

Efficacy of bacterial cellulose membrane for the treatment of lower limbs chronic varicose ulcers: a randomized and controlled trial

Eficácia da membrana de celulose bacteriana no tratamento de úlceras venosas de membros inferiores: estudo randomizado e controlado

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ABSTRACT

Objective: to evaluate the efficacy of Bacterial Cellulose (BC) membrane dressings in the treatment of lower limb venous ulcers. **Methods:** we carried out a prospective, randomized, controlled study of 25 patients with chronic venous ulcer disease in the lower limbs from the Angiology and Vascular Surgery Service of the Federal University of Pernambuco Hospital and from the Salgado Polyclinic of the County Health Department, Caruaru, Pernambuco. We randomly assigned patients to two groups: control group, receiving dressings with triglyceride oil (11 patients) and experimental group, treated with BC membrane (14 patients). We followed the patients for a period of 120 days. **Results:** There was a reduction in the wound area in both groups. There were no infections or reactions to the product in any of the groups. Patients in the BC group showed decreased pain and earlier discontinuation of analgesic use. **Conclusion:** BC membrane can be used as a dressing for the treatment of varicose ulcers of the lower limbs.

Keywords: Varicose Ulcer. Cellulose. Saccharum. Wound Healing.

INTRODUCTION

Chronic venous disease (CVD) of the lower limbs (LL) is common and occurs due to abnormal venous system function caused by valvular insufficiency, which may be associated with obstruction of blood flow^{1,2}. Its incidence is higher in women and only 30% of men are affected, which represents 3% to 5% of the population over 65 years old^{1,3-6}. It causes significant social impact, is prone to complications, such as infection and hemorrhage, limits quality of life and causes psychological changes.

The severity of LL CVD can be determined based on an international classification that considers clinical manifestation, etiological factors, anatomical distribution of the disease and pathophysiological findings (CEAP). By means of a score, the lesions can be divided into seven classes (0 to 6), the most severe clinical manifestation being the open ulcer (CEAP 6)⁷.

Currently, numerous materials are used as dressings for the treatment of chronic venous ulcers

(CVU), most of them expensive and, therefore, not available in the Brazilian Unified Health System (SUS)^{8,9}. The bacterial cellulose (BC) membrane, a biopolymer made from sugarcane molasses, has been developed at the Experimental Station of Sugar Cane in Carpina (EECC), Federal University of Pernambuco, Brazil (UFRPE)¹⁰. Several studies, including experimental analyzes and clinical trials have shown that BC is non-toxic, biocompatible and effective for tissue remodeling¹¹⁻¹⁴.

The aim of this study was to evaluate the efficacy of BC membrane dressing in the treatment of chronic varicose ulcers of the lower limbs.

METHODS

It is a prospective, randomized, controlled intervention study in which we evaluated 25 patients with CVD ulcers (CEAP 6)⁷ located in the lower limbs. These patients were treated at the Angiology and Vascular Surgery Service of the Clinics Hospital of the Federal

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University of Pernambuco (HC/UFPE) and at the Salgado Polyclinic, of the County Health Department in Caruaru, Pernambuco (PS / Caruaru / PE).

We randomly divided the participants in two groups: an experimental group that used BC membrane dressings (14 patients) and a control group that received conventional treatment with triglyceride oil (11 patients), a reference for the treatment of varicose ulcers in HC/UFPE and PS/Caruaru/PE. We performed the random selection with the software Randomizer (Urbaniak, G. C., & Plous, S. 2013, Version 4.0).

The sample was calculated based on the expected frequency of active or cured ulcers (3.6%) in the population with CVD⁵, considering the acceptable margin of error (5%), the confidence level (95%) and the level of heterogeneity (50%). The calculation was based on a normal distribution.

Research participants were submitted to anamnesis, including questions about previous treatments and clinical examinations. The study included adults, regardless of age and gender, with diagnosis of varicose ulcers of the lower limbs, CEAP 6, infected or not. The presence of peripheral pulses was the decisive criterion for inclusion.

We excluded children and adolescents, as well as patients with the following conditions: neuropathy, arterial, lymphatic or malignant ulcers, and anemia.

The BC membrane

The BC membrane is an exopolysaride obtained from sugarcane molasses, composed of stable polymerized sugars. Its size ranged from 2x2 to 6x60 cm and thickness, from 0.01 to 0.02 mm. It was perforated and packaged separately in surgical grade-type envelopes¹³. BC dressings were previously sterilized with 25kGy gamma irradiation and were donated by POLISA® Biopolymers for Health, and incubated at the EECC/UFRPE.

Dressing technique

We performed the clinical evaluation of the lesion based on the MEASURE¹⁵ methodology and

applied the dressing according to the standard operating procedures (SOP) of the HC/UFPE and PS/Caruaru/PE. We carried out the following steps: debridement; cleaning with saline solution (0.9%); wound swab for evaluation of contaminating bacteria; application of BC membrane or oils with essential fatty acids (EFA) or containing medium chain triglycerides (MCT).

After applying the coverage, we placed a secondary dressing (gauze) and elastic cotton bandage on the wounds of all patients. We performed weekly follow-up visits and instructed the patients to remain for 48 hours without changing the dressing. They were also instructed to remove the secondary bandage (gauze and bandages) prior to initiating personal hygiene and, during the bath, moisten the BC dressing by washing the area normally without removing it. BC membrane change was done weekly under medical supervision.

Evaluated outcomes

We considered the healing process within 120 days as the primary outcome. We collected sociodemographic information, medical history, primary diagnosis and comorbidities, as well as drug use, at the first clinical visit. We based the lesions clinical evaluation on the MEASURE¹⁵ acronym, evaluating the following parameters: M (measure), E (exudate), A (appearance), S (suffering), U (undermining), R (reevaluate) and E (edge).

We assessed the wound healing process by direct measurement of the lesion with a millimeter ruler and through the analysis of the images captured with a digital camera in all dressings exchanges during clinical consultation. We captured the lesion areas from the photographs with the software Image-Pro®, version 6.0 for Windows™.

We classified treatment efficacy according to: the degree of healing and size of the wound area; the characteristics of the tissue during the healing process; and the number of wounds completely healed.

We monitored confounding variables (presence of comorbidities and chronic and recurrent lesions) to limit variations in interpretation of the primary outcome. Comorbidities, represented by advanced diseases, can

interfere directly in the healing process. In addition, the presence of chronic and recurrent lesions may indicate resistance to other treatment protocols.

We performed a descriptive analysis for the sociodemographic data and statistical inference for the clinical data (MEASURE). We evaluated all data with the software GraphPad Prism®, version 3.0. We expressed the frequencies as percentages, using the Fisher exact test or the chi-square test. We presented continuous data as mean and standard deviation, studied by means of difference tests. We chosen the nominal level of 0.05 to reject the null hypothesis.

The study followed the ethical recommendations of the National Health Council, the Helsinki Declaration and the Nuremberg Code for studies with human beings and was approved by the Institutional Ethics in Research Committee (Nº 1.117.265, CEP/CCS/UFPE). We formally informed participants about the study and invited them to attend. All patients enrolled in the study signed an informed consent form (ICF).

RESULTS

Male participants constituted 54.5% of the control group and 50.0% of the experimental group, the majority with low level of schooling and retirees. The mean age of participants was 60 ± 17 years in the control group, compared with 61 ± 14 years in the experimental one. On the degree of functional independence, that is, the ability to walk without help, in the control group this corresponded to 72.7%, and in the experimental group, to 78.6%.

Regarding previous disease history, 18.2% had diabetes mellitus (DM), 18.2% had systemic arterial hypertension (SAH) and 9.1% had malignant neoplasms. In the BC group there were 35.7% with SAH, 28.6% with DM and 7.14% with malignant neoplasia. The mean body mass index (BMI) was 29.0 ± 8.0 kg/m² in the control group and 32.0 ± 8.0 kg/m² in the experimental group.

The swab culture was positive in 90.1% of the cases in the control group and in 100% in the experimental group (Table 1). The mean hemoglobin count was 13.0g/100ml in both groups.

Table 1. Bacteria found in secretion cultures (initial assessment).

Bacterial Profile (%)	Control	BC
<i>Pseudomonasaeruginosa</i>	30	42.9
<i>Providencia rettgeri</i>	20	0.0
<i>Acinetobacter</i>	10	0.0
<i>Proteus</i>	10	7.1
<i>Escherichia coli</i>	10	7.1
<i>Citrobacter</i>	10	7.1
<i>Providencia stuartii</i>	10	0.0
<i>Staphylococcusequorum</i>	0	7.1
<i>Gram negative bacilli</i>	0	14.4
<i>Staphylococcus aureus</i>	0	7.1
<i>Enterobacter</i>	0	7.1

Most ulcers were located in the right lower limb, seven (63.6%) in the control group and eight (57.1%) in the BC group. The most frequently affected site was the medial malleolus, five (45.4%) in the control and seven (50.0%) in the BC one. The wound area, measured during the initial clinical evaluation, was 50.0 ± 59.0 cm² in the control group and 54.0 ± 57.0 cm² in the BC. After 30 days (first reevaluation), the area was 31.0 ± 26.0 cm² in the control group and 55.0 ± 54.0 cm² in the BC group. After 120 days (second reevaluation), the wound area in the control group was 36.0 ± 27.0 cm² and 54.0 ± 49.0 cm² in the BC. There was no statistically significant difference between groups ($p=0.5748$). There was also no significant difference between the groups ($p=0.7120$) when the wounds were grouped by the mean area size at any of the evaluation times (initial, 1st or 2nd reevaluations).

The number of clinically healed wounds was similar in both groups, three (27.27%) in the control group and two (14.28%) in the BC membrane one. The analysis of the healing process by the Image-Pro Plus software revealed a statistically significant difference between the groups in the initial evaluation ($p=0.0096$), as well as in the first ($p=0.0096$) and in the second



Figure 1. Varicose ulcer, initial evaluation: A) Bacterial Cellulose Group; B) Control Group. Bright yellow fibrous tissue (red star), scarce granulation tissue (green arrow), macerated borders (black arrow) and signs of infection (redness and swelling) (purple arrow).

($p=0,0156$) reevaluations. The amount ($p=0.9928$) and the quality ($p=0.9921$) of exudates was not significant between the groups, although in the BC group the absence of exudates was more evident.

Pain intensity, measured by the analogue scale for pain, was lower in the BC group compared with controls ($p=0.0357$) in the second reevaluation, with earlier interruption of analgesic use by these patients. There was no difference in the other follow-up times (initial and first reevaluation).

In the control group, 63.6% of the patients had loss of subcutaneous tissue (deeper) in the initial evaluation. After 120 days, loss of epidermis (superficial wound) was more frequent (62.5%). In the BC group at baseline, participants with subcutaneous loss were also more common (57.14%) and, after 120 days, loss of epidermis was present in 83.33% of the cases. There was a significant difference between groups ($p<0.0001$). After 120 days of evaluation, patients with granulation tissue were 25% in the control group and 41.7% in the BC group. Epithelial tissue was present in 37.5% of the control group and 25.0% in the BC group. We also observed wounds with both types of tissue (granulation + epithelial) in the second reassessment in the control group, in 12.5% and in the BC group, in 25%, without statistical significance ($p=0.6946$).

All baseline and reevaluation measurement parameters (30 or 120 days after initial assessment) can be seen in Table 2 and are shown in Figures 1 and 2.

DISCUSSION

The assessment of the sociodemographic profile showed that the majority of patients with varicose ulcers of the lower limbs were, on average, 60 years old. They had a low level of education, evidenced by a high illiteracy rate, observed both in the control and in the experimental group (36% and 50%, respectively). These results are similar to those described in the literature^{16,17}. CVD of the lower limbs is insidious and progressive, and is usually aggravated by the difficulty presented by patients in taking proper care of their health, which determines the evolution to the disease's most severe forms^{16,18,19}. Low educational level is also related to the lack of access to medical care, since most of these patients depend exclusively on the Unified Health System (SUS) and therefore are often evaluated only when they present ulcers in advanced stages (CEAP 6).

In this study, most patients were male, contrary to the literature^{16,20}. Most were married, which may have contributed to adherence to treatment in both groups^{16,19}. A high percentage of patients, more than 60% in both groups, was unemployed and this data has also been widely described in the literature^{2,5,16,19}.

On the functional level, most participants were classified as independent, but almost all presented some degree of difficulty in walking, similar to what was found in the literature^{16,21,22}. Advanced CVD (CEAP 6) usually evolves with venous claudication (pain in walking), which,

Table 2. Evaluation of ulcers by MEASURE, initial assessment, after 30 and 120 days.

Parameters	Control			BC		
	Initial	1 ^a	2 ^a	Initial	1 ^a	2 ^a
	Assessment	Reassessment	Reassessment	Assessment	Reassessment	Reassessment
Lesion area ¹ (mean ± SD, cm ²)	50 ± 59	31 ± 26	36 ± 27	54 ± 57	55 ± 54	54 ± 49
Classification of area (mean±SD)						
up to 30cm ²	7.1 ± 5.7	12.8 ± 9.3	14.4 ± 8.7	8.6 ± 7.5	12.5 ± 7.5	12 ± 4.3
31 to 60cm ²	43.7 ± 4.7	43.8 ± 7.4	39.8 ± 3.2	44.1 ± 15.5	36 ± 0	37.3 ± 1.8
61 to 90cm ²	78 ± 0	71 ± 1.4	74 ± 5.7	96 ± 0	80.3 ± 0.4	77 ± 15.6
above 100cm ²	150 ± 70.7	0	0	145.3 ± 30.8	134.3 ± 36.3	119.7 ± 34.9
N ^o of clinically healed wounds	0	01	02	0	01	01
Healing process ² (%), pixel)						
healing ³	36.4	34.5	27.1	51.1 *	42.6 *	50.1 *
nothealed	63.6	56.4	61.7	48.9 *	40.9 *	38.6 *
completelyhealed	0	9.1	11.2	0	16.5 *	11.3
Exudate quantity (%)						
none	0	0	0	21.4	15.4	25.0
little	54.5	70	75	42.9	53.8	66.7
moderate	18.2	30	25	28.6	30.8	8.3
large	27.3	0	0	7.1	0	0
Exudate quality (%)						
none	0	0	0	0	15.4	25.0
serous	81.8	80.0	75.0	100	76.9	58.3
seropurulent	18.2	20.0	25.0	0	7.7	16.7
Pain intensity (analogue scale) (%)						
0	0	0	0	0	0	41.7 *
2	36.4	20.00	50.00	35.7	46.2	50.00 *
4	54.5	80.00	50.00	57.1	53.8	8.3 *
6	9.1	0	0	7.1	0	0
Appearance of wound (%)						
loss of epidermis	36.4	70.00	62.5	42.9	76.9	83.3 *
loss of subcutaneous tissue	63.6	30.00	37.5	57.1	23.1	16.7 *
Edge type						
epithelialized	9.1	60.0	50.0	14.3	15.4	16.7
bounded	45.5	10.0	37.5	57.1	30.8	33.3
irregular	45.5	30.0	12.5	28.6	53.8	50.0
Type of tissue						
integrity	0	0	0	0	7.7	0
Destroyed	18.2	0	12.5	14.3	15.4	0
Granulation	18.2	30.0	25.0	28.6	30.8	41.7
Epithelial	18.2	30.0	37.5	21.4	7.7	25.0
destroyed + granulation	27.3	20.0	0	0	0	0
Epithelial + granulation	9.1	10.0	12.5	7.1	7.7	25.0
Destroyed + epithelial	9.1	0	0	28.6	23.1	8.3
Destroyed + granulation + necrotic	0	10.0	12.5	0	7.7	0
Tissue color						
Red	36.4	40.0	75.0	50.0	46.2	50.0
Yellow	0	0	0	0	0	0
Mixed	63.6	60.0	25.0	50.0	53.8	50.0

The values are percentages (%) or average followed by the standard deviation (mean ± SD). * Statistically significant if $p < 0.05$. ¹ Manual evaluation of wound area, conducted by clinical evaluation. ² Evaluation of the healing process by Image-Pro Plus. ³ Evaluation on the amount of granulation tissue present in injury.

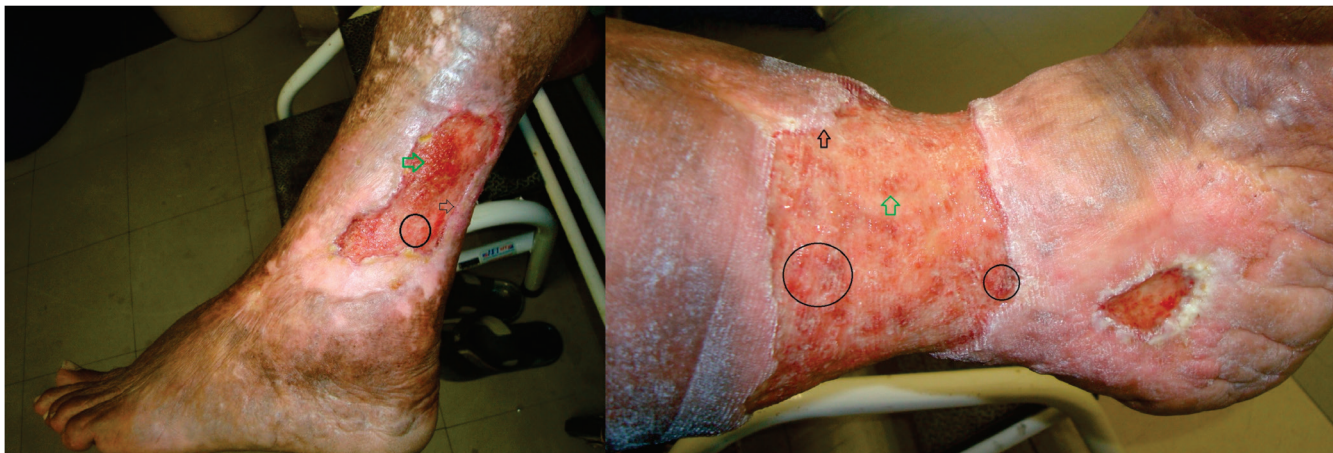


Figure 2. Varicose ulcer after 120 days: A) Bacterial Cellulose Group; B) Control Group. Granulation tissue more present in A than in B (green arrow), epithelial tissue lighter than surrounding tissue (that is, pink color) (black circle) and epithelialized borders (black arrow).

although not preventing ambulation, makes it difficult and slow.

As for comorbidities, the main ones were diabetes mellitus and arterial hypertension, common in the predominant age group of the studied patients²⁰. Although these diseases are not the cause of CVD, when present, they can aggravate the patient's condition and interfere with the ulcer healing process. Diseases that may interfere with wound healing have also been observed, such as rheumatoid arthritis and uterine cancer, in which therapy requires the use of steroidal anti-inflammatory agents and antineoplastic drugs^{23,24}.

Another factor that interferes with the healing process is obesity. In the control group, most participants had pre-obesity, whereas in the BC group, most were classified as grade-1 BMI²⁵. Several studies have shown that high BMI contributes to the prolongation of wound healing time²⁶. In a study that evaluated 50 patients with lower limb venous ulcers, the authors identified obesity in 46% of the patients²⁷.

The majority of the participants, in both groups (control: 90%, BC: 100%), had positive cultures for the wounds' secretion swabs. The microorganism most frequently found in both groups was *Pseudomonas aeruginosa*. This finding is expected and confirms the high rate of lower limbs CVU contamination^{27,28}. The longer the ulcer is active or the more frequent the relapses, the greater the chances of contamination, increasing the risk of infection, which in turn slows down the healing

process. The knowledge of the CVU's bacteriological profile can guide early empirical antibiotic therapy in cases where there is a clinical diagnosis of wound infection²⁹.

In the control group, the wounds were treated with substances based on essential fatty acids (EFA) or containing medium chain triglycerides (MCT), and then covered with gauze and bandages (foot and leg). Although this type of dressing may not be the gold standard for CVU treatment, it has been routinely used in other clinics in the SUS due to its low cost. Its use and advantages have been described in the literature^{5,8,18,22}.

The use of BC for the treatment of LL CVD is promising, since it is non-toxic¹¹, biocompatible¹² and promotes tissue remodeling. In addition, the BC membrane is made from a renewable source, whose raw material is the sugar cane, of low cost¹⁰, allowing its use in the SUS. There were no cases of cutaneous hypersensitivity reactions and BC-induced dermatitis. There have been reports of dermatitis and pain due to the use of MCT³⁰. There was no evidence of MCT dermatitis in this study.

Follow-up of with the MEASURE¹⁵ methodology occurred for 120 days. The healing process of this type of injury occurs slowly and, in many cases, complete wound healing is only obtained after a long period of time, sometimes more than 12 months^{5,27}, especially in cases of large ulcers⁶, similar to those presented by the majority of the participants of this study.

The 120 day period was chosen as sufficient to evaluate the CVU response to BC dressings. At the end of

the observation period, there was a reduction in the wound area in both groups. This difference was not statistically significant because several patients had extensive lesions and of different sizes in the first evaluation, which may justify the high standard deviation in relation to the mean area, which, therefore, compromises the results of the evaluation. To correct this potential error, wounds were classified according to their mean area or percentage (30cm², 31-60 cm², 61-90 cm² and above 100cm²) in each group, and then the comparison was made by group classification.

In the BC group, ulcers were more superficial at the end of the observation period in more than 80% of the patients (versus 60% in the control group). This may indicate that BC dressings acted as an inducer of tissue remodeling, stimulating the granulation process¹⁴. This is important because the ulcer healing depends not only on the epidermal proliferation at the margins of the lesion but also on the growth of the granulation tissue from the central area. Other studies have evaluated the application of BC membrane in animals and humans. The authors also observed an increase in granulation tissue, infection control and reduction of healing time^{12,13,31-35}.

All participants in the two groups reported decreased pain and discontinuation of analgesics. The participants who used BC dressing reported feeling more comfort and less pain than those in the control group. The BC membrane promoted self-care, including the possibility

of bathing, without having to worry about the dressing. There was no restriction on wetting the dressing, though were recorded some reports of dressing loss. The BC membrane is a wet dressing that favors hygiene, adheres well to the wound bed and spontaneously detaches once the wound is healed¹³. BC studies demonstrate that this is an innovative, effective, safe and low cost material^{13,31}.

This study is pioneer in the use of the BC membrane in the treatment of wounds resulting from peripheral vascular diseases in humans. It establishes the scientific basis for further research in the field of vascular surgery, including the use of BC for the treatment of other types of wounds caused by vascular diseases, such as ulcers, or even as dressings for other skin wounds, such as neuropathic ulcers and those caused by burns.

In addition, various structural modifications can be made to the BC membrane to optimize its properties as a dressing, increasing its water absorption capacity and antimicrobial activity or associating it with a controlled release system of antibiotics or other active principles.

Our study allowed us to observe that the Bacterial Cellulose membrane has the ideal properties as a dressing, for maintaining the humidity in the bed of the wound, absorbing excess exudates, limiting infectious processes and protecting the lesion against mechanical trauma. It is an effective alternative to the dressings used for the treatment of chronic varicose ulcers of the lower limbs.

R E S U M O

Objetivo: avaliar a eficácia de curativos com membrana de Celulose Bacteriana (CB) no tratamento de úlceras venosas de membros inferiores. **Métodos:** estudo prospectivo, randomizado e controlado de 25 pacientes com úlceras decorrentes de doença venosa crônica nos membros inferiores provenientes do Serviço de Angiologia e Cirurgia Vascular do Hospital de Clínicas da Universidade Federal de Pernambuco e da Policlínica do Salgado da Secretaria Municipal de Saúde, Caruaru, Pernambuco. Os pacientes foram distribuídos aleatoriamente em dois grupos: grupo controle, que recebeu curativos com óleo de triglicerídeos (11 pacientes) e grupo experimental, tratado com membrana de CB (14 pacientes). Os pacientes foram acompanhados por um período de 120 dias. **Resultados:** houve uma redução na área de ferida em ambos os grupos. Não houve infecção ou reações ao produto em nenhum dos grupos. Pacientes do grupo CB mostraram diminuição da dor e interrupção mais precoce do uso de analgésicos. **Conclusão:** a membrana de CB pode ser usada como curativo para o tratamento de úlceras varicosas dos membros inferiores.

Descritores: Úlcera Varicosa. Celulose. Saccharum. Cicatrização.

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