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Original article

# Use of bone marrow aspirate concentrate (BMAC) in the treatment of delayed unions and nonunions: a single-center case series

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**Abstract.** *Background and aim:* Surgical treatment of delayed unions and nonunions requires adherence to the principles of mechanical stability, as well as consideration of biological environment. Bone marrow aspirate concentrate (BMAC) provides cellular and growth factor supply acting as an osteoinductive and osteogenic stimulus in bone healing. The aim of the study is to analyze the outcome of delayed unions and nonunions treatment with autologous bone marrow concentrate supplementation at our institution. *Methods:* Study included all patients treated at the Orthopedic and Traumatology Unit of Cattinara Hospital-ASUGI (Trieste, Italy) between September 2015 and January 2022 for delayed union or nonunion who received bone marrow aspirate concentrate (BMAC) supplementation. Initial treatment, definitive surgical treatment, radiographic healing and complications were retrospectively evaluated. Data collection was conducted by clinical database searching. *Results:* The study population included 11 patients, F:M 7:4, mean age 61 years. Initial treatment was surgical in 82% of patients. Radiographic healing of the fracture occurred in 100% of cases. None of the patients presented complications. *Conclusions:* Bone marrow aspirate concentrate (BMAC) has shown encouraging results and a high safety profile. Thus, it could be an effective and safe method in the treatment of delayed unions and nonunion. However, further studies will be needed to clarify its role. (www.actabiomedica.it)

**Key words:** bone marrow aspirate concentrate, BMAC, delayed union, nonunion

## Introduction

Incidence of impaired healing has been variably identified and reported around the scientific community (1). Some authors estimated that up to 10% of fractures result in delayed unions and nonunions (2,3). Despite recent advances in general understanding of the bone healing complexity, the management of impaired union remains a challenge. Both appropriate biological environment and adequate mechanical stability are required for successful fracture healing.

Autologous iliac crest bone grafting remains a widely used augmentation for nonunion treatment. This method offers good results but is bound by inherently limited supply. Furthermore, it is associated with different complication such as donor site pain and infections (4-6).

Alternative techniques such as bone marrow aspirate concentrate (BMAC) have gained attention recently. The principle behind BMAC is that it enables recovery of osteogenic cells and osteoinductive factors from bone marrow using a minimally invasive approach. A centrifugation process concentrates nucleated cells separating them from non-nucleated cells such as erythrocytes. After BMAC is obtained it can be applied percutaneously or in combination with cancellous and/or structural graft (7-10). Several studies in both animals and humans have demonstrated

promising results in bone healing using this method (11-16). Nonetheless, there is a lack of larger studies that compare results to other available techniques (17).

The aim of this study was to retrospectively evaluate the outcomes of treatment with bone marrow aspirate concentrate (BMAC) for delayed unions and nonunion at out institution.

## Methods

The study included all patients treated between September 2015 and January 2022 at the Orthopedics and Traumatology Unit of Cattinara Hospital-ASUGI of Trieste (Italy) for delayed union or nonunion who received bone marrow aspirate concentrate (BMAC) supplementation. Non-union was defined according to the U.S. Food and Drug Administration (FDA) when a minimum of nine months has elapsed since the injury and the fracture site has not shown any signs of healing for the final three months (18). Conversely, a delayed union was diagnosed when a fracture showed no healing progression after six months or less in accordance with average anticipated time.

All the data were collected from the digitalized medical records. The variables considered were age, sex, fracture site, type of healing problem (delayed union/nonunion) and initial treatment that led to delayed union/nonunion. Subsequently, type of definitive surgical treatment was documented including fixation method and any use of allograft augmentation. In all cases bone marrow aspiration concentrate was obtained using a BMAC (Joint S.r.l., Italy) kit for aspiration and processing. After the percutaneous aspiration from iliac crest, preparation procedure according to the manufacturer's instructions was carried out. The resulting BMAC was mixed with allograft or was injected percutaneously in the fracture site. When mixed with cancellous allograft, BMAC was also added with fibrin glue to obtain a stable and cohesive construct.

Patients were followed up radiographically and clinically during the postoperative period. The primary outcome was fracture union, determined as the presence of valid bone bridges on ≥3 cortices. In addition, patients were monitored for any complications occurred during evaluation period.

*Statistical analysis*

All data were collected and analyzed using Microsoft Excel. In the present study only descriptive statistics were used. Data were presented as means for continuous variables or percentages for categorical variables.

## Results

The study population included 11 patients with mean age at the time of surgery of 61 years (range 46-84). There were seven female (64%) and four male patients (36%). Tibia was the most frequently involved fracture site (45% of cases), followed by femur (36%). Other fracture sites included humerus and clavicle. Majority of patients had fracture nonunion (73%), while delayed union was diagnosed in 27% of cases. Nine patients (82%) were treated surgically for their initial injury and two (18%) underwent a conservative treatment prior to the diagnosis of healing impairment (Table 1.).

Two patients (18%) were treated with circular external fixator and percutaneous injection of BMAC alone. All other patients (82%) received the combination of internal fixation (plate/nail) and cancellous allograft with BMAC supplementation (Table 2.).

All of 11 patients (100%) achieved union after treatment, with a mean time to radiographic union of 6.5 months (range 4–12). None of the patients presented complications during the evaluation period. In detail, no patients suffered from donor site morbidity, hematoma or wound complications at the iliac crest BMAC harvesting site (Table 2.).

## Discussion

Different factors can compromise the process of bone healing. Both mechanical stability and biological environment (availability of osteogenic cells, osteoinductive mediators and osteoconductive scaffold), as well as adequate vascularity and host systemic condition, are all important for successful bone healing(1). An accurate correlation between the exact cause of

**Table 1.** Patient demographic and baseline clinical data.

| **Age (mean)** | **61 years (range 46-84 years)** |
|---|---|
| **Sex** | 7 Female (64%) : 4 Male (36%) |
| **Fracture location:** | |
| **Femur** | 4 (36%) |
| **Tibia** | 5 (45%) |
| **Humerus** | 1 (9%) |
| **Clavicle** | 1 (9%) |
| **Type of healing disorder:** | |
| **Delayed union** | 3 (27%) |
| **Nonunion** | 8 (73%) |
| **Treatment prior to delayed union/nonunion:** | |
| **Surgical** | 9 (82%) |
| **Conservative** | 2 (18%) |

**Table 2.** Treatment and outcome results.

| **Treatment for delayed union/nonunion** | |
|---|---|
| **Internal fixation (plate/nail) and cancellous allograft with BMAC** | 9 (82%) |
| **External fixation with percutaneous injection of BMAC** | 2 (18%) |
| **Union rate** | 11 (100%) |
| **Mean time to radiographic union** | 6.5 months (range 4-12) |
| **Complications** | 0 (0%) |

nonunion and appropriate treatment strategy remains challenging (19). In fact, recent evidence suggests that simultaneous tackling of more than one healing factor can enhance the results and is preferable over 'monotherapy' (1,20). The autologous iliac crest bone graft (ICGB) is still considered to be the gold standard for treatment of nonunions providing osteo-inductive and osteoconductive stimuli together with osteogenic cells. However, it has limited harvest supply and in the setting of larger bone defects alternative methods need to be considered (22). BMAC represents a valid alternative since it can be combined with various forms of allografts for volume augmentation and administrated percutaneously in the cases where structural graft is not required (1,7-10,22). In the present study majority of patients (82%) received BMAC in association with cancellous allograft for osteoconductive purposes. Furthermore, all patients in this group underwent surgical revision of internal fixation to address the mechanical stability of the fracture site. Only two patients (18%) received BMAC percutaneously. This was consistent with the choice of external fixation for mechanical stability management in an attempt to preserve the vascularity of fracture site. In both patients soft tissue envelope was at risk and further disturbance could have compromised the healing potential.

All of the patients (100%) in this case series achieved union. The mean time to radiographic union was 6.5 months, ranging from 4 to 12 months. The literature reports comparably high union rates using BMAC, while time to union varies greatly between different studies. Hernigou et al. evaluated the outcome of 60 patients with nonunion of the tibia treated with percutaneous injection of BMAC. Bone healing was reached in 88% of patients. Time to union was 8 weeks for closed and stage I open fractures and 14 weeks for stage II and IIIA open fracture (10). In the study by Kassem, 20 patients underwent percutaneous injection of BMAC for delayed union or nonunion after open reduction and internal fixation. Reported radiographic union rate was 95% after a mean of 2.95 months (23). Singh et al. obtained 83 % consolidation within 7 months (range 4-12) after percutaneous injection of BMAC for delayed union and nonunion of 12 fractures (24). Other studies using percutaneous administration of BMAC report similar results. Braly et al. had 82 % union rate within 4.1 months (range 1.7–6.4) when treating delayed union and nonunion of 11 tibia fractures (9). Connoly et al. obtained 88 % consolidation of 17 tibia nonunion within 21 weeks (range 15–30) (7). To our knowledge there is a lack of published studies that evaluate union rates with a BMAC and allograft mixture for delayed union and/or nonunion. In the study by Lin et al. results were compared between two groups of patients with long bone nonunions. The first group of 26 patients was treated with open repair and BMAC in association with cancellous allograft. In the second group 25 patients were treated with open repair and autologous iliac crest bone graft (ICBG). In their analysis BMAC and


**Figure 1.** Case of distal femur nonunion with mechanical plate failure (A). Patient was treated with internal fixation and BMAC associated with cancellous allograft (B-C). A fibrin glue was added to BMAC-cancellous allograft to obtain a stable and cohesive construct (B). Post-operative control (C). Follow-up images taken at 4 months demonstrate gradual fracture healing (D). At 9 months fracture completely healed which allowed for nail removal due to an ipsilateral femoral neck fracture requiring partial hip replacement (E).

allograft had a healing rate of 75%. They also found no significant difference between two groups since union rate for the ICBG cohort was 78%. (25). Thua et al. conducted a clinical trial that involved 18 nonunion treated with BMAC and cancellous allograft. The control group was composed of 9 patients treated with autologous cancellous bone graft from the iliac crest. In the group of BMAC/allograft healing was obtained in

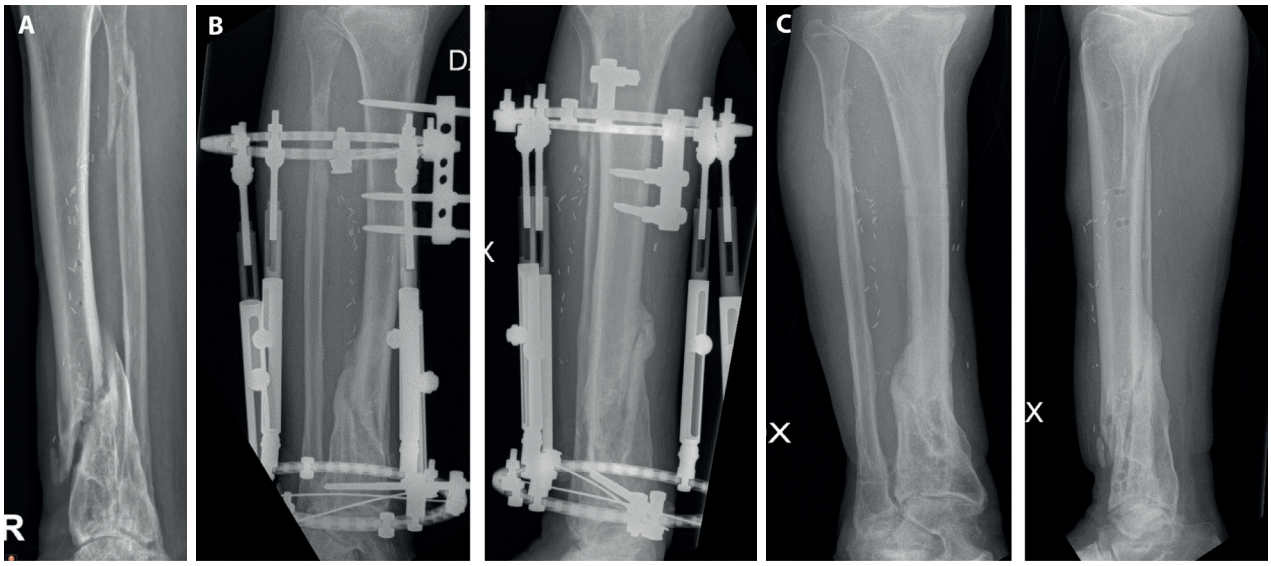


**Figure 2.** Case of distal tibia delayed union in patient initially treated conservatively (A). Patient underwent treatment with external fixator and percutaneous injection of BMAC: post-operative control (B). Fracture healed radiographically and clinically at 4 months (C).

94.4% of cases, while the time to union was 3.3 ± 0.9 months (range, 2 - 5 months). In the control group 88.9% fractures consolidated at mean 4.6 ± 1.5 months (range 3 - 7 months) (26). Possible reason for the variability in time of union could be linked to differences in scheduling of follow-up consultations between different studies. Longer periods between consecutive appointments means that consolidation could be confirmed later.

BMAC is generally considered to be a safe procedure, which is confirmed in our study. None of the patients presented complications at the iliac crest harvesting site or complications associated with BMAC administration. Nonetheless, adverse events are known to happen and have been reported in literature. The most common complication is hemorrhage followed by infection, donor site morbidity and persistent pain (27). In the study by Bain 54.890 cases of iliac crest biopsy procedures were evaluated retrospectively. In less than 0,05% of cases serious adverse events were reported (28). The complications associated with BMAC administration are scarcely documented and consist mainly of fat embolism, although such events have not been reported in humans (17).

Main limitations in this study include the retrospective design, limited sample size and substantial heterogeneity between analyzed subjects. Furthermore, there was no control group that received other types of treatment different than BMAC. Nonetheless, in our case series treatment with bone marrow aspirate concentrate was an effective and safe procedure.

## Conclusions

Current evidence supports bone marrow aspirate concentrate (BMAC) as a viable alternative for management of nonunions and delayed unions. Although this study has limitations, the results confirm that supplementary BMAC results in high rates of bone union and has a high safety profile. Nonetheless, further research is required to determine whether it performs better than other available solutions.

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**Ethic Committee:** Authors state that the protocol for the research project has been approved by a suitably constituted Ethics

Committee of the institution within which the work was undertaken and that it conforms to the provisions of the Declaration of Helsinki. The involved subjects gave informed consent to participate and patient anonymity has been constantly preserved.

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## References


1. Andrzejowski P, Giannoudis PV. The 'diamond concept' for long bone non-union management. J Orthop Traumatol. 2019 Apr 11;20(1):21.
2. Einhorn TA. Enhancement of fracture-healing. J Bone Joint Surg. 1995;77:940–956.
3. Bell A, Templeman D, Weinlein JC. Nonunion of the femur and tibia: an update. Orthop Clin N Am. 2016;47:365–375.
4. Harrell DB, Caradonna E, Mazzucco L, et al. Non-hematopoietic essential functions of bone marrow cells: A review of scientific and clinical literature and rationale for treating bone defects. Orthop. Rev. (Pavia) 2015, 7, 5691.
5. Fitzgibbons TC, Hawks MA, McMullen ST, et al. Bone grafting in surgery about the foot and ankle: indications and techniques. J Am Acad Orthop Surg. 2011;19:112–120.
6. Wilkins RM, Kelly CM. The effect of allomatrix injectable putty on the outcome of long bone applications. Orthopedics. 2003; 26(5 Suppl): s567-s570.
7. Connolly JF, Guse R, Tiedeman J, et al. Autologous marrow injection as a substitute for operative grafting of tibial nonunions. Clin Orthop Relat Res. 1991;266:259–270.
8. Gianakos A, Ni A, Zambrana L, et al. Bone marrow aspirate concentrate in animal long bone healing: an analysis of basic science evidence. J Orthop Trauma. 2016;30:1–9.
9. Braly HL, O'connor DP, Brinker MR. Percutaneous autologous bone marrow injection in the treatment of distal meta-diaphyseal tibial nonunions and delayed unions. J Orthop Trauma. 2013;27:527–533.
10. Hernigou PH, Poignard A, Beaujean F, et al. Percutaneous autologous bone-marrow grafting for nonunions. J Bone Joint Surg Am. 2005;87-A:1430–1437.
11. Agarwal R, Williams K, Umscheid CA, Welch WC. Osteoinductive bone graft substitutes for lumbar fusion: A systematic review. J Neurosurg Spine. 2009; 11(6): 729-740.
12. Burwell RG. The function of bone marrow in the incorporation of a bone graft. Clin Orthop Relat Res. 1985;(200) (200):125-141.
13. Lindholm TS, Urist MR. A quantitative analysis of new bone formation by induction in compositive grafts of bone marrow and bone matrix. Clin Orthop Relat Res. 1980;(150)(150):288–300.
14. Liebergall M, Schroeder J, Mosheiff R, et al. Stem cell-based therapy for prevention of delayed fracture union: A randomized and prospective preliminary study. Mol Ther. 2013; 21(8): 1631-1638.
15. Salama R, Weissman SL. The clinical use of combined xenografts of bone and autologous red marrow. A preliminary report. J Bone Joint Surg (Br). 1978; 60(1): 111-115.
16. Tiedeman JJ, Connolly JF, Strates BS, Lippiello L. Treatment of nonunion by percutaneous injection of bone marrow and demineralized bone matrix. an experimental study in dogs. Clin Orthop Relat Res. 1991 Jul;(268):294-302.
17. Imam MA, Holton J, Ernstbrunner L, et al. A systematic review of the clinical applications and complications of bone marrow aspirate concentrate in management of bone defects and nonunions. Int Orthop. 2017 Nov;41(11): 2213-2220.
18. Wittauer M, Burch MA, McNally M, et al. Definition of long-bone nonunion: A scoping review of prospective clinical trials to evaluate current practice. Injury. 2021 Nov;52(11):3200-3205.
19. Nicholson JA, Makaram N, Simpson A, Keating JF. Fracture nonunion in long bones: A literature review of risk factors and surgical management. Injury. 2021 Jun;52 Suppl 2:S3-S11.
20. Calori GM, Mazza E, Colombo M, Ripamonti C, Tagliabue L. Treatment of long bone non-unions with polytherapy: indications and clinical results. Injury. 2011 Jun;42(6):587-90.
21. Le Nail LR, Stanovici J, Fournier J, Splingard M, Domenech J, Rosset P. Percutaneous grafting with bone marrow autologous concentrate for open tibia fractures: analysis of forty three cases and literature review. Int Orthop. 2014 Sep;38(9):1845-53.
22. Benshabat D, Factor S, Maman E, et al. Addition of Bone Marrow Aspirate Concentrate Resulted in High Rate of Healing and Good Functional Outcomes in the Treatment of Clavicle Fracture Nonunion: A Retrospective Case Series. J Clin Med. 2021 Oct 16;10(20):4749.
23. Kassem MS. Percutaneous autogenous bone marrow injection for delayed union or non union of fractures after internal fixation. Acta Orthop Belg. 2013 Dec;79(6):711-7.
24. Singh AK, Shetty S, Saraswathy JJ, Sinha A. Percutaneous autologous bone marrow injections for delayed or non-union of bones. J Orthop Surg (Hong Kong). 2013 Apr;21(1):60-4.
25. Lin K, VandenBerg J, Putnam SM, et al. Bone marrow aspirate concentrate with cancellous allograft versus iliac crest bone graft in the treatment of long bone nonunions. OTA Int. 2019 Mar 12;2(1):e012.

26. Thua T, Bui D, Nguyen DT, et al. Autologous Bone Marrow Stem Cells combined with Allograft Cancellous Bone in Treatment of Nonunion. Biomed Res Ther 2015 Dec; 2, 29
27. Elattar O, Christophersen CM, Farber D. Pain and Complications Following Bone Marrow Aspirate Concentrate Harvested From the Iliac Crest in Foot and Ankle Surgery. Foot Ankle Spec. 2021 Jun 18:19386400211017379.
28. Bain BJ. Bone marrow biopsy morbidity and mortality. Br J Haematol. 2003 Jun;121(6):949-51.

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