in the photobiomodulation group had granulation tissue, while in the conventional group it was 0% ($p = 0.0014$). By ROC curve was possible to establish that the cut-off for the arising of granulation tissue is 4 weeks. In addition, up to 18 laser treatment sessions increases the likelihood of ulcer closure, but beyond 18 sessions the probability starts to decrease, falling below 40%. It was also possible to determine the glycemic limit for the success of photobiomodulation: up to 225mg/dL.

Conclusion: Laser photobiomodulation with the parameters used accelerated the arising of the granulation tissue and provided 100% lesion cure in 6 patients. This study was also instrumental in determining the ideal number of sessions to maximize the likelihood of ulcer closure: once a week, for up to 18 weeks and with greater affectivity in patients with capillary glycemia below 225mg/dL.

Keywords: Laser. Photobiomodulation. Ulcers. Amputations. Diabetes Mellitus.

RESUMO

Objetivo: Avaliar o efeito da fotobiomodulação a laser no fechamento de úlceras após amputações menores em pacientes com diabetes mellitus (DM).

Método: Dezesseis pacientes em tratamento ambulatorial em um hospital público terciário foram randomicamente divididos em dois grupos. O grupo convencional foi tratado com limpeza da lesão utilizando solução salina e curativo primário; o grupo fotobiomodulação recebeu o tratamento convencional associado ao laser com λ = 660 nm, I = 2,7 W/cm^2, H = 108 J/cm^2, t = 40 s, E = 4,32 J. Semanalmente, as lesões foram avaliadas por meio da mensuração da área, perímetro, temperatura, pH e níveis glicêmicos. Foi realizada análise estatística, considerando-se significância de $\alpha = 0,05$.

Resultados: Após 5 semanas, não houve diferença significativa entre os grupos; entretanto, 100% dos pacientes do grupo fotobiomodulação apresentaram tecido de granulação, enquanto no grupo convencional esse percentual foi de 0% ($p = 0,0014$). Pela curva ROC, foi possível estabelecer que o ponto de corte para o surgimento do tecido de granulação é de 4 semanas. Além disso, até 18 sessões de laser aumentaram a probabilidade de fechamento das úlceras, porém, após esse número, a probabilidade começou a diminuir, ficando abaixo de 40%. Também foi possível determinar o limite glicêmico para o sucesso da fotobiomodulação: até 225 mg/dL.

Conclusão: A fotobiomodulação a laser, com os parâmetros utilizados, acelerou o surgimento do tecido de granulação e proporcionou cura completa da lesão em 6 pacientes. O estudo também permitiu determinar o número ideal de sessões para maximizar a probabilidade de fechamento das úlceras: uma sessão semanal por até 18 semanas, com maior efetividade em pacientes com glicemia capilar inferior a 225 mg/dL.

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Palavras-chave: Laser. Fotobiomodulação. Úlceras. Amputações. Diabetes Mellitus.

RESUMEN
Objetivo: Evaluar el efecto de la fotobiomodulación láser en el cierre de úlceras posteriores a amputaciones menores en pacientes con diabetes mellitus (DM).

Método: Dieciséis pacientes en tratamiento ambulatorio en un hospital público terciario fueron divididos aleatoriamente en dos grupos. El grupo convencional fue tratado mediante limpieza de la lesión con solución salina y curación primaria; el grupo de fotobiomodulación recibió el tratamiento convencional asociado al láser con λ = 660 nm, I = 2,7 W/cm², H = 108 J/cm², t = 40 s, E = 4,32 J. Semanalmente, las lesiones fueron evaluadas mediante la medición del área, perímetro, temperatura, pH y niveles de glucemia. Se realizó análisis estadístico considerando un nivel de significancia de α = 0,05.

Resultados: Después de 5 semanas no se observaron diferencias significativas entre los grupos; sin embargo, el 100% de los pacientes del grupo de fotobiomodulación presentó tejido de granulación, mientras que en el grupo convencional fue del 0% (p = 0,0014). Mediante la curva ROC fue posible establecer que el punto de corte para la aparición del tejido de granulación es de 4 semanas. Además, hasta 18 sesiones de láser aumentaron la probabilidad de cierre de las úlceras, pero después de este número la probabilidad comenzó a disminuir, situándose por debajo del 40%. También se determinó el límite glucémico para el éxito de la fotobiomodulación: hasta 225 mg/dL.

Conclusión: La fotobiomodulación láser con los parámetros utilizados aceleró la aparición del tejido de granulación y proporcionó la curación completa de la lesión en 6 pacientes. El estudio también permitió determinar el número ideal de sesiones para maximizar la probabilidad de cierre de las úlceras: una sesión semanal durante un máximo de 18 semanas, con mayor efectividad en pacientes con glucemia capilar inferior a 225 mg/dL.

Palabras clave: Láser. Fotobiomodulación. Úlceras. Amputaciones. Diabetes Mellitus.

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1 INTRODUCTION

Data on morbidity and mortality from diabetes demonstrate the importance of the disease as a public health problem in the global population – globally, one in five people aged between 65 and 69 live with diabetes (approximately 136 million)1. It is projected that the number of individuals over 65 with diabetes will reach 195.2 million in 2030 and 276.2 million in 2045. This progressive increase is mainly due to the rise of type 2 diabetes mellitus (insulin resistance), which represents 90% to 95% of cases and predominantly affects adults and the elder adults (1).

Worldwide, the prevalence of diabetes is driven by a complex interplay of socioeconomic, demographic, environmental, genetic, and behavioral factors. Rising levels in the adoption of unhealthy lifestyles (unhealthy diets and physical inactivity, leading to obesity) and progressive urbanization significantly account for the increase in the incidence and prevalence of diabetes globally. Chronic complications or those that develop over a long period may present in people with diabetes (especially the elderly) at the very moment of diagnosis. In this sense, early detection and treatment are essential to prevent disability and death (2), (3).

The increased use of health services by individuals with diabetes, the loss of productivity, and the prolonged care required to treat chronic complications (renal failure, heart problems, diabetic foot, among others) represent, for most countries, an expenditure between 5% and 20% of total health spending, posing a major challenge for health systems5. In Brazil, in 2018, the Unified Health System (SUS) expenditures on hospitalizations, outpatient procedures, and medications corresponded to 30% for diabetes (over R$ 1 billion) and 11% for obesity (over R$ 370 million). The costs of obesity as a risk factor for diabetes are also high (4), (5).

As the disease evolves there are macro and microvascular complications, which compromise the structure and function of the eyes, kidneys, circulatory system, and peripheral nervous system (3). Changes in the lower limbs are common and are known as diabetic foot. The lesions are mostly chronic ulcers that worsen patients' quality of life, and increase long-term morbidity and mortality, as they may progress to amputations (3).

Diabetic foot ulcers (DFUs) have a high incidence in the word. Patients with DM present a 15-25% higher chance of developing DFUs throughout their life and an 85% higher risk of amputations resulting from ulcer infections. Every year, one million people with DM have a lower limb amputation (4), (5).

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The main goal of diabetic foot management is to perform local injury care, ensure adequate blood supply, prevent and control infections in order to ensure complete closure of the ulcer and concomitant control of the systemic disease (6).

The choice of treatment for DFU is based on the expected action of the medication on the lesion bed, such as protection of the ulcer bed, antimicrobial activity or exudate absorption. In this way, active-dressings, biologicals and negative pressure therapy can be used at different phases of treatment, namely: hygiene, debridement, reduction of bacterial colonies, exudate control and stimulation of the formation of granulation tissue (4).

Although there are a wide range of therapies available for DFU treatment, often the goal of maintaining limb homeostasis is not achieved. This mainly occurs because the treatment is lengthy, and not all patients adhere to the conventional therapies. Thus, amputation ends up being the only solution for containing the infection (6).

Photobiomodulation (PBM) is the application of light, generally in the visible or near-infrared spectra, to stimulate or inhibit cellular functions in order to achieve beneficial effects, such as relieve pain and reduce inflammation (8). The most widely accepted mechanism of action is that the photons are absorbed by the respiratory chain and increase ATP production, generating low levels of reactive oxygen species (ROS), which are responsible for stimulating cellular proliferation and metabolism (7).

PBM, when applied in the immediate postoperative period, is ideal for triggering inflammatory cascade events promoting wound contraction, phagocyte chemotaxis, macrophage polarization, fibroblast differentiation in myofibroblasts, and collagen organization. The three phases of wound repair can be modulated to promote rapid closure (7), (9), (10).

Diabetic patients have difficulty cicatrization process due to hyperglycemia, inhibition of inflammatory response, decrease in collagen production, extracellular matrix deposition and reduction in angiogenesis (11). Lasers have been used since the 1960s as an alternative lesion treatment for the closure of various types of wounds. Over the years, several studies (clinical and experimental) have reported the action of PBM on wound cicatrization, as presented in **Table 1.**

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Table 1

Action of photobiomodulation in wound healing - clinical studies

Study	Study Design	Participants	Intervention	Expected Results	Treatment Results
Minatel et al 2009	Randomized, Double blind; Placebo – controlled	23 patients with chronic diabetic ulcers.	LED: 2 times per week for 90 days. 660nm to 890nm (Cluster – red and infrared LEDs), 3J/cm² 100mW/cm², 30s	Granulation rate and cicatrization	Group treatment, total closure in 90 days of 100% of lesions whereas in placebo group only one lesion reached full closure.
Landau et al 2011	Randomized, Placebo – controlled, Double blind	14 patients with diabetic ulcers and 2 patients with venous ulcers.	Vireo (bulb): 2 times per day for 12 weeks, 400-800nm 43.2J/cm², 180mW/cm², 240s	Cicatrization rate, reduction of size, time for injury closure	Group treatment: 90% cicatrized, reduction in size of 89%, time of 7.14 weeks. Placebo group: 33% cicatrized, reduction in size of 54%, time: 11.5 weeks.
Kaviani et al, 2011	Randomized, Double blind; Placebo – controlled	23 patients with diabetic foot for more than 3 months.	Laser: 2 times per week for 2 weeks, 685nm 10J/cm², 50mW/cm², 200s	Reduction in ulcer size and time for cicatrization	Significant reduction in ulcer size in the laser group of 58 ± 10.4% to 23.5 ± 14.1% after two weeks of treatment, cicatrization after 11 weeks. Placebo group did not show significant results in 14 weeks.
Kajagar et al, 2012	Randomized, Group controlled	68 patients with chronic diabetic foot ulcers.	Laser: for 15 consecutive days. 2-4J/cm², 60mW, 5kHz	Reduction in lesion area	Larger reduction in lesion area in the laser group, 36% in relation to the initial lesion.
Feitosa et al 2015	Randomized, Controlled, Interventionist	16 patients with ulcerations in lower limbs.	Laser: 3 times per week for 4 weeks, 632.8nm 30mW, 4J/cm², 80s	Reduction in lesion area	Reduction in lesion area in the laser group (7.98cm² to 2.39 cm²); in the control group the lesion area grew (2,55cm² to 8,43 cm²).
Frangez et al 2017	Randomized, Placebo - controlled	79 patients with chronic lesions in lower limbs– diabetic and	LED: 3 times per week for 8 weeks. 625, 650 e 850nm	Increase in local blood flow	There was an increase in blood flow in the treated group (both diabetic

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		non-diabetic.	2.4J/cm² / placebo: 0.72J/cm², 300s		and non-diabetic) which did not occur in the placebo group.
Mathur et al 2017	Randomized, Placebo – controlled	30 patients, diabetic foot ulcers.	Laser: for 15 consecutive days, 660nm 50mW/cm², 3J/cm², 60s	Reduction in lesion area	Reduction in lesion area in the laser group (37.2%); placebo group (15.12%).

Source: Authors.

According to literature review, the PBM presents positive results in relation to the control group. However, more studies are needed to establish adequate dosimetry and, especially, the frequency and timing of treatment. Thus, the purpose of this study was to follow treatment until total closure of the ulcer. By doing so, the ideal number of irradiations was discovered, thus offering patients with DM, in the immediate postoperative period after minor, lower limb amputations, a more effective therapeutic option.

Therefore, to assess the action of photobiomodulation on the closure of minor ulcers post-amputation in patients with DM were used photographic images to measure the area, perimeter, arising of granulation tissue, temperature and pH of ulcers. Patient´s glycemic index was monitored, too.

2 METHODS

Recruitment was carried out from March to September of 2017, and was approved by the Research Ethics Committee of the Nove de Julho University and by the Ethics Committee from the Mandaqui Hospital Center (CAAE: 53351716.5.3001.5551), which is a public hospital, providing tertiary care. It is a reference for highly complex care in the city of São Paulo, Brazil. Each patient received a verbal explanation of the study and only participated in it after free acceptance, with the signing of the Informed Consent Form.

2.1 STUDY DESIGN

Study was a single-center, controlled, clinical trial with two parallel groups: the conventional group and the photobiomodulation group. Participants were randomly assigned to a group-allocated to the laser group, then to the conventional group, and so on, as amputation surgeries occurred. The sample consisted of 16 patients diagnosed with

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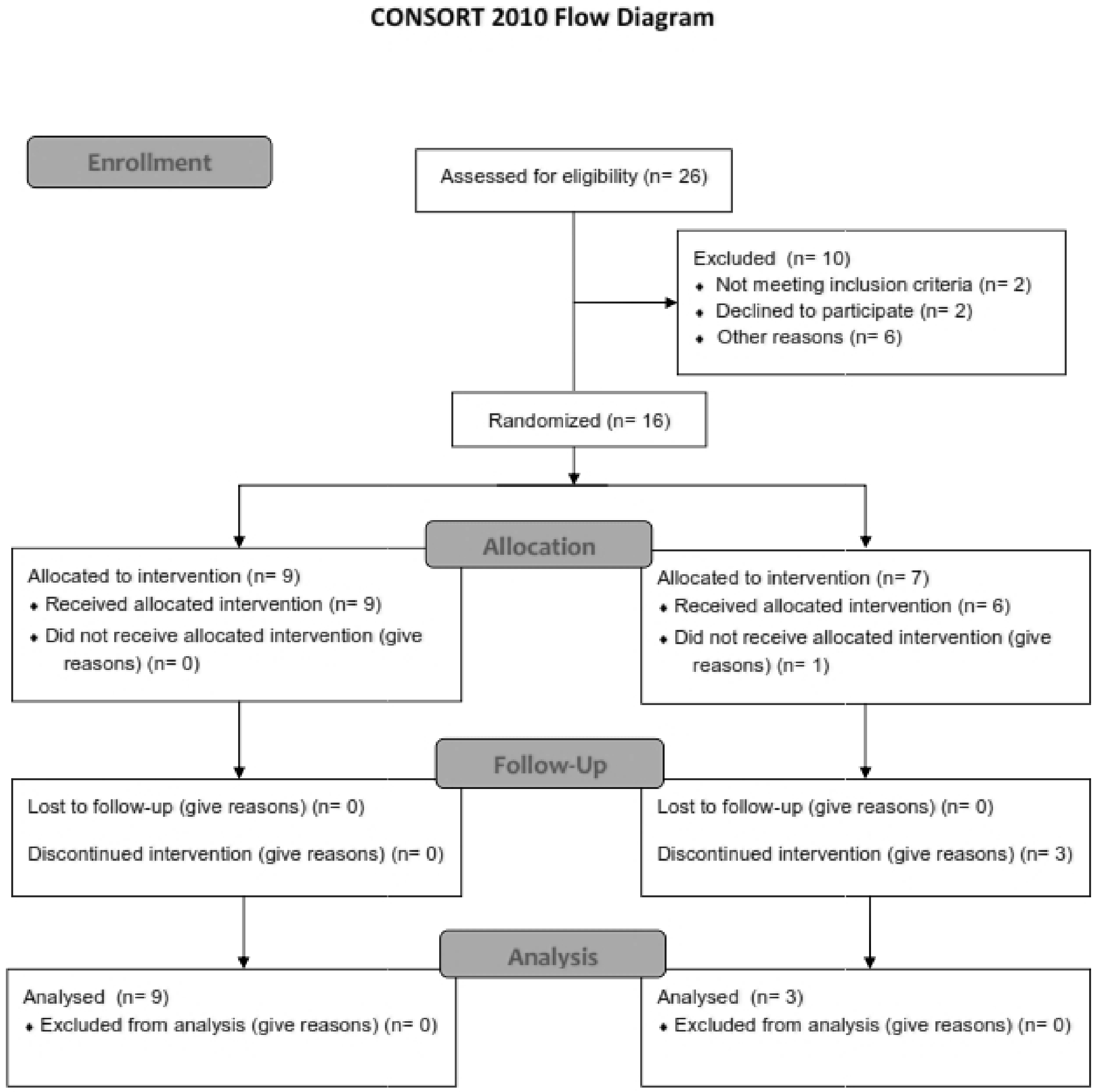
Diabetes Mellitus, in outpatient follow-up with the vascular surgery team and who fit the inclusion criteria.

The study was outlined according to CONSORT Statement Criteria **(Figure 1)**, and is registered at www.clinicaltrial.gov, ID NCT02883751, 29 Aug 2016.

A blind evaluator analyzed the results and photographic images.

Figure 1

Critérios da Declaração CONSORT



Source: Authors.

2.2 INCLUSION CRITERIA

Participants should be 18 years of age or older, have type I or II DM, and have undergone minor partial amputation at the level of fingers and toes, metatarsophalangeal or trans metatarsal disarticulation and be in immediate postoperative period.

2.3 EXCLUSION CRITERIA

Participants were excluded if they had infected lesions, were undergoing or had undergone antineoplastic treatment in the last 3 months, if pregnant or nursing, or had concomitant participation in another clinical trial or who were not in the immediate postoperative period.

2.4 EXPERIMENTAL GROUPS

The patients were divided into two groups: Conventional group (n = 7): Treatment consisted of cleaning the surgical lesion with 0.9% saline solution, once a week, a primary cellulose membrane dressing (Membracel®) or absorptive dressing with silver (Acticoat ®, Curatec ®, Aquacel ® - as available in the hospital) was applied to the lesion. The choice of dressing was made according to the surgical technique employed and the amount of secretion at the lesion site. Next, the secondary dressing, a cotton compress or gauze (depending on the size of lesion and amount of secretion), was secured with a crepe bandage.

Photobiomodulation group (n = 9): Treatment with laser and primary dressing with cellulose membrane (Membracel®) or absorptive dressing with silver (Acticoat®, Curatec®, Aquacel® - as available in the hospital), the choice of coverage was made according to the surgical technique employed and amount of secretion at the lesion site. Treatment consisted of cleaning the surgical lesion with 0.9% saline solution, followed by laser irradiation (Therapy EC, DMC®, Brazil) once a week. The application method was by contact along the edges of the lesion, with 1 cm between the irradiated points, as well as in the ulcer bed (points in the center and in the N, S, E and W directions, **Figure 2**). After laser application the lesion received primary dressing, then the secondary dressing.

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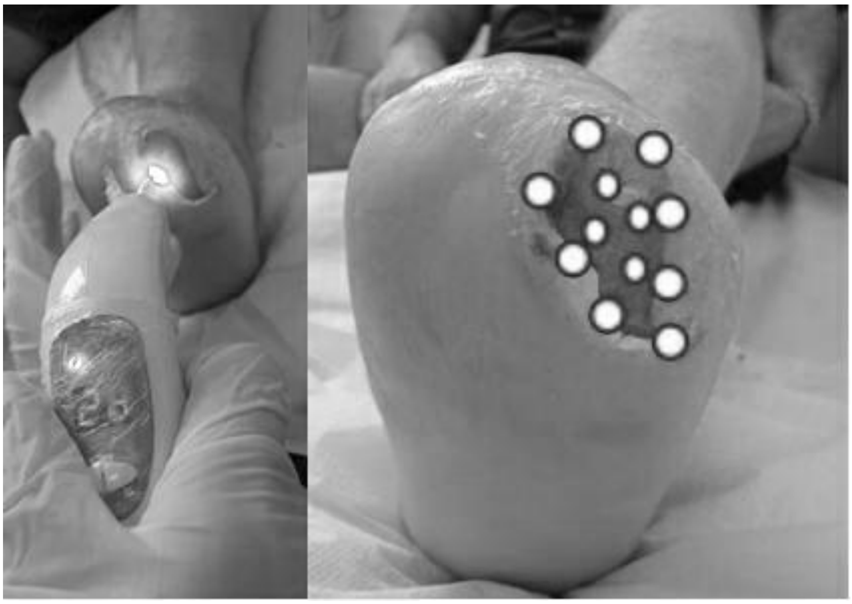
Figure 2

After laser application, with primary dressing, image 2 after secondary dressing



Source: Authors.

The laser was wrapped with disposable plastic film (transparent at the red wavelength) during application. This film was replaced with new film with each change in patient. Laser parameters were: λ= 660±10 [nm], continuous wave, average radiant power 108 mW, power density at aperture 2,7 W/cm^2, beam spot size at target 0,04 cm^2, irradiance at target 2,7 W/cm^2, exposure duration 40s, radiant exposure 108 J/cm^2, energy density at aperture 108 J/cm^2, radiant energy 4,32 J, once a week and number of irradiated points according to lesion area.

2.5 ANALYSIS

The primary study variable was the area of the lesion, measured using photographic records (Powershot S5 IS, Canon®, USA) taken after cleaning. A millimeter scale was used for reference and later analysis of the area and perimeter with ImageJ software (NIH, USA). The photographs were also used to record the arising of the granulation tissue.

The capillary glycemia measurement was performed using a glucose meter (Injex Sens II®, country).

The pH reading was performed before the lesion was cleaned by placing the reagent tape on the lesion for 5 seconds. The reading was then performed using the color scale (K36-014, KASVI®).

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Thermographic images were performed before the lesion was cleaned in both groups and, in the laser group, after laser application as well. A thermographic camera (C2 FLIR® Technology, USA) was used.

To verify variations in lesion area and perimeter in both groups, as well as temperatures before and after irradiation in the laser group, the following formula was used:

$$\Delta_{\%} = \frac{measurement\ 5th\ week - measurement\ the\ 1st\ week}{measurement\ the\ 1st\ week} . 100 \qquad (1)$$

2.6 STATISTICAL ANALYSIS

The data were checked for normality with the Shapiro-Wilk test. Found to be normal, the groups were compared using the t-Test for independent samples. The data were presented in the mean ± standard deviation format. Using the F-test for Variances Ratio, variance equality was compared between the groups, for each variable. The variables studied were variations in area, perimeter, pH, temperature and glycemic index, between the 1st and the 5th week of treatment.

The Receiver Operating Characteristic (ROC) curve was used to represent the relationship between sensitivity and specificity in respect to the presence of granulation tissue in the PBM and conventional groups, as well as to determine the number of sessions required for the arising of said tissue. It was also used to establish the cut off point for the blood glucose level at which successful closure of the lesion was still possible.

The Chi-square test corrected by Fisher was then performed to verify the proportion of presence and absence of granulation tissue between the PBM and conventional groups at the end of the five weeks of treatment.

The survival rate of ulcers treated with PBM was determined using the Kaplan-Meyer test.

The significance of all tests was $\alpha = 0.05$ and the OriginPro 2017 software (version b9.4.2.380, OriginLab Corp®., Northampton, USA) was used.

3 RESULTS

Out of 16 patients, 15 (93.75%) had diagnoses of type 2 Diabetes Mellitus and were taking human insulin and/or oral hypoglycemic agents. 1 patient (6.25%) had Type 1 Diabetes Mellitus and was taking human insulin.

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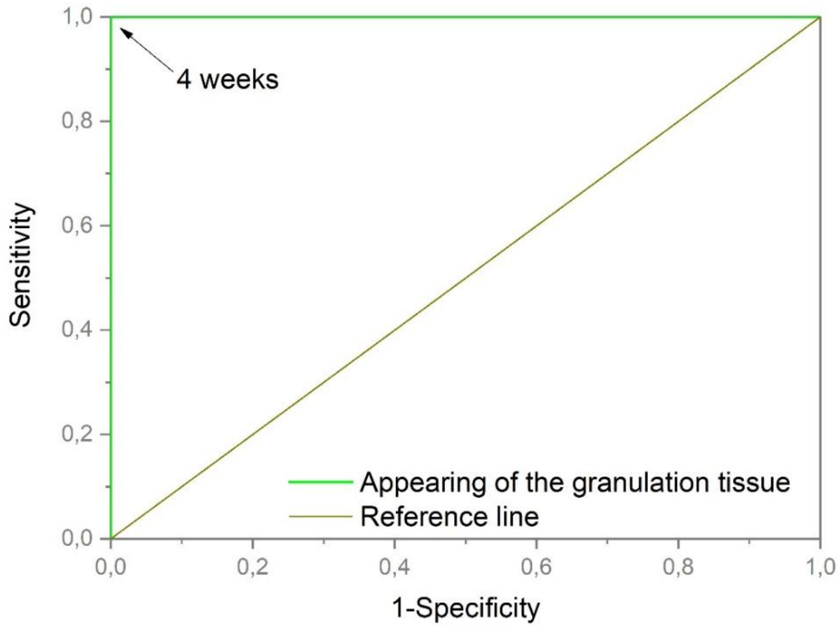
Using the ROC curve, it was possible to establish the cut off time for arising of granulation tissue, 4 weeks. That is, the period necessary for granulation tissue to appear is 4 weeks (**Figure 3**).

Figure 3

Granulation tissue after 4 weeks. 2018



Source: Authors.

After five weeks of treatment, 100% (9/9) of patients in the PBM group had granulation tissue, while in the conventional group 0% (0/4), this difference was significant ($p = 0.0014$). This led to the discontinuation of conventional treatment, to avoid new amputations, and the patients were transferred to the photobiomodulation group after a decision made by a multidisciplinary team. This step was taken in order to maintain the patients' physical and emotional well-being. In fact, the main predictor variable in the laser group was the arising of granulation tissue.

As for the other variables, there was no significant difference between groups in reference to changes in area ($p = 0.38467$), perimeter ($p = 0.07066$), pH ($p = 0.79164$), temperature ($p = 0.6703$) or glycemic index ($p = 0.09713$) up to the 5th week of treatment. In **Figure 4** it is possible to observe the results of these variables.

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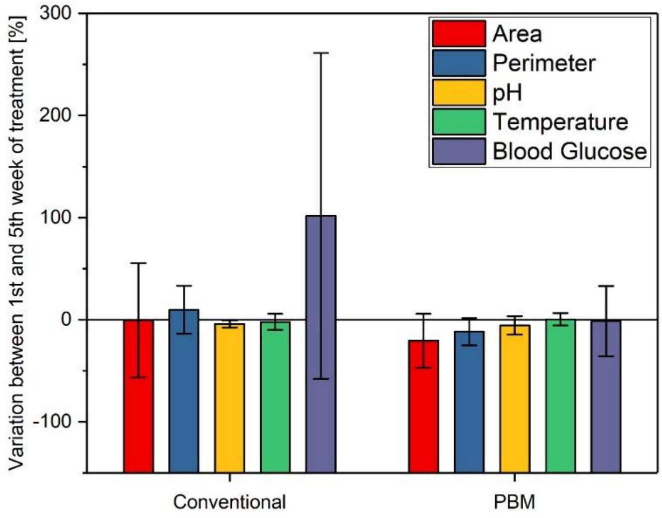
Figure 4

Relationship between changes in peripheral area, temperature, and glycemic index (up to the 5th week of treatment)



Source: Authors.

Between the 5th and the last treatment session, 6 patients presented 100% lesion closure .

The survival rate of ulcers treated with PBM was determined via the Kaplan-Meyer test. Up to the 18th session the probability of ulcer closure is over 70%. From the 18th session on, the probability becomes less than 40% (**Figure 5**).

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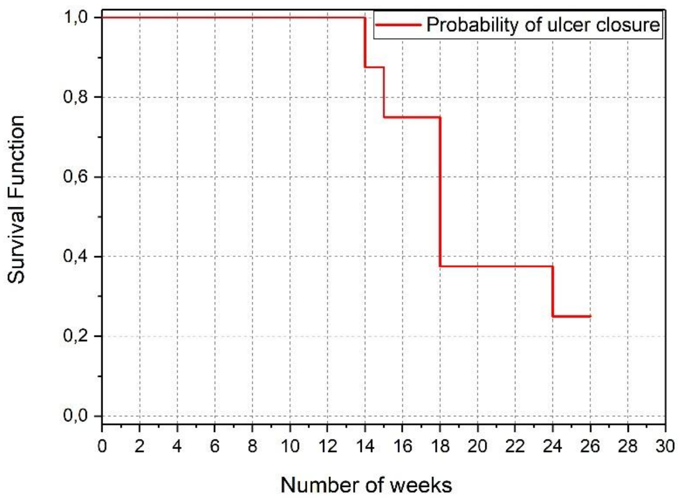
Figure 5

Survival rate of lesion improvement treated with photobiomodulation assessed by the Kaplan-Meier test at the 18th session.



Source: Authors.

Using the ROC curve, it was possible to establish the cut off point for the blood glucose level at which successful closure of the lesion was still possible, obtaining a value of 225 mg/dL. Thus, the data were categorized as 0 (values> 225 mg/dL) or 1 (values ≤ 225 mg/dL). The Chi-square test corrected by Fisher was then performed to verify the proportion of patients with glycemic index above and below 225 mg/dL among those who had 100% lesion closure and those who did not. Of the patients who did not have 100% of closure ulcer had glycemic index above 225 mg/dL, while those with 100% had a blood glucose level below 225 mg/dL. This proportion was statistically significant (p = 0.00216).

4 DISCUSSION

Diabetic foot ulcers represent one of the major health problems related to Diabetes Mellitus. It is characterized by infections and destruction of deep tissue associated with peripheral neuropathies (4). In Brazil, it accounts for 40-70% of lower limb amputations (12).

In the studies by Ramussen (13) and Parisi (14), it was shown that amputations are more frequent in male patients with type 2 DM and 60 to 70 years of age. These data corroborate our sample, which consisted of 14 men (87.5%) with type 2 DM (93.75%) and mean age of 55 years.

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Our research was performed immediately after the minor amputation surgery, precisely to treat the newly created ulcer and verify the action of the photobiomodulation in the acute period of the lesion. This type of surgery does not use flap rotation (rotation of the skin to close the lesion), and cicatrization by second intention is delayed in diabetic patients, justifying the search for therapies that reduce repair time.

There was no significant difference between the groups regarding area ($p = 0.38467$), perimeter ($p = 0.07066$), pH ($p = 0.79164$), temperature ($p = 0.6703$) or glycemic index ($p = 0.09713$) until the 5th week of treatment, although clinically it was possible to perceive the worsening of the lesion in the conventional group. This discrepancy between clinical and statistical observations is due to the large standard deviation verified in the data. This deviation could have been minimized if the sample had been more homogeneous; however, the maximum outpatient capacity of the hospital, for the type of patient, which met the inclusion criteria, had been reached. Thus, there was no way to recruit more patients so as to try to homogenize the sample.

Vitse (15) *et al* studied 24 patients divided into two groups (photobiomodulation and placebo) and after 12 weeks of treatment there was a reduction of the mean area of the ulcer in 77% in the PBM group and 69% in the placebo group. However, no statistically significant difference was found between the groups (15). In our study, the PBM group presented a reduction in the lesion area of 20.6 ± 26.4 (%), while the conventional group presented a reduction of 0.5 ± 55.9 (%), after 5 weeks of treatment.

Kaviani *et al* observed that the number of patients who presented total ulcer closure was higher in the PBM group (8 out of 13 patients) than in the placebo group (3 out of 9 patients) in 20 weeks of treatment. However, the authors also did not find a statistically significant difference, attributing this fact to the small sample size (16). For our research, 7 patients were allocated to the conventional group, but one patient died and two gave up the study due to transportation and food expenses, leaving four patients. In the PBM group, 9 patients were allocated and they remained until the end of the study. From the 5th to the 18th PBM treatment session, 6 patients' lesions closed 100% of these, 2 were originally from the conventional group and 4 already belonged to the PBM group. That is, our rate of ulcer closure was like that of Kaviani *et al*(15).

Despite the lack of statistical significance between the groups, it was possible to observe lower secretion in the PBM group and a greater amount of granulation tissue. This corroborates with (17), who observed that lesions treated with PBM presented a greater

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amount of granulation tissue and an absence of secretion, unlike the conventional group, which required debridement and more frequent dressing changes due to increased secretion.

Another important factor is that photobiomodulation stimulates the proliferation of fibroblasts and dermal keratinocytes, important in the cellular proliferation phase of the cicatrization process (18). In all patients, there was an increase in keratin production during laser treatment, especially during the first applications, requiring debridement when there was a large amount of tissue that could interfere with the contraction of the lesion. On the other hand, the same excess of keratin was important in protecting the lesion, especially for the patients who did not complete the necessary rest period and were ambulatory even before the ulcers had closed.

The pH of the ulcers stayed in the alkalinity range (8.0 to 8.5) and the temperature was around 33°C in both the PBM and conventional groups. According to the study by Dini et al., a lesion temperature below 33ºC promotes a decrease in the activity of epithelial cells, fibroblasts and neutrophils, interfering in the repair process. Nagoba et al. describe how the surface pH of a lesion plays a key role in cicatrization, helping to control infection and increasing antimicrobial activities, bacterial protease, angiogenesis and oxygen release. On the other hand, a very high pH makes cicatrization difficult, and a neutral pH is ideal (19). According to Power a better understanding of the relationship between pH and diabetic foot ulcers is essential for decreasing the duration and impact caused by possible infections (20).

Blood glucose measurements were not performed during fasting but were still above acceptable postprandial values in diabetics. According to the American Diabetes Association (21), the values should be lower than 180mg/dL. Of the patients who did not have a fully closure ulcer, 100% had glycemia above 225 mg/dL, while those who experienced total ulcer closure had a blood glucose level below 225 mg/dL.

Kruse *et al*. (2016) in an in vitro study, showed that fibroblast and keratinocyte migration was inhibited when glucose was added at a concentration of 5.6 mM/L, equivalent to 100 mg/dL. However, human skin cells can tolerate hyperglycemic conditions of up to 472 mg/dL and fibroblasts of up to 180 mg/dL, a level where they show increased cellular activity in relation to lower concentrations of glucose (22).

Huang et al showed that a high glucose concentration (635mg/dL) induced apoptosis in keratinocytes in vitro, which are important cells in the cicatrization process (23). Hyperglycemia (values greater than 100 mg/dL) favors immune dysfunction: neutrophilia,

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damage to the antioxidant system and humoral immunity and decreases antimicrobial activity, which permits infections that can affect all organism, but in the case of diabetic patients more frequently affects feet (4). In our study, despite elevated capillary glycemia values, granulation tissue appeared up to the fifth week in the laser treated patients, unlike in those in the conventional group. At the end of five weeks of treatment, 100% of patients in the PBM group had granulation tissue, while in the conventional group 0% had, this difference was significant (p = 0.0014).

Granulation tissue appears in the proliferative phase of the cicatrization process. It takes around 4 to 10 days to fill the lesion. However, in diabetic and hyperglycemic patients this process slows down or is absent, depending on blood glucose levels. Several studies have shown that the action of the laser in the inflammatory phase, 24 to 48 hours after injury, promotes an increase in granulation tissue. This reinforces the importance of initiating treatment in the acute phase of the lesion. Dahmardehei (25) evaluated the application of photobiomodulation on diabetic patients with injuries from 3rd degree burns, after skin grafting, and there was a significant increase in granulation tissue and total closure of the lesion in 8 weeks of treatment (24). Trajano *et al.* in an experimental study of 2nd degree burns in diabetics, demonstrated that the application of a laser in the proliferative phase promotes a significant increase of the granulation tissue in comparison to groups not treated with laser (25). Sousa et al in a systematic review (26) and Hazari et al in a Case Report (8) demonstrated that photobiomodulation decreases the number of cells in the inflammatory phase and increases collagen synthesis and formation of granulation tissue in the proliferative phase.

In the present study, despite the high glycemia values, the patients treated with laser presented granulation tissue, on average, in the 4th week of treatment. This did not happen in the conventional group. The absence of this tissue makes the lesion much more susceptible to infections and slows the onset of the remodeling phase, making it difficult for the lesion to contract and, therefore, to close.

It was observed that patients who did not present a significant decrease in the lesion area by the 18th week were found to have nutritional alterations and did not correctly follow the indicated diet for patients with DM. In addition, they did not adequately follow the proposed rest plan to reduce local pressure, and many of them became ambulatory too early, making the tissue repair process even more difficult. On the other hand, patients who fully or partially followed the guidelines showed a good response to treatment.

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5 CONCLUSIONS

The present study provides evidence that laser application accelerates the cicatrization process in ulcers caused by minor amputations in patients with DM, since it led to the early arising of granulation tissue even with high values of capillary glycemia. This confirms that even with glycemic index values as high as 225 mg/dL there can still be complete closure of the ulcer. In addition, it was possible to determine the optimal number of sessions for the greatest likelihood of total closure: once a week for a maximum of 18 weeks.

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