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Study of efficacy of bone marrow injection in delayed union of fractures of lower limb

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Abstract

Background and Objectives: Fracture healing is a complex series of events involving the array of biological as well as biomechanical processes. Some, in the setting of an unfavorable cellular microenvironment and mechanical instability, some fractures unpredictably end up in delayed union despite interventions. Stem cell therapy has been the choice of treatment in many conditions because of their regeneration potential into different cells and tissues. Bone marrow is one of the richest sources of these mesenchymal stem cells which act as osteoprogenitor cells. This study aims to present the functional outcome of autologous bone marrow injection in the treatment of delayed union of lower limb fractures.

Materials and Methods: After obtaining ethical committee permission and patient consent, the study was conducted on 30 patients aged above 18 years, who presented with delayed union of long bones of lower limb after 3 months at BIRRD Hospital Tirupati during January 2022 to January 2023. Patients with bone marrow disease, pathological fractures, and active infection were excluded.

Results: The average age of the subject was 40 years and male: female was 9:1. The average union time was around 18 weeks. 16.7% of the patients had union at 2 months, 36.7% at 4 months, 40% at 6 months and 6.7% had absent union. The result was satisfactory in 28 patients and poor in 2 patients.

Conclusion: After our follow up of 30 patients for a period of 6 months post bone marrow aspirate injection, we observed that there was accelerated bone healing. The procedure is simple, cost effective, easily reproducible with nil or minimal complications.

Keywords: Bone marrow aspirate, delayed union, tibia, femur

Introduction

Fracture healing includes a complex series of events involving the array of biological as well as biomechanical processes. Some, in the setting of an unfavourable cellular microenvironment and mechanical instability, some fractures unpredictably end up in delayed union or non-union despite interventions with internal / external fixation or cast application [1]. Various variables including the patient and fracture have been attributed for the delay in the process of fracture union. Different modalities of treatment are available for the management of the same. The biological environment has been shown to be affected by osteogenic, osteo-conductive and osteo-inductive substances which are collectively present in osteo-progenitor cells [2].

Goujon followed by McGaw and Harbin, first demonstrated the osteogenic potential of these osteoprogenitor cells in bone marrow and thereby, hold the key to the formation as well as healing of bone [3,4].

In view of this, open autologous bone grafting, where bone is harvested and then implanted at the site of fracture has been the gold standard method in the management of delayed union and non-union.

However, post-operative complications such as pain, hematoma formation, surgical site infection and scarring, meralgia paresthetica and gait changes have render this method less favourable, not to mention the high cost and also the need for prolonged hospital stay. Opening the non-union site where healing is already hampered also contributes to devascularisation of fracture fragments.

In contrast, stem cell therapy has been the choice of treatment in many conditions because of their regeneration potential into different cells and tissues [5]. Bone marrow is one among the richest sources of these mesenchymal stem cells which act as osteoprogenitor cells [6]. It was in 1955 Herzog first demonstrated the use of bone marrow injection for healing of fractures [7].

Injecting bone marrow, rich in osteo-progenitor cells is a simpler procedure having, lower post-operative complications, cost effective, as well as a shorter hospital stay.

This study was done with an aim to present the functional

outcome of only autologous bone marrow injection in the treatment of delayed union of fractures of lower limb, which were previously treated by internal / external fixation, or cast application.

Objectives

To evaluate the efficacy of bone marrow aspirate injection in delayed union of fractures using union scale score with reference to

1. Rate of healing
2. Functional and Radiological outcome

Table 1: Union Scale Score [8]

Score	Mobility	Tenderness	Radiological features
0	Frank mobility in both planes	Present	No call us at all
1	Restricted mobility in both planes	Absent	Minimum ensheathing callus
2	Minimum mobility in one plane	Absent	Good ensheathing callus and internal callus bridging at least two cortices
3	No mobility at all	Absent	Good ensheathing callus bridging all 4 cortices

Union scale score includes

1. Clinical scoring (tenderness and abnormal mobility)
2. Radiological scoring (callus formation)

Methods

Source of data

The study is conducted in 30 cases presented with delayed union of long bones of lower limb to Department of Orthopaedics surgery in BIRRD Hospital Tirupati during January 2022 to January 2023.

Method of collection of data

Inclusion criteria

Patients with

1. Lower limb long bone fractures with no signs of clinical and radiological union after 3 months
2. Age above 18 years

Exclusion criteria

Patients with

1. Bone marrow disease
2. Pathological fractures
3. Active infection

Patients refusal

Operative details

Position of the patient

Patient was in supine position. In order to stabilize the back, a sand bag was placed under the gluteal region. In this position, the donor site was made prominent which provides ease for the entry of needle through iliac crest. Risk of damaging pelvic organs would also be minimized. In the same way, a sand bag was also placed under the recipient site for stabilization.

Procedure in detail

Under Spinal anaesthesia, both donor and recipient sites were draped following the aseptic principles. Under C-arm guidance, the fracture site was localized. 2 needles (16G or 18G) were inserted into the fracture site, being visualized anteroposteriorly and mediolaterally. The bone marrow needle was inserted about 3cm posterior to the anterior superior iliac spine at the centre of the broadest portion of iliac crest. The needle was inserted up to the guard, followed by readjustment to a higher point and further insertion with rotatory thrust was done. This was repeated until

2-3 cm of the needle was inserted. The depth of the needle ensured sufficient bone marrow that was being harvested. Finally, the stiletto was removed and a 20 cc non-heparinised syringe was attached to the needle.

Once the needle was in position, aspiration of bone marrow was done by simultaneous retraction of syringe plunger and needle rotation to prevent back filling of venous blood. Bone marrow of about 40-80 mL depending on need at recipient site was aspirated and injected. Following aspiration and injection, sterile dressings were applied at both the donor and recipient sites.

Post-procedure, a single dose of Inj. Cefotaxime 1gm was administered. Patient's vitals and general well-being were monitored until recovery from anesthesia.

Follow up

Patients were followed up at 2nd, 4th, and 6th month both clinically and radiologically using union grade score. Patients were advised to avoid medications like NSAIDs that may hinder bone healing.

Sampling Procedure

All patients with delayed union fractures of lower limb who satisfied the inclusion criteria were taken up for the study.

A thorough history and clinical examination was done after taking informed consent. Ethical committee approval was taken for the study.

Results

The following were the observations in our study.

Table 2: Volume of Bone Marrow Aspirate Injected

Volume(ml)	Total no. of patients	Percentage
40-60	18	60%
61-80	12	40%

Among the volume of bone marrow aspirate injected, 60% of the patients were 40-60mL and 40% were 60-80mL.

Table 3: Time of Callus Appearance on X-Ray

Time	Total no. of patients	Percentage
2 months	18	60%
4 months	10	33.3%
6 months	2	6.7%

60% of the subjects had developed callus which was detected on X-ray at 2 months, 33.3% at 4 months and 6.7% at 6 months after bone marrow injection.

Time of Fracture Union

16.7% of the patients had union at 2 months, 36.7% at 4 months, 40% at 6 months and 6.7% had absent union.

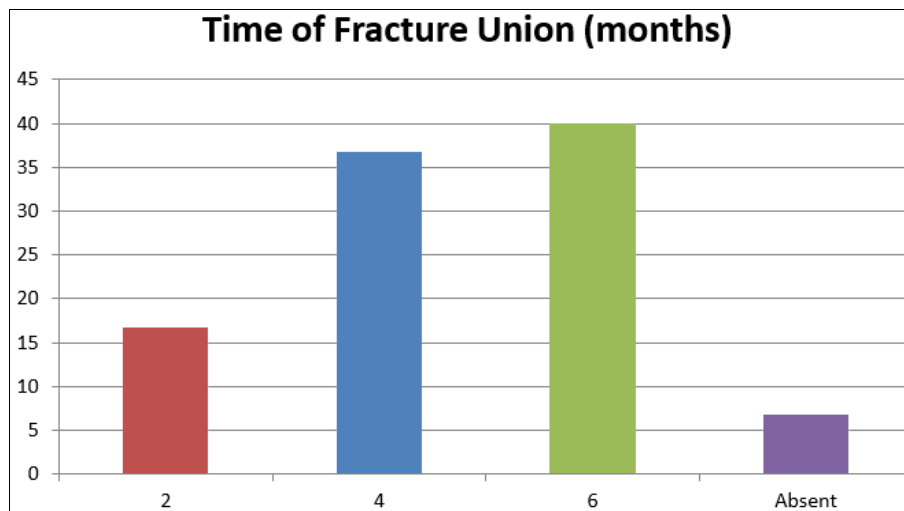


Fig 1: Bar Diagram Showing Distribution of Time of Fracture Union

Union scale grading

In this study, 90% of the patients had union of grade 7, 3.3%

between 5 to 6 and 6.7% were grade less than 5.

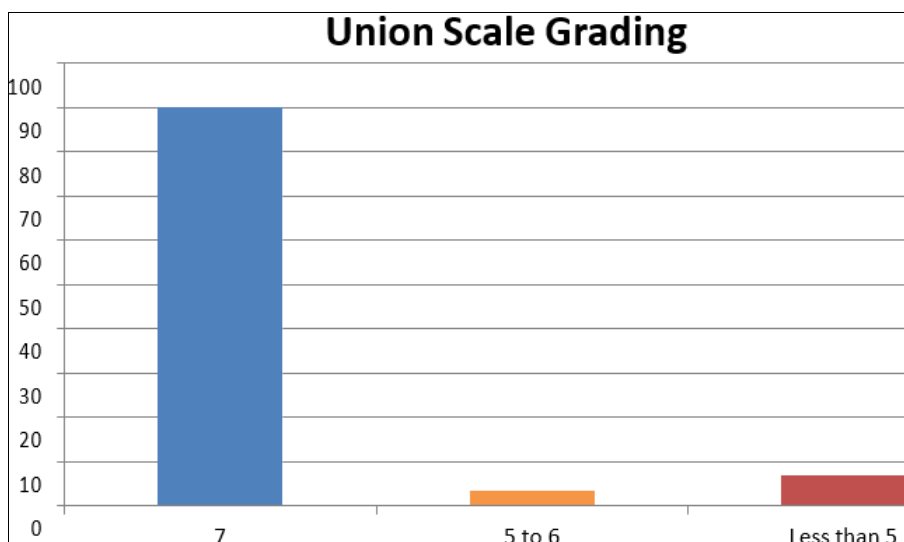


Fig 2: Bar Diagram Showing Distribution of Union Scale Grading

Table 4: Outcome

Outcome	Total no. of patients	Percentage
Good	27	90%
Fair	1	3.3%
Poor	2	6.7%

In this study, 90% of the patients had good outcome, 3.3% had fair outcome and 6.7% had poor outcome.

Discussion

Most of the delayed unions in the long bones are treated by various ways like bone stimulators i.e. ultrasonic or pulsed electromagnetic waves, Platelet rich plasma (PRP) injections, bone marrow injection, bone grafts, and bone graft substitutes. This study is performed to know the effectiveness of the bone marrow injection and the outcome in the delayed unions^[9]. For proper and adequate bone healing, re-establishment of the biology at the fracture site is necessary. It is proposed as

diamond concept by Giannoudis, which includes “cell recruiting molecules, bone matrix, osteogenic cells and vascularity^[10].”

Age Distribution

In the present study the mean age is 40 years which is similar to other studies.

Gender Distribution

In our study, the male to female ratio is 9:1 similar to study done by Sim *et al*^[11].

Site of Fracture

In this study, 10% of the fractures involved proximal 1/3rd, 50% involved middle 1/3rd and 40% involved distal 1/3rd which is comparable to other studies.

Type of Fracture

In our study, 76.7% of the fractures are of simple type while

23.3% are of compound type which is comparable to other studies.

Time for Union

In our study, average time of fracture union is 18 weeks which is comparable to other studies.

Table 5: Comparison of time of union

Authors	Year	Average Time of Union
Braly H L <i>et al</i> [12]	2013	17 weeks
Singh <i>et al</i> [2]	2013	16 weeks
Subash Y [13]	2018	13.4 weeks
Sim <i>et al</i> [11]	1992	17 weeks
Hernigou <i>et al</i> [14]	2005	12 weeks
Bhargava <i>et al</i> [8]	2007	12 weeks
Nazar [15]	2016	16 weeks
Rahimnia <i>et al</i> [16]	2016	12 weeks
Konde <i>et al</i> [17]	2017	20 weeks
Present study	2023	18 weeks

Duration of Initial Visit

In this study, the average time of visit after initial fracture management is about 4 months, which is comparable to other studies.

Table 6: Comparison average time of first visit

Authors	Year	Average time of first visit
Sim <i>et al</i> [11]	1992	4 months (17 weeks)
Denver [18]	2003	21 months
Bhargava <i>et al</i> [8]	2007	14-30 weeks
Present study	2023	4 months

Amount of Aspirate Injected

In the present study, the amount of bone marrow aspirate injected is between 40-80ml which is comparable to other studies.

Table 7: Comparison of BM aspirate

Authors	Year	Volume of BM aspirate(ml)
Braly H L <i>et al</i> [12]	2013	40-80
Sharma D <i>et al</i> [19]	2017	50-60
Sim <i>et al</i> [11]	1992	50-200
Bhargava <i>et al</i> [8]	2007	50-90
Present study	2023	40-80

Time of Appearance of Callus

In the present study, the average time of callus seen on X-ray is 12 weeks which is similar to a study by Upadhyay S *et al*.

Table 8: Comparison of time callus

Authors	Year	Time of Callus seen on X-ray
Upadhyay S <i>et al</i> [20]	2016	12 week
Wani H [21]	2013	21 weeks
Present study	2023	12 weeks

Union Scale Grading

In the present study, the clinical scoring at the end of 6 months follow up are 90% with 6-7 score, 3.3% with 4-5 score and 6.7% with less than 4 score. The radiological scoring is 90% with score 3, 3.3% with score 2 and 6.7% with score 1. Based on clinical and radiological scoring, the union scale grading is derived, which is comparable to other study.

Table 9: Comparison of union score

Author	Year	Union Scale Grading
Bhargava R [8]	2007	6-7: 23 (82.1%)
		Less than 6: 5 (27.9%)
Present study	2023	6-7: 27 (90%)
		Less than 6: 3 (10%)

Final Outcome

In the present study, the final outcome is 93.3% which is comparable to other studies.

Table 10: Comparison of final outcome

Authors	Year	Outcome
Sim <i>et al</i> [11]	1992	9/11 (81.8%)
Bhargava <i>et al</i> [8]	2007	25/28 (89.3%)
Elsattar <i>et al</i> [22]	2014	16/20 (80%)
Connolly <i>et al</i> [23]	1991	18/20 (90%)
Sahu [24]	2018	82/93 (88%)
Singh <i>et al</i> [2]	2013	10/12 (83.3%)
Thua <i>et al</i> [25]	2015	10/10 (100%)
Hernigou <i>et al</i> [14]	2006	88.3%
Sugaya <i>et al</i> [26]	2014	76%
Present study	2023	28/30 (93.3%)

Conclusion

Fracture healing is a diverse process which needs to be addressed depending on various variables related to patient, injury, tissue and treatment. Any imbalance in these variables will disturb the biology of bone healing leading to delayed union.

With increased high velocity and open injuries especially in the younger population, there is a increase in incidence of comminuted fractures which often go for delayed or non-union even after aggressive management. Even though the gold standard for the treatment of delayed or non-union is bone grafting, there is always an associated morbidity with the procedure.

After our short term follow up of 30 cases for a period of 6 months post bone marrow aspirate injection, we could observe that there is accelerated bone healing, even in patients with associated co-morbidities.

We also observed that even single dose of unconcentrated bone marrow aspirate injection is enough to achieve union. The procedure is simple, cost effective, easily reproducible with no or minimal complications. Even though all of our subjects underwent the procedure under spinal anaesthesia, many studies have concluded that this procedure can be done under local anaesthesia or short general anaesthesia on OPD basis. We preferred non heparinized syringes as the time interval between aspirations and injecting at the delayed union site is very short.

We finally conclude that, the earlier the intervention in delayed union faster the union and less chances of progression to non-union.

Although bone marrow aspirate injection at the delayed union of fractures of lower limb is found to be effective in our study, there are limitations from our observations, i.e. small sample size, inclusion of only lower limb fracture delayed unions which needs to be addressed.

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Declaration of Conflicting Interests

There are no other conflicts of interest. Funding the author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethical Review and hospital Consent

The study was approved by the local hospital institutional review board.

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