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Effectiveness of two bundles in venous leg ulcer healing: A randomized controlled trial

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The objective of this study was to compare the effectiveness of 2 bundles in venous leg ulcer healing.

This study is a open, randomized, controlled clinical trial with parallel treatment, 1:1 allocation rate, and 24-week follow-up. Twenty-eight patients with venous leg ulcers of the lower limbs were allocated to 2 groups: group A (n = 14) and group B (n = 14). The mean age of the participants was 59.67 ± 11.95 years, and the mean ulcer surface area was 29.32 (±98.43) cm^2. The primary outcome was ulcer healing. Secondary outcomes were wound area reduction rate, Pressure Ulcer Scale of Healing (PUSH) scores, and the presence and intensity of pain before, during and after dressing change. Two different bundles were applied in 2 phases to the randomized groups. All participants engaged in an educational activity, performed exercises, rested with legs elevated, received oral nutrition supplementation (Cubitan; Danone Nutricia), and had their ulcers cleaned with warm saline solution and biguanide polyhexanide solution (Prontosan; B. Braun). Topical therapy in the first phase was papain 2% or 4% for group A and 2% hydrogel for group B. Both groups received single-layer elastic compression therapy (SurePress; ConvaTec). In the second phase, group A received compression therapy with Unna boot (Viscopaste; Smith-Nephew) as the primary dressing, while group B received a cellulose membrane (Membracel; Vuelo Pharma) followed by the Unna boot (Viscopaste; Smith-Nephew).In group A, 71.42% of the ulcers healed; in group B, the figure was 64.28%. Wound area, PUSH scores, and the occurrence and intensity of pain decreased significantly and equivalently in groups A and B.Both bundles are effective in the treatment of venous leg ulcers and pain relief. (J Vasc Nurs 2019;37:232-245)

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INTRODUCTION

Venous leg ulcers (VLUs) are defined as wounds that develop on the leg, foot, or on an area affected by venous hypertension.[1] They are long-lasting sores,[2] which are also considered complex[3] and hard-to-heal wounds.[4]

These ulcers are a public health problem and cause frequent pain, edema, especially in the region of the ankles and feet, loss of mobility, and impairment of activities of daily living, labor, and leisure.[5] Symptoms such as pain, odor, and exudate can affect many aspects of the lives of people with VLU, such as sleep and relationships, thus negatively influencing quality of life and increasing the affliction experienced by these people.[6]

Study conducted in the United Kingdom between 2015 and 2016 found that the mean cost of wound care over 12 months was an estimated £7,600 per VLU, and the cost of managing an unhealed VLU increases 4 to 5 times in comparison to that of managing a healed VLU.[4] In Australia, a study that sought to identify VLU treatment costs in a specialized clinic, a hospital and 2 wound treatment services, from 2016 to 2017, found that the mean weekly cost was AUD 214.61 in community care services and AUD 294.72 in specialized services. Although the costs were higher in the latter, healing time was less.[7] Based on 4 randomized clinical studies using the Markov model, the study estimated and compared the costs of venous ulcer treatment with iodine together with multilayer compression therapy and the costs of standard treatment, which included multilayer

compression therapy and debridement, when necessary.[8] The costs were calculated in USD (based on 2014).[8] Iodine treatment together with multilayer compression therapy was USD 7.259 during one year compared to USD 7.901 for standard treatment.[8] Using the combined treatment, as opposed to the standard treatment, resulted in savings of USD 643 per patient.[8]

The treatment for VLU is multidimensional. It includes educational interventions,[9] rest with elevation of the affected lower limb, physical exercise,[10,11] compression therapy,[12] nutrition,[13] perilesional skin care,[14] and topical therapy.[15]

However, studies usually test 1 type of treatment or a combination of 2 or 3 types.[16–20] Some studies clearly indicate the combinations used,[10,11,16–18] while others only mention the standard treatment, leaving doubts about the use of combined therapies.[19,21,22]

Systematic reviews indicate that there is no "gold standard" topical therapy for treating VLU, and whatever the topical therapy chosen, it must be combined with compression therapy to promote healing.[15,23]

Using different protocols, consisting of a single topical therapy[17,18,24] or compression therapy[17] to combinations of 3 or 4 therapies,[19,25] the studies carried out so far report healing rates between 0%[18] and 65%[20] in a 12-week follow-up, suggesting that the most positive results were obtained in investigations that applied combinations of a certain number of therapies. The examined outcomes focus on the complete healing of the wound, but it is also important to understand the effect of therapies on pain handling.[26,27] In this regard, the greatest contribution has originated from studies that associate exercises using the legs with compression therapy.[10,28,29] There are different exercises[16,28,30] and compression therapies[31] that can be combined. A gold standard exercise program has not been defined, and although multilayer compression therapy offers a more effective action than other methods, all the procedures show positive effects and are recommended for the treatment of VLU.[31]

Although it is known that people with this type of wound show a higher risk of malnutrition in comparison with people who do not have the ulcer,[32] there is no evidence proving the effectiveness of nutritional supplementation in the improvement of healing in the affected population.[33] However, the daily consumption of 3 doses of a nutritional supplement enriched with immunonutrients led to positive results in the healing of pressure injury in adults and elderly people, even those who did not have malnutrition,[34–37] indicating the potential of this therapy to treat patients with VLU.

Also, research on wound healing shows that warm saline rinses should be used to clean the wounds[38] because hypothermia may occur during dressing changes,[39] affecting tissue repair.[40] Despite this recommendation, studies do not mention the use of this procedure.[10,11,16,19–22]

In this sense, it is important to test the effectiveness of bundles composed of a set of therapies combined to obtain an expected outcome.[41] As yet, no bundles for the treatment of VLU are available.

Testing bundles can generate knowledge for evidence-based practice and provide support for future recommendation in regard to the treatment of VLU aimed at the proper management of pain, a decrease in the time of healing, and an improvement in the venous circulation of the legs.

In light of the multidimensionality of VLU treatment, the objective of this study is to compare the effectiveness of 2 bundles to promote wound healing and pain relief on venous ulcers over a 24-week follow-up period.

MATERIALS AND METHODS

Design and location of the study

This is an open, randomized, controlled, comparative trial of 2 multidimensional bundles, with a 1:1 allocation ratio. This study was prepared according to the CONSORT, 2010 guidelines.[42]

The study was conducted in a wound dressing room within a public health unit in a large city in the Central-West region of Brazil, from June 2016 to March 2018.

Study participants and sample

A total of 118 people were evaluated for eligibility. The inclusion criteria were the presence of VLU (diagnosed by a medical professional using vascular echocardiography of the lower limbs or from clinical signs of impaired venous circulation); ankle circumference greater than 18 centimeters; age equal to or greater than 18 years; and a Mini-Mental State Examination score compatible with the education level.[43] Individuals (n = 82) were excluded if they presented hepatopathy, nephropathy, arterial pulse undetectable by manual Doppler, impeding the verification of the Ankle-Brachial Index (ABI), ABI <0.8 or >1.3, intermittent claudication when walking 250 meters or less, severe auditory or visual impairment, or if the affected limb went pale when elevated. Three people declined to participate in the study.

The convenience sample was composed of successive entries.

Randomization and blinding

Stratified randomization was applied according to VLU area (area < 20 cm^2; area ≥ 20 and < 60 cm^2; area ≥ 60 and < 90 cm^2 and area ≥ 90 cm^2). The participants were allocated into 2 treatment groups (group A and group B). To perform randomization, the Research Randomizer program (https://www.randomizer.org) was used according to the tutorial. Blinding was used in the randomization of participants and in the calculation and analysis of ulcer areas.

Instruments for data collection and evaluation

An instrument containing questions on social and demographic data (gender, age, level of education, years of education, and income) and exclusion-criteria diseases (liver and kidney diseases) was developed. A cognitive assessment was also performed by means of the Mini-Mental State Examination[44] to evaluate the eligibility criteria.

The outcomes were evaluated at baseline and then every week until complete healing or at the end of the 24-week follow-up period. Ulcers were evaluated every day for adverse events (clinical signs of deterioration, infection, and signs of allergy to the products used).

The data collected at baseline through the interview and physical examination were social and demographic data (civil status, occupation, and per capita income); self-reported medical diagnosis and ongoing treatment of diabetes, thyroid diseases, systemic arterial hypertension, pulmonary and cardiac diseases, problems in venous and arterial circulation, availability of vascular pulse in the lower limbs by Doppler, and history of deep vein thrombosis; clinical conditions of the lower limbs (varicose veins, reticular veins, telangiectasias,

hemosiderosis, lipodermatosclerosis, edema, perimeter of the ankle and calf, ABI); smoking and alcohol consumption; clinical conditions of the ulcers, including the healing state measured by the Pressure Ulcer Scale of Healing (PUSH)[45]; evaluation of ulcer pain during dressing change by a numeric pain scale,[46] planigraphy, and photography of ulcers; and venous blood collection for the biochemical measurement of glucose.

The software Image J version 1.51j8 was used to calculate the ulcer area.

Data on the clinical conditions of ulcers and pain were collected daily to monitor possible adverse reactions to treatment, as well as the general condition of the participant. Data on the outcomes of interest were collected weekly: ulcer healing, presence and intensity of ulcer pain during a dressing change, planigraphy, and wound photography.

Intervention

VLU was defined as a wound in the legs, associated with clinical signs such as edema, varicose veins, hemosiderosis, telangiectasias, reticular veins, white atrophy, and lipodermatosclerosis,[47] without any signs of arterial impairment, with ABI $\geq$ 0.8 a $\leq$ 1.3,[48] tibial posterior and pedis pulses palpable or detectable by manual doppler and the absence of intermittent claudication during ambulation.[47]

The 2 treatment bundles comprised educational intervention, lower limbs physical exercise, periods of rest with the leg elevated, and oral nutritional supplementation, combined with topical therapy associated with compression therapy for each group. Through stratified randomization, different topical therapies were applied to groups A and B.

The educational intervention consisted of a self-care manual containing guidelines on venous insufficiency, risk factors for VLU, dressing protection during showering, drinking 8 glasses of water per day, exercises, resting for 30 minutes with legs elevated 3 times a day, and daily walks.

The nutritional supplement (Cubitan; Danone Nutricia) was offered to the participants for 4 weeks, based on the initial wound area. People with ulcers $\leq$ 20 cm^2 received 2 vials a day, and those with wounds > 20 cm^2 received 3 vials a day. All participants received a booklet with healthy-eating guidelines based on the recommendations of the Brazilian Ministry of Health[49] and were instructed by a nutritionist or nurse on how to use the supplement.

Taking into account that there is not a protocol to calculate the dosage and that the clinical studies available used this supplement in people with pressure injury administering 3 daily doses,[36,37] the supplementation for the patients examined in the present study was determined based on the wound area.

The leg exercises were prescribed by a physical therapist, along with the nurses, and based on the available kinesiotherapeutic guidelines based on scientific evidence.[10,28–30] The objectives of these exercises were to increase the mobility of the ankle joint, to stimulate muscle pump, promoting venous circulation, and increase strength and muscular endurance. The exercises consisted of 1) (warm-up) in an orthostatic position with support, with leg extended or semiextended, ankle rotations for 30 seconds, in both directions, one foot at a time; 2) in an orthostatic position with support, simultaneous heel lifts (15 repetitions); 3) in a sitting position, resisted ankle plantarflexion, with an elastic band around the foot held in the hands, providing moderate resistance to movement (15 repetitions); 4) in a sitting position, triceps surae stretch with dorsiflexion using an elastic band for 15 seconds (3 repetitions); 5) in dorsal decubitus with 90° flexion of the hip and knee, lymphatic decongestive maximal ankle dorsiflexion, alternating between the lower limbs (15 repetitions with progression to 25); and 6) rotational movements of the ankles for 30 seconds each side in a sitting or lying position. The protocol consisted of 3 exercises sessions a day, with 1 under the supervision of the research team when the patient came for their dressing change.

Participants were also advised to take 1,000 to 1,500 meters daily walks in the morning or afternoon and to rest with legs elevated for 30 minutes 3 times a day (morning, afternoon, and night).

Participants were provided with a diary in which to record their exercises, periods of rest with elevated limbs, walks, and intake of the nutritional supplement as a means of monitoring the activities performed. On the day of their care, participants were administered with a supervised dose of the supplement, and the empty bottles from the previous day's consumption were collected. Participants were considered to have adhered to the exercise, rest, and nutritional supplementation regimen when they complied with at least 80% of the program in terms of frequency.

Different topical and compression therapies were applied according to the group. For group A, in the first phase, the wound was cleaned with a jet of warm 0.9% saline solution[50,51] and then compressed with a cotton gauze soaked in a solution of polyhexanide biguanide and betaine (Prontosan; B Braum),[52,53] which was left on the wound for 15 minutes. After removal of the dressing, the perilesional skin was wiped and skin protective powder (Stomahesive; from ConvaTec)[54] was applied. Then, a primary wound dressing was applied with either 2% or 4% papain,[55–57] as prepared in a compounding pharmacy, depending on the percentage of slough in the VLU bed, determined by macroscopic evaluation (in $\leq$ 50%, 2% papain was used; in > 50%, 4% papain was used). Then, rayon gauze and cotton gauze were applied, and the dressing was sealed with crepe bandages. Finally, grade III compression therapy with one layer of elastic bandage was applied (Surepress; ConvaTec).[58,59] Group B received the same procedures, with the only difference being the application of 2% hydrogel,[60,61] as prepared in a compounding pharmacy, instead of papain.

In the second phase, approximately 14 to 21 days after the beginning of treatment, when the slough area had reduced and new epithelial tissue was apparent at the borders, the lesions were cleaned as previously described for groups A and B, and a different dressing was used. In group A, inelastic compression therapy (Unna's boot, Viscopaste; Smith-Nephew)[47,62] was applied directly on the ulcer. In group B, a cellulose membrane was applied as the primary dressing (Membracel, from Vuelo Pharma),[63] followed by inelastic compression therapy (Unna's boot, Viscopaste; Smith-Nephew).[47,62]

In both groups, cotton gauzes were used on the Unna boot in the area of the ulcer, for absorption of the exudate, and secured with crepe bandages. At this stage, dressing changes were performed at 3- and 4-day intervals (twice a week).

Saline solution is the solution most commonly used to clean up wounds. It can be used in the long run and does not damage the granulation tissue.[50] The temperature in the microenvironment of the surface where the wound is located may decrease as a consequence of the loss of the thermal protective barrier, which occurs by both skin rupture and the action of external factors such as the environment temperature and the temperature of the substances used in the dressing. Saline solution can minimize the interferences in maintaining the temperature suitable for cell proliferation.[51]

Polyhexanide biguanide solution (Prontosan) is considered effective in treating colonized or infected wounds, providing favorable

conditions to the healing process, decreasing healing time and inflammatory signs of infection or colonization,[52] and may be used until wounds heal.[53]

Papain is a selective debriding agent which does not harm the healthy tissue of wounds, has anti-inflammatory properties, decreases the volume of exudate, and favors wound healing by stimulating the formation of granulation tissue.[56] The action of papain depends on the concentration used. In granulation tissue, it is recommended to use a concentration between 2% and 4%, and in the presence of purulent exudate and/or infections papain, concentrations may vary from 4% to 6%.[55] Papain also has the function of inhibiting and reducing the formation of biofilms or interrupting the growth of biofilms already formed.[57]

Hydrogels act as a chemotactic agent for leukocytes, favoring angiogenesis and promoting autolytic debridement,[60] showing positive effects on healing.[61] Cellulose membranes (Membracel) protect wounds from mechanical traumas, with no direct effects on healing.[63]

The Stomahesive (ConvaTec) skin protector has been used as a barrier in the care to peristomal skin.[60] In the VLU treatment context, it was used to protect perilesional skin, which is in contact with exudate, to prevent maceration.

Surepress is a monolayer elastic bandage that can be considered as an option for compression therapy, with a lower cost in comparison with multilayer bandage.[58,59]

The Unna boot is a bandage soaked in zinc oxide, gelatin, and glycerin. It is recommended to treat VLU and lymphedema[60] because it reduces edema as it presses the legs during exercises, improving blood pumping through the calf muscles.[47]

Outcomes

The primary outcome analyzed was the healing of VLUs, with healing defined as the complete closure of the wound, verified by epithelization of the wound sustained for 1 week.

The other analyzed outcomes were:

- Wound area reduction rate (initial area minus the area found in the subsequent evaluation, multiplied by 100)[64];
- Healing evolution, verified by PUSH scores media and the delta of the total PUSH scores (calculated based on the difference in the scores from week to week);
- Pain occurrence;
- Intensity of wound pain, before, during, and after dressing change, verified by an 11-point numeric pain scale, in which zero means absence of pain and 10 the worst possible pain.[46]

The variables studied for the homogeneity analysis of the groups were gender, age, level of education (years of education), per capita income, occupation, fasting glycaemia, diabetes, hypertension, smoking, body mass index, pain in the wound before dressing, lipodermatosclerosis, use of venotonic medications, duration and initial area of the ulcer, and initial PUSH score.

Ethical aspects

This study complied with Brazilian and international guidelines for research involving human beings. It is part of a matrix project approved by the Research Ethics Committee of the Federal University of Goiás (opinion 797.280/2014), registered in the Brazilian Clinical Trials Registry (ReBec), linked to the International Clinical Trials Registry Platform and to the World Health Organization (register number: RBR-5d4s4f).

The project received financial support from the Research Support Foundation of the State of Goiás (PPSUS 201410267000321) and the National Council for Scientific and Technological Development (CNPq) (487093/2013–5), as well as partial donations of Cubitan (Danone Nutricia Brasil).

The participants were monitored for adverse events. Therapy was continued when mild adverse events occurred and suspended in cases with moderate adverse events. The adverse events observed were allergy to the Unna boot or to the crepe bandage and onset, worsening, or uncontrolled clinical signs of infection.

Data analysis

Data were analyzed through descriptive statistics (absolute frequency, percentage, mean, median and standard deviation) and analytical statistics. The Shapiro-Wilk test was used to test normality of the quantitative variables. The Fisher Exact test or the Chi-Squared test and the Mann-Whitney *U* test or the Student's t-test were used to test the homogeneity of the groups A and B.

The outcomes (healing, wound area reduction rate, PUSH score evolution, wound pain intensity before, during and after dressing change) were compared intra and inter groups.

The Kaplan-Meier estimator and hazard ratio and its 95% confidence interval were used to evaluate the time required for ulcer healing. The Wilcoxon test was used in the intragroup analysis. The Chi-Squared test, the Fisher's exact test, and the Mann-Whitney *U* test or the Student's t-test and Cohen's D were used in the analysis between the groups. To compare the effect of bundles in the presence of pain, the Cochran Q test with post hoc analyses was used in intragroup analyses. The value of $P < .05$ was adopted. The Statistical Package for the Social Sciences for Windows (version 17.0) and Stata programs (version 14.0) were used for the statistical analysis of the data.

RESULTS

Of the 118 people assessed for eligibility, 82 were considered ineligible, and 3 refused to participate. Therefore, only 33 were randomly assigned to group A (n = 15) and group B (n = 18). Five participants were discontinued from the study before completing the first week of evaluation (4 due to adverse reaction/worsening of clinical signs of infection and 1 abandoned treatment). Thus, 28 subjects were included, group A (n = 14) and group B (n = 14) (Figure 1).

Characteristics of the participants

The characteristics of the participants at baseline are described in Table 1, which shows the homogeneity between the groups.

Bundles effectiveness

Healing. Ulcer healing occurred in 19 (67.85%) participants, of whom 10 (71.42%) were in group A and 9 (64.28%) were in group B ($P = 1.00$) in 24-week follow-up. After 12 weeks, the healing rate was 7 (50.0%) in group A and 9 (64.28%) in group B. There was no difference between the 2 groups in terms of healing proportion in the follow-up study ($P = 1.000$) (Figure 2).

Wound area reduction rate. Between the baseline period and the fourth week (period established for wound healing prognosis[19]), the ulcer reduction rate was 50.21% (±58.28) in group A and 65.19% (±42.05) in group B ($P = .642$). Comparing the

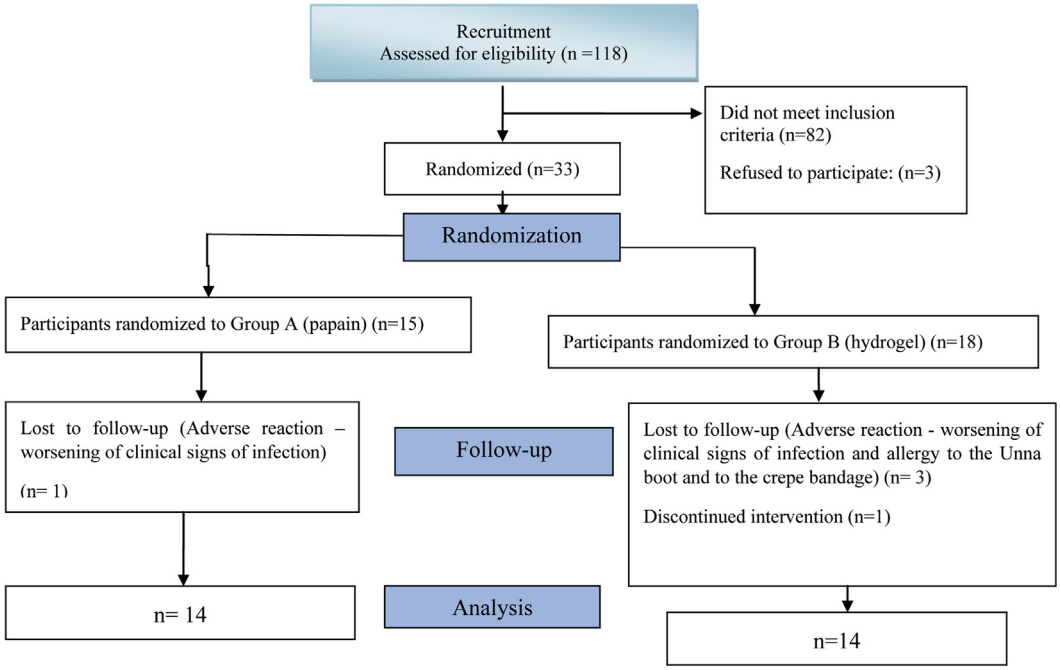

Figure 1. *Participants' flowchart during clinical trial participation.*

TABLE 1

DEMOGRAPHIC, SOCIAL, AND CLINICAL CHARACTERISTICS OF PARTICIPANTS AT BASELINE

Variables	*Group A (n = 14)*	*Group B (n = 14)*	*Total (n = 28)*	P *value*
Female (n, %)	10 (71.4)	9 (64.3)	19 (67.9)	1.000‡
Age in years*	62.14 (12.03)	57.07 (11.75)	59.6 (11.95)	.821§
Years of education*	5.64 (3.45)	6.53 (5.18)	6.08 (4.34)	.473‖
Income per capita*,†	201.70 (124.31)	225.51 (108.26)	213.60 (115.02)	.434‖
Occupation (n, %)	3 (21.4)	6 (42.9)	9 (32.1)	.420‡
Fasting glycaemia*	107.77 (35.28)	113.28 (76.13)	110.53 (58.29)	.679‖
AH (n, %)	6 (42.9)	7 (50.0)	13 (46.4)	.705¶
DM (n, %)	5 (35.7)	2 (14.3)	7 (25.0)	.385‡
Smoking (n, %)	2 (14.3)	1 (7.1)	3 (10.7)	1.000‡
PUSH score*	11.14 (3.71)	12.50 (2.50)	11.82 (3.18)	.056§
Wound pain before dressing change*	1.57 (2.70)	2.14 (3.00)	1.85 (2.82)	.537‖
Duration of lesions*	47.64 (56.85)	51.07 (97.49)	49.35 (78.33)	.333‖
Area of lesions	11.50 (14.01)	47.15 (138.71)	29.32 (98.43)	.383‖
BMI*	31.91 (5.52)	31.21 (3.73)	31.56 (4.64)	.072§
Lipodermatosclerosis (n, %)	4 (28.6)	5 (35.7)	9 (32.1)	1.000‡
Use of venotonic drugs (n, %)	8 (57.1)	11 (78.6)	19 (67.9)	.420‡

AH = arterial hypertension; DM = diabetes mellitus; PUSH = Pressure Ulcer Scale Healing; BMI = body mass index.

*mean (standard deviation).

†Per capita income calculated in dollars. Dollar (U$) to real (R$) in 2016: R$ 3.49.

‡Fisher's Exact test.

§Student's t-test.

‖Mann-Whitney *U* test.

¶Chi-square test.

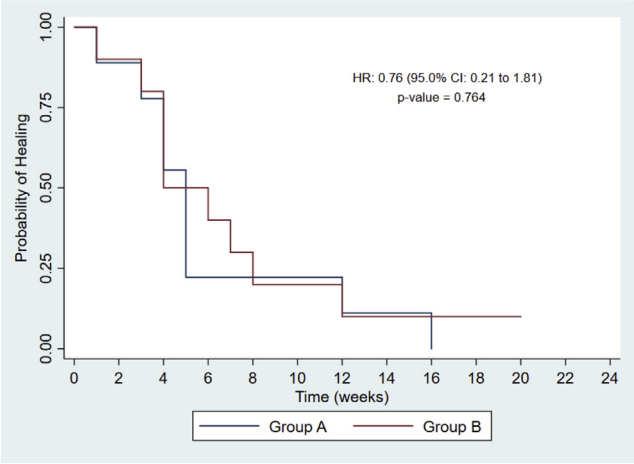

Figure 2. *Probability of healing of venous ulcers in groups A and B over 24-wk follow-up.*

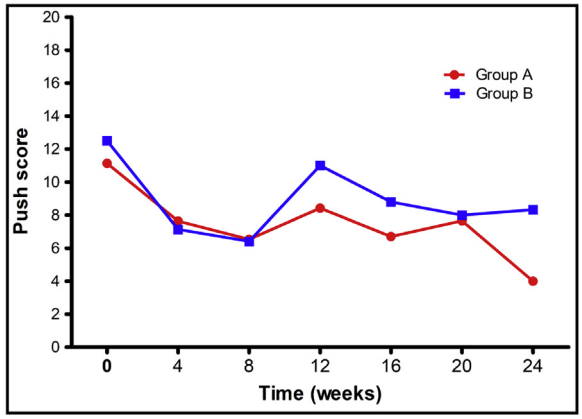

Figure 3. *Analysis of the evolution of mean PUSH scores between groups A and B over a 24-wk follow-up.*

baseline and the 12th week of follow-up (period generally used in effectiveness studies[11,16,37]), the mean ulcer reduction rate was 88.30% (±19.18) in group A and 80.88% (±35.67) in group B (Table 2), with no difference between groups.

PUSH scores. Figure 3 shows the comparative analysis of the evolution of mean PUSH scores between groups.

The mean PUSH scores decreased during the follow-up period, up to the eighth week for both groups and up to the 12th week for group A. There was no difference in the comparison between groups (Table 3 and Figure 4).

Pain. There was a significant reduction in the occurrence of pain in the first 4 weeks. In the 20th week, there was no report of pain among the participants, and in the last week, only one participant in group A reported pain (P = .549) (Figure 5). (Note: P value > 0.5 in all times; Fisher's exact)

There was no statistically significant difference in the presence of pain in both groups (P value > .05) (Table 4).

Pain intensity. There was no difference in pain intensity between groups A and B before, during, and after dressing change in the follow-up period (Table 5). At baseline, the mean pain intensity reported before dressing change was 1.57 ± 2.71 in group A and 2.14 ± 3.0 in group B (P = .537). During dressing change, it reached 3.36 ± 3.39 in group A and 3.43 ± 3.52 in group B (P = 1.000). After dressing change, pain intensity was 1.21 ± 2.00 in group A and 2.14 ± 3.20 in group B.

Pain intensity before dressing change decreased in group A between the fourth, eighth, and twentieth weeks, and in group B, pain intensity decreased between baseline and all other weeks, with no statistical difference between groups and no significant differences in the other periods (Table 5 and Figure 6).

During dressing change, the pain intensity decreased between the fourth, eighth, twelfth, 16th, 20th, and 24th weeks in group A and group B (Table 5 and Figure 6).

After dressing change, decreased pain intensity was observed in group A only between the baseline and the 16th, 20th, and 24th weeks (Table 5). In group B, pain intensity decreased between baseline and all other weeks, with no statistical difference between groups (Table 5 and Figure 6).

TABLE 2

COMPARISON OF ULCER AREA REDUCTION RATES BETWEEN GROUPS A AND B OVER 24-WK FOLLOW-UP

Weeks	*Group A μ (SD)*	*Group B μ (SD)*	P *value**
0–4	50.21 (58.28)	65.19 (42.05)	.642
0–8	76.96 (38.77)	78.29 (32.72)	.881
0–12	88.30 (19.18)	80.88 (35.67)	.741
4–8	46.31 (73.82)	62.38 (40.35)	.757
8–12	−308.96† (1,008.02)	35.44 (54.83)	.886
12–16	39.31 (65.70)	10.55 (39.60)	.449
16–20	22.12 (67.12)	42.95 (33.83)	.655
20–24	−10.83 (129.62)	38.19 (47.90)	.827

SD = standard deviation.

*Mann-Whitney U test.

†Negative rates indicate an increased ulcer. A patient with an almost epithelialized lesion had intense pruritus and traumatized the area by scratching it.

DISCUSSION AND LIMITATIONS

The bundles tested in groups A and B promote favorable healing, reduce pain in VLU, and are effective for healing these wounds. No differences were found in the comparison between the groups (all P values > .05). In 24 weeks, the bundle tested in group A promoted the healing of 71.42% of the VLU, while the bundle tested in group B promoted the healing of 64.28%. There was also a reduction in ulcer area, the PUSH scores, and in pain intensity.

Different healing rates have been observed in studies involving people with VLU,[16–19,21,25] with values generally smaller than those found in the present study.

TABLE 3

COMPARISON OF THE MEAN PUSH SCORES IN EACH GROUP AND THE DIFFERENCE IN PUSH SCORES BETWEEN GROUPS A AND B OVER THE 24-WK FOLLOW-UP TREATMENT

	*Group A**	*Group B**				
Time (wk)	*μ (SD)*	*μ (SD)*	*Difference (95.0% CI)*	t[†]	P *value*	*Cohen's D*
0	11.14 (3.72)[a]	12.50 (2.50)[c]	−1.36 (−3.81; 1.10)	−1.133	.268	0.428
4	7.64 (4.95)[b]	7.14 (6.01)[d]	0.50 (−3.78; 4.79)	0.240	.812	0.091
8	6.54 (5.42)	6.42 (6.29)	0.13 (−4.99; 5.24)	0.052	.959	0.022
12	8.42 (4.16)	11.00 (5.44)	−2.57 (−8.42; 3.29)	−0.966	.355	0.537
16	6.71 (5.02)	8.80 (5.89)	−2.09 (−9.11; 4.94)	−0.661	.523	0.387
20	7.67 (4.68)	8.00 (7.00)	3.85 (−9.43; 8.77)	−0.087	.933	0.062
24	3.67 (3.21)	8.33 (6.66)	−4.67 (−18.56; 9.23)	−1.093	.336	0.892

SD = standard deviation; CI = confidence interval.

*Intragroup comparisons performed by the Student's t-test for dependent samples; a, statistical difference at 4 wk (*P* value = .003), 8 wk (*P* value = .002), 12 wk (*P* value = .021), and 20 wk (*P* value = .042); b, statistical difference with 8 wk (*P* value = .012); c, statistical difference with 4 wk (*P* value = .001) and 8 wk (*P* value = .001); d, statistical difference with 8 wk (*P* value = .018) and 16 wk (*P* value = .037).

[†]Intergroup comparison performed for each week of follow-up by Student's t-test for independent samples.

Studies that used 2% to 4% papain not associated with compression therapy reached a healing level between 12.5%[18] and 20.0% in the treated VLU[24] in a 12-week follow-up. By using 2% carboxymethylcellulose hydrogel only, with no compression therapy, no ulcer healed in 12 weeks.[18]

Although these studies have reported positive effects, the healing percentages were lower than those found in the present investigation. This may be explained by the fact that the mentioned studies did not apply compression therapy. In addition, the dressings were applied by both patients at home and professionals at the health unit, alternately.

Comparison between the application of elastic compression therapy associated with an inert therapy (Petrolatum gauze) and the use of the Unna boot as an exclusive therapy showed that each group had a healing rate of 11.1% in a 13-week follow-up.[17]

Higher healing rates were obtained in a study that associated compression therapy using the Unna boot with different coatings containing nanocrystalline silver and educational actions in the context of care to patients with VLU through nursing appointments, as reported in the descriptive and retrospective investigation, which included 80 VLU, showing healing of 51.3% of the wounds in 12 weeks.[62]

These examples indicate that it is necessary to combine actions for concomitant use to obtain better results.

The bundles tested in the present study showed higher effectiveness than the intervention with proper topical care to the conditions of the ulcers' bed and high compression therapy, in some cases associated with surgery of superficial veins, which promoted healing of 44% of the 94 treated VLU, in 24 weeks.[19]

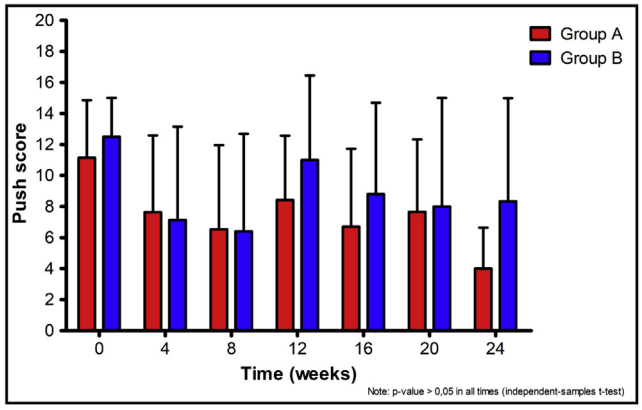

Figure 4. *PUSH scores presented by group A and group B over 24-wk follow-up.*

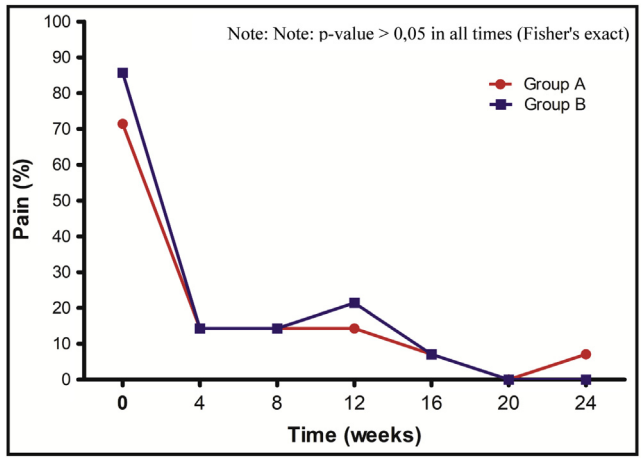

Figure 5. *Self-reported pain among participants of groups A and B over 24 wk of follow-up.*

TABLE 4

PAIN SELF-REPORTED IN GROUPS A AND B OVER 24-WK FOLLOW-UP

	*Group A**	*Group B**			
Time (wk)	*n (%)*	*n (%)*	*Difference (95% CI)*	P *value*[†]	*V Cramer*
0	10 (71.4)[a]	12 (85.7)[a]	14.29 (−16.41; 42.32)	.648	0.174
4	2 (14.3)	2 (14.3)	0.00 (−27.64; 27.64)	1.000	0.000
8	2 (14.3)	2 (14.3)	0.00 (−27.64; 27.64)	1.000	0.000
12	2 (14.3)	3 (21.4)	7.14 (−22.02; 35.25)	1.000	0.093
16	1 (7.1)	1 (7.1)	0.00 (−25.02; 25.02)	1.000	0.000
20	—	—	—	—	—
24	1 (7.1)	—	7.14 (−15.17; 32.47)	1.000	0.192

CI = confidence interval.

*Intragroup comparisons performed by the Cochran Q test; a, statistical difference at week 4 (P value ≤ .001), week 8 (P value < .01), week 12 (P value ≤ .001), week 16 (P value < .01), week 20 (P value < .01), and week 24 (P value < .001).

[†]Intergroup comparison performed for each week of follow-up by Fisher's exact test.

Although the bundles examined in the present study resulted in a healing rate similar to that reported by an investigation which tested topical care associated with high, medium, and low compression therapy or pneumatic compression,[21] the procedures described in the present study have the advantage of producing this effect in a shorter time. In the mentioned study, healing of 70% of the VLU occurred in 48 weeks, whereas in the present investigation, the same result was reached in 24 weeks.

A faster healing process implies cost savings for health systems and patients, increases the number of days with a higher quality of life, and means a reduced negative social impact of venous insufficiency.

In some studies, referred to previously,[19,21] the topical therapies were not described in the method, which prevented the reproduction of these studies. We believe that this information should not be omitted in study design descriptions as bed preparation and the topical therapy used may promote healing.[14]

In the present investigation, the total percentage of wounds healed after 12 weeks reached 62.5%, demonstrating that the association of the measures used in bundles, which had not been tested previously in other research, increased the success of the treatment.

The best results found in the literature taking into account a 12-week follow-up were reported in a cohort study involving 217 participants with venous and mixed ulcers[20] that used 4-layer (69.0%) and 3-layer compression bandages (13.0%) and the Unna boot (18.0%). However, the study did not disclose the selection criteria for the compression modalities nor the information on the topical therapy used. In this study, approximately 65% of ulcers were healed within 12 weeks and 75% after 16 weeks.[20] Multilayer compression therapy was not included in the bundles tested in the present investigation; however, a similar healing percentage was achieved after 12 weeks of follow-up, with 50.0% healing in group A and 64.28% in group B. In the 16th week, 64.28% of wounds had healed in group A and 64.28% in group B, suggesting that this method could be adopted in developing countries in the later stages of treatment, with the aim to achieve its rational use.

The differences observed in the studies regarding healing percentages may result from both the therapeutic approach used and the severity of the VLU included in the investigation. Ulcer duration, wound area, and microbial load, as well as the presence of comorbidities and the condition of the affected limb, such as lipodermatosclerosis, are intervening factors for healing of VLU.[21,39]

The present study included people who showed hindering factors for the healing of VLU.[65] However, the association of the therapeutic measures proposed in the bundles could promote a high healing rate.

A wound reduction rate of more than 30% up to the fourth week of treatment is considered a favorable outcome, with a good prognosis in VLU healing.[19] In the present study, between baseline and the fourth week of follow-up, the mean rate of ulcer reduction was well above this percentage (50.21 ± 58.28% in group A and 65.19 ± 42.05% in group B), indicating that the bundles tested are associated with good prognoses.

Regarding the ulcer reduction rate, the results obtained by using bundles were similar to those found in a 12-week follow-up study that obtained a 77.10% (±25.70) reduction in ulcer area in the intervention group and 69.20% (±40.03) in the control group by using laser photobiomodulation. However, the final results for full healing reach were inferior: 18% healing in the control group and 29% in the intervention group, and it was not clear whether compression therapy was associated with photobiomodulation throughout the follow-up.[25]

TABLE 5

INTERGROUP AND INTRAGROUP COMPARISON OF DIFFERENCES IN PAIN INTENSITY BEFORE, AFTER, AND DURING DRESSING CHANGE

	*Group A**	*Group B**				
Time (wk)	*μ (SD)*	*μ (SD)*	*Difference (95.0% CI)*	H[†]	P *value*	*Cohen's D*
Before						
0	1.57 (2.71)[a]	2.14 (3.00)[b]	−0.57 (−2.79; 1.65)	109.500	.603	0.201
4	0.29 (1.07)	0.36 (1.34)	−0.07 (−1.01; 0.87)	89.500	1.000	0.148
8	0.00 (0.00)	0.21 (0.80)	−0.21 (−0.65; 0.23)	105.000	.769	0.122
12	0.36 (1.08)	0.21 (0.80)	0.14 (−0.60; 0.88)	91.000	.769	0.122
16	0.14 (0.53)	0.00 (0.00)	0.14 (−0.15; 0.44)	91.000	.769	0.122
20	0.00 (0.00)	0.00 (0.00)	—	98.000	1.000	0.000
24	0.29 (1.07)	0.00 (0.00)	0.29 (−0.30; 0.87)	91.000	.769	0.122
During						
0	3.36 (3.39)[c]	3.43 (3.52)[c]	−0.07 (−2.76; 2.61)	98.000	1.000	0.000
4	0.71 (1.86)	1.07 (2.89)	−0.36 (−2.25; 1.53)	99.000	1.000	0.017
8	0.07 (0.27)	0.39 (1.07)	−0.21 (−0.82; 0.39)	98.500	1.000	0.009
12	0.36 (1.08)	0.43 (1.16)	−0.07 (−0.94; 0.80)	98.500	1.000	0.009
16	0.39 (1.07)	0.50 (1.87)	−0.21 (−1.40; 0.97)	98.500	1.000	0.009
20	0.00 (0.00)	0.00 (0.00)	—	98.000	1.000	0.000
24	0.00 (0.00)	0.00 (0.00)	—	98.000	1.000	0.000
After						
0	1.21 (2.00)[e]	2.14 (3.20)[f]	−0.93 (−3.00; 1.14)	110.500	.571	0.218
4	0.79 (2.00)	0.50 (1.87)	0.29 (−1.22; 1.79)	92.000	.804	0.104
8	0.43 (1.60)	0.00 (0.00)	0.43 (−0.45; 1.31)	91.000	.769	0.122
12	0.36 (1.34)	0.00 (0.00)	0.36 (−0.38; 1.09)	91.000	.769	0.122
16	0.00 (0.00)	0.36 (1.24)	−0.36 (−1.09; 0.38)	105.000	.769	0.122
20	0.00 (0.00)	0.00 (0.00)	—	98.000	1.000	0.000
24	0.00 (0.00)	0.00 (0.00)	—	98.000	1.000	0.000

SD = standard deviation; CI = confidence interval.

*Intragroup comparisons performed by the Wilcoxon test; a, statistical difference at week 4 (*P* value = .046), week 8 (*P* value = .046), and week 20 (*P* value = .046); b, statistical difference at week 4 (*P* value = .025), week 8 (*P* value = .014), week 12 (*P* value = .014), week 16 (*P* value = .014), week 20 (*P* value = .014), week 24 (*P* value = .014); c, statistical difference at week 4 (*P* value = .001) and week 8 (*P* value = .005), week 12 (*P* value = .034), week 16 (*P* value = .020), week 20 (*P* value = .003), week 24 (*P* value = .003); d, statistical difference at week 4 (*P* value = .020), week 8 (*P* value = .011), week 12 (*P* value = .011), week 16 (*P* value = .020), week 20 (*P* value = .030), week 24 (*P* value = .030); e, statistical difference at week 16 (*P* value = .046), week 20 (*P* value = .046), and week 24 (*P* value = .046); f, statistical difference at week 4 (*P* value = .025), week 8 (*P* value = .025), week 12 (*P* value = .025), week 16 (*P* value = .025), week 20 (*P* value = .025), week 24 (*P* value = .025).

[†]Intergroup comparison performed for each week of follow-up by Mann-Whitney *U* test.

Regarding healing evolution, there was a reduction in PUSH scores during follow-up, especially between baseline and the eighth week. This evolution profile was identified in another study; however, it only occurred after the 12th week of follow-up,[25] suggesting that the tested bundles can promote the healing process more quickly.

The bundles proposed in the present study included cleaning procedures that may have contributed to the management of the inflammatory phase. Warm 0.9% saline solution may prevent hypothermia in the wound, which has been described as an event that decreases the activity of leukocytes and favors infection.[40]

A double-blind randomized controlled trial showed that Prontosan reduces inflammation signs and contributes to speeding up the healing of vascular ulcers. Consequently, the update of protocols addressing care to people with chronic wounds including this product is recommended.[66]

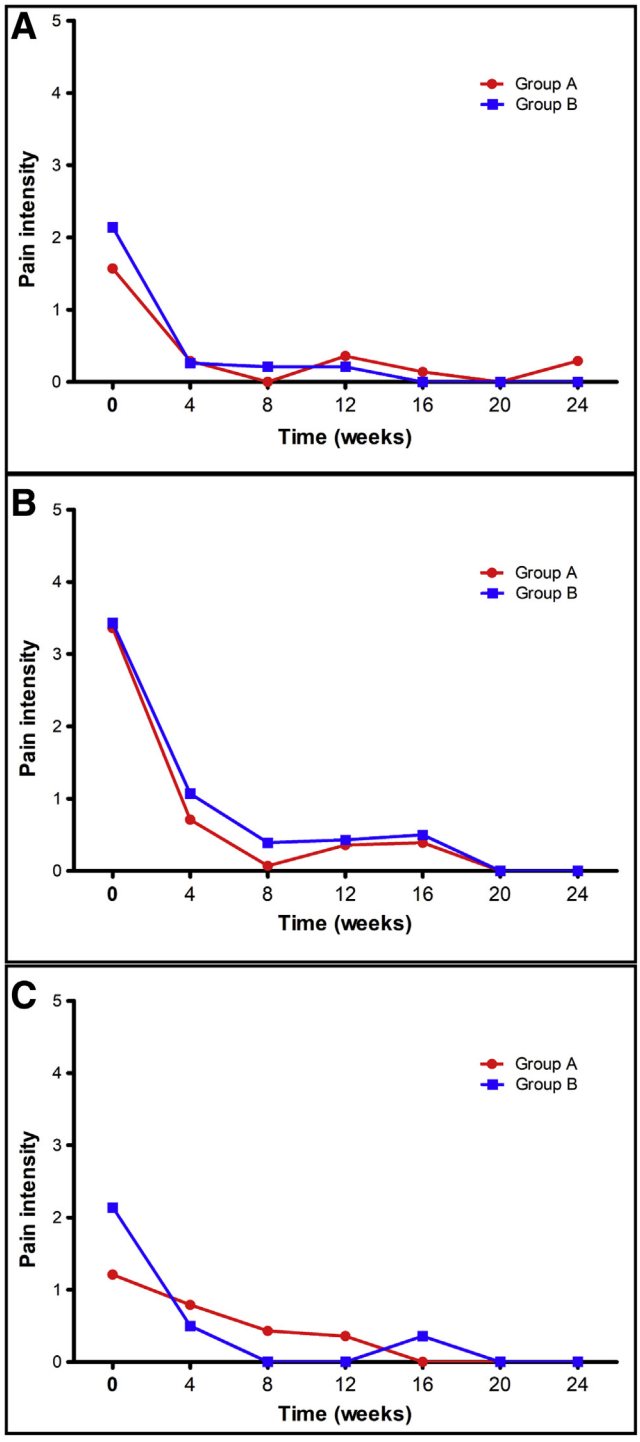

Figure 6. *Pain intensity before (A), during (B), and after (C) dressing changes over 24 wk of follow-up.*

In combination with elastic compression, Prontosan significantly helped improve the control of bacterial load, as indicated clinically, by a microbiological evaluation and by the reduction of pain as of the second week until the end of treatment in the intervention group ($P < .05$).[64] The explanation of this result was based on pH changes, which decreased from 8.9 ± 0.6 to 7.0 ± 0.3 after 4 weeks of treatment.[67]

In an acidic environment, nitric oxide is released, which stimulates collagen deposition, bacterial control, and the formation of new blood vessels.[68,69]

Regarding the topical therapy used in the present study, made up of papain and hydrogel, there are investigations emphasizing their benefits in wound treatment.[55,56]

Compression therapy is considered the gold standard to treat VLU[31,47] because it reduces venous hypertension, thus decreasing edema.[47]

There are different types of compression therapy. Multilayer therapy is considered more effective than single-layer dressings.[31] However, it is necessary to consider that multilayer bandages are more expensive than single-layer bandages, which are better options in contexts where financial resources are scarce.[58] In underdeveloped or developing countries, such as Brazil, reusable compression therapy can be an accessible option for the current public health system, with universal access.

A multicenter study involving 53 people with VLU compared one-layer compression therapy (SurePress) to a standard short-stretch system (Comprilan) and found that the proportion of ulcers that healed in 12 weeks was 44.4% among people treated with SurePress and 17.2% among people treated with the standard system ($P = .027$). The study concludes that the SurePress system was more effective than the standard system in healing VLUs.[59]

There are several exercise protocols for the legs indicated for improving the functioning of the calf muscle bomb and the ankle articulation mobility, reducing venous hypertension and edema.[16] They promote a positive effect on tissue perfusion in VLU, which is enhanced when compression therapy is applied.[11]

The combination of exercises and compression therapy was tested in studies, leading to different healing proportions varying from 30%[8] to 83.0%[14] in 24 weeks. These studies failed to clarify the topical therapy used.

The combination of physical activity and compression has the potential to reverse the effects of venous hypertension, decreasing healing time, and preventing functional limitations.[27] Exercises and compression therapy can decrease edema,[10,16,28,70] improve calf muscle function and ankle range of motion,[71] increase oxygenation at the wound site,[11] and reduce inflammation[72] and, consequently, pain.[10,16,28,70]

Active exercise of moderate intensity, such as those adopted in the present study, may affect the profile of cytokines and growth factors in the limb affected by mechanotransduction.[73] In particular, there was an increase in the production of anti-inflammatory cytokines such as interleukin 10, defensins D1 and D2, and transforming growth factor β of fibroblasts in the thoracolumbar fascia and deep muscles by means of low-amplitude cyclic stimuli.[74,75]

The exercises also contribute to reducing the fear of active movement and of exposing the leg to strain, optimizing the return to daily and professional activities.[29]

Another fundamental aspect in the therapeutic approach for people with venous ulcers is nutrition.[13,76] As mentioned previously, evidence on the effects of oral supplements on healing in this population is scarce, and comparisons between results may be hindered.

A case series study investigated the effect of individually designed nutritional support programs associated with nutritional

supplementation on the healing of therapy-resistant VLU in the legs in primary health care. Six people participated in the study, with ten venous ulcers that had been open for 1.5 to 8 years.[77] Participants were asked to follow an individualized diet plan that included the use of dietary supplements (Fortimel; Nutricia AB), taken once or twice daily between meals, containing 9.7 grams of protein, 10.4 grams of carbohydrate, 2.1 grams of fat per 100 mL, 17 milligrams of vitamin C, and 1.7 milligrams of zinc per 100 mL. After 9 months, all the ulcers had improved, showing a decreased area, and 2 had healed, indicating the benefits of this therapy.[77]

We emphasize that the nutritional supplement was used in the present study for 4 weeks only, 2 or 3 times a day, which generates higher costs in the first month, with a decrease in subsequent months.

The treatment of individuals with VLU should provide adequate pain control as pain is a frequent occurrence in this population.[26,27] The bundles tested significantly reduced pain in the first 4 weeks of treatment, and the number of people for whom this symptom persisted was reduced, with full resolution up to 20 weeks.

Pain in people with vascular ulcers can derive from the injury itself, from an underlying vascular disease and from external factors such as the dressing. Manipulation during wound cleaning, the application and removal of dressings, the type of dressing used, debridement, and the presence of infection can also cause and exacerbate pain.[78,79]

A study found a mean pain intensity of 5.43 (±2.97) during dressing change and of 4.77 (±2.85)[72] before the procedure, values higher than the ones found in the present study. The study also showed a positive and moderate correlation (r = 0.57, P = .001) between self-reported pain intensity before dressing change and during the procedure,[78] which points to the importance of bundles that include care in the 24 hours after dressing change, avoiding pain before the subsequent dressing change. In addition, care during cleaning and debridement, which must be atraumatic and performed with warm saline solution, is important and was included in the bundles tested in the present study.

The reduction of pain intensity during dressing changing in both groups may be related to the effect of polyhexanide biguanide solution (Prontosan®), debridement, and reduction of microbial load, probably enhanced by the anti-inflammatory action of papain in group A and hydrogel in group B. We stress that these effects are known, but combining therapies may promote a quicker relief as a consequence of a synergistic action.

In addition, the therapies offered to both groups, including exercises[10,16,28,70] and compression therapy,[59] may have contributed to reducing pain, given that they are commonly indicated to solve this problem.

Finally, we highlight the importance of educational activities such as the 1 included in this bundle. These increase adherence to the treatment plan[80] and promote self-care by providing the knowledge and ability to administer it,[9] supporting the healing process and reducing pain.

Studying the effect of bundles is a complex task. It requires financial investment and a heavily dedicated staff, available over an extended period. However, this must not discourage health professionals from seeking better practices to treat people who are suffering.

The present study has some limitations that must be stressed, such as lack of blinding and the small number of participants. Given the nature of the treatments used, it was not possible to establish the double-blind. Studies with combined interventions need greater financial support or inputs from various institutions to include large samples, which is rarely possible. Despite these limitations, the present investigation represents a breakthrough for combining several therapies recommended in the literature.

CONCLUSIONS

The tested bundles improved the ulcer healing conditions from the fourth week of the treatment onwards, when a significant decrease in PUSH scores and pain was observed in both groups, a reduction in pain intensity before and after the dressing in group B was noted, and a decrease in pain intensity during this procedure in group A was registered. The wound reduction rate had an average value higher than 50.0% after 4 weeks and higher than 80.0% in 12 weeks, with healing levels of 71.42% in group A and 64.28% in group B.

The tested bundles promoted healing and reduction of pain in the VLU, and no differences were found between them. Thus, both bundles are an effective approach to the treatment of VLU. Health services may choose the most suitable bundle according to the expected action of the products, wound bed conditions, cost, ease of application and changes, and their institutional possibilities.

Taking into consideration the VLU healing percentage and the reduction of occurrence and intensity of pain obtained in the present study after the treatment with the bundles in a 24-week follow-up, the authors suggest the inclusion of warm saline solution and polyhexanide biguanide in the cleaning of the wounds, 2% hydrogel or 2% to 4% papain as a possibility of primary coating, and the promotion of compression therapy using washable elastic bandage and the Unna boot in settings marked by lack of access or contraindication of multilayer compression therapy.

The present study poses the challenge of performing new investigations to estimate the contribution of the association of each specific action included in the tested bundles and the share related to the inclusion of new elements to the bundle, such as individual nutritional therapy, psychoemotional support, and integrative and complementary practices, among others.

Knowing that there are regions around the world with reduced access to health services, the present study prompts the development of new investigations to test the application of bundles in the modality of shared management of VLU care, including families and patients themselves, merging home care and care provided by multidisciplinary teams, to strengthen self-care skills, and the engagement of families in the care to people with VLU.

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REFERENCES

1. O'Donnell Junior TF, Pasman MA, Marston WA, et al. Mangement of venous leg ulcers: clinical pratice guidelines of the Society for Vascular Surgery® and the American Venous Forum. J Vasc Surg 2014;60(2):3-59.
2. Apollonio A, Antignani PL, Di Salvo M, et al. A large Italian observational multicentre study on vascular ulcers of the lower limbs (Studio Ulcere Vascolari). Int Wound J 2016; 13:27-34.
3. Ferreira MC, Tuma Junior P, Carvalho VF, et al. Complex wounds. Clinics 2006;61(6):571-8.
4. Guest JF, Fuller GW, Vowden P. Venous leg ulcer management in clinical practice in the UK: costs and outcomes. Int Wound J 2018;15(1):29-37.
5. Joaquim FL, Camacho ACLF, Sabóia VM, et al. Impact of home visits on the functional capacity of patients with venous ulcers. Rev Bras Enferm 2016;69(3):439-47.
6. Phillips P, Lumley E, Duncan R, et al. A systematic review of qualitative research into people's experiences of living with venous leg ulcers. J Adv Nurs 2018;74:550-63.
7. Barnsbee L, Cheng Q, Tulleners R, et al. Measuring costs and quality of life for venous leg ulcers. Int Wound J 2019;16: 112-21.
8. Nherera LM, Woodmansey E, Trueman P, et al. Estimating the clinical outcomes and cost differences between standard care with and without cadexomer iodine in the management of chronic venous leg ulcers using a markov model. Ostomy Wound Manage 2016;62(6):26-40.
9. Gonzalez A. The effect of a patient education intervention on knowledge and venous ulcer recurrence: results of a prospective intervention and retrospective analysis. Ostomy Wound Manage 2017;63(6):16-28.
10. Azoubel R, Torres GV, Silva LWS, et al. Effects of the descongestive physiotherapy in the healing of venous ulcers. Rev Esc Enferm USP 2010;44(4):1085-92.
11. Mutlak O, Aslam M, Standfield N. The influence of exercise on ulcer healing in patients with chronic venous insufficiency. Int Angiol 2018;37(2):160-8.
12. Ratliff CR, Yates S, McNichol L, et al. Compression for primary prevention, treatment, and prevention of recurrence of venous leg ulcers: an evidence-and consensus-based algorithm for care across the continuum. J Wound Ostomy Continence Nurs 2016;43(4):347-64.
13. Barber GA, Weller CD, Gibson SJ. Effects and associations of nutrition in patients with venous leg ulcers: a systematic review. J Adv Nurs 2018;74(4):774-87.
14. Costa I, Dantas D, Melo G, et al. Protocol of assistance to persons with venous ulcer in primary care: integrative literature review. J Res: Fundam Care Online 2017;9(2):566-74.
15. Borges EL, Caliri MHL, Haas VJ. Systematic review of topic treatment for venous ulcers. Rev Latinoam Enfermagem 2007;15(6):1163-70.
16. Klonizakis M, Tew GA, Gumber A, et al. Supervised exercise training as an adjunct therapy for venous leg ulcers: a randomized controlled feasibility trial. Br J Dermatol 2018;178(5):1072-108.
17. Abreu AM, Oliveira BGRB. A study of the Unna Boot compared with the elastic bandage in venous ulcers: a randomized clinical trial. Rev Latinoam Enfermagem 2015; 23(4):571-7.
18. Rodrigues ALS, Oliveira BGRB, Futuro DO, et al. Effectiveness of papain gel in venous ulcer treatment: randomized clinical trial. Rev Latinoam Enfermagem 2015;23(3):458-65.
19. Chaby G, Senet P, Ganry O, et al. Prognostic factors associated with healing of venous leg ulcers: a multicentre, prospective, cohort study. Br J Dermatol 2013;169(5):1106-13.
20. Marston WA, Carlin RE, Passman MA, et al. Healing rates and cost efficacy of outpatient compression treatment for leg ulcers associated with venous insufficiency. J Vasc Surg 1999;30(3):491-8.
21. Moffatt CJ, Doherty DC, Smithdale R, et al. Clinical predictors of leg ulcer healing. Br J Dermatol 2010;162(1):51-8.
22. O'Brien J, Finlayson K, Kerr G, et al. Evaluating the effectiveness of a self-management exercise intervention on wound healing, functional ability and health-related quality of life outcomes in adults with venous leg ulcers: a randomised controlled trial. Int Wound J 2017;14(1):130-7.
23. Norman G, Westby MJ, Rithalia AD, et al. Dressings and topical agents for treating venous leg ulcers. Cochrane Database Syst Rev 2018;6:CD012583.
24. Ribeiro APL, Oliveira BGRB, Soares MF, et al. Effectiveness of 2% and 4% papain gels in the healing of venous ulcers*. Rev Esc Enferm USP 2015;49(3):394-400.
25. Vitse J, Bekara F, Byun S, et al. A double-blind, placebo-controlled randomized evaluation of the effect of low-level laser therapy on venous leg ulcers. Int J Low Extrem Wounds 2017;16(1):29-35.
26. Joaquim FL, Camacho ACLF, Silva RMCRA, et al. Reflections on home care provided by nurses for treating venous ulcers. [Reflexão acerca do atendimento domiciliar realizado por enfermeiros no tratamento de úlceras venosas]. Revista de Enfermagem UFPE 2016;10(2):664-8.
27. Salomé GM, Ferreira LM. Impact of non-adherent Ibuprofen foam dressing in the lives of patients with venous ulcers. Rev Col Bras Cir 2017;44(2):116-24.
28. Davies JA, Bull RH, Farrelly IJ, et al. A home-based exercise programme improves ankle range of motion in long-term venous ulcer patients. Phlebology 2007;22(2):86-9.
29. Roaldsen KS, Biguet G, Elfving B. Physical activity in patients with venous leg ulcer- between engagement and avoidance. A patient perspective. Clin Rehabil 2011;25(3):275-86.
30. Szewczyk MT, Jawień A, Cwajda-Białasik J, et al. Randomized study assessing the influence of supervised exercises on ankle joint mobility in patients with venous leg ulcerations. Arch Med Sci 2010;6(6):956-63.
31. Mauck KF, Asi N, Elraiyah TP, et al. Comparative systematic review and meta-analysis of compression modalities for the promotion of venous ulcer healing and reducing ulcer recurrence. J Vasc Surg 2014;60:71-90.
32. Szewczyk MT, Jawien A, Kedziora-Kornatowska K, et al. The nutritional status of older adults with and without venous ulcers: a comparative, descriptive study. Ostomy Wound Manage 2008;54(9):34-42.

33. Holt IGS, Green SM, Nelson EA. Oral nutritional supplements for treating venous leg ulcers. Cochrane Database Syst Rev 2016;5:CD012210.
34. Cereda E, Gini A, Pedrolli C, et al. Disease-specific, versus standard, nutritional support for the treatment of pressure ulcers in institutionalized older adults: a randomized controlled trial. J Am Geriatr Soc 2009;57:1395-402.
35. Cereda E, Klersy C, Serioli M, et al. A nutritional formula enriched with arginine zinc, and antioxidants for the healing of pressure ulcers. Ann Intern Med 2015;162:167-74.
36. Van Anholt RD, Sobotka L, Meijer EP, et al. Specific nutritional support accelerates pressure ulcer healing and reduces wound care intensity in non-malnourished patients. Nutrition 2010;26:867-72.
37. Heyman H, Van De Looverbosch DEJ, Meijer EP, et al. Benefits of an oral nutritional supplement on pressure ulcer healing in long-term care residents. J Wound Care 2008;17(11): 476-8.
38. Silva D, Hahn G. Treating venous ulcers: reality in Brazil and Portugal. Revista de Enfermagem da UFSM 2012;2(2): 330-8.
39. Mcguiness W, Vella E, Harrison D. Influence of dressing changes on wound temperature. J Wound Care 2004;13(9): 383-5.
40. Esclamando RM, Damiano GA, Cummings CW. Effect of local hypothermia on early wound repair. Arch Otolaryngol Head Neck Surg 1990;116(7):803-8.
41. Rodrigues AN, Fragoso LVC, Beserra FM, et al. Determining impacts and factors in ventilator-associated pneumonia bundle. Rev Bras Enferm 2016;69(6):1108-14.
42. Schulz KF, Altman DG, Moher D. Consort 2010 Statement: updated guidelines for reporting parallel group randomized trials. Br Med J 2010;340:698-702.
43. Bertolucci PHF, Brucki SMD, Campacci SR, et al. The Mini-Mental State Examination in an outpatient population: influence of literacy. Arq Neuro-Psiquiatr 1994;52(1):1-7.
44. Seabra MLV, Concílio GV, Villares JB, et al. Assessment of the Mini-Mental State Examination in Brazilian volunteers and patients. [Avaliação do teste "Mini-Mental State" em voluntários e pacientes brasileiros]. Rev ABPAPAL 1990; 12(1-4):1-7.
45. Santos VLCG, Sellmer D, Massulo MME. Inter rater reliability of Pressure Ulcer Scale for Healing (PUSH) in patients with chronic leg ulcers. Rev Lat Am Enfermagem 2007;15(3):1-7.
46. Huskisson EC. Measurement of pain. Lancet 1974;9(7889): 1127-31.
47. CONUEI. Conferencia nacional de consenso sobre las úlceras de la extremidad inferior (C.O.N.U.E.I.). Consensus document 2018. [Documento de consenso 2018]. 2th ed. Madrid: Ergon; 2018:127; https://gneaupp.info/conferencia-nacional-de-consenso-sobre-las-ulceras-de-la-extremidad-inferior-c-o-n-u-e-i/. Accessed June 20, 2018.
48. Harding K, Dowsett C, Fias L, et al. Simplifying venous leg Ulcer management. Consensus recommendations. London, England: Wounds International Enterprise House; 2015:25; https://www.woundsinternational.com/resources/details/simplifying-venous-leg-ulcer-management-consensus-recommendations. Accessed September 5, 2019.
49. Ministério da Saúde, Secretaria de Atenção à Saúde, Departamento de Atenção Básica. Food guide for the Brazilian population. [Guia alimentar para a população brasileira]. Brasília, Brasil: Ministério da Saúde; 2014:156; http://bvsms.saude.gov.br/bvs/publicacoes/guia_alimentar_populacao_brasileira_2ed.pdf. Accessed January 20, 2018.
50. Ovens L, Irving S. Advances in wound cleansing: an integrated approach. Wounds UK 1990;14(1):58-63.
51. Zhu LY, Guo SX, Wu P, et al. Advances in the research of the relationship between wound temperature and wound healing. Chin J Burns 2018;34(11):829-32.
52. Santos E, Silva M. Treatment of colonized/infected wounds using polyhexanide. Referência 2011;3(4):135-42.
53. Moore K, Gray D. Use of the antimicrobial agent PHMB for preventing wound infections. [Uso del agente antimicrobiano PHMB para prevenir la infección de heridas]. Gerokomos 2008;19(3):145-52.
54. Ohura N, Kurita T, Takushima A, et al. Efficacy of a skin-protection powder for use as a dressing for intractable ulcers. J Wound Care 2006;15(10):471-6.
55. Rol JLR, Oliveira KA, Vieira LC, et al. Topical wound therapy: use of papain. [Terapia tópica de feridas: utilização de papaína]. Revista CuidArt 2008;2(1):100-10.
56. Leite AP, Oliveira BGRB, Soares MF, et al. Use and effectiveness of papain in the wound healing process: a systematic review. [Uso e efetividade da papaína no processo de cicatrização de feridas: uma revisão sistemática]. Rev Gaucha Enferm 2012;33(3):198-207.
57. Oliveira HLCD, Fleming MECK, Silva PV, et al. Influence of papain in biofilm formed by methicillin-resistant Staphylococcus epidermidis and methicillin-resistant Staphylococcus haemolyticus isolates. Braz J Pharm Sci 2014;50(2):261-7.
58. Pereira BEM, Sousa ATO, França JRFS, et al. Cost comparison of three kinds of compression therapy in venous ulcer. An Bras Dermatol 2016;91(4):544-6.
59. Polignano R, Guarnera G, Boneado P. Evaluation of Sure-Press Comfort: a new compression system for the management of venous leg ulcers. J Wound Care 2004;13(9):387-91.
60. Mandelbaum SH, Santis EP, Mandelbaum MHS. Cicatrization: current concepts and auxiliary resources - Part II. An Bras Dermatol 2003;78(5):525-42.
61. Andrade MR. Adaptation process of patients with venous ulcers to hydrogel treatment: a case study. [Processo adaptativo de pacientes com úlceras venosas ao tratamento com hidrogel: um estudo de caso [Dissertação na Internet]]. Niterói: Escola de Enfermagem de Afonso Costa/UFF; 2011:119.
62. Danski MTR, Liedke DCF, Vayego SA, et al. Unna boot technology in the healing of varicose ulcers. Cogitare Enfermagem 2016;21(3):1-9.
63. Cavalcanti LM, Pinto FCM, Oliveira GM, et al. Efficacy of bacterial celulose membrane for the treatment of lower limbs chronic varicose ulcers: a randomized and controlled trial. Rev Col Bras Cir 2017;44(1):72-80.
64. Ramsey DT, Pope ER, Wagner-Mann C, et al. Effects of three occlusive dressing materials on healing of full-

thickness skin wounds in dogs. Am J Vet Res 1995;56(7):941-9.
65. Jenkins DA, Mohamed S, Taylor JK, et al. Potential prognostic factors for delayed healing of common, nontraumatic skin ulcers: a scoping review. Int Wound J 2019;16:800-12.
66. Bellingeri A, Falciani F, Traspedini P, et al. Effect of a wound cleansing solution on wound bed preparation and inflammation in chronic wounds: a single-blind RCT. J Wound Care 2016;25(3):160-8.
67. Romanelli M, Dini V, Barbanera S, et al. Evaluation of efficacy and tolerability of a solution containing Propyl Betaine and Polihexanide for wound irrigation. Skin Pharmacol Physiol 2010;23(1):41-4.
68. Frank S, Kämpfer H, Wetzler C, et al. Nitric oxide drives skin repair: novel functions of an established mediator. Kidney Int 2002;61(3):882-8.
69. Kumar S, Singh RK, Bhardwaj TR. Therapeutic role of nitric oxide as emerging molecule. Biomed Pharmacother 2017;85:182-201.
70. Domingues EAR, Kaizer UAO, Lima MHM. Effectiveness of the strategies of an orientation programme for the lifestyle and wound-healing process in patients with venous ulcer: a randomised controlled trial. Int Wound J 2018;15:798-806.
71. Orr L, Klement KA, McCrossin L, et al. A Systematic review and meta-analysis of exercise intervention for the treatment of calf muscle pump impairment in individuals with chronic venous insufficiency. Ostomy Wound Manage 2017;63(8):30-43.
72. Alavi A, Sibbald G, Phillips TJ, et al. What's new: management of venous leg ulcers. J Am Acad Dermatol 2016;74(4):643-64.
73. Ingber DE. Tensegrity and mechanostransduction. J Bodyw Mov Ther 2008;12(3):198-200.
74. Corey SM, Vizzard MA, Bouffard NA, et al. Stretching of the back improves gait, mechanical sensitivity and connective tissue inflammation in a rodent model. PLoS One 2012;7(1):e29831.
75. Berrueta L, Muskaj I, Olenich S, et al. Stretching impacts inflammation resolution in connective tissue. J Cell Physiol 2016;231(7):1621-7.
76. Dryden SV, Shoemaker WG, Kim JH. Wound management and nutrition for optimal wound healing. Atlas Oral Maxillofac Surg Clin North Am 2013;21(1):37-47.
77. Wissing UE, Ek A-C, Wengström Y, et al. Can individualised nutritional support improve healing in therapy-resistant leg ulcers? J Wound Care 2002;11(1):15-20.
78. Oliveira PFT, Tatagiba BS, Martins MA, et al. Assessment of pain during leg ulcers' dressing change. Texto Contexto Enferm 2012;21(4):862-9.
79. Salvetti MG, Costa IKF, Dantas DV, et al. Prevalence of pain and associated factors in venous ulcer patients. Rev Dor 2014;15(1):17-20.
80. Smith D, Team V, Barber G, et al. Factors associated with physical activity levels in people with venous leg ulcers: a multicentre, prospective, cohort study. Int Wound J 2018;15(2):291-6.