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## A study on effects of percutaneous bone marrow injection in delayed union and non-union of long bone fractures- observational study

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### Abstract

**Background:** Bone marrow is a good source of osteoprogenitor cells. Being a simple and minimally invasive technique with lesser complications, this study is intended to evaluate the effectiveness of bone marrow injection in delayed union and non-union and thus decrease the period of morbidity for the patients those are likely to go for non-union.

**Aim and Objectives:** The study effects of percutaneous bone marrow injection in delayed union and nonunion of long bone fractures”

**Materials and Methods:** This prospective study was conducted in Pujitha Hospital, Vijayawada over a period of 2 years. We had 34 patients in our series treated by percutaneous bone marrow injection. Based on the amount of initial displacement, comminution, soft tissue injury and post op reduction and alignment we graded the cases likely to go in for non-union. Such cases when failed to show expected amount of clinical and radiological union within a certain period we chose them for bone marrow injection. Bone marrow was aspirated from the iliac crest or tibial tuberosity using a bone marrow aspiration needle. Later this marrow aspirate was injected to the fracture site under C -arm guidance. Patients were followed up in the 1st month and then every 3rd month after the procedure and were clinically and radiographically assessed. Cases with pathological fractures, infected non-unions, malignancy and age under 15 years were excluded from our study. The collected data was analysed statistically.

**Results and Conclusion:** We compared our study with other similar studies. We had 72.7% union achieved, another 18.2% showed progression towards healing and 9.1% showed non-progression for union. Union was better when bone marrow injection was given in a case of delayed union as compared to non-union cases. This is a simple, easy and valuable technique to enhance bone healing and this reduced the period of morbidity due to delayed union and non-union.

**Keywords:** Hip fracture, bone turnover markers, CTX, PINP, vitamin D

### Introduction

Bone is a tissue in which the ability to regenerate is more predictable than in any other tissue of the body. Fracture healing is a specialized type of wound healing in which the regeneration of the bone leads to restoration of the skeletal integrity. There are three stages of healing in a fractured bone: Stage of hematoma, Stage of subperiosteal and endosteal cellular proliferation, Stage of callus formation.

The time in which a given fracture will unite cannot be arbitrarily stated as different bones heal in variable period of time depending upon many factors. In delayed union there is clinical and radiological evidence that healing is taking place but it has not advanced at the average rate for the location and type of fracture. Non-union is said to exist only when actual evidence of cellular activity at the fracture site ceases and fracture is not uniting. The diagnosis of the non-union is based on the presence of one or more of the following criteria like painless abnormal mobility, bony defect, sclerosis surrounding the bone ends and obliteration of the medullary canal. FDA panel has defined non-union has established when a minimum of 9 months have elapsed since injury and the fracture shows no visible progressive signs of healing for last 3 months.

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There are various factors that is used to enhance union such as drugs, electro- magnetic fields, distraction and compression osteogenesis by Ilizarov, low intensity ultrasound therapy, autogenous bone graft [1, 2, 3, 4]. Autologous bone grafting has been the standard operative method for decades since the work of Phemister<sup>5</sup> which involves operative removal of bone from the donor site usually pelvis and operative implantation at the site of delayed union or non-union. Autologous bone potentially contributes three vital components for healing which are osteoconduction, osteoinduction and osteogenesis. The need to open the non-union site has added the risk of infection or devascularization of the fracture fragments where healing is already impaired. Hence a continuous search has been made to find out such an alternative method of treating delayed and non-union which is easy, economical and safe. Current search in basic science provides understanding of the factors needed for osteogenesis in bone substitutes. The osteoblast is very well known as chief bone forming cell, but now it has shown that osteoblast, fibroblasts and reticular cells etc have the common precursor cells and these common precursor cells are found in bone itself, in bone marrow and in certain areas of connective tissue framework [5]. The cells aspirated from bone marrow are being shown to provide stimulus for osteogenesis in animal experiments [6].

The ability of marrow to form bone has been known for more than a century since the experimental work of Goujon [7] in 1869. Burwell used the osteogenic potential of autologous red marrow to create osteogenesis in allogenic cancellous grafts [8]. Bone marrow has also been used in combination with osteoinductive materials such as bone morphogenic protein (BMP) [9], demineralised bone matrix [10] and as a composite graft with bioceramics [11].

Percutaneous autologous bone marrow grafting offers advantage of decreased morbidity associated with classical open grafting techniques. Other advantages include decreased cost and hospital stay, as the procedures are performed in an outpatient setting.

The aim of study is to present our experience in the effects of percutaneous bone marrow injection in delayed and non-union of long bone fractures.

**Materials and Methods**

This prospective study was done in Department of Orthopedics Pujitha Hospital, Vijayawada over a period of 2 years. 40 patients with non-union or delayed union were treated with percutaneous bone marrow injection. 30 out of 40 patients were males. One case was lost in follow up. Cases were considered as delayed union if there was no sufficient callus formed in the first 3 months of follow up. In cases of delayed union bone marrow injections were given at a minimum of 3 months after the initial treatment with closed or open technique. Cases were considered as nonunion or anticipated to result in nonunion if there was no improvement in progression towards healing for consecutive 3 months. The average age of the patients were 42.8 years (18-79 years). This study included 16 femur, 14 tibia, 6 humerus, 3 radius. The time period from fracture treatment to bone marrow injection varied from 2 to 24 months. Study included 28 closed fractures, 9 cases of Gustilo Anderson Type 1 open fracture, and one each of type 2 and type 3. There were 32 cases of delayed union and 7 cases of non- union. Open procedures were done in 14 and closed in 25 fractures.

**Inclusion criteria**

1. Patients above 15 years.
2. Patients with clinical and radiological evidence of

delayed union or nonunion.

**Exclusion criteria**

1. Patients below 15 years
2. Patients who are not fit for surgery/anesthesia
3. Infection, Malignancy
4. Patients who are not available for follow up.

**Operative procedure**

All patients were admitted and procedure was done in operation theatre after obtaining written informed consent. Patient was placed in supine position and under Spinal anesthesia. Iliac crest or the tibial tuberosity was painted and draped along with the site of delayed or non-union. About 25-40ml of bone marrow aspirated from these sites and injected into the recipient site using aspiration needle under radiological control. Post operatively dressing was applied and patients were discharged in 2-4 days. Patients were followed up clinically and radiologically at an interval of 6 weeks till an average of 8 months (3- 15 months). Clinically patients were checked for tenderness, abnormal mobility, pain on weight bearing. Radiologically patients were evaluated for callus formation. Patients were also evaluated based on musculoskeletal society scoring system as well as hammers table [12, 13].

**Results**

This study included 40 patients, out of which one case was lost in follow up. 24 out of 33 cases bone union was achieved (72.7%). Among the 33 patients 26 were males (78.8%).

**Table 1: Sex**

Sex	Frequency	Percentage
Female	10	25
Male	30	75
Total	40	100.0

The age of the patients varied from 18-79 years with mean age being 41.8 years.

**Table 2: Type**

Type	Frequency	Percentage
Closed	28	71.79
Type 1 open	9	23.07
Type 2 open	1	2.56
Type 3b open	1	2.56
Total	39	100.0

In this study 28 cases were closed fractures and there were 11 cases of open fractures at the time of injury. Open fractures included 9 cases of Gustilo Anderson type 1, 1 case each of type 2 and type 3.

Out of 40 cases of delayed union or non-union, 16 cases were femur, 14 cases were tibia, 6 humerus cases and 4 cases of radius

Type	Frequency	Percentage
Closed	28	64.1
Open	11	35.89
Total	39	100.0

**Table 3: Pattern of fracture**

Pattern	Frequency	Percentage
Communitied	12	30.76
Simple	27	69.23
Total	39	100.0

Comminuted fractures were seen in 12 cases and simple fractures in 27 patients.

**Table 4:** Initial treatment

Initial Rx	Frequency	Percentage
Casting	2	5.12
Closed IMIL	16	41.02
Ex-Fix	4	10.25
Open plating	17	43.58
Total	39	100.0

Closed procedures were done in 16 cases and open procedures done in 17 cases at the time of injury.

**Table 5:** State of union

State of union	Frequency	Percentage
Delayed	32	82.05
Non-union	7	17.94
Total	39	100.0

32 patients were diagnosed to have delayed union and 7 were diagnosed with non-union at the time of injection of bone marrow

**Table 6:** Age

Age in years	Outcome			Total
	United	P.H	Non-union	
25 and above	5	0	1	6
	83.33%	.0%	16.66%	100.0%
26-45	16	4	0	20
	80%	20%	.0%	100.0%
46-65	6	3	0	9
	66.66%	33.33%	.0%	100.0%
Above 65	2	0	2	4
	50%	.0%	50%	100.0%
Total	29	7	3	39
	74.35%	17.94%	7.69%	100.0%

Among the 26 patients below 45 years, 21 showed good union (80.76%) compared to patients above 45 years. Out of 13 patients above 45 years only 8 patients showed good union (61.53%).

**Table 7:** Sex

Sex	Outcome			Total
	United	P.H	Non-union	
Female	5	3	2	10
	50.0%	30%	20%	100.0%
Male	22	6	1	29
	75.86%	20.68%	3.44%	100.0%
Total	28	8	3	39
	71.79%	20.51%	7.69%	100.0%

**Table 8:** Site of fracture

Site	Outcome			Total
	United	P.H	Non-union	
Ankle	1	0	0	1
	100.0%	.0%	.0%	100.0%
Both bone Forearm	1	0	0	1
	100.0%	.0%	.0%	100.0%
Femur	12	0	3	16
	75%	.0%	25%	100.0%
Humerus	5	1	0	6
	83.3%	16.66%	.0%	100.0%
Radius	3	0	0	3
	100.0%	.0%	.0%	100.0%
Tibia	7	5	0	12
	58.3%	41.7%	.0%	100.0%
Total	29	6	4	39
	74.35%	15.38%	10.25%	100.0%

Out of the 16 femur cases, 12 cases showed good union (75%). About 90% of the radius and humerus cases also showed bony union. Among the 12 cases of tibia, 7 showed good union (58.3%). 5 showed progression towards healing.

**Table 9:** Type of fracture

Type	Outcome			Total
	United	P.H	Non-union	
Closed	18	5	2	25
	72%	20%	8%	100.0%
Open	9	3	2	14
	64.28%	21.42%	14.28%	100.0%
Total	27	8	4	39
	69.23%	20.51%	10.25%	100.0%

Among the 25 closed fractures, 18 showed total union, 5 showed progression towards healing and 2 cases resulted in non-union as compared to the 14 cases of open fractures which showed union in 9 cases (64.28%), progression towards healing in 3 cases and non-union in 2 case.

**Table 10:** Fracture pattern

Pattern	Outcome			Total
	United	P.H	Non-union	
Communitized	9	2	1	12
	75.0%	16.6%	8.3%	100.0%
Simple	20	5	2	27
	74.07%	18.51%	7.4%	100.0%
Total	29	7	3	39
	74.35%	17.94%	7.69%	100.0%

There were 12 Communitized fractures out of which 9 showed good union (75%). Out of the 27 simple fractures, 20 showed good union (74%).

**Table 11:** Initial Treatment

Type	Outcome			Total
	United	P.H	Non-union	
Casting	0	2	0	2
	.0%	100.0%	.0%	100.0%
Closed IMIL	13	1	2	16
	81.25%	6.25%	12.5%	100.0%
Ex-Fix	4	0	0	4
	100.0%	.0%	.0%	100.0%
Open plating	12	4	1	17
	70.5%	23.5%	5.88%	100.0%
Total	29	7	3	39
	74.3%	17.9%	7.69%	100.0%

The fractures treated by closed methods initially at the time of injury showed better union with 13 out of 16 cases showing good union (81.2%), where as those cases treated by open procedures showed union in only 12 out of 17 cases (70.5%).

**Table 12:** State of union

State of union	Outcome			Total
	United	P.H	Non-union	
Delayed	26	5	1	32
	81.25%	15.6%	3.1%	100.0%
Non-union	4	1	2	7
	57.14%	14.28%	28.5%	100.0%
Total	30	6	3	39
	76.92%	15.38%	7.69%	100.0%

There were 32 cases of delayed union and 7 cases of non-union. Out of 32 cases of delayed union, 26 cases showed good union (81.25%), 5 showed progressive healing. Only 4 cases out of 7 cases of non-union showed good bony union after bone marrow injection (57.14%).

**Table 13:** Quantity of Bone marrow

Quantity	Outcome			Total
	United	P.H	Non-union	
30ml and below	20	4	0	24
	83.3%	16.6%	.0%	100.0%
Above 30ml	10	2	3	15
	66.6%	13.3%	20%	100.0%
Total	30	6	3	39
	76.92%	15.38%	7.69%	100.0%

**Table 14:** Callus formation

Callus	Outcome			Total
	United	P.H	Non-union	
1st	26	7	3	36
	72.2%	19.4%	8.33%	100.0%
3rd	2	0	0	2
	100.0%	.0%	.0%	100.0%
6th	0	0	1	1
	.0%	.0%	100.0%	100.0%
Total	28	7	4	39
	71.79%	17.94%	10.25%	100.0%

Out of 36 cases, callus was seen on the x ray in 1<sup>st</sup> month in 26 cases

**Table 15:** Clinical Union

Clinical	Outcome			Total
	United	P.H	Non-union	
3	15	5	0	20
	75%	25%	.0%	100.0%
6	12	3	2	17
	70.5%	17.6%	11.7%	100.0%
9	1	0	0	1
	100.0%	.0%	.0%	100.0%
Nil	0	0	1	1
	.0%	.0%	100.0%	100.0%
Total	28	8	3	39
	71.79%	20.51%	7.69%	100.0%

**Table 16:** Radiological Union

Radiol	Outcome			Total
	United	P.H	Non-union	
3	2	1	0	3
	66.6%	33.3%	.0%	100.0%
6	20	7	1	28
	83.33%	29.16%	4.1%	100.0%
9	5	0	0	5
	100.0%	.0%	.0%	100.0%
Nil	0	0	3	3
	.0%	.0%	100.0%	100.0%
Total	27	8	4	39
	69.2%	20.51%	10.25%	100.0%

Clinical union was seen in an average of 28 weeks (12-36 weeks) and radiological union in 27 weeks (11-36weeks).

**Discussion**

Various methods of treatment were sorted for delayed and non-union from decades which includes exchange nailing, bone grafting, stimulation by electric current and electromagnetic field, ilizarov fixation [1, 2, 3, 4] etc. However, the standard procedure of bone grafting was found to have associated complications as mentioned. The osteogenic and osteoinductive property of bone marrow were first described by Mcgaw and Habin [14]. Conolly [15] and Healy [16] Who have demonstrated that percutaneous bone marrow injection can successfully treat 78%-95% of non-union cases. The work of Hernigou *et al.* [17] showed experimentally that marrow produces optimal effect when used early in fracture healing process.

Other similar recent studies [18] has shown good union in their series of patients and concluded that percutaneous bone marrow injection is safe and easy procedure. The only complications noticed were infection and pain at the donor site which were subsided by analgesics and antibiotics.

In this study which included 40 patients, we observed union in 24 patients (72.7%) which is comparable to other similar studies.

Most of the cases in our study were diagnosed to have delayed union. Bone marrow was injected in most of the cases at a minimum of 3 months following the initial treatment. Fractures which failed to show expected progression towards healing were selected for the study. Only cases with minimal gap and displacement were selected for the study.

Although there was high selection bias in favour of union, it cannot be said that union in these cases would have occurred even without the procedure as the mean time duration between the procedure and injury was about 22 weeks (5.4 months). After bone marrow injection the fractures united in mean of 27 weeks. Hence it is clear that the percutaneous bone marrow injection had helped the fracture to unite, it has definitely accelerated the healing process.

The fractures treated previously by closed technique had union in 72% and those treated with open procedure, the union was seen in 64.28%. Out of the 7 non-union cases, 4 cases showed union, 1 case showed progressive healing and 2 resulted in non-union. Out of the 32 delayed union cases 26 united (81.25%). The average hospital stay was 4 days ranging from 2-5 days.

Bone marrow injection was found to be more useful in cases of delayed union as compared to nonunion cases.

The effect of bone marrow injection in cases with non-union of fractures cannot be commented upon as the sample size was less. The age of the patient, state of union, type of fracture, quantity of bone marrow injected played a significant role with p value < 0.5. There were no donor site or recipient site infections noticed in this study.

**Conclusion**

Bone marrow injection is a minimally invasive procedure done percutaneously. It is easy, safe procedure with no associated complications that may occur in bone grafting, thus reduced hospital stay and expenditure. Learning curve is short. It can be considered as an alternate method for bone grafting in delayed and non-union of fractures.

It can be given in cases in which delayed union is diagnosed or anticipated so as to prevent those fractures resulting in non-union and thus reducing the morbidity associated with non-union.

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**Conflict of Interest**

None

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Nil

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