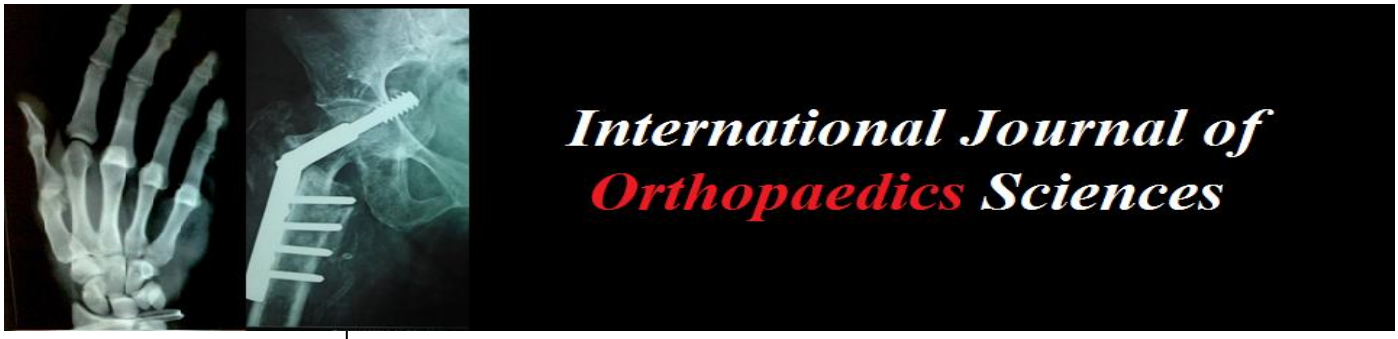

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To study the union rates and complications of percutaneous bone marrow injection in delayed union of long bone fractures: A prospective study

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Abstract
Introduction: Fracture healing is a form of wound healing that involves bone regeneration and leads to the restoration of skeletal integrity. Despite recent developments fracture stabilisation and understanding of biological healing processes, delayed union remains a challenging clinical condition. Bone marrow being abundant in osteoprogenitor cells is being tried to enhance the fracture healing. This study emphasizes the proficiency of bone marrow injected at the fracture site with delayed union and to reduce the time of morbidity for patients who are at the risk of development of non-union.
Aim: To study the union rates and complications of percutaneous bone marrow injection at the site of delayed union of long bone fractures.
Materials and Methods: This is a prospective observational study at BLDEU'S Shri B. M. Patil Medical College, Hospital and Research Centre, Department of Orthopaedics between November 2020 TO March 2022.
Patients who were admitted with delayed union of long bone fracture and were assessed clinically and radiologically at 6 weeks,3 months, 6 months & 9 months.
In this research 35 patients had percutaneous bone marrow injection who were in delayed union based on clinical assessment and radiographs depending on extent of the initial displacement, communition, soft tissue loss, postoperative reduction, and alignment.
Such instances were chosen for bone marrow injection when they failed to demonstrate the anticipated clinical and radiological union level within a predetermined time frame. The iliac crest or tibial tuberosity was used as the site for the bone marrow aspiration.
This Bone marrow injection was given into the fracture site under fluoroscopic guidance, distance between the fractured segments and signs of callus formation were assessed. The data obtained will be entered into a Microsoft Excel sheet, and statistical analysis will be performed using a statistical package for the social sciences (Version 20). Results are presented as Mean (Median) ±SD, counts and percentages and with p value of 0.05.
Results: Amongst 35 patients, 28(80%) showed complete bony union, another 4(11.4%) indicated progressive healing, and 3(8.5%) showed non union. This simple, effective method shortens the amount of time that morbidity develops as a result of delayed union and allows faster bony union Complications like surgical site infections and anaesthetic complications were not encountered. Postoperative pain was managed with adequate analgesia with NSAIDS.
As a result, it is concluded that effective union can be achieved in delayed union of long bones with percutaneous autologous bone marrow injection, without any complications at donor or recipient site. Bone marrow injection is a safe and secure method to treat delayed union of long bone fractures.

Keywords: callus**,** morbidity, non union, osteoprogenitor cells, skeletal integrity

Introduction
The healing of fractures is a special type of wound-healing process which restores the integrity of the skeletal system by regeneration of bones. The stages of healing of a fractured bone includes Stage of haematoma formation, Stage of endosteal and periosteal cellular multiplication Stage of formation of callus, Consolidation stage, Remodelling stage
However, in a small proportion of cases, it is delayed or impaired. It is said that there is an occurrence of delayed union when the fracture has not united in the expected time, but still has the potential to unite.

The clinical and radiological signs of healing in a patient with delayed union are slower compared to a similar fracture in a similar bone among regular patients. This depends on the involvement of a particular bone and its anatomic region, the fracture pattern involved, the energy of the original injury and the amount of surrounding soft tissue damage and the modality of treatment. Only a few known methods to improve union are mentioned in literature such as medications, electromagnetic field, Ilizarov technique (compression and distraction osteogenesis), low-intensity ultrasonographic therapy, and autologous bone transplantation [1. 2. 3. 4]. Since Phemister's work [5] autologous bone grafting, which entails surgically taking bone from the graft donor site, typically from the iliac crest of pelvis, and surgically implanting it at the place of fracture site showing delayed union.

Three important elements for fracture healing are osteoconduction, osteoinduction, and osteogenesis contributed by autologous bone grafting [6].

Nevertheless, there have been issues with the surgical harvesting and implantation at the fracture site, both at the donor and recipient locations. It has been documented that issues at the donor site include painful scars, hematomas, infections, muscle herniations, fractures or subluxations, and gait abnormalities, prolonging hospital stay and cost [7].

Since the delayed union site must be opened, the already compromised healing process now faces the increased risk of infection or devascularisation of the fracture fragments. This has led to a continuous search for an alternate, simple, affordable, and secure technique of treating delayed union.

The osteoblast is the primary bone-forming cell, but recent research has demonstrated that it shares a common ancestor with fibroblasts, retinacular cells, and other bone-forming cells as well as bone marrow and other regions of the connective tissue framework [10, 11, 12, 13]. Therefore autologous bone marrow which has sufficient amount of osteoprogenitor cells can be used to treat delayed union by supplementing required growth factors for fracture healing.

This research is aimed to study the union rates and complications of percutaneous bone marrow injection into the site of delayed union of long bone fractures.

Materials and Methods

This is a prospective observational study was done at Department of Orthopaedics B. L. D. E. (Deemed to be University) Shri B.M. Patil's Medical College, Hospital and Research Centre, Vijayapura, Karnataka from November 2020 to March 2022. All patients provided written informed consent after being informed about the plan of treatment, its expenses, morbidity after surgery, and anaesthetic and procedural complications. Institutional ethical clearance was taken with reference number IEC/NO-09/2021

Sample size calculation with 90% (ref) confidence level and margin of error of ±10%, a sample size of 35 subjects will allow the study the long bone fractures….

with finite population correction. By using the formula:

$$\frac{n=z^2\ p*q}{d^2}$$

Where Z= Z statistic at α level of significance

d^2= Absolute error

p= Proportion rate 0.05

q= 100-p [14]

Total of 40 patients were administered with percutaneous bone marrow injection out which 5 were lost in follow up. 35 patients were included in this study above 18 years of age, diagnosed with delayed union by the means of clinical and radiological examination. Physically fit for surgery and willing to participate in study.

Patients age less than 18 years, medically unfit for surgery/anesthesia, patients with active infection or malignancy and those who did not complete follow up were excluded.

Under spinal anaesthesia, the patient was made to lie in the supine position. The iliac crest or tibial tuberosity, as well as the site of the delayed union were painted and draped, under radiological supervision, approximately 25-40 millilitres of the bone marrow was aspirated in a sterile fashion from these sites and was injected into the delayed union site by the aspiration needle. Union was determined based on fracture site movement, pain, and radiographic characteristics. When the fracture gap was healed and the patient was able to put weight or utilise the limb without pain or instability at the fracture site, the fracture was called unified. [Table/Figure 1].

Fig 1: Aspiration of Bone marrow from Antero- superior iliac spine with Jamshidi Needle

The patients were evaluated clinically and radiologically for fracture healing after surgery at 6 weeks,3 months, 6 months & 9 months.

Statistical Analysis

The data obtained will be entered into a Microsoft Excel sheet, and statistical analysis will be performed using a statistical package for the social sciences (Version 20). Data is presented as Mean (Median) ±SD, counts and percentages and diagrams.

The Chi square test was used to compare categorical variables. The diagnostic tests were chosen based on their sensitivity, specificity, positive predictive value and negative predictive value. P value of <0.05 was considered statistically significant. All statistical tests were performed two-tailed.

Results

In this study, 40 patients were involved of whom 5 were lost in follow-up. Out of 35 cases there were 15 fractures of femur, 10 of tibia, 8 of humerus, and 1 of each radius and ulna. There were 27 closed fracture cases and 8 open fracture cases at the time of the injury. Simple fractures were detected in 27 individuals, while comminuted fractures occurred in 8 cases. In 21 cases, closed procedures were carried out as the first line of treatment. Ex-Fix was performed at the time of injury in 8 cases, while open procedures were performed in 6 cases. Among 35 patients, 28 of the 35 patients were men

(80%), and 7 were women (20%), 28(80%) showed complete bony union, another 4(11.4%) indicated progressive healing, and 3(8.5%) showed non union. Complications like surgical site infections and anaesthetic complications were not encountered. Postoperative pain was managed with adequate analgesia with NSAIDS. [Table 2a]

Table 2a: Age of patients

Age (Years)	No. of patients [n]	Percentage
< 30	1	2.8
30 - 39	16	45.7
40 - 49	9	25.7
50 - 59	4	11.4
>60	5	14.2
Total	35	100.0

Table 2b: Association between Age and outcome

Age (Yrs)	Outcome				Chi square test	P value
	Non-Union	P.H	United	Total		
< 30	0	0	1	1	22.444	0.004*
	0.0%	0.0%	100.0%	100.0%		
30 - 39	0	0	14	14		
	0.0%	0.0%	100.0%	100.0%		
40 - 49	0	0	9	9		
	0.0%	0.0%	100.0%	100.0%		
50 - 59	1	1	3	5		
	20.0%	20.0%	60.0%	100.0%		
More than 60	2	3	1	6		
%	33.3%	50.0%	16.7%	100.0%		
Total	3	4	28	35		
%	8.6%	11.4%	80.0%	100.0%		

*: Statistically significant

Table 3a: Gender of Patients

Gender	No. of patients	Percentage
Female	7	20
Male	28	80
Total	35	100.0

Table 3b: Association between Sex and outcome

Sex	Outcome			Total
	Non-Union	P.H	United	
Female	0	0	8	8
	0.0%	0.0%	100.0%	100.0%
Male	3	4	20	27
	11.1%	14.8%	74.1%	100.0%
Total	3	4	28	35
	8.6%	11.4%	80.0%	100.0%
Pearson Chi-Square	2.593	0.274		

*: Statistically insignificant

Table 4: Final outcomes

Result	Number of Patients	Percentage (%)
United	28	80
Progressive Healing	4	11.4
Non-union	3	8.5
Total	35	100

The mean age of the subjects of this study was 43.38 years, the youngest being 29 years and the eldest being 63 years, and the mean quantity of bone marrow injection given was 27.75 ml. Radiological union occurred at an average of 22 weeks (12 to 36 weeks) and clinical union at an average of 18.5 weeks (12 to 36 weeks). Patients with higher age and co-morbidities with other habits like alcohol & tobacco consumption had a predilection for fracture non-union

Among 35 patients 27(77.1%) presented with closed fractures, 8(22.8%) open fractures. 27(77.1%) were simple & 8(22.8%) comminuted fractures, which were treated with Closed IMIL Nail for 22(62.8%), External Fixation for 7(20%), Open reduction and plating for 6 (17.1%) patients.

Case Illustrations

Case

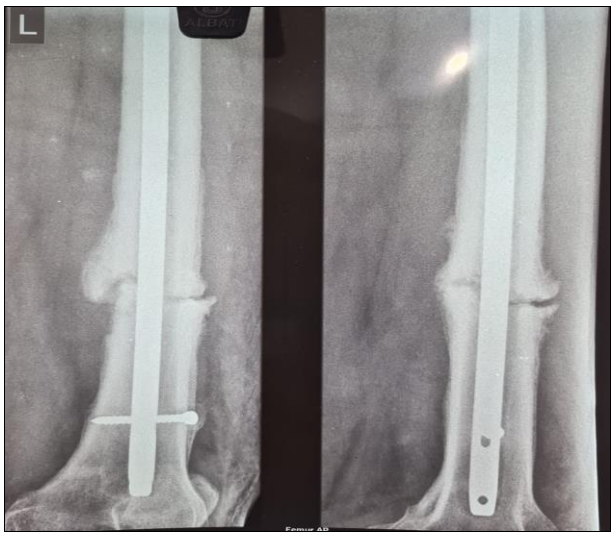

Fig 2: 3 Months old delayed union of Left Femur shaft with Long Proximal Femoral Nail In Situ

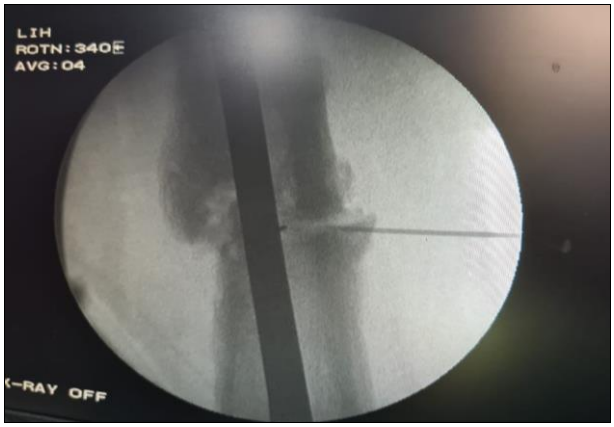

Fig 3: Bone marrow injection under fluoroscopic guidance

Fig 4: Aspiration of bone marrow from Ipsilateral Tibial tuberosity

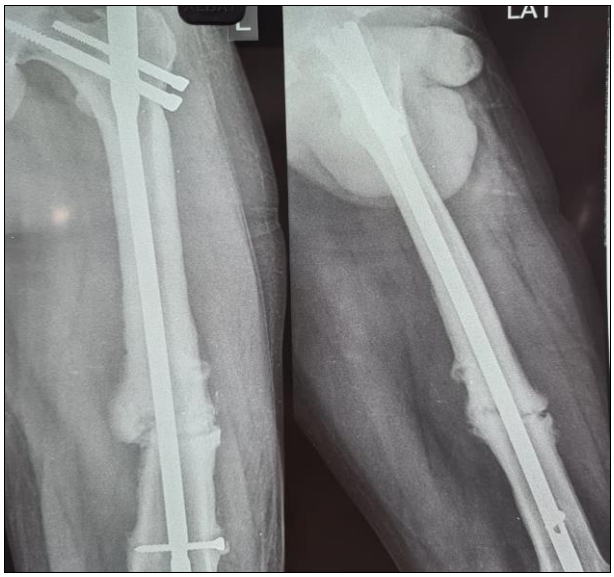

Fig 5: Achievement of Bony union after 3 Months

Discussion

In the present study, 35 patients with radiological evidence of delayed fracture union were managed with the injection of percutaneous bone marrow in which 15 fractures of the femur, 10 of the tibia, 8 of humerus, and 1 of each radius and ulna were present.

Patients were examined clinically for signs of discomfort, unusual movement, and pain on activities. Patients had their radiological callus formation checked. Many orthopaedic surgeons find it difficult to treat delayed union, which is a serious clinical issue.

Factors like Age of the patient, state of bone at the time of bone marrow injection and comorbidities like hypertension and diabetes were significant in determining the result.

The delayed union site requires both mechanical and biological support, which must be given at all costs. The biological stimuli for bone regeneration involves the interplay of osteo-inductive growth signals, signal-responsive stem cells, viable vascularity, and a scaffold that promotes cellular proliferation and growth [13]. It is proven that flexible multipotent mesenchymal stem cells (MSCs) show the potential to differentiate into a wide variety of cells including cartilage, bone, tendon, muscle, and nerve [15]. In a variety of orthopaedic specialities, this multipotent cell has the ability to play a significant therapeutic regime in healing and regeneration of different tissues [16]. Since bone marrow aspirate is the most common source of mesenchymal stem cells, many doctors have utilised un-processed bone marrow aspirate (BMA) to aid in the healing process [17]. Currently, the iliac crest is where BMA is most usually found. Both the anterior and posterior pelvis yield the same total number of cells, but the posterior crest has a higher proportion of connective tissue progenitors. By aspirating the marrow, only a little portion of the mesenchymal stem cells (MSCs) may be preserved. MSCs make up around 0.01% of BMA cells, and as people age, they recover fewer and fewer viable cells.

In this study an amount of 30 cm3 bone marrow was used patients, and resulted in significant amount of enhancement of bone union. In order to treat 60 patients with atrophic tibial non-union, Hernigou *et al*. investigated the effects of injecting 20 cm3 of bone marrow aspirate concentrate (BMAC) collected from the iliac crest. Among the findings were the callus formation volume and clinical union rate. Four months after the treatment, 88% of the patients had effective bone union. The concentration (p=0.001) and total number (p=0.01) of progenitor cells injected were considerably lower in the seven non-united tibias than in the united ones. The quantity of hard callus was shown to be positively linked with the quantity of fibroblast colony-forming (FCF) units in the graft (p = 0.04) and their concentration (p = 0.01)

Additionally, the researchers found a negative correlation (p = 0.04) between the number of Fibroblast Colony Forming units present at the graft site and the time required for union. They came to the conclusion that BMAC was a single-step process that might avoid issues with in vitro cultivation such as de-differentiation, pre-ageing, and diminished viability. Hernigou *et al*. reported injecting BMAC at the location of fracture non-unions in 86 diabetes individuals ankle in a different recent study [18]. The effectiveness of the procedures was assessed in light of 86 diabetic non-unions that had iliac crest bone grafts. They discovered that 82.1% of the ankles treated with BMAC healed, as opposed to only 62.3% of the ankles treated in the control group. The control group suffered from serious problems, such as amputations (5.8%), avascular necrosis (12.7%), and infection (20%). The BMAC group reported less problems.

This study promotes the use of percutaneous bone marrow injection as an better adjuvant for fracture healing in delayed union compared to conventional bone grafting. The researchers came to the conclusion that, given the elevated risks of serious complications associated with iliac bone grafting by open surgical method in this cohort, BMAC injection would be recommended. Moreover, when compared to conventional iliac bone auto-graft therapy, percutaneous BMAC treatment is linked to greater healing rates.

Bone marrow injection was successfully employed by Ma *et al*. to improve healing in a variety of long bone fractures involving the tibia, the femur, the metatarsals, or humerus. In certain cases, these fractures were linked to distinct clinical conditions such infections or pathological fractures [19]. Concerning the side effects, neither an infection nor discomfort at the injection sites nor the donor sites were noted. Kassem [20] examined the result of the method of percutaneous injection of BMAC in 20 patients who had fractures managed with open reduction and internal fixation (ORIF) with implant that had delayed union. After ORIF, the BMAC injection was started on average 9.65 months later (4 to 24 months). Under the supervision of a fluoroscopy, BMAC was percutaneously administered into the fracture site. After an average of 2.95 months, the patients reported a 95% accomplished clinical and radiological union rate. Additionally, BMAC and platelet rich plasma (PRP) have been proved to work well together in the treatment of non-union [21]. However, because they were not assessed independently, it is unclear if BMAC, PRP, or both produce this result.

Bone marrow aspiration from Iliac crest is a skilled procedure and requires experience, in this study no complications occurred while withdrawing and injecting bone marrow, and no surgical site complications were encountered. Hernigou *et al*. developed the sector rule, which is based on the safety zones, for aspirating bone marrow from the iliac crest [22]. They divided the six equal sections of the crest of the ilium bone into anterior and posterior directions. The 480 entry points tried by a total of six surgeons on 120 different patients were examined by the authors. The safe and unsafe areas for placing the trocar into the iliac crest were consistently envisioned using the sector approach. They found that obese patients had a higher chance of breaches, but this risk is lower

for surgeons with more experience. Out of 480 access locations, 94 breaches happened, with the thinner iliac crest sectors showing higher risks. The first through fourth sectors also carry a higher risk of damaging the external iliac artery, especially in females. However, when the trocar was kept greater than 6 cm into the posterior part of the iliac crest, posterior sectors were linked to a higher risk of neurovascular injury to sciatic nerve and gluteal vessels. The sector rule provides a strong framework for the BMA purpose, they concluded. Even while preoperative antibiotic use is widespread practise and overall risk is low, particularly with percutaneous delivery, infection at the administration site is a potential problem. Since bone is permeable to liquid substances, fat embolization when used intraosseously is a potential problem [23]. Consideration should be given to whether certain people, such as those with cardiac shunts, are suitable candidates for intra-osseous BMAC because they pose a higher risk of embolization. Patients should be closely watched in every instance of intra osseous injection for any clinical indications of a fat embolism [24]. In research by Reichert [25] *et al*., 37 patients with delayed union received bone marrow injection therapy. Under radiologic supervision, 10 ml of marrow was aspirated and injected percutaneously into the site of delayed union. 28 out of 37 patients had successful bone union after percutaneous bone marrow injection; the average time it took was 16 weeks. At the donor location, there were no infections or problems [25]. This study has a few restrictions. Despite the fact that the study's prospective nature, the sample size was modest. The prospective randomised clinical trials are required to assess the effectiveness of our treatment for various sites of delayed union. Last but not least, the generalizability of our findings may be hampered by the possibility that the surgical approach employed in our department had an impact on the results of the current investigation. According to a study by Ramji Lal Sahu [14] *et al*., a sufficient amount of bone marrow injection is required for each individual bone in order to treat a simple bone cyst, congenital pseudoarthrosis of the tibia, and delayed union in patients with challenging diseases like cancer.

In a research project by Thua *et al*. Healing time after bone marrow injection was significantly shortened. There were no systemic or local side effects from the intervention. There was no sign of infection or hematoma growth at the aspiration site. Persistent discomfort has not been reported after iliac crest bone marrow aspiration [26].

According to a study by Han Y [27] *et al*., the majority of children who underwent percutaneous autologous bone marrow transplantation (PABMT) had their bones healed after following a meticulous surgical process, and the proper rehabilitation training. The literature and empirical findings of this study indicate that the technique of PABMT is a simple, safe, minimally invasive, inexpensive and effective therapeutic alternative for kids who have delayed union of their long bones. Early bone marrow transplants also minimise the duration of the treatment, reduce the need for additional transplants, and hasten the healing process.

SD Ramavat & B Gangajaliya [28] it was established that bone marrow injections could hasten fracture repair. It is a method for using tissue engineering in orthopaedics that shows promising results. Infusion of bone marrow which has the osteoinduction property is used during treatment, but with less complexity and morbidity than gold standard bone grafting. When there is a suspicion of a delay in fracture healing, the method developed by Dr. Karma Uden Bhutia and colleagues [29] can be employed as an early intervention. This treatment has a low risk of donor and recipient site morbidity and can even be performed under local anaesthesia in an outpatient setting. Susheel Kumar Pathak & Meeta Agnihotri [30] concluded that reactivating osteogenesis with autologous marrow grafting is a successful strategy. Fracture cases with the highest likelihood of delayed union had outstanding union potential scores. There are no limitations for this study. There is no conflict of interest among the authors.

Conclusion

The current research shows 80% of patients showed complete bony union, another 11.4% indicated progressive healing after administration of percutaneous bone marrow injection. The ability to self-renew, engage in clonal proliferation, and specialise into diverse musculoskeletal tissues are all characteristics of bone marrow. In contrast to iliac bone grafting, no further surgical incision is needed, and there is no donor site morbidity. The fracture site is not altered by subcutaneous bone marrow injection. Several studies have found a correlation between the number of progenitor cells in the bone marrow aspirate and accelerated wound healing. Percutaneous bone marrow injection, a promising tissue engineering technique for the orthopaedic community, which is a safe and dependable technique with high patient compliance.

Conflict of Interest

Not available

Financial Support

Not available

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