

Management of Chronic Non-Healing Ulcers by Topical Application of Platelet Rich Plasma (PRP)

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ABSTRACT

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Disturbance of the normal anatomic structure and functional integrity of the skin can be described as wound. Chronic or non-healing ulcers are defined as ulcers which are failed to heal in less than 3 weeks of duration .If normal healing process is interrupted ulcer can become chronic in nature due to lack of growth factors and cytokines which is results in delay of wound healing. Conventional treatment for chronic non-healing ulcers includes wound cleansing and necrotic tissue debridement. The use of patient's own body cells for ulcer treatment relies upon the components present in the blood and platelet concentrate, which contains various cytokines and growth factors. Autologous PRP is a platelet suspension in plasma derived from whole blood that is increasingly being used in clinical practice for the treatment of chronic non healing ulcers.

OBJECTIVE: To assess the efficacy of topical application of autologous platelet rich plasma in wound healings.

METHODOLOGY: The study was conducted in the department of General Surgery, GREAT EASTERN MEDICAL SCIENCES during the period of February 2021 to February 2022 .

Ten patients between 18-80 yrs ,of any sex, with chronic non-healing ulcers of different etiologies were treated with topical application of PRP.

RESULTS : Ten patients each having ulcer of varying etiology were included .Treated with Topical administration of AUTOLOGOUS PRP solution over the ulcer. Among the included patients 6(60%) were males and 4 (40%) were females with a mean age of 62.5 ± 13.53 years. Out of 10 patients 4(40%) were in 61-80 years age group,2(20%)were in 41-60 years age group and 4(40%) patients was less than 40 years .The duration of the chronic non healing ulcers presented by the patients range from 9 to 24 weeks with a mean duration of 16weeks.After application of PRP solution ,the mean healing time was found

to be almost 8.2 weeks \pm 1.9weeks. After the application of PRP solution small islands of granulating tissue appeared over the wound and a significant reduction in ulcer size was observed as a sign of healing and improvement.

CONCLUSION: In our study, the results showed that PRP is a safe and effective treatment modality for chronic non-healing ulcers. Delivering of growth factors to target site enhances the wound healing rates of chronic non healing ulcers. PRP seems to be efficient to treat chronic non healing ulcers which are non responsive to classical conservative treatments. Using PRP to treat chronic wounds/ulcers may not only enhance healing, but also prevent lower extremity amputations caused by nonhealing wounds. There by reducing over all hospital stay, inconvenience of constant medication and morbidity.

Keywords: Chronic Or Non-Healing Ulcers, Cytokines, Chronic Non-Healing Ulcers, Platelet Rich Plasma, PPP

I. INTRODUCTION

Skin is the largest organ in human body it covers the entire surface area and comprising 10% of total body mass.^{1,2} It has self repairing and self renewing capacity act as important barrier

between outer and inner environment ³It plays a crucial role in defense. Disturbance of the normal anatomic structure and functional integrity of the skin can be described as wound.⁴ Chronic or non-healing ulcers are defined as ulcers which are failed to heal in less than 3 weeks of duration ^{5,6} Typically occurs in lower extremities that are unresponsive to therapy and persist despite appropriate care. This ulcer does not heal in a defined time period. There are many types of non-healing ulcers that may include venous, arterial, diabetic, pressure and traumatic ulcer. The normal wound healing process is dynamic and having three phases : inflammation ,proliferation and re-modelling. If normal healing process is interrupted ulcer can become chronic in nature due to lack of growth factors and cytokines which is results in delay of wound healing.⁷ The incidence of chronic ulcers is expected to increase as the population ages

and due to increased risk factors for atherosclerotic occlusion such as smoking, obesity and diabetes. Majority of the chronic lower extremity ulcers are accounted by venous disease.⁶ The goal of ulcer treatment is to obtain wound closure. Conventional treatment for chronic non-healing ulcers includes wound cleansing and necrotic tissue debridement ^{8,9} A wide variety of advanced treatment for non-healing ulcer available viz: hyperbaric oxygen therapy, skin grafting and VAC (vacuum assisted closure).^{10,11} Despite treatment many chronic ulcers fail to heal and persist for months/years . Cellular therapy for the treatment of non-healing ulcer has been a major breakthrough. The use of patient's own body cells for ulcer treatment relies upon the components present in the blood and platelet concentrate, which contains various cytokines and growth factors. These modular treatment options are safe and effective . Autologous PRP is a platelet suspension in plasma derived from whole blood that is increasingly being used in clinical practice for the treatment of chronic non healing ulcers. The concentration of platelets in PRP is 2–6 folds higher than that of whole blood.¹² Platelets

contain proteins known as growth factors that trigger biological effects of wound healing PRP facilitates wound healing by providing essential growth factors. In addition to acceleration of wound healing, platelets exert antimicrobial activity against bacteria and clinical data shows that the presence of infection is reduced in PRP-treated wounds. The advantages of PRP is easy, cost-effective and much more lasting compared to other standard treatments. Being autologous in nature it is free from communicable pathogens, making it a safe treatment modality with good clinical results.

II. METHODS AND MATERIAL

The study was conducted in the department of General Surgery, GREAT EASTERN MEDICAL SCIENCES during the period of February 2021 to February 2022. Ten patients between 18-80 yrs, of any sex, with chronic non-healing ulcers of different etiologies were treated with topical application of PRP.

Inclusion criteria:- Age groups between 18 to 80, Both sexes are included, Patient belonging to outpatient and inpatient with chronic or non healing ulcers due to various etiologies (such as arterial, venous, pressure or diabetic foot ulcers).

Exclusion criteria :- Smokers and individuals with systemic disease. Patients who are on anticoagulants/on immunosuppressive therapy/Pregnant women, patients with severe cardiovascular disorder/bleeding disorder / Uncontrolled sugar levels were excluded. Patient who receive radiation of chemotherapy within last 3 months. Patient with evidence of malignancy, ulcer with exposed tendons/ligaments/Bones, evidence of gangrene and limbs with selective ankle brachial index (ABI > 0.8 and < 1.5).

Preparation of Prp :- Depending upon the size of ulcer, under strict aseptic conditions peripheral blood was drawn in syringes containing anticoagulant (Acid Citrate Dextrose – ACD-A) in the ratio of 3:17

(anticoagulant: whole blood) from patient's antecubital vein. Blood and anticoagulant were thoroughly mixed before transferring to the processing device to prevent formation of blood clots. The aspirated whole blood was then processed using a centrifugation device. Centrifugation at a rate of 4000 RPM for 10 minutes. After centrifugation sample was transferred to the sterile field.

Treatment procedure :- The chronic non-healing ulcers were first debrided to remove necrotic and infected tissues. And the wound area was cleaned thoroughly with betadine solution. PRP solution was prepared based on the size of the ulcer. Then PRP solution is applied topically over the ulcer. After application of PRP Solution a non-absorbent dressing was used to cover the ulcer area (non-absorbent sterile transparent sheet, Tegaderm). The dressing was changed on day 3 post-treatment. The wound was irrigated with normal saline and assessed for the presence of any form of infection. Patients were followed on every 2nd week to assess the improvement of ulcer healing till 24 weeks of post treatment. Wounds were photographed before treatment and at each follow-up visit after treatment using a digital camera.

III. RESULTS AND DISCUSSION

RESULTS

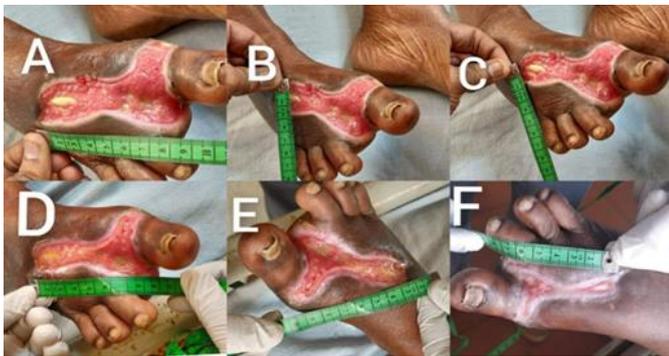
Ten patients each having ulcer of varying etiology were included. Treated with Topical administration of AUTOLOGOUS PRP solution over the ulcer. Among the included patients 6(60%) were males and 4 (40%) were females with a mean age of 62.5± 13.53 years. Out of 10 patients 4(40%) were in 61-80 years age group, 2(20%) were in 41-60 years age group and 4(40%) patients were less than 40 years. Among the ulcers treated, there were 4(40%) venous ulcers, 2(20%) diabetic ulcers, 2(20%) arterial ulcers and 2(20%) pressure ulcers. The duration of the chronic non-healing ulcers presented by the patients range from 9 to 24 weeks with a mean duration of

16weeks.After application of PRP solution ,the mean healing time was found to be almost 8.2 weeks±1.9weeks.After the application of PRP solution small islands of granulating tissue appeared over the wound and a significant reduction in ulcer size was observed as a sign of healing and improvement.

Duration of ulcer persisted before prp treatment :

| Duration of ulcer (weeks) | No of patients |
|----------------------------|----------------|
| 9-12 | 6 |
| 13-16 | 4 |

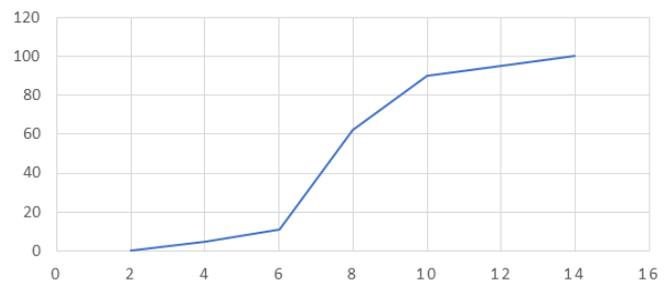
Ulcer Healing time following PRP Treatment :-



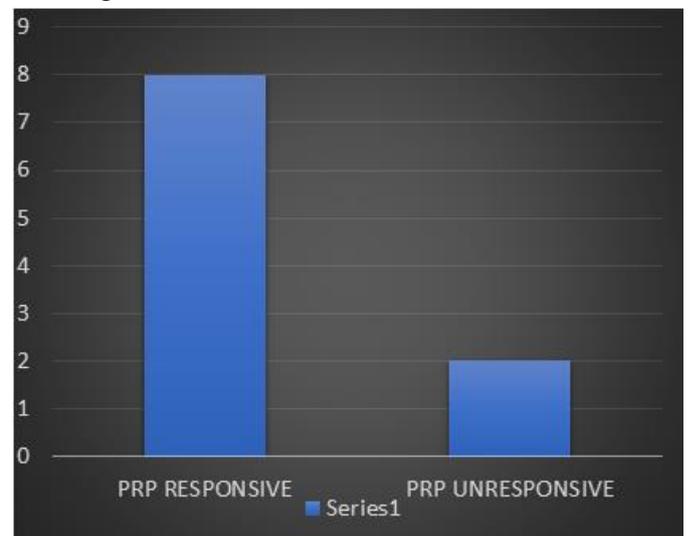
Out of 10 ,8 patients showed signs of healing of the ulcer(reduction in wound size) Where more than 90% reduction in wound size was observed in 6 (60%) patients ,followed by 80-90 % reduction in wound size in 2 (20%) patients over the 24 weeks follow up post PRP application.Patients tolerated the procedure well and there was no procedure related complication. Almost five fold increase in the platelet counts were observed in the final PRP product. There was a statistically significant reduction in the Red Blood Cell (RBC) counts in the post processed sample as compared to whole blood(less than 80%). The mean White Blood Cell (WBC) Count of all the patients was considerably higher than the mean WBC count in whole blood.Reduction in pain and serous discharge from wounds was noted within 1 week post-treatment.This could be due to the anti-inflammatory property of PRP which contains leukocytes. Also no

adverse effects were reported on the day of treatment and during the patient's follow up period. This as a safe and effective treatment method for chronic non-healing ulcers. The overall quality of life of the treated patients improved tremendously post PRP therapy.

PICTURE SHOWS THE PATIENT FOLLOWUP PRE AND POST PRP TREATMENT



20 % of Patients were unresponsive to PRP therapy ,undergoes interval debridement's and regular dressings.



DISCUSSION

Ulcers are classified as acute or chronic according to the duration they have persisted. Chronic non healing ulcers come with significant cost and morbidity for the patients.Typically occurs in lower extremities that are unresponsive to therapy and persist despite appropriate care.These chronic non

healing ulcers of lower extremity develop as a result of peripheral neuropathy, ischemia, or trauma and are often difficult to treat¹³. The main goal of any treatment modality is to obtain wound closure. The conventional treatment includes adequate debridement, re-vascularization of ischemic tissue and avoidance of undue pressure on the wound. Skin grafting has shown some efficacy, however they are not capable of providing the necessary growth factors to modulate the healing process and are expensive.¹⁴ Platelets contain a large number of growth factors and cytokines that play key roles in inflammation and wound healing by contributing towards haemostasis at sites of vascular injury. PRP is a rich concentrate of platelets, cytokines and growth factors dispersed in a very small amount of plasma which can be prepared from a sample of centrifuged autologous blood. The α -granules of platelet rich plasma contain various growth factors primarily Platelet Derived Growth Factor (PDGF), Vascular Endothelial Growth Factor (VEGF), Transforming Growth Factor- β (TGF- β), Insulin-like Growth Factor (IGF) and Fibroblast Growth Factor (FGF). Platelets initiate the wound healing process through release of locally active growth factors that attract undifferentiated cells to the site of injury and promote their cell division. PRP may also limit inflammation by suppressing cytokine release at the site of injury. Improve the wound healing process by promoting capillary angiogenesis and reepithelization because of the presence of large amount of leukocytes.¹⁵

The growth factors released from PRP are important in modulating mesenchymal cell recruitment, proliferation and extracellular matrix synthesis during the healing process¹⁶. PDGF stimulates chemotaxis, proliferation and new gene expression in monocytes, macrophages and fibroblasts, these cell types are considered essential for tissue repair. Platelet derived angiogenesis factor is a polypeptide capable of stimulating new capillary growth by inducing migration of endothelial cells. Transforming growth factor- β stimulates cell

proliferation, protein synthesis and collagen synthesis. It also inhibits growth of many epithelial tumor cells and fibroblastic cell lines. Platelet derived epithelial cell growth factor partially responsible for the initial influx of neutrophils into the wound space. It is also a mitogen for many cells including epithelial cells and fibroblasts. More recently, it was suggested that this was the mechanism by which platelet factors influence the process of angiogenesis and re-vascularisation, thus promoting granulation tissue formation.

Apart from growth factors platelets also release large amounts of elements that contribute to primary homeostasis, like fibrinogen, serotonin, fibronectin, factor V, factor VIII (Von Willebrand factor) and calcium (factor IV). These result in formation of platelet aggregates (clots), causing platelet stabilization by crosslinked fibrin and sticky glycoproteins. The formed fibrin matrix promotes cell permeation with monocytes, fibroblasts and other progenitor cells that play an important role in ulcer healing. In our case series, 10 patients with ulcer were treated with an topical administrators of autologous PRP solution. 80% of patients showed healing of the wound with reduction in ulcer size.

Reduction in pain was observed in post PRP treatment. And also the quality of life of the patients significantly improved. The results demonstrated the safety and efficacy of autologous PRP in treating chronic non-healing ulcers. PRP is an autologous preparation making it a safe treatment modality as compared to allogenic preparations and is free from concerns over transmissible diseases. Moreover PRP requires no special considerations regarding antibody formation. There by effectively preventing the risk of graft vs host disease and leading to better acceptance by patients.

IV. CONCLUSION

In our study, the results showed that PRP is a safe and effective treatment modality for chronic non-healing ulcers. Decrease in pain was observed in post PRP

treatment. Delivering of growth factors to target site enhances the wound healing rates of chronic non healing ulcers. PRP seems to be efficient to treat chronic non healing ulcers which are non responsive to classical conservative treatments. Using PRP to treat chronic wounds/ulcers may not only enhance healing, but also prevent lower extremity amputations caused by nonhealing wounds. There by reducing over all hospital stay, inconvenience of constant medication and morbidity.

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