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Role of prophylactic autologous bone marrow aspirate injection in accelerating union and rehabilitation in long bone fractures in surgically unfit patients

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Abstract
Background: Autologus Bone grafting is a commonly performed second surgery in non-union of operated long bones fractures. In some patients surgery is not possible because of anaesthetic complications and other co-mobid conditions, a simple plaster immobilisation may not be sufficient. a simple bone marrow aspiration and fracture site injection would be an alternate to bone graft in these patients.
Materials and Methods: This Study included 50 patients divided into two groups A and B, 25 in each group, having fractures of long bones except femur managed with closed reduction and cast application. 13 patients of group A and 14 of B had poor prognosis for union. Group A were treated with immobilisation alone and Group B treated with Immobilisation and Bone marrow aspirate injection.
Results: 30.77% patients of poor prognosis attained union at 6 months without Bone marrow aspirate injections(Group A) and 92.86% patients attained union with Bone marrow aspirate injections (Group B). Patients in Group A on an average took 10.3 months to perform full weight bearing whereas Patients in Group B took 6.8 months.
Discussion: Bone marrow aspirate injection definitely increase the union rates and decrease the period of immobilisation in long bone fractures. It can be a blessing in patients with medical limitation to surgery.
Conclusion: Bone marrow aspirate injection definitely increase the union rates and decrease the period of immobilisation in long bone fractures managed conservatively It can be a blessing in patients with medical limitation to surgery.

Keywords: Bone marrow aspiration, long bones fractures, surgically unfit patients

1. Introduction
Long bone fractures such as shaft of tibia fractures, both bones and single bone forearm fractures, shaft of humerus fractures and shaft of femur fractures are commonly encountered in the emergency room. There is a trend to operate and fix these fractures to enable early mobilisation of the patient so as to prevent the morbidity associated with prolonged recumbency and also to reduce the financial burden on the family due to prolonged period of unemployment. However, the patients who are already debilitated and unfit for surgery due to medical conditions like heart diseases, chronic respiratory ailments are at double disadvantage because they are surgically unfit and fracture immobilisation further complicates the already existing medical problems. These patients are usually managed conservatively with plaster immobilisation, prolonged traction, and other forms of external immobilisation such as Thomas knee splint, Bohler Braun splint etc. These methods require a longer duration of treatment and also risk the fracture with possibility of non-union.
Bone tissue is itself capable of self repair. However if the primary attempt of fracture healing made by the fracture hematoma itself fails, then bone grafting is generally the second line of management to avoid non-union or delayed union, an event that is otherwise inevitable. Bone grafting is called the second wounding procedure [1]. Operative harvesting of bone graft and placing it at fracture site is successful in most cases in accelerating fracture union. The diamond concept holds that the fracture union or filling of a gap defect by autologous bone grafting occurs because of a interaction of osteogenic cells, cytokines, an osteo-conductive matrix, and a mechanically stable environment with a good blood supply [2].

Autologous bone grafting is a commonly practiced method of osteoinduction in cases of nonunion of long bones. This method is however faced with donor site morbidity and requires a full surgical anaesthetic preoperative preparation and the surgical, anaesthetic complications that comes along with any surgery. This may not be the method in the patients already unfit for fracture fixation surgery. A simple percutaneous aspiration of iliac crest bone marrow and injection of the aspirate at the fracture site is an alternative to the more elaborate procedure of bone grafting. Cells isolated from all the aspirates express positive MSC (mesenchymal cell) surface markers (CD105, CD90, and CD73) and a low level of negative MSC markers (CD34 and CD45). The cells maintain the ability to proliferate and differentiate into cells of mesenchymal lineages [3]. They are being shown to provide stimulus for osteogenesis in animal experiments and in clinical evaluation of bone graft and bone substitutes [4]. This technique is simple, quick, can be done on outpatient basis and can be done in local anaesthesia.

In this study, we intervened the process of bone healing in debilitated patients being managed conservatively by injecting bone marrow aspirate. The intervention was done not after non-union or delayed union was established but when the bone was still in the process of union, with the idea that it would augment the union and rehabilitation speed of already uniting bone.

2. Materials and Methods: This study was a prospective randomised control trial conducted in Kalpana Chawla Government Medical college and Hospital, Karnal, Haryana between June 2012 and June 2015. Institutional review board clearance was obtained. Informed written consent was taken prior to procedure. This study had a total of 50 patients who had sustained traumatic long bone fractures and because of medical comorbidities were unfit for surgery. Long bone fractures included shaft of tibia fractures with or without fibula fractures, shaft of humerus fractures, both bone forearm and single bone forearm fractures. Patients with shaft of femur fractures were not included. Only patients with satisfactory Bony alignment and Reduction were included in the study. Exclusion criteria were gross malalignment on post-reduction radiographs which even otherwise would have remote possibility of fracture union, patients with segmental fracture, open fractures, pathological fractures and the patients who lost to follow up any time before 6 months. None of the patients had any myeloproliferative disorder, fanconi's anaemia, aplastic anaemia or other medical illness that could diminish Bone marrow stock. The patients were randomised equally in to two groups, A and B, of 25 patients each. Irrespective of the group all the patients were reduced by traditional methods of closed reduction and maintained on cast immobilisation for the first two months.

At the end of two months, all the patients were assessed for the tenderness at fracture site and abnormal mobility of fracture fragments. Routine anteroposterior and lateral radiographs were taken at 2 monthly interval for all patients and corroborated with clinical findings. Those patients in which clinically bony tenderness persists and no radiological signs of nonunion were there are categorized as poor prognosis cases for nonunion.

The standard procedure of aspiration of bone marrow from the anterior iliac blade and injecting percutaneously at fracture site was adopted. The procedure was carried out as an outpatient procedure. To aspirate the marrow from the iliac crest, a 16-gauge bone marrow aspiration needle was used and to inject the marrow at fracture site the standard disposable needle of 16-gauge in cases of tibia or ulna. Image intensifier was used to locate the area of bone marrow injection. Only in a few cases of tibial fractures, the procedure was done without image intensifier as the fracture site was distinctly palpable. The volume of bone marrow injected was between 50-60 ml in cases of tibia, 30-40 ml for both bone forearm fractures (divided into two equal quantities for each forearm bone), for ulna the amount injected was 15-20 ml only. The limiting factor for the amount of bone marrow injection was the volume that could be injected at a particular site. The marrow was aspirated in 5-10 ml aliquots and injected at the fracture site simultaneously. Multiple entry portals were needed on one or both the iliac crests to harvest the marrow.

The postoperative management consists of a compression bandage for two or three days. After two or three days a well-fitting patellar tendon-bearing cast was applied in cases of fracture leg bones. The patient with fracture shaft ulna was given a functional cast brace.

After the assessment at the end of two months the patients in group A were further continued on cast immobilisation without any intervention and those of group B were injected with the bone marrow aspirate. Bone marrow was aspirated from the anterior iliac blade under local anaesthesia using a 16 gauge bone marrow aspiration needle. The target was to aspirate around 50-60 ml of bone marrow for tibia fractures, 30-40 ml for humerus fractures, 30-40 ml for both bone forearm fractures (divided into two equal quantities for each forearm bone) and 15-20 ml for single bone forearm fractures. Injections for aspirating the marrow could be single or multiple in one or both the iliac crests depending on the amount of aspirate required. The aspirate was quickly injected at the fracture site using a 16 gauge needle under fluoroscopic guidance. Fibular fracture site in cases of both bone leg fractures was not injected. In both bone forearm fractures, radial and ulnar sites were separately injected. Aseptic precautions were followed for aspiration as well as injection. These patients were again given cast immobilisation after bone marrow injection for two month.

At the end of four months, cast was removed in both the groups and reassessed for abnormal mobility at fracture site. The ones with no abnormal mobility were put on the rehabilitation protocol; functional braces (irrespective of the group), patellar tendon braces for leg fractures, arm brace for humeral shaft fractures and forearm braces for both bone or single bone forearm fractures. Tibia fracture patients were mobilised weight bearing as tolerated initially till full weight bearing was possible. Upper limb fracture patients were gradually allowed weight bearing activities like lifting a glass of water, lifting a bottle of water to lifting a bucket of water till the patient was comfortable using the fractured limb with same strength as the normal limb. The brace was discarded when the patient was confident of full weight bearing. The time of confident full weight bearing was noted. Patients who persisted to have fracture site mobility at end of completed 4 months in group A were given another 2 months of immobilisation. If patients of group B had abnormal mobility at end of 4 months they were given a repeat injection of bone marrow aspirate and given cast for 2 months followed by reassessment.

At the end of 6 months the patients with loss of abnormal mobility were put on rehabilitation protocol. Those with abnormal mobility in group A were also treated with bone marrow injections. This was because we found the results of bone marrow injections satisfactory in group B and we didn't

want the patients of group A to be at disadvantage. All but 3 of these fractures also united in a year time but the follow up of these patients is not a part of this study. Bone marrow aspirate injection was declared a failure if despite two shots of bone marrow aspirate injection i.e., 6 months in group B, abnormal mobility persisted.

3. Results: There were 24 cases of both bone leg fractures, 11 cases shaft of humerus fractures, 10 cases of both bone forearm fractures, 3 cases of shaft of radius and 2 cases of shaft of ulna fractures. Group A had 10 cases of leg fractures, 7 cases of humerus fractures, 5 cases of both bone forearm fractures and all 3 cases of radius fractures. Group B had 14 cases of leg fractures, 4 cases of humerus fractures, 5 cases of both bone forearm and both the cases of shaft ulna fractures. The mean age of patients in group A was 61.5 years and in group B was 65.6 years.

Assessment at 2 months: After cast removal, 13 patients of group A persisted to have abnormal mobility and 14 patients of group B had similar signs of non union. These clinical signs were consistent with the radiological signs of non union like variable amount of sclerosis at fracture ends, persistence of fracture gap, absence or scarcity of callus, lack of trabecular continuity etc. These patients were said to have a high chance of non-union and labelled 'poor prognosis cases (Table 1). The intervention of bone marrow aspirate was studied in these patients.

Table 1

	Group A	Group B
Poor Prognosis Patients At 2 Months	13	14
Poor Prognosis Patients United At 4 Months	3 (23.08%)	10 (71.43%)
Poor Prognosis Patients United At 6 Months	4 (30.77%)	13 (92.86%)

Assessment at 4 months: Of the 13 patients having 'poor prognosis' in group A, only 3 patients (23.08%) showed signs of union in form of loss of abnormal mobility. Rest 10 patients persisted to have abnormal mobility and these patients were continued with immobilisation for 2 months. 10 out of the 14 patients (71.43%) of group B who had 'poor prognosis' at 2 months, lost abnormal mobility and 4 continued to have it (Table 1). Radiologic signs were consistent with the clinical features. These 4 patients received their second shot of bone marrow injection at 4 months and were further immobilised for 2 months. The patients who showed clinical signs of union at 4 months (irrespective of their group) were changed to a functional cast brace and gradual weight bearing. Correspondingly, 15 patients of group A and 21 patients of group B were converted to a functional brace and weight bearing as tolerated was started. Only 4 of the 15 patients of group A (26.67%) could perform full weight bearing before 6 months whereas 15 of the 21 patients(71.43%) could do it before the sixth month was over (Table 2).

Table 2

	Group A	Group B
United Cases Bearing Full Weight At 4-6 Months	26.67%	71.43%
United Cases Bearing Full Weight At 6-8 Months	50%	91.67%

Assessment at 6 months: 1 out of the 10 patients (10%) of group A showing abnormal mobility at 4 months ceased to have it after 6 months and 9 continued to have it. These 9 patients were managed with bone marrow injections and 6 of them united in a year but their follow up is not a part of this study. Only one patient out of the 4 of group B having abnormal mobility at 4 months continued to have it at 6 months following second shot of marrow aspirate and 3 were united (75%) (Table 1). We found that only 30.77% of poor prognosis cases of group A united (4 of 13) whereas in Group B 92.86% of poor prognosis cases united (13 0f 14). Of the united 16 united cases in group A, 8 (50%) could do full weight bearing before 8 months whereas 22 out of 24 in group B (91.67%) could do it before 8 months were over (Table 2). United patients in group A on an average took 10.3 months to perform full weight bearing whereas that of group B took 6.8 months.

4. Discussion: Most long bones should ideally be fixed with internal fixation methods keeping in mind, the high rates of failure of the conservative methods in these cases, and also the morbidity, psychological and financial upset to the patient associated with conservative methods. However an orthopaedician is faced with situations where he has no choice than to follow a conservative method. In such a case, there is a search for ways that if used as supplements to conservative methods, should increase the chances of fracture union. Gene therapy is an attractive but seeing the difficulties involved in using embryonic stem cells and second the cost factor, using bone marrow injections is a good alternative.

Bone marrow aspirate has proved to be helpful in animal studies in increasing the bone formation seen radiologically and histologically. Also application of bone marrow aspirate concentrate increases the torsional stiffness of the new formed bone [5]. Boyd said that bone grafting is primarily a second wounding procedure, in which surgeon hopes that the response of the body will be more favourable than the response following the original trauma (1). The same principle was used in our study. We therefore didn't inject the bone marrow aspirate at the time of fracture itself because fracture itself releases hematoma that most times is sufficient for providing precursors of fracture union. Only if abnormal mobility persisted at 2 months, it was assumed that the fracture hematoma was not capable alone and the fracture requires a second supplementation of growth factors in form of bone marrow aspirate injections. Also this '2 months' time frame was chosen on the assumption that in this time the fracture is not so sclerosed and the fracture is still trying to unite but at the same time fracture hematoma is exhausted. These poor prognosis patients were 13 in group A and 14 in group B. The number of poor prognosis cases in the two groups were comparable. We found a union rate of as high as 71.43% at 4 months and 92.86% at 6 months in the intervened cases. This was consistent with the study of Bhargava *et al* who found a union of 23 out of 28 patients in their study [6]. Only 4 cases required a second shot of bone marrow injection at 4 months out of which 3 united, suggesting that a second shot of bone marrow aspirate wouldn't be required in most cases.

Bone marrow aspirate not only increased the union rate but also accelerated the rehabilitation of the patients. Around 71% cases of group B who had attained union could bear full weight by 4-6 months as against 23% cases in group A. The difference is drastic. Average time period, for full weight bearing in group A was 10.3 months as against 6.8 months in group B. Previous studies on the effect of bone marrow aspirate injection supplementation in core decompression in AVN have also proved that it allows early weight bearing

compared to decompression alone [7].

The patients enrolled in the study were already high risk of prolonged immobilisation because of their pre-existing medical ailments and this treatment proved a blessing to them as it drastically reduced the immobilisation period and morbidity that would have occurred if they were on immobilisation alone.

As is clear from the study, the patients in group B were far happier than the patients in group A and to avoid this disadvantage to patients of group A, the cases of non-union in group A were also given bone marrow aspirate injections at 6 months and then at 8 months if required. Within a year, 6 of the non-united 9 cases successfully achieved union.

Role of bone marrow aspirate in pure non-union where implant fixation has been used, has already been established in many studies [8, 9]. This study was one of its kind to study the role of bone marrow aspirate injections in patients managed with plaster and having a high possibility of non-union. Seeing the results, we recommend the use of prophylactic bone marrow aspirate injections in healthy patients getting managed conservatively by choice. The drawbacks of the study could be the small sample size.

5. Conclusion: Bone marrow aspirate injection definitely increase the union rates and decrease the period of immobilisation in long bone fractures managed conservatively It can be a blessing in patients with medical limitation to surgery.

6. Conflict of Interest: None.

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