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**Original Research Article**

# Study of Percutaneous Autologous Bone Marrow Injection in the Treatment of Delayed Union of Long Bone Fractures after Definitive Fixation

**Kishore Kunal[1], Vikash Ranjan[2]**

[1]Assistant Professor, Department of Orthopaedics, Radha Devi Jageshwari Memorial Medical College & Hospital, Turki, Muzaffarpur, Bihar

[2]Associate Professor, Department of Orthopaedics, Radha Devi Jageshwari Memorial Medical College & Hospital, Turki, Muzaffarpur, Bihar

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**Corresponding Author: Dr. Vikash Ranjan**

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**Abstract:**

**Background:** A wide range of biological sectors are paying more and more attention to the potential benefits of human mesenchymal stem cells. For many orthopedic surgeons, managing delayed union and non-union is a problem. Osteoprogenitor cells that can create bone are found in bone marrow. This study aimed to evaluate the effects of percutaneous autologous bone marrow injection for the management of long bone fractures that did not heal following final fixation.

**Methods**: From December 2019 to July 2020, the study was conducted in the orthopaedic department of Radha Devi Jageshwari Memorial Medical College & Hospital, Turki, Muzaffarpur, Bihar. Following final fixation, a total of 23 patients were treated for delayed union of long bone fractures. Percutaneous autologous bone marrow injection was used to treat these 23 individuals, and they were monitored for six months.

**Results**: Based on the clinico-radiological criteria of union, the findings were assessed and determined to be good in 17.39% (4/23) of the cases, poor in 21.73% (5/23) of the cases, and excellent in 60.86% (14/23).

**Conclusion**: Without needing to access the fracture site, the percutaneous autologous bone marrow injection stimulates cells and aids in the repair of fractures. As a result, it is a useful technique for achieving the satisfactory outcome of delayed union of long bone fractures following final fixation without posing a serious risk to the patient or the fracture site.

**Keywords**: Bone Marrow, Definitive Fracture, Injection, Delayed Union.



## Introduction

The German doctor first documented the presence of nonhemopoietic stem cells in bone marrow more than a century ago. His work established the theory that fibroblasts from bone marrow can produce collagen fibers and accelerate the healing of wounds. [1] Human mesenchymal stem cells (MSC) have drawn growing interest recently in a number of scientific domains due to their potential benefits. [2] The Food and Drug Administration defines nonunion as the fracture not healing over the course of the last three months and nine months after the injury. [3]

Clinical and radiological evidence in delayed union indicates that healing is occurring, but it is not progressing at the typical pace for that particular location and kind of fracture. Many orthopedic surgeons find it difficult to manage delayed union and nonunion, which is a serious clinical issue. [4] Low-intensity ultrasound, electromagnetic waves, and mechanical stimulation are examples of mechanical treatments used to improve union. [5] Biochemical methods such as osteoconductive biomaterials and osteoinductive agents are used to facilitate and accelerate growth. Tricalcium phosphate, hydroxyapatite, demineralized bone matrix, and autologous bone transplant are the components of osteoconductive materials.[6] Bone morphogenic proteins, whether sourced externally or from within the bone transplant, are licensed osteoconductive factors. [7] Osteoprogenitor cells that can create bone are found in bone marrow. [8]

In order to treat the delayed union of long bone fractures following final fixation, a safe and efficient method is the percutaneous autologous bone marrow injection.

## Material and Methods

From December 2019 to July 2020, this study was conducted in the orthopedics department of Radha Devi Jageshwari Memorial Medical College & Hospital, Turki, Muzaffarpur, Bihar. Percutaneous autologous bone marrow injections were used to treat a total of 25 patients with long bone fractures who had been fixed with both internal and external fixation devices and had experienced delayed union. There were six female patients and nineteen male patients in the adult patient group, ages 18 to 65. However, the total number of patients was reduced from 25 to 23 after two male patients were eliminated. One of them was lost to follow-up, and the other underwent revision surgery.

To rule out any active infection, all standard pre-procedure examinations, including radiological investigations, were completed. Every patient who satisfied the inclusion criteria had a thorough clinical and biochemical evaluation performed to rule out any co-morbidities that might be impeding the union's progress. Every patient gave written informed consent after receiving a thorough explanation of the entire process, its cost, and any risks associated with anesthesia. In the operating room, all of the percutaneous bone marrow injections were administered. In order to prevent cross-contamination, the patient was put in the supine position and the fracture and graft sites were prepped and draped independently. 2% lignocaine injection was used for local infiltration during the entire process. Under fluoroscopic guidance, an 18-gauge I.V. cannula was now placed into the location of the delayed union.

Between the outer and inner tables in the anterior iliac crest, a manually inserted 16-gauge Thomas bone marrow aspiration needle [9] was placed. A 10 ml preheparinized plastic syringe was used to aspirate the bone marrow, and each aspiration required a 45 degree rotation of the needle. To minimize the amount of dilution by peripheral blood and to increase the number of progenitors in the graft site, the marrow was drained in small fractions at a time (about 5 ml).

Next, using the 18-gauge I.V. cannula in the delayed union site, the aspirated bone marrow is gradually administered into the previously indicated site in order to prevent cellular extravasation. Following the treatment, the patient received a compression dressing and was released the same day. The bone marrow aspiration and injection into the transplant site were always done by the same surgeon. In every case of delayed union, we injected 40–50 cc of bone marrow into the femur and tibia, 20 cc into the humerus, and 10 cc into the radius and ulna. [10] Every three to four weeks, the patients were checked on in order to evaluate the union's clinicoradiological status. In order to do a clinico-radiological examination of the union, Heckman's description of painless total weight bearing without macromobility at the fracture site was followed by radiographic evidence of healing on at least three of the four cortices. [11,12] The criteria state that a fracture is rated as excellent if it unites within 16 weeks of a bone marrow injection, as good if it unites within 24 weeks, and as poor if it takes more than 24 weeks. In the event that the union does not advance following this operation, the patients were advised to pursue alternative approaches.

## Results

Percutaneous autologous bone marrow injections were used to treat 25 patients with lengthy bone fractures with delayed union in this case series investigation. The patients were monitored for six months after the injections. Of these twenty-five patients, one underwent revision surgery and one patient was lost during follow-up. Therefore, we limited the trial to 23 individuals who received bone marrow injections and were regularly followed up for up to six months following those injections. Of the 23 patients, 17 were male (73.91%), and 6 were female (26.08%). 73.91% (17/23) had experienced a traffic accident, 21.73% (5/23) had experienced a fall, and 4.34 (1/23) had sustained injuries when participating in sports. 60.86% (14/23) of the fractures were on the right side, and 39.13% (9/23) were on the left. According to Table 2, of these 23 patients, 39.13% (9/23, Gustilo and Anderson8 type 1=4, type 2=1, type 3A = 2, and type 3B = 2) had open fractures, while 60.86% (14/23) had closed fractures. 17.39% (4/23) of the participants in this study suffered fractures to their femurs, 39.13% (9/23) to their tibias, 17.39% (4/23) to their humerus, 17.39% (4/23) to their radius, and 8.69% (2/23) to their ulnas.

For the sake of convenience, the patients were split into three age groups based on their age (Table 1). 47.82% (11/23) of the study's participants had linear fractures, 39.13% (9/23) had comminuted fractures, and 13.04% (3/23) had segmental fractures. As shown in Table 3, of the 23 instances, 43.47% (10/23) had open reduction and internal fixations at first, 43.47% (10/23) had closed reduction and internal fixations, and 13.04% (3/23) had open reduction and external fixations.

**Table 1: Age and sex distribution in the study group (n=23)**

| Age (years) | Male | Female | Total | Percentage |
|---|---|---|---|---|
| 18-20 | 3 | - | 3 | 13.04% |
| 21-40 | 9 | 2 | 11 | 47.82% |

| | | | | |
|---|---|---|---|---|
| 41-65 | 5 | 4 | 9 | 39.13% |
| Total | 17 | 6 | 23 | 100% |

**Table 2: Type of fractures and their distribution (n=23)**

| Type of fracture | Overall number | Tibia | Femur | Humerus | Radius | Ulna |
|---|---|---|---|---|---|---|
| Closed fracture | 14 | 4 | 2 | 3 | 4 | 1 |
| Open type 1 fracture | 4 | 2 | - | 1 | - | 1 |
| Open type 2 fracture | 1 | - | 1 | - | - | - |
| Open type 3A fracture | 2 | 1 | 1 | - | - | - |
| Open type 3B fracture | 2 | 2 | - | - | - | - |
| Linear fracture | 11 | 3 | 3 | 2 | 2 | 1 |
| Comminuted fracture | 9 | 4 | 1 | 2 | 2 | |
| Segmental fracture | 3 | 2 | | | | 1 |

**Table 3: Types of initial fixation and their distribution (n=23)**

| Type of fixation | Overall number | Tibia | Femur | Humerus | Radius | Ulna |
|---|---|---|---|---|---|---|
| Open reduction and internal fixation | 10 | 1 | 1 | 4 | 3 | 1 |
| Closed reduction and internal fixation | 10 | 6 | 2 | - | 1 | 1 |
| Open reduction and external fixation | 3 | 2 | 1 | - | - | - |
| Plate fixation | 8 | - | - | 4 | 3 | 1 |
| Nail fixation | 12 | 7 | 3 | | 1 | 1 |
| Open reduction and internal fixation with nail | 2 | 1 | 1 | - | - | - |

The average duration between injury and percutaneous autologous bone marrow injection was 4.29 months, with a minimum of 3 months and a maximum of 6 months. A few patients experienced some pain and discomfort at the donor site, but it finally went away after a few days. Table 4 shows that the method resulted in the union of femur fractures in 100% (4/4) cases, tibia in 77.77% (7/9) cases, humerus in 50% (2/4) cases, radius in 75% (3/4) cases, and ulna in 100% (2/2) cases.

**Table 4: Results according to individual bone (n=23)**

| Bone | Number | United | Percentage |
|---|---|---|---|
| Femur | 4 | 4 | 100% |
| Tibia | 9 | 7 | 77.77% |
| Humerus | 4 | 2 | 50% |
| Radius | 4 | 3 | 75% |
| Ulna | 2 | 2 | 100% |

As previously indicated, we injected varying amounts of bone marrow into various bones, and the outcomes are shown in Table 5.

**Table 5: Results according to the amount of bone marrow injection (n=23)**

| Bone | Amount of bone marrow injection (cc) | Number | United | Percentage |
|---|---|---|---|---|
| Femur | <50(>40) | 4 | 4 | 100% |
| | <40 | 0 | - | - |
| Tibia | <50(>40) | 6 | 6 | 100% |
| | <40 | 3 | 1 | 33.33% |
| Humerus | <20 | 1 | 0 | 0 |
| | >20 | 3 | 2 | 66.66% |
| Radius | <10 | 3 | 2 | 66.66% |
| | >10 | 1 | 1 | 100% |
| Ulna | <10 | 2 | 2 | 100% |
| | >10 | 0 | - | - |

Table 6 shows that the findings were deemed to be poor in 21.73% (5/23) instances, good in 17.39% (4/23) cases, and excellent in 60.86% (14/23) cases.

**Table 6: Outcome of bone marrow injection (n=23)**

| Result | Number | Percentage |
|---|---|---|
| Excellent | 14 (T5, F3, H2, R2, U2) | 60.86% |
| Good | 4 (T2, F1, R1) | 17.39% |
| Poor | 5 (T2, H2, R1) | 21.73% |

**T= Tibia, F= Femur, H= Humerus, R= Radius, U= Ulna**

**Figure 1: Two 18G I.V cannula was fixed into the delayed union siteunder fluoroscopic guidance**


**Figure 2: (a): Bone marrow aspiration from anterior iliac crest with 16G Thomas bone marrow aspiration needle and collected in 10ml pre-heparinised plastic syringe; (b): Bone marrow injection at the delayed union site with 18G I.V cannula (which had been previously located under fluoroscopic guidance)**

## Discussion

A fracture that has not shown any discernible radiographic healing for three months following the injury is said to have delayed union. [13] Various techniques are available to treat delayed union, including extracorporal shock waves, demineralized bone matrix (DBM), recombinant bone matrix protein (rhBMP), platelet-rich plasma, ultrasound, and traditional autologous bone grafting, which is widely considered the gold standard for treating non-union. All of these techniques, nevertheless, are somewhat expensive, time-consuming, problem-free, and labor-intensive to complete. [15,16,17,18,19,20] Conversely, the process of autologous bone grafting entails a significant risk of severe morbidity at both the donor and recipient sites. [21]

In this study, we used autologous bone marrow injection to treat 23 cases of delayed union of long bone fractures without experiencing any major post-procedural complications. Of the twenty-three cases, four had humerus fractures, three had radius fractures, and one had an ulna fracture. The initial surgery in all of these instances was open reduction and plate fixation. Two examples of femur shaft fractures, six cases of tibia fractures, one case of each of the radius and ulna fractures, all underwent close reduction and nail fixation. One open type 2 fracture of the femur shaft and one open type 3A fracture of the tibia were treated with open reduction and nail fixation. Two examples of open type-3B fractures of the tibia were treated with open reduction and external fixation using an Ilizarov fixator. One open type-3A fracture shaft of the femur was treated with open reduction and external fixation using an LRS fixator.

Comparable to the average union rates of 65% and 62.2% in the studies by Laurent Galois et al. [20] and Jean-Baptiste Gross et al. [11], respectively, is the average union rate of 78.26% in our cases.

The average union time in our cases was 3.53 months, which is quite comparable to the Ramji Lal Sahu et al. study's average union time of 3 months (12 weeks). [10]

In our instances, the average duration from injury to bone marrow injection was 4.29 months, which is similar to the average period of 4.1 months reported by John F. Connolly et al. [13] in their publication. Our study 43.47% of patients had both open and closed reductions with internal fixations when they first came to us; the remaining 13.04% had open reductions with external fixations. These results are strikingly similar to those of studies by Ashok K. Singh et al. [23] and Ramji Lal Sahu et al. [10]

17.39% of the patients in our study had femur fractures when they first came to see us. After receiving a bone marrow injection, 100% of these patients had unions with an average union duration of 3.35 months. In contrast, a study by Joao Antonio Matheus Guimaraes et al. [22] of 16 cases with non-unions of the femur shaft following locked intramedullary nailing revealed a 50% union rate and an average union duration of 5 months following bone marrow injection.

Our results are somewhat comparable to the 90% union rate and 4 month average union time reported by John F. Connolly et al. [13] in their study of delayed union of tibia treated with autologous marrow injection. We achieved 77.77% of union rate in tibia fractures following bone marrow injection.

According to our observations, each bone needs a sufficient amount of bone marrow injection to produce a useful result, which is consistent with the findings of Ramji Lal Sahu et al. [10] We discovered that 60.86% of our cases with percutaneous autologous bone marrow injection were excellent, 17.39% were good, and 21.73% were poor. These results are comparable to those reported by Ramji Lal Sahu et al. [10] in their study.

Numerous studies have shown that percutaneous bone marrow injection with composite graft is a successful treatment for minor bone cysts, congenital pseudoarthrosis of the tibia, and delayed union in challenging cases such as cancer patients. [10]

Numerous studies, including Park et al. have demonstrated the effectiveness of bone marrow injection as a therapy option for conditions including non-union, bone cysts, etc. when combined with composite bone graft or other ceramics. [24-26]

Our work is justified by Laurent Galois et al. [15] statement that bone marrow injections can produce the best results when administered during the delayed union phase as opposed to the non-union phase.

In their investigation on autologous marrow injection for delayed unions of the tibia, John et al. suggested that early bone marrow injection for high-risk fractures provides an optimal prophylactic approach to promote osteogenesis with no morbidity. [13]

Because autologous bone marrow injection is a relatively straightforward procedure that can be carried out in a single office visit under local anesthetics, it is incredibly economical. Additionally, it eliminates several major issues with the donor or recipient location that the conventional bone grafting method could cause. [13]

Since the substance being injected is autogenous, there is no chance of an immunological reaction or the spread of illness, making the bone marrow injection safe.10 Autologous bone marrow injection plays a crucial function in treating fractures promptly when there is a possibility of future non-union at the fracture site. As such, it can be utilized as a preventive measure for non-union in susceptible patients. [13]

## Conclusion

Orthopaedic surgeons face a difficult challenge when treating lengthy bone fractures that do not fuse together immediately after definitive treatment. Traditional bone grafting, the induce membrane technique, ultrasound therapy, electric shock wave therapy, demineralized bone matrix (DBM), recombinant bone matrix protein (rhBMP), platelet rich plasma, external compression by external fixators, dynamization, etc. are some of the treatment modalities used to manage delayed union. However, each of these methods is rather costly and calls for a skilled and knowledgeable hand. Conversely, the autologous bone marrow injection, which can be done under local anesthesia without needing to explore the fracture site and potentially avoiding a major surgical risk, is a straightforward and efficient method for treating delayed union. It is a day care procedure that offers cellular stimulation at the fracture site, promotes fracture healing, and is very cost-effective. Most importantly, though, because it can prevent the fracture from future nonunion.

However, a lengthy multicentric investigation with a comparison group using the other approaches is required to reach a firm conclusion.

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