International Journal Dental and Medical Sciences Research
Volume 3, Issue 1, Jan-Feb 2021 pp 514-521 www.ijdmsrjournal.com ISSN: 2582-6018

Percutaneous Bone Marrow Injection in Delayed Union and Slow Union of Long Bone Fractures

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Submitted: 10-01-2021 Revised: 18-01-2021 Accepted: 21-01-2021

ABSTRACT: Objective: To study the role of percutaneous bone marrow injection in delayed and slow union[1] of long bone fractures.
Design of study: Prospective study
Results and observation: In this study, thirty-four patients with a slow union or delayed union were treated with percutaneous bone marrow injection. 26 out of 34 patients were males. One case was lost in follow up. In cases of delayed union management[2], bone marrow injections were given at a minimum of 3 months after the initial treatment with closed technique. Slow Unionimpliesthatfractureunionispresentbutslow.Ins lowunion,afracturethatmaintains the appearance of the early stages of healing for more than a few weeks. In this study, 24 out of34 patients showed good union (72.7%), which is consistent with the other similar studies. Out of 28delayedunionandslowunioncases,22showedgood union(78.6%)comparedto40%union in 5 of the Non-union cases. The fractures that were treated by closed reduction methods showed better union compared to open reduction. Patients below 45 years showed good union compared to older age groups. Patients were also evaluated based on the radiographic evaluation scale[3] by hammer etal.
Keywords: Delayed Union, Bone marrow aspirate, Callus, Fracture healing, Radiographic evaluation.

Conclusion: Percutaneous bone marrow injection[4] is effective in stimulating the union of bone withlowmorbidityandearlymobilizationcomparedto routinebone-graftingtechniques.P-value <0.05showssignificanceinthisstudyfortheage,stateof theunionatthetimeofpercutaneous bone marrow injection and quantity of bone marrow given, callus formation, and radiological outcome.

I. INTRODUCTION

Thepercutaneousbonemarrowinjectioncon ceptwasintroducedbyHerzog[5]in1951.McGaw[6] and Habin were among the first to demonstrate the osteogenic activity of bone marrow. Bone is a tissue in which the ability to regenerate is more predictable than inanyother tissue of the body. Fracture healing occurs as a specialized type of wound healing in which the regeneration of the bone leads to the restoration of skeletal integrity**.**

R D Russell[1] in the year 1980 slow union can be caused by impaired blood supply, delayed union by inadequate immobilization, whether external or internal, and infection. Non-union, as well as delayed union, may be caused by prolonged movement and interposition of soft tissue. Slow Union and delayed union with too early cessation of immobilization cause non-union.

The management of delayed, slow, non-union of long bone fractures is to promote a sound union at the fracture site and to restore the good functional capacity of the affected limb to an optimum level. Various non-invasive methods such as pulsed ultrasound, magnetic field induction, and growth factor therapy are available and have been used with encouraging results. Though the Gold standard of management of delayed, slow, and non-union[7]ofthesefractureshasbeenautologousbonegraft ing,itisaninvasiveprocedurethatis associatedwithitsownsetofcomplications,especially atthedonorsitesuchasapainfulscar, infection, hematoma formation, muscle herniation, fracture or subluxation, and gait disturbances. These complications decrease morbidity for the patient and could also increase the expenditure to the patient and prolong the hospital stay. A procedure that is minimally invasive, cost-effective, enhances good union at the fracture site and improves with better functional results is percutaneous autologous bone marrow injection fulfilling the criteria and gives goodresults.
Union is considered delayed when the healing has not advanced at the average rate forthelocationandtypeoffracture,usually3to6months ,whereasslowunionimpliesthat afractureunionispresentbutslow.Thisisafracturethat

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Volume 3, Issue 1, Jan-Feb 2021 pp 514-521 www.ijdmsrjournal.com ISSN: 2582-6018

maintainstheappearanceoftheearly stages of healing for more than a few weeks. The fracture line remains clearly visible, but there is no unusual separation of the fragments and no cavitation of the surfaces, decalcification, or sclerosis. A slow union does not necessarily result in a delayed union or non-union. Such fractures often unite if immobilization is maintained long enough.

II. MATERIALS AND METHODS

A prospective study of Thirty-four patients with a slow union or delayed union during the period from June 2018- November 2020 and followed up to November 2020, at Narayana general hospital attached to Narayana medical college, Nellore. The patients were prospectively analysed and followed up bothclinicallyandradiologicallyataregularintervalof 6weeksforup to an average of 8 months. At every visit, check radiographs to be taken to assess the radiologicalhealing.

Selection of cases: The patients of age group more than 15 years who are diagnosed as delayed union or slow union with clinical and radiological evidence were selected.

Inclusion criteria:1) All patients aged more than 15 yrs.2) Patients with clinical and radiological evidenceofdelayedUnionorslowUnion.,3)Patientswhoarewillingtoparticipateandcangive consent.

Exclusioncriteria:1)Pregnantwomen,2)Patientswith neurologicaldeficits.3)Patientsbelow15 years 4). Infection, Malignancy 5) Patients who are not fit forsurgery/anaesthesia

Surgery procedure: All patients were admitted, and the procedure was done in an operation theatre after obtaining written informed consent. Patient was positioned in a supine position under Spinal anaesthesia. The iliac crest was painted and draped along with the surgical site. About 25-40ml of bone marrow aspirated from donor sites and injected into the recipient site using an aspiration needle under image guidance. Postoperatively dressing was applied under sterile precautions, and patients were discharged after 2-4 days. Patients followed up clinically and radiologically at an interval of 6 weeks until an average of 8 months ranging between 3- 15 months. During follow ups clinically patients were checked for tenderness, abnormal mobility, pain on weight-bearing. Radiologically, union assessed with hammers table.

Figure 1: Bone marrow Aspiration and Injecting into the Lt. Tibia.

III. OBSERVATION AND RESULTS

This study included 34 patients, out of which one case was lost to follow up. The age of the patients ranging from 18-79 years, with the mean age being 41.8 years, was included. Among the33patients,26weremales(78.8%).Inthisstudy,23caseswereclosedfractures,andthere were 11 cases of open fractures at the time of injury. Open fractures included nine Gustilo Andersontype1,onecaseeachoftype2,andtype3.Outof34casesofdelayedUnionorslow Union, 11 cases were a femur, 13 cases were tibia, six humerus cases, and 4 cases of the radius. In the type of fractures, 12 were comminuted fractures, and 21

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are simple fractures. 12 out of 9 in comminuted fractures showed union (75%), and out of the 21 simple fractures, 15 showed good union (71.4%). The fractures treated byclosedmethodsinitiallyatthetimeofinjury showed better union, with 14 out of 17 cases showing good union (85%). In contrast, those casestreatedbyopenproceduresshowedunioninonly10outof15cases(67%).Outofthe11 femur cases, 8 cases showed good union (72.7%). About 90% in 10 cases of the radius and humerus casesalsoshowedbonyunion.Amongthe13casesofthetibia,8showedgoodunion (61%).5showedprogressiontowardshealing.Outofthe11femurcases,8casesshowedgood union (72.7%). The clinical union was seen in an average of 18 weeks (12-36 weeks) and radiological union in 22 weeks (11-36weeks). Out of 33 cases, callus was seen on the x-ray in 1st month in 23cases.

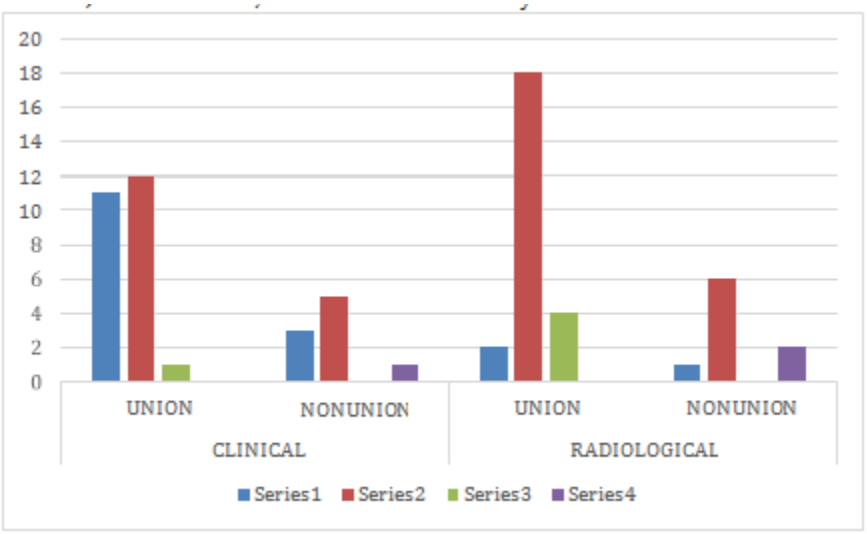

FIGURE2: CLINICAL AND RADIOLOGICAL UNION

There was total 28 cases of delayed union and slow union and 5 cases of non- union. Among the 28 cases of delayed union, 22 cases were good union (78.6%), 5 showed non-union and 1case was lost to follow up. Only 2 out of 5 cases of non-union showed good bony union after bone marrow injection (40%) at the end of follow up at 6th month.

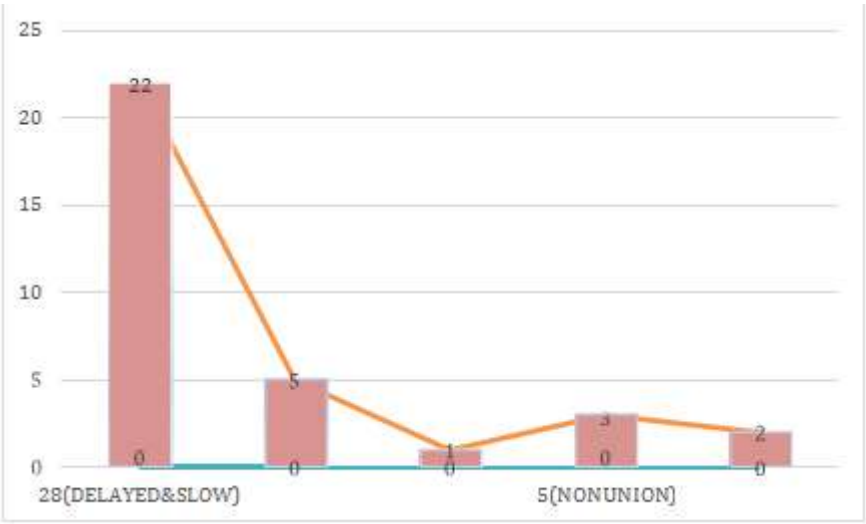

FIGURE 3: UNION AND NONUNION AT END OF FOLLOW UP

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PARAMETER	P-VALUE	CONCLUSION
Age * outcome	.030	Significant
Type * outcome	.834	Non-Significant
Pattern * outcome	.976	Non-Significant
Callus * outcome	.031	Significant
Clinical * outcome	.284	Non-Significant
Radiological * outcome	.037	Significant

Table1: Fishers exact test P-value

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CASE 1: A Delayed union of fracture shaft of Lt. Tibia treated with bone marrow injection

1) Pre-op X-ray

2) Three months following bonemarrowinjection **3) Six months followup**

Case :2 Slow union of Lt. Forearm both bones fracture treated with bone marrow injection

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Pre-opX-ray

Three months following bone marrow injection Six months follow up (final followup)

IV. DISCUSSION

Fracture healing occurs in two ways.

Primaryhealing/directhealing-

Boneformationoccursdirectlywithoutthecallus formation. This type of fracture healing occurs particularly in stable, aligned, and closely approximated fractures. It can roughly be compared to the recovery ofsoft tissuebyprimaryintention.E.g.,Fracturerigidlystabilized byplates.Thisisoftwo types.

a) **Contact healing/ Haversian remodeling-** when there is direct contact between the cortical bone ends, lamellar bone forms directly across the fracture line, parallel to the long axis of the bone, by direct extension of osteons.

b) **Gap healing-** Osteoblasts differentiate and start depositing osteons onthe exposed surfaces of fragment ends, mostly without preceding osteoclastic resorption. In big significant gaps

of 200um-1mm, the cells fill the gap with wovenbone,andHaversianremodelingbeginstodepositthelamellarbone.

Secondary healing/indirect healing- It is the usual type consisting of the formation of callus either of cartilaginous or fibrous type. Lamellar bone (Enchondral/indirect bone formation) replaces callus later. It is comparable to the healing of soft tissue by fillinggaps with vascular granulationtissue.

When the fracture is not rigidly fixed, the callus is replaced by bone by secondary bone healing, radiologically characterized by abundant callus formation, temporary widening of fracture gap, and the slow disappearance of radiolucent fracture line due to fibrocartilage mineralization.

The bone healing occurs in successive stages in a sequence of steps activated by and depending on the previous steps. Each stage depends on different kinds of differentiated cells to make new capillaries (including endothelial and smooth muscle cells), local connective tissue (including fibroblasts, lipoblasts, and intercellular materials), and the bone and cartilage matrices (made of osteoblasts and chondroblasts). In some situations, bone healing can arise without being caused by a fracture. E.g., Myositis ossificans, myelofibrosis, Paget's disease, and growth plates where woven bone formation occurs without a fracture. Osteoinduction is the initial step in bone healing; it causes mesenchymal cells to differentiate into various cells, which then proliferateandproducemessengersubstances,whichfurtherstimulatesthemesenchymalcellsto differentiate. This cycle continues until healing. In Osteoconduction, a scaffold of the collagenous network develops, upon which the reparative cells produce callus and bone, facilitating the deposition of bone in an orderly fashion and helps to bridge the gap. Allografts have powerful osteoinductive and osteoconductive properties. Various methods of treatment were developed for delayed, slow Union and non-union for decades, which includes exchange nailing, bone grafting, stimulation by electric current and electromagnetic field, Ilizarovfixation[1,2]

· Hernigou et al.[21] conducted a study between 1990 and 2000, which included 60 patients with the established slow union, non-union of the tibial shaft. Marrow was aspirated from the iliac crest. Each non-union and slow union site received a relatively constant volume of 20cm^3 of concentrated marrow. The number of progenitor cells that were transplanted was estimated by counting the fibroblast colony-forming units. The volume of bone formation was determined by comparing preoperative computerized tomography scans with scans performed four months following the injection. The bone union is observed in 53 patients. He concluded that percutaneous bonemarrowgraftingisaneffectiveandsafemethodforthetreatmentofslowunionandnon-union.

A study conducted by Siwach[22] RC et al. in 2001, which included 72 patients of post-traumatic delayed unions, slow unions, established non-unions, poor regenerate in segmental bone transportation, and limblengtheningproceduretreatedbypercutaneousinjectionsofautogenous bone marrow at the site of failed healing with an average follows up of four years. Bone union observed in 68 patients. Overall, 72.2% of the patients had an excellent result, 11.1% a good result, 11.1% a fair result, and 5.5% unfortunate result orfailure.

The work of Paley et al[26] showed that marrow produces an optimal effect when used early in the fracture healing process.Conolly[27]andHealy[28]havedemonstratedthatpercutaneousbonemarrow injection can successfully treat 78%-95% of slow unioncases.

Inthepresentstudy,thirty-fourpatientswithaslowunionordelayedunionweretreated with percutaneous bone marrow injection. 26 out of 34 patients were males. One case was lost in followup.The fracturelineremains visible, butthereisnoexcellentseparationofthefragmentsandnocavitationofthesurfaces, decalcification, orsclerosis.Suchfracturesoftenuniteifimmobilization is maintained long enough. The mean duration between the procedure and injury was about 22 weeks(5.4months).After percutaneousbonemarrowinjection,thefracturesunitedinthemeantime of 17 weeks. Therefore, it is clear that the percutaneous bone marrow injection had helped the fracture to unite; it had accelerated the healing process, radiologically evaluated by a scale developed by hammer[3] et al. Cases were considered as non-union or anticipated to result in non- unionifthere was noimprovement in the progressiontowardshealingforthreeconsecutivemonths.

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GROUP	CALLUS FORMATION	FRACTURE LINE	STAGE OF UNION
1	HOMOGENOUS BONED STRUCTURE MASSIVE,	OBLITERATED BARELY	ACHIEVED
2	BONY TRABECULAE CROSSING FRACTURE LINE	DISCERNIBLE	ACHIEVED
3	APPARENT	DISCERNIBLE	UNCERTAIN
4	TRACE	DISTINCT	NOT ACHIEVED
5	NO CALLUS	DISTINCT	NOT ACHIEVED

TABLE 2: HAMMER SCALE FOR RADIOLOGICAL EVALUATION

Percutaneousbonemarrowinjectionwasfoundtobemorebeneficialincasesofdelayed Unionandslow Unionascomparedtonon-unioncases.Theageofthepatientinyears,stateofunion at time of percutaneous bone marrow injection, type of fracture, the quantity of bone marrow injected played a significant role with a p-value < 0.05. There were neither in donor site nor in the recipient site infection noticed in thisstudy.

V. SUMMARY

In the present study, 24 out of 34 patients showed good union (72.7%), which is consistent with the other similar studies. The fractures that were treated by closed reduction methods initially showedbetterunioncomparedtoopenreduction.Patientsbelowtheage45yearsshowedgood union compared to older age groups. P-value found significant (<0.05) for the age, state of the union at the time of percutaneous bone marrow injection and quantity of bone marrow given, callus formation, and radiologicaloutcome.

VI. CONCLUSION

Bonemarrowinjectionasaminimallyinvasiveproceduredonepercutaneouslyisasafeprocedure with no related complications that might occur with traditional bone grafting procedure, thus reduced hospital stay, expenditure, and early mobilization. It can be considered an alternate methodtobonegraftingindelayedandSlowUnionoffractureswithnosurgicalscarandsurgical siteinfectionindonorandrecipientsites.Itcanbegivenincasesinwithdelayeduniondiagnosed or anticipated to prevent the fractures resulting in non-union andthereby reducingthemorbidityassociatedwithnon-union P-value calculated was <0.5 value was found to be significant for age, state of the union at the time of percutaneous bone marrow injection, the quantity as well as the appearance of callus.

VII. LIMITATIONS

The study duration was limited to 6 months, which might be insufficient to study the union in long bones like femur. Small sample size as larger sample of patients would possibly be essential to consolidate better and evaluate the effectiveness of this procedure. The study is conducted as a single Centre study not a multicentric study. Not a comparison study which might limit the accurate benefits and risk of this study.

VIII. ACKNOWLWEDGEMENT

The authors received no financial support for this research, authorship, and/or publication of this article. Declaration of Conflicting Interests the authors declare no potential conflicts of interest with respect to this research, authorship, and/or publication of this article.

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