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Bacterial cellulose biopolymer film and gel dressing for the treatment of ischemic wounds after lower limb revascularization.

Curativo com filme e gel de biopolímero de celulose bacteriana no tratamento de feridas isquêmicas após revascularização de membros inferiores.

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A B S T R A C T

Objective: to evaluate the use of a bacterial cellulose biopolymer film and gel dressing in the treatment of patients with ischemic wounds submitted to lower limb revascularization. **Methods:** we conducted a randomized clinical trial in the Angiology and Vascular Surgery outpatient clinic of the Clinics Hospital of the Federal University of Pernambuco, between January 2017 and December 2018. We followed 24 patients after lower limb revascularization, divided into two groups: Experimental, treated with bacterial cellulose biopolymer film and gel, and Control, treated with essential fatty acids. Patients attended weekly appointments to change dressings and had their wound healing processes evaluated over a period of 90 days. **Results:** the reduction of the ischemic wounds' areas after 30 days was 4.3cm^2 (55%) on average for the experimental group, and the 5.5cm^2 (48.5%) for the control group (p>0.05). The complete healing rate at 90 days was 34.8%, 50% in the experimental group and 18.2% in the control group (p=0.053). **Conclusion:** the bacterial cellulose biopolymer film associated with gel can be used as a dressing in the treatment of ischemic wounds of patients undergoing revascularization of the lower limbs.

Keywords: Peripheral Arterial Disease. Saccharum. Cellulose. Biopolymers. Leg Ulcer. Lower Extremity. Biological Dressings.

INTRODUCTION

The most severe manifestation of lower limbs (LL) peripheral obstructive arterial disease (PAD) is the ischemic wound (IW). It occurs most often in the foot and leg and is associated with a high risk of limb loss[1]. Most patients with IW are candidates for open or endovascular arterial revascularization surgery, which aims to restore blood flow to the lower limb and thus avoid major amputations (above the ankle joint), which cause a significant deterioration in quality of life and increased mortality. Hardly accessible, alternative therapy already exists, such as the use of stem cells, but this is still not able to replace revascularization procedures[1-3].

In addition to arterial revascularization surgery, patients with IW often undergo surgical debridement and minor amputations. These procedures are performed after revascularization surgeries and aim to promote the removal of devitalized and infected tissues, and to facilitate the healing process[1-3]. Thus, there is need for dressings, performed at the outpatient level. There are many materials used in these dressings, most also used in venous and lymphatic ulcers. There is no standardization as to the material used in the dressings of such wounds, and several protocols are used[1-3].

The bacterial cellulose biopolymer film with associated gel (CBFG) is a nontoxic and biocompatible material that has been studied in various areas of medicine. It has been used in animal experiments as an arterial substitute and to fill eviscerated eyeballs.

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In humans, it has been tested in several areas of medicine, including dressings. It had satisfactory results in patients with venous ulcers, but had not yet been used as IW cover, which presents a distinct behavior from venous ulcers.

The aim of this study is to evaluate the use of CBFG in the treatment of IW after revascularization of the lower limbs[4-10].

METHODS

We study 24 patients presenting IW in the lower limbs and undergoing revascularization surgery of the lower limbs (endovascular or open) in the Vascular Surgery Service of the Clinics Hospital of the Federal University of Pernambuco (HC-UFPE). The study was a simple, prospective, randomized intervention study.

We randomized and distributed patients as follows: 13 patients in the group with film and gel biopolymer dressing (Experimental Group - EG) and 11 in the control group, with essential fatty acids (EFA) and gauze (Control Group - CG). We followed all individuals at the HC-UFPE Vascular Surgery Outpatient Clinic in weekly appointments, when we performed the clinical evaluation and dressing change, for a period of 90 days. We assessed the IW using the MEASURE[11] methodology.

CG patients underwent application of EFA to the wound and covered with gauze and fixed with bandages. EG patients were treated by applying a primary dressing composed of biopolymer gel applied directly to the IW bed and covered with the same biopolymer film (membrane) (Figure 1). This primary dressing was also covered with gauze and fixed with bandage, used only as a secondary dressing in this group.

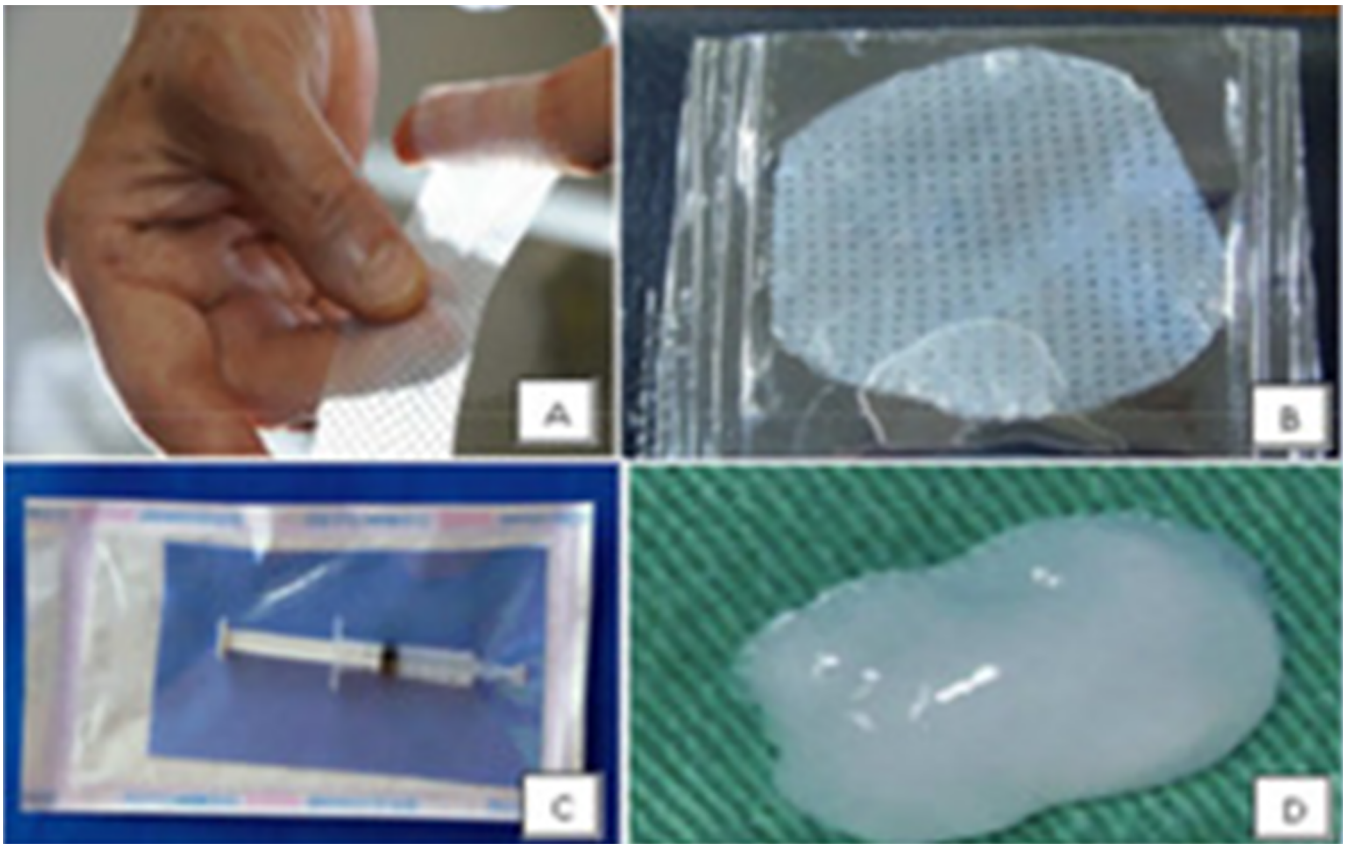

Figure 1. *Bacterial cellulose biopolymer film and gel: ease of membrane handling (A); sterile presentation (B); sterile bacterial cellulose gel (C); appearance of bacterial cellulose gel (D).*

We instructed CG patients to daily and completely change the dressing after the bath, cleaning the wound, reapplying EFA and a new cover with gauze, according to the Service protocol. We oriented EG individuals to the same procedure, but only by changing the secondary dressing (gauze), without removing the membrane directly adhered to the ulcer (primary dressing). We photographed all wounds with the same NIKON 3200 digital camera at baseline and at reevaluations for monitoring responses to the therapeutic measures.

We performed the statistical analysis with the GraphPad Prism 4.0 (GraphPad Software Inc., USA) and SigmaPlot 12.0 (Systat Software, Inc., Germany) softwares. We expressed continuous variables as mean and standard deviation or median and interquartile range 25%-75%, and mean difference and 95% confidence interval. We expressed categorical variables as number of cases and frequency per group studied. For data distribution analysis, we performed the Shapiro-Wilk normality test. To compare categorical variables between groups, were used the Pearson's chi-square test or Fisher's exact test. To compare continuous variables between groups, we used the Student's t-test or Mann-Whitney test for independent samples, and paired Student's t-test or Wilcoxon test for paired data to compare evaluations. We conducted the two-way ANOVA test with the Holm-Sidak multiple post-test comparisons, for comparisons between interventions (Control and CBFG) and effect of time within each intervention (pre- and post-intervention). We considered values of $p<0.05$ as significant.

The study was approved by the UFPE Human Research Ethics Committee (opinion number 1,117,265). All patients were informed about all the details of the research. Those who agreed to participate signed an Informed Consent Form.

RESULTS

Among the 24 evaluated patients, the ages ranged from 49 to 90 years (mean 67.4), and 12 (50%) were female. Regarding the risk factors for PAD, the most frequently found was systemic arterial hypertension (SAH), present in 20 (83.3%) patients, ten (90.3%) patients from the CG and ten (76.9%).%) from the EG ($p=0.59$). Smoking, diabetes *mellitus* (DM) and dyslipidemia were present in 19 (79.2%), 18 (75%) and 16 (66.6%) patients, respectively, with no significant difference between groups ($p>0.05$) (Table 1).

Endovascular surgical treatment (percutaneous transluminal angioplasty) was predominant in both groups, being more frequent in the EG, in ten (76.9%) patients, compared with CG, in six (54.5%) patients, but without statistical significance ($p=0.39$) (Table 2).

As for the evaluation through MEASURE, there was no statistical difference between the two groups on the first day of evaluation (Table 3).

There was also no statistical difference in any MEASURE parameter between groups over a 30-day period. Both dressings showed a significant reduction in length and width (EG of -0.7cm and -0.7cm, and CG, -0.9cm and -0.9cm, respectively) ($p<0.05$). EG had a depth reduction of 0.4cm, while CG had a reduction of 0.1cm, with statistical significance in favor of EG ($p=0.046$) (Figures 2 and 3).

Table 1. *Comorbidity profile and medical history.*

Variables	Control Group (n=11)	Experimental Group (n=13)	p-value
Smoking			
Yes	9 (81.8%)	10 (76.9%)	1.000
No	2 (18.2%)	3 (23.1%)	
Diabetes *mellitus*			
Yes	9 (81.8%)	9 (69.2%)	0.649
No	2 (18.2%)	4 (30.8%)	
Systemic arterial hypertension			
Yes	10 (90.9%)	10 (76.9%)	0.596
No	1 (9.1%)	3 (23.1%)	
Acute myocardial infarction			
Yes	9 (81.8%)	9 (69.2%)	0.339
No	1 (9.1%)	4 (30.8%)	
Stroke			
Yes	2 (18.2%)	1 (7.7%)	0.560
No	8 (72.7%)	12 (92.3%)	
Dyslipidemia			
Yes	6 (54.5%)	10 (76.9%)	0.650
No	4 (36.4%)	3 (23.1%)	
Thrombophilia			
Yes	0	0	-
No	10 (90.9%)	13 (100%)	
Neoplasia			
Yes	0	0	-
No	10 (90.9)	13 (100%)	
Previous surgery			
Yes	11 (100%)	11 (84.6%)	-
No	0	2 (15.4%)	
Use of medications			
AAS	11 (100%)	13 (100%)	-
Plavix	4 (36.4%)	12 (92.3%)	0.008
Cilostazol	8 (72.7%)	11 (84.6%)	0.630
Simvastatin	10 (90.9%)	13 (100%)	0.458
Others	9 (81.8%)	13 (100%)	0.435

** Fisher exact test.*

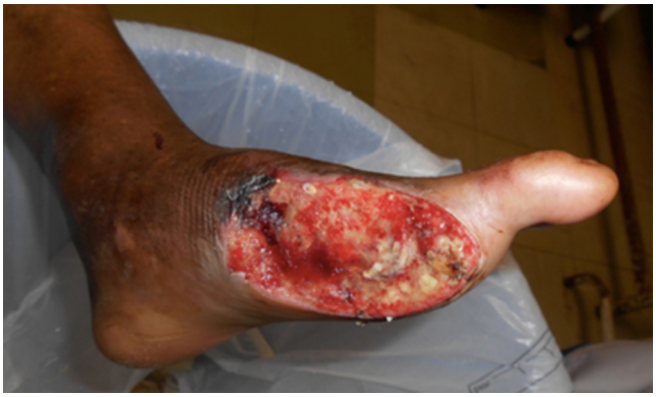

Figure 2. *Ischemic wound after limb revascularization and left hallux amputation. There is already a predominance of granulation tissue.*

Figure 3. *Appearance of ulcer after 30 days of outpatient follow-up: increased granulation tissue (CG).*

Table 2. *Surgical treatments for IW (data expressed as median with interquartile range 25%-75%).*

Variables	Control Group (n=11)	Experimental Group (n=13)	p-value
Amputation			
Yes	11 (100%)	10 (76.9%)	0.223[a]
No	0	3 (23.1%)	
Amputation site			
One toe	6 (54.6%)	8 (61.6%)	-
More than one toe	4 (36.4%)	2 (15.4%)	
Forefoot	1 (9.1%)	3 (23.0%)	
Debridement			
Yes	10 (90.9%)	10 (76.9%)	0.596[b]
No	1 (9.1%)	3 (23.1%)	
Revascularization type			
Bypass	5 (45.5%)	3 (23.1%)	0.390[a]
Transluminal angioplasty	6 (54.5%)	10 (76.9%)	

[a]*: Chi-square test;* [b]*: Fisher exact test.*

There was no statistical difference in the reduction of IW area within 30 days. It was 4.3 cm^2 (55%) in average for EG, and 5.5cm^2 (48.5%) or CG ($p>0.05$). Both groups showed a significant IW area reduction (Tables 4 and 5).

The 90-day complete healing rate was 34.8% (8 cases), 50% (6 cases) in the EG and 18.2% (2 cases) in the CG, but without statistical significance (p=0.193). We could not assess one EG patient because he died of cardiac complications (acute myocardial infarction) at 45 days of follow-up (Figures 4 and 5).

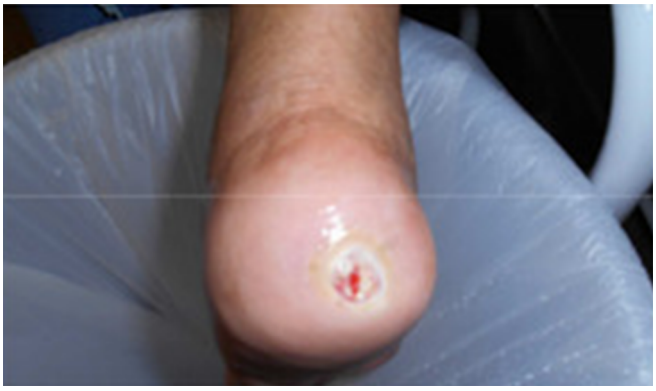

Figure 4. *Ischemic heel wound after left lower limb revascularization.*

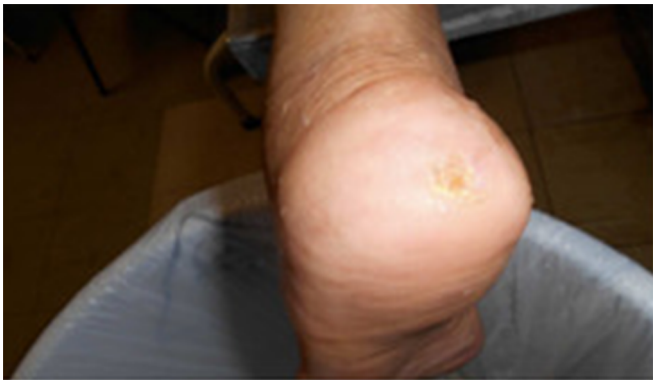

Figure 5. *Healed wound after six weeks of outpatient follow-up (EG).*

DISCUSSION

PAD affects patients of full age, the average age of patients in this study being 67.4 years. This result is similar to those found in the literature and is justified because PAD has a higher prevalence from the sixth decade of life on[12-14].

The evaluated sample had an equal number of patients in both sexes. Atherosclerosis is known to affect men earlier, but after menopause, the incidence in women tends to equal the opposite sex.

Table 3. *MEASURE-related aspects on the first assessment day. Data expressed as mean ± standard deviation or median (interquartile range 25%-75%).*

Variables	Control Group (n=11)	Experimental Group (n=13)	p-value
Wound measures			
Length	4.4±2.1(cm)	4.3±2.6 (cm)	0.974[a]
Width	2.3±1.3 (cm)	2.3±1.3 (cm)	0.900[a]
Depth	0.3 (0.0-0.5) (cm)	0.4 (0.3-0.8) (cm)	0.320[b]
Area	7.9 (2.2-24.8) (cm2)	8.3 (2.9-15.5) (cm2)	0.862[b]
Exudate amount			
None	1 (9.1%)	0	-
Little	10 (90.9%)	12 (92.3%)	
Moderate	0	1 (7.7%)	
Exudate quality			
Serous	10 (100%)	12 (92.3%)	1.000[c]
Seropurulent	0	1 (7.7%)	
Pain intensity			
0	0	1 (7.7%)	-
1-3	6 (54.5%)	7 (63.4%)	
4-6	4 (36.4%)	3 (23.1%)	
7-9	1 (9.1%)	2 (15.4%)	
Pain Period			
Continuous	1 (9.1%)	1 (7.7%)	-
Dressing change	4 (36.4%)	7 (63.4%)	
Did not mention	2 (18.2%)	2 (15.4%)	
Lesion aspect			
Appearance			
Partial skin loss	2 (18.2%)	0	-
Subcutaneous loss	9 (81.8%)	11 (84.6%)	
Skin loss	0	2 (15.4%)	
Border type			
Delimited	11 (100%)	12 (92.3%)	1.000[c]
Irregular	0	1 (7.7%)	
Kind of tissue			
Granulation	10 (90.9%)	12 (92.3%)	-
Epithelial	1 (9.1%)	0	
Necrotic	0	1 (7.7%)	
Coloring			
Red	10 (90.9%)	11 (84.6%)	1.000[c]
Yellow	1 (9.1%)	2 (15.4%)	
Detachment			
Present	0	0	-
Absent	11 (100%)	13 (100%)	

[a]: *Student's t-test;* [b]: *Mann-Whitney;* [c]: *Fisher's exact test.*

Table 4. *Comparison of MEASURE-related, quantitative data between the two groups after 30 days. Data expressed as mean ± standard deviation and mean difference (95% confidence interval).*

	Control Group (n=11)				Experimental Group (n=13)				p-value** (between groups)
	Pre-treatment	Post-treatment	Post/Pre-treatment difference	p-value*	Pre-treatment	Post-treatment	Post/Pre-treatment difference	p-value*	
Length (cm)	4.1±2.4	3.2±2.3	-0.9 (-1.5 a -0.3)	0.011	4.4±2.7	3.7±3.2	-0.7 (-1.3 a -0.1)	0.025	0.687
Width (cm)	2.3±1.3	1.4±1.1	-0.9 (-1.2 a -0.6)	<0.001	2.2±1.5	1.5±1.2	-0.7 (-1.1 a -0.3)	0.002	0.324
Depth (cm)	0.2±0.2	0.1±0.2	-0.1 (-0.2 a 0.1)	0.250#	0.5±0.5	0.1±0.2	-0.4 (-0.6 a -0.1)	0.011	0.046[a]
Area (cm^2)	12.2±11.9	6.7±7.6	-5.5 (-8.7 a -2.2)	0.004	13.0±15.9	8.7±13.1	-4.3 (-6.9 a -1.6)	<0.001#	0.543

** Paired t test; ** Two-way ANOVA; [a]: difference between conventional versus BP pre groups; # non-parametric tests (Kruskal-Wallis or Wilcoxon).*

Table 5. *Comparison of MEASURE-related, qualitative data between the two groups after 30 days. Data expressed as median (interquartile range 25-75%).*

	Control Group (n=11)			Experimental Group (n=13)			p-value (between groups)
	Pre-treatment	Pos-treatment	p-value	Pre-treatment	Pos-treatment	p-value	
Pain	2 (0-4)	0 (0-2)	0.157	2 (0-4)	0 (0-2)	0.096	0.978*
Exudate amount							
None	1 (9.1%)	4 (36.4%)	-	2 (15.4%)	4 (30.7%)	-	-
Little	10 (90.9%)	6 (54.5%)		10 (76.9%)	9 (69.3%)		
Moderate	0	1 (9.1%)		1 (7.7%)	0		
Exudate quality							
Serous	10 (100%)	7 (100%)	1.000#	10 (92.3%)	8 (88.9%)	1.000#	-
Seropurulent	0	0		1 (7.7%)	1 (11.1%)		
Appearance							
Erythema	0	2 (18.2%)	-	0	1 (7.7%)	-	-
Partial skin loss	2 (18.2%)	0		0	4 (30.8%)		
Total skin loss	9 (81.8%)	7 (63.3%)		11 (84.6%)	8 (61.5%)		
Total cutaneous loss	0	0		2 (15.4%)	0		
Edge							
Delimited	11 (100%)	11 (100%)	1.000#	12 (92.3%)	13 (100%)	0.474#	-
Irregular	0	0		1 (7.7%)	0		
Type							
Slaps	0	1 (9.1%)	-	0	0	-	-
Granulation tissue	10 (90.9%)	10 (90.9%)		13 (100%)	13 (100%)		
Epithelial tissue	1 (9.1%)	0		0	0		
Coloring							
Red	10 (90.9%)	9 (81.8%)	0.582#	11 (84.6%)	12 (92.3%)	1.000#	-
Yellow	1 (9.1%)	2 (18.2%)		2 (15.4%)	1 (7.7%)		

*Student's t-test or # Mann-Whitney test and Chi-square test or # Fisher's exact test; * two-way ANOVA.*

These facts make the groups equal in the prevalence of PAD in the older ages strata, as revealed in this research. Another aspect to be noted is that men die earlier than women due to atherosclerotic disease[12-14].

The most prevalent risk factors for PAD in the study sample were SAH, DM and smoking. These results are similar to those described in the literature and are related to the development of atherosclerosis. In addition, several studies link smoking and DM to progression to more severe forms of PAD. There fore, diabetic patients and/or smokers have increased risk of developing gangrene or IW[12-14].

Lower limb revascularization surgery is chosen according to the type, location and extent of PAD. The proximal and shorter lesions have good response both to the direct arterial bypass, and to endovascular treatment, the latter being less invasive. The most important consensus comparing open and endovascular surgery (Transatlantic Intersociety Consensus II) presented anatomical criteria for the selection of revascularization type.

One should also consider the patients' clinical conditions. Patients with high cardiovascular risk should be selected for less invasive endovascular treatment[12].

The average healing time of IW is usually 90 to 180 days, although there is a great divergence in the literature. In this study, healing after 90 days of follow-up occurred in about half of EG patients and in less than 20% of CG patients, but without statistical difference. The small sample may have influenced the non-statistical significance, despite the significant difference obtained in the percentage of total healing in EG[15-19].

The evaluation through the MEASURE[11] protocol was better applied in the 30-day period, when there was a greater presence of patients included in the study. Some patients could not attend all visits, making visits more spaced in the 90-day observation period, which only allowed the evaluation of the healing rate, rendering impossible to obtain quantitative data of a considerable part of the sample in that period.

The main factor for IW healing is good distal limb perfusion. The area of the lesions, the criteria for surgical reintervention used and the follow-up of the graft or treated artery patency may also influence IW healing[20-22].

We used The MEASURE method to standardize the IW assessment. We found a predominance of delimited wounds, with little exudate, rich in granulation tissue and without detachment. After adequate revascularization of the limb affected by PAD and surgical debridement to remove devitalized tissues, there is an expected decrease in the frequency of exudative wounds, which are more superficial an prone to granulation progression. In this study, we randomized patients only after surgical treatment of ischemia and wounds and, therefore, characteristics such as good granulation, little exudate and IW delimitation were similar in both groups[23].

The fact that CBFG was changed weekly without impairing healing results seems to be an important factor in patient adherence to treatment. In addition, the sensation of pain during dressing change causes suffering and even the onset of cardiac angina in arteriopathic patients. In the present study, patients had pain episodes during dressing change. The literature describes that anxiety on the eve of dressing change can be a trigger for death from acute myocardial infarction. Therefore, the spacing of dressing changes may even favor greater patient survival[9,20].

The gel-associated coverage favors better dressing fixation, providing longer permanence time and more spaced changes. In addition, longer-lasting coverage over the injury reduces treatment costs. Therefore, the association of CBFG provides better adhesiveness and, because it is translucent, it maintains an important feature of the dressing that is allowing wounds' evaluation, even covered[21].

Considering that the CBFG has been used with good results in venous disease in previous studies and considering the results of this study, CBFG becomes a good alternative in the treatment of wounds of various etiologies. Ulcers of different pathophysiology treated with CBFG demonstrated similar responses to conventional treatment[9,21].

The various materials produced by the Carpina Sugarcane Experimental Station (UFRPE) showed good response in clinical research applied to humans, which accredits the material to be widely explored in medical practice[9].

A limitation of this study was the non-classification and comparison of patients according to angiosome revascularization criteria, which is a current trend in vascular surgery[23]. We did not proceed this way because we included for evaluation only patients whose surgical treatment was successful, and probably the affected angiosome had been adequately revascularized. Another limitation to be considered is the small number of patients evaluated, which may have influenced the statistical results obtained as described in the previous paragraph.

The good results achieved by CBFG in IW healing and its good tolerance by patients increase the possibility of its use in the short/medium term. We conclude that the sugarcane biopolymer gelatinous film-based dressing can be used for the treatment of ischemic wounds after revascularization of the lower limbs.

R E S U M O

Objetivo: *avaliar o uso do curativo de filme e gel de biopolímero de celulose bacteriana no tratamento de pacientes com feridas isquêmicas submetidos à revascularização dos membros inferiores.* **Métodos:** *ensaio clínico randomizado realizado no ambulatório de Angiologia e Cirurgia Vascular do Hospital das Clínicas da Universidade Federal de Pernambuco, entre janeiro de 2017 e dezembro de 2018. Foram acompanhados 24 pacientes após revascularização de membros inferiores, divididos em dois grupos: Experimental, tratado com filme e gel de biopolímero de celulose bacteriana, e Controle, tratado com ácidos graxos essenciais. Os pacientes foram acompanhados em consultas semanais para troca dos curativos e o processo de cicatrização das feridas foi avaliado em um período de 90 dias.* **Resultados:** *a redução da área das feridas isquêmicas no período de 30 dias foi de 4,3cm² (55%), em média, para o grupo experimental, e de 5,5cm² (48,5%) para o grupo controle (p>0,05). A taxa de cicatrização completa, em 90 dias, foi de 34,8%, sendo 50% no grupo experimental e 18,2% no grupo controle (p=0,053).* **Conclusão:** *o filme de biopolímero de celulose bacteriana associada a gel pode ser utilizado como curativo no tratamento de feridas isquêmicas de pacientes submetidos à revascularização de membros inferiores*

Descritores: *Doença Arterial Periférica. Saccharum. Celulose. Biopolímeros. Úlcera da Perna. Extremidade Inferior. Curativos Biológicos.*

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