SOCIEDADE BRASILEIRA DE ORTOPEDIA E TRAUMATOLOGIA

RBO REVISTA BRASILEIRA DE ORTOPEDIA

www.rbo.org.br

Original Article

Percutaneous autogenous bone marrow injection for delayed union or non-union of long bone fractures after internal fixation☆

Ramji Lal Sahu

Department of Orthopaedics, Sharda University, Greater Noida, India

ARTICLE INFO

Article history:
Received 3 June 2017
Accepted 5 September 2017
Available online 29 December 2017

Keywords:
Bone nails
Femoral fractures
Fracture fixation, internal
Fractures, ununited

ABSTRACT

Objectives: 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.

Methods: This prospective study was carried out at the Orthopeedics Department from June 2005 to June 2010. A total of 93 patients with delayed union and non-union (56 delayed unions and 37 non-unions) of the long bone were recruited from the Emergency and Outpatient Departments and treated with percutaneous autologous bone marrow injections. The clinical results of this study were rated on the basis of the criteria of union. All patients were followed for 24 months.

Results: All the fractures (delayed union and non-union) were united within 12 weeks. Most of the patients had discomfort at the donor site for few days; none had problems of persistent pain. The results were excellent in 68.81% (64/93) of cases, good in 19.35% (18/93) of cases, and poor in 11.82% (11/93) of cases.

Conclusion: Percutaneous autologous bone marrow injection is an effective and safe method for the treatment of diaphyseal non-union and delayed union. Thus, it is concluded that with an adequate amount of autologous bone marrow injection, successful union in delayed union and non-union of fractures of long bones can be achieved.

☆ Study conducted at Department of Orthopaedics, Sharda University, Greater Noida, India.

E-mail: drrlsahu@gmail.com

https://doi.org/10.1016/j.rboe.2017.09.004

Injeção percutânea de medula óssea autóloga para tratamento de retardo de consolidação ou pseudoartrose de fraturas de ossos longos após fixação interna

Palavras-chave:
Hastes ósseas
Fraturas femorais
Fixação interna de fratura
Fraturas com pseudoartrose

RESUMO

Objetivos: O objetivo deste estudo foi avaliar os resultados da injeção percutânea de medula óssea autóloga no tratamento de fraturas com retardo de consolidação ou pseudoartrose após fixação interna.

Métodos: Esse estudo prospectivo foi realizado no Departamento de Ortopedia de junho de 2005 a junho de 2010. Um total de 93 pacientes com retardo de consolidação e pseudoartrose (56 retardos de consolidação e 37 pseudoartroses) de osso longo foram recrutados dos Departamentos de Emergência e Ambulatórios e tratados com injeções de medula óssea autóloga percutânea. Os resultados clínicos desse estudo foram avaliados com base em critérios de consolidação. Todos os pacientes foram seguidos durante 24 meses.

Resultados: Todas as fraturas (retardo de consolidação e pseudoartrose) apresentaram consolidação dentro de 12 semanas. A maioria dos pacientes apresentava desconforto na região doadora por alguns dias; nenhum caso de dor persistente foi observado. Os resultados foram excelentes em 68,81% (64/93), bons em 19,35% (18/93) e ruins em 11,82% (11/93) dos casos.

Conclusão: A injeção de medula óssea autóloga percutânea é um método efetivo e seguro para o tratamento da pseudoartrose e do retardo de consolidação diafisários. Assim, conclui-se que uma quantidade adequada de injeção autóloga de medula óssea pode levar a uma consolidação bem sucedida em casos de retardo de consolidação e pseudoartrose de fraturas de ossos longos.

Introduction

Nonunion and delayed union are common problem seen in fracture healing and may be caused by several factors with or without any obvious cause. Numerous methods have been adopted to overcome this problem such as bone graft, electrical stimulation, ultrasound, bone transport and bone marrow injection. The concept of bone marrow graft and the percutaneous grafting method were subsequently combined in many studies, taking into account the fluid nature of the bone marrow. Some studies stated that percutaneous bone marrow injection could be used with composite graft with good results in the treatment of simple bone cyst congenital tibial pseudoarthrosis and in the management of delayed union in difficult clinical circumstances such as cancer patients.[1–4] The aim of this prospective study was to assess the results of percutaneous bone marrow injection in the treatment of fractures presenting with delayed union and non-union following internal fixation.

Material and methods

This prospective study was carried out at Orthopaedics department from June 2005 to June 2010. Institutional medical ethics committee approved it. A total of 93 patients with delayed and non-union (56 delayed unions and 37 non-unions) of long bone were treated with percutaneous autologous bone marrow injections. Written informed consent was taken from each patients and study was conducted according to world medical association declaration of Helsinki. The mean age of the patients was 46 years (range: 16–86 years) and sex distribution was 67 males and 26 females.

Inclusion criteria

1. Patients with delayed and non-union of long bone fractures.
2. Age between 16 and 86 years.
3. All fractures had acceptable alignment, good bone opposition and stable fixation.
4. Bone marrow aspiration was done from anterior or posterior iliac crest.
5. Bone marrow was injected at interval of four to six weeks after radiological evaluation for union under image intensifier control.
6. The clinical results of this study were rated on the basis of the criteria of union; Union was defined clinically by the absence of bony tenderness and abnormal mobility at the fracture site, and no pain at the fracture site on weight bearing. Radiological fracture union was defined by the presence of callus bridging the fracture and partial obliteration of the fracture line in 2 views perpendicular to each other.[5]
7. Patients were followed up for 24 months.

Exclusion criteria

1. Patients with pathological fractures.
2. Malnourished patients and those with open fractures, arterial injuries, nerve injuries, infected fractures.

A written informed consent was obtained from all the patients; they were explained about treatment plan, cost of operation, and hospital stay after surgery, and complications of anaesthesia. They were followed up after surgery, were clinically and radio logically assessed for fracture healing, joint movements and implant failure. According to the criteria the results are graded as excellent when the fractures unites within 16 weeks without any complication, good when union occur within 24 weeks with treatable complications like superficial infection and knee/ankle stiffness and poor when union occur before or after 24 weeks with one or more permanent complications like infection (osteomyelitis), implant failure, non-union, limb shortening and permanent knee/ankle stiffness. Delayed union was recorded when the fracture united between three to six months while nonunion was noted when a minimum of nine months have elapsed since injury and the fracture shows no visible sign healing for 3 months. Out of 93 long bones, 6 fracture shaft of the femur were treated with interlocking nail and 15 supracondylar fracture of femur were treated with lower femoral locking plates. 19 tibial shaft fractures were treated with dynamic compression locking plates. All the 17 humeral shaft fractures were treated with low contact dynamic compression locking plate (LC-DCP). Seven cases of radius and ulna fractures were treated conservatively with pop application. 13 radius and 16 ulnas were treated with dynamic compression plates. We injected 40–50 cc bone marrows for femur and tibia, 20 cc for humerus and 10 cc for radius and ulna in all the cases of delayed and nonunion fractures.

The procedure was carried out in operation theatre (OT). The patient was placed in supine position, fracture site and graft site were draped separately to avoid cross contamination. A 2 mm K-wire was used to drill the bone with T handle and then a needle of gauge 16 was used for aspiration and a lumber puncture needle of gauge 16 was used for injection. The entire procedure was done under local infiltration with 2% xlocaine or ketamine or spinal anaesthesia. The recent site was marked prior to the injection and immediately after aspiration, 40–50 ml of the non-heparinised bone marrow was injected into the previously marked site under image intensifier guidance. A compression dressing was given postoperatively and the patient was discharged in the evening and reviewed after every 6 weeks. Serial X-rays were taken at review till the fracture got united. Fracture site mobility, tenderness and radiological features were assessed for union. The fracture was considered united when bone crossed the fracture gap and the patient was able to weight bear or used the limb without local pain or instability.

Statistical analysis

Statistical analysis was conducted using chi-square test. A p value of less than 0.05 was considered to be statistically significant.

Table 1 – Age and sex distribution in study group ($n = 93$).

Age	Male	Female	Total	%
<20	7	3	10	10.75
20–40	14	5	19	20.43
40–60	18	8	26	27.95
60–80	16	6	22	23.65
>80	12	4	16	17.20
Total	67	26	93	100

Results

In this prospective study, 93 long bone fractures of delayed or nonunion were treated with percutaneous autologous bone marrow injections and followed for a period of two years. 72.04% (67/93) patients were males and 27.95% (26/93) patients were females. The patients were aged sixteen years to eighty-six years. 60.21% (56/93) had met with a road traffic accident, 13.97% (13/93) had a fall from a height and 25.80% (24/93) patients got injured from sport injuries. There were 53.76% (50/93) right sided and 46.23% (43/93) left sided fractures. Out of 100% (93/93), 13.97% (13/93) patients were open fractures (Gustilo and Anderson type I) and 86.02% (80/93) were closed fractures. In this study, 22.58% (21/93) patients had fracture shaft of the femur, 20.43% (19/93) fracture shaft of the tibia, 18.27% (17/93) fracture shaft of humerus, 21.50% (20/93) fracture shaft of radius and 17.20% (16/93) patients had fracture shaft of ulna.

The patients were divided into five groups according to their age for simplicity (Table 1). The clinical results of our study were based on the criteria of union, nonunion[5] delayed union or malunion. The patients were followed according to their clinical status. In this study, 73.04% (67/93) cases were linear fractures, 25.80% (24/93) comminuted fracture and 2.15% (2/93) cases were segmental fractures. None of the fracture with bone loss was included in the present study. 53.76% (50/93) of the long bones were initially treated by open reduction and internal fixation, 21.50% (20/93) by close reduction and internal fixation, 13.97% (13/93) by close reduction and plaster cast and 10.75% (10/93) by open reduction and external fixation. Out of 93 long bone studied, 60.21% (56/93) were delayed union, 25.80% (24/93) were hypertrophic nonunion and 13.97% (13/93) were atrophic non-union. 11.82% (11/93) long bone fractures in our study were infected.

The minimum time elapsed before the percutaneous autologous bone marrow injection was 4 months and maximum 24 months with an average of 8.2 months. Most of the patients had discomfort at the donor site for few days; none had problems of persistent pain. 53.76% (50/93) patients were injected once, 21.50% (20/93) were injected twice, 13.97% (13/93) were injected thrice and 10.75% (10/93) patients were injected four times at monthly interval. All the fractures (Delayed union and nonunion) were united within 12 weeks. The minimum time for union was 8 weeks and maximum 16 weeks with an average of 12 weeks. With this bone marrow injection, femoral fractures united in 85.71% (18/21) cases, tibia in 89.47% (17/19) cases, humerus in 88.23% (15/17) cases, radius in 90% (18/20) cases and ulna 87.5% (14/16) cases (Table 2). Delayed union were united in 100% (56/56) cases, Non-union hypertrophic

Table 2 – Results according to individual bone (n = 93).

Bone	Number	United	Percentage
Femur	21	18	85.71
Tibia	19	17	89.47
Humerus	17	15	88.23
Radius	20	18	90
Ulna	16	14	87.5

p value: 0.96. Result: not significant.

Table 3 – Result according to the type of defect in union (n = 93).

Defect in union	Number	United	Percentage
Nonunion hypertrophic	24	18	75
Nonunion atrophic	13	8	61.53
Delayed union	56	56	100

p value: <0.45. Result: significant.

united in 75% (18/24) cases and nonunion atrophic were united in 61.53% (8/13) cases (Table 3). We injected 40–50 cc bone marrows for femur and tibia, 20 cc for humerus and 10 cc for radius and ulna in all the cases of delayed and nonunion fractures (Table 4).

Comparison of results with other studies showed that the success rate of our study is similar to that of other studies (Table 5). The results were excellent in 68.81% (64/93) cases, good in 19.35% (18/93) cases and poor in 11.82% (11/93) cases (Table 6). In subjective overall assessment 68.81% (64/93) patients were full satisfied and 19.35% (18/93) patients were satisfied with the outcome of treatment.

Discussion

Nonunion or delayed union of long bone fractures always has been a challenging problem. Autogenous bone grafting has been the most commonly used procedure in the operative treatment. It involves morbidity at donor site such as haemorrhage, infection, the need for additional 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 method.[6] Few studies focused on less invasive methods such as ultrasound, bone growth factors (e.g. bone morphogenic protein), extracorporeal shock waves and bone marrow injection, aiming to achieve similar results but with fewer complications.[7] In our study, 93 delayed and non-union of long bone fractures were treated with bone marrow injection without infection, haemorrhage and ugly scar.

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.[8] The time to union was significantly less in female patients compared to male patients ($p = 0.041$). In our study, 11 long bone fractures were not united because of heavy smoking habits of the patients. The tibia represented 20.43% 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. The higher incidence of open tibial fractures due to their subcutaneous anatomical location as well as the specific aspects of vascularisation of the tibia is among the important causes of this relatively frequent delay in healing.

In our study, out of 93 long bones, 6 fracture shaft of the femur were treated with interlocking nail and 15 supracondylar fracture of femur were treated with lower femoral locking plates. 19 tibial shaft fractures were treated with dynamic compression locking plates. All the 17 humeral shaft fractures were treated with low contact dynamic compression locking plate (LC-DCP). Seven cases of radius and ulna fractures were treated conservatively with pop application. 13 radius and nine ulnas were treated with dynamic compression plates. The 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 locking plating, if not performed using a minimal invasive surgical approach, damages the soft tissue much more than IM nailing done under image intensifier without opening the fracture site.[9] 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-union following locked plate fixation included in this study may also be related to the bicortical locking screw fixation of the plate inserted close to the fracture site, leading to very rigid fixation and not allowing enough micro motion at the fracture site to induce an osteoblastic activity.

Majority of the studies stated that in specific patient the failure may be related to the improper reduction of the fracture

Table 4 – Results given according to amount of bone marrow injection given (n = 93).

Bone	Amount of bone marrow (cc)	Number	United	Percentage	*p* Value	Result
Femur	<50	6	3	60%	<0.05	Significant
	>50	15	15	100%		
Tibia	<50	7	5	71.42%	0.05	Not significant
	>50	12	12	100%		
Humerus	<20	7	5	71.42%	0.07	Not significant
	>20	10	10	100%		
Radius	<10	10	8	80%	0.13	Not significant
	>10	10	10	100%		
Ulna	<10	8	6	75%	0.13	Not significant
	>10	8	8	100%		

Table 5 – Comparison of results with other studies (*n* = 93).

Study and year	No. of bones studied	No. of bones united (%)
Present study (Ramji lal sahu)	93	88.17
Rakesh Shrivastav, 2013	33	87.87
Healy et al., 1990	8	62.5
Connolly et al., 1991	20	90
Garg et al., 1993	20	85
Bieniek et al., 1993	30	87
Husseini	71	72

p value: 0.94. Result: not significant.

Table 6 – Outcome of results of bone marrow injection (*n* = 93).

Result	Number	Percentage
Excellent	64	68.81
Good	18	19.35
Poor	11	11.82

p value: <0.05. Result: significant.

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 to achieve early union. Bajada et al. and others stated that percutaneous bone marrow injection could be used with composite graft with good results in the treatment of simple bone cyst congenital tibial pseudoarthrosis and in the management of delayed union in difficult clinical circumstances such as cancer patients.[1–4] In our study, there is no gap at the fracture site after reduction and rigid internal fixation with implant. Garnavos et al. 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.[10] In other studies (such as Kim et al.),[11] the aspirate was cultured in vitro before injection of the osteoprogenitor cells into the fracture site. 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 ml through redirection of the needle into the iliac crest to make sure the bone marrow aspirate remained concentrated. Muschler et al.[12] 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 88.12% success to achieve union following the bone marrow injection, this study has showed the efficacy of autogenous bone marrow to accelerate fracture healing.

Ma et al.[13] 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.[13,14] As for the complications, there was no reported infection or pain related to the donor sites or injection sites. The use of bone marrow is considered a simple and minimal 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 orthopaedic field, which avoids many of the complications of the traditional bone grafting method commonly used so far. Hernigou et al.[15] Reported that hematopoietic stem cells are pluripotent and are able to differentiate; however, the number of pluripotent cells is decreased in patients who smoke or use alcohol or steroids. Sinning down the donor sample will increase the number of pluripotent cells (located in the buffy coats). They have demonstrated that success is dependent on the number (concentration) of stem cells available for injection.[15] A potential limitation of our study was the absence of a control group treated by a different modality. We injected 40–50 cc bone marrows for femur and tibia, 20 cc for humerus and 10 cc for radius and ulna in all the cases of delayed and nonunion fractures (Table 4). Comparison of results with other studies showed that the success rate of our study is similar to that of other studies (Table 5).

The results were excellent in 68.81% (64/93) cases, good in 19.35% (18/93) cases and poor in 11.82% (11/93) cases (Table 6). In subjective overall assessment 68.81% (64/93) patients were full satisfied and 19.35% (18/93) patients were satisfied with the outcome of treatment. We recommend that the good results achieved in this study (88.12% union) were related to the good selection of the 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.

Conclusion

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 orthopaedic field, which avoids many of the complications of the traditional bone grafting method commonly used so far.

Conflicts of interest

The authors declare no conflicts of interest.

REFERENCES

1. Bajada S, Harrison PE, Ashton BA, Cassar-Pullicino VN, Ashammakhi N, Richardson JB. Successful treatment of refractory tibial nonunion using calcium sulphate and bone

marrow stromal cell implantation. J Bone Joint Surg Br. 2007;89(10):1382–6.
2. Di Bella C, Dozza B, Frisoni T, Cevolani L, Donati D. Injection of demineralized bone matrix with bone marrow concentrate improves healing in unicameral bone cyst. Clin Orthop Relat Res. 2010;468(11):3047–55.
3. Park IH, Micic ID, Jeon IH. A study of 23 unicameral bone cysts of the calcaneus: open chip allogeneic bone graft versus percutaneous injection of bone powder with autogenous bone marrow. Foot Ankle Int. 2008;29(2):164–70.
4. Siegel HJ, Baird RC 3rd, Hall J, Lopez-Ben R, Lander PH. The outcome of composite bone graft substitute used to treat cavitary bone defects. Orthopedics. 2008;31(8):754. PubMed PMID: 19292421.
5. Brumback RJ, Toal TR Jr, Murphy-Zane MS, Novak VP, Belkoff SM. Immediate weight-bearing after treatment of a comminuted fracture of the femoral shaft with a statically locked intramedullary nail. J Bone Joint Surg Am. 1999;81(11):1538–44.
6. Ebraheim NA, Elgafy H, Xu R. Bone-graft harvesting from iliac and fibular donor sites: techniques and complications. J Am Acad Orthop Surg. 2001;9(3):210–8.
7. Roussignol X, Currey C, Duparc F, Dujardin F. Indications and results for the Exogen™ ultrasound system in the management of non-union: a 59-case pilot study. Orthop Traumatol Surg Res. 2012;98(2):206–13.
8. Hernigou J, Schuind F. Smoking as a predictor of negative outcome in diaphyseal fracture healing. Int Orthop. 2013;37(5):883–7.
9. Seyhan M, Unay K, Sener N. Intramedullary nailing versus percutaneous locked plating of distal extra-articular tibial fractures: a retrospective study. Eur J Orthop Surg Traumatol. 2013;23(5):595–601.
10. Garnavos C, Mouzopoulos G, Morakis E. Fixed intramedullary nailing and percutaneous autologous concentrated bone-marrow grafting can promote bone healing in humeral-shaft fractures with delayed union. Injury. 2010;41(6):563–7.
11. Kim SJ, Shin YW, Yang KH, Kim SB, Yoo MJ, Han SK, et al. A multi-center, randomized, clinical study to compare the effect and safety of autologous cultured osteoblast (Ossron) injection to treat fractures. BMC Musculoskelet Disord. 2009;10:20.
12. Muschler GF, Boehm C, Easley K. Aspiration to obtain osteoblast progenitor cells from human bone marrow: the influence of aspiration volume. J Bone Joint Surg Am. 1997;79(11):1699–709.
13. Ma JT, Yu M, Zhang MC, Zhu XJ, Xu HY, Liang GJ. Clinical observation on percutaneous autologous bone marrow grafting for treatment of fracture nonunion. Zhongguo Gu Shang. 2009;22(11):862–4.
14. Murawski CD, Kennedy JG. Percutaneous internal fixation of proximal fifth metatarsal jones fractures (Zones II and III) with Charlotte Carolina screw and bone marrow aspirate concentrate: an outcome study in athletes. Am J Sports Med. 2011;39(6):1295–301.
15. Hernigou P, Mathieu G, Poignard A, Manicom O, Beaujean F, Rouard H. Percutaneous autologous bone-marrow grafting for nonunions. Surgical technique. J Bone Joint Surg Am. 2006;88 Suppl. 1 (Pt 2):322–7.