Evaluation of treatment with carboxymethylcellulose on chronic venous ulcers*

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Abstract: Background: Among the chronic leg ulcers, venous ulcers are the most common and constitute a major burden to public health. Despite all technology available, some patients do not respond to established treatments. In our study, carboxymethylcellulose was tested in the treatment of refractory chronic venous ulcers.
Objective: To evaluate the efficacy of carboxymethylcellulose 20% on the healing of chronic venous ulcers refractory to conventional treatments.
Methods: This is an analytical, pre-experimental study. Thirty patients were included with refractory venous ulcers, and applied dressings with carboxymethylcellulose 20% for 20 weeks. The analysis was based on measurement of the area of ulcers, performed at the first visit and after the end of the treatment.
Results: There was a reduction of 3.9 cm^2 of lesion area (p=0.0001), corresponding to 38.8% (p=0.0001). There was no interruption of treatment and no increase in lesion area in any patient.
Conclusions: Carboxymethylcellulose 20% represents a low cost and effective therapeutic alternative for the treatment of refractory chronic venous ulcers. However, controlled studies are necessary to prove its efficacy.
Keywords: Carboxymethylcellulose sodium; Leg ulcer; Varicose ulcer; Wound closure techniques; Wound healing

INTRODUCTION

Chronic leg ulcers affect about 1% to 3% of the world population, and it is estimated that this data worsen with increasing longevity of individuals. Among them, venous ulcers are the most common and constitute a major burden to public health, because they are related to absenteeism and absence from work.[1,2]

Occurrence of chronic venous insufficiency is closely related to the emergence of ulcers, but this process is still not fully understood.[1,3,4]

Various aspects that affect the healing process, such as location, depth and extent of the lesion, presence or absence of infection, nutritional status, co-existence of chronic degenerative diseases and age of the patient, are crucial to the development of treatment protocols.[5]

Treatment of chronic skin ulcers aims to anticipate the healing process and prevent recurrences and complications.[6,7,8]

The main therapeutic methods currently available are compression, local treatment, use of systemic drugs and surgery to correct the changes of the venous system.[6,9]

After the healing of the ulcer, the greatest challenge is to avoid relapse. Thus, health services should offer monitoring and guidelines to help patients in the

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incorporation of everyday practice, such as the use of compression stockings, mediation between activity and rest periods, as well as care to avoid trauma.[6]

Treatment of choice for venous ulcers is compression therapy, requiring the exclusion of artery disease and neuropathic processes for its application. Compressive dressings, elastic stockings and pneumatic compression are the methods available. [6,10-13]

New and different technologies, some with high costs, are provided in the market. [14] Therefore, carboxymethylcellulose, a component substance of several products used in the treatment of wounds and easy handled, has been tested in the treatment of venous ulcers. [15,16]

This article presents the results of using CMC 20% in 30 patients with chronic venous ulcers refractory to compression therapy and to conventional local treatments.

The research, which complies with the resolution 196/96 of the National Health Council, was approved by the Ethics Committee in Research of the University Hospitals Clementino Fraga Filho, of the Universidade Federal do Rio de Janeiro, and Pedro Ernesto, of the Universidade Estadual do Rio de Janeiro. All patients signed the informed consent.

OBJECTIVE

To evaluate the effectiveness of CMC 20% in the healing of chronic venous ulcers refractory to conventional treatments.

METHODS

Analytical, pre-trial study, conducted from January 2011 to June 2013. We included 30 patients with 40-73 years who presented chronic venous ulcers, with an area ≥3 cm^2, with >3 months of evolution and who were refractory to compressive treatments, including Unna boot, and to local treatments with essential fatty acids (EFA), silver sulfadiazine 1%, and collagenase, among others. Patients did not have signs of malignant transformation and/or skin or bone infection; presented hemoglobin ≥10 g/dl; maximum blood glucose 200 mg/dl; absence of signs and symptoms of congestive heart failure or deep vein thrombosis; ankle-brachial index (ABI) >0.8; and minimum sensitivity to violet monofilament (Semmes-Weinstein 2.0 g).

Protocol of service

1. Delivery of an illustrated brochure containing guidance on performing the dressing at home and outpatient treatment for patients and families.
2. Weekly dressing performing in the clinic, under aseptic technique, by one of the researchers associated with the project.
   - Cleaning of the area adjacent to the lesion with liquid soap with triclosan 1% and saline solution 0.9%.
   - Abundant irrigation of the wound bed with saline solution 0.9%.
   - Drying of the perilesional areas.
   - Application of CMC 20% on the wound bed.
   - Perilesional skin hydration with petrolatum.
   - Lesion covering with gauze and fixation with crepe dressing.
3. Daily change of dressing at home in accordance with previous guidance.
4. Weekly monitoring of the healing process: measure of the wound extension, assessment of number and characteristics of exudate, photographic documentation and observation of local adverse events such as redness, pain, discomfort and maceration of the wound edges.

Patients were instructed verbally about the need for alternating rest and activity. Limb elevation and ankle joints mobilization were recommended during the rest period alternated with physical activities, such as walking, according to individual tolerance.

The material used in the home dressing was offered to patients weekly.

Evaluation of development criteria:

- Optimal healing: 100% (wound closure)
- Good healing: 60-99% reduction of the ulcer area
- Regular healing: 30-59% reduction of the ulcer area
- Poor healing: <30% reduction of the ulcer area

The analysis of the evolution occurred by comparing the ulcer area measured at the first visit and after a maximum of 20 weeks.

Statistical analysis

In the descriptive analysis, observed data were presented in the form of table, expressed as mean, standard deviation, median, interquartile range, minimum and maximum for numeric data, and the frequency (n) and percentage (%) for categorical data. [17]

In inferential analysis, to verify if there was significant variation in the area of the lesion from the beginning to the end of the treatment, we used the Wilcoxon signed-rank test. [17] To assess whether there was a significant variation in the response and in the response time to the treatment regarding the development of ulcers, we used the Kruskal-Wallis ANOVA test.

The significance determination criterion used was the level of 5%. Statistical analysis was performed with SAS 6:11 software (SAS Institute, Inc., Cary, NC).

RESULTS

In the study sample, the mean age of patients was 59.9 years. In median values, the ankle-brachial index (ABI) was 1.1 and the initial area of lesion was 10.3 cm^2.

Table 1 shows the mean, standard deviation (SD), median, minimum and maximum of numeric clinical variables.

There was a predominance of female patients: 16 (53.3%) women versus 14 (46.7%) men. Regarding comorbidities, systemic hypertension was present in 40% of cases, diabetes mellitus and heart disease, in 16.7% each, and smoking in 26.7% of cases.

In 53.3% of cases, ulcers had >10 years, a fact to be considered in the analysis of responses to treatment. Pain was reported by 80% of patients.

Table 2 provides the frequency (n) and percentage (%) of categorical clinical variables.

Regarding clinical course, we observed optimal healing (wound closure) in 6.7% of patients (n=2); good healing (reduction of the ulcer area from 60% to 99%) in 23.3% (n=7); and regular healing (reduction from 30% to 59%) in 36.7% (n=11). Poor healing (reduction of <30% of the lesion area) was found in 33.3% of patients (n=10).

Regarding the healing evolution, expressed from median values, a 3.9 cm^2 absolute reduction was observed in lesion area, corresponding to 38.8% relative reduction. Mean absolute reduction was 9.6 cm^2, corresponding to 44.7% of relative reduction (p=0.0001). The p value was established by the Wilcoxon signed-rank test.

Treatment response was differentiated regarding time of ulcers evolution. Relative reduction of lesion area (%) in the group that developed lesions <1 year was higher than the group that developed lesion from 1 to 10 years and for >10 years. Interquartile range shows no variation in treatment time of groups 1-10 years and >10 years, unlike what happened with the group <1 year. However, there was no significant difference (Table 3).

Table 1: Numeric clinical variables: age, ankle-brachial index (ABI), initial lesion area in cm^2 and treatment duration in weeks

Variable	M (DP)	Med(Min/Max)
Age (years)	59.9 (8.7)	63 (40-73)
ABI	1.11 (0.19)	1.09 (0.80-1.4)
Initial lesion area (cm^2)	19.7 (24.2)	10.3 (3-11.5)
Treatment duration (weeks)	19.4 (2.4)	20 (9-20)

M: mean; SD: standard deviation; Med: median; Min/Max: minimum/maximum

Table 2: Categorical clinical variables

Variable	N (%)
Gender	
Male	14 (46.7)
Female	16 (53.3)
Smoking	8 (26.7)
SAH	12 (40.0)
Heart disease	5 (16.7)
DM	5 (16.7%)
Time of ulcer evolution (years)	
< 1	5 (16.7)
1 to 10	9 (30.0)
> 10	16 (53.3)
Pain	24 (80.0)

SAH: systemic arterial hypertension;
DM: diabetes mellitus

Table 3: Response and response time to treatment according to the duration of ulcer evolution

Variable	Time of ulcer evolution (years)	n	median	Q1	Q3	IIQ	p value[a]
Absolute delta of lesion area (cm^2)	< 1	5	10.5	0.8	42.7	41.9	0.76
	1 a 10	9	3.5	1.2	5.4	4.2	
	> 10	16	4.0	1.9	10.6	8.7	
Relative delta of lesion area (%)	< 1	5	64.0	15.5	89.9	74.4	0.74
	1 a 10	9	37.1	25.1	62.2	37.1	
	> 10	16	41.2	18.5	56.3	37.8	
Duration (weeks)	< 1	5	20.0	14.5	20.0	5.5	0.34
	1 a 10	9	20.0	20	20	0	
	> 10	16	20.0	20	20	0	

IIQ: interquartile range a: Kruskal-Wallis ANOVA test

Duration of treatment was 20 weeks, on median values. It is noteworthy that 2 patients did not reach the maximum estimated time, because they achieved complete healing of ulcers, one in 9 weeks and another in 12 weeks. No patient stopped treatment during the study and there were also no cases of increasing in the lesion area.

DISCUSSION

In accordance with other studies, in our sample patients' mean age was 59.9 years and there was a predominance of female patients (53.3%).[12,18-20]

Regarding the existence of comorbidities, we highlight the occurrence of systemic hypertension, present in 40% of cases. Diabetes mellitus and heart disease were present in 16.7% of cases and smoking in 26.7%. In the study of Frade et al, an association between chronic venous insufficiency and hypertension was found in 43.7% of cases.[18]

Pain, a relevant clinical data for the humanization of care and planning of interventions, was identified in 80% of cases.[21]

The high prevalence of venous ulcers and the occurrence of relapses generate individual and collective negative impacts.[6] Actions for proper patient care should include new therapeutic measures or new technologies with best cost/benefit for wound healing.

Carboxymethylcellulose is an anionic polymer derived from cellulose, a macromolecule formed by primary and secondary repeating units. It has the qualities of polysaccharides such as solubility, viscosity, and ability to form gels. Also, it is produced via Williamson reaction, by treating the cellulose with monochloroacetic and/or monochloroacetate acid (sodium salt) in the presence of sodium hydroxide excess.[22,23]

This polymer can be obtained from cheap and abundant biomass such as sugarcane bagasse. It is found in the form of white powder that, when dissolved, forms a clear gel, non-toxic, colorless and odorless. It acts as a thickener, stabilizer, nonstick, sliding, water retainer and rheology controller. Also, it forms resistant films, being very soluble in cold or hot water and physiologically inert. It is one of the most versatile polymers with applicability in various industrial sectors, including food industry.[22,23,24]

In this study, the application of dressing with CMC 20% promoted, in 2 cases, the complete wound closure, in the 9 and 12 weeks, also promoting reduction of the lesion area in approximately two thirds of patients, considering those who had a good healing (60-99%) and regular healing (30-59%)

Improvement in the appearance of the ulcer bed was also observed, with reduction of the amount of devitalized tissues and increase in granulation tissue. These aspects are also expected in an effective treatment.

No patient stopped treatment, which may indicate good tolerance of the product. Mild sensation of "stinging" or "burning" was reported by only 2 patients and was the only adverse event identified. It is considered, therefore, a need for further investigations to establish its effect from formulations with different concentrations, based on the characteristics of the wounds.

We did not find in the literature studies that have evaluated the use of CMC alone in the treatment of wounds. However, the property to facilitate cellular rehydration and debridement is attributed to CMC, reason why it is one of components of different coverings, including hydrocolloid plates and hydrogel, whose function is to maintain moisture in the wound bed and promote autolytic debridement, facilitating healing. [15,16] These properties led us to investigate its applicability in the treatment of patients in the public healthcare system who were refractory to other treatments.

The polymer (CMC) presents low cost and can be produced in compounding pharmacies, such as university, Brazilian Public Healthcare System (SUS) or Ministry of Health pharmacies. The manipulation of CMC granted the product an expiration date of approximately 4 months. Its use is simple and requires no special training, thus it can be provided to the patient for use at home.

Production of CMC in concentration of 20% determined the optimum texture for application limited to the wound area. At higher concentrations, such as CMC 40%, the formation of a paste with thick, sandy texture, and difficult to handle, was observed. The use of lower concentrations, 1% and 5.5-6%, has been related to the treatment of nystagmus and healing of corneal ulcers. [25,26]

Spending on treatment, considering all inputs inherent to the dressings, ranged from R$ 463.53 to R$ 1023.40 per patient, according to the time (maximum of 20 weeks) and the extent of lesion.

Response to treatment was weakly correlated with the time of development of ulcers. However, the prolonged existence of the lesion has been associated with suffering and loss of working conditions, which constitutes an important socio-economic problem.[21,27,28] Interdisciplinary work is necessary, as a way to provide assistance centered on patient needs.[29] Prevention is the focus. Nevertheless, when this is not possible, we must contribute to healing and to facing the reality. Establishing techniques and technologies with good cost-benefit ratio is an important way to do so.[30]

Study limitations

In this study, the absence of a control group and the consequent possibility of the occurrence of selection bias, as well as those related to behavioral changes in subjects in nonrandomized studies (Hawthorne effect), prevented conclusions about the effectiveness of the product.[31-33]

Diabetic patients were included and, despite the measurement of ABI >0.8 indicates lower risk of arterial impairment, vascular abnormalities caused by diabetes can interfere with the accuracy of this method.[34] Moreover, it was not possible to establish monitoring of cases in the long run.

CONCLUSION

This study presents CMC 20% in paste as a possible low-cost therapeutic alternative for the treatment of refractory venous ulcers. However, to establish its effectiveness, it is recommended to conduct controlled studies. It is also suggested studies to assess the implementation of the substance at different concentrations.❑

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