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Combining Concentrated Autologous Bone Marrow Stem Cells Injection With Core Decompression Improves Outcome for Patients with Early-Stage Osteonecrosis of the Femoral Head: A Comparative Study

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ABSTRACT

The management of early-stage osteonecrosis of the femoral head (ONFH) remains challenging. This study aimed to evaluate the effects of core decompression and concentrated bone marrow implantation on ONFH. The study recruited 28 hips with early ONFH randomly assigned into two groups of core decompression with (group A) and without (group B) bone marrow injection. Patients were evaluated using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) questionnaire, Visual Analogue Scale (VAS) pain index, and MRI. The mean WOMAC and VAS scores in all patients improved significantly ($P < 0.001$). MRI showed a significant improvement in group A ($P = 0.046$) and significant worsening in group B ($P < 0.001$). Bone marrow stem cell injection with core decompression can be effective in early ONFH.

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Avascular necrosis (AVN) or osteonecrosis of femoral head (ONFH) is a relatively common disease that has multiple etiologies. The disease is usually bilateral. This condition usually affects the young [1]. The first presentation of ONFH may be painless, but ultimately severe pain and loss of movement occur. The disease usually advances with time and can result in the collapse of the femoral head and lead to end stage arthritis of the hip [1].

The pathogenesis and etiology of non-traumatic ONFH is not completely understood but stem cell involvement has been implicated as the initiating event [2].

There are various grading classifications of the disease with the Association Research Circulation Osseous (ARCO) proposing a new classification for ONFH based on magnetic resonance imaging (MRI) [3].

There is a number of treatment options proposed for this condition that includes the administration of bisphosphonates, anticoagulants, vasodilators, and biophysical modalities [4]. In addition, surgical treatment options such as the core decompression, vascularized

cortical bone graft implantation, and femoral osteotomies have been described [5].

The exact mechanism by which core decompression works is unknown. It is believed that core decompression leads to a reduction in the intraosseous pressure and also stimulates stem cell regeneration. In recent years modified core decompression is one of the most reliable and most commonly used methods for treating the early stages of ONFH [6]. However, modified core decompression does not always have satisfactory results because of the inadequate bone remodeling and reconstruction of the necrotic area [7]. This may be related to the relative inadequacy of osteoprogenitor cells in the osteonecrotic proximal femur [2]. Using bone morphogenic proteins and demineralized bone matrix may improve the results of modified core decompression [8–10].

The undifferentiated bone marrow mesenchymal stem cells (BMSCs) have been used for tissue regeneration in recent years because of their ability to differentiate into multiple cell lineages, including osteoprogenitor cells [2,8,11]. There are reports of encouraging outcome related to the injection of the BMSCs into the femoral head of patients with after drilling a hole into the avascular area in patients having atraumatic osteonecrosis [2,12–15]. It is known that an adequate number of autologous stem cells need to be injected into the femoral head with 2 million cells being considered as optimal [11].

The aim of the current prospective, randomized study was to evaluate the effect of implanting concentrated autologous bone marrow containing mononuclear cells (MNCs) in combination with a core decompression procedure on patients with early stage ONFH.

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Table 1
Baseline Characteristics of the Patients.

Variable	Group A (N = 14)	Group B (N = 14)
Side of treated hip		
Left (%)	10 (71.4%)	4 (28.6%)
Right (%)	4 (28.6%)	10 (71.4%)
Age (mean ± SD)	31 ± 11.4	26.8 ± 5.8
Gender (male/female)	9/5	10/4
Etiology		
Corticosteroids (%)	10 (71.4%)	9 (64%)
Idiopathic (%)	4 (28.6%)	5 (36%)
MRI findings (ARCO classification) ^a		
Class I (%)	3 (21.4%)	2 (14.3%)
Class II (%)	9 (64.3%)	7 (50%)
Class III (%)	2 (14.3%)	5 (35.7%)
VAS score (mean ± SD)	35.9 ± 4.5	38.6 ± 4.6
WOMAC score (mean ± SD)	32 ± 3.8	35.9 ± 2.7

^a At the baseline, the MRI findings in group A were not significantly different from the findings in group B. (*P* = 0.24).

Materials and Methods

This study was a prospective, randomized clinical trial, which included patients with non-traumatic ONFH with ARCO classification stages I, II, or III. The stages of ARCO classification are as follows:

- Stage 0—Positive histology with normal radiograph, computer tomography (CT), MRI, or scintigraphy
- Stage I—Positive MRI and/or bone scintigraphy with normal radiograph or CT
- Stage II—Radiographic changes in the femoral head including sclerosis, cysts, or osteoporotic changes of the femoral head
- Stage III—Radiographic sign of subchondral fracture (“crescent sign”)
- Stage IV—Radiographic sign of flattening of the femoral head
- Stage V—Radiographic sign of flattening of the femoral head and osteoarthritic changes such as decreased joint space and acetabular changes
- Stage VI—Complete joint destruction [3]

Patients with traumatic osteonecrosis and patients who were continuing steroid use were excluded from the study. All eligible patients were approached and consented for participation in the study. The hips were randomly assigned to two treatment groups: core decompression combined with injection of concentrated autologous bone marrow containing MNCs in to the femoral head (group A) or core decompression alone (group B). After inclusion, envelope technique was used to randomize the patients into either group. Only the surgeon

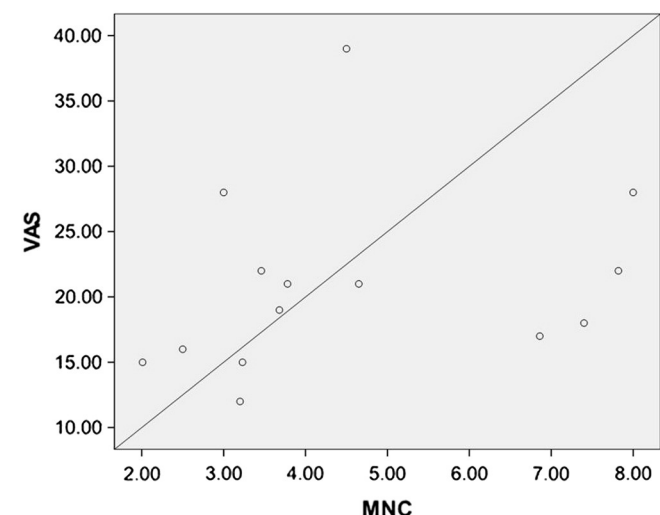


Fig. 1. The diagram showing the correlation between Total MNC count and VAS score. MNC, mononuclear cell; VAS, visual analogue scale.

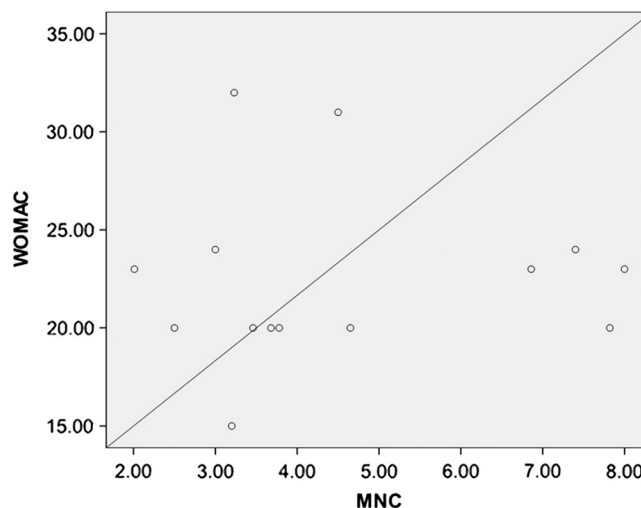


Fig. 2. The diagram showing the correlation between total MNC count and WOMAC score. MNC, mononuclear cell; WOMAC, Western Ontario and McMaster Universities.

and the operating room staff were aware of the group assignment and they were not involved in further follow-up of the patients. All surgical procedures were undergone under general anesthesia. So, the patients and physicians evaluating them were unaware of the group assignment. The study was approved by the ethical committee of the university and informed consent was obtained from the patients.

Twenty-eight hips in 18 patients were enrolled in the study. Ten patients had bilateral ONFH. After inclusion, a nurse was asked to open an envelope containing the study-group assignment for each hip and reveal it to the surgeon. A statistician who was not involved in the trial prepared the sequentially numbered, sealed, opaque envelopes. Group A contained 14 patients (14 hips) with ONFH who underwent core decompression therapy combined with injection of concentrated autologous bone marrow containing MNC into the femoral head. Group B consisted of 13 patients (14 hips) who were treated with core decompression therapy alone. Ten patients had bilateral ONFH. Nine patients with bilateral ONFH had 1 hip in group A and 1 hip in group B. There were 9 men's and 5 women's hips in group A and 10 men's and 4 women's hips in group B, respectively. The mean age of the patients in the study was 29.08 years (range, 18 to 56 years) with no statistically significant difference between the two groups (*P* = 0.22) (Table 1).

Surgical Procedure

Stem cells were obtained by bone marrow aspiration of the iliac crest. Following the preparation of the skin, a small incision was made over the iliac crest and a needle was advanced between the cortical tables of the crest. Approximately 200 ml of bone marrow aspirate was obtained. The aspirated bone marrow was kept in a sterile bag containing cell anticoagulant solution (citric acid, sodium citrate, dextrose) and sent to the bone marrow transplantation laboratory for processing. The aspirated bone marrow was filtered and washed to remove fat, clot

Table 2
VAS Score At The Baseline and After Intervention.

	Group A (mm)	Group B (mm)	Difference (95% CI)	<i>P</i> Value
Preoperative	35.9 ± 4.5	38.6 ± 4.6	-2.7 (-6.2 to -0.8)	0.13
6 months	15.1 ± 3.6	28.2 ± 3.9	-13.1 (-16 to -10.2)	<0.001
12 months	20.2 ± 4.8	31.4 ± 5.1	-11.2 (-15 to -7.4)	<0.001
18 months	18.7 ± 3.2	31.5 ± 4.7	-12.8 (-15.9 to -9.7)	<0.001
24 months	16 ± 3.7	32.1 ± 4.1	-16.1 (-19.4 to -12.8)	<0.001

Note: The changing trend was significantly affected by intervention (*P* < 0.001). Group A, bone marrow graft group; group B, control group; VAS, visual analogue scale; CI, confidence interval.

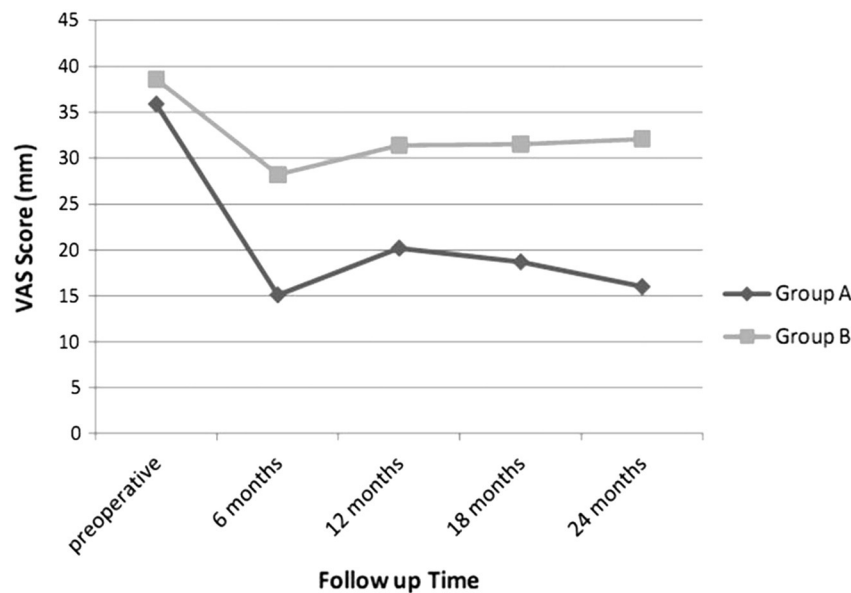


Fig. 3. VAS changing trend during 24 months after the intervention. Group A, bone marrow graft group; group B, control group.

debris, and red blood cells (RBCs). The bone marrow was centrifuged for 5–10 min at 400g. The heavier polynuclear cells were removed from the periphery at a flow rate of 100 ml/min for about 50 seconds. The lighter anucleated RBCs and plasma were collected from the center. All these procedures were done under sterile conditions. The prefabricated tubing set, centrifuge bowl, and seal were sterilized before each procedure. After separating MNCs containing stem cells, cell count was done. If the mean MNC count per ml was at least 2 million cells, the concentrated MNCs were sent back to the operation room in a sterile plastic bag containing anticoagulants for injection. The processing of the bone marrow aspirate took place in less than 60 minutes.

Core decompression was done using the classic technique. After the preparation of the skin a small incision was made on the lateral aspect of the hip, just below the greater trochanter. The lateral cortex was drilled using a 2.7 mm drill, and the drill advanced into the necrotic aspect of the femoral head under fluoroscopy. At this point a spinal needle was inserted and aimed at the necrotic femoral head through the opened canal and advanced within 2–3 mm of the joint line. Concentrated bone marrow cells were then injected into the lesion slowly and the entrance of the canal was closed with an allograft bone plug obtained from the corticocancellus iliac crest to prevent back leakage of the injected materials.

Postoperative Follow-Up

Patients were instructed to refrain from full weight bearing for three weeks.

Patients were evaluated with visual analog scale (VAS) and Western Ontario and McMaster Universities (WOMAC) osteoarthritis index preoperatively and immediately after surgery and at 6, 12, 18, and

24 months after the intervention. MRI images of the hip were obtained prior to surgery and at 6, 12, 18, and 24 months postoperatively. The MRI findings were staged based on the ARCO classification.

Statistical Analyses

Comparison between the two groups was performed using independent samples t-test for continuous data and Mann–Whitney U test for non-parametric data. The results at the last follow-up evaluation were compared to the baseline using paired t-test (for continuous data) and Wilcoxon (for non-parametric data). Repeated analysis of variance (ANOVA) (for continuous data) and Friedman (for non-parametric data) were used to evaluate the effects of intervention type on changing trend of outcomes during follow-up. A *P* value less than 0.5 was considered significant. All analyses were performed using SPSS v.16 (Chicago Inc).

Results

In group A, the mean volume of bone marrow aspirate obtained was 230 ± 6.7 ml which was concentrated to 58 ± 13 ml after processing. The aspirate contained 249 ± 112 white blood cells (WBC) per milliliter after concentration, which contained $33 \pm 8\%$ MNC. Total WBC was $13 \pm 5 \times 10^8$ and contained $5 \pm 2 \times 10^8$ MNC for each patient. The correlation between the total MNC count and outcomes, including VAS and WOMAC scores, was analyzed. The correlation coefficient and *P* value were 0.47 and 0.09 respectively for total MNC count and VAS score and 0.078 and 0.79 for total MNC count and WOMAC score. There was no significant correlation between the total MNC count and outcomes (Figs. 1 and 2).

VAS Changes During Follow-Up

The mean VAS score was 35.9 ± 4.5 in group A and 38.6 ± 4.6 in group B at the baseline (*P* = 0.13) and reduced to 16 ± 2.5 in group A and 32 ± 4.4 in group B at 24 months post-intervention (*P* < 0.001). The mean VAS score in group A was significantly lower than group B at 24 months (*P* < 0.001). The trend of VAS scores from baseline to 24 months post-intervention were significant (*P* < 0.001) and their trends were significantly affected by therapeutic methods (*P* < 0.001) (Table 2, Fig. 3). In bilateral cases, the mean VAS score was 36.7 ± 3.4 in group A hips 37.9 ± 3.3 in group B hips (*P* = 0.19) and reduced

Table 3

WOMAC Score at the Baseline and After Intervention.

	Group A	Group B	Difference (95% CI)	<i>P</i> Value
Preoperative	32.2 ± 3.8	35.9 ± 2.7	−3.7 (−6.3 to −1.1)	0.006
6 months	12.7 ± 2.7	24.5 ± 5.1	−11.8 (−15 to −8.6)	<0.001
12 months	10.2 ± 1.8	23.5 ± 3.5	−13.3 (−15.5 to −11.1)	<0.001
18 months	10 ± 1.4	25.4 ± 4	−15.4 (−17.7 to −13.1)	<0.001
24 months	9.7 ± 1.8	27.2 ± 3.7	−17.5 (−19.8 to −15.2)	<0.001

Note: The changing trend was significantly affected by intervention (*P* < 0.001). WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; group A, bone marrow graft group; group B, control group; CI, confidence interval.

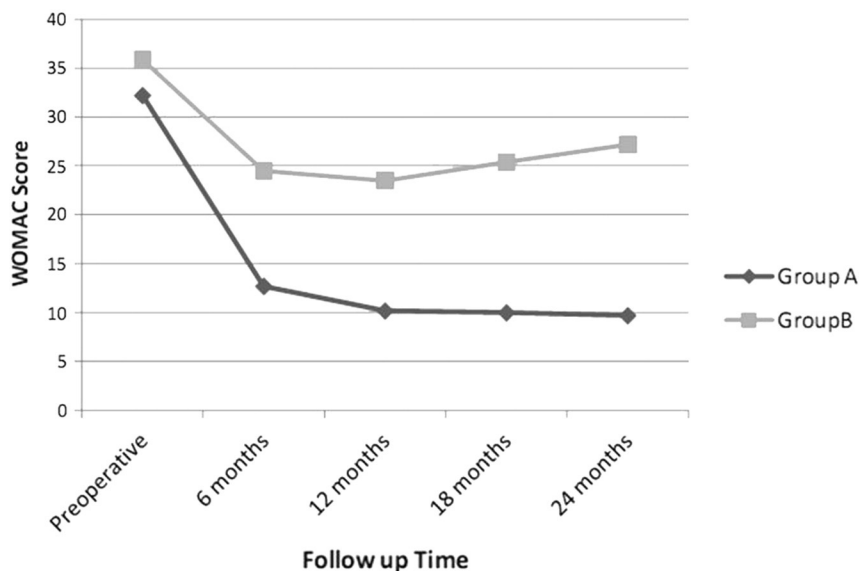


Fig. 4. WOMAC changing trend during 24 months after the intervention. Group A, bone marrow graft group; group B, control group.

to 17 ± 3.5 in group A and 33 ± 3.4 in group B at 24 months post-intervention ($P < 0.001$).

WOMAC Changes During Follow-Up

The WOMAC scores of group A improved from 32 ± 3.8 at the baseline to 9.7 ± 1.7 at 24 months ($P < 0.001$). In group B, scores improved from 35.9 ± 2.7 at baseline to 27.2 ± 3.7 at 24 months. The changing trend of WOMAC was significant in groups A ($P < 0.001$) and B ($P < 0.001$) for 24 months and their trends were significantly different ($P < 0.001$) (Table 3, Fig. 4). In bilateral cases, The WOMAC scores of group A hips improved from 30 ± 3.6 at the baseline to 11.4 ± 2.6 at 24 months ($P < 0.001$) and in group B hips, scores improved from 34.3 ± 3.1 at baseline to 26.8 ± 1.6 at 24 months.

MRI Changes During Follow-Up

At baseline, the mean MRI score was 1.93 and mean rank was 12.9 (median = 2) in group A and was not significantly different from group B with a mean score of 2.2, and mean rank of 16 (median = 2) ($P = 0.24$). Mean MRI scores and mean rank changed to 1.7 and 8.5 (median = 2) in group A and 2.8 and 18.6 (median = 3) in group B ($P < 0.001$). In bilateral cases, the mean MRI score was 1.89 and mean

rank was 11.9 (median = 2) in group A hips at baseline and was not significantly different from group B hips with a mean score of 2.1, and mean rank of 15 (median = 2) ($P = 0.26$). Mean MRI scores and mean rank changed to 1.74 and 8.9 (median = 2) in group A hips and 2.9 and 16.3 (median = 3) in group B hips of bilateral cases ($P < 0.001$).

The MRIs of patients in group B did not show changes within 6 months of intervention but some began to worsen after 6, 12, and 18 months (10 patients, 71%) out of which 3 patients (21%) underwent subsequent THA. The other 4 patients in the control group (28%) did not have any changes after 24 months. The changing trend in the control group was significant during follow-up ($P < 0.001$). In group A, no patient had an alteration in their MRI within 12 months but at 18 months one patient was found to have improved from stages III to II and at the last evaluation 2 patients had experienced marked improvement (one of them from stages II to I and the other one from stages III to II). There was no change in the MRI of the other 12 patients (85%) at the latest follow-up. The changing trend of group A was significant during follow-up ($P < 0.001$). The changing trend differed significantly in group A compared to group B ($P < 0.001$) (Figs. 5 and 6).

Table 4 shows the baseline and final stages of ONFH in the patients in both groups. The distribution of stages in the groups was not significant at baseline ($P = 0.58$). In both groups, the distribution significantly changed at 24 months ($P = 0.005$).

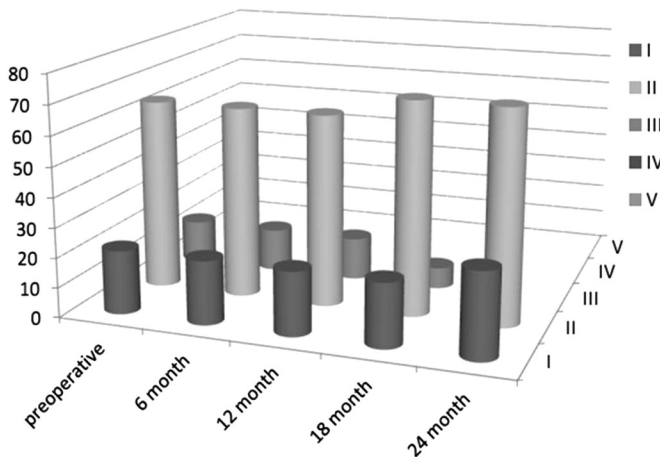


Fig. 5. MRI results according to ARCO classification in group A. The diagram shows the percentage of hips in each stage at 6-month intervals after surgery in group A.

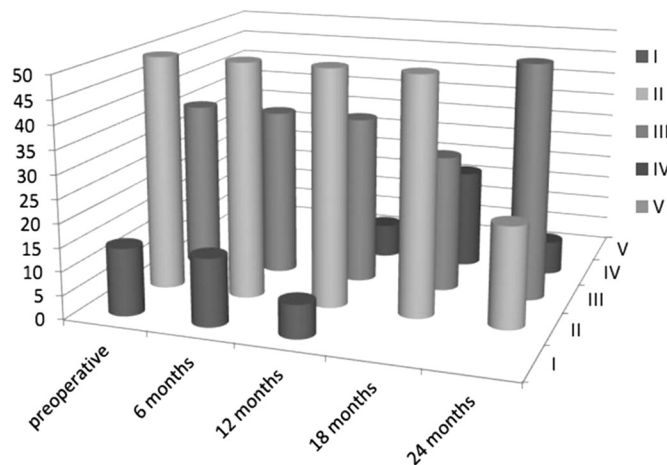


Fig. 6. MRI results according to ARCO classification in group B. The diagram shows the percentage of hips in each stage at 6-month intervals after surgery in group B.

Table 4
The Distribution of ARCO Stages of Femoral Head Osteonecrosis in Groups A and B.

Initial stages	No. of Hips	Group A						No. of Hips	Group B							
		Final Stage After 24 months							Final Stage After 24 months							
		I	II	III	IV	V	THA		I	II	III	IV	V	THA		
Stage I	3	3						2	1	1						
Stage II	9	1	8					7	2	4					1	
Stage III	2		2					5		2	1			2		

Discussion

Based on the results of the present study, it appears that injection of concentrated autologous bone marrow containing MNCs in combination with core decompression is an effective therapy for the early stages of ONFH. This treatment reduced pain and joint symptoms, delayed disease progression, and even improved the clinical and paraclinical condition of some patients.

Implanting of BMCs combined with core decompression for ONFH was proposed by Hernigou et al [16] in 2000. Subsequently some investigators have reported on their experience with stem cell therapy for osteonecrosis [12–14,23]. Gangji et al [12], in a small series, noted the progression of the disease in patients who received core decompression alone versus those who underwent core decompression combined with stem cell injection. This was consistent with the MRI findings of the present study showing that the disease did not progress in group A who received core decompression combined with stem cell injection versus those who received core decompression alone. In fact 3 patients in the stem cell injection group witnessed marked improvement in their symptoms as well as the MRI appearance. Two patients had an improvement from stage III to stage II and another patient improved from stage II to stage I. In contrast, ten patients in group B who underwent core decompression alone had a deterioration of their symptoms and the MRI appearance, of whom three patients required subsequent conversion to THA. Interestingly, two patients with ARCO stage III in group A also noted a marked improvement in their condition and the MRI appearance. So the improvement may be more marked in patients with worse MRI findings. The findings of our study are in keeping with those of some other studies [13–15,22].

The reason for the stem cell to result in an improved outcome may relate to the pathophysiology of ONFH. Decreased mesenchymal and progenitor cells have been reported in the proximal femur of patients with ONFH [17–19]. This may in turn lead to a reduction in angiogenesis, intramedullary vascularization, and osteoblasts, which could predispose patients to osteonecrosis. Loss of stem cells with osteogenesis potential may also adversely affect bone repair after osteonecrosis [19].

Thus, mesenchymal stem cells implanted into the necrotic area of the proximal femur can potentially differentiate into multiple cell lineages, resulting in bone formation vascularization and oxygen flow to the ischemic tissues, and accelerate fracture healing [8,20]. In a study by Song et al [21], histologic evidence of new bone formation in the femoral head after 6 weeks of mesenchymal cell transplantation has been shown. In the present study, 3 patients in the bone marrow-grafted group showed improvement, indicating the effectiveness of this treatment method as reported in the previously published literature.

Different methods of MNC instillation into the osteonecrotic area have been described, including direct injection through core cannal or via catheterization of the medial or lateral femoral circumflex artery or obturator artery [11]. Contrary to direct instillation of MNC through the core cannal, selective catheterization of the blood vessels is difficult, technically de-

manding, and largely limited because of low feasibility. The only essential step is to instill at least 2 million MNCs per ml into the necrotic area for effective regeneration [11]. In our study, the cell count of the final suspension ensured delivery of this recommended dosage.

The safety of autologous BMNC instillation into the necrotic area is supported by this study. There has been no report of infection or allergic reaction associated with BMNC instillation in the literature except for a case of superficial infection in a study by Yan et al [13].

In conclusion, implanting concentrated autologous bone marrow containing MNC in ONFH added to core decompression surgery could be effective in the early stages of ONFH. A small number of patients and short period of follow-up are the main limitations of the present study. More studies with larger sample size and longer follow-up are required to accept the role of stem cell therapy in ONFH. This treatment strategy could result in enrollment of stem cells and osteogenic cell progenitors in the treatment of osteonecrosis.

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