

Multidirectional percutaneous drilling and autologous bone marrow injection for the treatment of femoral diaphyseal nonunions: a prospective interventional study

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Background: To examine the outcomes of multidirectional percutaneous drilling and autologous concentrated bone marrow (BM) transplantation for atrophic femoral diaphyseal nonunion characterized by intact hardware and mechanical stability at the nonunion site.

Methods: Fourteen patients (22–63 years of age) were admitted to our hospital with atrophic femoral diaphyseal nonunion. All patients were treated with a combination of multidirectional percutaneous drilling and autologous concentrated BM transplantation. Radiographic evaluation was conducted every month after transplantation until bone healing was achieved.

Results: Bony union was achieved in 13 of the 14 patients (92.9%) after an average of 3.9 months (range: 2.5–6 months). The average radiographic union scale in tibial (RUST) scale score improved significantly from the preoperative period (6.15 ± 1.21) to follow-up (11.23 ± 0.73 ; $P < 0.05$). The mean follow-up after transplantation was 31.4 ± 9.5 months (range: 18–50 months). At the final follow-up, the quality of function had improved significantly, allowing a return to normal activities.

Conclusion: Combined multidirectional percutaneous drilling and autologous concentrated BM transplantation is an easy, safe, inexpensive, and efficacious method to treat atrophic femoral diaphyseal nonunion characterized by intact hardware and mechanical stability at the nonunion site.

Trial registration number: ISRCTN29808592

Keywords: autologous bone marrow injection, multidirectional percutaneous drilling, femoral diaphyseal fracture, nonunion

Introduction

Diaphyseal femoral fractures occur in both the young and the elderly. Their causes are diverse, as are the treatment options used to treat both the fractures and the associated injury.¹ Current methods include intramedullary nailing, plate fixation, and external fixation. While the results are generally favorable, delayed union or nonunion occurs in some cases. Böstman et al reported a 4% delayed or nonunion rate in fractures treated with locking plate fixation.² Reamed interlocking intramedullary nailing was shown to yield better clinical results than plate fixation, with a nonunion rate of 0.9–1.1%.^{3,4} However, despite these improved outcomes, patients with nonunion of the diaphyseal femur will inevitably suffer serious complications,

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including limb deformity or shortening, degeneration of neighboring joints, and local pain.

The treatment of nonunion is a challenge to orthopedic surgeons. In patients with nonunion of diaphyseal femoral fractures, various treatment strategies based on the above-described methods have been proposed. A prerequisite is careful classification of the nonunion, as this will guide the treatment choice. For patients with atrophic femoral diaphyseal nonunion, autologous cancellous bone is a fairly common practice, with the most common autologous graft donor site being the iliac crest.⁵ Autologous bone grafts, analogous bone grafts, and bone substitutes are additional therapeutic options.⁶ The complications that follow treatment include donor site pain, blood loss, increased operative time, and a risk of infection.^{7,8} The incidence of morbidities related to bone grafts is as high as 22%, with 12-month donor site pain occurring in up to 45% of patients.^{9,10}

To minimize the drawbacks associated with traditional bone grafting, percutaneous approaches have been developed for harvesting autologous bone marrow (BM).^{11–13} These approaches are based on osteo-inducing cells harvested from the iliac crest and injected directly into the fracture site. BM grafted using this method is easy, safe, and relatively non invasive and can be performed under local anesthesia with minimal secondary local damage. However, not all patients who undergo this procedure experience satisfactory healing, and the incidence of nonunion after BM injection continues to be high, at 18–37%.^{14–16}

One difficulty in treating nonunion is that the involved site is stiff and not easily handled. In standard bone-grafting

procedures, resection of nonviable bone and the intervening nonunion tissue is necessary.¹⁷ However, in previously reported percutaneous BM grafting procedures, no attempts were made to remove the intervening callus or fibrous tissue from the nonunion site.^{13,16,18–20} This omission would make it difficult to inject the entire volume of BM, and the injected marrow may leak through the gap between bone and soft tissue. We, therefore, hypothesized that multidirectional percutaneous drilling of the nonunion site would produce an ideal incubation bed for fixing the BM graft in position while simultaneously promoting the revascularization of intervening fibrous tissue and inducing osteoinductive factors locally in the bone matrix, thus enhancing bone healing.

Materials and methods

Study population and protocol

This study was a single-center, single-group interventional study conducted at our hospital, a university teaching hospital, from January 2009 to September 2013. Patients aged >18 years with atrophic nonunion, and who underwent percutaneous autologous BM grafting with multidirectional percutaneous pre drilling procedures, were voluntarily enrolled in the study. Patients with local angular deformity, shortening, fixation problems, or mental comorbidities resulting in poor compliance were excluded. Thus, the final study population consisted of 14 patients with atrophic femoral diaphyseal nonunion who agreed to undergo this novel procedure. The characteristics of the patients are listed in Table 1. The nine males and five females had a

Table 1 Patient characteristics

Case	Sex	Age	Initial injury	Initial treatment	Time since injury (months)	Comorbidities
1	Male	44	Open	Plate	10	None
2	Male	25	Closed	IMN	13	Tobacco use
3	Male	30	Closed	IMN	19	Tobacco use
4	Female	28	Closed	IMN	18	None
5	Female	28	Closed	Plate	10	None
6	Male	38	Open	Plate	10	None
7	Male	22	Closed	IMN	17	Tobacco use
8	Male	29	Closed	IMN	11	None
9	Female	38	Closed	IMN	16	None
10	Male	63	Closed	Plate	10	Tobacco use
11	Male	39	Open	Plate	9	None
12	Female	42	Closed	Plate	9	Tobacco use/DM
13	Female	25	Closed	IMN	11	None
14	Male	22	Closed	IMN	9	None

Abbreviations: IMN, intramedullary nailing; DM, diabetes mellitus.

mean age of 33.8 years (range: 22–63 years). Eight non-unions involved the left femur and six the right femur. All patients had previously undergone plate or intramedullary nail fixation. Atrophic nonunion of a diaphyseal femoral fracture (International Classification of Diseases 10th edition [ICD-10] code M84.151) was diagnosed according to clinical signs and radiographic examinations. In all of the patients, >9 months had passed since the initial fixation. No visible progressive signs of healing at the fracture site had appeared during the 3 previous consecutive months, thus fulfilling the Food and Drug Administration's definition of nonunion. All data in this study were collected prospectively. Informed consent was obtained from all individual participants included in the study.

BM aspiration and concentration

BM was harvested according to a previously published method.²¹ Briefly, after the patients were placed under general anesthesia, a BM aspiration needle was inserted into the posterior iliac crest. The needle was reoriented repeatedly within the iliac crest to optimize the number of BM cells harvested. Samples obtained from each puncture point were pooled into a BM collection bag containing anticoagulant. Erythrocytes were removed by centrifugation for 10 mins at 1200 g. The remaining aggregates were then centrifuged for 10 mins at 3000 g to remove supernatant plasma and anticoagulants. Finally, a concentrate of BM aspirate (30–40 mL) was collected in a syringe for injection.

Multidirectional percutaneous drilling at the nonunion site and BM grafting

Under fluoroscopic guidance, multiple 4.0-mm steinmann pins were drilled into the nonunion site in various directions to push the intervening soft tissue away. After repeated drilling, a concentrated BM syringe needle was placed in the nonunion gap; the BM was slowly injected for 1 min, and the needle was gradually withdrawn. Figure 1 shows the steps of the procedure, and Figure 2 provides intraoperative photographs of a patient with femoral shaft nonunion.

Radiographic evaluation

Radiographic evaluation (plain anteroposterior and lateral radiographs) was conducted every month for 1 year after transplantation until bone healing was achieved. Healing at the four cortices (medial/lateral/anterior/posterior) was evaluated using the Radiographic Union Scale for Tibial fractures (RUST) classification system,²² which employs 4- to 12-point scales and sums the score for each of the four cortices. Three senior orthopedists judged the healing independently, with the final diagnosis based on the majority opinion.

Statistical analyses

All data were expressed as mean and SD of the mean using SPSS 22.0 software (IBM Corporation, Armonk, NY, USA). The univariate significance of the comparison between the preoperative and postoperative of RUST score was established through a independent-samples *t*-test.

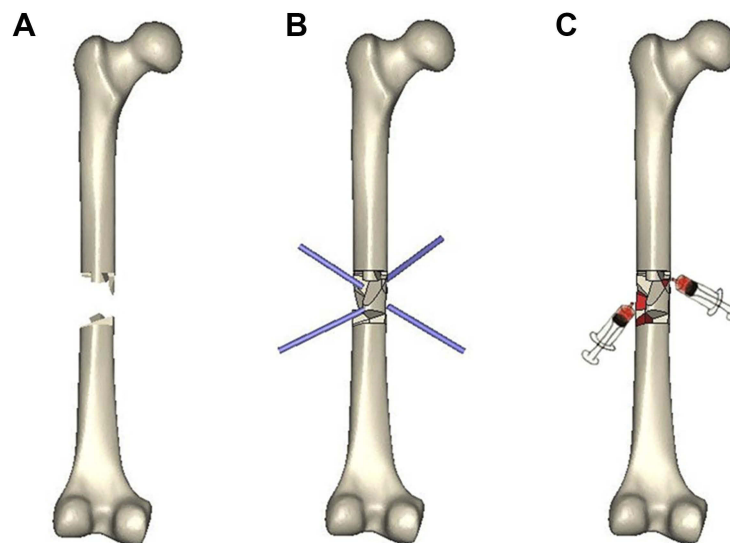


Figure 1 The steps of the procedure. (A) Fracture nonunion; (B) multiple drilling of the nonunion site from different angles; (C) autologous bone marrow grafting.

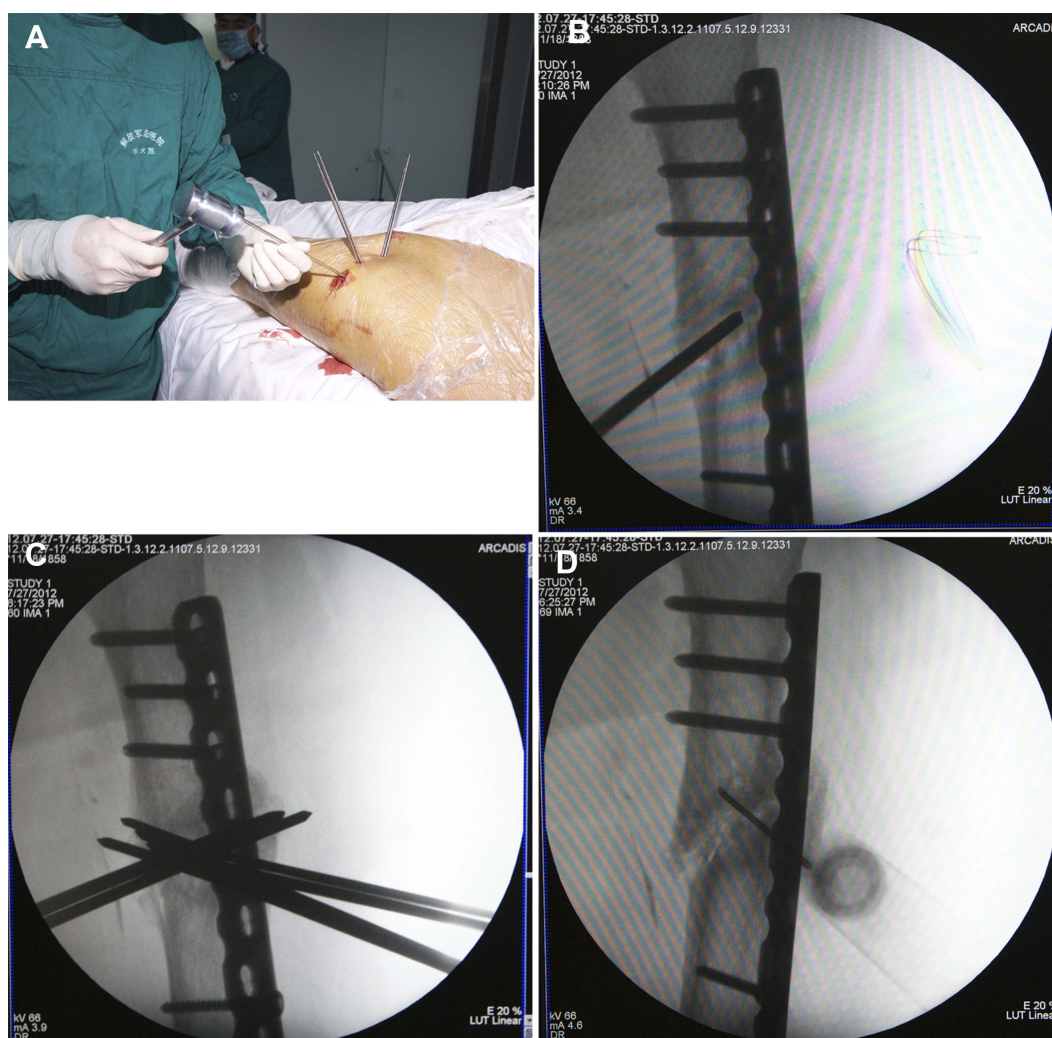


Figure 2 Intraoperative photographs of a patient with femoral shaft nonunion. (A) The drilling process; (B and C) fluoroscopy during drilling; (D) fluoroscopy-guided placement of the tip of a concentrated bone marrow (BM) syringe needle in the nonunion gap.

Results

All patients reported slight discomfort at the donor site for the first 2 days postoperatively, but the pain was managed sufficiently with oral pain killers administered during the first 24 hrs. No major complications were identified. Of the 14 patients, bony union was achieved in 13 (92.9%) after an average of 3.9 months (range: 2.5–6 months) (Figures 3, 4). Radiographic union was diagnosed by a RUST score ≥ 10 , and the results were confirmed by clinical examination. The average RUST score improved significantly, from 6.15 ± 1.21 preoperatively to 11.23 ± 0.73 at follow-up ($P=0.000$, $P<0.05$) (Figure 5). The mean final follow-up duration was 31.4 ± 9.5 months after transplantation (range: 18–50 months). By the final follow-up examination, the patients' quality of life had significantly

improved and a return to normal activities was possible. Only one patient failed to achieve bony union without signs of healing 3 months after BM injection. This patient received an additional plate and autogenous bone grafting at 3 months and achieved bony union within 6 months after the latter procedure.

Discussion

Femoral diaphyseal nonunion has long been a challenging clinical problem. Effective surgical treatment of these patients requires a detailed understanding of the pathophysiology and classification of nonunion.²³ Fracture union mainly depends on adequate mechanical stabilization and the biological environment (pro-osteogenic cells, growth factors, and vascularization) of the fracture site.^{24,25}

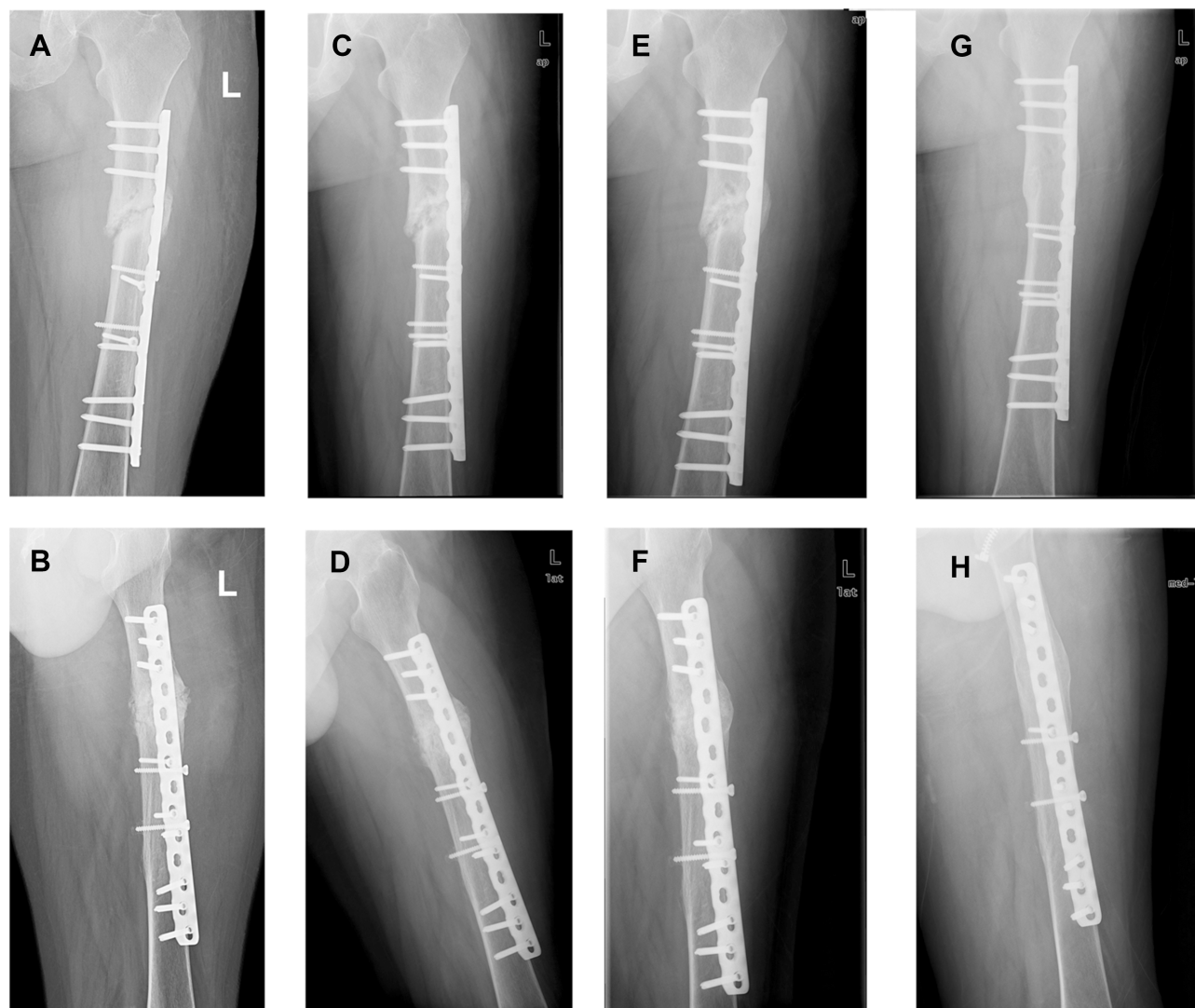


Figure 3 BM transplantation of a 44-year-old male patient. (A and B) Postoperative result immediately after multidirectional percutaneous drilling and autologous concentrated bone marrow (BM) transplantation in a 44-year-old male patient; (C and D) 1 month postoperatively; (E and F) bony union, achieved 3 months postoperatively; (G and H) complete remodeling of the callus obtained at 19 months postoperatively.

Hypertrophic nonunion is considered to arise from insufficient stability; in these cases, treatment primarily involves stabilization of the fracture. However, atrophic nonunion has a primarily biological, rather than mechanical, etiology²⁶ and thus requires a biological approach to treatment. In this study, the mechanical properties of the nonunion were carefully evaluated by radiographic examination. There were no fixation problems, and all cases were identified as atrophic nonunion. The lack of an appropriate biological stimulus was thus hypothesized to be a major factor leading to nonunion in the study patients.

The standard treatment for nonunion is autologous bone grafting, which is performed to accelerate osteogenesis by stimulating the local microenvironment at the

nonunion site. However, the autogenous bone originates mainly from the iliac spine and is harvested during a procedure that is relatively invasive and may cause pain, neurovascular injury, infection, or other complications at the donor site.

To minimize the drawbacks associated with traditional bone grafting, autologous BM grafting for nonunion has been employed, with mixed results. The first report of percutaneous BM grafting of delayed union and nonunion was by Healey et al, in 1990. Their patients had undergone lower-extremity resections for sarcomas affecting bone. Bony union was finally achieved in five of the eight patients (63%).¹⁴ With gradual improvements to the technique, bony re union rates after autologous BM grafting



Figure 4 Bone marrow (BM) transplantation of a 25-year-old female patient. (A and B) Radiographs of femoral shaft nonunion in a 25-year-old female patient; (C and D) postoperative result immediately after multidirectional percutaneous drilling and autologous concentrated BM transplantation; (E and F) 1 month postoperatively; (G and H) bony union, achieved 4 months postoperatively; (I and J) radiological results after removal of the intramedullary nail.

have reached 76–82% according to recent studies,^{15,16} but there remains considerable room for improvement.

Prior to this study, we carefully assessed the drawbacks associated with previously reported autologous BM grafting procedures.^{13,16,18–20,27,28} A major problem was that in none

of them, an attempt had been made to remove the intervening calluses or fibrous tissue from the nonunion site. We, therefore, designed a new procedure that combined the advantages of multidirectional percutaneous drilling with minimally invasive percutaneous supplementation of autologous

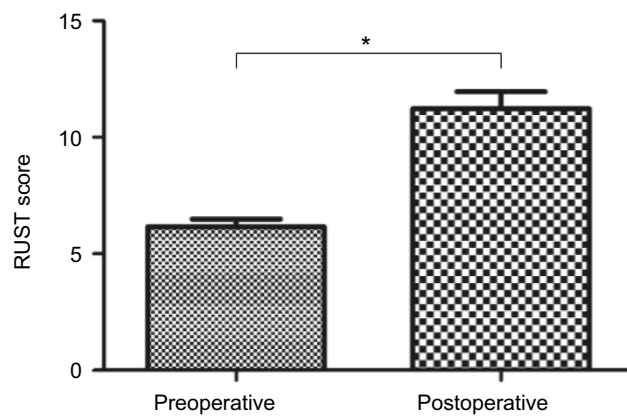


Figure 5 Analysis of the RUST score between preoperative and postoperative follow-up. Each bar represents the mean $\pm$ SD. * $P=0.000$, $P<0.05$.

Abbreviation: RUST, radiographic union scale in tibial.

concentrated BM, thus providing an ideal incubation bed and a strong biological stimulus. Patients treated by this technique achieved a bone union rate of 92.9% (13/14).

BM contains osteogenic progenitors, and its implantation can lead to effective bone regeneration. Both preclinical investigations and clinical studies have demonstrated that BM cells can differentiate into osteoblasts.^{29–33} In clinical practice, autologous BM is harvested from the iliac crest and implanted at the fracture site. Previous studies have shown a link between the number of progenitors in the graft and the volume of the callus around the nonunion site. In failed cases, the number of transplanted BM stem cells was low.³⁴ In our approach, with the aim of grafting as many osteogenic stem cells as possible, we grafted concentrated aspirates. Hernigou et al demonstrated that mononuclear cells could be concentrated by centrifugation of the BM aspirate, resulting in improved osteogenesis.²⁷ They also hypothesized that the concentrated BM includes stem and other mononuclear cells with osteogenic or angiogenic properties that influence the clinical outcome. Although culture-expanded human BM stromal cells have been used successfully for enhanced fracture healing in nonunion,³⁵ they must be expanded in vitro for several weeks to achieve a sufficient number of cells for transplantation. This delays treatment and increases both the culture-related contamination risk and therapy cost. By contrast, BM concentration is a simple, safe, clean, and low-cost procedure that allows the harvest and transplantation of cells shortly after their aspiration. This advantage recommends the use of BM cell concentrates, instead of expanded purified BM stromal cells, for bone cell therapy.

Resection of the scar and fibrous tissue at the nonunion site is considered essential for the treatment of atrophic nonunion.¹⁷ However, for percutaneous cellular transplantation, additional surgery to refresh the nonunion site may disrupt already compromised tissues and increase the risk of continued nonunion, or even lead to further complications such as infection. Moreover, a previous study in humans showed that nonunion tissue at the fracture gap contains osteogenic or chondrogenic progenitor cells.¹⁷ Three factors are thought to be essential to the healing process: an adequate number of osteoprogenitor cells, an appropriate scaffold (cell incubation bed), and biologically active molecules.²⁸ In nonunion treated with BM, the marrow is injected both into the gap in the nonunion and around the bones. However, it may be difficult to inject the entire graft and the BM may leak through the gap between the bone and soft tissue. Therefore, the existing fibrous tissue in the fracture gap should be removed, by chipping or drilling, to obtain an ideal cell incubation bed for placement of the concentrated BM. In our procedure, multidirectional percutaneous drilling was performed to cause local damage (microfracture), promote the revascularization of fibrous tissue, and accelerate the inflow of BM cells or growth factors from normal peripheral bone. In addition, hematomas caused by local microfracture help restart the healing process, while cells in the concentrated BM secrete angiogenic cytokines, which promote angiogenesis and thus improve osteogenesis.³⁶

The best indication for the combined use of multidirectional percutaneous drilling and autologous concentrated BM is the treatment of nonunion, especially oligotrophic or atrophic nonunion, which are less biologically active. In our study, this approach led to complete healing in 92.9% of the patients, all of whom had been diagnosed with atrophic nonunion. While the infection may be considered the main risks of the procedure, our study showed that it is safe, simple, and less invasive, and that local or systemic complications did not develop in any of the treated patients. Hernigou et al reported the clinical results of >1000 patients who underwent BM aspiration and none developed complications.¹⁹ There are also no reports of infection among any of the published studies on autologous BM grafting for nonunion.^{11–13,16,18–20,27–29,35} Additionally, because the material injected is autologous BM, there is no risk of disease transmission or an immune reaction.

Conclusion

The therapy proposed in this study combined two simple techniques: multidirectional percutaneous drilling and autologous concentrated BM transplantation under fluoroscopy. Together, they constitute a simple, minimally invasive, and inexpensive method to successfully treat femoral diaphyseal nonunion. Because the results were at least as good as those achieved with other methods, our study demonstrates the utility of this combined technique for treating aseptic nonunion characterized by intact hardware and mechanical stability at the nonunion site.

Ethical approval and informed consent

Ethical approval was obtained by the ethics committee of the Ethics Review Board of Chinese PLA General Hospital. Written informed consent was obtained from all participants.

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Disclosure

The authors report no conflicts of interest in this work.

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