ISSN: 1676-4285

OBJN Online Brazilian Journal of Nursing
ENGLISH
Federal Fluminense University
AURORA DE AFONSO COSTA NURSING SCHOOL
uff

Platelet-rich plasma in the treatment of venous ulcers: a case series

Beatriz Guitton Renaud Baptista de Oliveira[1], Silvia Regina Secoli[2], Andrea Pinto Leite Ribeiro[3],Alcione Matos de Abreu[4], Jane Marcy Neffá Pinto[1]

1 Universidade Federal Fluminense
2 Universidade de São Paulo
3 Fundação Oswaldo Cruz
4 Universidade Federal do Estado do Rio de Janeiro

ABSTRACT

Objective: To assess the viability of the treatment of venous ulcers with platelet-rich plasma (PRP). **Method:** A descriptive case series study conducted as a pilot study for a clinical trial. With a sample of three patients, allocated after randomization, two for intervention and one for control. The cost was collected by means of direct observation. **Results:** In patients who received the intervention (PRP), two venous ulcers were followed-up, one presented complete healing, with a cost of US$ 550.35, and the other exhibited a rate of area reduction of 33.33%, with a cost of US$ 1,070.32. In the control patient, there was an 83.33% reduction in the venous ulcer area, with a cost of US$ 361,53. **Discussion:** The pilot test made it possible to adequate the protocols and to determine the supplies required for the completion of the study. **Conclusion:** The assessment of the clinical protocols is pivotal for the development of controlled clinical trials.

Keywords: Platelet-Rich Plasma; Varicose Ulcer; Nursing; Biomedical Technology Assessment; Costs and Cost Analysis; Cost-Effectiveness Evaluation

Oliveira LBGRB, Secoli SR, Ribeiro APL, Abreu AM, Pinto JMN. Platelet-rich plasma in the treatment of venous ulcers: case series. Online Braz J Nurs [Internet]. 2018 [cited year month day];17(3):e20186005. Available from: https://doi.org/10.17665/1676-4285.20186005

INTRODUCTION

Chronic Venous Insufficiency (CVI) is a highly prevalent disease often leading to the development of leg venous ulcers[1]. The compression therapy is considered the gold standard for the treatment of CVI and should be associated with a topical product that keeps the ulcer bed moist, thus favoring healing. Several studies show that the compression therapy is effective in healing existing venous ulcers and that it reduces the likelihood of wound recurrence[1-2].

One of the most important substances that may be used in the topical treatment of chronic venous ulcers is platelet-rich plasma (PRP), which consists of an autologous platelet concentrate in a limited volume of plasma obtained by blood centrifugation[3].

PRP contains many growth factors that may act in the processes of hemostasis, wound healing, and tissue re-epithelialization[4-5]. The three main platelet growth factors involved in the healing process are: platelet-derived growth factor (PDGF), transforming growth factor beta (TGFβ), and vascular endothelial growth factor (VEGF). They stimulate the production of collagen and extracellular matrix with minimum amounts of plasma and are an important alternative when conventional treatments for chronic ulcers have failed[6].

The search for cost-effective technologies is crucial for the sustainability of the health systems, especially in the case of chronic diseases, whose incidence and recurrence increase as population ages, leading to higher costs both for patients and their families and for the health system.

The analysis of the scientific grounds for clinical decisions and knowledge of Health Economy by nurses contribute to the practice of their attributions and to decision-making in nursing care[7]. Nurses are able to articulate the value and the relationship of costs, time, and efficacy of the clinical practice procedures to improve the care provided[8].

The economic assessment of health technologies provide information to guide the health professionals on the need and means to reduce costs within the health system by making the best choice in terms of technology considering the lowest cost and the greatest effectiveness for the treatment of venous ulcers[8].

The effectiveness of the use of PRP in venous ulcers was assessed in three international clinical trials[9-11], and the outcome of complete healing was found in 50.11% of the venous ulcers treated with PRP versus 48.24% in the control group[9-11].

There are few studies on the cost of treatment with PRP in venous ulcers; in fact, there is only one cost-effective analysis comparing the standard treatment for venous ulcers (cleaning, necrotic tissue debridement, prevention, diagnosis, and, if appropriate, treatment of infection and application of materials to cover the wound) with PRP[12]. In Brazil, there is no evidence on the cost of this technology for the treatment of venous ulcers. Therefore, this study arose from the need of contributing with a cost-effective assessment of two technologies for the treatment of venous ulcers, in order to provide evidence for decision-making of nurses and managers and to contribute to the development of new investigations on the topic.

Objective: To assess the viability of the treatment of venous ulcers with PRP.

METHOD

This is a case series of an integrated project on PRP that will conduct a controlled randomized clinical trial. A pilot study was conducted in order to make adjustments to the research protocol of this trial. Descriptive case series studies comprise from three to ten cases and present a detailed report of the disease and of the treatment, allowing for future larger investigations and more elaborate study designs[13].

A pilot study is a small-scale test that will be used to adjust the procedures, materials and methods proposed for the investigation[14]. The mini-version of the complete study comprises the execution of all the procedures foreseen in the methodology so as to predict results, evaluate the viability of the collection methods in each execution phase, and address the issues requiring review and improvement[14].

The study was conducted in the wound outpatient clinic at a university hospital in the state of Rio de Janeiro, Brazil, from May to September 2016. With a sample of three participants, allocated after randomization, two for the intervention with PRP and one for control with Petrolatum® gauze.

The study participants were selected according to the following inclusion criteria: medical diagnosis of CVI; ankle brachial index (ABI)≥0.9; presence of palpable pulses in the lower limbs, such as pedal and posterior tibial pulses; age ≥18 years old; venous ulcer measuring at least 2.0 cm² and less than 100 cm². The ABI is used as a criterion for the diagnosis of peripheral artery disease (PAD) and is calculated from the data obtained using the following formula: ABI = (SBPa/SBPb) [SBPa = SBP of the ankle; SBPb = Brachial SBP] (Wound, Ostomy and Continence Nurses Society)[1].

The exclusion criteria were the following: pregnancy; infectious/communicable disease; venous ulcer with necrotic tissue covering the entire wound bed and in the rounded shape; suspected malignancy or infection at the wound site; hypercoagulability; having received transfusion in the last three months. The discontinuation criteria were the following: signs of allergy to the use of the products for wound treatment; presenting severe pain; patients who expressed interest in withdrawing from the study, had irregular attendance to medical appointments, or discontinued product use; occurrence of serious adverse event and clinically significant local adverse events (severe pain).

Data collection took place from May 2016 to September 2016, with a follow-up time of 12 weeks. PRP was applied every 15 days; and Petrolatum® gauze, once a week. The participants were instructed to change the secondary dressing at home whenever the gauze and bandage were saturated.

The intervention (PRP) consisted of blood collection and PRP preparation by blood centrifugation. Subsequently, the PRP was applied to the previously cleaned ulcer, and the ulcer was covered with sterile gauze and fixed with crepe bandages. On the following day, patients were instructed to change the dressing, irrigate the ulcer with 0.9% physiological solution, and apply Petrolatum® gauze, which was changed once a week. The control

participant was treated only with Petrolatum® gauze once a week. Compression therapy with elastic bandages, considered the gold standard for the treatment of venous ulcers, was administered to all the participants, and they were instructed on how to apply and wash the bandages.

An area of venous ulcers in cm^2 was considered the primary outcome for the assessment of effectiveness; and treatment expenses for the assessment of costs. The secondary outcomes were the following: type of tissue present in the bed and borders of the ulcer, aspect of the exudate (amount and type), characteristics of the skin adjacent to the ulcer, and its depth.

The study outcomes were assessed using specific instruments and research protocols applied in the wound outpatient clinic, and later validated. The reduction in ulcer areas in cm^2 over the 12-week treatment was assessed using decals taken from intervention and control participants in weeks 1, 6 and 12.

The treatment costs were collected by means of direct observation of the dressing procedure, using the following steps: identification, measurement, and valuation of direct cost items related to outpatient dressing change. Direct cost is to be understood as expenses directly applied in the production of a service or a product, such as material resources and workforce[15].

Costs were estimated considering the sum of the direct costs used in each stage: time to apply the dressing, products (PRP and/or Petrolatum® gauze), and supplies for each stage of the process.

For the participants undergoing treatment with PRP, cost estimation also included the direct cost related to collection of blood for centrifugation and preparation of PRP on a fortnight basis.

The time the professional spent to perform the procedure was measured by direct observation using a chronometer and considering the units hour/minute/second (h/min/sec). The estimation only considered the duration of dressing application, blood collection, and preparation of the PRP.

Thus, costs the procedure were calculated as follows:

Procedure (PRP) = Wage per minute x time to perform the procedure (puncture + preparation of PRP + dressing)

Procedure (control) = Wage per minute x time to apply the dressing

The measures used to compute the supplies were the following: units (u) for products sold individually or in packages; milliliters (mL) for liquids and semiliquids; and centimeters (cm) for plaques and other materials such as adhesive tapes.

The use of the elastic compression therapy was also computed. The material for changing dressings daily at home was provided according to the participant's demand and was computed weekly, each time the patients returned to the outpatient clinic.

The perspective of the paying sources of public health services (Unified Health System) was adopted. The study time frame was the same as its follow-up duration: 12 weeks.

The items were valued after consulting data from an electronic auction involving the university hospital where the research was conducted.

The currency used was the American dollar, considering its mean quote from May to

September (US$ 1.00 equals R$ 3.34), in order to achieve a better generalization of the findings with the international investigations, using the conversion rates applied at the time of collection.

The research protocol was approved by the Research Ethics Committee of the Medical School of the Fluminense Federal University, under CAAE number 45478515. 0.0000.5243. The study participants signed the Free and Informed Consent Form and the authorization form for photographic recording.

RESULTS

The sample of this pilot study consisted of three patients, of which two received intervention (PRP, Petrolatum® gauze, and elastic bandages), and one was allocated as control (Petrolatum® gauze and elastic bandages), with 12 weeks of follow-up, totaling 12 nursing outpatient visits, 66 days of household treatment, and 72 days of follow-up for each patient.

Intervention - PRP (Patients 1 and 2)

Patient 1

Male, (A.A.F), 65 years old, illiterate, and informal worker. He had a medical diagnosis of CVI and hypertension, ABI=0.9, and palpable pulses in the lower extremities. He presented a small, recurrent venous ulcer, located at the lower third of the left lower limb, measuring approximately 3 cm^2, with partial depth and irregular borders, presence of granulation tissue (76-100%) and small crumbled areas in the ulcer bed (1-25%), with little exudate. Adjacent skin with characteristics of vitiligo, lipodermatosclerosis, and eczema. The treatment with PRP started on May 3rd, 2016. The application and preparation of the PRP in gel form were conducted according to the proposed protocol. Subsequently, a dressing with sterile gauze was applied and fixed with crepe bandages wrapped in upward circles. On the following day, the patient was instructed to change the dressing according to the protocol and to apply Petrolatum® gauze. On July 19th, 2016, after 12 weeks of regular treatment with PRP, the ulcer was healed (100% reduction rate), with an estimated cost of US$ 550.35.

Patient 2

Female, (M.S), 56 years old, with complete elementary education, kitchen-maid, poor hygiene conditions. He had a medical diagnosis of CVI and hypertension, ABI =1.1, and palpable pulses in the lower extremities. She presented small, recurrent venous ulcers located at the right and left malleoli, measuring approximately 25 cm^2 of total area, with partial depth and irregular and macerated borders, as well granulation tissue (76-100%) and small crumbled areas in the ulcer bed (1-25%), with little exudate. The adjacent skin was dry, with characteristics of lipodermatosclerosis and eczema. The treatment with PRP started on May 31st, 2016. The application and preparation of the PRP in gel form were conducted according to the proposed protocol. Subsequently, a dressing with sterile gauze was applied and fixed with crepe bandages wrapped in upward circles. On the following day, the patient was instructed to change the dressing according to the protocol and to apply Petrolatum® gauze. On

August 16th, 2016, after 12 weeks of regular treatment with PRP, the ulcer had an approximate size of 17 cm^2 of total area, presenting granulation tissue (51-75%), small crumbled areas in the ulcer bed (1-25%), and areas with epithelialization tissue (1-25%), with little exudate. The adjacent skin was hydrated. The rate of venous ulcer reduction was 33.33%. The estimated cost of the treatment was US$ 1,069.93.

During the visit on July 12th, 2016, patient 2 presented improved exudate production, fetid odor, flushing, heat and pain of intensity 8, as assessed using the visual analogue scale, thus requiring a medical visit, in which ciprofloxacin 500 mg 12/12 h for 14 days, with an additional cost of US$ 20.96 for the medication and US$ 2.99 for the outpatient visit, totaling US$ 1,093.88.

Control

Control patient

Female, (S.A.S), 75 years old, with complete high school education, and retired. She had a medical diagnosis of CVI and hypertension, ABI = 1.05, and palpable pulses in the lower extremities. She presented a small, recurrent venous ulcer located at the malleolus in the right lower limb, measuring approximately 6 cm^2, with partial depth and irregular borders, presence of granulation tissue (75-100%) and small crumbled areas in the ulcer bed (1-25%), with little exudate. The adjacent skin presented lipodermatosclerosis and eczema. The patient was instructed to change the secondary dressing whenever necessary. The treatment with Petrolatum® gauze started on July 12th, 2016, and the dressing was changed on a weekly basis. After 12 weeks of treatment, on September 27th, 2016, the venous ulcer measured 1 cm^2, presented granulation tissue (1-25%) and epithelialization tissue (76-100%), and had a superficial depth.

The rate of venous ulcer reduction was 83.33%. The estimated cost for treating the control patient was US$ 361.53.

Graph 1 shows the evolution of the venous ulcer area over the 12-week treatment in intervention and control patients.

Table 1 shows the direct costs of outpatient and household treatment of the venous ulcers. The secondary outcomes are presented in Table 2.

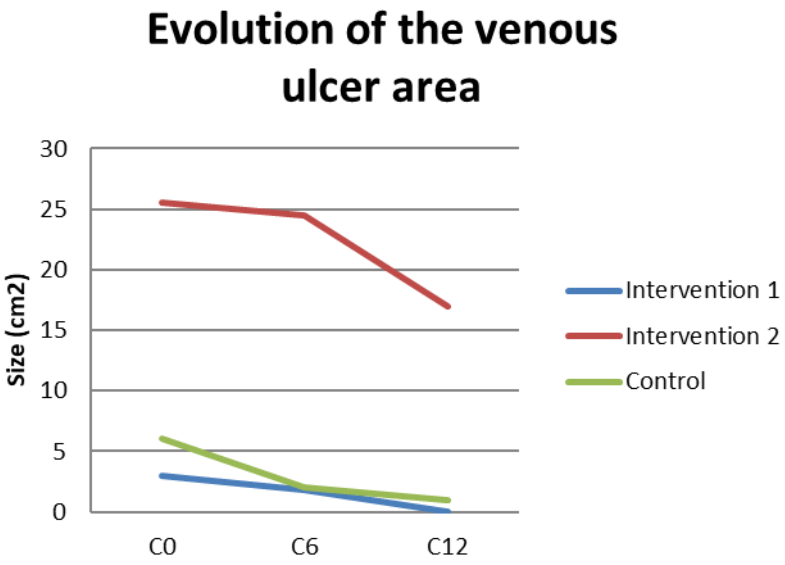
The pilot study allowed for the introduction of changes to the method, with the refining of the inclusion, exclusion, and discontinuation criteria. The changed items are listed in Chart 1.

The changes related to the procedure lead to the development of a new protocol to define the frequency of changing Petrolatum® gauzes and are summarized in Table 3.

In addition to the outcome predicted for the analysis of the data, which initially was venous ulcer area in cm^2, another outcome was introduced after the pilot study: the number of healed ulcers. Additionally, the healing rate was maintained as an outcome and was assessed by measuring the area (in cm^2) of the ulcers that did not have complete healing during the treatment period.

DISCUSSION

In this study, there was predominance of elderly and female individuals, and the disease most predominantly associated with CVI was systemic arterial hypertension. Several



Graph 1. Evolution of the venous ulcer area over the 12-week treatment, Niterói, RJ, Brazil, 2016

studies involving patients with the same profile as that of this sample have shown that systemic arterial hypertension is the chronic disease that most affects patients with venous ulcers, with percentages as high as 61%[16].

The prevalence of CVI is closely related to the aging process, meaning that the elderly are the most affected population. Furthermore, belonging to the female gender is considered a risk factor for the development of this chronic disease[17].

With regard to the number of healed ulcers over the 12-week treatment, one intervention patient experienced complete healing of the venous ulcer. The rates of area reduction in the other two patients were 33.33% (intervention) and 83.33% (control).

The assessment of the tissue in the venous ulcer bed at the end of the treatment showed that the three patients presented granulation and/or epithelialization tissue. This was a positive finding, because areas of devitalized tissues were observed at the beginning of the study.

The exudate present in the ulcers during the first and the last assessment was of the serous type, and its amount ranged from small to little.

The production of exudate tends to decrease throughout the normal process of healing, and should be assessed after removing the dressing and before cleaning the ulcer[18]. An increase in exudate production is common and may occur when elastic compression is added as adjuvant therapy in the treatment of venous ulcers[16].

With regard to the adjacent skin, there was an improvement in dryness for all the patients, because they used a moisturizer with vitamins A and B and essential fatty acids throughout the entire treatment period.

As for the depth item, one intervention patient had complete ulcer healing, and the control patients improved depth from partial to superficial.

Based on the results observed during the study follow-up, there was the need to make the following change to the final clinical protocol:

Table 1. Distribution of the cost (in American dollars) according to the following categories: procedure, product, outpatient and household supplies, and compression therapy, Niterói, RJ, Brazil, 2016

Category	Cost (Interv. 1)	%	Cost (Interv. 2)	%	Cost (Control)	%
Human resources (procedure)	452.71	82.3	834.75	78.0	278.89	77.1
Product (Petrolatum)	8.96	1.6	26.06	2.4	9.77	2.7
PRP supplies (collection + preparation)	11.96	2.2	11.38	1.1	-	-
Outpatient supplies	29.74	5.4	110.20	10.3	27.64	7.6
Household supplies	33.22	6.0	60.00	5.6	31.46	8.7
Compression therapy	13.77	2.5	27.54	2.6	13.77	3.8
Total	550.35	100.0	1,069.93	100.0	361.53	100.0

Table 2. Characteristics of the venous ulcers in the first and twelfth weeks, Niterói, RJ, Brazil, 2016

Parameters evaluated	1st week			12th week		
	Pt. 1	Pt. 2	Pt. 3 Control	Pt. 1	Pt. 2	Pt. 3 Control
Exudate	Serous	Serous	Serous	Absent	Serous	Serous
Amount of exudate	Small	Small	Small	Absent	Small	Small
Tissue present in ulcer bed	Granulation (75-100%) Devitalized (1-25%)	Granulation (75-100%) Devitalized (1-25%)	Granula-tion (75-100%) Devitalized (1-25%)	100% of epithelia-lization	Granula-tion (51-75%), Devitali-zed (1-25%), epithelia--lization (1-25%)	Epithelia-lization (76-100%) Granula-tion (1-25%)
Adjacent skin	Vitiligo, lipoderma-tosclerosis, eczema, and dry	Lipoderma-tosclerosis, eczema, and dry	Lipoderma-tosclerosis, eczema, and dry	Vitiligo, lipoder-matos-clerosis, eczema, and hydrated	Lipoder-matos-clerosis, eczema, and hydrated	Lipoder-matos-clerosis, eczema, and hydrated
Depth	Partial	Partial	Partial	Healed	Partial	Superficial

the frequency for changing the Petrolatum® gauze will depend on the amount of exudate produced by the venous ulcer, and the nurses' assessment will be based on the following parameters: absent, when the ulcer bed is dry; small, when the ulcer bed is moist and drainage covers less than 25% of the dressing; moderate, when the ulcer bed are wet and drainage involves from 25 to 75% of the dressing; and large, when ulcer bed is filled with fluid and drainage involves more than 75% of the dressing[19].

Cost management is a key tool for the analysis of the spreadsheets including the costs of the resources used[15].

The analysis of the direct cost items related to the procedure allowed for the prediction of the required supplies and their costs.

Table 1. Criteria for the selection of the participants changed by the pilot study. Niterói, RJ, Brazil, 2016

Inclusion criteria		
Initial protocol	**Final protocol**	**Observations**
Hematocrit>34%, hemoglobin>11g/dL, and platelet count above150,000/mm³ proven by blood cell count with retroactive date of up to 3months; Presenting ulcers with an evolution time greater than threemonths.	Partial thromboplastin time (TAP/TP)>70-80% 10-13s and partial thromboplastin time (PTT)<15-30% 25-35s; No history of alcoholism or psychiatric diseases that may interfere with self-care; Availability to attend the outpatient clinic once a week.	This criterion was included despite the fact that most of the patients used medications of chronic use like platelet antiaggregants (acetylsalicylic acid). A history of alcoholism and/or psychiatric diseases may hamper patient adherence to the visits. The weekly frequency of visits is necessary for the follow-up of patients and their ulcers.
Exclusion criteria		
Initial protocol	**Final protocol**	**Observations**
Being pregnant or breastfeeding; Having coagulation disorders; Using corticosteroids or platelet antiaggregants; Presenting an ulcer with suspected malignancy; Presenting a rounded ulcer; Not adhering to the treatment plan.	Presenting an infectious/communicable disease; Presenting a venous ulcer with necrotic tissue covering the entire ulcer bed; Presenting hypercoagulability.	This criterion was included because the procedure involves handling biological material. The presence of necrosis in the ulcer bed may indicate artery complications (mixed). Presenting coagulation disorders, autologous platelets cannot be obtained from patients with thrombocytopenia, during pregnancy, and in hypercoagulability states.
Discontinuation		
Presenting signs of infection; Patient who had irregular attendance to medical appointments or discontinued product use; Occurrence of serious adverse event and of clinically significant local adverse events (severe pain); occurrence of pregnancy during follow-up.	Presenting signs of allergy to the products used in wound treatment; Patient who expressed interest in withdrawing from the study.	It is considered a mild adverse event. According to the ethical principles, the patient may decide to withdraw from the study at any time.

Table 3. Protocol for the frequency of change of Petrolatum® gauzes, Niterói, RJ, Brazil, 2016

Frequency of change		
Initial protocol	**Final protocol**	
Weekly	First week: daily change, regardless of the amount of exudate. After the second week, the proposed protocol should be followed:	
	Amount of exudate	Frequency of change per week
	Absent	One
	Small (less than 25%)	One
	Moderate (25 to 75%)	Alternate days
	Large (more than 75%)	Daily

The category human resources (procedure), which represents the cost of the nursing workforce, was the one that accounted for the highest percentage of costs, with 77.1% of the total treatment costs for the control patient, 82.3% for intervention patient 1, and 78.0% for intervention patient 2.

The time spent performing the procedure was computed, but it should be considered with caution, because the technique for blood collection and PRP preparation and the application of products for dressing were being improved, which demands an increased time for performing the procedure. This time will be calculated in the clinical trial again, because the procedure time is likely to decrease as the technique improves.

The supplies category, represented by the sum of the material resources used, accounted for the second highest cost. It was observed that the costs of outpatient dressings were higher than those of household dressings, and that expenses with nursing workforce were the main contributing factor for this difference, according to another study that evaluated patients with venous ulcer[20].

Since the compression therapy is the gold standard in the treatment of venous ulcers, its costs, including its several modalities, have been assessed in many papers. In this study, the elastic bandage was used and its cost represented 2.5% of the total treatment cost in the intervention patients and 3.8% of the control cost, thus representing the third highest treatment cost.

The introduction of cost studies and concepts on health economic assessment are important in the nursing field, because they provide a great amount of information that may be used in management and decision-making, with the purpose of improving service and care, favoring a greater efficiency in equal allocation of resources[8].

CONCLUSION

The pilot test enabled to adjust the method and the protocols and to determine the supplies required for the development of the clinical trial, modifying the protocol for the use of Petrolatum® gauze according to the type and amount of exudate, in order to prevent the risk of infection in the wound bed.

The assessment of health technologies by means of cost studies and economic assessments is another activity that may be performed by nurses and that changes nursing care from a perspective focused on efficiency and better resource allocation.

REFERENCES

1. Wound, Ostomy and Continence Nurses Society (WOCN). Guideline for management of wounds in patients with lower-extremity arterial disease. Mount Laurel (NJ): Wound, Ostomy and Continence Nurses Society (WOCN); 2014. 204 p. (WOCN clinical practice guideline series; no. 1).

2. Ratliff CR, Yates S, McNichol L; Gray M. 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 of Wound, Ostomy & Continence Nurs. 2016 July/Aug; 43(4): 347–364. doi: 10.1097/WON.0000000000000242

3. Olszewer E, Arroyo E, Nakamura F. PRP--Plasma rico em plaquetas. 1a. ed. São Paulo, SP: Editora Fapes Books; 2015.

4. Vendramin FS, Franco D, Nogueira CM, Pereira MS, Franco TR. Plasma rico em plaquetas e fatores de crescimento: técnica de obtenção e utilização em cirurgia plástica. Rev. Col. Bras. Cir. 2006; 33 (1): 24-8.

5. Pinto JMM, Pizani NS. Aplicabilidade em dermatologia do plasma rico em plaquetas. Surg. Cosmet. Dermatol. 2015; 7 (1): 61-4.

6. Pinto JMN, PIZANI NS, KANG HC, SILVA LAK. Application of platelet-rich plasma in the treatment of chronic skin ulcer - Case report. An. Bras. Dermatol. [Internet]. 2014 [Cited 2017 Jun 5];89(4):638-640. ISSN 0365-0596. Available from: http://www.scielo.br/pdf/abd/v89n4/0365-0596-abd-89-04-0638.pdf

7. Porzsolt F. Clinical Economics and Nursing. Rev Lat Am Enfermagem [Internet]. 2015 [Cited 2017 Jun 5];23(6):989–90. Available from: http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0104--11692015000600989&lng=en&nrm=iso&tlng=en

8. Mata VE, Schutz V, Peregrino AAF. Dificultades y oportunidades para la enfermería: una revisión narrativa sobre evaluación económica en salud. Enfermería Glob [Internet]. 2013 [Cited 2017 Jun 5]; 12(29):392–403. Available from: http://scielo.isciii.es/scielo.php?script=sci_arttext&pid=S1695--61412013000100021&lng=es&nrm=iso&tlng=es

9. Bogdan VG, Tolstov DA. Prospective randomized clinical trials of efficiency of autologous platelet-derived concentrates to stimulate regeneration of trophic ulcers of venous etiology. Novosti Khirurgii. 2014 maio;22(3):344–350.

10. Senet P, Bon F-X, Benbunan M, Bussel A, Traineaus R, Calvo F, et al. Randomized trial and local biological effect of autologous platelets used as adjuvant therapy for chronic venous leg ulcers. Journal of Vasc Surgery. 2003; 38(6):1342–1348.

11. Stacey MC, Mata SD, Trengove NJ, Mather AC. Randomised double-blind placebo controlled trial of topical autologous platelet lysate in venous ulcer healing. Eur J Vasc Endovasc Surgery. 2000; 20(3):296–301.

12. Campos RC, Diez NP, Barandiaran FA. Platelet-rich plasma in skin ulcer treatment. Wounds. 2013 Sep;25(9):256-62.

13. Oliveira MAP, Velarde GC, Sá RAM. Entendendo a pesquisa clínica V: relatos e séries de casos. FEMINA [Internet] Setembro/Outubro 2015 [Cited 2017 Jun 5];43(5). Available from: http://files.bvs.br/upload/S/0100-7254/2015/v43n5/a5320.pdf

14. Bailer C, Tomitch LMB, D'Ely RCS. Planejamento como processo dinâmico: a importância do estudo piloto para uma pesquisa experimental em linguística aplicada. Rev Intercâmbio [Internet]. 2011 [Cited 2017 Jun 5]; 24:129-146. ISSN 2237-759x. Available from: https://revistas.pucsp.br/index.php/intercambio/article/download/10118/7606

15. Castilho V, L AFC, Fugulin FMT, Peres HHC, Gaidzinski RR. Total staff costs

to implement a decision support system in nursng. Rev. Latino-Am. Enfermagem [Internet]. 2014 Feb [cited 2017 June 06]; 22(1):158-164. Available from: http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0104-11692014000100158&lng=en. doi: http://dx.doi.org/10.1590/0104-1169.3074.2383.

16. Abreu AM, Oliveira BGRB. A study of the Unna Boot compared with the elastic bandage in venous ulcers: a randomized clinical trial. Rev. Latino-Am. de Enfermagem. 2015;23:571–577.

17. Evangelista DG, Magalhães ERM, Moretão DIC, Stival MM, Lima LR. Impacto das feridas crônicas na qualidade de vida de usuários da estratégia de saúde da famìlia. R. Enferm. Cent. O. Min. [Internet]. 2012 mai/ago [Cited 2017 Jun 5]; 2(2):254-263. Available from: http://www.seer.ufsj.edu.br/index.php/recom/article/view/15/308

18. Santos V, Marques J, Santos A, Cunha B, Manique M. Exudate Control in Chronic Wounds: Evidence Based Approach. Journal of Aging & Inovation. [Internet]. 2012 [Cited 2017 Jun 5];1(2):61-67. Available from:http://journalofagingandinnovation.org/wp-content/uploads/7--Controlo-do-exsudado.pdf.

19. Harris C, Bates-Jensen B, Parslow N, Raizman R, Singh M, Ketchen R. The Bates--Jensen Wound Assessment Toll: pictorial Guide validation project. J Wound Ostomy Continence Nurs. 2010;37(3):253-9.

20. Oliveira AP, Oliveira BGRB. Cost of the treatment for venous ulcers in an outpatient clinic and in the household: a descriptive study. Online Braz J Nurs [Internet]. 2015 October [Cited 2017 Jun 5]; 14 (3): 221-8. Available from:http://www.objnursing.uff.br/index.php/nursing/article/view/4842. doi:http://dx.doi.org/10.17665/1676-4285.20154842

Received: 2017/07/08

Reviewed: 2019/03/19

Approved: 2019/10/21