Research Paper

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Functional outcome and results of Platelet rich plasma (PRP) in Treatment of Delayed Union

Medical Science

KEYWORDS : PRP, Delayed union, VEGF

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ABSTRACT

Objective: *To assess functional outcome & results of injection of platelet rich plasma (PRP) in delayed union.*
Design: *Prospective clinical study with 12 months of follow-up.*
Methods: *Clinically proven six patients of delayed union participating in study included in study according to inclusion and exclusion criteria on OPD basis after getting written and informed consent , treated by 6 mL of autologous PRP injection thrice weekly for 4 weeks by single author*, evaluation done clinically as well as radiologically (at baseline, 1 month , 3 months, 6 month and 12 month interval).*
Results: *The median follow-up period was 10 months (range 8–12 months) .The fractures of five patients (83.3%) achieved union at median 12 weeks (range 8–20 weeks). There was non-union of the fractures of 1 patient (16.6%), grafting and revision surgery was done in this patient.*

Conclusions: *Thrice weekly injection of 6 ml of autologous PRP for 4 weeks is a safe and effective mean of treatment of delayed union. But to establish PRP as a definitive treatment modality larger studies with longer duration needed in future.*

INTRODUCTION

Bone healing, or fracture healing is a proliferative physiological process in which the body facilitates the repair of a bone fracture[1,2,3]. For normal fracture healing to occur a number of requirements must be met eg viabilty of fragments (i.e. intact blood supply), mechanical rest this can be achieved by not moving and external immobilization, e.g. cast or internal fixation and absence of infection. The process of healing is different depending on the configuration of the fracture fragments and can be divided into three main categories (i)spontaneous (indirect/ secondary) healing, (ii) contact (angiogenic/primary) healing (iii) gap healing[1,3,4]. Fracture healing is a complex physiological process involving a coordinated interaction of hematopoietic and immune cells within the bone marrow, in conjunction with vascular and skeletal cell precursors [5]. Several different cytokines and growth factors play role in healing of a fracture[6]. Delayed union is a fracture that requires more time than standard to heal but over time it shows progression toward healing[7]. Average healing times of common fractures are as follows phalanges(3 weeks), metacarpals(4-6 weeks),distal radius(4-6 weeks), lower arm(8-10 weeks), humerus (6-8 weeks), femoral neck(12 weeks), femoral shaft(12 weeks), tibia(10 weeks) [1,4] .Non-union is defined by the United States Food and Drug Administration as established when a minimum of nine months has elapsed since injury and the fracture shows no visible progressive signs of healing for three months [4,8]. Non-union is generally classified as hypertrophic, oligotrophic or atrophic according to the radiological appearance [4,8]. Atrophic non-union is characterized by little or no callus and resorption in the bone ends while in oligotrophic and hypertrophic non-union, blood flow is sufficient and an excessive amount of callus is seen. Insufficient mechanical stability is a reason which leads to non-union [9]. In the treatment of delayed union or non-union, the biological and mechanical factors should be evaluated first. After achieving mechanical stability with internal or external fixation, an attempt is made to achieve union with grafts, growth factors or with physical means[7]. Platelet Rich Plasma (PRP) stimulates natural healing process through growth factors contained in the platelets. PRP applied to the wound area accelerates the physiological healing process, provides support for the connection of cells, reduces pain and has an anti-inflammatory and anti-bacterial effect[10]. Studies in literature have reported the use of PRP in the treatment of non-union [11-14]. The aim of this study was to determine the effects of autologous PRP on union in the treatment of patients diagnosed with delayed union.

MATIRIALS AND METHODS-

After approval from institutional ethical committee (IEC), clinically & radiologically diagnosed fifteen adult patients of both sexes of delayed union with at least 3 months since fracture in conservatively treated patient or 3 months since last operation included in study .Exclusion criteria were pathologic fractures, clinical or laboratory signs of infection, a history of anticoagulant use, patient having significant cardiovascular disease, anemia, renal or hepatic disease, pregnancy, any local infection or malignancy, diabetes, hypothyroid, neuropathy or any vascular insufficiency , bleeding or platelet disorder. All the patients were explained about the study and an informed consent was obtained. Only those providing consent to participate in the study were enrolled in the study. Paticipents were treated with 6 ml of autologous injection PRP thrice weekly for 4 weeks at the site of fracture by single author*. Patients were followed up for 12 months post injection PRP. No analgesic was prescribed during follow up except tab paracetamol (650 mg) SOS.

The PRP was prepared by withdrawing 20 cc of whole blood under aseptic precautions atraumatically from antecubital vein, mixed with 2.8 ml of Acid Citrate Dextrose solution (ACD solution)[15] in sterile vials, centrifuged in centrifuge machine @ 1500 rpm for 15 minutes[16], PRP was made and collected in fresh vial by pipette. After waiting for one hour at 20-22° (air condition room) so that platelets come in resting phase[17].PRP was injected intralesionally and surrounding tendons by aseptic technique without prior activation by mean of pharmacological agents[18]. In PRP, concentration of platelets should increase 3-5 times than that in whole blood for proper effect.

STATISTICAL ANALYSIS-

The statistical analysis was done using SPSS (Statistical Package for Social Sciences) Version 15.0 statistical Analysis Software. The values were represented in Number (%) and Mean±SD.

RESULTS-

Table-1 Baseline data

Demography Male/Female	5/1 Total 6
Age of patients Median	32 yrs, Range 19-57 yrs
Median time since fracture/last operation (Months)	4.8, Range 4-6
Median follow up (Months)	10 , Range 9-12
Union	5/6

Out of six enrolled patients 5 were male (83.3%) and 1 was fe-

male (16.6%) and median age of participants was 32 years, ranged from 19 to 57 years. PRP was applied at median 4.8 months (range 4–6 months) after the last operation or after fracture in conservatively treated patient. The median follow-up period was 10 months (range 8–12 months) (Table 1). The fractures of five patients achieved union at median 12 weeks (range 8–20 weeks). There was non-union of the fractures of 1 patient, grafting and revision surgery was done in this patient. No side effect during treatment with injection PRP was noticed except pain at injection site in two patient which lasted for ten minutes and relived spontaneously.

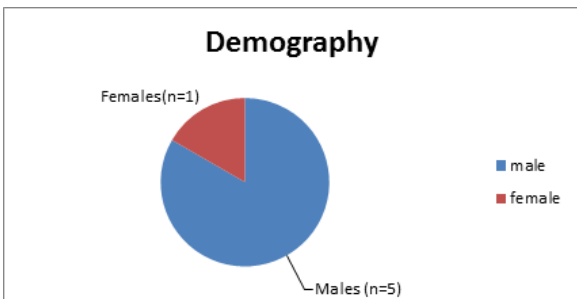

Figure-1 Demography

DISCUSSION-

There are several factors which affect fracture healing. These can be grouped as factors related to the fracture (open fracture, infection, type of fracture),

factors related to the patient (smoking, diabetes mellitus, connective tissue diseases, systemic infection) and iatrogenic factors (medications such as non-steroid anti- inflammatories and steroids) [19]. In the treatment of

non-union, autologous bone grafting is the first choice, studies have reported the use of bone marrow injection, bone morphogenetic protein (BMP), PRP, and demineralised bone matrix in fracture union[11,12,13,20,21,22]. PRP was first used in 1987 in heart surgery to prevent excessive blood transfusion [23]. More than 30 bioactive proteins are found within the alpha granules of platelets [24]. Transforming Growth Factor beta (TGFβ) and Platelet Derived Growth Factor (PDGF) are growth factors with a major role in fracture healing [5,6]. PRP, which includes growth factors such as primarily TGFβ and PDGF, vascular endothelial growth factor, and insulin-like growth factor and proteins such as fibrin, fibronectin, vitronectin and thrombospondin plays a role at several stages of tissue healing [25]. The growth factors activate some of the cells which have a function in tissue healing and thus provide soft tissue healing and bone regeneration [26]. PRP activates repair cells in the blood circulation [27]. With the effect of growth factors which it contains, it stimulates local stem cells and activates the repair cells in the circulation and the bone marrow. In a study by Bielecki et al[11] of a single dose application of PRP to 32 cases of delayed and non-union, results were reported of union in all the delayed union group and in 65% of the non- -union group. They recommended the application of PRP within 11 months after surgery. Sanchez et al[13] applied revision surgery, grafting and PRP to 13 of 16 cases of non hypertrophic non-union and repeated PRP injections to three patients. Union was obtained in all cases and at least three injections were recommended in cases where injection was applied. In a study by Calori et al[12] in which revision surgery together with PRP was compared with the application of BMP7. In 120 cases of atrophic non- -union, union was achieved in 86.7% of the BMP group and 68.3% of the PRP group and clinical and radiological healing was reported earlier in the BMP group. Griffin et al[29] reviewed the use of PRP in clinical studies and reported that PRP use was safe but no clinical evidence was shown of benefit in acute or delayed fracture union. Different results have been reported from the application of PRP together with allograft or autograft in surgical treatment. While some researchers have maintained that PRP has positive effects[30,31], others have claimed that there is no benefit [32,33].

In our study in 83.3% of delayed union patient union was achieved after thrice weekly autologous injection of PRP at fracture site for 4 weeks while in 16.6% cases delayed union was progressed to nonunion which was treated by revision surgery with autologous cancellous bone grafting , the results are consistent with other studies[11,30,31]. In our study no side effect of PRP injection noted except pain in injection site which lasted for ten minutes is consistent with studies which states that autologous PRP is devoid of potential side effects[28]. In vivo studies also suggest that PRP helps in healing of musculoskeletal system and even promotes regeneration.

In our study sample size and follow-up duration is less so we suggests further study should be carried out with larger sample size and longer follow up for making autologous injection PRP as an established treatment option for delayed union.

CONCLUSION-

Thrice weekly injection of 6 ml of autologous PRP for 4 weeks is a safe and effective mean of treatment of delayed union. But to establish PRP as a definitive treatment modality larger studies with longer duration needed in future.

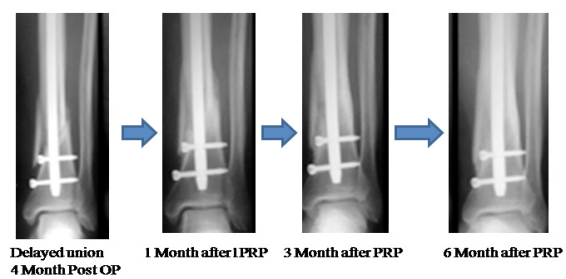

Figure 1- Post op delayed union treated by inj PRP

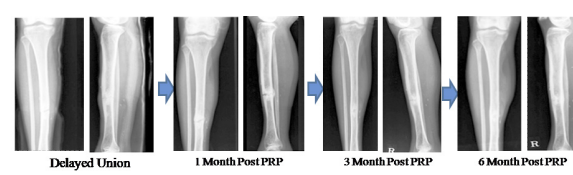

Figure 2 – Delayed union treated by inj PRP

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BenjaminII; Leandro MaiaIII; Aécio C. de OliveiraII; José de O. PintoII; José I. Ribeiro JúniorIV 19. TAITSMAN, L. A., LYNCH, J. R., AGEL, J., BAREI, D. P., NORK, S. E.: Risk factors for femoral nonunion after femoral shaft fracture. J. Trauma, 67: 1389–1392, 2009. 20. BRALY. H. L., O'CONNOR, D. P., BRINKER, M. R.: Percutaneous autologous bone marrow injection in the treatment of distal metadiaphyseal tibial nonunions and delayed unions. J. Orthop. Trauma, 27: 527–533, 2013. 21. ROLDAN, J. C., JEPSEN, S., MILLER, J., FREITAG, S., RUEGER, D. C., ACIL, Y., TERHEYDEN, H.: Bone formation in the presence of platelet-rich plasma versus bone morphogenetic protein-7. Bone, 34: 80–90, 2004. 22. WILKINS, R. M., KELLY, C. M.: The effect of allomatrix injectable putty on the outcome of long bone applications. Orthopedics, 26: 567–570, 2003 23. FERRARI, M., ZIA, S., VALBONESI, M., HENRIQUET, F.,VENERE, G., SPAGNOLO, S., GRASSO, M. 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