The Journal of Arthroplasty xxx (2019) 1–6

Contents lists available at ScienceDirect

The Journal of Arthroplasty

journal homepage: www.arthroplastyjournal.org

Platelet-Rich Plasma-Incorporated Autologous Granular Bone Grafts Improve Outcomes of Post-Traumatic Osteonecrosis of the Femoral Head

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ARTICLE INFO

Article history:
Received 27 June 2019
Received in revised form
24 August 2019
Accepted 2 September 2019
Available online xxx

Keywords:
platelet-rich plasma
autogenous bone graft
core decompression
post-traumatic osteonecrosis of the femoral head
clinical results

ABSTRACT

Background: To investigate the effects of platelet-rich plasma (PRP)-incorporated autologous granular bone grafts for treatment in the precollapse stages (Association of Research Circulation Osseous stage II–III) of posttraumatic osteonecrosis of the femoral head.
Methods: A total of 46 patients were eligible and enrolled in the study. Twenty-four patients were treated with core decompression and PRP-incorporated autologous granular bone grafting (treatment group), and 22 patients were treated with core decompression and autologous granular bone grafting (control group). During a minimum follow-up duration of 36 months, X-ray and computed tomography were used to evaluate the radiological results, and the Harris hip score (HHS) and visual analog scale were chosen to assess the clinical results.
Results: Both the treatment and control groups had a significantly improved HHS ($P < .001$). The minimum clinically important difference for the HHS was reached in 91.7% of the treatment group and 68.2% of the control group ($P < .05$). The HHS and visual analog scale in the treatment group were significantly improved than that in the control group at the last follow-up ($P < .05$). Successful clinical and radiological results were achieved 87.5% and 79.2% in the treatment group compared with 59.1% and 50.0% in the control group ($P < .05$), respectively. The survival rates based on the requirement for further hip surgery as an endpoint were higher in the treatment group in comparison to those in the control group ($P < .05$).
Conclusion: PRP-incorporated autologous granular bone grafting is a safe and effective procedure for treatment in the precollapse stages (Association of Research Circulation Osseous stage II–III) of post-traumatic osteonecrosis of the femoral head.

Post-traumatic osteonecrosis of the femoral head (ONFH) is one severe complication of femoral neck fractures, which often causes femoral head collapse and osteoarthritis if left untreated. Prevention of the collapse of the femoral head and preservation of the function of the hip joint are 2 major therapeutic purposes in the early stages of ONFH [1]. To date, however, there is no ideal surgical approach to treat post-traumatic ONFH. Early recognition and surgical intervention for patients in the precollapse stages of post-traumatic ONFH are essential to improve clinical outcomes in hip salvage.

In recent years, core decompression is the most commonly used hip-preserving approach for treatment in the precollapse stage of ONFH [2–5]. The therapeutic theory of core decompression is to reduce intramedullary pressure, thereby preventing neurovascular compression and promoting new bone formation [6]. Although core decompression is beneficial for delaying or preventing the progression of ONFH, its effect in the natural course of precollapse ONFH remains unclear [7]. Since its implementation, core decompression has evolved from a simple technique to multiple techniques [8], and core decompression combined with autologous bone grafting through the core decompression track is becoming the most commonly used method [9]. Fresh autografts contain surviving cells

Hang Xian and Deqing Luo contributed equally to this work.

No author associated with this paper has disclosed any potential or pertinent conflicts which may be perceived to have impending conflict with this work. For full disclosure statements refer to https://doi.org/10.1016/j.arth.2019.09.001.

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https://doi.org/10.1016/j.arth.2019.09.001
0883-5403/

and osteoinductive proteins, such as bone morphogenetic proteins 2 and 7 (BMP-2, BMP-7), insulin-like growth factors (IGFs), fibroblast growth factors (FGFs), and platelet-derived growth factors (PDGFs). They contain the best material available for autografts from a biological point of view [10].

Platelet-rich plasma (PRP) is an autologous concentration of human platelets in a small volume of plasma at supraphysiologic levels. PRP is rich in autologous growth factors, such as PDGFs, transforming growth factor beta 1 and 2 (TGF-β1, TGF-β2), IGFs, and epidermal growth factors (EGFs), and it has been shown to have positive effects on the stimulation of tissue healing [11–13]. Because PRP is readily available and autologous PRP therapy is considered safe, the use of PRP in combination with autologous bone grafts could increase bone regeneration and bone density [14]. Based on the theory that autologous bone grafts and PRP could stimulate the growth and formation of bone, one procedure containing both of their advantages may have a reduplicated effect on treating post-traumatic ONFH. The purpose of this study is to conduct a randomized, single-blinded, prospective trial to investigate the efficacy and safety of PRP-incorporated autologous granular bone grafts for treatment in the precollapse stages of post-traumatic ONFH.

Materials and Methods

Subjects

A randomized, controlled trial was conducted between January 2008 and December 2013 at the single university teaching hospital. This study protocol was approved by our institutional review board, and written informed consent was obtained from all study participants. The inclusion criteria were post-traumatic ONFH of Association of Research Circulation Osseous (ARCO) stages II to III in patients aged between 18 and 55 years. The exclusion criteria were age older than 55 years, previous pathologic fractures, severe metabolic diseases (such as hemophilia, rheumatic arthritis, and diabetes mellitus), autoimmune diseases, blood disorders, and receiving invasive or surgical treatment on a hip for treatment of ONFH. To achieve good intraobserver and interobserver reliability, 1 experienced orthopedic surgeon and 1 experienced radiologist, who were blinded to the treatment protocol, worked together to make the final decision of the Tonnis grade/ARCO stage of the affected hip joints. The final diagnosis of ONFH mainly depended on the image findings from X-ray and computed tomography (CT) scanning, and all the patients underwent the same preoperative X-ray and CT imaging.

A population-based cohort in a single institution was established between January 2008 and December 2013 with a minimum follow-up of 36 months. Patients fulfilling the inclusion criteria were randomly divided into 2 groups: the core decompression and PRP-incorporated autologous granular bone graft group (treatment group), and the core decompression and autologous granular bone graft group (control group). The patients were randomized depending on randomized numbers generated using a sealed-envelope method. Sixty patients with post-traumatic ONFH were assessed for eligibility. Fourteen patients were excluded because they did not meet the inclusion criteria (7 patients), declined to participate (3 patients), or were lost to follow-up (4 patients). The remaining 46 patients were eligible and enrolled in the study. Twenty-four patients were treated with core decompression and PRP-incorporated autologous granular bone grafting, and the remaining 22 patients with core decompression and autologous granular bone grafting (Fig. 1). All the surgeries were carried out by the same surgical team.

PRP Preparation

Before inducing anesthesia, 90 mL of peripheral venous blood was withdrawn and collected in 9-mL tubes containing 3.8% (w/v) sodium citrate. The blood samples were centrifuged by a single spin at 500 g for 8 minutes at room temperature to separate the blood into 3 layers. The PRP was located in the intermediate layer between the layer of red blood cells and layer of acellular plasma (platelet-poor plasma). PRP was then collected in sterile tubes for the surgeries. The platelet counts in this plasma were 1.5-2 times greater than those in peripheral blood, with no leukocytes. About 8-10 mL of PRP was finally harvested using this method. Ten percent calcium chloride was used to activate the platelets just before application. The preparation and formulation of PRP were completed by the same surgeon for all surgeries in the treatment group.

Surgical Procedure

Under regional or general anesthesia, all patients underwent surgery on a fracture table. The hip was exposed through a lateral approach in the supine position. With excision of subcutaneous tissue and the lateral fascia, followed by blunt dissection of the vastus lateralis muscle, a longitudinal capsular incision exposed the anterior aspect of the hip. Previously cannulated screws or dynamic hip screws (DHSs) were removed. Core decompression was performed as observed using the C-arm radiograph. During the core decompression, a large single drill, the diameter of which was 12.5 mm, was used to remove the necrotic tissue of the femoral head. If the previous treatment method used DHSs, the existing large drill of the DHSs could be used to perform core decompression after removal of the previous fixation. The necrotic bone was then removed locally. The fresh autologous granular bones were harvested from an about 4 cm × 3 cm × 1.5 cm-sized piece of autogenous iliac crest and cut into an about 5 mm × 5 mm × 5 mm granular volume.

In the treatment group, the fresh autologous granular bones were mixed with the PRP and well packed in the necrotic area, and a bone tamp was used to pack the autologous granular bones in an appropriate density through the core decompression channel. In addition, sterilized medical bone wax was applied to block the end of the channel in order to avoid PRP and granular bone loss in all patients during the procedures. An intraoperative C-arm fluoroscope was used to confirm the adequacy of the grafting. The surgical procedure in the control group was the same as that in the treatment group, but without the PRP.

Postoperative Management

All patients received cefazolin for 24 or 48 hours. Postoperatively, active movements of the knee and hip were encouraged. Non-weight-bearing movements for 6 weeks were instructed, after which partial weight-bearing with the aid of a mobility aid was allowed for the following 10 weeks. Full weight-bearing was allowed after 16 weeks.

Assessment of Treatment Effects

We employed the Harris hip score (HHS) and visual analog scale (VAS) of hip pain to evaluate the function recovery of the hips. Patients were assessed preoperatively and at routine postoperative intervals of 3, 6, 12, 24, and 36 months by an experienced resident who was blinded to the patients' treatment. X-ray images including posteroanterior and lateral views and CT scans of the hips were also obtained at the same time points for each patient. The prime outcomes of the study were clinical and radiological failure. Clinical failure was defined as an HHS <70 points or a requirement for

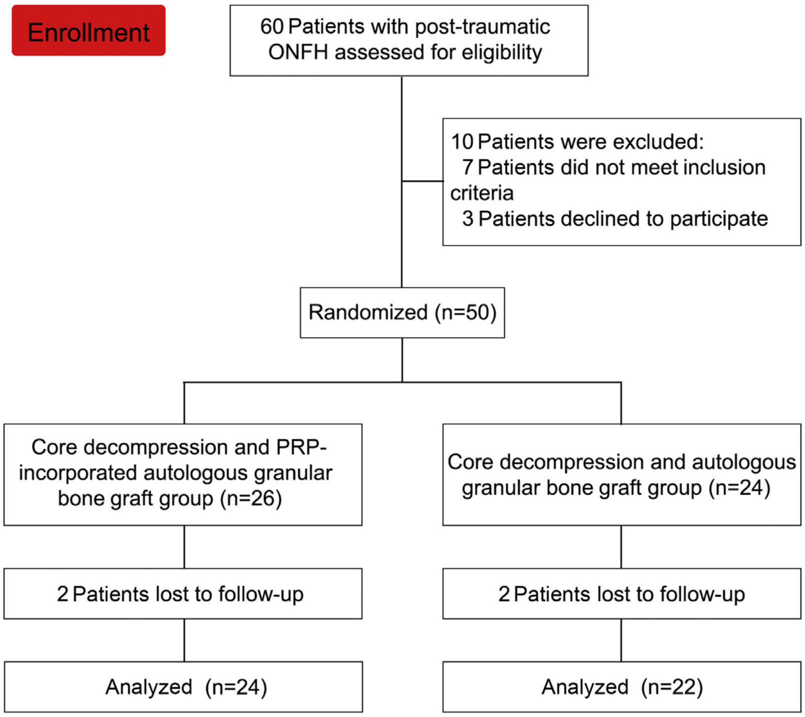

Fig. 1. Distribution of the study subjects from enrollment to the end of the study. ONFH, osteonecrosis of the femoral head; PRP, platelet-rich plasma.

further hip surgery. For each group, the percentage of patients who achieved the minimum clinically important difference (MCID) was also analyzed. The MCID was defined as a 10-point increase in the HHS. Radiological failure was defined as new collapse occurrence or increased collapse occurrence of greater than 2 mm [15]. The image reviewer and resident who performed follow-up were all blinded to the treatment protocol to achieve good intraobserver and interobserver reliability.

Statistical Analysis

Statistical analyses were performed using SPSS 19.0 for Windows. Descriptive statistics were used to record the baseline characteristics. The chi-square test was chosen to compare nominal data. Metric data were evaluated using the Mann-Whitney *U* test. Any values of *P* less than .05 were considered statistically significant.

Results

Detailed baseline patient characteristics are shown in Table 1. No significant differences were found in the baseline characteristics of the 2 groups, including age, gender, side of treated hip, Garden classification, time to original surgery, previous treatment method, follow-up period, ARCO stage, and preoperative HHS and VAS scores. The presence of poly trauma at the time of original injury included 2 cases of chest injury, 1 case of head trauma, and 5 cases of soft tissue contusion in the treatment group, and 1 case of chest injury, 1 case of clavicle fracture, and 4 cases of soft tissue contusion in the control group. The poly traumas were not contraindications of the surgical procedure. Patients who had undergone previous treatment including cannulated screw fixation and DHS fixation had undergone only 1 surgical procedure to treat the primary injury. All patients achieved primary wound healing after surgery, and there were no other complications due to the surgical procedure.

During a minimum duration of follow-up of 36 months after surgery, both the treatment and control groups had a significantly improved HHS ($P < .001$). The MCID for the HHS reached 91.7% in the treatment group and 68.2% in the control group ($P = .0449$). In addition, the HHS in the treatment group was significantly higher

Table 1
Baseline Patient Characteristics.

Characteristic	Treatment Group (N = 24)	Control Group (N = 22)	*P* Value
Mean age (range), y	28.3 ± 1.4 (16-39)	29.6 ± 1.7 (18-42)	.5723
Female/male, n	9/15	6/16	.4598
Right/left hip involved, n	17/7	12/10	.2529
Garden classification (III/IV)	10/14	7/15	.4894
Presence of poly trauma	8	6	.7539
Time to original surgery (range), h	25.1 ± 3.0 (6-64)	24.2 ± 3.6 (4-60)	.8563
Previous treatment			.8452
Cannulated screw fixation	17	15	
DHS fixation	7	7	
Time between fixation and onset of ONFH (range), mo	15.7 ± 0.7 (12-24)	17.1 ± 0.8 (10-24)	.2309
ARCO stage			.9868
IIa + IIb + IIc	6/3/2	6/2/1	
IIIa + IIIb + IIIc	8/4/1	7/5/1	
Lesion location			.9759
Medial	7	6	
Central	9	8	
Lateral	8	8	
Tonnis grade (0/1/2)	13/10/1	12/9/1	.9972
Follow-up period (range), mo	44.9 ± 1.7 (36-60)	46.2 ± 2.2 (36-60)	.6466
Harris hip score			
Preoperation (range)	70.3 ± 1.2 (59-82)	71.3 ± 1.3 (56-79)	.8077
Last follow-up (range)	86.5 ± 1.6 (68-96)	79.3 ± 2.4 (63-96)	.0254
The percentage of patients reaching the MCID (%)	22/24 (91.7)	15/22 (68.2)	.0449
VAS score			
Preoperation	4.1 ± 0.2	4.1 ± 0.2	.8859
Last follow-up	0.9 ± 0.2	2.0 ± 0.4	.0125
Successful clinical results (%)	21/24 (87.5)	13/22 (59.1)	.0284
Successful radiological results (%)	19/24 (79.2)	11/22 (50.0)	.0380

ARCO, Association of Research Circulation Osseous; VAS, visual analog scale; MCID, minimum clinically important difference; DHS, dynamic hip screw.

than that in the control group at the last follow-up ($P = .0254$). The VAS score significantly declined in the treatment group when compared with that in the control group ($P = .0125$). There was a higher percentage of successful clinical results in the treatment group in comparison to that in the control group. Successful clinical results were achieved in 21 of 24 patients (87.5%) in the treatment group. Three patients required total hip arthroplasty because of secondary degenerative arthritis at 12, 14, and 19 months after surgery, respectively, and were considered as cases of clinical failure. In the control group, successful clinical results were achieved in 13 of 22 patients (59.1%). Nine cases of clinical failure were present in the control group, and 7 cases were resolved with total hip arthroplasty due to secondary degenerative arthritis at 9, 11, 12, 18, and 20 months after surgery, respectively. Two patients underwent transtrochanteric rotational osteotomy 11 and 16 months after surgery, respectively. The radiological outcomes in the treatment group were also better than those in the control group ($P = .0380$). Successful radiological results were achieved in 19 of 24 patients (79.2%) in the treatment group compared with 11 of 22 patients (50.0%) in the control group (Table 1). The survival rates based on the requirement for further hip surgery as an end point were higher in the treatment group in comparison to those in the control group ($P = .0260$; Fig. 2). A typical case is shown in Figure 3.

Discussion

Post-traumatic ONFH is a major complication of femoral neck fractures that is difficult to cure and requires various solutions. There is no consistency in the reported incidence of post-traumatic ONFH, which has been about 20%-40% following femoral neck fractures [16], and even up to 86% [17]. Patients experience hip pain and hip joint dysfunction once collapse of the femoral head occurs. Therefore, preservation of the femoral head is the great predominant principle to treat patients in the precollapse stages of ONFH [18]. Core decompression is the most frequently used approach for treatment in the precollapse stage of ONFH, which can confer a therapeutic effect mainly through a reduction in intramedullary pressure, thereby alleviating pain and improving blood flow, leading to the regeneration of the necrotic zones, and finally delaying or preventing the development of ONFH [6,19].

Autologous harvested bones are frequently used for treating bone defects and promoting bone fusions as they promote bone regeneration and repair [20]. Grafting can be performed through the channel of core decompression, as well as by means of opening a small window in the femoral head or neck; the former is the most common method [7]. It is well known that many growth factors for

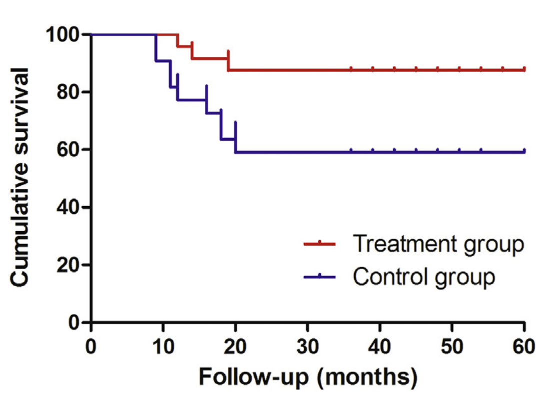

Fig. 2. Survival with the requirement for further hip surgery as the end point. The survival rate was significantly different between the treatment group (87.5%) and control group (59.1%) at 60 mo ($P = .0260$).

osteoinduction are contained in fresh bone autografts, such as BMP-2, BMP-7, FGFs, IGFs, and PDGFs; they form the best material available from a biological point of view, because they neither need exogenous donors nor have the problem of immune rejection [10,21]. Therefore, combination treatment including core decompression and autologous bone grafting shows great potential for the treatment of ONFH [22,23]. Fresh autologous bone can also be harvested easily and contains fresh red bone marrow, from which stem cells can be obtained [24,25]. Additionally, many studies have suggested that treating patients using stem cells in combination with core decompression shows significant improvements in the HHS in comparison to treating patients with core decompression only [23,26,27]. Hence, the use of fresh bone autografts seems to be a better choice than the use of other bone grafts. However, the handling of granular fresh autologous bone is of great importance in this procedure. Autologous bone graft absorption is a tough problem that needs careful consideration. The granules of autologous bones should not be too small in case of easy absorption. Bone scaffolds are necessary for newborn osteoblasts to migrate to and repair necrotic areas of the femoral head. The granules should be small enough to pass through the decompression channel and be large enough to respond to mechanical stimulation and avoid being absorbed in a short time. A granule size of about 5 mm × 5 mm × 5mm could meet the requirements, such that they are not absorbed until formation of the new bone trabecula.

The standard platelet concentration for transfusion has been based on PRP, and it has been reported that the concentrations of growth factors in PRP release and form lysates in patients with ONFH as much as in healthy individuals [28]. That is, PRP contains a high level of platelet, as well as the full complement of clotting factors. Several studies have demonstrated that PRP has a positive role in bone generation, and the use of PRP in combination with autologous bone grafts could effectively promote bone regeneration and improve bone density [29]. Platelets begin to secrete these proteins actively 10 minutes after clotting, and more than 95% of the presynthesized growth factors are secreted within 1 hour [30]. TGF-β and PDGFs could help facilitate in chemotaxis and mitogenesis of stem cells and osteoblasts, angiogenesis for capillary ingrowth, and bone matrix formation [31]. Although it is generally believed that platelets do not contain BMPs, Sipe et al [32] identified both BMP-2 and BMP-4 in platelet lysates, suggesting the possibility that these might contribute to the role of platelets in bone formation. TGF-β and PDGFs therefore represent a mechanism for sustaining long-term healing and bone regeneration, and even evolving into a bone remodeling factor over time [14]. During the process of bone repair and healing, platelets act as an exogenous source of growth factors that stimulate the activity of bone cells, based on their association with bone growth. The life span of a platelet in a wound and the period of the direct influence of its growth factors are always less than 5 days. It has been proven that with a combination of platelet growth factors including TGF-β, FGFs, and EGFs, an optimum condition is created for the stimulation of differentiation and proliferation of osteoblasts into osteogenic cells. Equally, proliferation is increased by the mitogenic action of PDGFs in mesenchymal stem cell differentiation, because TGF-β and EGFs are added [33]. Osteogenesis and osteoinduction of the decompression site may depend on the increase in and activation of marrow stem cells into osteoblasts, which also secrete TGF-β [34]; the extension of healing and activation of macrophages then replace the role of platelets as the primary source of growth factors after the third day [35]. Finally, bone regeneration is accomplished. In this study, fresh autologous granular bones in combination with PRP have the combined benefit of core decompression together with an osteoinductive and osteoconductive graft in the devitalized femoral head. Most patients exhibited a better HHS and VAS score

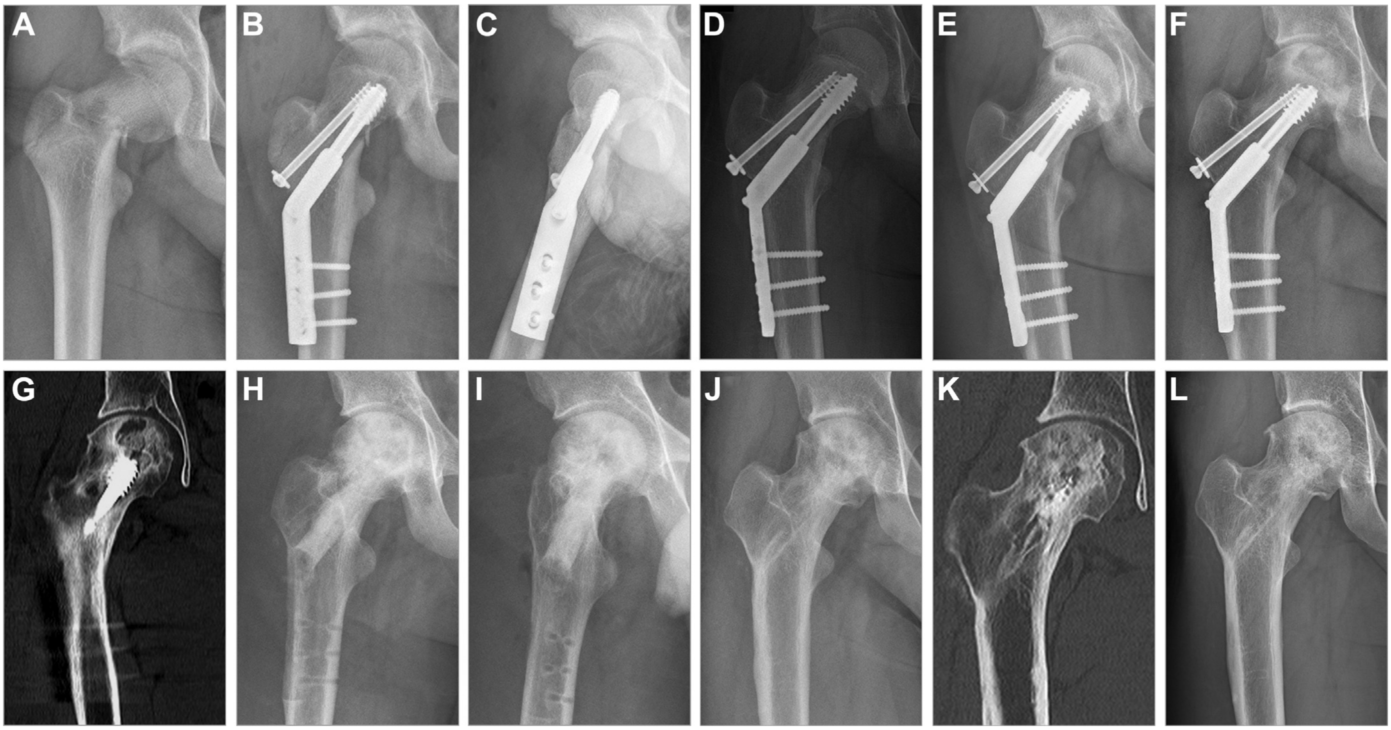

Fig. 3. Representative radiographic images from an 18-y-old male patient treated with core decompression and PRP-incorporated autologous granular bone grafting. (A) X-ray shows a femoral neck fracture with comminution in the previous injury. (B and C) X-ray on the day of previous treatment with DHS fixation. (D and E) X-ray at 6 and 12 mo after DHS fixation for the femoral neck fracture. (F and G) X-ray and CT show ARCO stage III ONFH 18 mo after DHS fixation for the femoral neck fracture. (H and I) X-ray on the day of core decompression and PRP-incorporated autologous granular bone grafting. (J and K) X-ray and CT scans 12 mo after surgery show consistency. (L) X-ray at 36 mo after surgery shows no further advanced femoral head collapse or osteoarthritis. PRP, platelet-rich plasma; DHS, dynamic hip screw; CT, computed tomography; ARCO, Association of Research Circulation Osseous; ONFH, osteonecrosis of the femoral head.

than those in the control group, which is a good predictor of hip function in the long-term follow-up.

However, this study presents several limitations. The sample size of this study was small, and there is still the need for a large number of patients to support the further advantages of core decompression and PRP-incorporated autologous granular bone grafting, which can also further reveal the mechanisms of treatment factors in this procedure. Meanwhile, the shape of the bone graft granules still needs further studies to be evaluated and explored in order to find a more rational shape. Lastly, we focused on the treatment of ONFH secondary to trauma when we first designed the study. This may be one underlying limitation of our study because whether it could be used to treat other causes of ONFH still has to be considered with caution and must be further validated, which could be the scope of future research.

Conclusions

In summary, PRP-incorporated autologous granular bone grafting appears to be an effective and safe method for treatment in ARCO stages II to III of post-traumatic ONFH, which could achieve better clinical and radiological results compared with autologous granular bone grafting alone. Combining fresh autologous granular bone and PRP may provide the void filler and structural support after necrotic bone removal, which offers a chance for the PRP and fresh bone graft to combine their advantages together during the core decompression procedure. The present study has demonstrated encouraging effects of this method and provides another choice for treatment in ARCO stages II to III of post-traumatic ONFH.

Acknowledgments

We acknowledge the key projects from the Nanjing Military Region during the 12th Five-Year Plan Period (No. 10MA073 and No. 12MA067).

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