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Original Article

A Combination Therapy for Osteonecrosis of the Femoral Head and Short-Term Results

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ABSTRACT

Objective: The purpose of this study is to report the clinical and radiological outcomes of patients who underwent core decompression in combination with bone marrow aspiration concentrate injection at the decompressed site and medical treatment and to compare these outcomes with a matched cohort of patients who underwent isolated core decompression.

Methods: Patients were divided into 2 groups according to their health insurance's coverage. Patients were treated with core decompression in combination with bone marrow aspiration concentrate injection and medical therapy (group A) or with core decompression alone (group B) for patients whose insurance did not cover bone marrow aspiration concentrate treatment. The extent of osteonecrosis was estimated by a modification of the combined necrosis-angle method of Kerboul.

Results: A total of 29 hips in group A and 27 hips in group B were evaluated. The groups showed similar demographic data and follow-up time. A total of 3 patients from group A and 10 from group B underwent revision. Revisions were significantly more common in group B ($P=.018$) and time to revision was also significantly shorter ($P=.005$). There was a significant difference in survival between the groups. Patients had better scores on average in the first postoperative year. There was no difference in clinical scores between the groups. Type of surgery was found to be a risk factor for revision.

Conclusion: Core decompression combined with bone marrow aspirate concentration and mixed medical treatment consisting of alendronate, lovastatin, and enoxaparin resulted in better clinical outcomes, lower pain scores, and significantly lower revision rates compared with core decompression alone. Core decompression alone was a risk factor for revision.

Keywords: bone marrow aspirate, core decompression, osteonecrosis of femora head

INTRODUCTION

Osteonecrosis of the femoral head (ONFH) is a progressive, multifactorial, and disabling disease that causes significant clinical morbidity and particularly affects young and active patients. Delayed diagnosis and treatment often lead to collapse of the femoral head. To avoid such complications, it is critical to focus on early diagnosis and appropriate treatment.[1] Although the most appropriate treatment method for ONFH remains controversial, conservative and some surgical methods have been tried over the years with varying success rates.[1-3] A systematic review reported that only 28% of hips treated conservatively had no radiographic changes 4 years after initial diagnosis, and 33% required no surgical intervention.[3]

Surgical treatment can be broadly divided into femoral head-sparing procedures and total hip arthroplasty (THA).[4] Sparing procedures include core decompression (CD), nonvascularized bone grafts, vascularized bone grafts, and rotational osteotomies.[5] Core decompression is the most commonly performed surgical technique for the treatment of ONFH.[6,7] It is a relatively simple and inexpensive procedure with a low risk of complications.[7] It reduces intraosseous pressure in the femoral head and increases blood flow to the necrotic region.

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A 15-year survival rate of 63% has been reported in the literature.[3,8-10] To increase survival and achieve better clinical outcomes, a combination of medical and nonsurgical therapies has often been combined with a CD procedure.[11] Bone marrow aspirate injection, extracorporeal shock wave therapy, hyperbaric oxygenation, anticoagulants, lipid-lowering agents, bisphosphonates, growth factors, antioxidants, and vasoactive agents have been reported in the literature to increase the survival rate of CD.[11,12]

Injection of bone marrow aspirate concentrate (BMAC) into the decompressed site has shown particularly promising results. The 12-year follow-up of patients treated with CD and BMAC injection showed a volumetric decrease in the necrotic area by more than 50% with an overall survival rate of 83%.[13] It has also been reported that isolated medical treatments increase the survival rate of ONFH, but to our knowledge, no study has yet reported results on medical treatment combined with a CD procedure and BMAC injection.

The purpose of this study is to report the clinical and radiographic outcomes of patients who underwent CD in combination with BMAC injection at the decompressed site and medical treatment, and to compare these outcomes with a matched cohort of patients who underwent isolated CD.

METHODS

Patient Selection

Patients who were treated for osteonecrosis of the femoral head at our medical center between January 2016 and January 2019 were eligible for this study. The classification system of modified Ficat and Arlet was used throughout the study. Inclusion criteria were patients at the precollapse stage (grade 1-2A). Exclusion criteria were chronic or acute necrotic site collapse, >2 mm collapse, grade 2B, 3, and 4 cases, previous surgery for ONFH, pregnancy, history of malignancy, and immunosuppression. The study was carried out with the ethical approval of Ankara Bilkent City Hospital (Ethics committee decision dated March 17, 2021 and numbered E1.21.1606). Surgery was indicated in grade 1 patients who presented with a painful hip and in all grade 2A patients who had acute onset of pain symptoms and were at a precollapse stage.

Patients were divided into 2 groups according to their health insurance's coverage. Patients were treated with CD in combination with BMAC injection and medical therapy (group A) or with CD alone (group B) for patients whose insurance did not cover BMAC treatment. All data collected were retrospectively analyzed. Demographic data and associated clinical risk factors such as additional comorbidities, corticosteroid use, and alcohol consumption were obtained from medical records.

All operations were performed by a single surgical team. Measurements and scores were calculated by a single experienced surgeon in order to avoid difference between individuals.

Surgical Technique

Patients scheduled for surgery were placed supine on a standard radiolucent table. One gram of cefazolin was administered intravenously 1 hour before surgery, and spinal anesthesia was routinely administered. Surgical procedures were performed by a single surgeon in a standard manner.

A small lateral incision was made on the proximal thigh, and the lateral femoral cortex was palpated. Decompression was performed with a multiple drilling technique using 2.7 mm diameter K-wires. Starting from the trochanteric region, the necrotic area of the femoral head was first approached to within 2-3 mm of the joint with multiple wires. To further reduce femoral neck edema and pressure, the wires were also advanced divergently within the bony structures (Figure 1). The position of the wires was routinely checked on antero-posterior and lateral radiographs.

In group A, bone marrow was aspirated from the ipsilateral iliac crest. A total of 32 mL of bone marrow was

MAIN POINTS

- Combined therapy has better functional components in the short term than isolated decompression.
- Core decompression alone was a risk factor for revision.
- Medical agents to be added to core decompression and bone marrow aspiration concentrate treatment improve outcomes.

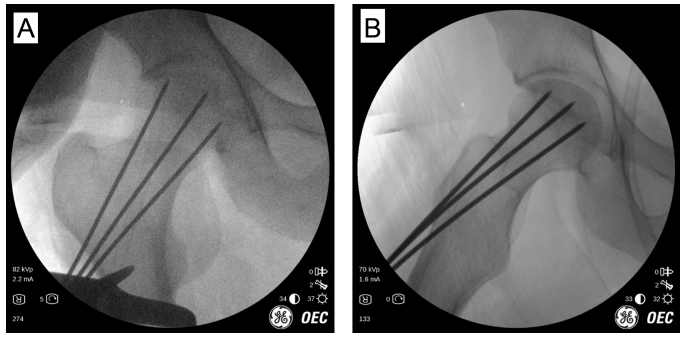

Figure 1. Intraoperative antero-posterior (A) and lateral (B) views of the wires advanced toward the necrotic region and in a divergent way throughout the femoral neck to decrease the pressure and the edema.

aspirated from 3 different sites using a trocar (Figure 2a). The aspirate was then filtered through a 41-micron mesh filter and was evenly distributed among 4 injectors. The injectors were then placed in a centrifuge and centrifuged at 1000RCF. The bone marrow was thus separated into layers. The layer at the bottom of the buffy coat rich in nucleated cells and progenitor cells, the buffy coat itself, and a very small amount of plasma were taken from each injector (1-2 mL in total) and then combined into one (Figure 2b). A total of 5-6 mL of BMAC was obtained from the original bone marrow. The BMAC content was injected with a hip arthroscopy needle through the wire holes aligned with the lesion. To prevent the injection contents from flowing back, the entrances of the tunnels were sealed with bone wax. The wound was then closed in a standard fashion.

Supplementary Medical Therapy

Low-molecular-weight heparin (enoxaparin sodium) at a dosage of 4000 IU was administered to both groups of patients within 12-24 hours after surgery and given once daily. Treatment was continued for 30 days and then replaced by 100 mg acetyl salicylic acid for a total of 3 months. Group A also received 70 mg of alendronate administered orally weekly and 20 mg of lovastatin administered orally and daily. Each drug was continued until 3 months postoperatively and then discontinued.

Postoperative Rehabilitation

Patients received the same postoperative rehabilitation protocol and were discharged on the second postoperative day. Immediately after surgery, isometric exercises for the lower extremities were started, and patients received a nonweight-bearing rehabilitation protocol with crutches or a walker for 12 weeks. After 12 weeks, all patients were allowed partial WB under the supervision of a rehabilitation physician. Weight bearing was gradually increased according to clinical and radiological results. Patients were examined at their 6th week, 3rd, 6th, and 12th month postoperatively and at routine annual visits thereafter.

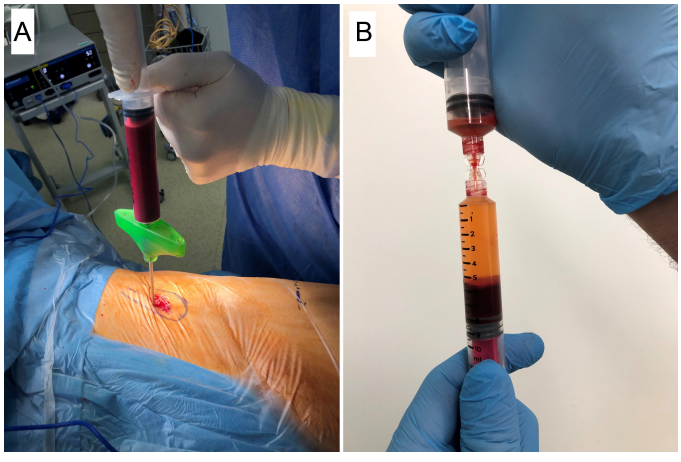

Figure 2. Bone marrow being aspirated from the iliac crest with a trocar (A). After centrifugation, the cellulated dense layer at the bottom, the buffy coat in the middle, and a small portion of the plasma were gathered from each injector and combined in a single one (B).

Radiologic Evaluation

Routine preoperative and postoperative radiographs of the pelvis AP and lateral frog legs were obtained in all patients. The preoperative radiographs were evaluated for minimal osteoporosis/blurring, subcortical cyst, patchy sclerosis, collapse and the extent of collapse, flattening of the femoral head, and narrowing of the joint space.

Preoperative MRI images were available for all patients and were repeated at postoperative year 2. The Ficat–Arlet classification system was used for staging. Decreased signal intensity on T1-weighted images, lines on T2-weighted images, the "double density sign" on T2-weighted images, joint effusion, subcortical collapse, and its extent were examined.

The extent of osteonecrosis was estimated by a modification of the combined necrosis-angle method of Kerboul et al.[15] The necrotic angle was measured on coronal and sagittal MR images rather than on AP and lateral radiographs. Mid-coronal and mid-sagittal sections showing the largest diameter of the femoral head were used for the measurements. These images showed the largest area of abnormal signal intensity within the femoral head. The arc of the necrotic portion was measured in both the mid-coronal and mid-sagittal views, and then the sum of the 2 angles was calculated (Figure 3). Depending on the size of the combined necrotic angle, the hips were divided into 4 categories: stage 1 (<200°), stage 2 (200°-249°), stage 3 (250°-299°), and stage 4 (≥300°).[16]

These data were recorded preoperatively and postoperatively. All radiological data measurements were performed by a single senior physician on 2 separate occasions and 1 week apart.

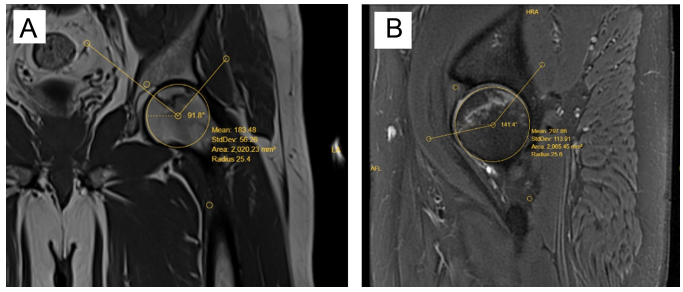

Figure 3. The necrotic angle was measured on mid-coronal (A) and mid-sagittal (B) MR images and then the total of the 2 angles was calculated.

Functional and Clinical Evaluation

Clinical function was assessed preoperatively and postoperatively at each follow-up with a visual analog scale (VAS), the Hip Disability and Osteoarthritis Outcome Score, and the Harris hip score (HHS). For practical reasons, data from the first and second postoperative years were included in this study. Failure and revision criteria were the formation of a new collapse area visible on radiographs, an increase in collapse of more than 2 mm, the development of progressive osteoarthritis, and worsening of clinical scores during follow-up. Data collection was terminated in patients who underwent arthroplasty.

Statistical Analysis

Statistical analysis was performed with Statistical Package for Social Sciences 22.0 (IBM SPSS Corp., Armonk, NY, USA) and Microsoft Excel. Categorical data are presented as number and percentage, whereas continuous data are presented as mean and standard derivation with minimum and maximum values. Nonparametric tests such as the Wilcoxon rank sum test were used to calculate significance between nonnormally distributed data (clinical scores, classifications, and angles). The chi-square test and its nonparametric version, the Mann–Whitney *U*-test, were used to analyze categorical data. A Spearman's RHO correlation analysis was used to analyze the relationship between study variables and revision. A univariate and then a multivariate Cox regression analysis was used to identify potential risk factors associated with revision cases. Finally, a Kaplan–Meier analysis was performed to compare survival between the 2 study groups. Interobserver reliability was calculated, and an intraclass correlation coefficient of 0.921, showing excellent interobserver reliability, was obtained. Results were evaluated with a 95% confidence interval and a *P*-value of $<.05$ was considered significant.

RESULTS

Fifty-nine patients who underwent surgery within the specified time period were initially eligible for the study. Four patients refused to participate in the study, 6 patients were lost to follow-up, and 1 patient had died because of an occupational injury. Twenty-nine hip joints from 26 patients diagnosed with ONFH who underwent combined treatment (group A-CD, bone marrow stem cell implantation, and medical treatment) and 27 hip joints from 22 patients who underwent CD only (group B) were collected and analyzed.

Demographic data revealed a mean follow-up time of 30.4 $\pm$ 11.29 months for group A and 29.8 $\pm$ 11.12 months for group B. In both groups, a majority of patients were male (62.1% vs. 51.9%) and the most common etiology was related to corticosteroid use (48.3% vs. 37%). Revisions were significantly more common in group B ($P=.018$) and time to revision was also significantly shorter ($P=.005$). Demographic data are shown in Table 1.

Radiological measurements were performed based on preoperative MRI scans and patients were graded. No significant difference was found between groups, with the majority of patients having a preoperative grade 2A (96.6% and 96.3%, respectively). Kerboul angle was also measured in all preoperative patients and graded accordingly. Again, the angle data were similar for both groups. All data on preoperative classifications are shown in Table 2.

Three patients from group A and 10 patients from group B underwent revision surgery. All revisions were due to progression of osteonecrosis or collapse and consisted of hip replacement surgery. Spearman correlation analysis was performed between all preoperative variables and revision. It was found that type of surgery (group) and preoperative HHSs correlated with failure (Table 3).

A Kaplan–Meier analysis was performed to compare survival between groups (Figure 4). There was a significant difference in survival between the groups (log rank = 0.009). Regression analysis was then performed to investigate whether correlations could translate into a risk factor for failure and thus for revision. All preoperative variables were subjected to univariate regression analysis. While surgery type/group was found to be significant, other variables such as BMI and HHS were close to significance. The variables were then analyzed in a multivariate regression model and type of surgery was found to be a risk factor for failure ($P=.003$). All data are presented in Table 4.

Clinical scores were recorded preoperatively for all patients and postoperatively for surviving cases in the first and second year of follow-up. There was significant improvement in both groups of patients ($P > .05$), although patients had better scores on average in the first postoperative year than in the second. There was no difference in clinical scores between the 2 groups, either preoperatively or postoperatively. All results are shown in Figure 5.

DISCUSSION

This study showed that a combination of CD, injection of bone marrow concentrates, and medication had a significant effect on the short- and medium-term survival of patients with osteonecrosis of the femoral head. The greatest risk factor for revision was the type of surgery. Clinical and functional scores improved significantly in all surviving cases, with better scores in the first postoperative year.

Table 1. Demographic Data of Study Patients

	Cor Decompression + Bone Marrow Aspiration (n = 29)	Cor Decompression Alone (n = 27)	*P*
Age			*n.s.**
Mean ± SD	38.2 ± 9.91	38.5 ± 10.22	
Median (min–max)	38 (23–62)	40 (23–64)	
Side			*n.s.*+*
Right	15 (51.7%)	17 (63%)	
Left	14 (48.3%)	10 (37%)	
Sex			*n.s.*+*
Male	18 (62.1%)	14 (51.9%)	
Female	11 (37.9%)	13 (48.1%)	
BMI			*n.s.**
Mean ± SD	25.9 ± 2.73	25.4 ± 2.60	
Median (min–max)	25.6 (20.1–30.3)	25.2 (20.5–30.4)	
Mean follow-up of surviving cases			*n.s.**
Mean ± SD	30.4 ± 11.29	29.9 ± 11.12	
Median (min–max)	25 (20–53)	25 (21–53)	
Revised			*.018*+*
Yes	3 (10.3%)	10 (37%)	
No	26 (89.7%)	17 (63%)	
Time to revision (months)	n = 3	n = 10	*.005**
Mean ± SD	30.3 ± 10.26	11.2 ± 7.74	
Median (min–max)	33 (19–39)	9.5 (3–29)	
Etiology			*n.s.*+*
Idiopathic	9 (31%)	6 (22.2%)	
Corticosteroids	14 (48.3%)	10 (37.0%)	
Sistemic lupus eritematozus	2 (6.9%)	2 (7.4%)	
Trauma	2 (6.9%)	4 (14.8%)	
Kidney disease	2 (6.9%)	2 (4.1%)	
Sickle cell anemia	0 (0%)	3 (11.1%)	

BMI, body mass index.
+Chi-square; *Mann–Whitney *U* test; n.s., non-significant.

Early interventions for ONFH are attracting increasing interest.[6-8,11,17,18] While conservative procedures such as controlled weight bearing and medical therapy are often the first line of treatment, joint collapse is inevitable in most cases.[1] CD is a relatively simple procedure and has long been used in the treatment of ONFH.[19] The goal is to relieve the increased intraosseous pressure within the femoral head and improve blood supply.[7] Although it has shown better clinical results compared with conservative treatment,[20] it is clear that there is still room for improvement. The combination of BMAC injection with a CD was first advocated by Hernigou et al,[21] and their subsequent studies showed better clinical outcomes with a lower rate of hip replacement.[7] They concluded that the use of autologous BMAC in combination with CD for ONFH slowed disease progression and femoral head collapse, significantly reduced the need for THA, and found that the combined use was superior to CD treatment alone.[22,23]

Inspired by these results, researchers later sought to enhance this success with new treatment combinations. Anticoagulants, fibrinolytics, vasodilator, and

Table 2. Classifications and Angles

	Cor Decompression + Bone Marrow Aspiration (n = 29)	Cor Decompression Alone (n = 27)	*P*
Preoperative Kerboul Angle			*n.s.**
Mean ± SD	193.5 ± 45.04	184.0 ± 40.31	
Median (min–max)	180 (130–305)	180 (135–270)	
Postoperative Kerboul Angle			*n.s.**
Mean ± SD	202 ± 53.77	208.1 ± 48.84	
Median (min–max)	180 (130–340)	205 (135–305)	
Preoperative Kerboul Grade			*n.s.*+
1	17 (58.6%)	19 (70.4%)	
2	9 (31.0%)	6 (22.2%)	
3	2 (6.9%)	2 (7.4%)	
4	1 (3.4%)	0 (0%)	
Postoperative Kerboul Grade			*n.s.*+
1	16 (55.2%)	13 (48.1%)	
2	9 (31.0%)	8 (29.6%)	
3	1 (3.4%)	4 (14.8%)	
4	3 (10.3%)	2 (7.4%)	
Preoperative Ficat–Arlet Grade			*n.s.*+
1	1 (3.4%)	1 (3.7%)	
2A	26 (96.6%)	24 (96.3%)	

BMI, body mass index.
*Mann–Whitney *U* test; +Chi square; n.s., non-significant.

Table 3. Correlations Between Revision Cases and Study Variables

	Revision	
	Correlation Coefficient *R**	Significance *P*
Type of surgery/Group	**0.316**	.018
Age	0.017	*n.s.*
Gender	0.067	*n.s.*
Etiology	-0.109	*n.s.*
BMI	-0.188	*n.s.*
Preoperative Kerboul Angle	-0.127	*n.s.*
Preoperative Kerboul Grade	-0.136	*n.s.*
Preoperative Ficat–Arlet Grade	0.106	*n.s.*
Preoperative Harris Hip Score	-0.292	**0.029**
Preoperative Hip Disability and Osteoarthritis Outcome Score	-0.101	*n.s.*
Preoperative Visual Analogue Scale	0.141	*n.s.*

BMI, body mass index; n.s., non-significant.
*Spearman's rho.

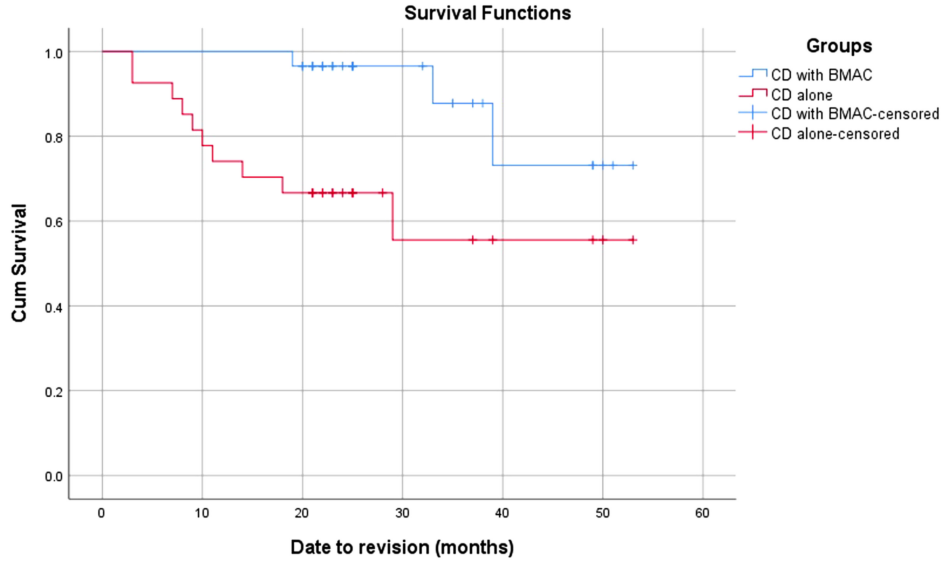

Figure 4. A Kaplan–Meier analysis a significant difference in survival between the groups (long rank = 0.009).

lipid-inhibiting drugs were tried as adjunctive medical treatment with mixed results.[11] Glueck et al[24] introduced enoxaparin to facilitate fibrinolysis of intravascular thrombi. He hypothesized that this would improve blood flow, leading to regression of hypoxia and eventual healing of the dead bone. A similar study was also performed by Chotanaphuti et al,[25] who reported a rate of 57.7% without progression of osteonecrosis. Although no serious adverse effects such as bleeding were reported in these studies, the use of anticoagulants should be approached with caution, especially in patients with thrombophilia. Lipid-lowering agents such as statins are commonly used to prevent cardiovascular disease, and some studies have reported their efficacy in steroid-induced ONFH.[26,27] Despite promising initial results, it has been reported that osteonecrosis rates were similar in patients with and without a history of chronic steroid use who were taking statins for prevention.[28] Randomized controlled trials are still lacking, and the clear protective role of statins remains controversial.

Lai et al[29] reported that bisphosphonates such as alendronate may delay and even prevent ONFH collapse because of their ability to inhibit osteoclast activity. While other authors also reported improvement in clinical outcomes and disappearance of pain with relatively

Table 4. Univariate and Multivariate Cox Regression Analysis on Risk Factors for Revision Surgery During Follow-up Period

	Univariate Cox Regression Analysis		Multivariate Cox Regression Analysis Model		
	HR (95% CI)	*P*		Adjusted HR (95% CI)	*P*
Age	*0.96 (0.92–1.03)*	*n.s.*	Age	0.95 (0.90–1.02)	*n.s.*
Gender	*0.85 (0.28–2.52)*	*n.s.*	Gender	1.37 (0.38–4.96)	*n.s.*
Etiology	0.78 (0.48–1.27)	*n.s.*	Etiology		
BMI	*0.83 (0.68–1.01)*	*n.s.*	BMI	0.90 (0.69–1.17)	*n.s.*
Preoperative Kerboul Angle	0.99 (0.98–1.01)	*n.s.*	Preoperative Kerboul Angle		
Preoperative Kerboul Grade	0.67 (0.26–1.73)	*n.s.*	Preoperative Kerboul Grade		
Preoperative Ficat–Arlet Grade	21.1 (0.00–3314)	*n.s.*	Preoperative Ficat–Arlet Grade		
Preoperative HHS Score	*0.95 (0.90–1.01)*	*n.s.*	Preoperative HHS Score	0.93 (0.87–1.00)	*n.s.*
Preoperative HOOS Score	0.98 (0.91–1.04)	*n.s.*	Preoperative HOOS Score		
Preoperative VAS Score	1.15 (0.78–1.69)	*n.s.*	Preoperative VAS Score		
Type of surgery/group (CD & BMAC vs. CD alone)	0.21 (0.06–0.77)	0.018	Type of surgery/group (CD & BMAC vs. CD alone)	0.10 (0.23–0.46)	.003

BMAC, Bone marrow aspirate concentrate; CD, Core decompression; BMI, body mass index; HR, hazard ratio; n.s., non-significant.

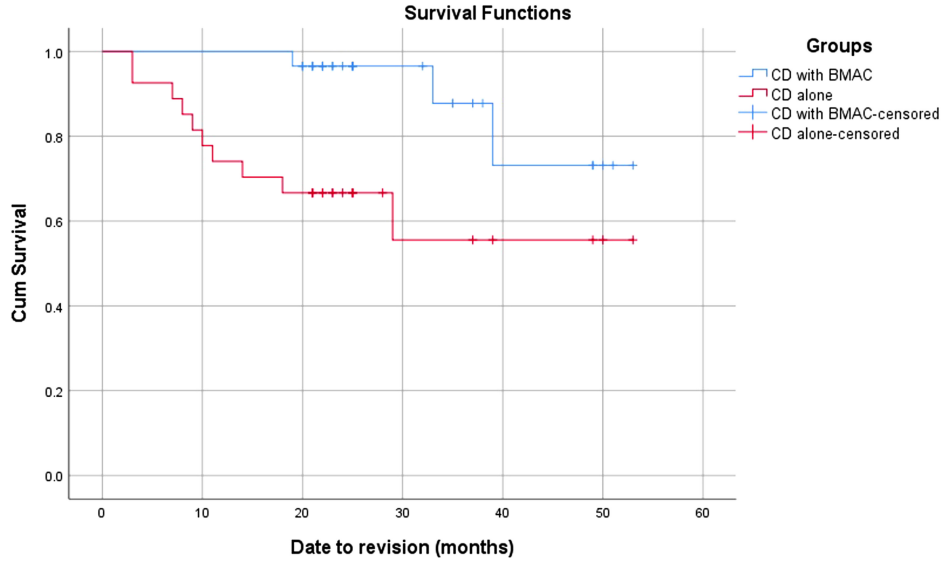

Figure 5. Kaplan–Meier survival analysis showing overall progression and revision cases of the 2 groups. Group A (upper/blue line) had significantly longer survival and fewer revision cases compared to Group B (bottom/red line).

minor THA conversions,[30,31] 2 important prospective randomized controlled trials showed no differences in disease progression, clinical scores, and revision rates.[32,33] The authors concluded that more evidence is needed to determine whether bisphosphonates prevent femoral head collapse or lead to clinical improvement at all. In this study, we opted for a mixed-medicine approach and used a combination of alendronate, lovastatin, and enoxaparin in conjunction with a CD procedure. The initial results are satisfactory overall and suggest that the combination provides better results than CD alone in the first 2 years, with no adverse effects reported.

Although femoral head-sparing procedures are rarely effective in patients with a collapsed femoral head, there is still no consensus on treatment in very early stages.[11] Procedures such as CD (with or without BMAC injection), drug therapies, grafting, and osteotomies show better clinical outcomes when used in early stages of the disease.[5] The success rate also decreases with increasing width of the necrotic area (Kerboul angle). Yoon et al[3] reported that an advanced stage according to the Ficat–Arlet classification and a wide initial Kerboul angle were correlated with poorer overall outcomes and a higher failure rate. Most patients in this study had grade 2A by the Ficat–Arlet classification. We performed a subanalysis examining the relationship between preoperative grade and postoperative clinical scores and revisions (data not shown here), but no significant results were found.

Wang et al[7] reported in their meta-analysis that clinical outcomes improved significantly after CD and a BMAC procedure compared with CD alone. At 12 and 24 months after the procedure, patients had significantly higher HHS scores, significantly lower VAS and WOMAC scores, and similar rates of adverse effects. Patients with BMAC injection had an overall reduction in final necrotic area and a lower failure rate. This study also showed similar results. Patients reported significantly higher clinical scores and lower pain scores at follow-up when treated with combined therapy. The number of revisions was higher in the CD group, which was statistically significant.

Our study has some limitations. First, the number of patients included was relatively small. A larger sample would have led to more significant results, especially with regard to risk factors. Second, the majority of patients in this study were grade 2A. A larger and less homogeneous patient sample would have led to a more comprehensive result. Nevertheless, performing CD in grade 1 patients in whom more conservative therapies have not been tried could sometimes be considered too aggressive. Further studies are needed to guide and orient surgical interventions at these early stages. On the other hand, performing a relatively expensive procedure in grade 3 patients in anticipation of poor outcomes could further disable the patient and complicate future THA. Finally, this was a retrospective study, and patients' treatment modality was determined by their health insurance options. Despite its limitations, this study shows that a combination of surgical and therapeutic treatment modalities leads to good clinical outcomes in patients with osteonecrosis of the femoral head after 2 years.

Core decompression combined with bone marrow aspirate concentration and mixed medical treatment consisting of alendronate, lovastatin, and enoxaparin resulted in better clinical outcomes, lower pain scores, and

significantly lower revision rates compared with CD alone. CD alone was a risk factor for revision.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Ankara Bilkent City Hospital (Date: March 17, 2021, Number: E1-21-1606).

Informed Consent: Written informed consent was obtained from the patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – H.A., E.V.; Design – H.A., Y.E.; Supervision – H.A., A.F.; Resources – H.A., İ.S.; Materials – H.A., A.Ş.; Data Collection and/or Processing – H.A., K.K.; Analysis and/or Interpretation – H.A., E.V.; Literature Search – H.A., A.F.; Writing Manuscript – H.A., Y.E.; Critical Review – H.A., A.Ş.; Other – H.A., İ.S.

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