

A PROSPECTIVE RANDOMISED STUDY BETWEEN AUTOLOGOUS PLATELET RICH PLASMA VERSUS PLACENTA EXTRACT GEL ON WOUND HEALING IN DIABETIC ULCER

Madhuri Panchakshari^{1*}, Dr. N. J. Patel², Dr. Nimesh Thakkar³

¹*Research Scholar, S.K. Patel College of Pharmaceutical Education and Research, Ganpat University, Kherva

²Associate Professor, S.K. Patel College of Pharmaceutical Education and Research, Ganpat University, Kherva

³Assistant Professor, Department of General Surgery, GMERS Medical College, Gandhinagar

***Corresponding Author:** Madhuri Panchakshari

*Research Scholar, S.K. Patel College of Pharmaceutical Education and Research, Ganpat University, Kherva

ABSTRACT- Diabetic ulcer is still challenging to manage even with all recent treatment modalities. Many newer substances are coming out with more and more research. PRP and Placenta extract Gel are examples of them. Many studies have been conducted for their efficacy and potency with standard dressing material and substances like betadine and hydrogen peroxide, EUSOL etc. we came out with study to compare both the newer regimen with each other regarding its outcome, patient safety as well as compliance to each modality.

KEY WORDS- Diabetic ulcer, non-healing Ulcers, Autologous PRP, Placenta Extract Gel, Wound Management

INTRODUCTION-

One of the most common causes of chronic wounds is growth factor abnormality. Platelets are considered a rich source of growth factors. Platelet-rich plasma (PRP) enhances wound healing by the barrier effect to prevent bacterial invasion into the wound or the growth factors stimulate wound healing.⁽¹⁾ Diabetes has become a major public health problem worldwide, and the prevalence of diabetes, according to epidemiological studies, continuously increases worldwide. Therefore, the prevention of diabetes and its related complications has become a fundamental issue for both developed and developing countries. Although standard treatments for ulcers have been well applied in patients with diabetic ulcers, such as revascularization, debridement, the use of antibiotics, offloading of the affected legs, and the intensive management of blood glucose^(2,3) a considerable number of patients with diabetic ulcers would eventually undergo lower extremity amputation despite these treatments. The unsatisfying efficacy of these conventional treatments to patients with diabetic ulcers has been attributed to the lack of wound healing-related growth factors in these patients, including vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF).⁽⁴⁾ PRP is a product derived from fresh whole blood that contains a high concentrate of platelets, which can release a variety of highly concentrative growth factors, including PDGF, transforming growth factor (TGF)-b, VEGF, epidermal growth factor (EGF), fibrinogen, osteocalcin and insulin-like growth factor (IGF). It is noteworthy that these factors are essential for the 3 regulations of important cellular processes involved in the healing of wounds, including cell proliferation, chemo-attractant, and cell metabolism. The use of placenta as a therapeutic agent has been prevalent for a long time. It is an immunologically privileged organ and has unique pharmacological effects such as enhancement of wound healing, anti-inflammatory action, and analgesic effect. A variety of substances with biological and therapeutic activity present in human placenta have been isolated and identified as hormones, proteins, glycosaminoglycans, nucleic acids, and polydeoxyribonucleotides (PDRNs).



Hence, this study intends to demonstrate and compare the therapeutic role of platelet rich plasma/allogeneic platelet concentrate and Placenta extract in healing of diabetic ulcers.

MATERIALS AND METHODS-

This study was conducted as a randomized clinical study at Tertiary care hospital during the study period from October,2022 to July,2023. The Patients diagnosed to have Diabetic ulcer attending the Surgery Out Patient Department (OPD) of a tertiary care hospital.

A total of 90 patients with diabetic ulcer at different locations on extremities were randomized and distributed into study. Patients were randomly distributed in Autologous Platelet Rich Plasma and Placenta Extract Gel groups of 45 each. These groups were studied for the effect of Autologous PRP and Placenta Extract Gel (PEG) on epithelialization, reduction and complete healing of the ulcer. The wound was debrided mechanically (both groups) and all dead necrotic material was removed and cleaned thoroughly with antiseptic solution.

PRP was administered once a week for a total of 8 weeks and the ulcer/raw area was covered with saline gauze covered with Vaseline (petroleum jelly) to provide adequate moisture. The dressing was changed every 3rd day and was cleaned with normal saline and covered with Vaseline gauze subsequently. For the Placenta Extract gel group, ulcer was cleansed with saline and Placenta Extract gel was applied once weekly directly over the ulcer area. The dressing was changed every 3rd day and was cleaned with normal saline and covered with Vaseline gauze subsequently. Patients were followed up for a total of 8 weeks and the healing was recorded twice weekly.

Objectives of the study

Primary objectives:

1.To compare the efficacy and safety of Autologous Platelet rich plasma and Placenta Extract gel in diabetic ulcer.

Secondary objectives:

1. To assess the time taken for wound closure or obtaining healthy ulcer base, sufficient enough to accept split skin graft in the experimental (PRP) and Placenta Extract gel groups.
2. To compare the rates of wound healing during the study in either group.
3. To evaluate the incidence of complications including adverse events and serious adverse reactions.

Patient selection:

Inclusion criteria

1. Patients in the age group of 35- 75 years with long standing diabetic foot ulcers.
2. Diabetic patients with type 1 or type 2 diabetes mellitus.
3. Ulcer of more than-equal to 4 weeks duration.
4. Ulcers have to be clinically non infected, full thickness and not exposing bones, tendons, ligaments.
5. Individuals with systemic disease or history of anticoagulant, immunosuppressive, or antibiotic therapy in the last 3 months to be excluded.
6. Haemoglobin more than-equal to 10 g%.
7. Diabetes should be well controlled with HbA1c less than equal to 8.

Exclusion criteria -

1. Screening platelet count < 1,00,000 per cubic mm
2. Patients who are diagnosed or are suspected of osteomyelitis.
3. Patients with serum creatinine of > 1.5 mg/dL.

4. Patients with severe infected wounds (presence of visible pus or excessive wound exudates).
5. Patients infected presently/previously with maggots.
6. Patients with changes of cellulitis, ischemia or gangrene.

Method used to prepare PRP:

Autologous Platelet Rich Plasma (PRP) was prepared by drawing <20 mL of blood, amount depending on the wound size, from the patient. Under all aseptic conditions the blood was drawn in regular 10cc syringes with a 24G needle and expressed into Sodium citrate bulbs of quantity 2.7 ml containing 3.2% sodium citrate as anticoagulant. The blood and anticoagulant were mixed adequately to prevent blood clot formation. A well-mixed sample provide higher quality PRP. The blood was centrifuged to separate the PRP from the whole blood which was then applied to the wound followed by a sterile dressing. Centrifugation separates the contents in blood, where the erythrocytes sediment at the bottom as the substrate and there is platelet rich concentrate as the top layer. We were using the REMI 8c centrifuge available in the Pathology central laboratory of tertiary care hospital to prepare PRP. Patient’s blood in the citrate bulbs was arranged against equal weight saline containing plain bulbs for equivalent gravity distribution and centrifuged at 1500 RPM (soft spin) followed by 3000 RPM (hard spin). The supernatant thus obtained is the platelet rich concentrate which was used to inject in the patient’s ulcer. This platelet rich concentrate was drawn in regular insulin (subcutaneous injection) syringes and was injected in the margins and bed of the diabetic ulcer.

RESULTS:

Age Distribution- In our study of 90 patients, age ranged from 30 to 80 years with the maximum number of patients ranging between 50 – 70 years. This shows that maximum number of patients of diabetic ulcer lay in older age group or in older age group ulcer are unresponsive to initial therapy and persist despite appropriate care and do not proceed towards healing in adefined time period.

AGE	PRP	PEG
31-40	1	2
41-50	10	13
51-60	12	13
61-70	16	12
71-80	8	5
Mean	60	57
Standard deviation	10.07	11.36

Table no. 1. Age distribution in both groups

Sex Distribution- Out of 90 patients, 68 patients were males and 22 patients were female i.e., our study showed male preponderance of diabetic ulcer.

Sex Distribution (%)	No. of patients	
	PRP	PEG
Male	37	31
Female	8	14
Total	45	45

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Table no. 2. Sex distribution in both groups

Hb Concentration- In our study patients with HB > 10gm% were taken since low amounts of hemoglobin affects wound healing. A range of 10-14 g % was found in majority of the patients in our study with the female population having low hemoglobin as compared to men.

Hb concentration	PRP	PEG
Mean	12.1	12.6
Standard deviation	1.3	1.7

Table no. 3. Hemoglobin Concentration in both groups

HbA1c level: The target HbA1C during the course of study and including patients for study was <8 mmol/mol to prevent bias of having uncontrolled blood sugar affecting the rate of healing in either group. To prevent bias of this parameter we have included measurement of HbA1C at the initiation of the study and at the terminal stage of study.

Parameter- HbA1c	PRP		PEG	
	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
Mean	6.9	6.8	6.6	6.6
Standard deviation	0.3	0.3	0.19	0.28

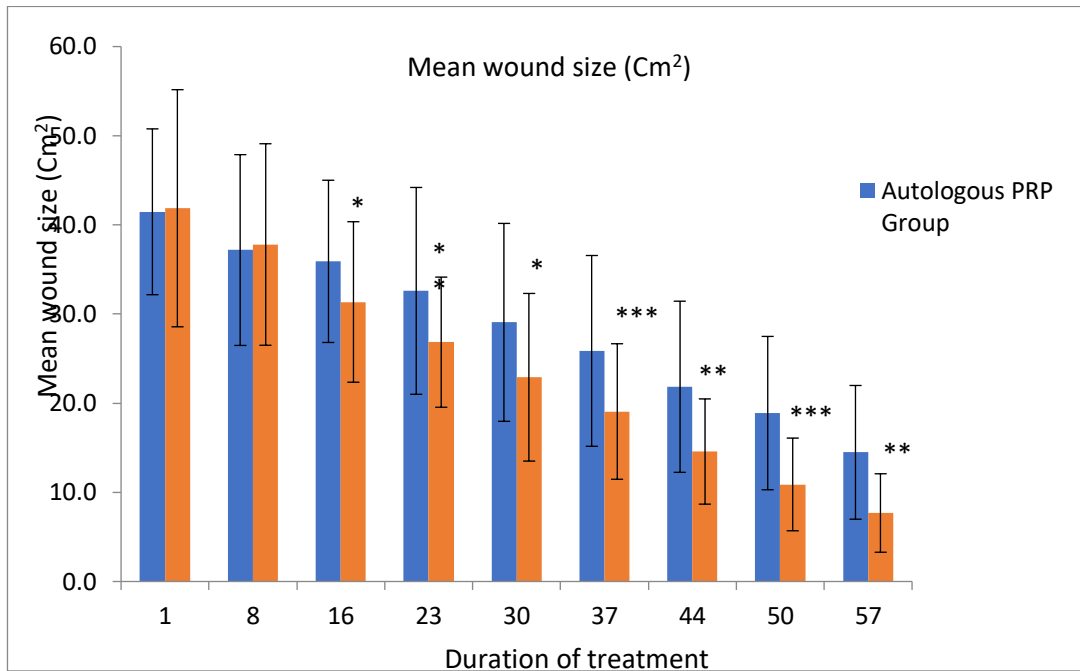
Table no. 4. HbA1c Values in both groups

Ulcer size comparison at end of 8 weeks of treatment:

Ulcer size	PRP	PEG
Mean	14.5	7.7
Standard deviation	7.5	4.4
P value	0.0001	
Significant	*** significant	

Table no. 5. Ulcer Size comparison at end of eight weeks in both groups

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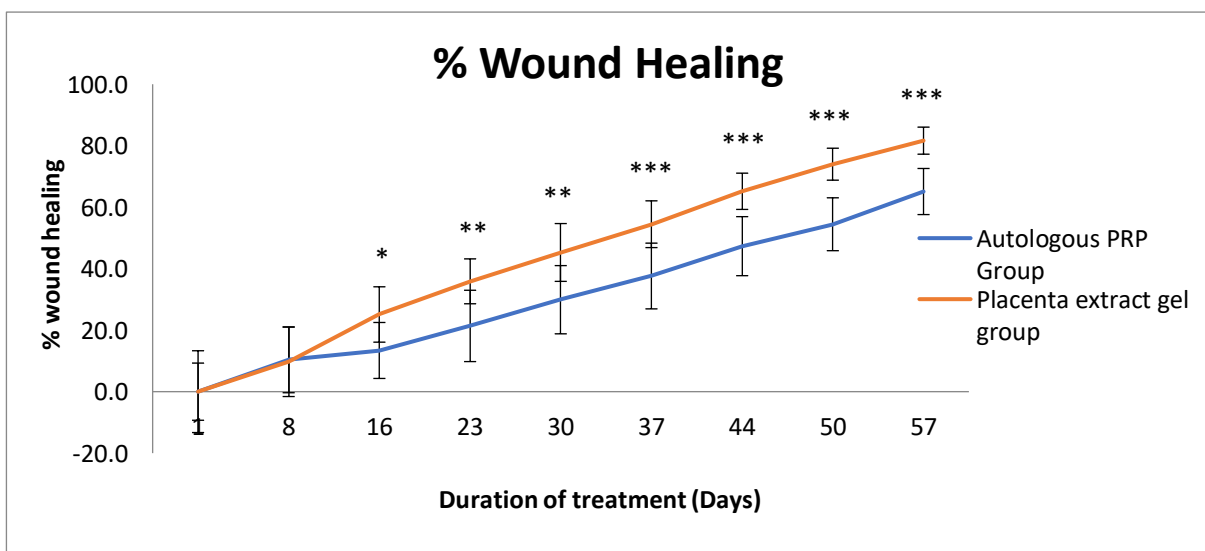
*Difference from the PRP group at $p < 0.05$, ** Difference from the PRP group at $p < 0.001$ and *** Difference from the PRP group at $p < 0.0001$ by t-test analysis.

Healing of Ulcer and Rate of Contracture of Ulcer:

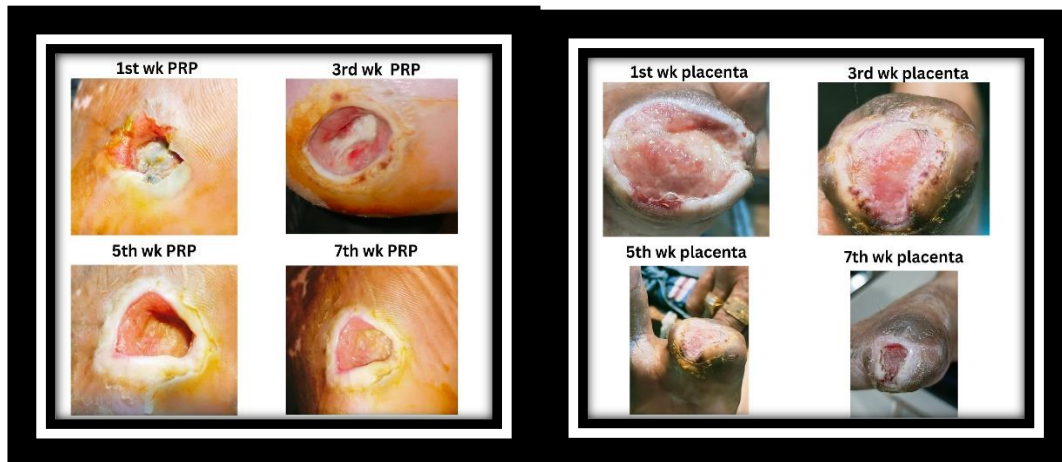
At the time of admission PRP and PEG groups have almost equal mean wound size that is 41.5 cm² and 41.9 cm² respectively. While after giving both the treatment over 8 weeks' time duration as per protocol, PRP group showed 65% and PEG grouped showed 81.5% reduction in ulcer size. This shows % wound healing or Rate of contraction of wound in patients.

	PRP	PEG
Mean Area on admission	41.5	41.9
Mean Area on 8 th week of treatment	14.5	7.7
Percentage contraction of wound	65%	81.5%

Table no. 6. Wound contraction comparison at end of eight weeks in both groups



*Difference from the PRP group at $p < 0.05$, ** Difference from the PRP group at $p < 0.001$ and *** Difference from the PRP group at $p < 0.0001$ by t-test analysis



Clinical Photographs of wound healing in both group patients

DISCUSSION:

The study was conducted as a randomized clinical study at tertiary care hospital during the study period from October, 2022 to July, 2023. The Patients diagnosed to have Diabetic ulcer attending the Surgery Out Patient Department (OPD) and emergency of a tertiary care hospital. Diabetic Ulcer wound is a common clinical problem. Because of population aging and an increase in risk factors and co-morbidities such as tobacco use, obesity, hypertension, and atherosclerosis, there is a clear trend toward increased risk of chronic wounds. The social and economic effects are inevitable.⁽⁵⁾

Managing the diabetic Ulcer should adopt a multidisciplinary approach to manage diabetes and its associated complications. Optimum glycemic control is important. Although direct evidence linking improved glycemic control and healing is lacking, there is sufficient agreement to suggest this would help indirectly by a number of mechanisms. First, chronic hyperglycemia has been shown to impair leucocyte function, a key player in wound healing⁽⁶⁾. Secondly, poor glycemic control has been shown to be associated with micro-vascular complications, with nephropathy patients having a 3-fold higher risk of amputations in comparison to those without nephropathy.

An experimental tool used in combination with standard wound care, topically applied working platelet concentrate or plasma (PRP), may be used to boost chronic inflammatory wounds into the state of proliferation and healing as they release multiple growth factors and cytokines into the wound mimicking natural healing conditions^(7,8). Presently as for pressure ulcers, standard treatment consists of pressure relief, surgical debridement and maintenance of a clean wound environment along with systemic antibiotics. Dressings containing antimicrobial or pain-relieving substances used beneath compression bandages are currently being developed.⁽⁹⁾

A total of 90 patients with diabetic ulcer at different locations on extremities were randomized and distributed into study. Patients were randomly distributed in Autologous Platelet Rich Plasma and Placenta Extract Gel groups of 45 each. These groups were studied for the effect of Autologous PRP and Placenta Extract Gel (PEG) on epithelialization, reduction and complete healing of the ulcer. Analysis was done by using students paired 't' test for continuous variables within the groups and unpaired 't' test for continuous variables between two groups.

As per our study of 45 patients in each group, 8 weeks of study, maximum number of patients ranging from 50-70 years of group with chronic ulcers, majority being male patients. We have selected

patients having Hb more than 10 gm% in both groups so that delayed healing due to anaemia can be ruled out. So, in our both groups, mean of Hb was almost insignificant for healing differences. In both groups, we have selected patients with controlled DM to avoid bias. During treatment all patient had controlled parameter in both groups.

Size of the ulcer at the end of 8 weeks of treatment was significantly reduced in placenta Extract group compared to autologous PRP group. Mean Area of wound at the starting of study for both groups was almost equal. While percentage contraction of wound was 65% with PRP and 81.5 % for PEG, which is significant for PEG at the end of 8 weeks. No Adverse reaction was noted with any of the group.

CONCLUSION:

As per our study, it comes to our notice that both PRP as well as PEG fastens recovery for ulcer in diabetic patients. But for comparison between both, PEG stands better in terms of wound healing and contracture. Patient's compliance is also good with PEG as it is commercially available in market and easy to apply while for Autologous PRP, we need to withdraw blood every time to make it. Moreover, Self-application and less hospital visits can be possible for PEG, while for PRP needs medical personnel from blood withdrawal to preparation and application. We should study even for large volume of patients and for longer duration of time for much more and precise details.

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