

The Role of Autologous Platelet Rich Plasma in Treatment of Chronic Non Healing Diabetic Foot Ulcers

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Abstract:

Introduction: Chronic ulcers are a major health problem worldwide and have great impact at personal, professional and social levels, with high cost in terms of human and material resources. Application of autologous Platelet Rich Plasma (PRP) has been a major breakthrough for the treatment of non-healing and diabetic foot ulcers, as it is an easy and cost-effective method, and provides the necessary growth factors that enhance tissue healing. To study the role of effectiveness of autologous platelet rich plasma in healing of chronic ulcers. Also to study the percentage of reduction of area of the ulcer.

Methods: Patients admitted in surgery ward for chronic ulcer were studied. Individuals with systemic disease or history of anticoagulant, immunosuppressive, pregnant women, patients with severe cardiovascular disorder, bleeding disorder and anemia were excluded. Detailed history, clinical examination and lab investigations were taken and analyzed. Autologous platelet rich plasma was prepared from the patients and was applied to the ulcer and regular dressings were done. Wound area was calculated. The treatment outcome was defined as a percentage change of the area, which was calculated as initial measurement minus assessment day measurement divided by initial measurement.

Conclusion: 50 cases were studied. Various factors like age group, gender, etiology of the ulcer, percentage change of area of the ulcer is calculated and found that autologous platelet rich plasma is effective in healing of chronic ulcers. The mean percentage area of reduction of ulcer in the study is 79.33%, which is a very significant reduction in the area of the ulcer.

Keywords: Platelet rich plasma, Ulcer.

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Introduction

Chronic ulcers typically occur in lower extremities that do not respond to initial therapy or continue despite adequate care and do not progress towards healing with an underlying aetiology that may be associated with systemic disease or regional disorders within a defined time span [1,2]. Some forms of chronic ulcers can include venous, arterial, inflammatory, stress, or traumatic ulcers. The normal process of wound healing is dynamic and complex with three phases: inflammation, tissue formation and remodelling of tissue. However, if the normal healing process is disrupted, due to the lack of growth factors and cytokines that hinder the healing process, an ulcer can become recurrent in nature [3].

The aim of ulcer care is to achieve the closure of wound as quickly as possible. Conventional treatment of chronic ulcers includes wound washing, necrotic tissue debridement, prevention, diagnosis, and, where possible, infection control, mechanical off-loading, blood glucose regulation,

and regional dressing ulcer care [2,4,5]. These types of ulcers not only affect the quality of life and productivity of the patient but also become a substantial financial burden for the patient and the healthcare system [6]. Nonetheless, some risk factors generally influencing and leading to slow wound healing include: 1) local causes such as the involvement of debris or necrotic tissue, ulcer infection, tissue hypoxia, and repetitive trauma; 2) systemic diseases such as diabetes mellitus, immunodeficiency, or malnutrition; and 3) medications such as corticosteroids [3].

The standard treatment modalities available for non-healing ulcers address these issues and provide adequate local ulcer therapy with necrotic tissue debridement and moist wound healing setting, wound area pressure relief, antibiotic infection control, antiseptics and topical antibacterial agents, ischemic management, and co-morbidity medical management. A wide range of innovative non-healing ulcer treatments include hyperbaric oxygen

therapy, skin grafting. Following treatment, most chronic ulcers fail to heal or linger for months/years and/or recur after healing, requiring additional advanced wound care therapies for sufficient healing.

Over the past two decades, novel cell therapies such as platelet-rich plasma (PRP) therapy have gained significant interest for their potential use in regenerative medicine [7,8]. Autologous PRP is a plasma-derived platelet suspension that is commonly used in clinical practice to treat recurrent ulcers in whole blood. The PRP platelet density is 2–6 times greater than the whole blood concentration [9]. PRP's curative effects are based on the fact that platelets are a cellular reservoir of a variety of growth factors with healing roles that play an active role in the regeneration of tissues. Several studies have also been published on the role of platelet rich plasma for the treatment of non-healing ulcers with positive response [10].

PRP is most often mixed with thrombin before application in order to generate a fibrin gel, and a platelet-growth-factors-rich exudate [11]. Thrombin-activated platelets release numerous growth factors from their α -granules [12] that can modulate cell proliferation and differentiation and accelerate soft tissue repair in vivo [13] Based on this aim and objectives of the study is to assess reduction in wound size of chronic non-healing ulcers by autologous platelet rich plasma and to evaluate the safety of autologous platelet rich plasma in treatment of chronic non-healing ulcers.

Materials and Methods

This study was done for a period of two years in 50 cases of chronic non healing foot ulcers were chosen through purposive sampling at a tertiary care teaching hospital. A detailed history, clinical examination and investigations were done. And the decision for platelet rich plasma (PRP) injection into wound for wound therapy was decided based on the history, clinical examination findings, laboratory and other diagnostic test report. Adequate diabetic control obtained with insulin therapy and oral hypoglycemic agent with diabetologist opinion. Treated with IV and oral antibiotics according to wound swab culture and sensitive report.

Weekly PRP application and saline dressing done (maximum 6 weeks). Patients were followed up till discharge. Duration of healing and the size of the ulcer before and after treatment were considered as outcomes of the study. The study population consists of patients admitted in the surgical ward diagnosed with chronic non healing ulcer. Patients with DM type 2 with non-healing chronic foot

ulcers (For more than 4 weeks) showing no signs of healing (Reduction in size, Formation of granulation tissue, Epithelization) with intact distal pulsation. Ulcers grade 1 & grade 2 according to Wagner grading system were included in the study.

While patients with liver cell failure, Renal impairment, Heart failure, bleeding or platelet disorders, Malignancies, Short life span, peripheral vascular disease, Major lower limb amputation low immunity or corticosteroid therapy and ulcers (Grade 3,4,5), Patients with evidence of gangrene in ulcer are any part of foot. Patients has known or suspected osteomyelitis. Ulcers that are clinically infected were excluded.

Preparation of PRP

Patients were thoroughly examined and ulcer size (length and breadth) was measured. Under aseptic precautions 20 ml of venous blood was drawn and added to a test tube containing EDTA centrifuged at 3000 rpm for 15 min to separate the red blood cells from the platelets and plasma. The supernatant and the buffy coat composed of platelets and plasma was collected and centrifuged again at 2000 rpm for 5-10 min.

The bottom layer of about 5-8 ml was taken. This contains plasma that is rich in platelets, the supernatant fluid is discarded that is poor in platelet concentrate. The prepared PRP is applied onto the wound after proper surgical debridement and was dressed with a non-absorbent dressing (paraffin gauze). The treatment outcome was defined as a percentage change of the area which was calculated as initial measurement minus assessment day measurement divided by initial measurement. An ellipse is closer to a wound shape than a square or rectangle that would be described by simple length \times width.

Results

The sex distribution of non-healing ulcers among the patients studied was, out of 50 patients, 39 patients were male (78%) and 11 patients were female (22%). The mean age of the male patients affected was 56.26 years with the standard deviation of 11.19 years. The mean age of female patients affected was 58.19 years with the standard deviation of 8.55 years. The maximum number of male patients affected with ulcers is between 40 to 70 years. The maximum number of female patients affected with ulcers is between 50 to 70 years.

Coming to etiology for chronic ulcers was diabetes in 86 %, venous causes in 12 % of the patients. The level of random blood sugar of the patient has an inverse relationship with the percentage of reduction of area of the ulcer.

Table 1: Site of ulcer

Site of Ulcer	Frequency	Percent
Above Left Medial Malleolus	9	18.0
Above Right Medial Malleolus	1	2.0
Below Left Knee Amputation Stump	3	6.0
Below Right Knee Amputation Stump	3	6.0
Dorsum Of Left Foot	10	20.0
Dorsum Of Right Foot	6	12.0
Lateral Aspect Of Left Leg	8	16.0
Lateral Aspect Of Right Leg	1	2.0
Medial Side Of Right Foot	8	16.0
Medial Side Of Right Leg	1	2.0
Total	50	100.0

The commonest site of ulcer is dorsum of left foot in our study followed by left medial malleolus and lateral aspect of left leg. The mean duration of ulcer when patients came to treatment was 8.28 weeks, the mean duration of time taken for healing was 6.9 weeks in our study.

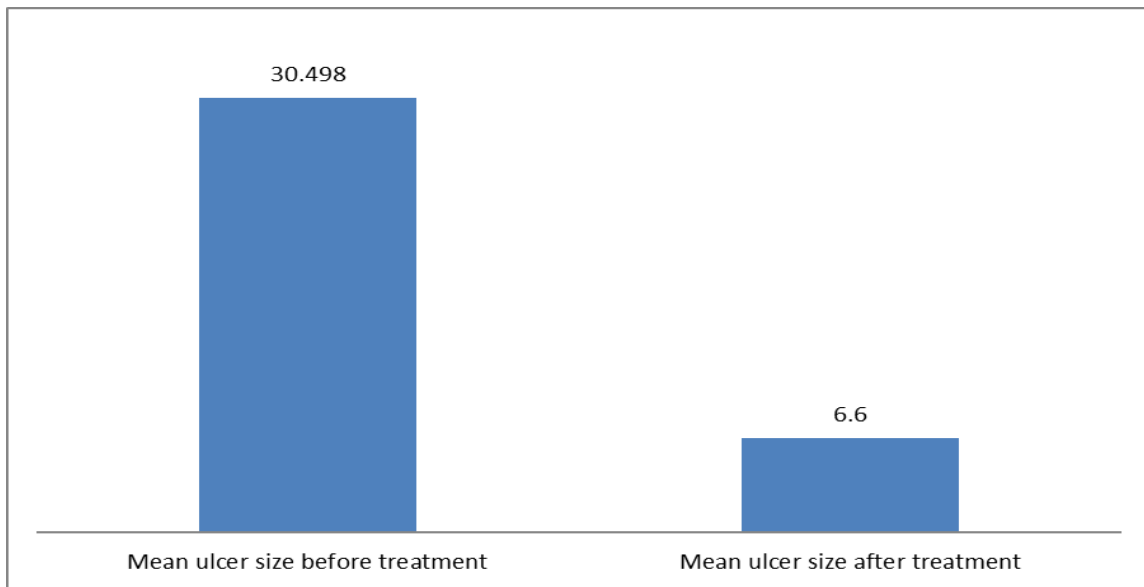


Image 1: Mean size of ulcer before and after

The mean ulcer size before treatment was 30.49cm³ with SD of 24.63 which reduced to 6.6 cm³ with SD of 2.26 after treatment. This was statistically significant with a p value of < 0.001.



Image 2: Ulcer before and after treatment with PRP

Discussion

Diabetic foot is a serious condition with a high morbidity and affects quality of life. In spite of the treatment advances in managing diabetes, the complications from diabetic foot are very serious and are a significant contributor of lower limb amputations. The initial point is the development of ulcer in the foot. The ulcer is a culmination of a number of neurovascular changes. Management of diabetic foot ulcers is of great significance in clinical setting as it leads to serious socioeconomic consequences. Therefore finding a potential solution to heal foot ulcers is of great importance.

Leg ulcers are classified as acute or chronic according to their duration; however, there is no consensus as to a specific length of time to define chronicity. An acute ulcer usually should heal in less than a month. Among chronic ulcers, duration of 6 months or more seems to define the most recalcitrant ulcers. Among diabetic patients, 2-3% will develop a foot ulcer each year, 15% will develop a foot ulcer during their lifetime.

Although the pathogenesis of peripheral sensory neuropathy is still poorly understood, there seem to be multiple mechanisms involved, including the formation of advanced glycosylated end products and diacylglycerol, oxidative stress and activation of protein kinase C β . The frequency and severity of wound infection is increased in diabetes, which may be related to high glucose levels or impairment of granulocytic function and chemotaxis. In addition, there seems to be a prolonged inflammation, impaired neovascularization, decreased synthesis of collagen, an abnormal pattern of synthesis of extracellular matrix proteins and decreased fibroblast proliferation

The main principles of treatment are relief of any pressure from the wound by total contact casting, adequate control of infection, debridement of devitalized tissue and control of blood sugar levels. If the standard measures fail, new therapeutic options such as recombinant human growth factors and bioengineered skin substitutes may be benefited but cost is the limiting factor.

Autologous PRP is a cost-effective method. PRP enhances wound healing by promoting the healing process by seven growth factors present in it. They are platelet-derived growth factor (PDGF- $\alpha\alpha$, $\alpha\beta$, $\beta\beta$), fibroblast growth factor, vascular endothelial growth factor, epidermal growth factor and transforming growth factor. These growth factors are important in modulating mesenchymal cell recruitment, proliferation and extra-cellular matrix synthesis during the healing process. Platelet-derived angiogenesis factor is a polypeptide capable of stimulating new capillary growth by inducing migration of endothelial cells. Platelet-derived epithelial cell growth factor is 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 revascularization, thus promoting granulation tissue formation.[14] In addition to growth factors, leucocytes also help in wound healing as they have and also help in preventing infections. The percentage of reduction of area of ulcer in venous ulcer was 79.33% which is comparable to the Yilmaz et al [15] study where the area of reduction of ulcer was 94.7% in 6 weeks. Also comparable to Kakudo et al [16] study where the percentage of area of reduction was 83% in 5 weeks.

The management of non-healing ulcers is a challenging issue. Delayed healing of wounds is the major problem in the community besides causing morbidity and disability in the patient, burden on our health resources. The platelet rich plasma containing the important growth factors has a positive impact on wound healing by enhancing granulation tissue formation also acts an anti-inflammatory agent and helps in reducing the wound size. Nowadays PRP is being used in various fields like Orthopedics, Sports medicine, Dentistry, Otolaryngology, Neurosurgery, Ophthalmology, Urology, Wound healing, Cosmetic, Cardiothoracic and Maxillofacial surgery.

Conclusion

This study shows that PRP is effective in healing foot ulcers with a considerable reduction in the ulcer area in a short duration of time. Being an autologous preparation, it is safer than other preparations. Future studies should focus on large multicentric studies with random sampling with comparison of other treatment options. PRP is a safe, simple, inexpensive and biocompatible procedure. In our study, PRP is found to be useful in enhancing the wound healing in chronic ulcers without any adverse events.

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