Original article

Concentrated autologous bone marrow aspirate transplantation versus conservative treatment for corticosteroid-associated osteonecrosis of the femoral head in systemic lupus erythematosus

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Abstract

Objective: To compare the outcomes of steroid-associated osteonecrosis of the femoral head in patients with systemic lupus erythematosus who underwent conservative treatment and concentrated autologous bone marrow aspirate transplantation

Methods: Osteonecrosis of the femoral head was classified according to the Japanese Investigation Committee system. Concentrated autologous bone marrow aspirate transplantation was performed by aspirating the bone marrow from both iliac crests and then transplanting it to the necrotic area after the core decompression. Patients with >2-year follow-up after the concentrated autologous bone marrow aspirate transplantation in our institution (Group I) and those with >2-year follow-up after the first hospital visit in a cooperative institution (Group II) were included in this study. After a randomized matching based on age, sex, type, stage, and etiology, the collapse rate in pre-collapsed stages and total hip arthroplasty conversion rate in all stages were compared between the two groups.

Results: After the matching adjustment, 33 pairs of hips were included. Preoperatively, 1, 2, 16, and 14 hips were classified as types A, B, C1, and C2, respectively, and 15, 13, 2, and 3 hips were classified as stages 1, 2, 3A, and 3B, respectively. The collapse rates in the pre-collapsed stages were 68% and 39% in Groups I and II, respectively. Total hip arthroplasty conversion rates were 33% and 45% in Groups I and II, respectively. However, Group I had significantly higher and lower conversion rates in stages 1 and 3, respectively (both $P<0.05$).

Conclusion: Conservative treatment may be preferable in stage 1 hips. In addition, concentrated autologous bone marrow aspirate transplantation may prevent further collapse in stage 3.

Key words: Osteonecrosis of the femoral head, joint-preserving surgery, concentrated autologous bone marrow aspirate transplantation, matching adjusted comparison

Introduction

In Japan, non-traumatic osteonecrosis of the femoral head (ONFH) is classified as ischemic, aseptic, and atraumatic and is mainly associated with corticosteroid use (51%). Among patients with steroid-associated ONFH, 31% were diagnosed with systemic lupus erythematosus (SLE), the most common underlying disease[1–3]. The peak ages of ONFH onset are aged 40 years for men and 30 years for women[1].

ONFH with broad necrotic areas is associated with unsatisfactory prognosis, with a collapse rate of 60–86%[4–6].

Accordingly, total hip arthroplasty (THA) is frequently performed for collapsed hips, with a THA conversion rate of 44%[7]. As ONFH onset occurs at younger ages than osteoarthritis, the duration of prosthetic survival in THA is a problem for patients with ONFH. THA is not the first-line treatment for patients aged 20–30 years based on the prosthetic lifespan and dislocation risk. In addition, compared to osteoarthritis, osteonecrosis is highly associated with the long-term durability of THA[8]. Joint-preserving therapy is preferred for young patients with ONFH. However, the outcomes of these joint procedures are poorer for collapsed than for pre-collapsed hips[9, 10]. To prevent or reduce collapse, various joint-preserving therapies have been proposed, including femoral osteotomy, core decompression, vascularized bone grafting, and bone marrow transplantation. Bone marrow transplantation combined with core decompression has also been reportedly effective[11]. In 2003, concentrated autologous bone marrow aspirate transplantation (CABMAT) was first performed in our institution.

Although the outcomes of CABMAT-treated ONFH, including short-term CABMAT results in patients with SLE, have been reported[11, 12], these studies are greatly limited due to the lack of a control group.

The therapeutic effects of CABMAT were compared with those reported in a previous study on natural history, core decompression, and another method of bone marrow transplantation[12]. However, because age, sex, stage, type of ONFH, underlying disease, and follow-up period all differed among reports, a precise comparison was difficult. Although our institution (Group I) treated idiopathic ONFH with CABMAT, conservative management was performed in the cooperative institution (Group II). Accurate patient data (age, sex, etiology, follow-up period, type, and stage) were obtained from both institutions. Hence, the outcome of CABMAT is comparable with that of conservative therapy using a matching-adjusted approach.

This study aimed to compare the collapse rate and THA conversion rate of steroid-associated ONFH in patients with SLE treated by CABMAT with those of treated conservatively and to examine the curative effects of CABMAT.

Material and Methods

Patients

The study design was approved by the institutional ethical review committee of both institutions. Written informed consent to participate was obtained from all enrolled patients.

For precise matching comparisons, the Japanese Investigation Committee classification was used to independently define the types and stages of ONFH diagnosis and classification, respectively[13, 14]. Using these criteria, ONFH was classified into types A, B, C1, and C2 based on the location of necrosis using T1-weighted coronal images obtained by magnetic resonance imaging (MRI) and categorized into stages 1, 2, 3A, 3B, and 4 using anteroposterior and lateral plain hip radiographs. The types and stage classifications are defined as follows: type A, a necrotic lesion occupying one third or less of the weight-bearing portion; type B, a necrotic lesion occupying two thirds or less of the weight-bearing portion; type C1, a necrotic lesion occupying more than two-thirds of the weight-bearing portion but not extending laterally to the acetabular edge; type C2, a necrotic lesion extending laterally to the acetabular edge; stage 1, an abnormality detected not only in the plain radiograph but also in MRI; stage 2, femoral head sclerosis without collapse observed in a plain radiograph; stage 3A, hips with collapse of <3 mm, including the crescent sign; stage 3B, hips with collapse of ≥3 mm, without osteoarthritic changes; and stage 4, osteoarthritic changes[13].

The inclusion criteria were steroid-associated ONFH in patients with SLE treated with CABMAT in our institution from January 2003 to December 2015 (for Group I) or treated conservatively in the cooperative hospital from January 1988 to December 2015 (for Group II). Patients not followed up for >2 years were excluded from this study.

Regarding the CABMAT group (group I), 58 patients (92 hips) treated with CABMAT were retrospectively examined and followed up for >2 years postoperatively. The mean postoperative follow-up period was 5.1 (2.0–12) years, and the mean age was 35.4 (16–77) years. All ONFH was associated with corticosteroid use for the treatment of SLE. Preoperatively, 3, 5, 40, and 44 out of 92 hips were analyzed as types A, B, C1, and C2, respectively, whereas 19, 23, 48, and 2 hips of 92 hips were analyzed as stages 1, 2, 3 (3A+3B), and 4, respectively. In another institution, the conservative treatment group (group II) comprised of 59 patients (103 hips) treated conservatively and followed up for >2 years after the diagnosis. In the conservative therapy for ONFH, hip muscle training, load limitation of the hip joint using crutch, and pharmacotherapy with nonsteroidal anti-inflammatory drugs are performed. The mean follow-up period and age were 11.4 (2–25) and 36.1 (15–63) years, respectively. All ONFH was caused by corticosteroid use due to SLE. Preoperatively, 3, 16, 51, and 33 of 103 hips were classified as types A, B, C1, and C2, respectively, whereas 80, 17, 6, and 0 hips were classified as stages 1, 2, 3 (3A+3B), and 4, respectively.

After the matching based on age, sex, type, stage, and underlying disease, the collapse rate and THA conversion rates were compared between the two groups.

Bone marrow aspiration, concentration, and transplantation

CABMAT was performed according to an established protocol[15]. Approximately 300 mL of bone marrow was

aspirated from the iliac crest using a bone marrow harvest needle (Medical Device Technologies, Inc., Gainesville, FL, USA) and transferred into a bone marrow collection bag (Baxter, Deerfield, IL, USA). After the centrifugation at 1,200 g for 10 min (KUBOTA 9800; Kubota, Osaka, Japan), erythrocytes were transferred from the main bag to a satellite bag (Terumo, Tokyo, Japan). After the second centrifugation (3,870 g for 7 min), the plasma was transferred from the main bag into another satellite bag; therefore, approximately 30 mL of the buffy coat was left in the main bag. Core decompression using a 4.8-mm-diameter trephine (Iso Medical Systems, Tokyo, Japan) was performed to transport the buffy coat to the necrotic area. The drill was inserted percutaneously into the center of the necrotic area. After the core decompression, multiple drillings toward the necrotic site from the core decompression hole were performed using 2.4-mm-diameter Kirschner wires. Using the core decompression tract, a cannulated metal rod with four small holes at the top (Iso Medical Japan, Tokyo, Japan) was inserted into the necrotic area. Through the metal rod, the buffy coat was manually inserted and slowly infused over several minutes using a syringe. Approximately 18 ± 5.7 mL of the buffy coat was transplanted using a monitor with biplane fluoroscopy. Weight bearing was limited for 6 weeks postoperatively. Non-weight-bearing exercises were allowed. Full weight bearing was allowed 10 weeks postoperatively. Adaptation criteria of CABMAT principles are stages 1–3A of ONFH.

Femoral head collapse rate

Anteroposterior and lateral radiographs of the affected hip were obtained during each clinical evaluation. Radiographic progression of the femoral head collapse (preoperatively to the most recent follow-up) was evaluated considering the ONFH classification and staging. All radiographs were independently evaluated by two observers who were orthopedic surgery specialists and were authorized by the Japanese Orthopaedic Association. Progression of the femoral head collapse was evaluated using a template overlay circle, according to Aaron et al.'s study[16]. The chi-squared test was used to compare collapse rates between Groups I and II.

THA conversion rate

The χ^2 and log-rank tests were used to compare the THA conversion rate between Groups I and II using. A P-value of <0.05 was considered statistically significant.

Statistical analysis

All statistical analyses were performed using the JMP Statistics version 13.2.1 (SAS Institute Inc., Cary, NC, USA).

Results

Matching-adjusted groups

Between Groups I and II, hips were matched in a 1:1 ratio according to age within 10 years, sex, etiology, and preoperative types and stages. Overall, 33 hips were recruited from each institution; therefore, 66 hips were included in the matching-adjusted group. Preoperatively, 1, 2, 16, and 14 of 33 hips were classified as types A, B, C1, and C2, respectively, whereas 15, 13, 2, and 3 hips were classified as stages 1, 2, 3A, and 3B, respectively. All ONFH due to corticosteroid use occurred during the SLE treatment. The overall duration of steroid use was 12.7 (4.8–23.3) and 17.5 (4.4–31.4) years in groups I and II, respectively. The average maximum steroid doses were 60 (30–80) and 56.5 (40–80) mg in Groups I and II, respectively. The matched patients' characteristics between Groups I and II are shown in Table 1.

Collapse rate of the pre-collapsed femoral head

The collapse rates in stages 1 and 2 were 67% (10/15) and 69% (9/13), respectively, in Group I and 7% (1/15) and 77% (10/13), respectively, in Group II. The collapse rate in the pre-collapsed stages in Group I was significantly higher than that in Group II (68% [19/28] vs. 39% [11/28]; P<0.05, χ^2 test).

THA conversion rate

THA conversion rates were 33% (11/33) and 45% (15/33) in Groups I and II, respectively, exhibiting no significant difference (P=0.31, χ^2 test). In stage 1, the THA conversion rate was significantly higher in group I (33% vs. 7%;

Table 1 Patient characteristics of Groups I and II after matching

		Group I	Group II
Number of hips		33	33
Sex	Male	2	2
	Female	31	31
Mean age (years)		35.1 (22.6–53.5)	35.7 (20.5–57.1)
Side	Right	10	17
	Left	23	16
Preoperative type			
A		1	1
B		2	2
C1		16	16
C2		14	14
Preoperative stage			
1		15	15
2		13	13
3 (3A+3B)		5	5
Mean follow–up period (years)		5.9 (2.0–14.5)	8.7 (2.1–24.8)*

*P<0.05, unpaired t-test.

$P<0.05$, χ^2 test). Conversely, in stage 3 (3A and 3B), the THA conversion rate was significantly lower in group I (40% vs. 100%; $P<0.05$, χ^2 test) (Table 2).

Survival rates (end-point: THA conversion)

No significant differences were observed in survival rates between Groups I and II (Figure 1) ($P=0.75$, log-rank test). In stage 1, survival rates were significantly higher in Group II ($P<0.05$, log-rank test). In stage 2, no significant difference was observed. In stage 3 (3A+3B), survival rates were significantly higher in group I ($P<0.005$, log-rank test) (Figure 1). For types A and B, survival curves could not be drawn, and the log-rank test was not performed. For types C1 and C2, no significant differences were observed between Groups I and II.

Discussion

The exact mechanism of steroid-associated ONFH is unclear. Blood supply insufficiency due to thrombus, fat

Table 2   Total hip arthroplasty conversion rate for each type and stage in Groups I and II

Stage		Type				Total
		A	B	C1	C2	
Group I	1	0/1 (0%)	0/2 (0%)	2/8 (25%)	3/4 (75%)	5/15 (33%)
	2	-	-	2/7 (29%)	2/6 (33%)	4/13 (31%)
	3 (3A+3B)	-	-	0/1 (0%)	2/4 (50%)	2/5 (40%)
Total		0/1 (0%)	0/2 (0%)	4/16 (25%)	7/14 (50%)	11/33 (33%)
Group II	1	0/1 (0%)	0/2 (0%)	0/8 (0%)	1/4 (25%)	1/15 (7%)
	2	-	-	3/7 (43%)	6/6 (100%)	9/13 (69%)
	3 (3A+3B)	-	-	1/1 (100%)	4/4 (100%)	5/5 (100%)
Total		0/1 (0%)	0/2 (0%)	4/16 (25%)	11/14 (79%)	15/33 (45%)
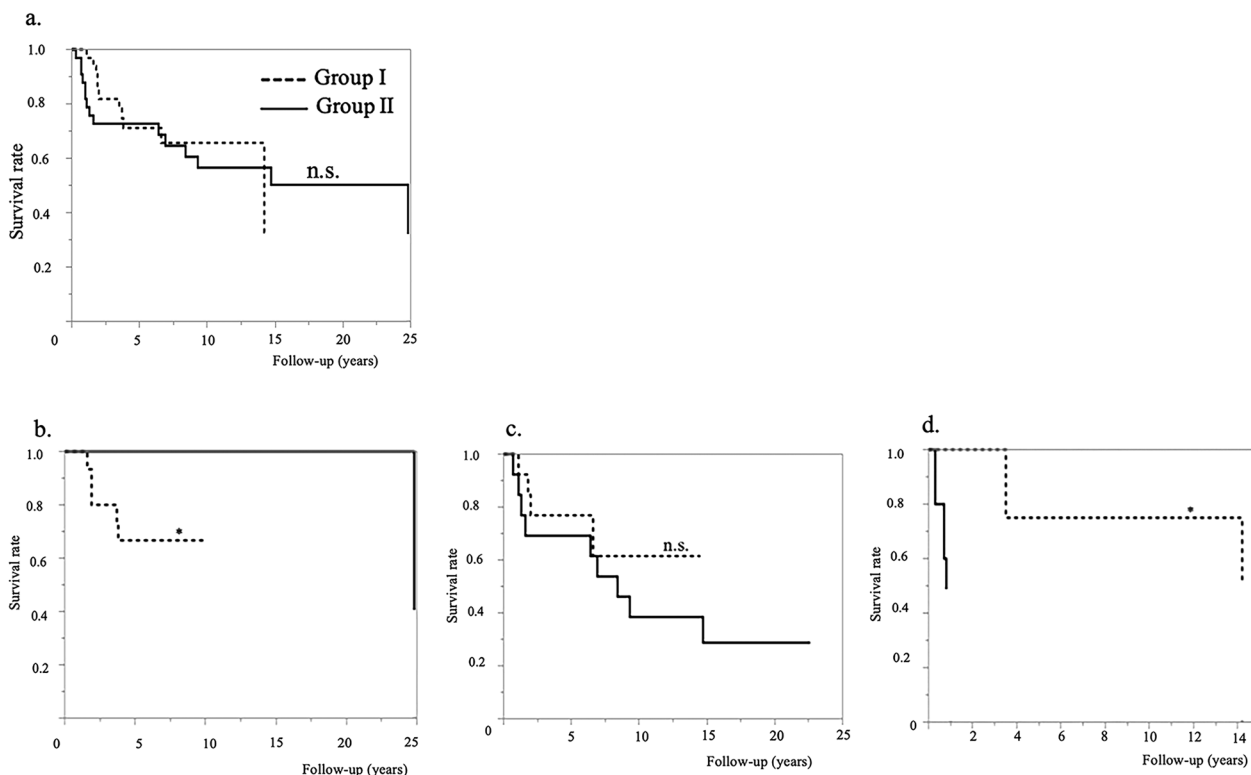
Figure 1   (a) Overall survival curve of groups I and II. (b) Survival curve in stage 1 (*$P<0.05$, log-rank test). (c) Survival curve in stage 2 (n.s., not significant). (d) Survival curve in stage 3 (*$P<0.005$, log-rank test). Short dashed line, group I; continuous line, group II. End point: total hip arthroplasty conversion.

embolism, and endothelial dysfunction decreases the mesenchymal stem cell (MSCs) and growth factor levels; and bone cell apoptosis is all advocated as causes of necrosis in ONFH[17–20].

Although the exact mechanism of the therapeutic effect of bone marrow transplantation remains unknown, several theories have been proposed. The differentiation potency of MSC may possibly play an important role. MSCs have the potential to differentiate various cells[21]. Osteoblasts and/or vascular endothelial cells, differentiated from transplanted MSC, can possibly improve osteogenesis and cardiohemodynamics in the necrotic area, contributing to its therapeutic effects. Sugaya et al. reported that transplanted MSCs could differentiate osteoblasts and induce tissue repair in the rabbit model[22].

Furthermore, the secretory function of MSCs could provide a therapeutic effect. MSCs secrete wide-spectrum factors with antiapoptotic, proangiogenic, proliferative, and chemoattractive capacities[23].

In addition to MSCs, the buffy coat (concentrated bone marrow used for transplantation) contains not only MSCs but also various growth factors (basic fibroblast growth factor [FGF], platelet-derived growth factor-BB, vascular endothelial growth factor, transforming growth factor β1, and bone morphogenetic protein[24]. These multifunctional, wide-spectrum growth factors might contribute to osteogenesis and angiogenesis, preventing the femoral head collapse.

CABMAT has been performed in our institution since 2003, expecting therapeutic effects attributable to the MSC and growth factor complementation using buffy coat transplantation. Revascularization and migration of MSC and growth factors from the healthy bone via core decompression were also expected. Yoshioka et al. reported a THA conversion rate of 11% after CABMAT, with a mean follow-up period of 3.4 years[11]. Tomaru et al. reported a THA conversion rate of 29%, with a mean follow-up of 5.5 years[9]. Hernigou et al. reported that THA conversion rates after the concentrated bone marrow transplantation were 6.2% and 57% in the pre- and post-collapsed stages, respectively, with a mean follow-up of 7 years[25].

Sen et al. reported that outcomes of mononuclear cell instillation with core decompression were better than core decompression alone[26]. Papakostidis et al. reported the effects of bone marrow transplantation in a systematic review[27]. Several studies reported the effectiveness of bone marrow transplantation; nevertheless, no head-to-head trials have been conducted on the effects of bone marrow transplantation on ONFH. The lack of the control group was a limitation of a previous study that aimed to verify the effectiveness of CABMAT[28].

The collapse rate in the pre-collapsed stages was significantly lower in group II. The higher collapse rate in the pre-collapsed stage and higher THA conversion rate in stage 1 in group I are unclear. The first hypothesis involves differing recruitment methods. Although no screening system existed for ONFH in patients who received high corticosteroid doses in our institute (Group I), a screening system was available in the cooperative institute (Group II). The hypothesis is that core decompression before buffy coat transplantation might induce mechanical bone fragility and/or accelerate osteoclast cell activity in the weight-bearing area of the femoral head. Several studies reported that the core decompression, including its outcomes, is not always stable. Mont et al. reported that core decompression had a significant effect on the early stage of ONFH[29]. The clinical success was defined as >80 points in the Harris hip score or >80% in other similar scoring systems. The success rates of nonoperative treatment ranged from 0% to 44%, whereas that of the core decompression ranged from 32% to 92%. Despite the high success rates in several studies, low success rates had also been reported. Furthermore, Mont et al. did not compare the core decompression results with those of conservative treatment; nevertheless, core decompression might result in poor prognosis.

In stage 3, the THA conversion rate was low in group I. In the conservative treatment group, the prognosis of the hips that reached stage 3 was poor, with collapse progression and high THA conversion rate. In these cases, CABMAT might improve the prognosis. The exact mechanism of this improvement remains unclear. Osteogenesis induced by CABMAT might prevent the substantial collapse that leads to THA conversion. Indeed, osteogenetic changes in the buffy coat donor site may occur in some patients (Figure 2). Furthermore, as sclerotic changes in ONFH cause stress concentration, triggering subchondral fractures at the lateral boundary, the core decompression to the sclerotic change may improve stress concentrations[30].

In stage 2, no significant difference was observed in the THA conversion rates between the two groups. The core decompression disadvantage and osteogenesis advantage could have offset one another, clinically suggesting that careful observation of stage 1 hips is preferable. If changes are detected on plain radiographs, including osteosclerosis, subchondral fracture, and minor collapse, CABMAT should be considered. Hernigou et al. reported a significantly lower THA conversion rate and higher number of implantation of fibroblastic colony-forming units (CFU-F) in the concentrated bone marrow than those in our previous study (i.e., ONFH treated by CABMAT)[25]. In their report, a cell separator concentrated on the bone marrow, whereas only a simple blood bag was used in the CABMAT method. As a result, the number of CFU-Fs was approximately 10 times greater in the concentrated bone marrow[9, 25], which may account for the low THA conversion rate. Kuroda et al. reported a low collapse rate of pre-collapsed ONFH treated by
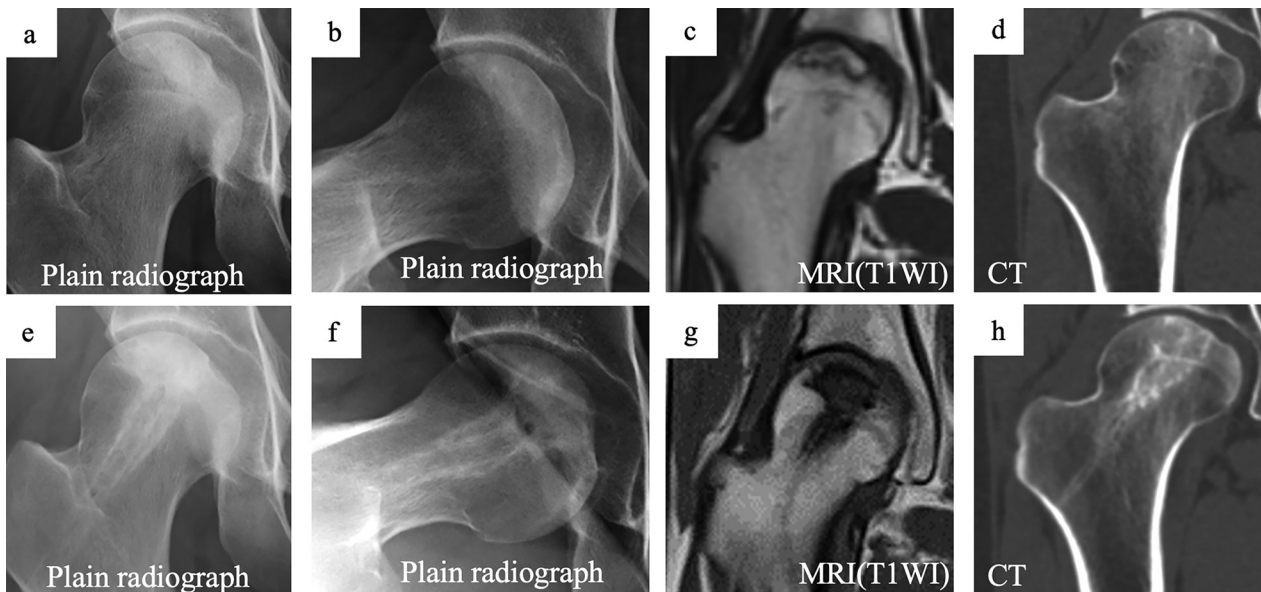
Figure 2 A 23-year-old woman with preoperative stage 1 and type C1.
Bone formation at the most recent follow-up can be seen. (a–d) Preoperative image. (e–h) Eight years after CABMAT. MRI (T1WI), magnetic resonance image T1-weighted image; CT, computed tomography; CABMAT, concentrated autologous bone marrow aspirate transplantation.

recombinant human FGF 2 (rhFGF-2)-impregnated gelatin hydrogel[30]. The amount of FGF was much higher in rhFGF-2-impregnated gelatin hydrogel than that in the buffy coat of the CABMAT method. Moreover, the buffy coat is liquid, whereas the gelatin hydrogel is a semisolid substance. Gelatin is expected to have higher retention rate than the buffy coat. Although the short-term result of FGF gelatin hydrogel treatment is good, the long-term outcome is slightly unclear. Considering the FGF gelatin hydrogel characteristics, they could be combined with CABMAT to improve the outcomes. Therefore, the use of a cell separator, gelation of the buffy coat, and combination with artificial bone for mechanical reinforcement of the drilled femoral head may be considered to improve the outcomes.

This study had limitations. First, the study design is retrospective; thus, matching the follow-up periods is difficult. Nevertheless, the use of the log-rank test could correct the difference during the follow-up period to some extent. Second, the number of patients and the follow-up period were small and short, respectively. The survival analysis in the subgroups (stages 1 and 2) might be unreliable due to the inadequate number of samples. Therefore, a study with a larger number of patients should be conducted to validate these results.

Core decompression is needed for historical control to investigate the therapeutic effect of bone marrow transplantation itself. However, it is not yet widely performed in Japan. Conservative treatment is the standard treatment in Japan, whereas bone marrow transplantation and rhFGF-2-impregnated gelatin hydrogel treatment are performed in only a few hospitals[30]. Therefore, patients who underwent core decompression cannot be considered as the control group; hence, we decided to set those who underwent conservative treatment as the control group in this study as the next best policy.

Conclusion

Based on the collapse and THA conversion rates, conservative therapy was more favorable for stage 1, whereas CABMAT was more favorable for stage 3. A prospective randomized control study comparing CABMAT and core decompression is needed to verify the treatment effect of CABMAT with more accurately.

Conflict of interest: The authors declare that they have no conflict of interest.

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