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A study of use of platelet rich plasma and bone marrow aspirate in management of delayed union of tibial diaphyseal fractures

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Abstract:
Background: *A Delayed union is defined as a fracture which has not united in the time in which one would expect it to unite. Of the long bones, Tibia is the most common site for delayed union development. These often results in need for secondary intervention or additional treatment to stimulate bony union. Percutaneous autologous bone marrow injection is minimally invasive and can promote bone healing. PRP is autologous blood product containing very high concentration of platelets. There is currently no well established, less invasive approach available to foster fracture healing in patients with delayed unions. In view of the above facts and to find a cheap, non invasive and patient compliant solution we undertook the study of use of Autologous Bone Marrow aspirate and Platelet Rich Plasma in management of delayed union of tibial diaphyseal fractures.*
Materials and Methods: *In this prospective randomised controlled study, 22 patients of delayed union tibial diaphyseal fractures belonging to age group 18 to 60 years who were follow up cases of closed or compound tibial diaphyseal fractures managed conservatively or operatively (with no implant at present) were randomly allocated to 2 groups of 11 patients each based on computer based randomization chart. Group A received platelet rich plasma and Group B received bone marrow injection. 2 doses were given at an interval of 4 weeks. Clinical and radiographic evaluation done at 3, 6 and 9 weeks. The initial pattern of fracture, management, time for radiological and clinical union was compared between the groups.*
Results: *The number of cases which resulted in union between the two groups was compared and a statistically significant difference was found between the two groups.The results of our study showed a significant advantage of using bone marrow in management of delayed union of tibial diaphyseal fractures*
Conclusion: *Percutaneous autologous bone marrow injection resulted in union in cases of delayed union of tibial diaphyseal fractures as compared to platelet rich plasma aspirate*
Key Word: *Delayed union, Tibia fracture, Bone Marrow Aspirate, Platelet Rich Plasma*

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I. Introduction

Fracture healing involves a well-orchestrated cascade of molecular and cellular events that recapitulate the process of embryonic endochondral bone formation and results in formation of new bone across the fracture site. The majority of fractures heal uneventfully, but it has been reported that 5% to 10% of all fractures either fail to unite or demonstrate a delay in healing.[1, 2]Complications in fracture healing such as delayed union occur in majority of tibial shaft fractures. These often results in need for secondary intervention or additional treatment to stimulate bony union. Reoperations are an example of such secondary intervention which can often result in a considerable impact in patient function and quality of life.[3] Currently the gold standard treatment to stimulate bone healing is rescue surgery with autologous graft. However, the open grafting method has multiple disadvantages, including the limited availability of bone autografts and osteoprogenitor cells and donor site morbidity associated with autograft harvest.[4] Hence, to find a cheap, non invasive and patient compliant solution we undertook the study of use of autologous bone marrow aspirate and platelet rich plasma in management of delayed union of tibial diaphyseal fractures.

II. Materials and Methods

A prospective randomized controlled trial study was conducted in Gauhati Medical College and Hospital. All patients reporting with delayed union tibial diaphyseal fractures at Orthopaedics OPD were chosen for the study. The study was conducted for a period of 18 months from 1st November 2020 to 31st May 2022. 22 patients were chosen and randomly divided into two groups of 11 each. Randomization ensured that both the groups were comparable with respect to age, sex, mode of injury, side of injury, previous treatment etc.

Study Design: Prospective randomized controlled study
Study Location: This was a tertiary care teaching hospital based study done in Department of Orthopaedics, at Gauhati Medical College and Hospital, Bhangaghar, Guwahati, Assam.
Study Duration: November 2020 to May 2022.
Sample Size: 22 patients.
Subjects & selection method: All patients reporting with delayed union tibial diaphyseal fractures at Orthopaedics OPD were chosen for the study. The study was conducted for a period of 18 months from 1st November 2020 to 31st may 2022 after getting clearance from the ethical clearance committee. Minimum follow up period was 9 months. 22 patients were chosen and randomly divided into two groups of 11 each.

Inclusion criteria:
1. Age more than 18 years and less than 60 years
2. Willing to participate to undergo the procedure and study
3. Follow up cases of closed or compound tibial diaphyseal fractures manged conservatively or operatively (with no implant at present)
4. More than 4 months and less than 9 months of initial trauma
5. Clinically presence of the following at the fracture site:
   Pain
   Tenderness on stress at the fracture site
   Motion at the fracture site
6. Radiographically, presence of radiolucent line at the fracture site.

Exclusion criteria:
1. Age less than 18 years or more than 60 years
2. Less than 4 months or more than 9 months of initial trauma
3. History of drug abuse
4. Pathological fractures
5. Active systemic or local infection
6. Evidence of malignancy in the past 5 years
7. Pregnant
8. Lactating
9. On corticosteroid drugs
10. On immunosupressants

Procedure methodology:
Patients were counselled about the procedure and after informed and written consent in their own understandable language, standard proforma was filled. Patients were divided into two groups based on computer based randomization chart. 11 patients were taken in each group.
Group A- Received platelet rich plasma (n=11)
Group B- Received bone marrow aspirate (n=11)

Preparation and administration of Platelet rich plasma
Preparation of the venipuncture site and blood sample collection
- Proper vein was selected and the venipuncture site was cleaned with sterile cotton swabs soaked in spirit and betadine in sequential manner
- 40 ml of venous blood was drawn from the selected vein and dispensed in sodium heparin vials

PRP separation procedure
- Differential centrifugation technique with two spins using BEXCO centrifuge machine was used
- Blood collected in sodium heparin vials were used in centrifugation
- The first spin was performed at 1500 rpm for 15 minutes. This spin separated the red blood cells from the rest of the components
- The upper part containing the plasma was carefully transferred to another vial and the lower red blood cell layer discarded

Concentration procedure
- The vials containing plasma were spinned at 2500 rpm for 10 minutes.
- The upper half of the supernatant (the platelet poor plasma) was discarded
- The lower half was collected in two 10 ml sterile syringes and kept in constant agitation

Administration of PRP

- Administration of PRP injection was performed in the Major Operation Theatre of the Department of Orthopaedics.
- Patient was placed on OT table in supine position
- The affected limb was painted and draped
- Prilox ointment (lidocaine and prilocaine) ointment was applied tropically.
- Under fluoroscopic (C-arm) guidance the site of delayed union was localized
- Under all aseptic and antiseptic conditions prepared PRP was injected into the site of delayed union
- Sterile bandaging was given and above knee casting was done for immobilization

Figure 1: Centrifuge Machine

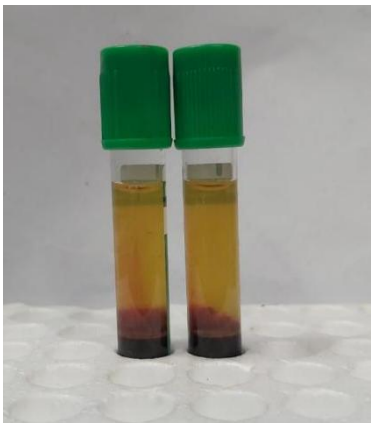


Figure 2: Platelet Rich Plasma in Heparin Vial

Figure 3: Injection of PRP at fracture site

Preparation and administration of Bone marrow aspirate

Collection of BMA

- Procedure was carried out in the Major Operation Theatre of the Department of Orthopaedics
- Patient was placed on OT table in supine position
- Short general anaesthesia was administered
- Painting and draping of the iliac region was done
- Under all aseptic and antiseptic conditions a 2mm incision was given over the anterior iliac crest
- BMA needle (Jamshidi) was introduced into cancellous part of iliac crest in between inner and outer tables
- 20ml of aspirate is collected
- The incision site was stapled and antiseptic dressing done

Administration of BMA

- Done in the same setting as collection of BMA
- Under fluoroscopic (C-arm) guidance the site of delayed union was localized
- The affected limb was painted and draped
- Under fluoroscopic (C-arm) guidance the site of delayed union was localized
- The collected BMA was injected directly into the site of delayed union
- Sterile bandaging was given and above knee casting was done for immobilization

Figure 4: Aspiration of Bone Marrow from Illiac Crest Figure 5: Localization of Fracture

Follow Up (PRP & BMA): The same procedure is repeated after 4 weeks

- After 4 weeks of the 2nd injection patient is evaluated radiographically. If there is presence of callus partial weight bearing with Patellar Tendon Bearing (PTB) casts is allowed. If there is no callus, above knee cast is continued and patient is asked to review after 4 weeks and the same procedure is followed.
- Follow up is done after 3, 6 and 9 months from the initial injection

Both clinical and radiographic evaluation was done. Anterior-posterior as well as lateral view x-rays were taken.
Clinical Union*:* Painless total weight bearing without macro mobility at the fracture site
Radiological Union*:* Bridging callus formation across 3 of the 4 cortices on anteroposterior and lateral radiographic views.

Statistical analysis: Data was analyzed using SPSS version 20 (SPSS Inc, Chicago). Student t-test was used to ascertain the significance of differencs between mean values of two continuous variables. P value less than 0.05 was considered as the cut-off value for significance.

III. Result

The efficacy of platelet rich plasma and bone marrow aspirate in management of delayed union tibia diaphyseal fracture was studied. 11 patients received two doses of platelet rich plasma at an interval of 4 weeks and other 11 patients received two doses of bone marrow aspirate at an interval of 4 weeks.

Table no 1 shows that59.1 % of cases were initially compound fractures. Similar results were found by Marc Jayankura et al in their study. They found 82.8 % of cases to be initially compound fractures. .Majority of the cases in our study were caused due to road traffic accidents; it is fairly common for compound fractures to happen in such cases.

Table no 1: Type of Fracture:

	Frequency	Percent	Valid Percent	Cumulative Percent
Compound	13	59.1	59.1	59.1
Closed	9	40.9	40.9	100.0
Total	22	100.0	100.0	

Type of fracture	PRP	BMA
Closed	7	6
Compound	4	5
Total	11	11

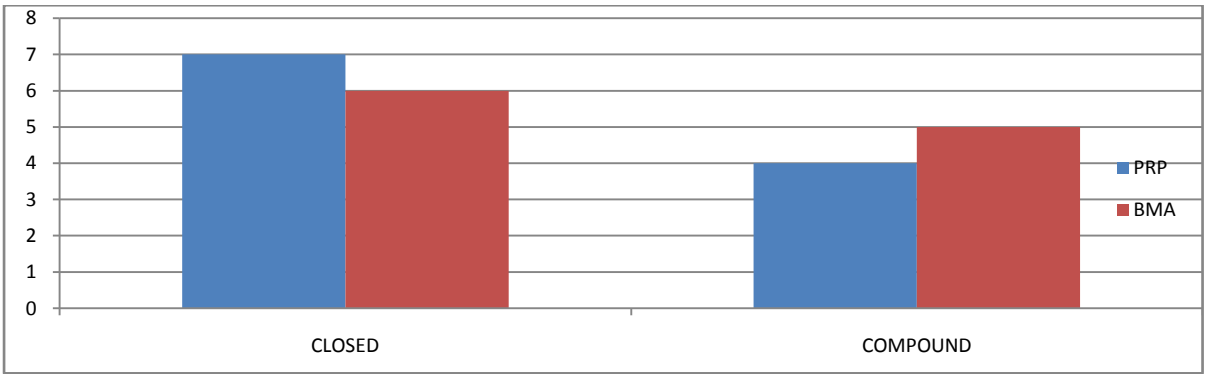


Table no 2 shows that Most of the cases in our study had fracture of both tibia and fibula **(**81.8%**)**

Table no 2: Bones Fractured

	Frequency	Percent	Valid Percent	Cumulative Percent
Tibia + Fibula	18	81.8	81.8	81.8
Tibia	4	18.2	18.2	100.0
Total	22	100.0	100.0	

Bones Fractures	PRP	BMA
Tibia + Fibula	8	10
Tibia	3	1
Total	11	11

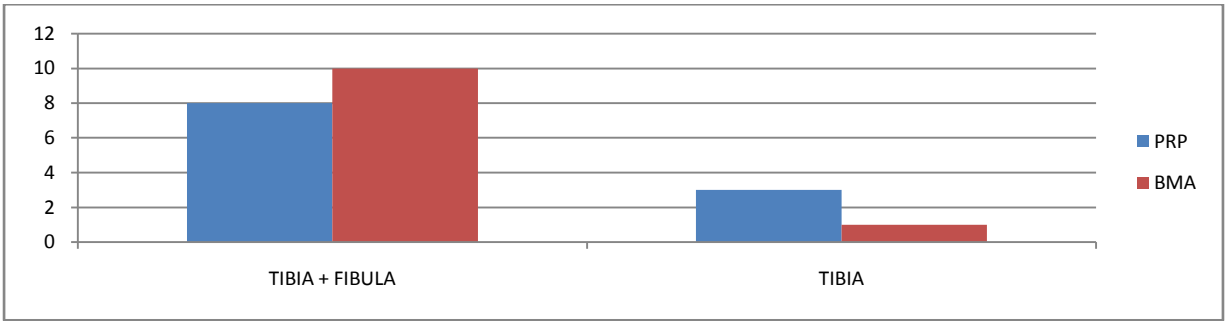


Table no 3 describes the initial treatment received by patients. Patient who had internal fixation devices operated were not included in the study to maintain uniformity regarding immobilization (with pop casts only) after administration of bone marrow aspirate and platelet rich plasma. As majority of the cases had history of hospitalization following initial trauma, most of the cases were managed with external fixators (54.5 cases). Majority of closed cases were managed with pop casts only

Table no 3: Preliminary Treatment:

	Frequency	Percent	Valid Percent	Cumulative Percent
No Treatment	1	4.5	4.5	4.5
External Fixator	12	54.5	54.5	59.1
Conservative (POP)	9	40.9	40.9	100.0
Total	22	100.0	100.0	

Preliminary Treatment	PRP	BMA
No Treatment	0	1
External Fixator	7	6
Conservative	4	4

Total	11	11

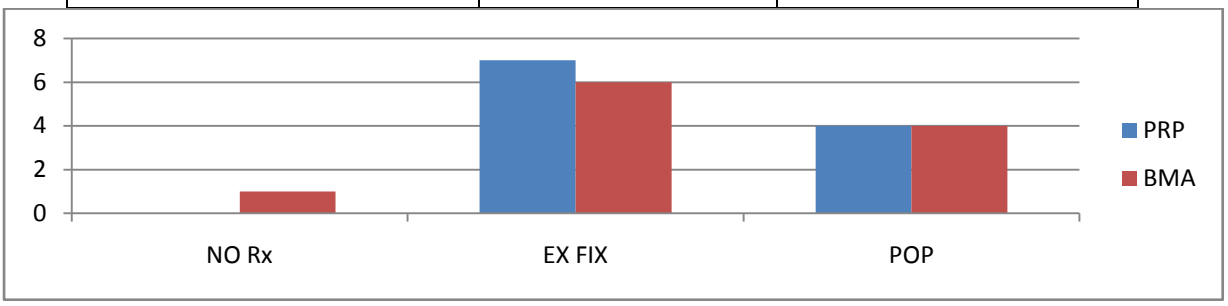


Table no 4 shows the time interval from initial injury to presentation in hospital by the patients. Majority of the cases (40.9%) presented to us after 5 months of initial trauma. (Mean = 5.36 months). 2 patients presented to us as early as 4 months from initial trauma. 1 patient presented following 8 months from initial trauma. Patients presenting before 4 months and beyond 9 months were not considered for the study as they did not qualify to be defined as delayed union fracture.

Table no 4: Interval (Time from initial injury to presentation in hospital)

	Frequency	Percent	Valid Percent	Cumulative Percent
4 m	2	9.1	9.1	9.1
5 m	9	40.9	40.9	50.0
6 m	7	31.8	31.8	81.8
7 m	3	13.6	13.6	95.5
8 m	1	4.5	4.5	100.0
Total	22	100.0	100.0	

Mean: 5.36

Interval	PRP	BMA
4 m	1	1
5 m	6	3
6 m	3	4
7 m	1	2
8 m	0	1
Total	11	11

Mean (PRP): 5.37

Mean (BMA): 5.91

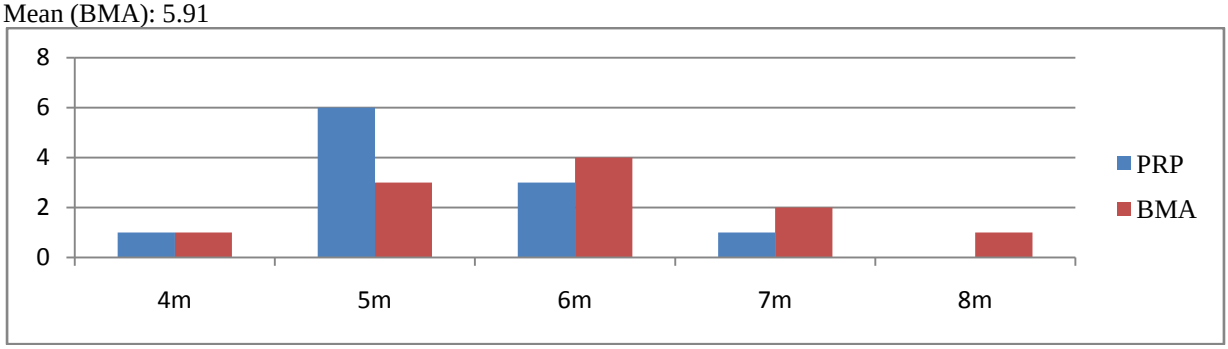


Table no 5 depicts the results of our study. 9 out of 11 cases (81.8 %) resulted in union of their fractures in the bone marrow aspirate group where as 5 out of 11 cases (45.5 %) achieved union in the platelet rich plasma group. On statistical analysis, the p value was found to be 0.046, indicating a significant difference in results between the two groups.

Table no 5: Results:

	Frequency	Percent	Valid Percent	Cumulative Percent
Union	14	63.6	63.6	63.6

Non Union	8	36.4	36.4	100.0
Total	22	100.0	100.0	

Intervention * Result Cross tabulation						
			Result		Total	**P-value**
			U	NU		
Intervention	BMA	Count	9	2	11	**0.046**
		% within Intervention	81.8%	18.2%	100.0%	
	PRP	Count	5	6	11	
		% within Intervention	45.5%	54.5%	100.0%	
Total		Count	14	8	22	
		% within Intervention	63.6%	36.4%	100.0%	

Results	PRP	BMA
Union	5	9
Non Union	6	2
Table	11	11

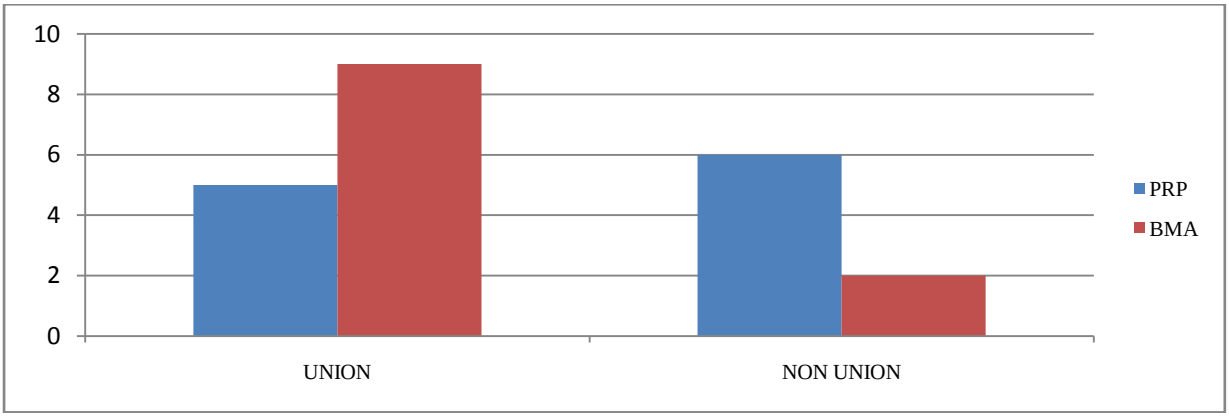


Table no 6 show the time taken for clinical union.. Clinical union is said to have occurred when there is Painless total weight bearing without macro mobility at the fracture site

Table no 6: Time for Clinical Union:

Time	PRP	BMA
3 months	1	1
6 months	1	5
9 months	3	3
Total	5	9

Mean (PRP) : 7.2 months
Mean (BMA): 6.66 months

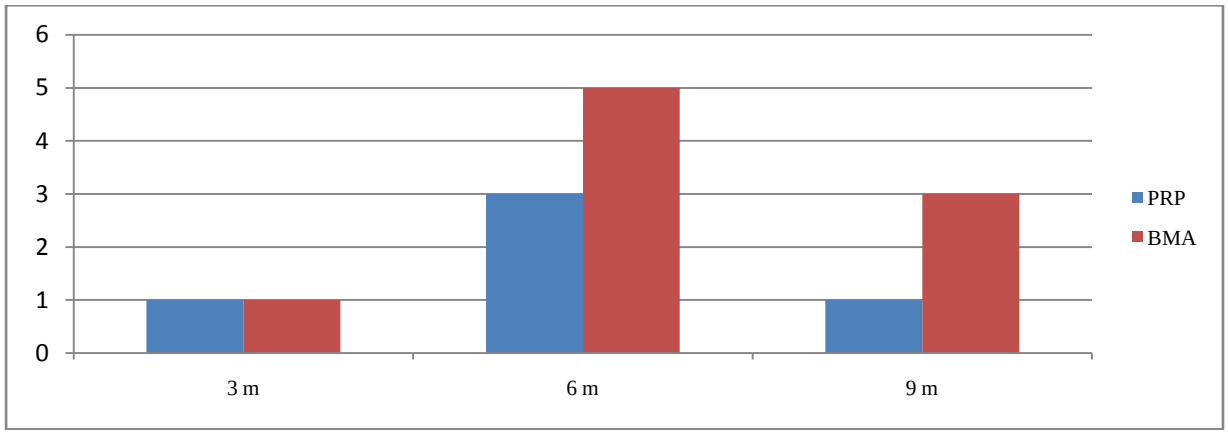
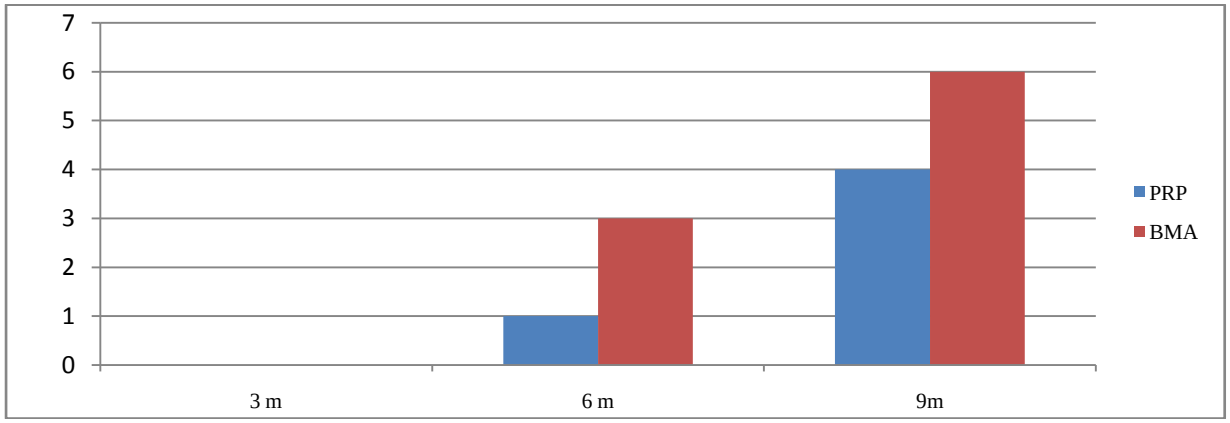


Table no 7 shows the time taken for radiological union. A fracture is considered to be radiologically united if there is bridging callus formation across 3 of the 4 cortices on anteroposterior and lateral radiographic view**s.**

Table no 7: Time to Radiological Union:

Time	PRP	BMA
3 months	0	0
6 months	1	3
9 months	4	6
Total	5	9

Mean (PRP): 8.4 months
Mean (BMA): 8.0 months



IV. Discussion

Tibial fracture union is a lengthy process that begins with the initial trauma and continues for months following clinical and radiological union until the bone regains its previous structure and function. Delayed union and non-union are two typical issues that any surgeon dealing with fracture healing may encounter. Delay in the union is caused by systemic and local reasons, including insufficient reduction, inappropriate immobilization, distraction and loss of blood supply due to open fractures, infection and drug consumption. . Various circumstances can cause delayed healing, but it can also happen for no apparent reason[5]

There are several options for the therapy of delayed union, each with a distinct level of invasiveness and outcome. Currently, the gold-standard treatment to stimulate bone healing in delayed unions is rescue surgery with autologous bone grafts.[4] However, the open grafting method has some disadvantages, including the limited availability of bone autografts and osteoprogenitor cells, and the donor-site morbidity associated with autograft harvest.[6] Bone allograft is a second option, but it has less osteo-inductive properties than autologous grafts, and it may lead to graft rejection and potential transmission of infections. Such operative interventions may delay the patient's return to a normal life and lead to a significant burden on society.[7] Although there is currently no well-established, less invasive treatment approach available to foster fracture healing in patients with delayed unions, alternatives have been developed (e.g. synthetic bone substitutes, biological factors, platelet-rich plasma, biodegradable scaffolds/biomaterials in combination with osteogenic factors,

electromagnetic field stimulation, low-intensity pulsed ultrasounds, cell therapy and tissue engineering products).[8]

Our study relied on injecting bone marrow aspirate and platelet rich plasma in delayed union tibial diaphyseal fracture site and monitoring for signs of union.

The concept of percutaneous bone marrow injection was born out of a desire to avoid the drawbacks of traditional autogenous open bone grafting. Adult bone marrow contains mesenchymal stem cells, called marrow stromal cells.[9] MSCs can differentiate into connective tissue cells such as osteocytes, osteoblasts, adipocytes and chondrocytes.[10] The potential of MSCs to differentiate into bone-producing cells has generated interest in using them in orthopaedic injuries to promote fracture repair and treat bone disorders.[11]

Platelet-derived growth factors are a class of signalling molecules that participate in the cell repair process by activating the proliferation and chemotaxis of mesenchymal cells, osteoblasts, and chondrocytes.[12]After activation, PRP releases many growth factors, supplementing the allogeneic bone with insufficient activity.[13]

The results of our study showed a significant advantage of using bone marrow in management of delayed union of tibial diaphyseal fractures.

The use of bone marrow aspirate for fracture healing is a very good procedure for treatment of delayed union of fractures. Bone marrow aspirates are the major source of osteoinductive factors produced by resident cells such as endothelial cells, MSCs, osteoblasts, platelets and macrophages. It is essentially an autograft without the bone matrix and clinical proof of its ability to mend is accumulating. Our study demonstrated that autogenous BMA extended bone healing.

V. Conclusion

Percutaneous autologous bone marrow injection is less invasive, safe and cost-effective therapeutic option for management of delayed union of tibial diaphyseal fractures.

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