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Autologous platelet injection in the treatment of long bone nonunion: A prospective interventional study

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Abstract
Introduction: Union of fracture is a complex process involving many systemic as well as local factors. Disturbance in any of these factors may lead to failure of process of union. This non-union is associated with increased morbidity, pain and functional disability. Autologous platelet injection at local site has been reported to be one of the effective measures in managing the cases of fracture of long bones complicated by non-union. We conducted this prospective study to know the effectiveness of autologous platelet injection at the fracture site in cases of fracture of long bones complicated by non-union.
Materials and Methods: This was a prospective interventional study comprising of 30 cases of fracture of long bones complicated by non-union. The patients were included in this study on the basis of a predefined inclusion and exclusion criteria. The patients with established nonunion after fracture femur, tibia, humerus, radius and ulna were included in this study. Patients who were treated either by, by internal fixation, bone grafting or conservatively were added in this study. Imaging was done by X-rays and if needed by computerized tomography. Imaging was done till definite evidence of union was obtained.
Results: Out of 30 cases there were 18 males and 12 females with a M:F ratio of 0.66. The most common bones involved were femur (60%), tibia (16.67%) and humerus (16.67%). Combined fractures of Radius and Ulna were seen in 3 (10 %) patients. The mechanism of injury was Road traffic accidents (66.66%) followed by direct blow and fall from height. All patients initially were treated conservatively or by surgery depending upon type of fractures. Non-union of fractures were treated by autologous platelet injection. All fractures showed radiological evidence of union within 4 months of treatment.
Conclusion: Autologous platelet injection at local site is an effective management strategy in patients of fracture of long bones complicated by non-union. A non-infected site is the pre-requisite of this treatment.

Keywords: Long bone fractures, non-union, autologous platelet injection, outcome

Introduction
With increased motorization and industrialization there is an exponential increase in road traffic accidents and industrial trauma. Fractures following road traffic and other accidents frequently result in long bone fractures. These fractures usually unite and heal over a period of time. These cases of non-union may result in significant morbidity, cause functional deficits in patients and may require multiple operative procedures [1]. Though there is no strict time period to diagnose non-union, usually absence of evidence of union on imaging after 4-6 months needs intervention. This entity needs to be differentiated from delayed union where union is slow but will eventually occur without additional surgical or nonsurgical intervention [2]. The various factors which may be responsible for delayed or non-union include local site infection, soft tissue interposition at the fracture site, bone loss leading to loss of bony contact between fractures ends, faulty fixation, inadequate immobilization and also factors such as immunocompromised status, smoking, anemia, steroid use, patients on chemotherapeutic agents, cachexia, severe peripheral vascular diseases and metabolic bone disease [3]. Patients usually present with pain, stiffness and various degrees of functional disabilities. The workup of these patients must include a through history to search for a cause of non-union as well as a comprehensive clinical examination to find out presence of factors such as local infection, faulty fixation and presence of bone loss.

Imaging studies are crucial for diagnosis of non-union. X-Ray anteroposterior and lateral views showing absence of healing over a period of 4-6 months is diagnostic of non-union. In doubtful cases and in cases with rotational component computerized tomography with 3D reconstruction can be useful [4]. Magnetic resonance imaging is preferred in cases where osteomyelitis is suspected. Moreover, MRI may show soft tissue details more accurately than X-ray and Computerized Tomography. Use of radioisotope scanning for the diagnosis of infection as a cause of non-union is not routinely done but may be useful in selected cases [5].

One of the difficulties with managing patient of non-union is ambiguity with its diagnostic criteria. There is no standardized criteria for defining non-union. FDA (Food and Drug Administration) defines a non-union as the incomplete fracture healing within 9 months following injury, along with absence of progressive signs of healing on serial radiographs over the period of three consecutive months [6]. Once this criterion is met patient needs some or the other form of intervention without which the union of fractured bone is unlikely.

Management of Non-Union generally depends upon the site and cause and may comprise of procedures such as excision of infected bone, removal of infected hardware, bone transplant, antibiotic beads, nailing. Plating and Ilizarov etc [7]. Recently the interest in use of biologic agents such as aspiration concentrate of bone marrow, platelet rich plasma, fibroblast growth factors, stem cells and bone morphogenic protein for treatment of nonunion has increased due to encouraging results in various clinical trials [8]. The use of local injection of platelets has been shown to be effective in treatment of non-union of long bones. Platelets contain granules which contain multiple growth factors and cytokines [9]. These growth factors and cytokines play a crucial role in the bone repair and also help in healing of fracture [10]. We conducted this prospective study to find out the effectiveness of autologous platelet injection at the fracture site in cases of fracture of long bones complicated by non-union.

Materials and Methods

This was a prospective interventional study conducted in the department of orthopedics of a tertiary care medical college situated in an urban area. The patients were included in this study on the basis of a predefined inclusion and exclusion criteria. After excluding the patients on the basis of exclusion criteria 30 patients were included in this study. Demographic details like age and gender were noted. Mechanism of fracture and treatment details of all the patients were also noted. A detailed history was taken specially to know presence of risk factors for non union. A thorough clinical examination was done. Investigations like CBC, BT CT, HIV, HBsAg and preanesthetic evaluation was done in all cases. Oral antibiotics were given to all patients before the procedure. All patients received low molecular weight heparin for prevention of deep vein thrombosis. NSAIDs were strictly avoided before and after the procedure.

Fracture fixation method was chosen on the basis of site of fracture, age of patient and according to clinical decision of the operating surgeon. The procedure consisted of open reduction and internal fixation, screwing or nailing depending upon the type of fractures. In addition to operative procedure all patients received platelets rich plasma (approximately 10 ml) was injected around the fracture site in the periosteum. It was outpatient department procedure and patients were instructed to follow physiotherapy and rehabilitation programs to minimize the risk of pseudoarthrosis. When needed plaster cast was given for immobilization. Partial weight bearing was allowed after 4 weeks. Patients were followed up monthly for initial 3 months and after that every 45 days till 1 year. During follow up visits, clinical as well as radiological evaluation (anteroposterior and lateral views) was done in all the cases. In each visit pain relief was measured using visual analogue scale (VAS). Clinical union was defined as pain-free, full-weight bearing and full functional recovery for lower extremity fracture non-unions, and pain-free movements and full functionality for fracture non-unions of the upper extremity. Radiological union was defined as the presence of bridging callus on at least 3/4 cortices on the AP and lateral radiographic views. Computed Tomography was done in cases where X-ray findings were non-conclusive or ambiguous. Failure of treatment was defined as absence of clinical and radiological union till 9 months of platelet injection. The results were studied using appropriate statistical methods. Data analysis was carried out using SPSS16.0 version software. Microsoft word and excel were used for generating charts and graphs. P value less than 0.05 was taken as statistically significant.

Inclusion Criteria

1. Patients having fractures of long bones complicated by non-union.
2. Age over 18 years of age.
3. Patients given informed consent to be part of the study.

Exclusion Criteria

1. Patients less than 18 years of age.
2. Patients who refused consent to be part of the study.
3. Patients lost to follow up.
4. Active autoimmune disorders and large bone defects
5. Patients with large skin defects of fracture site, musculoskeletal disorders, malignancies, and pathological fractures.
6. Patients having contraindications to surgical procedures such as severe thrombocytopenia, deranged bleeding or clotting time were also excluded.

Results

This was a prospective observational study in which the patients who had been diagnosed with non-union of long bones were included. The clinical details, operative management and outcome was studied. A total of 30 patients who fulfilled the inclusion criteria were included in this study. Out of these 30 patients there were 18 males and 12 females with a M:F ratio of 0.66

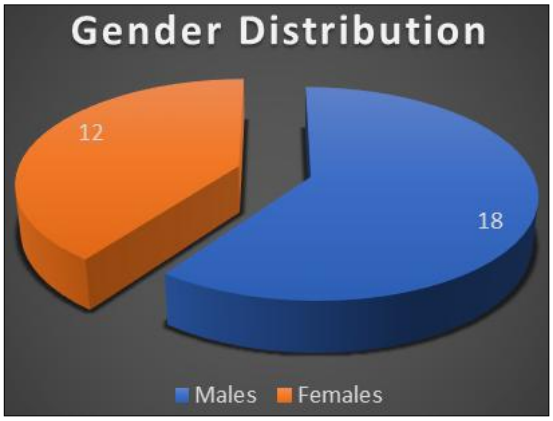

Fig 1: Gender Distribution of the studied cases.

The analysis of the age groups of the patient showed that the most common age group to be affected was between the age group of 35-45 years comprising of 40.00 % of all the cases followed by 35-45 (33.33%) years and > 45 years (16.67%).

Table 1: Age groups of the affected patients.

Age group	No. of patients	Percentage
18 -25 years	3	10.00%
25-35 years	12	40.00%
35-45 years	10	33.33%
>45 years	5	16.67%
Total	30	100%

The analysis of mechanism of injury showed that the most common mode of injury was road traffic accidents (63.33%) followed by fall of heavy object (16.67%), Direct blow like assault (13.33%) and other injuries (6.67%).

Table 2: Mode of injury

Mode of injury	No of patients	Percentage
Road Traffic Accidents	19	63.33%
Fall of heavy objects	5	16.67%
Direct impact	4	13.33%
Others	2	6.67%
Total	30	100%

The analysis of presence of risk factors for nonunion in the studied cases showed that there were no risk factors in 12 (40.00%) patients while 8 (26.67%) patients had either diabetes, hypertension or both. Inadequate immobilsation after surgery (10.00%), faulty fixation (6.67%), bone loss (6.67%), fracture site infection (6.67%) and anemia (3.33%) were other factors seen in studied cases.

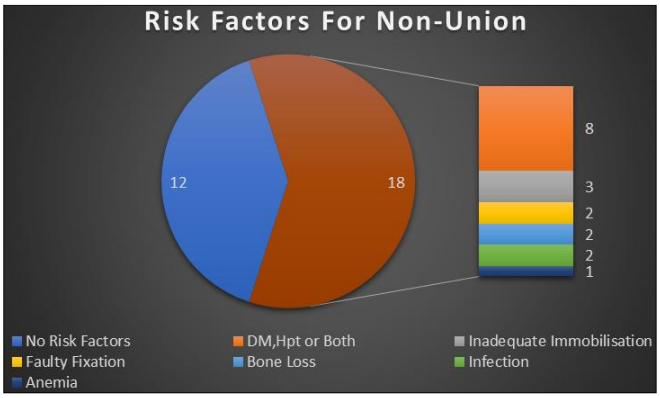

Fig 2: Risk Factors present in the studied cases

The bone primarily affected by non-union most commonly were Femur (33.33%) followed by tibia (16.67%), humerus (16.67%), radius (13.33%), ulna (10.00%) and combination of radius and ulna (10.00%).

Table 3: Affected Bone in the studied cases.

Affected Bone	No of Case	Percentage
Femur	10	33.33%
Tibia	5	16.67%
Humerus	5	16.67%
Radius	4	13.33%
Ulna	3	10.00%
Radius and Ulna	3	10.00%
Total	30	100.00%

Spiral fractures (23.33) followed by type III open fractures (20.00%) were the most common fractures complicated by non-union. The other common fractures complicated by nonunion were Type II open fractures (20.00%), simple fractures (13.33%) and wedge fractures (10.00%).

Table 4: Types of fractures in studied cases.

Fracture	Type	No Of Cases	Percentage
Closed Fracture	Simple	4	13.33%
	Oblique	2	6.67%
	Spiral	7	23.33%
	Wedge	3	10.00%
	Comminuted	1	3.33%
Open Fracture	Type I	3	10.00%
	Type II	4	13.33%
	Type III	6	20.00%
Total		30	100%

All patients were treated by closed reduction, open reduction and internal fixation with the help of screws or plating depending upon the type of fractures. Patients received injections of platelet rich plasma periosteally and around the fracture sites. Within 4 months of treatment union occurred in all of the patients.

Fig 3: Nonunion of fracture of radius and ulna (Left), After local injection of platelet Radiological union noted (Right).

Radiographic Union was noted at an average of 65.25 days in closed fractures and 93.25 days in open fractures. The difference in duration of radiological union was found to be statistically significant (P<0.05)

Table 5: Mean Duration of radiological healing in Open and Closed Fractures.

	Mean Duration Of Radiological Union (days)	Std Deviation (days)
Closed Fractures	65.25	3.96
Open Fractures	93.25	2.94
P value < 0.05 - Significant		

Proximal fractures showed early evidence of radiological union with mean time of radiological union of 61.78 while distal fractures showed radiological union at an average time of 98.46 days. The difference in duration of radiological union in proximal and distal fractures was found to be statistically significant (P<0.05).

Table 6: Mean Duration of radiological healing in Proximal and Distal Fractures.

	Mean Duration Of Radiological Union (days)	Std Deviation (days)
Proximal Fractures	61.78	2.76
Distal Fractures	98.46	3.12
P value < 0.05 - Significant		

Patients with no Risk Factors showed early evidence of radiological union with mean time of radiological union of 62.34 while distal fractures showed radiological union at an average time of 92.76 days. The difference in duration of radiological union in patients with or without risk factors was found to be statistically significant (P<0.05).

Table 7: Mean Duration of radiological healing in Patients with and without risk factors.

	Mean Duration Of Radiological Union (days)	Std Deviation (days)
Patients With Risk Factors	62.34	2.92
Patients Without Risk Factors	92.76	3.46
P value < 0.05 - Significant		

During follow up VAS scores of all the patients were determined to know the reduction in pain. While during post-operative period 11 patients had VAS score more than 6 (Severe pain), at 1 month follow up only 5 patients had severe pain. At 6 months follow up only 7 patients had mild pain and 23 patients had no pain.

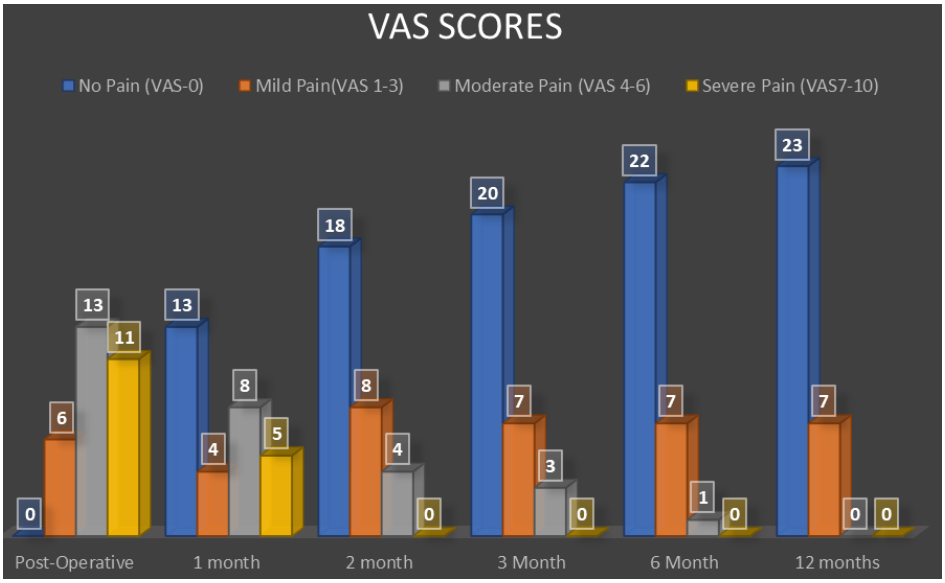

Fig 4: VAS scores in Postoperative period and during follow up.

Discussion

Nonunion of the fractured bones is one of the common problems encountered in orthopedics practice. The incidence of non-union is more in patients of advanced age, those with peripheral vascular diseases, patients on steroids or immunosuppressants and in individuals with local wound infection [11]. While it is important to identify and treat the cause of non-union such as bone loss (bone grafting), infection (antibiotics) and faulty fixation (proper internal fixation), there are certain biological agents which may hasten the process of union in fractured bones [12]. These biological agents include aspiration concentrate of bone marrow, platelet rich plasma, fibroblast growth factors, stem cells and bone morphogenic protein. As far as use of these biological agents in the patients of delayed and nonunion is concerned there is tremendous increase in the interest of researchers [13].

These biological a different mechanism of actions by which they improve healing of fractured bones. Aspiration concentrate of bone marrow act by virtue of presence of stem cells that have the ability to differentiate into osteoblasts after it is injected at the fracture site. Similarly platelets contain multiple growth factors and cytokines that play an important role in healing process and hence aid in union of fractured bones. Fibroblast growth factors help in union of bone by expression of multiple genes involved in osteogenesis [14].

Ghaffarpasand F *et al.* [15] conducted randomized double-blind placebo controlled clinical trial involving 75 adults patients having fractures complicated by Non-union. Patients were randomly assigned to receive 5mL PRP (n=37) or 5mL normal saline as placebo (n=38) in the site of fracture after intramedullary nailing or open reduction and internal fixation (ORIF) along with autologous bone graft. The author found that healing rate was significantly higher in group which received platelet injections as compared to placebo. Injection of PRP was also associated with lower pain scores and shorter healing duration. The authors concluded that platelet injection results in higher cure rate, shorter healing duration, lower limb shortening and less postoperative pain. Similar results were reported by authors like Say F *et al.* [16] and Calori GM *et al.* [17]

Hakimi M *et al.* [18] conducted a study to assess the effect of platelet rich plasma in combination with autologous cancellous graft on bone defect healing in a critical metaphyseal long bone defect the authors found that Platelet rich plasma combined with autologous cancellous graft leads to a significantly better bone regeneration compared to isolated application of autologous cancellous graft in an *in vivo* critical size defect on load-bearing long bones.

Conflicting outcomes were reported by other who found that platelet rich plasma may not enhance healing process by itself. Lenza M *et al.* conducted review of literature to evaluate effectiveness of the use of platelet-rich plasma as coadjutants for union of long bones. The authors included randomized clinical trials that evaluated the use of platelet-rich plasma as coadjuvant medication to accelerate union of long bones. At the end of review the authors found no conclusive evidence that sustained the use of platelet-rich plasma as a co-adjuvant to aid bone regeneration of fractures, pseudoarthrosis, or bone defects [19].

Despite conflicting conclusions of the studied there is ample evidence to show that platelets injected locally improves the healing of fractured bone. The process of healing aided by platelets has sound scientific basis (presence of growth factors in platelets) [20]. Our study unequivocally found beneficial effects of platelet injection in cases of bone fractures complicated by nonunion. More extensive research is needed to understand the effects of platelet injections on the healing process.

Conclusion

Our study showed that percutaneous transplantation of platelets is safe treatment for non-unions of long bone diaphysis. The relative ease of preparation, applicability in the clinical setting, favorable safety profile and possible beneficial outcome makes local injection of platelets a promising therapeutic approach for managing long bone fractures complicated by non-union.

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