

Effect of the cream based on *Croton lechleri* Müll. Arg. in the treatment of diabetic patients' ulcers: a case study

Efeito da pomada à base de *Croton lechleri* Müll. Arg. no tratamento de úlceras de pacientes diabéticos: um estudo de caso

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ABSTRACT

*Ulcers development in lower limbs is a potential complication known in Diabetes mellitus patients. Conventional medicines frequently do not show desired efficacy, resulting in adverse effects. In this sense, the seek for natural treatments, effective, easy to obtain and handle and at the same time with low cost, becomes a therapeutic alternative for the ulcers treatment. The aim of this study was to verify the healing potential of a cream made with *Croton lechleri* Müll.Arg. sap, when applied in diabetic patients' ulcers. It is concluded that the cream made with *Croton lechleri* Müll.Arg. sap showed healing potential, however, several variables should be evaluated and considered simultaneously, since diabetes is a multifactorial disease.*

Keywords

Diabetes mellitus. Wounds. Ointment. Dragon's blood.

RESUMO

O desenvolvimento de úlceras nos membros inferiores é uma complicação potencial conhecida em pacientes com diabetes mellitus. Medicamentos convencionais frequentemente não mostram a eficácia desejada, resultando em efeitos adversos. Nesse sentido, a busca por tratamentos naturais, eficazes, de fácil obtenção e manuseio e, ao mesmo tempo, com baixo custo, torna-se uma alternativa terapêutica para o tratamento das úlceras. O objetivo deste estudo foi verificar o potencial cicatrizante de uma pomada feita com a seiva de *Croton lechleri* Müll.Arg., quando aplicada em pacientes com diabetes mellitus. Conclui-se que a pomada à base de seiva de *Croton lechleri* apresentou potencial curativo, no entanto, diversas variáveis devem ser avaliadas e consideradas simultaneamente, pois o diabetes é uma doença multifatorial.

Palavras-chave

Diabetes mellitus. Feridas. Pomada. Sangue de dragão

Como você deve citar?

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1 INTRODUCTION

Diabetes Mellitus (DM) is actually considered a global epidemic, because it is one of the main chronic diseases, responsible for high rates of morbidity and mortality. Its most prevalent form is Type 2 (T2DM), which concentrates approximately 90% of all cases. According to the World Health Organization (WHO, 1999), the number of people affected by the disease tends to increase in the coming years. The global estimate for the future is that, in 2030, 366 million people will have the disease (LI et al., 2012).

The main clinical manifestations found in patients with T2DM are characterized by metabolic disorders, such as hyperglycemia, and complications of the clinical outcome including neuropathic, visual and mainly vascular disorders, such as ulcers (RAMAN et al., 2012). Researches indicate that diabetic patients have up to 25% of chance of developing an ulcer on the lower limbs (SINGH; ARMSTRONG; LIPSKY, 2005; FERNANDO et al., 2015) and the annual incidence of foot-diabetic ulcers is approximately 3% in patients (SARINNAPAKORN et al., 2016).

Once an ulcer has developed, there is an increased risk of wound progression that can lead to amputation of the affected limb. Diabetic ulceration has been indicated to precede amputation in up to 85% of cases (SARINNAPAKORN et al., 2016). At least 40% of the amputations in diabetic patients can be prevented with a team approach to wound treatment and subsequent healing (VAN NETTEN et al., 2016). The investment in wound care, combined with the loss of productivity of individuals affected and the families that care for them and their quality of life, entails a great cost to society (AGENCY, 2006; FIFE; WEITR, 2007).

It is worth to mention that conventional therapeutic agents have generally inadequate efficacy, with an incidence of serious adverse effects (STRAND; KIMBERLY; ISAACS, 2007). In this sense, medicinal plants have been used since the dawn of civilization with studies proving their efficacy and potential to promote healing and prevent infection, with minimal side effects. Thus, herbal treatment may be an alternative strategy in the healing process of ulcers (BUDOVSKY; YARMOLINSKY; BEN-SHABAT, 2015).

In this context, together with the fact that Brazil has a large plant biodiversity, the Ministry of Health (MS in Portuguese) in February 2009 promulgated the National Relation of Medicinal Plants of Interest to SUS (RENISUS in Portuguese) (MARMITT et al., 2016), composed of 71 native plant species, originated from different biomes of the country, which includes the genus *Croton*, represented by two species, *Croton cajucara* Benth and *Croton zehntneri* Pax & K.Hoffm. The sap of *Croton lechleri* Müll. Arg (Euphorbiaceae) species may be an alternative for the treatment of ulcers in diabetics, since it is already known to have a healing effect (CAI et al., 1991; CAI; CHEN; PHILLIPSON, 1993; CHEN; CAI; PHILLIPSON, 1994; PIETERS et al., 1992), antihemorrhagic (CAI et al., 1991; CAI; CHEN; PHILLIPSON, 1993), antimicrobial (CHEN; CAI; PHILLIPSON, 1994) and anti-inflammatory (RISCO, 2003).

Thus, the aim of this study was to verify the healing potential of a cream made with a sap extracted from the stem of the dragon-blood tree (*C. lechleri*), applied topically to ulcers of diabetics' lower limbs.

2 MATERIAL AND METHODS

2.1 Overview

A total of four individuals with T2DM, all leaving in Lajeado, a city in Rio Grande do Sul state, Brazil, who had chronic ulcer in one of the lower limbs, were analyzed. *C. lechleri*® sap cream was applied daily

for three months, being the assessment of lesion retraction as well as plantar pressure performed once a week during the three months.

2.2 Sample and bioethical aspects

Seventy-five diabetic people enrolled in the Primary Care Information System (SIAB in Portuguese) from Lajeado, who were older than 45 years and had at least one chronic ulcer in the lower limb already treated or with undergoing treatment, with no signs of healing for more than three months were randomly selected.

Anamnesis and physical examination were performed individually in each patient previously to the beginning of the treatment by a team composed by a nurse and a biologist. Individuals that after medical screening were not given the cream-based treatment due to the lesion type were excluded from the sample. Out of a total of 12 people who fit the inclusion criteria, only four female subjects accepted to participate in the study and were named by patients I, II, III and IV.

All patients involved in this study signed the Free and Informed Consent Form (TCLE in Portuguese), according to the Resolution number 466/2012 approved by the Plenary of the National Health Council (CNS in Portuguese) regarding research and testing involving human beings. Likewise, the study was approved by the Research Ethics Committee (COEP in Portuguese) at Universidade do Vale do Taquari, - Univates -, (number 688.474), as well as by the Municipality Health Department (SESA in Portuguese).

2.3 Treatment

Debridement with clamp aid was performed on necrotic tissues. Afterwards, the ulcers were hygienized with 0.9% saline solution, followed by application of cream made with *C. lechleri*, and were protected with gauze and bandages till the next procedure.

Daily curative bandage with the applied treatment were done during a three month period. The daily amount of applied cream varied according to the size of the lesion and the individual need of each patient. *C. lechleri*® cream consists of 10% *C. Lechleri* sap extracted from latex, 1% vitamin E, 10% lanolin (10 g solid vaseline). Alkaloids, diterpene, and phenolic compounds are the main active compounds found in *C. lechleri* latex. Taspine is an alkaloid that assists in the healing of cellular tissues (AZEVEDO et al., 2008). In addition to taspine, other compounds present in sap, such as proanthocyanidins, may be involved in the exposed actions (RISCO et al., 2003). Proanthocyanidin SP-303 is related to the control of diarrhea (FISCHER et al., 2004). The sap has antioxidant and immunomodulatory properties (RISCO et al., 2003). Phenolic compounds, under certain conditions, may promote DNA damage, therefore studies are indicated to ensure the use of this sap (ROSSI et al., 2003).

2.4 Morphometric analysis

The lesions were photographed on days 0, 21, 49, 77 and 91 of the study (using a Sony semi-professional Camera), with standardized way of shooting and distance of 30 cm. The images obtained were analyzed macroscopically with AutoCAD® software, through the delimitation of the lesion areas. Subsequently, the calculation of the areas was done in square centimeters (cm²), evaluating the contraction of the lesions, in duplicate. The initial evaluation at day 0 was considered as control of each patient. All images were examined by a single blind investigator. The characterization of the lesions followed the classification of Wagner (LEVIN, 1998).

2.5 Baropodometer

Through the static baropodometry examination it was possible to analyze qualitatively and quantitatively the weight distribution exerted by patients in the lower limbs, as well as to verify the center of pressure exerted by them.

On the first day of treatment (day 0) as well as on days 14, 28, 42 and 56 during treatment, the baropodometer analysis (Arkipelago, *Footwork Pro*, AM CUBE, France) was performed in duplicate.

All participants were previously oriented to remain in a stand up position, with minimal or no movement, with bipodal support, free support base, arms along the body and with a single vision direction during the 10 seconds they remained on the electronic platform.

In order to investigate the relationship between the body and the support site, it was possible to verify the standard posture of each patient and how they oscillated in the posture and other variables. After stabilizing the baropodometer, the average pressure (kpa), average maximum pressure (kpa), surface (cm²), stabilometry (cm²) and maximum pressure (%) were measured for both lower limbs. Data were analyzed with FootWork Pro software version 3.7.

2.6 Statistical analysis

A database was structured, and the results were statistically analyzed using GraphPad Prism® (version 5.0 GraphPad Software, Inc.) and expressed as average \pm EPM, using Analysis of Variance (ANOVA). Values of $p \leq 0.05$ were considered significant.

3 RESULTS AND DISCUSSION

The prevalence of T2DM in Lajeado is around 3%, below the national average that is 6.2% (BRASIL, 2015), occurring frequently in elderly, hypertensive and literate women (MORESCHI et al., 2015). The low number of patients included in this study can be justified by the fact that, after medical screening and due to the lesion type, other possible patients did not receive an orientation to use the cream as treatment. The sample number was a limitation factor for the research, once in order to detect significant differences in the lesions contractions the minimum sample expected to the variance of the lesion sizes should be 55 patients.

Through the evaluation of the feet performed previously to the beginning and in the end of the study, it was observed that none of the participants carried out foot hygiene and skin hydration adequately. Regarding the characteristics of the lesions (Table 1), all patients presented liquefaction necrosis, without smell, with serous appearance and moderate exudation (patient I and III) or mild exudation (patient II and IV). Perilesional skin was dehydrated in all patients.

Table 1. Characteristics of the patients' lesions.

Patient I	Lesion involving the foot dorsum and malleolus of the left lower limb, with irregular borders and presence of hyperpigmentation and hyperemia areas.
Patient II	Injury involving the middle portion of the right lower limb, with irregular borders. Perilesional skin, with lipodermosclerosis.
Patient III	Injury in the internal malleolus of the left lower limb, with oval and irregular shape, presence of varicose veins in the lesion bed and granulation tissue. Perilesional skin was macerated, hyperemic, scaly, and swollen.
Patient IV	Flat lesion, in the anteromedial portion of the left lower limb, irregular shape, with discreet maceration of edges. Perilesional skin with hyperemic aspect.

Source: Author.

According to Wagner classification (LEVIN, 1998), patients I, II e III had grade 2 ulcers (Figures 1, 2 and 3), and the patient 4 was considered grade 1 (Figure 4).

Figure 1. Appearance of the patient I wound



A: at the beginning of the treatment with the cream (23/July/14, the lesion measure was 16 cm); **B:** at the end (23/October/2014, the lesion measure was 14 cm).

Source: Author

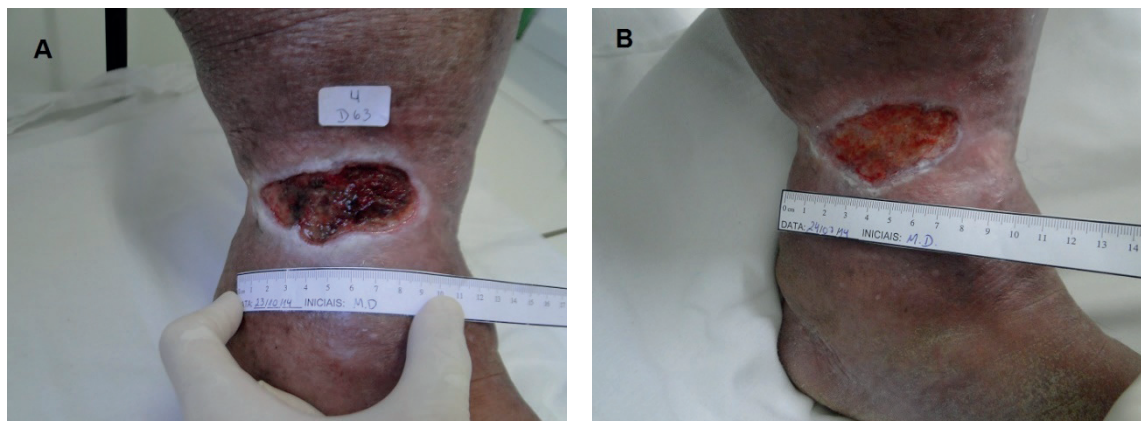
Figure 2. Appearance of the patient II wound.



A: at the beginning of treatment with the cream (23/July/14, the lesion measure was 12 cm); **B:** at the end (23/October/2014, the lesion reduced to 10.5 cm).

Source: Author.

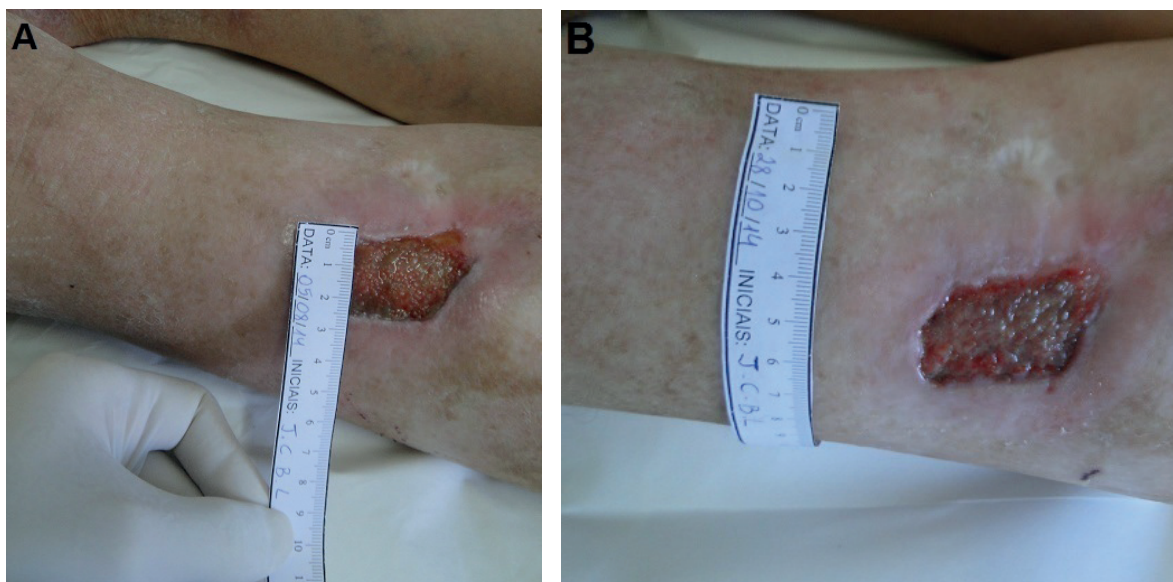
Figure 3. Appearance of the patient III wound.



A: at the beginning of treatment with the cream (23/July/14, the lesion measure was 8 cm); **B:** at the end (23/October/2014, the lesion increased to 9 cm).

Source. Author.

Figure 4. Appearance of the patient IV wound.

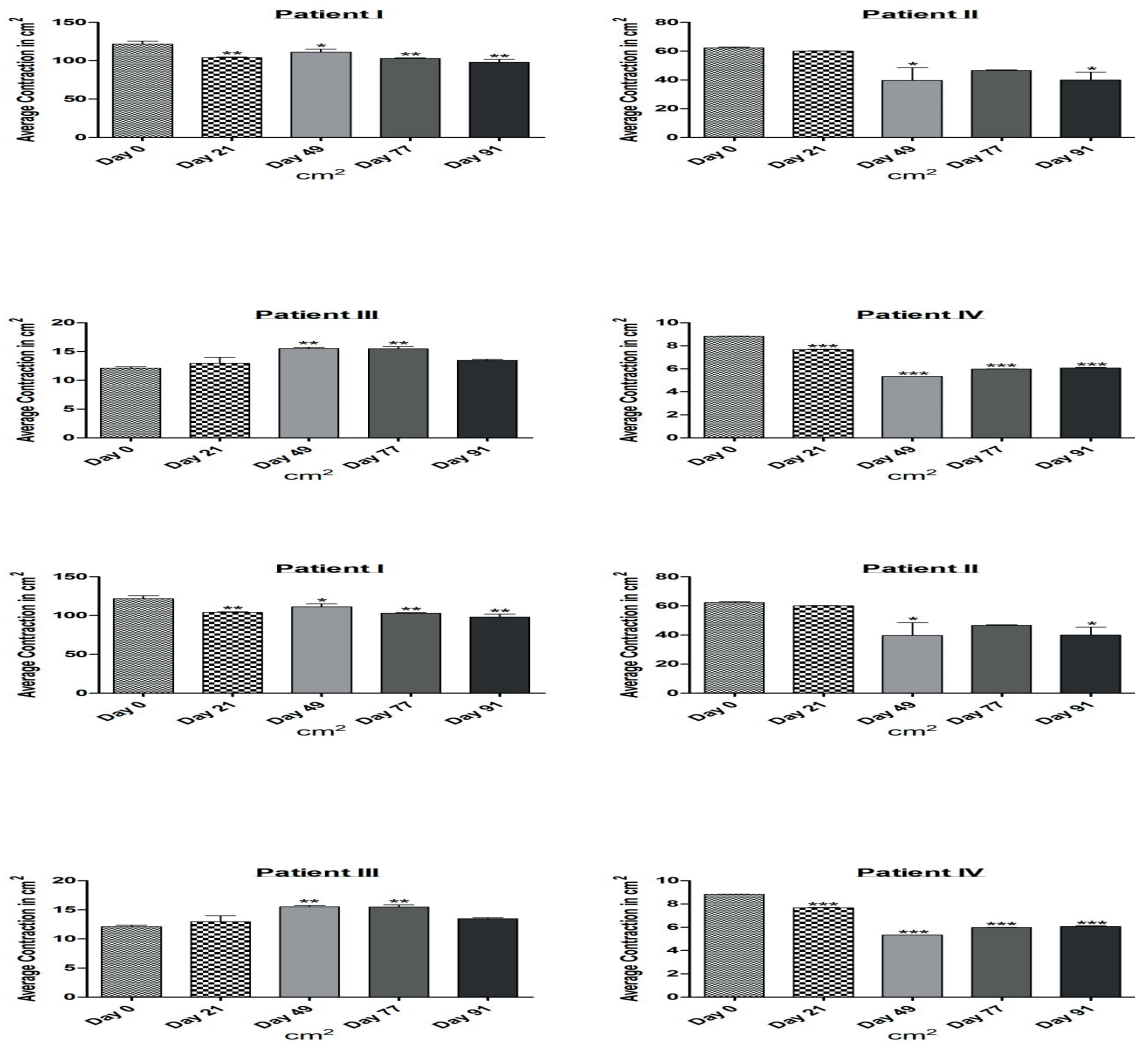


A: at the beginning of treatment with the cream (23/July/14, the lesion measure was 2,7 cm); **B:** at the end (23/October/2014, the lesion reduced to 2,5 cm).

Source. Author.

Among the evaluated patients, only patient III had an increase in the lesion size (plus 1.36 cm²), which can be explained by the fact that this participant presented a local infection during the investigation, causing her lesion to increase considerably (11.23%). In the other patients, a contraction was observed in the size of the lesions, and this reduction was more evident in patient II, 22.39 cm² (35.93% compared to the control, day 0). Patients I (23.51 cm² - 19.34%) and IV (2.76 cm² - 31.24%) also presented a reduction in ulcer size compared to the control, day 0 (Figure 5).

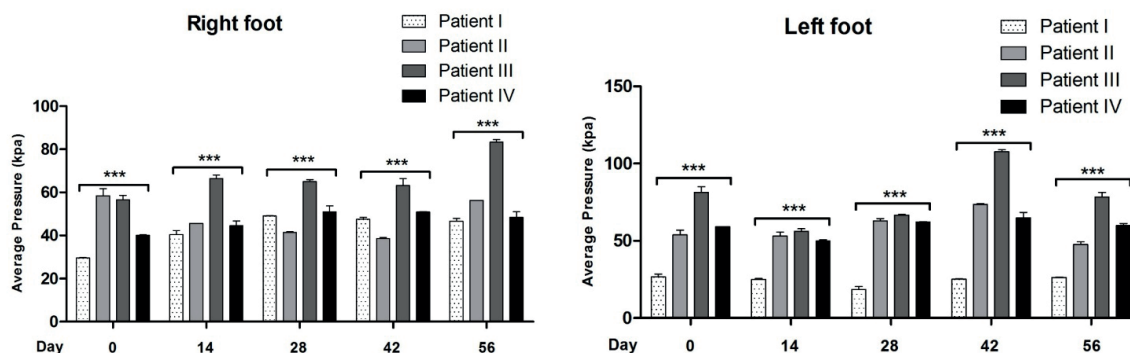
Figure 5. Average level of contraction of the patients' lesions in cm². Data presented as average ± standard error for two distinct measurements. ANOVA followed by Dunnet. *** p <0.05; ** p <0.01; *** p <0.001, compared to the control (day 0).



Source. Author.

The early identification of pressure points (redness, blistering, callosities), which can lead to subsequent development of lesions in the plantar region of the lower limbs can be avoided through the use of appropriate treatments (CAIAFA et al., 2011). Analyzing the data of static baropodometry tests, which showed the distribution of the patients' weight in the lower limbs, no significant difference was observed in the pressure area before and after the use of the cream, in both feet of the patients (Figure 6). In addition, when considering only the foot affected by the ulcer (patients I, III and IV - left foot, and patient II - right foot), there was no significant difference when comparing before and after the treatment period (56 days).

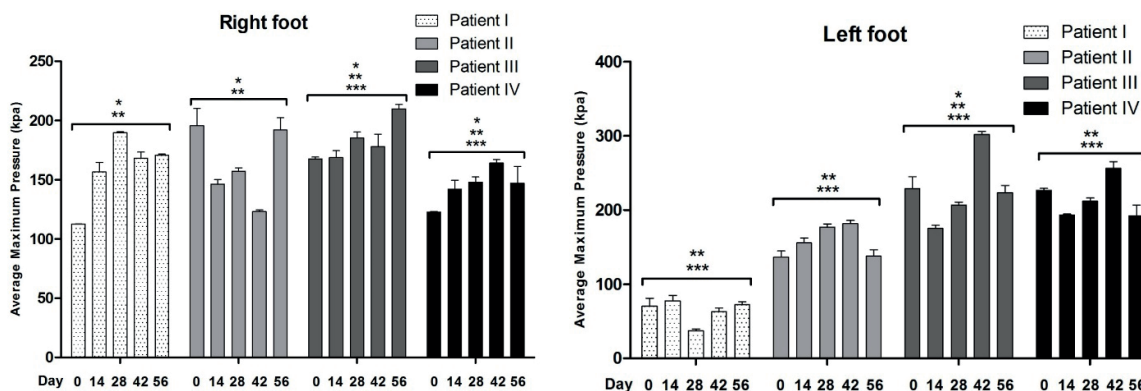
Figure 6. Average left and right plantar patients pressure estimated in kilopascal (kPa). Data presented as average \pm standard error for two distinct measurements. ANOVA followed by Bonferroni. *** $p < 0.05$, compared to the other patients during the evaluated days.



Source. Author.

Researches show that the peak of greater plantar pressure in normal individuals occurs in the posterior region of the foot, in static situation (CAVANAGH; RODGERS; IIBOSHI, 1987; TRIBASTONE, 2001). Others still indicate that high plantar pressure is the main ulcers causal factor in patients with DM (VEVES et al., 1992; BOULTON et al., 2005; MAYFIELD et al., 1998). Regarding the average of the maximum pressure (kpa), it was observed that there was oscillation in the maximum pressure of the patients during the period of evaluated treatment (Figure 7). When comparing day 0 and day 56, it is possible to observe a decrease in the maximum left foot pressure of patient IV (226.61- 192.24 kpa). This result can be justified because this lesion is classified as grade 1 by Wagner's classification. On the right foot (non ulcerated) of patient I (112.6 - 170.6 kpa), III (167.8 - 209.8 kpa) and IV (122.6 - 147.2 kpa), there was an increase in maximum pressure average, a signal of possible ulcers development in these previously unaffected limbs.

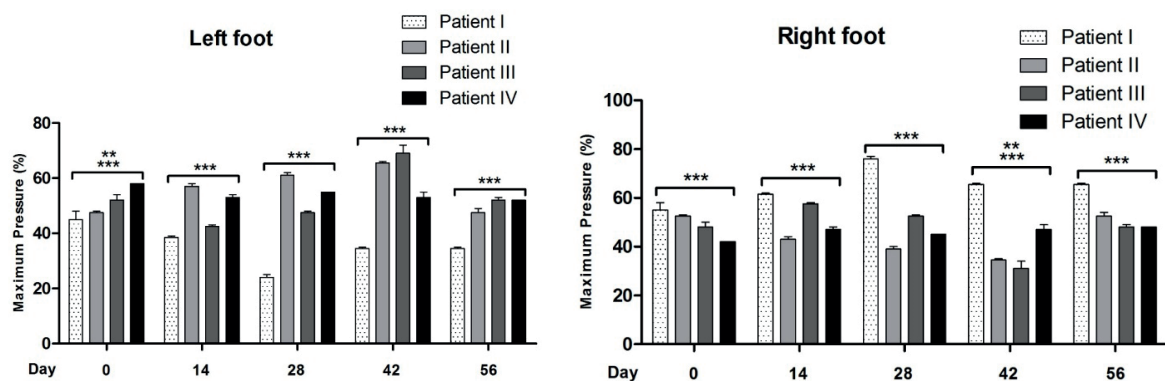
Figure 7. Average of maximal plantar pressure (left foot and right foot) of patients estimated in kilopascal (kPa). Data presented as average \pm standard error for two distinct measurements. ANOVA followed by Bonferroni. *** $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$, in relation to each patient during the evaluated days.



Source. Author.

It is described that the high rate of ulcerations in diabetic feet is caused by the increase in plantar pressure peaks, detected by researches through baropodometer (BOULTON et al., 2005; DIAS et al., 1999). The evaluation of the plantar weight distribution is necessary for patients who have an ulceration risk in the lower limbs and consequent prescription of shoes with a preventive purpose (VEVES et al., 1992). In patients I and IV, the percentage of maximal pressure during the treatment period decreased in the left foot (ulcerated foot) and increased in the right foot (Figure 8) during the treatment, once both patients had lesion in the left foot, and consequently, due to the pain, they pressed more the healthy foot (right).

Figure 8. Average of maximal plantar pressure (left and right foot) of patients. Data presented as average \pm standard error for two distinct measurements. ANOVA followed by Bonferroni. *** p <0.05; ** p <0.01; *** p <0.001, in relation to each patient during the evaluated days.



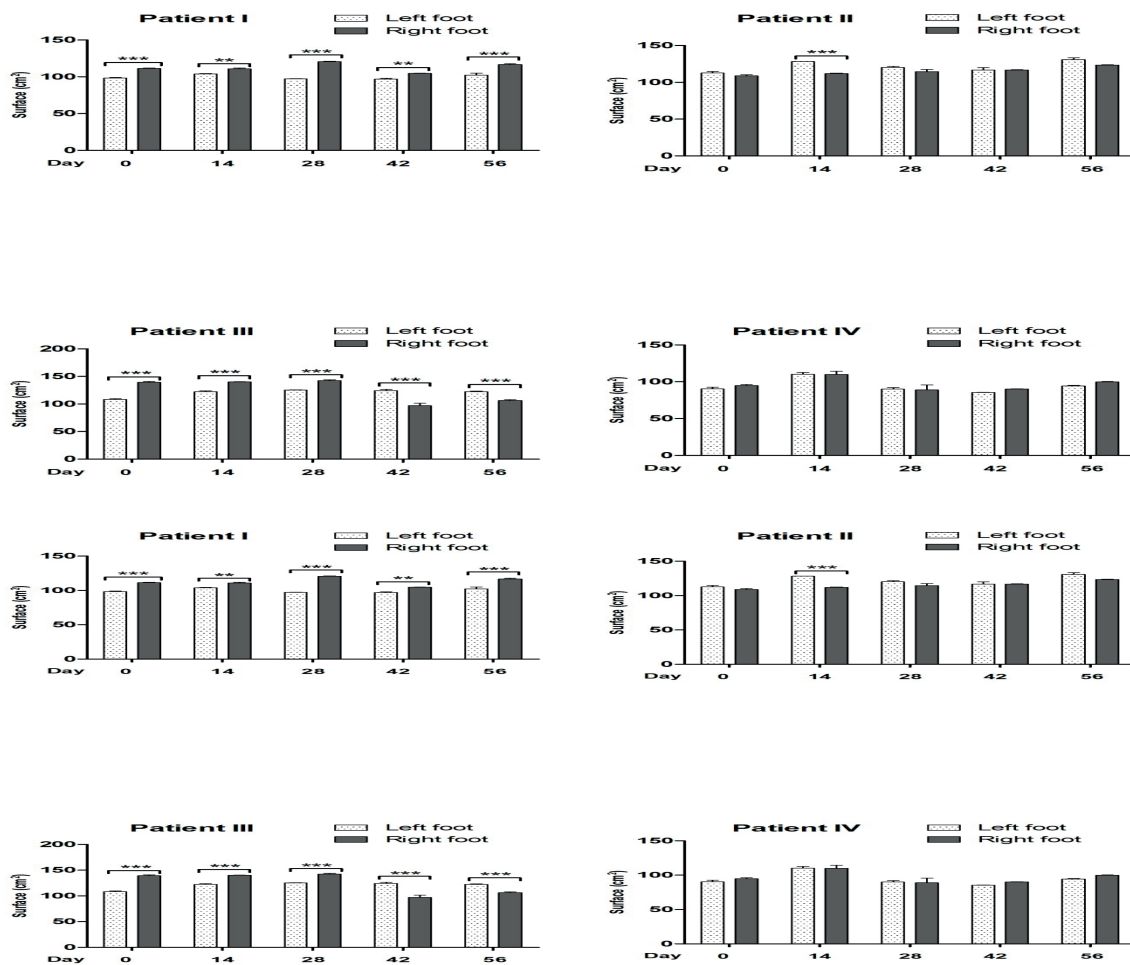
Source. Author.

Patient I lesion extension was to the underside of the foot, which possibly generated pain when establishing pressure. In addition, ulcers debridement was performed weekly and it could have generated pain and consequently discomfort while stepping and supporting the foot.

Due to clamp debridement, the tissue around the wound was manipulated, stimulating the proliferation of proinflammatory cytokines at the injured site, inducing tissue contraction. The stages that aim to achieve the tissue repair as a consequence of a damage are based on: aggregation, platelet activation and subsequent degranulation; inflammatory activity; matrix deposition; collagen synthesis; contraction of the injured site; epithelization; and remodeling (EVERTS et al., 2006).

Regarding the plantar surface dimension (cm²), there is a small increase of the surface (Figure 9) in the foot affected by the ulcer (patient I, III and IV - left foot and patient II - right foot). When walking, diabetics increase the contact with the soil in certain areas and decrease the contact in opposite areas of the plantar surface. These changes, associated with loss of sensitivity, detract the biomechanics of the feet, allowing an increase in plantar pressure (CAVANAGH; RODGERS; IIBOSHI, 1987; VEVES et al., 1992). However, static baropodometry data (Figure 6) showed no difference in the area of plantar pressure before and after the use of the cream, which in patients I, II and IV may be related to the contraction of the lesion area, once in diabetic patients, the healing process is fundamental and there is a consequent control of the infection (SCOTTISH INTERCOLLEGIATE GUIDELINES NETWORK, 1997).

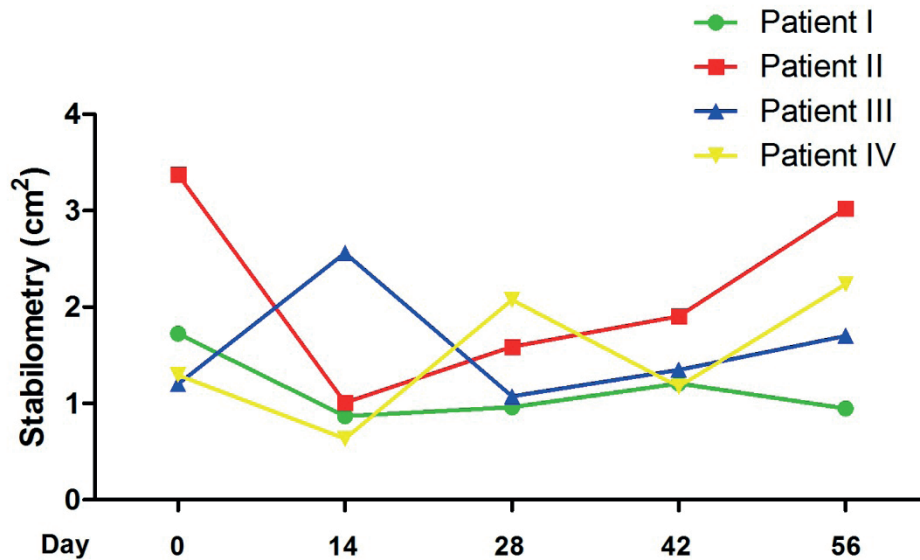
Figure 9. Plantar surface (cm²) of the patients. Data presented as average ± standard error for two distinct measurements. ANOVA followed by Bonferroni. *** p <0.05; ** p <0.01, in relation to both feet during the evaluated days.



Source. Author.

The stabilometry evaluated the balance in the orthostatic posture, which consists in the quantification of the anteroposterior and lateral oscillations of the body, while the individual remains standing on a force platform (OLIVEIRA, 1996). During this trial, through the comparison of the first and the last day of treatment, patients I (1,725 - 0.9475 cm²) and II (3.3745 - 3.0245 cm²) had a decrease in the stabilometric rate, while patients III (1,202 - 1.7025 cm²) and IV (1.2945-2.239 cm²), showed increase in this rate (Figure 10). The result in patients III and IV may be related to the plantar surface rate (Figure 9), once a small surface increase was observed in the foot affected by the ulcer (patients III and IV - left foot). Research has shown that elevated glycemic levels may contribute to ototoxicity, a fact that explains the difficulty of balancing, which can be affected not only by the plantar support but also by vestibular disorders that diabetics may eventually have (GARCIA-QUIROGA et al., 1978; TADA, 1997).

Figure 10. Stabilometry analysis of patients (cm²). Data presented as average \pm standard error for two different measurements. ANOVA followed by Bonferroni. *** p <0.05; ** p <0.01, in relation to both feet during the evaluated days.



Source. Author.

There is still low number of prescriptions and use of phytotherapics in Vale do Taquari, region where Lajeado city is located, including for the DM control (REMPEL et al., 2010), even after a sequence of analyzes carried out by the research group with diabetic individuals at Universidade do Vale do Taquari in Lajeado (BENINI et al., 2009); BENINI et al., 2010; HELLER et al., 2013; MARMITT et al., 2015; MIRALLES; BOSCO; REMPEL, 2011; MORAES et al., 2010; MORESCHI; REMPEL; CARRENO, 2015; NAVA et al., 2015; POZZOBON et al., 2014; POZZOBON et al., 2012; REMPEL et al., 2015; REMPEL et al., 2010; RODRIGUES et al., 2010; VANZETTO et al., 2011; WOLLINGER et al., 2015; ZACCARON et al., 2014). It should be emphasized that studies indicate healing potential for the sap of *C. lechleri* (CAY et al., 1991; CAI; CHEN; PHILLIPSON, 1993; CHEN; CAI; PHILLIPSON, 1994; PIETERS et al., 1992; SILVA et al., 2019).

The study has limitations since the inclusion criteria was people over 45 years old who had at least one chronic ulcer in the lower limb which had already been treated or under treatment and without evidence of healing for more than three months, resulting in a sample of four patients.

There was no control group, however, the four patients under treatment have had the ulcers for more than three months and were undergoing treatment, before the experiment, with Essential Fatty Acids (EFA) as oil (participants I and II) with vaginal gel with metronidazole (participant III) and participant IV treated with neomycin.

4 CONCLUSION

When the cream was used continuously, the lesions retracted in three of the four patients analyzed. Considering only the affected ulcer foot, there was no significant difference in static baropodometry examinations, comparing before and after the treatment period with *C. lechleri* cream. The results can be useful as a subsidy to assist primary care providers, in the determination of adequate approaches for the treatment of ulcers in diabetic patients.

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