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*ORIGINAL STUDY*

# Percutaneous autogenous bone marrow injection for delayed union or non union of fractures after internal fixation

Mohamed Samir KASSEM

*From Al Hadara University Hospital, Alexandria University, Egypt*

**The aim of this study was to assess the results of percutaneous injection of autologous bone marrow in the treatment of fractures presenting with delayed union or non union after internal fixation.**

**Twenty consecutive patients presenting to our outpatient clinic with internally fixed fractures with delayed union or non union were included in the study. The time between the index surgery and the bone marrow injection ranged from 4 to 24 months with a mean of 9.65 months. The bone marrow aspirate was injected percutaneously into the fracture site under fluoroscopy control.**

**Nineteen out of the twenty fractures achieved clinical and radiological union, on average after 2.95 months. In this series, percutaneous bone marrow injection appeared as a simple and effective method to accelerate fracture healing in patients with delayed union and nonunion of fractures.**

**Keywords** : bone marrow ; internal fixation ; fractures ; stem cell.

## INTRODUCTION

Fracture union is a complex process which starts with the initial injury and continues for several years after clinical and radiological union until the bone retains its original structure and function. Delayed union and non-union are two of the common problems that may face any surgeon dealing with fracture healing. Delayed healing may be caused by several factors ; it may also occur without any obvious cause. Several methods of treatment have been adopted to overcome this problem (e.g. bone graft, electrical stimulation, ultrasound, bone transport, and bone marrow injection).

The osteogenic potential of bone marrow has been investigated as early as the late decades of the nineteenth century (*13*).

McGraw and Harbin (*23*) were among the first to demonstrate the osteogenic activity of bone marrow in 1934. They used bone marrow as a graft to fill a defect in dog's fibulae and compared this with a contralateral non-grafted defect. The bone marrow grafted side was progressively filled with bone, unlike the non-grafted side.

Percutaneous bone grafting was first introduced by Herzog in 1951, with the use of a large bore needle and small cancellous chips to graft a nonunion (*18*).

■ Mohamed Samir Kassem, MD, Consultant Orthopaedic surgeon, Lecturer of Orthopaedics.
*Orthopaedic Department, Faculty of Medicine, Al Hadara University Hospital, Alexandria University, Egypt.*
Correspondence : Mohamed Samir Kassem, Orthopaedic department, Alhadara University Hospital, Alhadara, Lambrouzou, Alexandria, Egypt. E-mail : mokassem21@yahoo.com / mohamed.samir@alexmed.edu.eg


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The bone marrow graft concept and the percutaneous grafting technique were subsequently combined in many studies, taking into account the fluid nature of the bone marrow. In 1998, Connolly (4) in a review of his 15 years research into various methods and techniques of using marrow osteoprogenitor cells showed that marrow injection in and about the nonunion site can be useful to treat numerous skeletal healing problems e.g.tibial delayed unions or nonunion, either infected or not (5,6). Other studies showed that percutaneous bone marrow grafting could be used with promising results in other conditions such as the treatment of simple bone cysts (21). congenital tibial pseudoarthrosis (11) and in the management of delayed union in difficult clinical circumstances such as cancer patients (15).

The aim of this study was to assess the results of percutaneous bone marrow injection in the treatment of fractures presenting with delayed union or non union following internal fixation. This study was approved by the Ethics committee of our faculty of Medicine.

## MATERIAL AND METHODS

The study included twenty consecutive patients who presented to our outpatient clinic with delayed union or non union of a closed fracture following internal fixation. The union of the fracture was considered delayed when a slower than expected rate of union was seen when comparing the last two follow-up plain radiographs, with a time lapse of six months or less since internal fixation. The fracture was considered non united when there was no progression of union over the last three months, with a time lapse of more than six months since internal fixation.

Exclusion criteria included fractures with delayed or non union due to a mechanical cause related to the internal fixation necessitating revision of the fixation, active infection associated with the delayed union or the non union necessitating removal of the fixation, and the presence of a gap at the fracture site more than 10 mm which needed to be filled with a structural graft.

The time interval between the index surgery and the bone marrow injection ranged from 4 to 24 months with an average of 9.65 months.

The study included thirteen tibial fractures, five femoral fractures and two ulnar fractures. The fractures fixed with a distal tibial locked plate and a proximal tibial locked plates had been operated using a minimally invasive technique. A limited open approach had been used in two of the three femoral nailings included in this study to reduce the fracture ; a closed technique had been used in the third case.

The demographic data of the patients are listed in Table I.

Under general or spinal anaesthesia, bone marrow was aspirated from the anterior iliac crest using a special bone marrow aspiration needle (Downs,Yorkshire, U.K.), into heparinized syringes to avoid clotting of the aspirate. The bone marrow was aspirated from multiple sites to minimize dilution of the aspirate with blood. The aspirate was injected percutaneously into and around the fracture site under fluoroscopy control.

A minimum of 30 milliliters of bone marrow aspirate was injected in two patients with ulnar fractures and up to 80 milliliters in patients with tibial and femoral fractures.

Clinical union was assessed by the ability of the patient to weight bear unsupported for the lower limb fracture or to use the upper limb in daily activities without any pain or tenderness at the fracture site.

Radiological union of the fracture was assessed through serial monthly plain radiographs. The fracture was considered united radiographically when callus was seen crossing the fracture line, indicating cortical union at least at three cortices in the two planes radiographs.

Data were fed into the computer using the Predictive Analytics Software (PASW Statistics 18). Association between categorical variables was tested using Chi-square test. For normally distributed data, comparison between two independent populations was done using independent t-test. For abnormally distributed data, Mann-Whitney Test was used to analyze two independent populations. The significance level was set at $p < 0.05$.

## RESULTS

Nineteen out of the twenty fractures went on to clinical and radiological union, and the patients were mobilizing without any walking aid or any support at the end of their follow-up with no pain or tenderness at the fracture site.

One patient did not show any radiological evidence of new bone formation at his fracture site after three months and was considered a failure (Fig. 3).

The time to union following the bone marrow injection ranged from 2 to 5 months with an average of 2.95 months.

Table I. — Demographic data of the patients in the study group

| | Age (years) | Sex | Time lag (months) | Type of fixation | Bone affected | Time to union (months) |
|---|---|---|---|---|---|---|
| 1 | 45 | M | 12 | AFN | femur | – |
| 2 | 50 | M | 10 | DFLP | femur | 3 |
| 3 | 30 | M | 8 | DTLP | tibia | 4 |
| 4 | 26 | M | 4 | DTLP | tibia | 2 |
| 5 | 45 | F | 9 | DTLP | tibia | 3 |
| 6 | 30 | M | 8 | PTLP | tibia | 5 |
| 7 | 25 | M | 9 | DCP | ulna | 3 |
| 8 | 41 | F | 12 | DCP | ulna | 2 |
| 9 | 42 | M | 10 | RFN | femur | 4 |
| 10 | 38 | M | 24 | AFN | femur | 3 |
| 11 | 45 | M | 15 | DTLP | tibia | 2 |
| 12 | 62 | F | 7 | DTLP | tibia | 2 |
| 13 | 62 | F | 7 | PTLP | tibia | 2 |
| 14 | 35 | F | 6 | PTLP | tibia | 2 |
| 15 | 34 | M | 5 | DTLP | tibia | 4 |
| 16 | 38 | F | 7 | DTLP | tibia | 3 |
| 17 | 52 | M | 5 | DTLP | tibia | 3 |
| 18 | 66 | M | 9 | DTLP | tibia | 3 |
| 19 | 55 | M | 14 | PTLP | tibia | 4 |
| 20 | 25 | M | 12 | DFLP | femur | 2 |
| Mean ± SD | 42.3 ± 12.7 | | 9.65 ± 4.5 | | | 2.95 ± 0.9 |

AFN : antegrade femoral nail, DFLP : distal femoral locked plate, DTLP : distal tibial locked plate, PTLP : proximal tibial locked plate, DCP : dynamic compression plate, RFN : retrograde femoral nail.

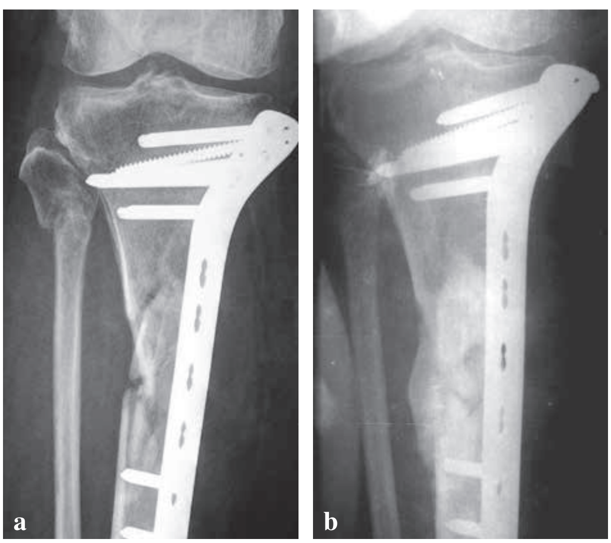


*Fig. 1.* — Plain AP radiograph showing a comminuted fracture of the proximal tibia internally fixed with a locked plate with a varus angulation which was accepted in this specific patient : a) no signs of union 8 months post fixation ; b) union of fracture 5 months post injection of bone marrow.

The relation between the different factors and the time to union is presented in table II.

Infection did not occur in any patient. There were no other complications related to either the donor site or the site of injection.

All patients were safely discharged on the same day of the marrow injection.

## DISCUSSION

Delayed union or non union of fractures has always been a challenging problem. Autogenous bone grafting has been the most commonly used method used in the surgical management up to now. This often involves a significant donor site mobidity, which may include haemorrhage, infection, the need for an additional surgical procedure, a painful and ugly scar, which adds to the disturbance of the vascularity of the fracture site when delivering the graft through an open technique (*2,9*).

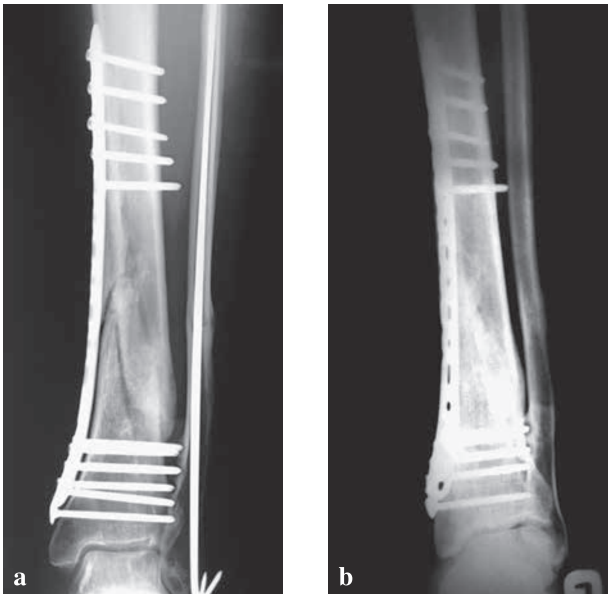


***Fig. 2.*** — Fracture of the distal third of the tibia internally fixed with a locked plate. a) non union 15 months post fixation ; b) radiological union 4 months post injection of bone marrow.

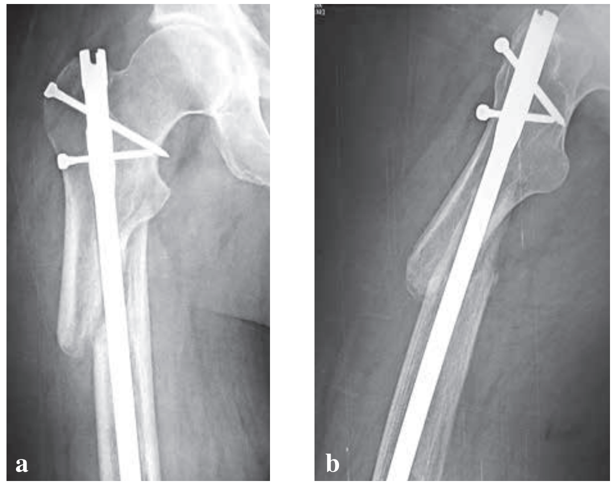


***Fig. 3.*** — Fracture of the proximal femur fixed with antegrade femoral nailing (AP and lateral view) with no signs of new callus formation 3 months post injection. This was the only fracture which failed to unite following bone marrow injection in our series.

Table II. — Relation between time to union and sex, age, type of fixation and bone affected

| | Time to union (months) | |
|---|---|---|
| | Mean ± SD | p |
| Sex | | |
| Male | 3.23 ± 0.93 | 0.041* |
| Female | 2.33 ± 0.52 | |
| Age | r = -0.155 | 0.526 |
| Habits | | |
| Non smoker | 2.50 ± 0.53 | 0.081 |
| Smoker | 3.27 ± 1.01 | |
| Type of fixation | | |
| Femoral Nail | 3.50 ± 0.71 | 0.737 |
| DCP | 2.50 ± 0.71 | |
| DTLP | 2.89 ± 0.78 | |
| PTLP | 3.25 ± 1.50 | |
| DFLP | 2.50 ± 0.71 | |
| Bone affected | | |
| Femur | 3.0 ± 0.82 | 0.773 |
| Tibia | 3.0 ± 1.0 | |
| Ulna | 2.50 ± 0.71 | |

*Statistically significant at $p < 0.05$.

DFLP : distal femoral locked plate, DTLP : distal tibial locked plate, PTLP : proximal tibial locked plate, DCP : dynamic compression plate.

Recent studies have focused on less invasive techniques such as pulsed low-intensity ultrasound, extracorporeal shock waves, bone growth factors (e.g. bone morphogenic protein), and bone marrow injection, aiming to achieve similar results but with less complications (*24,28,31*).

In our study, twelve out of fourteen male patients including the patient whose fracture did not unite were smokers. None of the six female patients included in the study were smokers but four of them were living with a husband who is a smoker. The time to union after bone marrow injection was longer in smoking patients compared to non smoking patients. This relation was however not statistically significant ($p = 0.081$). The relation between smoking and delayed and non union of fractures has been reported in several previous studies (*1,8,17*).

The time to union was significantly less in female patients compared to the male patients ($p = 0.041$). This could be explained with the smoking factor as previously discussed.

The tibia represented 65% of the cases included in this study. The relatively high incidence of delayed and non union associated with tibial fractures compared to the other long bones fractures has been reported in previous studies (*10,14*). The higher incidence of open tibial fractures due to their subcutaneous anatomical location as well as the specific aspects of vascularisation of the tibia are among the important causes of this relatively frequent delay in healing.

This study included 15 fractures fixed with locked plates (13 tibial and 2 femoral plates) out of a total of 20 internally fixed fractures. The relatively high proportion of delayed unions related to locked plating compared with intramedullary nailing has been noted and explained in previous studies by the fact that locked plating, if not performed using a MIS approach, damages the soft tissues much more than IM nailing done under fluoroscopy without opening the fracture site (*20,29*). In this specific patient, the failure may be related to the improper reduction of the fracture and to the long time interval the delayed unions or non unions following locked plate fixation included in this study may also be related to the bicortical locking screws fixation of the plate inserted close to the fracture site, leading to very rigid fixation and not allowing enough micromotion at the fracture site to induce an osteoblastic activity.

The patient who failed to unite had a segmental fracture of the femur fixed with an antegrade interlocking intramedullary nail. The distal fracture was already united at the time of inclusion into the study, which was 12 months after his first surgery. The proximal fracture was injected with 80 milliliters of bone marrow and was followed up for three months without showing any radiological signs of new callus formation (Fig. 3). We think that, in this specific patient, the failure was related to the improper reduction of the fracture and the long time interval since the index surgery, leading to incipient atrophy of the fracture end of the proximal fragment. We recommend the early management of delayed union of fractures once diagnosed, as it should provide a better chance to achieve union.

The bone marrow aspirate can be used alone or as a composite graft e.g. with a synthetic scaffold. This composite graft is usually introduced using an open technique and is indicated in non-united fractures with gaps or in osteolytic lesions such as large bone cysts (*3,7,27,30*).

Some authors have recommended the use of concentrated bone marrow obtained by centrifugation, in order to increase the number of osteoprogenitor cells in the bone marrow injected (*12,16*). In other studies, the aspirate was cultured *in vitro* before injection of the osteoprogenitor cells into the fracture site (*3,19*). Considering the increased cost and the risk of infection, we think that these techniques are more indicated in case of small bones non union e.g. scaphoid due to the limited space available to deliver the graft at the fracture site._

The aspiration needle used in this study has multiple holes at its end, allowing aspiration of the bone marrow from multiple sites at the same time. Through the same skin entry point, we also changed the site of aspiration every 4 milliliters through redirection of the needle into the iliac crest to make sure the bone marrow aspirate remained concentrated. Muschler *et al* (*26*) have studied the effect of the aspiration volume on the concentration of the number of osteoprogenitor cells ; they recommended the aspiration of the bone marrow from multiple sites to avoid its dilution with the peripheral blood.

With 95% success to achieve union following the bone marrow injection, this study has showed the efficacy of autogenous bone marrow to accelerate fracture healing.

Other studies have used bone marrow injection to promote healing in different types of fractures affecting the tibia, femur, metatarsals, or humerus, in some cases associated with various clinical situations such as infection or pathological fractures, with similar good results (*6,12,16,22,25*). As for the complications, there was no reported infection or pain related to the donor sites or the injection sites.

The use of bone marrow is considered a simple and minimally invasive technique. The bone marrow injection is safe, as the material injected is autogenous, so there is no risk of disease transmission or immune reaction. When compared to iliac bone grafting there is no additional surgical incision, and no donor site morbidity. The bone marrow is injected percutaneously, which does not disturb the fracture site.

The use of bone marrow to accelerate fracture healing is one of the applications of the stem cell technology. It represents a promising method of application of tissue engineering in the orthopedic field, which avoids many of the complications of the traditional bone grafting method commonly used so far.

We think that the good results achieved in this study (95% union) were related to the good selection of cases, in which the causes for delayed union were essentially biological, thus excluding cases with mechanical causes for the delayed union or the non union.

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