

New Age Treatment For An Age-Old Problem – PRP For Post-Surgery Non-Healing Venous Ulcers

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Abstract: Introduction: One of the major complications of varicose veins is the non-healing ulcer of the leg. The traditional treatment for this is regular dressing, foot end elevation with appropriate antibiotics and local application of silver-based ointments. The gold standard treatment for these patients is surgery (Trendelenburg surgery with or without venous stripping and subfascial perforator ligation and endovenous procedures). Surgeons usually reach a crux when a patient develops persistent ulcers which does not heal even after all these efforts.

Aim: Our objective in this study was to study the effects of Platelet Rich Plasma (PRP) in chronic non-healing post-surgical venous ulcers.

Methodology: This was a case control study with 40 patients conducted over 2019 and 2020, after institutional ethical clearance. All patients were treated with appropriate antibiotics prior to the study and obtained a culture negative status. PRP was separated and injected locally into the borders of the ulcer in cases, while controls were given regular dressings with silver-based ointments.

Results: We found that patients who were given PRP had a significantly faster healing rate and a lower infection rate.

Conclusion: Hence PRP can be safe, effective and reasonably cost effective in treating post-surgical venous ulcers.

1. INTRODUCTION:

Varicose veins are a common problem in the Indian population. Venous ulcers are often treated sub-optimally and progressed to large non-healing ulcers which ultimately require complex plastic surgical procedures. Left untreated these wounds, though not fatal, increases morbidity reduces productivity which in turn increases the cost and this has a negative impact on the quality of life of the patient.

Untreated varicose veins lead to lipodermatosclerosis. In this there is hypoxic skin break down and thus forms a varicose or venous ulcer. Venous ulcers have been categorized by the 'CEAP' classification as advanced form of venous insufficiency and defined as "Full-thickness defect of the skin most frequently in the ankle region, that fails to heal spontaneously and is sustained by chronic disease, based on the venous duplex ultrasound testing". Compression is considered first-line therapy for venous ulcers. Compression relieves edema and stasis by reducing distention in superficial veins and assisting the calf muscle pump action. Other managements include regular dressings, debridement, appropriate antibiotics and surgical management (Juxta femoral flush ligation with venous stripping and perforator ligation) of varicose veins. These are the conventional modes of treatment. (1)

Many hypothesis have been proposed and postulated to explain the causative mechanisms of venous ulcers. Regardless of the mechanism, these ulcers do not contract and / or refuse to epithelize as in any other ulcer. Hence these must be actively treated in order to promote healing. (2)

On the other hand, we have Plasma Rich Protein which is also called as PRP or platelet-enriched plasma or platelet-rich concentrate. PRP's have healing property because they contain a full complement of clotting and growth factors and a high concentrate of platelets. Hence these are a physiological reservoir of growth factors and these have an active role in tissue regeneration. These have been used to treat wounds since 1985. PRP serves as a growth factor agonist and has both mitogenic and chemotactic properties.(3,4)

Hence the aim of this study was to find the effectiveness of PRP in chronic venous ulcers.

2. MATERIALS AND METHODS:

This was a case control prospective study conducted at ACS medical college and hospital, Chennai, from Jan 2019 to Jan 2020 after obtaining institutional ethical clearance. Patients were explained about the study in detail and their written informed consent was obtained prior to the study.

The study was conducted in 40 patients which included 20 cases and 20 controls. Detailed history including the name, age, sex, address, contact number, occupation, and history of medication was noted. Age, size of ulcers and other parameters were matched for cases and controls.

Prior to start of the study all legs were documented with photographs and ulcer size was measured and quantified manually by taking templates on a tissue paper. This was done prior to every dressing.

Inclusion criteria:

- Any ulcer, persistent for more than 6 weeks (chronic ulcer).

- Patient should be from an accessible area so as to attend all the office dressings once in 4 days for 8 weeks of intervention and 3 months of follow up at the end of intervention.
- Age >18 but <80 years.
- Chronic venous insufficiency corresponding to C6 on the CEAP classification.
- Venous ulcer that either refused to heal or recurred following interventional procedure, both surgical and endovenous procedures.
- Normal blood test results in terms of platelet and red blood cell counts and hematocrit.
- Any ulcer whose diameter in the greatest dimensions were between 2 and 6 cms.

Exclusion criteria:

- Arterial insufficiency.
- Patients in whom doppler studies revealed residual varices.
- Diabetic neuropathic ulcers.
- Patients with severe cardiovascular disorders.
- Patients with syphilis, Hepatitis B, Hepatitis C and HIV.
- Chronic use of immunosuppressants or anti-retroviral drugs.
- Clotting disorders, anemia and hypoproteinemia.
- Chronic infectious diseases.
- Treatment with radiotherapy or chemotherapy.
- History of cancer.
- Active infection or fever at the beginning of the study.
- critically ill patients.
- patients who refuse to consent.

For all patients in group A, the following were done: PRP was prepared from the patients own blood 1 hour prior to the procedure. Then it was injected about 3/4th of a cm away from the edge of the ulcer with the needle pointed towards the base in a tangential manner at every 0.75 cm interval, this was followed by a simple gauze dressing. This was done on Mondays. The patient was asked to come for a follow-up on the 4th day. A regular silver-based dressing was done on Fridays and again the patient was asked to come for a follow-up on the following Monday again. This protocol was followed up to 8 weeks.

Group B patients were treated with conventional silver-based dressing. These patients were asked to come for dressings twice a week and follow-up.

During the study period, patients were allowed to do their day-to-day activities with compression bandages.

These patients were observed for a period 6 months from the date of initiation of the study.

The production of platelet-rich plasma:

20ml of venous blood was drawn in a syringe containing 0.1 ml of anticoagulant to avoid clotting. Whole blood was centrifuged at 3000 RPM for 5 min at 23°C and this is called a “soft spin”. This separated the blood into two layers: the bottom layer of PRBC’s, the top layer comprised of cellular plasma. The plasma alone is pipetted out and subjected to a second round of centrifugation at 4500 RPM for 10 mins. This is called a ‘hard spin’. The upper two third portion constitutes the Platelet Poor Plasma which was discarded while the lower one third portion constitutes the PRP, which is used for the PRP treatment. (5) This is aspirated in a syringe with a 24-gauge needle and is ready to be injected as per the above-mentioned protocol.



Figure 1: After the first centrifuge, showing PRBC’s and cellular plasma.

3. RESULTS:

Our study consisted of 20 cases and 20 controls. Of these, 8 patients belonged to 40 – 60 years, 8 patients belonged to 60 – 80 years and 4 patients belonged to 20 – 40 years of age in the control group. In the cases group, 7 patients belonged to 40 – 60 years, 9 patients belonged to 60 – 80 years and 4 patients belonged to 20 – 40 years of age

In our study about 10% were females and 90% were males.

Parameters compared:

The amount of exudate at the time of each dressing was found to be higher in the cases group than the control group.

There was a marginal increase in the cost of the cases group.

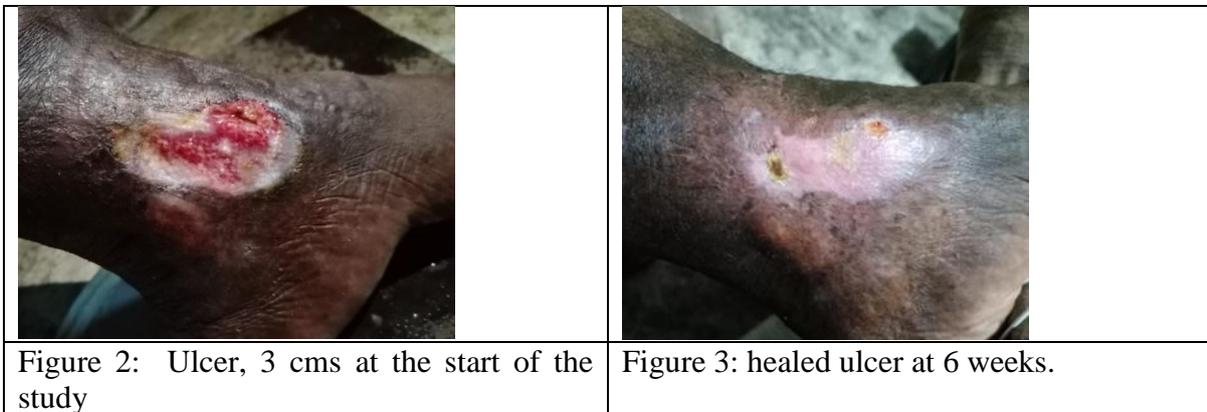
Patients were divided into two groups based on the ulcer size for assessment purpose.

	Total no of patients		No. of healed ulcers		No. of residual ulcers	
	2 -4 cms	4 – 6 cms	2-4 cms	4-6 cms	2-4 cms	4-6 cms
Control group	11	9	6	3	5	6
Cases group	12	8	12	6	0	2

Size of the wound: the average size of the wound was found to be decreasing faster in cases group than in controls group with reduction in the ulcer perimeter which was observed from the second week.

Table 2: Size of the wound over the period of study

Group		Average wound diameter @ Day 0	Average wound diameter @ 4 weeks	Average wound diameter @ 6 weeks	Average wound diameter @ 8 weeks	Average wound diameter @ 10 weeks	Average wound diameter @ 12 weeks
Conventional group (Controls)	2 – 4 cms	3.2	2.8	2.3	2.0	1.6	1.2
	4 – 6 cms	5.2	5.0	4.9	4.5	3.9	3.4
PRP Group (cases)	2 – 4 cms	3.3	2.4	1.2	0.0	0.0	0.0
	4 – 6 cms	5.3	4.2	2.3	1.1	0.5	0.7



Following observations were made during the study period.

1. One patient from the cases group who had an ulcer of 4 – 6 cms, whose ulcer healed during the study period, had a recurrent ulcer of >1 cm which healed with conservative management.
2. Patients who had a residual ulcer on completion of the PRP regimen also healed gradually with conservative management in the subsequent weeks.
3. Patients who had recalcitrant ulcers from the control group were given an option for PRP treatment.
4. Two patients from the control group with an ulcer size of 2 – 4 cms and two patients from the same group with an ulcer size of 4 – 6 cms, came back with a recurrent ulcer of less than 1 cm during the observation period. These patients were managed conservatively.
5. Patient satisfaction was higher with cases group, their reason being the faster wound healing, reduction in pain, swelling and discomfort.

4. DISCUSSION:

Venous leg ulcers account for more than half of lower extremity ulcerations, with overall prevalence in the general population ranging from 0.06% to 2%. (6,7) Multiple therapies have been proposed for their treatment. The first line of management being compression therapy for which compression bandage was first introduced by Unna in 1885.(6) This reduces

venous blood pooling and hence decreases venous hypertension. (5–9) Therapy with compression dressing is always not successful leading to chronic venous ulcers.

Surgery is still considered as a treatment protocol for varicose veins. But in the presence of deep vein thrombosis (DVT), this may not be possible. A doppler helps in identifying the presence or absence of DVT, SFJ incompetence and perforator incompetence. (1) Surgical management includes saphenofemoral flush ligation, saphenous vein stripping and subfascial ligation of incompetent perforators. (1) Post-surgery there is a lower recurrence rate of ulcer development. (10) But when such an unfortunate ulcer develops in a patient, surgeons are left with very few treatment options. This made us to take the initiative to conduct the current study.(11)

Since these post-surgical ulcers require regular dressings and repeated hospital visits, this causes lower productivity in younger people and produces a disability in older people. A study by Jones et al., suggested that odour and soaked dressings produce a negative effect on the patients psycho-socially. (7,12,13) It is during this time that we would like to explore the other treatment options for the patient.

Knighton et al., was among the first few to study the effects of autologous PRP on chronic cutaneous ulcers. (9,12,14–16) PRP has a platelet concentration five times above normal. (5,6,9,14–17) PRP has various types of growth factors in it which are important in modulating mesenchymal cell recruitment, proliferation and extra-cellular matrix synthesis during the healing process. (6,13,14)

Crovetti et al. also studied the effects of platelet gel in chronic ulcers among 24 patients. They had also suggested a once weekly platelet gel application like in our study. They had seen a complete response among 9 of these patients. (5,8,9,12,16)

Frykberg et al. studied 49 patients with ulcers of various etiologies and bigger diameters. They found that 97% of the wounds showed improvement. (6,14–16)

De Leon et al. studied 200 patients with chronic ulcers with various etiologies and found that 90.5% of wounds had a 63.6% volume reduction after PRP therapy.(5)

An Indian Study conducted by Sarvajnamurthy et al, on 17 patients with venous ulcers, who were treated with activated PRP, found better and faster wound healing compared to the conventional treatments. (5)

A study by Prakasam et al, in the year 2018, have explored the healing properties of autologous PRP and have suggested that PRP therapy for DFU have been very effective and the rate of recurrence is also low. (5)

Most of the data in literature pertaining to use of PRP in venous ulcers have been done in upfront cases. Our study shows the option of using PRP in recalcitrant cases where all the available options have been tried upon including antibiotics, compression therapy and surgery.

5. CONCLUSION:

The principles of wound care are thorough assessment with medical and nutritional optimization, debridement, compression, management of ischemia, management of infection, and appropriate wound bed preparation. But a major share of the wounds does not heal with conventional measures alone. Non-healing cutaneous ulcers which do not heal within 6 weeks with conventional treatments may require advanced wound care therapies. Most of the advanced therapies like vacuum assisted systems, skin grafting require hospitalization and

use of sophisticated equipments consuming time and resources. In this scenario PRP therapy has shown to be promising. It can be done as an office procedure without any hospitalization. Autologous PRP as weekly injections for 8 weeks is an effective therapy with significant reduction in the area and volume of the ulcer and is comparable with the advanced modes of treatment. Thus, PRP is an effective, safe, readily available procedure for the treatment of chronic recalcitrant and recurrent ulcers which improves the quality of life of patients and reduces their financial burden. Our study shows that PRP is effective in venous ulcers but due to the inclusion criteria, proper follow up and being a single institution study the sample size was small. A multi institutional study with increased number of patients and randomization is necessary to further validate the results.

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