Role of Percutaneous Autologous Bone Marrow Injection in Treatment of Delayed Union and Non Union of Long Bones

Dr. Karma Uden Bhutia¹, Dr. Ashik A Bary¹, Prof. Arun Kumar Singh², Prof. A Mahendra Singh², Dr. Raghvendra Raghuvanshi¹, Dr. Christopher Hmar¹

¹ Post Graduate Trainee, ² professor, Department of Orthopaedics, Regional institute of medical sciences, Manipur University, Lamphelpat, Imphal, 795004, Manipur, India

Abstract:
Background: Bone marrow contains osteoprogenitor cells that can be obtained with aspiration and appear to arise from a population of pluripotential connective-tissue stem cells.

Objectives: The purpose of the study was to evaluate the efficacy of autologous bone marrow injection in the treatment of delayed union and non union of long bones.

Methods: Thirty patients, twenty five delayed union and five non union of long bones were treated with this procedure. Of these, 23 had fracture tibia, 4 fracture ulna, 2 fracture humerus and 1 fracture femur. The average time duration between injury and procedure was 25.53±10.75 weeks (range 14 to 46 weeks). The bone marrow was aspirated from the anterior iliac crest and injected percutaneously in the fracture site under guidance of II tv.

Results: Union was achieved in 26(86.67%) out of 30 cases. The average time of clinical union was 11.31±4.52 weeks and radiological union was 14.92±4.62 weeks.

Conclusion: Bone marrow injection technique is simple technique which has high osteogenic potential. This minimally invasive procedure is safe, easy, simple, economical and short procedure.

Keywords: Bone marrow injection, delayed union, non union, osteoprogenitor cells

I. Introduction

Bone healing is a simple but endlessly complex biologic phenomenon.¹ Fracture healing requires the recruitment of appropriate cells( fibroblasts, macrophages, chondroblasts, osteoblasts, osteoclasts) and the subsequent expression of the appropriate genes (genes that control matrix production and organisation, growth factors, transcription factors) at the right time and in the right anatomical location.²

The major complications in fracture treatment were delayed union and non union. Union is considered delayed when healing has not advanced at the average rate for the location and type of fracture (usually 3 to 6 months). Non union is defined by US FDA as established when a minimum of 9 months has elapsed since injury and the fracture shows no visible progressive signs of healing for 3 months.²

There are various factors used to enhance union, such as drugs, electromagnetic fields, distraction and compression osteogenesis by ilizarov, autogenous bone graft and bone graft substitutes like bone morphogenetic protein.³

The concept of percutaneous bone graft was introduced by Herzog in 1951.⁴ McGaw and Habin were among the first to demonstrate the osteogenic activity of the bone marrow.⁵The osteogenic precursor cells which are capable of producing bone have been demonstrated among the stromal and endosteal cells of the bone marrow which are the key element in the process of bone formation and fracture healing.

Since percutaneous bone marrow injection is a simple and easy technique, we have taken up this study to ascertain its effectiveness in treatment of delayed union and non union.

II. Materials And Methods

The present study was conducted in the Department of Orthopaedics, RIMS, Imphal, Manipur over a period of two years from September 2012 to August 2014. This was a prospective study in which thirty (30) cases of delayed and non union of long bones, irrespective of sex and age, fitting in the inclusion criteria was subjected to percutaneous autologous bone marrow injection after obtaining written informed consent.

Inclusion Criteria
• Both genders were eligible.
• Age of fracture more than 12weeks.
Role of Percutaneous Antilogous Bone Marrow Injection in Treatment of Delayed Union...

- Clinically –abnormal mobility at the fracture site
  -tenderness at the fracture
  -pain on applying bending stresses.
Radiologically - insufficient amount of callus - sclerosis of fracture ends.
  -obliteration of bone marrow cavity at the fracture site.

Exclusion Criteria
- Infected fracture.
- Malignancy.
- Hepatitis B, Hepatitis C, HIV at the time of screening.
- Segmental bone loss.
- Smoking.
- Other major comorbidity.

Method
Ethical approval was taken from Institution Ethical Committee, RIMS, Imphal, Manipur. Informed consent were taken from all participants. All details of participating individuals were recorded. The fractures were assessed by antero-posterior and lateral radiographs of the long bone and clinically in delayed or non union. All routine investigations were done on all patients.

Patient were primarily treated for the fracture by external fixators, plating, plaster cast and nailing. The bone marrow injection was performed under spinal or local anaesthesia or general anaesthesia with monitoring by Image intensifier Television (ITV).

Under aseptic precautions, patient was kept in supine or lateral position. Painting was done around the site of aspiration i.e. over the iliac crest and injection site i.e. over the fracture site followed by draping. Bone marrow was be aspirated from the patient’s iliac crest with a bone marrow aspiration needle connected to a 20ml syringe. Required amount (10-30ml) of bone marrow was aspirated and injected immediately at the site of delayed or non union with a 16G spinal needle under the guidance of Image Intensifier. After bone marrow injection, the recipient site was either immobilised by a Plaster of Paris cast or the primary treatment was continued.

III. Assessment Of Results
All cases were followed after an interval of 4 weeks post injection for 6 months. The union was assessed clinically and radiologically.

Clinically - No abnormal mobility at the fracture site.
  - No tenderness at the fracture sites on applying bending stresses.
Radiologically - No gap at the fracture site.
  - Sufficient amount of callus.

The final results were based on whether union was achieved clinically and radiologically or not.

Results
Between September 2012 to August 2014, thirty patients, 25 with delayed union and 5 with non union of long bones were subjected to percutaneous autologous bone marrow injection in the Department of Orthopaedics, RIMS, Imphal. In 15 patients bone marrow injection was done under local anaesthesia, 10 patients under spinal anasaesthesia and 5 patients under general anaesthesia.

Bone marrow aspiration was done from anterior iliac crest and injected percutaneously at the fracture site. Patients were followed up at 4weeks interval till 6 months in the outpatients department of Orthopaedics, RIMS.

The mean age of the patients was 36.43±11.04 years with the range of 18 to 54 years. There was 18 males and 12 females. The study subjects comprised of higher percentage of male (60%) as compared to female (40%). Majority of the fractures were due to Road Traffic Accident which accounted for 80% (24), 13.33% (4) had injury following fall and 6.67% (2) had occupational injury. 23 out of 30 cases i.e. (76.67%) were of tibia, 4 (13.33%) were of ulna, 2 (6.67%) were of humerus and 1(3.33%) of femur. 14(46.67%) were closed fractures and 16 (53.33%) were open fractures. The initial treatment given was plating in 10(33.33%) patients, external fixation in 9(30%) patients, casting in 9(30%) patients and nailing in 2(6.67%) patients. The mean time interval between injury to bone marrow injection was 25.53±10.75 weeks in the range of 14 to 46 weeks. The amount of bone marrow injected was 20-30 ml for tibia and femur, 15-20 ml for humerus and 10-15 ml for ulna. The mean time for callus formation was 5.92±1.87 weeks ranging from 4 to 11weeeks. It is represented in Table 1.
Role of Percutaneous Antilogoous Bone Marrow Injection in Treatment of Delayed Union...

and Figure 1. The mean time for clinical union was 11.31±4.52 weeks ranging from 6 to 22 weeks. It is represented in Table 2 and Figure 2. The mean time for radiological union was 14.92±4.62 weeks ranging from 8 to 24 weeks. It is represented in Table 3 and Figure 3. Union was achieved in 26(86.67%) out of 30 cases. 2 out of 25 delayed union and 2 out of 5 nonunion (3 hypertrophic and 2 atrophic) failed to achieve union as shown in Table 4 and Figure 4. The two non union cases which failed to achieve union were atrophic type (one in ulna and other in tibia both initially treated by casting). Both the delayed union cases that failed to achieve union was in tibia (both type III open treated by external fixators). The two non-union cases were then managed by plating and interlocking nail with bone grafting for ulna and tibia respectively. The two delayed union cases were later managed by plating and bone grafting.

IV. Discussion

In this study 30 patients of which 25 cases were of delayed union and 5 cases were of non union were given percutaneous bone marrow injection. Patients were between 18 to 54 years of age, with a mean age of 36.43 ± 11.04 years. This is similar to the findings of Sim R et al10 where the mean age was 38 years (range, 19-62 years). Braley Houston L et al7 reported reported a mean age of 40.1 years (range, 24-51 years). There were 12 female and 18 male patients (m:f = 1.5:1). Majority of other studies showed marked male predominance. The study showing findings similar to ours was of Singh Ashok K3 where the male to female ratio was 1:1. The mean time between injury and bone marrow injection in this study was 25.53±10.75 weeks ranging from 14 to 46 weeks. This is similar to Bhargava R et al9 where the mean time was 25 weeks (range, 14-53 weeks). According to Padha Vikas et al10 the mean age was 28.1 weeks (range, 4-52 weeks). The fracture site involved in this study was tibia in 23 out of 30 patients (76.67%), ulna in 2 patients (6.67%), humerus in 2 patients (6.67%) and femur in 1 patient (3.33%). The findings were similar to Sim R et al10 where tibia comprised 72.7 % of the total fracture sites. In study by Bhargava R et al9 also tibia comprised majority of the bone involved i.e. 25 patients had fracture tibia out of 28 patients. In this study of 30 cases, there were 14 closed (46.67%) and 16 open (53.33%) out of which 4 were type I, 8 type II and 4 type IIa. In the study by Ismaeel Firas T et al11, 50% were open and 50% were closed fractures. In study of Bhargava Rakesh et al9 also 8 patients had type II open fracture out 28 cases. In this study the initial treatment given was plating in 10 patients (33.33%), external fixators in 9 (30%), POP casting in 9 (30%) and nailing in 2 (6.67%). In other studies also these were used as initial forms of treatment but the percentage of different types of treatment varied. In this study 15 patients (50%) were given local anaesthesia, 10 patients (33%) were given spinal anaesthesia and 5 patients (17%) general anaesthesia. In study by Bhargava R et al9 also majority of patients (76.67%) were given local anaesthesia. The amount of bone marrow injected in this study was 20-30 ml in tibia and femur, 15-20 ml in humerus and 15-30 ml in ulna. No definitive conclusion can be made regarding the amount of marrow to be injected because different investigators have injected different amounts of bone marrow with good results but now it has been shown that the efficacy of injected marrow is directly related to the number of progenitor cells.11 Larger volume aspirates contribute little to the overall number of bone marrow cells and result in unnecessary blood loss.12 In our study volume of injection depended mostly on the space available at the fracture site. Space had to be created in most cases by the inserted needle by breaking up the fibrous tissues between the fragments of bone. Only one injection was given like in studies of Padha V et al10, Bhargava R et al9, Braley H et al11, Srivastav R et al11 and Sim R et al11. In studies by Braley H et al11, Srivastav R et al11 and Sim R et al11 heparinised syringes were used. Heparin was not required in our study because of short interval between aspiration and injection, thereby avoiding the potential impairment of bone healing associated with heparin reported by Stinchfield et al11. In this study bone marrow was injected directly. According to Conolly et al13 osteogenic capacity of marrow is related to cell density and that concentration of marrow by simple centrifugation can enhance the rate and amount of bone formation. In this study the time taken for callus formation was 5.92 ± 1.87 weeks ranging from 4 to 11 weeks. 77% of successful cases showed callus between 4 to 6 weeks. In study by Singh Ashok K et al8, the time taken for callus formation was 5.8 weeks (range, 3-10 weeks). The mean time taken for clinical union in this study was 11.31 ± 4.52 weeks ranging from 6 to 22 weeks. 38.5% of successful cases showed clinical union between 9 to 11 weeks. According to Sim R et al10’s and Ahmed HH et al16 studies the time taken for clinical union was 10 weeks (range, 4-23 weeks). The mean time for radiological union in this study was 14.92 ± 4.62 weeks ranging from 8 to 25 weeks. Among other studies the ones that matched to ours closely were study of Sim R et al10 and Ahmed HH et al16 where mean time for radiological union was 17 weeks (range, 9-29 weeks). Goel A et al17 showed bony union following percutaneous injection in an average time of 14 weeks.

In this study union was achieved in 26 (86.67%) out of 30 cases. In delayed union cases union was successful in 23 (92%) out of 25 cases. In non union cases union was successful in 3 (60%) out of 5 cases. Similar findings were found by Shrivastav R et al11 where union was achieved in 87.87% of cases, Garg et al18 where union was achieved in 85% of cases, Singh Ashok K et al8 where where union was achieved in 83.33%
cases and Sim R et al\textsuperscript{6} in 81.8\% of cases. The 2 failed non union cases were of atrophic type. Husseini et al\textsuperscript{19} has observed that atrophic type of non union shows lower success rate to achieve union.

V. Conclusion

Delayed union and non-union are rare but well known complications of long bone fractures which present a major challenge to an orthopaedic surgeon despite continued advances in their treatment. For long, autologous cancellous bone grafting has been the standard of treatment. But this bone grafting has not been without complications such as painful scar, hematoma, infection, fracture or subluxation and guilt disturbances. Various methods of treating delayed and non-unions have been described such as Onlay bone grafting with or without internal fixation (Campbell, 1939; Phemister, 1947), cancellous insert grafts (Nicoll, 1956), subcortical iliac bone grafts (Forbes, 1961), dual only bone grafts (Boyd, 1941), stimulation by direct current through implanted electrodes (Peterson and Lewis, 1980) and by an electro magnetic field about the site of fracture (Sharrard et al., 1982). In bone grafting, the bone grafts mainly act as a scaffold with most of the cellular elements dying out and being replaced by creeping substitution (Chars, 1992).

Although there are several treatment options for patients with delayed and non union, bone marrow injection is a simple technique which has high osteogenic potential and can be grafted percutaneously. This minimally invasive procedure is safe, easy, simple, economical and short procedure. It is both patient as well as surgeon friendly procedure. In short, it is an easy substitution of a complex problem.

Our study has established that bone marrow has high osteogenic potential and can be grafted percutaneously successfully. Our study showed success rate of 86.67\%. In two cases of atrophic non union and two cases of delayed union, union was not seen. This procedure can be used as an early intervention , whenever one suspects a delay in healing of fracture. This procedure can be done on an outpatient basis and even under local anaesthesia with minimal donor and recipient site morbidity.

References

Role of Percutaneous Autologous Bone Marrow Injection in Treatment of Delayed Union...

VI. Tables

Table 1: Showing time for appearance of callus in successful cases:

<table>
<thead>
<tr>
<th>Period in weeks</th>
<th>No. of cases</th>
<th>Percentage(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 to 6</td>
<td>20</td>
<td>76.92</td>
</tr>
<tr>
<td>7 to 9</td>
<td>4</td>
<td>15.38</td>
</tr>
<tr>
<td>10 to 12</td>
<td>2</td>
<td>7.69</td>
</tr>
<tr>
<td>Total</td>
<td>26</td>
<td>100</td>
</tr>
</tbody>
</table>

Table 2: Showing time taken for clinical union in successful cases:

<table>
<thead>
<tr>
<th>Period in weeks</th>
<th>Delayed union cases</th>
<th>Non union cases</th>
<th>Percentage(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 to 8</td>
<td>7</td>
<td>0</td>
<td>26.92</td>
</tr>
<tr>
<td>9 to 11</td>
<td>10</td>
<td>0</td>
<td>38.46</td>
</tr>
<tr>
<td>12 to 14</td>
<td>10</td>
<td>0</td>
<td>11.53</td>
</tr>
<tr>
<td>15 to 17</td>
<td>6</td>
<td>0</td>
<td>3.84</td>
</tr>
<tr>
<td>18 to 20</td>
<td>1</td>
<td>0</td>
<td>7.69</td>
</tr>
<tr>
<td>21 to 23</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>24</td>
<td>2</td>
<td>100</td>
</tr>
</tbody>
</table>

Table 3: Showing time taken for radiological union in successful cases:

<table>
<thead>
<tr>
<th>Period in weeks</th>
<th>Delayed union cases</th>
<th>Non union cases</th>
<th>Percentage(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 to 10</td>
<td>5</td>
<td>0</td>
<td>19.23</td>
</tr>
<tr>
<td>11 to 13</td>
<td>5</td>
<td>0</td>
<td>19.23</td>
</tr>
<tr>
<td>14 to 16</td>
<td>10</td>
<td>0</td>
<td>38.46</td>
</tr>
<tr>
<td>17 to 19</td>
<td>1</td>
<td>0</td>
<td>3.84</td>
</tr>
<tr>
<td>20 to 22</td>
<td>2</td>
<td>0</td>
<td>7.69</td>
</tr>
<tr>
<td>23 to 25</td>
<td>1</td>
<td>2</td>
<td>11.53</td>
</tr>
<tr>
<td>Total</td>
<td>24</td>
<td>2</td>
<td>100</td>
</tr>
</tbody>
</table>

Table 4: Showing overall result:

<table>
<thead>
<tr>
<th></th>
<th>Delayed union</th>
<th>Non union</th>
<th>Percentage(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Union achieved</td>
<td>23</td>
<td>3</td>
<td>86.67</td>
</tr>
<tr>
<td>Union not achieved</td>
<td>2</td>
<td>2</td>
<td>13.33</td>
</tr>
<tr>
<td>Total</td>
<td>25</td>
<td>5</td>
<td>100</td>
</tr>
</tbody>
</table>

VII. Figures

Figure 1: Showing time for appearance of callus in successful cases

Figure 2: Showing time taken for clinical union in successful cases
Role of Percutaneous Antilogous Bone Marrow Injection in Treatment of Delayed Union...

Figure 3: Showing time taken for radiological union in successful cases

Figure 4: Showing final result of union

X ray showing delayed union (6 months) of tibia with plating as the initial treatment
Role of Percutaneous Antillogous Bone Marrow Injection in Treatment of Delayed Union...

X ray taken 8 weeks after bone marrow injection

X ray showing united tibia after removal of plate