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Bone Marrow Transplantation Followed by Growth Factors Injection in a Patient with Femoral Neck Nonunion: A Case Report

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Abstract

Background: Most fractures of femoral neck typically heal, but a significant proportion of fractures fail to heal, resulting in aseptic bone necrosis, delayed union or persistent nonunion. Specially, nonunion of fractured neck of femur in young adults is a serious problem. Some preclinical evidences show the therapeutic potential of autologous bone marrow for bone fracture healing; however, clinical outcome following of transplantation of bone marrow cells in patients with femoral neck nonunion has never been reported.

Case description: We describe a 57-year-old male who had a femoral neck nonunion and received autologous bone marrow transplantation, followed by growth factors injection. The primary endpoint of this study is to achieve radiological fracture healing (union) by evaluating anteroposterior images taken after and on 6th month, following bone marrow therapy and no serious adverse event occurred.

Literature review: To our knowledge, this is the first case in the literature of nonunion of femoral neck fracture treated with percutaneous autologous bone marrow transplantation.

Clinical relevance: This case suggests that autologous bone marrow transplantation, followed by plasma rich in growth factors (PRGF) could be considered as an exciting option to treat nonunion in femoral neck fracture.

Keywords: Femoral neck nonunion; Bone marrow; Transplantation; Plasma rich in growth factors

Introduction

With the increasing proportion of elderly people in the world, the number of hip fractures will approximate four million in 2025 [1,2]. Hip fracture, especially femoral neck fracture, gives rise to high morbidity, mortality, and more medical healthcare costs than other orthopaedic injuries [3-5]. Despite the ideal treatment for femoral neck fractures has been controversial since the early 20th century, arthroplasty is preferred for displaced fracture in patients older than 65 years, whereas nondisplaced fractures are managed with internal fixation [6]. While in young patients, the principles of treatment is to preserve the femoral head by anatomic reduction and stable fixation of the femoral neck [7,8]. The most common, early postoperative complications occurring after reduction and fixation are avascular necrosis (AVN) of the femoral head and nonunion, AVN being reported to range from 20% to 25% among patients [9]. Nonunion and osteonecrosis result in subsequent procedures, including revision surgery or arthroplasty, which lead more cost and risk to the patient [10]. In addition, there are challenges to prosthesis's lifespan life after prosthetic replacement in patients younger than 65 years old. Many scholars try some new approaches to the treatment of nonunion.

Autologous bone marrow transplantation has been proven to promote fracture healing in in vitro studies and also to significantly accelerate nonunion healing in animal studies [11,12] and clinical trials [10,13,14]. In this case, a patient with left femoral neck nonunion was successfully healed by percutaneous autologous bone marrow transplantation followed by growth factors injection.

Case Report

A 57-year-old male presented himself at our hospital complaining of left femoral neck delayed union with pain at the fracture site and disability of life. He had a left intra-capsular femoral neck fracture and had been treated by closed reduction and internal fixation with three cannulated screws at another hospital nearly 10 months before the initial presentation at our hospital. During the 8 months, after treatment in the hospital, the fracture site failed to heal in spite of being treated with low intensity pulsed ultrasound device and other conservative therapies. At the time of his presentation at our hospital, the patient complained of moderate pain at the fracture site causing disability of weight-bearing gait. The Harris score was only 28. He was clinically diagnosed as a nonunion according to the 1988 FDA Guidance Document Definition, he was clinically diagnosed as a nonunion because of requiring 9 months' duration of the nonunited fracture and with no evidence of progressive healing over the period of 3 months [15]. Anteroposterior and lateral radiographs led to diagnosis of non-infected bone defect type nonunion showing no bridging in fractured femoral neck (Figure 1A and 1B). The radiographs also revealed no apparent instability at the fracture site and absence of radiolucency around screws.

We obtained an informed consent from the patient for participating in clinical therapy regarding percutaneous transplantation of bone marrow in patients with nonunion. The clinical study protocol was approved by the ethics committees of our hospital. After the subject eligibility was confirmed, the patient was registered.

Material and Methods

The preparation of bone marrow gel

Surgery was performed under epidural anesthesia. The syringe

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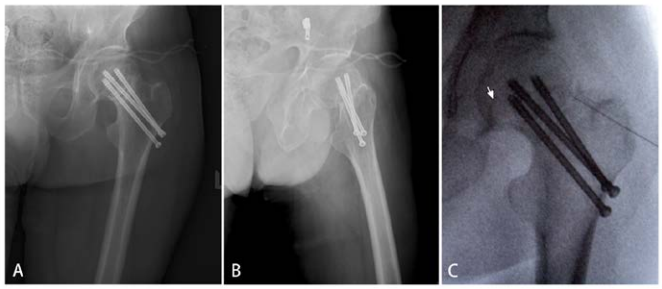

Figure 1: Images of femoral neck fracture non-union (A, B) and bone marrow gel injection (C).

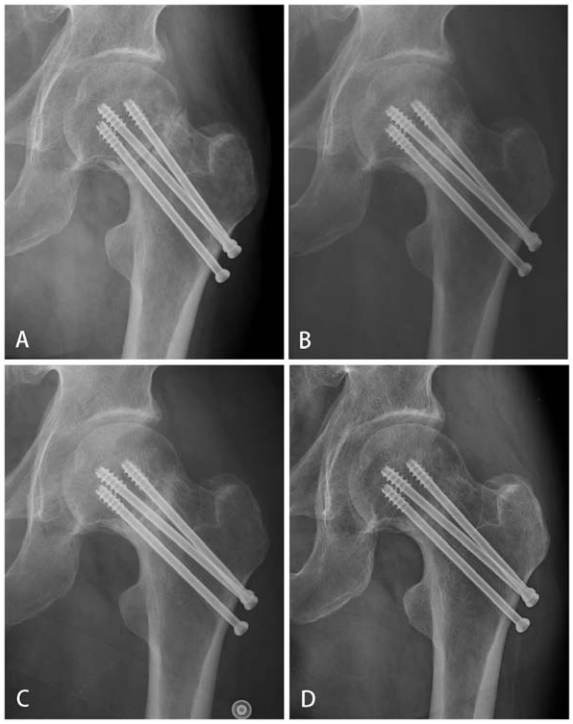

Figure 2: Aspect of the fracture after 3 months (A), 6 months (B), 8 months (C) and 12 months (D) of bone marrow gel injection.

was pre-added low molecular weight heparin (50 U/ml), and then 50-60 ml bone marrow was obtained by left anterior superior iliac spine paracentesis after the onset of anesthesia. Bone marrow was divided into three layers after centrifugation at 200 g for 6 minutes. After carefully removing the upper and middle interlayer into a new sterile centrifuge tube, the lower layer was centrifuged at 1000 g for 6 minutes. Then the serum supernatant was removed and added to the bone marrow centrifugate for the first time obtained by the first centrifugation. Myelomonocyte concentrates with a counted number of about 2-3×106 monocytes were prepared. After calcium chloride was added to a final concentration of 3 mg/ml and thrombin to 30 IU/ml, 14-16 ml bone marrow gel was obtained after completely mixed [16]. Then bone marrow gel was locally administered into the fracture site (bone defect site) using an injection needle under radiological fluoroscopic control (Figure 1C). Replacement of the original screws was not performed because of no apparent instability at the fracture site and absence of radiolucency around screws.

After 3 weeks, 2 courses of autologous cytokines and growth factors injections (one course per month) were followed. Infiltration was performed every 3 days for 3 times in one course.

The preparation of autologous cytokines and growth factors

Plasma rich in growth factors was prepared using two centrifugation techniques, similar to those described previously [17]. Heparinzed syringe was prepared in a Bio-safety Cabinet (Thermo scientific, USA) as follows: 100 μl 12500 U/ml low molecular weight heparin (Qilu pharmaceutical factory) was suck in a 50 ml sterile syringe (Weigao medical polymer materials production co.), then the skin was disinfected with alcohol or an iodine-based antiseptic solution before injection and 50 ml venous blood was collected into the heparinzed syringe.

The peripheral blood were centrifuged at 1048 $r \bullet min^{-1}$ for 25 min at room temperature (Thermo, USA) and then three layers were separated. Plasma rich in growth factors (PRGFs) in the middle layer (about 20 ml) was withdrawn and seperated into 3 vacuum tubes (Fisher, USA). The tubes were cryopreservation at -80°C overnight and then one of them was resuscitated in the 37°C water bath kettle in 5 minutes. After repeatedly freeze thawing more than twice, the plasma contains a variety of growth factors including platelet-derived growth factor, transforming growth factor-beta, vascular endothelial growth factor etc.

The thawing plasma was centrifuged at 3054 $r \bullet min^{-1}$ for 6 minutes (centrifugation radius is 9 cm) to separate the platelet fragmentation in the under layer. 10 $ug \bullet ml^{-1}$ deoxycycline (APP Pharm, USA) was added into the supernatant with a volume ratio of 1000:1 and then the plasma of autologous growth factors was obtained after filtration. The mean volume of autologous growth factors injected in our series was 4-5 ml for each infiltration.

Results

The patient was allowed to gait with partial weight bearing at 6 weeks and with full weight bearing at 6 months after PRGFs injection finished. 6 months after the treatment, the patient had no pain complaint with full weight-bearing gait, and Harris score was 88. At 3 months, anteroposterior radiograph showed some bone callus formation at fracture site after operation (Figure 2A). At 6 months, it provided diagnosis of achieved union showing the bony bridging in bone defect side (Figure 2B). At 8 and 12 months, we could not see the obvious fracture line on the X-ray (Figure 2C and 2D). At 16 months, fracture site of femoral neck had completed bony union (Figure 3A and 3B), then three cannulated screws were taken out at 16 months. The last anteroposterior radiograph was performed 3 months at three and a half month after the cannulated screws taken out (Figure 3C), and we could not see the fracture line at all, but only to see the faint outline of the cannulated screws in the femoral neck.

Taken together, the patient met the criteria of radiographical and clinical union as the primary end point in this treatment at 6 months. Eight months after the treatment, the patient had no symptoms relating to the fracture and autologous bone marrow transplantation. He could gait with full weight bearing. No serious adverse events relating to bone marrow administration, leukoapheresis, and transplantation occurred during the observation period.

Discussion

To the best of our knowledge, this is the first clinical report of

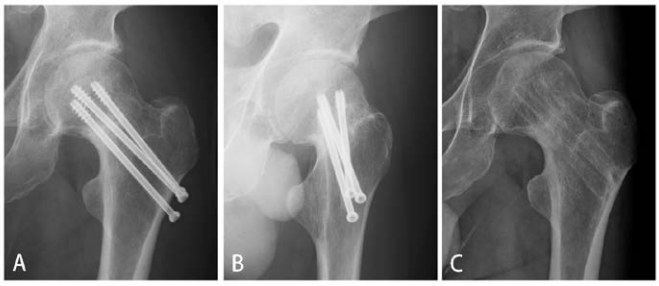

Figure 3: Fracture site of femoral neck had bony union afterat 16 months (A, B), and the three cannulated screws were taken out (C).

transplantation of autologous bone marrow, followed by autologous growth factors injection in a patient with femoral neck nonunion. The cell therapy successfully achieved bone union, which was confirmed by clinical symptoms and, radiograph as early as 6 months after the treatment. As for the safety evaluation in the first case, there were no serious adverse events for which could leada causal relationship to a denial of the cell therapy. could not be denied. In this case, no serious adverse events occurred during the 12-month follow up.

Femoral neck fracture is one of the most common hip fracture, of which the anatomy and, pathological characteristics have their particularities [18] has its particularity [16]. Femoral head and neck, mostly locate in the joint capsule. Once the femoral neck is fractured, the blood supply of the femoral head is damaged. What's more, the joint intracapsular bleeding increases intracapsular pressure, leading to further destruction of the femoral head blood supply. These are the reasons why the incidence of nonunion and osteonecrosis of the fracture of femoral neck is so high. The purpose of treatment of femoral neck fracture is to restore function and avoid fracture-related complications. Aseptic necrosis of the femoral head and nonunion are two major problems, especially in young patients [19]. Once osteonecrosis or nonunion happens, the patient oftenofen need total hip replacement. While, while the patient's age is relatively small, so the service lifespanlife of the prosthesis becomes a challenge. What's more, the prosthesis often requiresofen require further renovation treatmenttreatmen when it appearsappeares aseptic loosening [20].

In this case, the patient had gone to a number of hospitals, where he was suggested of the second surgery, including bone graft fixation or hemiarthroplasty. He refused because of the risks and complications caused due to surgery. In our hospital, taking into account the patient's wishes, as well as hospital stay and cost, we decided to carry out autologous bone marrow transplantation. Using autologous bone marrow transplantation for the treatment of femoral neck nonunion, several issues must be clear initially. Firstly, is autologous bone marrow transplantation treatment for femoral neck bone nonunion is valid? Several research groups have demonstrated the usefulness of local transplantation of total BM cells for fracture healing [21]. Tiedeman et al. tested the effectiveness of bone marrow or demineralized bone matrix(DBM) or both when injected percutaneously into a canine nonunion model and healing of the defect was evaluated roentgenographically, biomechanically, histologically, and biochemically 13 weeks postsurgery. They found bone marrow and DBM stimulated defect healing [11]. Percutaneous bone marrow injections were also able to heal bone defects in rabbit models [12]. Several clinical studies have also demonstrated that transplantation bone marrow can provide bone healing in nonunion [22]. This strategy has been supported by other investigators and bone marrow injections were widely used for tibial [13,14,21,23-25], femoral [25-27], humeral [13,26-28], and also for nonunionnonunions of radius and ulna [13,14,29]. Many surgeons now use bone marrow because of its biological value and low risk, so we decided to use autologous bone marrow transplantation instead of other surgeries.

PRGF has been used in delayed healing and in nonunion of fractures. Our clinical data are consistent with recent work by Seijas et al. who reported a case of delayed union fracture of the clavicle in which PRGF biological treatment was chosen before considering surgery. Three months after the final dose, final data showed healing of the bone completely [30]. In our study, PRGF-treated femoral neck continued to exhibit a greater rate of bone ingrowth compared to routine surgeries for delayed union or persistent nonunion treatment. Platelet-derived growth factors and transforming growth factors may stimulate the synthesis of collagen and fibronectin, followed by collagen deposition. Further preclinical/clinical studies would be warranted to compare the feasibility, safety and efficacy of the various modalities for bone repair.

A nonunion of femoral neck fracture in a young adult is difficult to treat. This case describes a successful use of percutaneous autologous bone marrow transplantation followed by growth factors injection in revision surgery. Based on this case report we suggest autologous bone marrow transplantation followed by growth factors injection as a possible approach for nonunion in femoral neck fractures, and it could be used as an alternative and, less invasive technique.

Acknowledgments

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References

1. Cooper C, Campion G, Melton LJ 3rd (1992) Hip fractures in the elderly: a world-wide projection. Osteoporos Int 2: 285-289.
2. Støen RØ, Lofthus CM, Nordsletten L, Madsen JE, Frihagen F (2014) Randomized trial of hemiarthroplasty versus internal fixation for femoral neck fractures: no differences at 6 years. Clin Orthop Relat Res 472: 360-367.
3. Osnes EK, Lofthus CM, Meyer HE, Falch JA, Nordsletten L, et al. (2004) Consequences of hip fracture on activities of daily life and residential needs. Osteoporos Int 15: 567-574.
4. Burge R, Dawson-Hughes B, Solomon DH, Wong JB, King A, et al. (2007) Incidence and economic burden of osteoporosis-related fractures in the United States, 2005-2025. J Bone Miner Res 22: 465-475.
5. Shi N, Foley K, Lenhart G, Badamgarav E (2009) Direct healthcare costs of hip, vertebral, and non-hip, non-vertebral fractures. Bone 45: 1084-1090.
6. Heetveld MJ, Rogmark C, Frihagen F, Keating J (2009) Internal fixation versus arthroplasty for displaced femoral neck fractures: what is the evidence? J Orthop Trauma 23: 395-402.
7. Lowe JA, Crist BD, Bhandari M, Ferguson TA (2010) Optimal treatment of femoral neck fractures according to patient's physiologic age: an evidence-based review. Orthop Clin North Am 41: 157-166.
8. Haidukewych GJ, Rothwell WS, Jacofsky DJ, Torchia ME, Berry DJ (2004) Operative treatment of femoral neck fractures in patients between the ages of fifteen and fifty years. J Bone Joint Surg Am 86-86A: 1711-6.
9. Ly TV, Swiontkowski MF (2008) Treatment of femoral neck fractures in young adults. J Bone Joint Surg Am 90: 2254-2266.
10. Daniel M, Mohammed S, Francis A, William Y, Joseph K, et al. (2015) Early result of hemiarthroplasty in elderly patients with fracture neck of femur. Niger Med J 56: 64-68.
11. Tiedeman JJ, Connolly JF, Strates BS, Lippiello L (1991) Treatment of nonunion by percutaneous injection of bone marrow and demineralized bone matrix. An experimental study in dogs. Clin Orthop Relat Res 268: 294-302.

12. Ma H-L, Chen T-H, Hung S-C (2004) Development of a new method in promoting fracture healing: multiple cryopreserved bone marrow injections using a rabbit model. Archives of Orthopaedic and Trauma Surgery 124: 448-454.

13. Sugaya H, Mishima H, Aoto K, Li M, Shimizu Y, et al. (2014) Percutaneous autologous concentrated bone marrow grafting in the treatment for nonunion. Eur J Orthop Surg Traumatol 24: 671-678.

14. Siwach RC, Sangwan SS, Singh R, Goel A (2001) Role of percutaneous bone marrow grafting in delayed unions, non-unions and poor regenerates. Indian J Med Sci 55: 326-336.

15. Guidance document for the preparation of investigational device exemptions and pre-market approval applications for bone growth stimulator devices. United States Food and Drug Administration, Rockville, USA.

16. Savarino L, Cenni E, Tarabusi C, Dallari D, Stagni C, et al. (2006) Evaluation of bone healing enhancement by lyophilized bone grafts supplemented with platelet gel: a standardized methodology in patients with tibial osteotomy for genu varus.[J]. J Biomed Mater Res B Appl Biomater 76: 364-372.

17. Soffer E, Ouhayoun JP, Dosquet C, Meunier A, Anagnostou F (2004) Effects of platelet lysates on select bone cell functions. Clin Oral Implants Res 15: 581-588.

18. Schweitzer D, Melero P, Zylberberg A, Salabarrieta J, Urrutia J (2013) Factors associated with avascular necrosis of the femoral head and nonunion in patients younger than 65 years with displaced femoral neck fractures treated with reduction and internal fixation. Eur J Orthop Surg Traumatol 23: 61-65.

19. Yang JJ, Lin LC, Chao KH, Chuang SY, Wu CC, et al. (2013) Risk factors for nonunion in patients with intracapsular femoral neck fractures treated with three cannulated screws placed in either a triangle or an inverted triangle configuration. J Bone Joint Surg Am 95: 61-69.

20. Hernigou P, Poignard A, Manicom O, Mathieu G, Rouard H (2005) The use of percutaneous autologous bone marrow transplantation in nonunion and avascular necrosis of bone. J Bone Joint Surg Br 87: 896-902.

21. Pountos I, Georgouli T, Kontakis G, Giannoudis PV (2010) Efficacy of minimally invasive techniques for enhancement of fracture healing: evidence today. Int Orthop 34: 3-12.

22. Nagoba BS, Selkar SP (2014) Autologous bone marrow-derived stem cells in wound healing. Int Wound J 11: 337.

23. Sebecic B, Gabelica V, Patrlj L, Sosa T (1999) Percutaneous autologous bone marrow grafting on the site of tibial delayed union. Croatian medical journal 40: 429-432.

24. Vaibhav B, Nilesh P, Vikram S, Anshul C (2007) Bone morphogenic protein and its application in trauma cases: a current concept update. Injury 38: 1227-1235.

25. Braly HL, O'Connor DP, Brinker MR (2013) Percutaneous autologous bone marrow injection in the treatment of distal meta-diaphyseal tibial nonunions and delayed unions. J Orthop Trauma 27: 527-533.

26. Matsuda Y, Sakayama K, Okumura H, Kawatani Y, Mashima N, et al. (1998) Percutaneous autologous bone marrow transplantation for nonunion of the femur. Nihon Geka Hokan 67: 10-17.

27. Wilkins RM, Chimenti BT, Rifkin RM (2003) Percutaneous treatment of long bone nonunions: the use of autologous bone marrow and allograft bone matrix. Orthopedics 26: s549-554.

28. Gross JB, Diligent J, Bensoussan D, Galois L, Stoltz JF, et al. (2015) Percutaneous autologous bone marrow injection for treatment of delayed and non-union of long bone: a retrospective study of 45 cases. Biomed Mater Eng 25: 187-197.

29. Sen MK, Miclau T (2007) Autologous iliac crest bone graft: should it still be the gold standard for treating nonunions? Injury 38 Suppl 1: S75-80.

30. Seijas R, Santana-Suarez RY, Garcia-Balletbo M, Cuscó X, Ares O, et al. (2010) Delayed union of the clavicle treated with plasma rich in growth factors. Acta Orthop Belg 76: 689-693.