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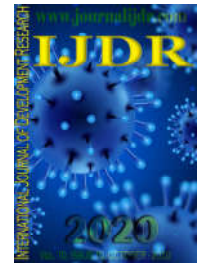
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COST OF TREATMENT AND REDUCTION ACHIEVED BY CHRONIC ULCER IN DIABETIC PATIENTS - A COMPARISON BETWEEN HYDROGEL AND HUMAN RECOMBINANT EPIDERMAL GROWTH FACTOR

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ABSTRACT

The study provides results from a double-blind clinical trial of 25 patients with diabetic or venous chronic ulcers. To evaluate the assessing cost of outpatient treatment with two technologies: 2% carboxymethylcellulose hydrogel or human recombinant Epidermal Growth Factor carbogel. Patients were randomly allocated to two ulcer treatment groups, human recombinant Epidermal Growth Factor treated (intervention group = 14), and 2% carboxymethylcellulose hydrogel (control group = 11); both treated during 90 days. To calculate the costs of each patient's procedures, direct costs and human resources costs were measured in Brazilian currency and converted into US dollars. Statistical analysis of clinical data was performed based on intention to treat. Were analyzed the proportion of cases with wound reduction; cost benefit of the treatment given by the average value of each 1cm² wound reduction; statistics on the cost of reducing each cm² of wound for each patient presenting wound reduction. In all evaluated periods, the proportion of cases with decreased lesion area was higher in the intervention group; It presented better cost-benefit ratio and lower average and median reduction cost for each reduced cm² of the wound. Data suggested that growth factor therapy may be cost-effective and innovative complement to standard wound care.

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INTRODUCTION

Among the various chronic complications associated with diabetes mellitus, various conditions, such as those resulting from peripheral neuropathy and venous disease, can lead to chronic ulcers [1]. These lesions may progress with infection, osteomyelitis and amputation associated with significant morbidity, mortality and high costs [2, 3]. Currently, in addition to the comorbidities associated with diabetes, the increasing life expectancy of these patients also increases the incidence of these conditions [4]. In developing countries such as Brazil, evidence suggests that lifetime occurrence of diabetic ulcers is between 19% and 34% [5].

These injuries and amputation are more common in low- and middle-income countries [6]. The health costs of treating chronic ulcers in diabetic patients with venous leg ulcers and diabetic foot ulcers are five times higher than in diabetic individuals with no ulcer [4, 7]. Those costs are mainly related to hospitalizations, more frequent in diabetics, but also to the care costs of treatment and follow-up of outpatient clinical management [8-11]. These injuries have received more and more attention from the multidisciplinary health team with the intention of developing advanced technology coverage in order to improve the healing result in the shortest possible time making it economically interesting [12]. These therapies

costs increase the importance of studies in search of new drugs and dressings capable of interacting with the injured tissue, aiming to accelerate the healing process [13, 14]. The topical Recombinant Human Epidermal Growth Factor (rhEGF) use has been highlighted in the wound healing process. It has been considered able to accelerate the rate of epidermal regeneration and reepithelialization with positive results in, Europe, Asia and Central and South America, expanding its worldwide acceptance to Europe [15-21]. RhEGF stimulates the proliferation and migration of keratinocytes and fibroblasts, improving wound healing [22]. Because it is a protein, it has low stability and spontaneously degrades [23] and therefore several technologies have been tested to allow its topical application on the lesions. The use of advanced and innovative technologies can increase the cost of products. In this sense, we sought to evaluate the cost of outpatient treatment of diabetic or venous ulcers of diabetic patients, using two technologies: 2% carboxymethylcellulose hydrogel (CMC) or rhEGFcarbogel.

MATERIALS AND METHODS

Data base: The database used for this analysis was originated in a randomized, double-blind, pragmatic clinical trial conducted at a public hospital located in Niteroi, Rio de Janeiro, Brazil. The results of the effectiveness of this study have already been approved in the other article that is awaiting approval from the journal. After approval by the Research Ethics Committee, all patients gave written informed consent and the collection process lasted 17 months starting in November 2016 and ending in April 2018. Participants were recruited for convenience during nursing consultations with diabetic outpatients who treated diabetic or venous chronic ulcers at the Wound Repair Outpatient Clinic of the hospital where the study was conducted. Follow-up time for each patient was 90 days. In addition to epidemiological data, detailed data on the material, supplies and covers used by each patient were retrieved from the clinical trial.

Clinical Trial Development: The study compared the cost of healing of diabetic and venous ulcers in diabetic patients using two different coatings: rhEGFcarbogel or 2% carboxymethylcellulose hydrogel (CMC). Both products favor the healing of chronic ulcers. The 2% CMC hydrogel is amorphous and used as a gold standard in the study hospital for the treatment of these lesions. Randomization was performed by randomly allocating participants into the groups, Intervention (rhEGFcarbogel) named product A and Control (2% CMC) named product B. The patients were instructed on how to change the dressing daily, reapplying the product in sufficient quantity to cover the lesion with a thin layer. The weekly change in the outpatient clinic, as well as treatment of the injury was performed by the nurse. With this conduct, we sought the closest possible approximation to the reality of treatment of the patient. The rhEGFcarbogel needs to be stored in pump, airless vial and refrigerated for up to 60 days to maintain active stability. In order to blind the patients, both products were stored the same way and kept refrigerated. Data related to product effectiveness and cost were collected. In all other nursing consultations, the wound was reevaluated, with the registration of the injury-specific data at weeks 01, 06 and 12. The participant and the two evaluators were blinded to the rate of reduction of the lesion area.

Wound Reduction: The wound reduction analysis was calculated through formula 1, considering the area of the initial wound and the area after 12 weeks of treatment [24, 25].

Formula 1: Wound Reduction = (final wound area - initial wound area)

To evaluate the reduction of the lesion area in square centimeters over the 12 weeks of treatment, the technique of manual planimetry and photography was performed. It consists of tracing the contour of the wound in sterile transparent material, calculating its final area by quantifying centimeter squares on squared paper [26].

The economic assessment

This study was based on the cost of a public agency in Brazil from the perspective of the Unified Health System (SUS). To calculate the treatment costs, data registration forms were established to observe how much material was used throughout the therapy considering both the outpatient care expenses and the material dispensed for home. The micro-costing survey was performed with all material dispensed for the patients' dressings. The calculation of these items was made from the average spent during treatment. The home kits supplies were delivered according to the demand at each outpatient visit for dressing. The home dressing supplies observed were sterile hydrophilic gauze pad, crepe bandage, waterproof tape roll, vial containing 0.9% saline solution and needle (40x12). To perform the outpatient dressing, the same household inputs were observed plus disposable surgical mask, surgical cap, disposable procedure gloves, sterile surgical gloves, number 20 scalpel blade. This material was accounted for both during outpatient consultation and throughout weekly home use of the patient. A survey was conducted to estimate the cost of supplies used by each patient in dressings by consulting purchase prices from a study hospital. An analysis includes direct costs: procedural costs considering test products, curative execution inputs, and human resource costs in outpatient consultations where the nursing time used in the consultation was recorded and calculated. As inputs, we considered the materials used in the dressing, at the outpatient clinic and at home. The measure used to account for or use was a Brazilian currency (Real). After accounting, the costs were converted to US dollars. For this conversion, a reference value was considered as an average between the highest closing value of the US dollar and the lowest locking value in May 2017, the month in which the cost data were collected in reais. Therefore, the reference value used in the conversion was 1 US dollar for 3,24225 reais. To evaluate the amount of gel used by the patients, a measure was made for home use, where the weekly return of the dispensed bottle was requested, which was weighed at the time of consultation, and its weight compared to the previous week. Outpatient use was measured at the time of dispensation.

During the weekly nursing consultation to perform dressings at the outpatient clinic, the time taken to perform this procedure was timed in minutes. The nursing workforce was calculated as the average between the base values of the fee table determined by Resolution 301/2005 of the Federal Nursing Council (COFEN), which regulates the profession, and the average value of the professional in the study hospital. To minimize the interpretation variables in the performance of

the timing, it was previously determined the moment considered the beginning and end of the procedure, defined as the opening and closing of the patient's bandage at the outpatient clinic. Statistical analysis of clinical data was performed based on the intention to treat. The choice of comparison tests between the groups was performed respecting the assumptions determined by the results, characteristics and behavior of the clinical study variables.

Calculation of cost-effectiveness of treatment given by the average cost of each 1cm² wound reduction

Average cost of 1 cm² wound reduction in period $\Delta t = \frac{\sum \text{costs in } \Delta t \text{ period}}{\sum \text{reductions in } \Delta t \text{ period}}$ = formula 2

\sum reductions in Δt period

This calculation took into consideration the entire sample, including the cost of cases in which there was no reduction or one with increased lesion size. In the latter case, the value was entered as a negative reduction in the denominator, which decreases the denominator, penalizing the cost-benefit ratio as it should be. Calculation of average (and other statistics) of cost of reduction of each 1 cm² of wound. For each patient who presented injury reduction, the total cost of treatment for each patient in the period was calculated. This calculation was made through the cost of reducing each 1 cm² in the period, divided by the total amount of reduced square centimeters in the same period.

RESULTS

Table 1 shows the frequency distribution of wound area variation over the evaluated time periods for both groups. In all periods considered, and for both control and intervention groups, there was at least 1 case of treatment failure, it means that, neither treatment was 100% effective in reducing the wound area over the 12 weeks. It was also possible to observe at least 1 case in which there was no alteration of the lesion area or in the same one that increased its area. Also, according to table 1, the treatment failure for each period were estimated for both groups. The probability of no wound reduction in the first 6 weeks for the control group was 18.2%; while in the intervention group it was 14.3%. The same calculation was made for the later period of the last 6 weeks, where the control group resulted in 54.5% while in the intervention group it was 28.5%. The probability of no wound reduction in the 12-week total study period was 45.5% in the control group and 14.3% for the intervention group. Thus, in all evaluated periods, the probability of failure is higher for the control treatment. The results suggest that in all evaluated periods the probability of success is higher than the treatment intervention.

Calculation of cost-effectiveness of treatment given by the average cost of each 1cm² wound reduction

Table 2 shows total reduction and average cost of each 1 cm² wound reduction in the control and treatment groups in each period evaluated.

Table 1. Frequency distribution of the variation of the wound area in the evaluated time periods, for both groups, N = 25, Niteroi, 2018

Group	Wound Area Variation	First 6 weeks	Last 6 weeks	12 weeks
Control*	Increased the area	1 (9,1%)	4 (36,4%)	4 (36,4%)
	Did not change area	1 (9,1%)	2 (18,2%)	1 (9,1%)
	Decreased area	9 (81,8%)	5 (45,5%)	6 (54,5%)
Intervention**	Increased the area	2 (14,3%)	3 (21,4%)	2 (14,3%)
	Did not change area	0 (0,0%)	1 (7,1%)	0 (0,0%)
	Decreased area	12 (85,7%)	10(71,4%)	12(85,7%)

* 2% carboxymethylcellulose hydrogel (CMC)

** rhEGFcarbogel

Table 2. Total cost, total reduction and average cost of each 1 cm² wound reduction in the control and treatment groups in each period evaluated

Variable	Period					
	First 6 weeks		Last 6 weeks		Total (12 weeks)	
	Control	Treatment	Control	Treatment	Control	Treatment
Sum of patient costs in this period (in US\$)	1.877,50	2.066,56	1.335,06	1.727,08	3.212,57	3.793,65
Sum of Reduced Areas over this period (in cm ²)	27,1	83,4	-17,4*	25,0	9,7	108,4
Average cost of 1cm ² reduction over theperiod	69,28	24,78	-	69,08	331,19	35,00

*In this group, the sum of the reduced areas in the last 6 weeks was negative, showing that, in fact, in total, the total area of wounds increased by 17.4 cm² for the control group patients during this period.

Then, for each patient who presented wound reduction, reduction cost values of each 1 cm² wound during the period were obtained and the statistics for this variable (minimum, maximum, average, median, standard deviation and coefficient of variation) were obtained. number of patients who presented wound reduction. In this calculation, the entire sample was not taken into account, since cases that had no reduction or when it was negative could not be included. The coefficient of variation is calculated by the standard deviation divided by the mean. The proportion of cases that presented wound reduction in each period with both treatments was analyzed. The distribution of the variable "cost of reduction of each 1 cm² of the wound" was also calculated for each patient who presented injury reduction.

It was observed that in the first 6 weeks, the control group spent US\$1877,50 dollars to obtain a total reduction of 27.1 cm²; In the same period, in the intervention group, an amount of US\$2066,56 was spent resulting in a total reduction of 83.4 cm². The average cost in this same period was US\$ 69,28 per 1cm² reduced in the control group while in the intervention group the value was US\$24,78 per cm². These values suggest that the cost-benefit ratio in the first 6 weeks is more positive in the intervention group than in the control group. The same calculations were performed for the last 6 weeks. During this period, US\$1727,08 was spent to achieve a total reduction of 25.0 cm² in the intervention group, leaving an average cost of US\$69,08 per cm². These results suggest that it is more expensive to reduce 1 cm² in the last 6 weeks.

Table 3. Key statistics of the cost of each reduced cm² in the wound in cases where there was a reduction in control and treatment groups in each period evaluated

Period	Group	n*	p*	Reduction cost statistics for each reduced wound cm ² (US / cm ²)					
				Minimum	Maximum	Mean	Median	Standard Deviation	C.V
First 6 weeks	Control	9	81,8%	13,42	440,98	132,87	66,11	139,89	1,05
	Intervention	12	85,7%	7,78	331,44	76,57	19,55	101,70	1,33
Last 6 weeks	Control	5	45,5%	42,33	333,29	180,35	178,51	110,34	0,61
	Intervention	10	71,4%	9,69	540,29	175,46	120,76	176,34	1,00
Total (12 weeks)	Control	6	54,5%	13,42	203,61	112,72	95,74	65,70	0,58
	Intervention	12	85,7%	9,02	534,42	110,96	38,26	150,75	1,36

n* = number of patients who presented wound reduction in this period

p* = proportion of patients who had wound reduction in this period, estimation of the probability of a patient receiving treatment to have wound reduction in this period.

For the control group such a relationship cannot be calculated, considering the total changes in the areas, wounds generally increased rather than reduced. The sum of the changes in area left an increase of 17.4 cm². Considering the total study period, over the 12 weeks, the total cost with the patients in the control group was US\$3212,57 dollars, for a total reduction of only 9.7 cm². In the same period, in the intervention group, a greater amount of US\$3793,65 was spent, however, it was possible to notice a total reduction of 108,4 cm². The average cost in the first 12 weeks was US\$331,19 per cm² reduced in the control group and US\$35,00 per cm² in the intervention group. These results suggest that the cost-benefit ratio at 12 weeks is better in treatment than in the control group.

Calculation of average (and other statistics) of wound reduction cost 1 cm²: As shown in table 3, considering only the cases that had wound reduction, according to the statistics displayed, it was possible to evaluate that in all periods, the proportion of cases that decrease the wound is higher in the intervention group. These results suggest that the likelihood of success, ie wound reduction, is greater with intervention than with control. In all periods evaluated, the mean reduction cost for each reduced wound cm² is also lower in the intervention group. The same was observed for the median reduction cost for each reduced cm². The reduction cost of 1 cm² presented high variability between patients in both groups in all evaluated periods, given the coefficients of variation well above 0.4. Considering the total period of 12 weeks, it was observed that the chance of a patient undergoing the intervention to have wound reduction is 85.7%. However, this 1 cm² reduction cost measure shows high variability (CV = 1.36) in the range of 9,02 to US\$534,42 / cm², with an average of US\$110,96 / cm² and a median of 38,26 US / cm². These results suggest that the chance of a patient undergoing control treatment to have wound reduction within 12 weeks of treatment is considerably lower, at only 54.5%. The cost of reduction of 1 cm² in this period presented high variability (CV = 0,58) in the range of 13,42 to 203,61 US / cm², with an average of US 112,72 / median of 95,74 US / cm². In all evaluated periods, the average and median reduction cost for each reduced wound cm² is lower in the intervention group.

DISCUSSION

Investigating the cost-benefit ratio of the treatments through the reduced average cost per R\$ / cm² showed that the cost-benefit ratio in the first 06 weeks had better results in the intervention group, with 24078 US / cm² lower than in the control group with 69,28 US / cm² reduced. Similar results were observed in the last 06 weeks as well, with favorable

relation to the intervention group, since in the total sum there was no reduction in the control group. Overall, the results suggest that it is more expensive to reduce 1 cm² in the last 06 weeks of treatment than in the first 06 weeks. These findings are consistent with another study that suggests that early initiation of growth factor treatment in diabetic patients may lead to lower overall health costs, improving wound healing outcomes [27]. When observing the total period evaluated, referring to the 12 weeks of the study, it is more evident that the cost-benefit ratio is better in the intervention group with 35,00 US / cm² reduced than in the control group with 331,19 US / cm² reduced. This result is in agreement with the literature, since other studies show that rhEGF favors the increase of granulation tissue in the lesion bed, favoring the healing process [19, 28-31]. These results also corroborate the fact that treatments that accelerate the healing of chronic ulcers in diabetic patients reduce the need for hospitalization, and consequently the costs of care [27, 32].

Calculation of average (and other statistics) of wound reduction cost 1 cm²: In all periods evaluated, the proportion of cases with decreased lesion area was higher in the intervention group. These findings suggest that the likelihood of success, ie wound reduction, is greater when treated with rhEGF (intervention product) than with control. Other studies using rhEGF in the intervention also observed similar results [18, 33]. Chronic ulcers in diabetic patients have a serious impact on the global burden of disease. The treatment of these patients generates high costs due to factors such as: possibility of long hospital stay, incident need for rehabilitation, frequently needed home care and the use of social services and possible complications of diabetic foot such as amputation. Although the short follow-up period and the small number of patients, the main limitations of this study, require caution in extrapolating these results, they suggest that growth factor therapy may be a cost-effective and innovative complement to standard wound care.

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List of abbreviations

Carboxymethylcellulose hydrogel (CMC)
National Health Council (CSN)
Recombinant Human Epidermal Growth Factor (rhEGF)
Unified Health System (SUS)
ADVFN Brazil (Brazilian Stock Exchange Portal, with Bovespa and BM&F quotes)
Federal Nursing Council (COFEN)

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