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ORIGINAL ARTICLE

The Efficacy of Bisphosphonates with Core Decompression and Mesenchymal Stem Cells Compared with Bisphosphonates Alone in the Treatment of Osteonecrosis of the Hip: a Retrospective Study

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Abstract *Introduction:* Osteonecrosis of the femoral head (ONFH) is a devastating disease with complete collapse of the femoral head often reported in greater than 70% of patients within 3 to 4 years of diagnosis. Early intervention prior to collapse may improve the chance of success of joint preserving procedures. *Questions/Purposes:* The purpose of this study was to evaluate whether core decompression with mesenchymal stem cells combined with bisphosphonate therapy can improve the clinical outcomes and reduce the risk of hip replacement when compared to treatment with bisphosphonate therapy alone. *Methods:* Between 2006 and 2014, 84 consecutive patients who were diagnosed with ONFH were identified from our institution's registry. Of these 84 patients, 49 patients (62 hips), fit inclusion/exclusion criteria. Twenty-nine patients (40 hips) were treated with bisphosphonate therapy only. Twenty patients (20 hips) were treated with bisphosphonates, core decompression, and mesenchymal stem cells. Functional outcomes were assessed using the Modified Harris Hip Score (MHHS), the visual analog score (VAS), and evaluation of support system. Clinical failure was defined as deterioration of the MHHS/VAS scores and support system used severe enough to require THR. Radiologic outcome measures included the XR and MR imaging staging of the hip. Survival analysis was performed with total hip replacement as the end point failure. Collapse was defined as progression from Ficat stage I or II to stage III and from Steinberg I, II, III to IV, V, VI. *Results:* Failure requiring THR occurred in 21/40 (52.5%) of bisphosphonates (BP)-treated hips at a mean follow-up of 25.3 ± 11.5 months and 5/22 (22.73%) of BP + CD + MSC-treated hips at a mean follow-up of 22.7 ± 19.5 months. The median (Q1, Q3) time to collapse was 24.9 (7.4, 33.0) months in BP-treated hips and 27.3 (27.3) months in BP + CD + MSC-treated hips. There was no evidence of a difference in functional outcomes between the two treatment groups. After adjusting for baseline Ficat stage, age, and sex, an unreplaced hip treated with BP + CD + MSC had 0.42 (95% CI 0.11, 1.57) times the risk of being replaced in the next moment compared to an unreplaced hip treated with bisphosphonates only ($P = 0.196$). *Conclusion:* Our results demonstrate that treatment with BP alone or BP + CD + MSC can postpone the need for total hip arthroplasty (THA) in the first 24 months in patients with ONFH compared to previously reported data, but there is no statistically significant difference between the two treatment groups. Combination therapy of BP + CD + MSC may be more effective in delaying the progression of collapse in early stage ONFH. Future prospective studies are warranted to determine the efficacy of these treatment strategies in the long term.

Keywords avascular necrosis · osteonecrosis · bisphosphonates · core decompression

Level of Evidence: III

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Introduction

Osteonecrosis of the femoral head (ONFH) has become both a challenging and devastating disease. Without treatment,

greater than 70% of femoral heads with osteonecrosis collapse and require prosthetic replacement within 3 years of diagnosis [17]. It is estimated in the USA that 20,000–30,000 new patients are diagnosed with osteonecrosis annually, and 5–12% of all total hip arthroplasties (THAs) are performed based on this diagnosis [28]. A variety of etiologies including microvascular damage, increased intraosseous pressure, adipogenic differentiation of the marrow stem cells, and mechanical stresses have been proposed as potential factors affecting the local blood supply [25]. Excessive alcohol use, coagulopathies, and chronic diseases requiring long-term corticosteroid use have been observed in patients with ONFH [27]. Treatment of ONFH varies according to disease stage, and early intervention prior to collapse is critical to achieve successful outcomes in joint-preserving procedures. Management alternatives include pharmacologic agents such as anticoagulants, lipid-lowering agents, and bisphosphonates; as well as joint-preserving procedures including core decompression, core decompression combined with concentrated stem cells, bone grafting, and/or osteotomy procedures [20]. Although THA is a definitive option for end-stage ONFH, higher revision rates in patients with associated risk factors have been reported [14].

Early reports on the efficacy of different treatment strategies have been controversial. Previous randomized control studies have reported statistically significant findings favoring core decompression with mesenchymal stem cells over conservative therapy (Table 1). The efficacy of bisphosphonates was initially deemed statistically significant in 2005 by Lai et al., but the same group later reported in 2012 controversial data (Table 1) [17]. The lack of high-level evidence in the literature makes it difficult to identify optimal treatment protocols to manage patients with pre-collapse ONFH, therefore it is crucial to evaluate whether these previously described treatments are effective.

We hypothesized that both bisphosphonate therapy alone and bisphosphonate therapy in combination with core decompression and mesenchymal stem cells can result in improved functional hip scores, lower level of pain scores, and a reduced risk of disease progression when compared with treatment of bisphosphonates alone. The primary aim of the current study was to retrospectively evaluate the reduction in the risk of hip replacement after treatment with either bisphosphonates alone or in combination with core decompression and mesenchymal stem cells in patients with ONFH at a pre-collapse stage. We also aimed to evaluate the radiologic progression of the disease between the two groups utilizing both X-ray and MRI. Lastly, we attempt to compare pre- and post-treatment Modified Harris Hip Scores, visual analog scores, and required support system used between BP alone and BP + CD + MSC groups.

Table 1 Favored treatments

Study	Favored odds ratio
Gangji et al. 2011 [9]	CD + MSC > CD[a]
Zhao et al. 2012 [29]	CD + MSC > CD[a]
Koo et al. 1995 [16]	CD = conservative
Neumayr et al. 2006 [19]	CD = conservative
Stulburg et al. 1991 [24]	CD = conservative
Chen et al. 2012 [6]	BP = conservative
Lai et al. 2005 [17]	BP > conservative[a]

[a] Denotes statistical significance

Patients and Methods

Institutional Review Board approval for this retrospective study was obtained via the Avascular Necrosis (AVN) of the Femoral Head Registry at our institution. Between 2006 and 2014, 84 consecutive patients who were diagnosed with AVN of the femoral head were identified from our institution's registry. Inclusion criteria were (1) diagnosed with ONFH, (2) over the age of 18 years, (3) idiopathic, steroid induced, ALL related, SLE related, sickle cell related, or alcohol induced, (4) baseline Ficat stage 1 or 2, and (5) treatment with either bisphosphonates (BP) alone or in combination with core decompression and mesenchymal stem cells (BP + CD + MSC). Exclusion criteria included patients (1) under the age of 18 years, (2) baseline Ficat stage 3 or 4, and (3) diagnosed with Ficat stage >2 in the contralateral limb. Of these 84 patients, 49 patients (62 hips), fit these criteria.

Twenty-nine patients (40 hips) were treated with bisphosphonate therapy only. Twenty patients (20 hips) were treated with bisphosphonates, core decompression, and mesenchymal stem cells. The mean age at presentation in the BP group was 43+/−12.1 years with 18 males and 11 females. The mean age at presentation in the BP + CD + MSC group was 38+/−14.7 with 9 males and 11 females. Underlying etiologies were recorded for each treatment group with the primary diagnosis being idiopathic in 37.50 and 54.70% in the BP and the BP + CD + MSC groups, respectively (Table 2). The mean follow-up for all patients including post-treatment hips after THR was 13.7+/−11.5 and 18.1+/−7.58 months in the BP and BP + CD + MSC groups, respectively. The mean follow-up for patients excluding those who had a THR was 25.3+/−11.5 and 22.7+/−19.5 months in the BP and BP + CD + MSC groups, respectively.

Clinical Evaluation

Initial visit evaluation was uniform for all patients and consisted of recording a detailed medical history and physical examination. Standard weight-bearing radiographs and magnetic resonance imaging (MRI) were performed at the discretion of the attending orthopedic surgeon. A complete history and physical was conducted with a particular focus on the clinical examination of the affected hip including range of motion and pain. Patients were then staged by the radiologist according to their radiological and MRI presentation as described previously by Ficat and Steinberg et al. [7, 8]. Functional outcomes were assessed using the Modified Harris Hip Score (MHHS), the visual analog score

Table 2 Demographic information

	BP	BP + CD + MSC	*P* value
Patients (*n*)	29	20	
Age	43 ± 12.1	38 ± 14.7	0.200
Mean follow-up (all patients)	13.7 ± 11.5	18.1 ± 7.58	0.113
Mean follow-up (excluding THR)	25.3 ± 11.5	22.7 ± 19.5	0.511
Female: male	1 (38%):18 (62%)	11 (55%):9 (45%)	0.238
Ficat stage			0.297
1	3 (10.3%)	1 (5.0%)	
2a	25 (86.2)	13 (65.0%)	
2b	1 (3.4%)	6 (30.0%)	
Hips (*n*)	40	22	
Etiology			0.602
Idiopathic	37.50%	54.70%	
Steroid induced	50%	36.2%	
Anticoagulation	10%	9.10%	
Trauma	2.5%	0	

(VAS), and evaluation of support system used. Scoring of the support system used included the following: 5—full weight bearing, 4—partial weight bearing with a walker, 3—partial weight bearing with a cane or one crutch, 2—two crutches, and 1—non-weight bearing with a wheelchair. Functional outcome data was collected at the initial office visit as well as at each consecutive visit following. The final follow-up outcome data was used for analysis.

Imaging

Diagnosis of ONFH was made based on available plain radiography anteroposterior (AP) and lateral frog views and MRI (sagittal and coronal views) assessing the stage and the extent of involvement of the femoral head. Outcome measures included the imaging staging of the hip and survival analysis. All imaging examination was analyzed by two experienced radiologists. Collapse was defined as progression from Ficat stage I or II to stage III and from Steinberg I, II, III to IV, V, VI. A radiographic failure was defined as the onset or the progression of collapse or progressive OA. The hips which did not fail were considered to be survived hips. Sixty-two patients had XR imaging at each follow-up, and 40 patients had MRI at each follow-up visit and were included for analysis.

Intervention

Patients were requested to initially obtain hematological lab reports to determine recent vitamin D levels in order to ensure proper medical management. Patients with low vitamin D levels were initially treated with over the counter vitamin D (1000 mg) twice a day and calcium citrate (1000 mg) twice a day. Follow-up visits with the surgeon were then performed within 1 month.

Bisphosphonate Protocol

If patient symptoms did not resolve and vitamin D levels were normal, the patients were then prescribed 35 mg of Actonel (bisphosphonate) taken orally once a week with follow-up visits every month. X-ray evaluation was done at each follow-up visit. Patients initially presenting with normal vitamin D levels, immediately were prescribed 35 mg of Actonel taken orally once a week. Follow-up was the same as above. Actonel was prescribed for a period of 1 year unless diagnosis of new onset of ONFH in the contralateral hip was made, then the treatment was extended.

Core Decompression/Mesenchymal Stem Cell/ Bisphosphonate Protocol

After vitamin D levels were corrected, patients underwent CD. Before beginning the CD procedure, the area of ON was carefully identified on AP and lateral radiographs as well as MRI. The procedure was performed with the patient supine on a fracture table under general anesthesia. The entire extremity including the ipsilateral hemi-pelvis was then prepared and draped in a sterile fashion. To obtain the mesenchymal stem cells, a stab incision was made 2 cm proximal to the anterior-superior iliac spine (ASIS) over the iliac crest. A fenestrated 11-G needle (BMAC–Harvest) was used to aspirate 60 cc of bone marrow from between the inner and outer tables of the iliac crest. All syringes had been previously treated with a solution of saline and heparin to avoid clotting. The aspiration was then concentrated into about 15 ml of the bone marrow cells using the bone marrow aspiration system (Harvest Technologies Corporation, Plymouth, MA).

Hip decompression was started during the time in which the bone marrow was concentrated and processed. The procedure was done under fluoroscopic guidance in two planes with two C-arms draped with sterile sleeves. After an initial fluoroscopic evaluation to determine the ideal entry point, an approximately 3-cm incision was made over the lateral aspect of the thigh. Dissection was carried down sharply to the fascia layer, which was posteriorly divided longitudinally. The vastus lateralis was then split midline distal to the vastus tubercle. With the use of fluoroscopic guidance, the guidewire

was then placed into the center of the previously identified necrotic lesion, typically in the anterosuperior region of the femoral head. A 4.5-mm cannulated reamer was then inserted over the guided wire stopping reaming at least 5 mm from the articular surface of the femoral head. The guided wire was then removed and exchanged with a trocar. Once the optimal position was identified, the concentrated marrow was injected into the core tract femoral head slowly in order to reduce leakage. The trocar and the wire were then removed, and the incision was closed in layers (Fig. 1a–d). Postoperatively, all patients were treated with an intravenous infusion of cefazolin and they were discharge from the hospital the same day of the operation. Patients were told to remain non-weight-bearing with crutches for 3 weeks after which were changed to weight bearing as tolerated. A course of 3 months physical therapy was indicated if the patient was presenting with any limitations, such as limited range of motion, muscle tightness, or gait balance abnormalities.

After the CD procedure, patients continued the prescribed regimen of 35 mg of Actonel taken orally once a week. Actonel was prescribed for a period of 1 year unless diagnosis of new onset of AVN in the contralateral hip was made, then the treatment was extended.

Statistical Analysis

Continuous variables are presented as means with standard deviations or medians with first and third quartiles, depending upon the data distribution, and categorical variables are presented as counts and percentages. Continuous baseline variables were compared between treatment groups using two-sample *t* tests or Wilcoxon rank-sum tests. Categorical baseline variables were compared between treatments using chi-square or Fisher's exact tests, as appropriate. The Kaplan-Meier analysis was used to calculate median time to event and produce survival curves. Cox proportional hazards modeling was used to compare hazard rates between treatments while adjusting for potential confounders. We used a marginal Cox model approach with a working independence assumption to account for the correlation between

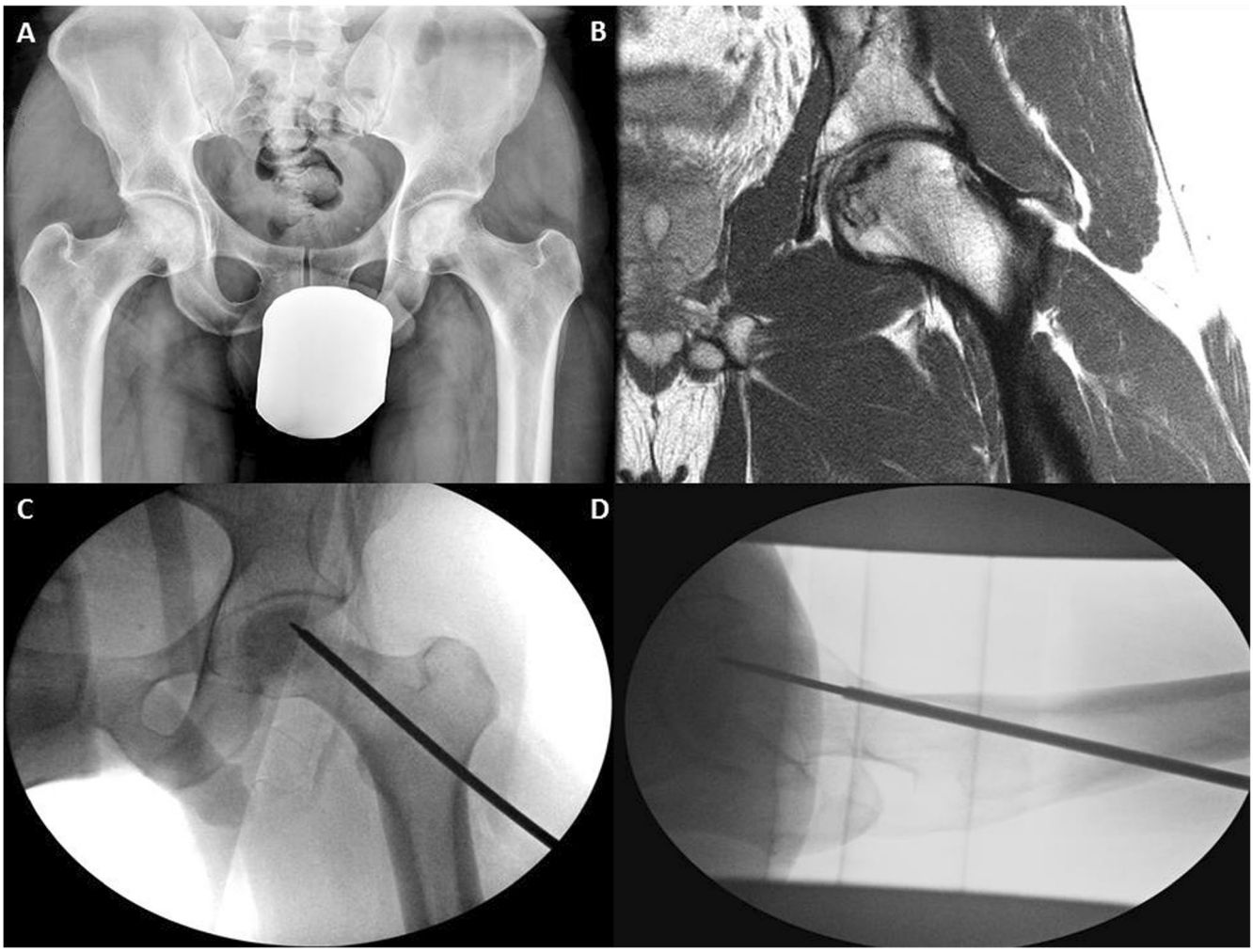

Fig. 1. **a** Anteroposterior X-ray of the pelvis demonstrating a Ficat stage IIb osteonecrosis of the left femoral head. **b** Same patient, left hip coronal MRI depicting the size of the lesion. **c**, **d** Same patient AP and axial fluoroscopic images taken during the femoral head decompression procedure.

outcomes on bilateral hips of the same patient. Multiple regression was used to compare change in functional outcome measures between groups while adjusting for potential confounders. All statistical hypothesis tests were two-sided, with statistical significance defined as $P<0.05$. Statistical analyses were performed with SAS Version 9.3 (SAS Institute, Cary, NC).

Results

There was no evidence of a difference in instantaneous risk of THR in unreplaced hips treated with BP + CD + MSC compared to BP alone. Adjusting for baseline Ficat stage, age, and sex, an unreplaced hip treated with BP + CD + MSC had 0.42 (95% CI 0.11, 1.57) times the risk of being replaced in the next moment compared to a hip treated with BP only ($P=0.196$). At a mean follow-up of 25.3+/−11.5 months, 19/40 (47.5%) of BP-treated hips had not required THR. At a mean follow-up of 22.7+/−19.5 months 17/22 (77.27%) of the BP + CD + MSC-treated hips had not required surgery. Failure requiring THR occurred in 21/40 (52.5%) of BP-treated hips and 5/22 (22.73%) of BP + CD + MSC-treated hips. The median (Q1, Q3) time to THR was 24.9 (7.4, 33.0) months in BP-treated hips and 27.3 (27.3) months in BP + CD + MSC-treated hips. Hips treated with BP + CD + MSC had a similar chance of progressing to the next stage on radiologic analysis compared to hips treated with BP alone ($P>0.7$). Adjusting for baseline Ficat stage, age, and sex, a hip treated with BP + CD + MSC and BP alone had similar odds of 0.83 (95% CI 0.45, 1.54 ($P=0.548$)) and 0.54 (95% CI 0.02, 15.47 ($P=0.719$)) times the odds treated with bisphosphonates only on XR and MRI analysis, respectively.

There was no evidence of a difference in the instantaneous risk of progressing to the next stage on radiologic analysis between hips treated with BP + CD + MSC vs. BP alone. Adjusting for baseline Ficat stage, age, and sex, an unreplaced hip treated with BP + CD + MSC had 0.83 (95% CI 0.45, 1.54; $P=0.548$) and 0.54 (95% CI 0.02, 15.47; $P=0.719$) times the risk of progressing to the next radiologic stage in the next moment on XR and MR, respectively, compared to hips treated with bisphosphonates only.

The clinical outcome measures after treatment are presented in Table 3. There was no evidence of a difference in functional outcomes between the two treatment groups.

Discussion

While a number of studies have successfully used bisphosphonate therapy to counter structural bone weakening in ONFH [1, 2], recent studies evaluating the effectiveness of core decompression in early stage ONFH remains controversial. To our knowledge, this is the first study that attempts to evaluate both treatment strategies to determine whether one results in greater improvements in clinical outcomes and a delayed progression of the disease.

In our study, 21/40 (52.5%) hips with a mean follow-up of 25.3 months following BP treatment, required a THA compared to 5/22 (22.73%) hips with a mean follow-up of 22.7 months treated with BP + CD + MSC. After adjusting for baseline Ficat stage, age, and sex, a hip treated with BP + CD + MSC had between a 17 and 46% reduction in risk of progressing to the next stage and a 58% reduction in risk of THR compared to a hip treated with BP only, but this finding was not statistically significant. Previous studies have reported that collapse of Steinberg stage II and III femoral heads typically occurs within the first 16–21 months after diagnosis without treatment [16]. Earlier studies have reported rates of collapse of the femoral head of 75 and 80% at 2 and 3 years, respectively [2]. In our present study, our results show that BP treatment alone and BP + CD + MSC treatment resulted in collapse rates and need for THR at 2 years in 43 and 21% of hips, respectively. Although there were no statistically significant differences, our results demonstrate that BP alone and BP + CD + MSC prevented or delayed THA in the first 24 months in 57 and 79% of hips, respectively. These results indicate both treatment options, BP alone and BP + CD + MSC, decrease the risk of collapse as well as the risk of the need for THR. The decision to proceed with a THR is multivariate and dependent on a careful discussion between the patient and their surgeon. While patients may choose to delay THR when presented with an alternate and less invasive option, our results show that both interventions decrease the risk of collapse and thus absolute need for THR. Even though there is no statistical difference between BP alone and BP + CD + MSC, the variations seen in the results between the treatment groups warrants prospective studies to evaluate possible differences in efficacy in delaying the progression of collapse in ONFH. These results indicate that both BP alone and BP + CD + MSC may postpone surgical intervention. This may be complicated by the fact that the treating physician is already providing an alternative therapy. The indications for THR are not entirely objective.

The data from this study also demonstrates no significant difference in clinical outcomes between the two treatment groups when evaluating MHHS, VAS, ROM, and support system. These results may indicate that clinically, there is no difference between the two treatment strategies, thereby questioning CD as necessary surgical intervention. In the BP group, a mean score of 0 (range 0–4) for support system was calculated. In contrast, a mean score of 2.5 (range 0–5) was calculated for the BP + CD + MSC group. Standardized evaluation with larger sample sizes along with the differentiation of the diagnosed stage is necessary to determine a more accurate determination of clinical functional outcomes.

Bisphosphonate therapy has been shown to counter the structural bone weakening caused by reparative osteocytic necrosis and apoptosis through anti-resorptive and anti-inflammatory actions [26]. Bisphosphonates function by inhibiting osteoclast activity, thereby curtailing bone resorption. Recent studies have demonstrated improvement and a reduction in patient disability scores, as well as an overall reduction in the rate of collapse in patients when compared to a control [1, 2, 17]. Lai et al. found that at a minimum of 24 months, only two of the 25 hips in the bisphosphonate group had loss of femoral head integrity compared with 19

Table 3 Clinical Outcomes

	BP			BP + CD + MSC								
	n	Mean ± SD	Median (Q1, Q3)	*n*	Mean ± SD	Median (Q1, Q3)	Unadjusted difference in means (95% CI)	*P* value	Adjusted difference in means (95% CI) [adjusted for follow-up time]	*P* value	Adjusted difference in means (95% CI) [adjusted for Ficat stage, age, and sex]	*P* value
MHHS initial	14	57.9 ± 25.9	60 (38, 84)	15	45.9 ± 17.8	47 (35, 57)	–	0.143	–	–	–	–
MHHS final	13	74.5 ± 25.7	84 (77, 91)	14	63.4 ± 23.5	69 (44, 84)	−11.0 (−30.5, 8.5)	0.255	−11.0 (−31.0, 9.0)	0.268	−12.3 (−33.6, 9.1)	0.246
MHHS change	13	15.3 ± 17.6	8.0 (4, 20)	14	16.8 ± 29.9	10 (0, 47)	1.5 (−18.2, 21.1)	0.878	1.2 (−18.7, 21.2)	0.638	−0.3 (−21.7, 21.2)	0.981
VAS initial	14	4.6 ± 3.9	5 (0, 8)	15	6.5 ± 2.4	6 (4, 9)	–	0.323	–	–	–	–
VAS final	12	2.4 ± 3.9	0 (0, 4)	14	4.3 ± 2.6	4.5 (2, 6)	1.9 (−0.8, 4.5)	0.154	1.8 (−0.8, 4.5)	0.171	2.2 (−0.9, 4.9)	0.164
VAS change	12	−2.5 ± 3.4	−0.5 (−5, 0)	14	−2.0 ± 3.6	−2 (−5, 1)	0.5 (−2.3, 3.3)	0.720	0.6 (−2.3, 3.5)	0.695	0.4 (−2.8, 3.6)	0.790
Support initial	14	1.4 ± 1.8	0 (0, 4)	15	2.3 ± 1.9	4 (0, 4)	–	0.138	–	–	–	–
Support final	12	0.3 ± 1.2	0 (0, 0)	14	1.9 ± 2.0	1.5 (0, 4)	1.5 (0.2, 2.9)	0.027	1.5 (0.1, 2.8)	0.031	1.5 (0, 3.1)	0.045
Support change	12	−1.2 ± 1.8	0 (−3, 0)	14	−0.3 ± 2.4	0 (−1, 1)	0.9 (−0.8, 2.6)	0.303	0.9 (−0.9, 2.7)	0.308	1.0 (−1.0, 2.9)	0.311

of the 25 hips in the control group [17]. Although these results have been promising, the role of bisphosphonates still has remained controversial. Chen et al. reported no significant difference in disease progression, functional outcomes, and radiologic outcomes. In addition, the optimal dosage of bisphosphonate therapy has not yet been established. Therefore, these drugs should be carefully administered. The dosage regimens used in this present study were chosen because they are currently recommended in the standard of care for the treatment of ONFH.

Although there is general agreement in the literature that core decompression is effective in earlier stages of the disease, evidence of its efficacy in preventing collapse has been controversial with the overall rate of success varying from as low as 40% to as high as 89% [5, 7, 8] A meta-analysis of 24 studies analyzing 1206 hips demonstrated that the best results of CD were in the treatment of early-stage lesions [18]. Eighty-four percent of patients with Ficat and Arlet stage I disease and 65% of patients with stage II disease had successful results [18]. The pathological mechanism underlying osteonecrosis has been associated with premature conversion of the red marrow to the fatty marrow resulting in an overall diminished number of progenitor cells in the affected bone [10, 16]. There has been documentation of decreased osteogenic stem cell concentrations beneath the sequestrum and in the inter-trochanteric region of the femoral head [12]. Therefore, the addition of autologous bone marrow along with core decompression may enhance repair of bone after osteonecrosis. Previous studies have demonstrated therapeutic effects of bone marrow implantation through marrow stromal cell secretion of angiogenic cytokines increasing both angiogenesis and osteogenesis. Hernigou et al. reported better outcomes in patients who had greater numbers of progenitor cells transplanted in their hips during CD procedures [13]. The addition of autologous mesenchymal stem cells as an adjunctive therapy may offer a potential safe and effective alternative in the treatment of ONFH.

Given the complex and variable nature of the pathogenesis of ONFH, it is not surprising that the variety of treatment modalities remain a controversial issue. The novel therapeutic approach of combining BP + CD + MSC may not only provide stability to the affected hip, but also may aid in reversing the disease process. CD reduces intra-medullary pressure, thereby increasing femoral head perfusion. This procedure allows for substitution to the necrotic area by bringing blood supply through the drill channel [20]. The mesenchymal stem cells augment osteogenic potential and when combined with CD, create an environment that enhances bone growth and delays disease progression. Furthermore, the addition of bisphosphonate therapy reduces marrow edema and the rate of remodeling, ultimately halting bone resorption. Our results were similar to some of the more recent studies evaluating CD in the treatment of ONFH in a comparable patient population (Table 4). Hernigou and Gangji pioneered the instillation of using MSCs along with CD in the treatment of ONFH. Our overall success rate of 77% for patients treated with BP + CD + MSC is comparable to the results reported by both Hernigou et al. and Gangji et al [9, 11]. A recent study by Kang et al. demonstrated an 83.6% overall success rate after treatment with BP + CD and reported a mean onset of progression of collapse at 23 months post-operatively [15]. The results of the current study, in addition to the evidence reported in the literature, support the belief that future prospective clinical trials are warranted to determine the efficacy and compare the outcomes of operative, medical, and conservative care in delaying the progression of ONFH. The data from this study can be used to help direct and inform hypotheses and power analyses for such studies.

This study has several limitations. Our study was retrospective and thus maintains the biases inherent to such a study design. Although this current study suggests that treatment with either BP or BP + CD + MSC are effective in delaying collapse within the first 24 months after diagnosis, the lack of long-term follow-up data makes it difficult to determine whether this effect can be maintained over longer periods of time. Future prospective studies are critical in determining whether these treatment strategies can prevent THR in the long term. While there is clinical and radiologic improvement, delaying THR in the younger, active population may not ultimately be the best option. Assuming that 50% of patients treated with BPs alone will undergo THR within 2 years post-treatment initiation, 109 patients per group (218 total) would be required to obtain 80% power at a two-sided alpha level of 0.05 to detect a 20 percentage

Table 4 Review of the current literature

	Follow-up	Method	Success rate
Aigner et al. (2002) [3]	68.9 months	CD	78%
Belmar et al. (2004) [4]	46 months	CD	63%
Sen et al. (2012) [21]	24 months	CD	40.36 weeks[a]
Steinberg et al. (1999) [22]	39 months	CD	64%
Gangji et al. (2011) [9]	60 months	CD + MSC	77%
Hernigou et al. (2002) [11]	26 months	CD + MSC	82%
Sen et al. (2012) [21]	24 months	CD + MSC	52 week[a]
Kang et al. (2012) [15]	23 months[b]	BP + CD	83.6%
Current study	22.7 months	BP + CD + MSC	77.3%
Current study	25.3 months	BP only	48%

[a] Mean survival time
[b] Followed patients up to 4 years

point decrease in THR within 2 years post-treatment initiation in the BP + CD + MSC group using logistic regression. The sample size estimate includes an adjustment for the assumption that a multiple regression of treatment group on the other predictors would produce a pseudo R2 of 0.15.

The lack of clinical evidence in the literature makes it difficult to identify optimal treatment protocols to manage patients with pre-collapse AVN of the femoral head. Our results demonstrate that treatment with BP alone or BP + CD + MSC have the potential to delay the need for THA in the first 24 months in patients with ONFH. Future prospective studies are warranted to determine the efficacy of these treatment strategies in the long term. Prospective studies should attempt to compare operative, medical, and conservative care in the treatment of ONFH to establish conclusive evidence.

Compliance with Ethical Standards

Conflict of Interest: Arianna L Gianakos, BS, Joaquin Moya-Angeler, MD, Shivi Duggal, BS, MBA, Lester Zambrana, BA, Kara G. Fields, MS, Douglas N. Mintz, MD, and Charles N. Cornell, MD have declared that they have no conflict of interest. Joseph M. Lane, MD reports other from Bone Therapeutics, SA and Emcyte; personal fees and other from Grafty's, ISTO and Kuros; personal fees from CollPlant Inc, outside the work.

Human/Animal Rights: All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008 (5).

Informed Consent: Informed consent was obtained from all patients for being included in the study.

Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

References

1. Agarwala S, Jain D, Joshi VR, Sule A. Efficacy of alendronate, a bisphosphonate, in the treatment of AVN of the hip. A prospective open-label study. *Rheumatology (Oxford)*. 2005; 44(3): 352-359.
2. Agarwala S, Shah S, Joshi VR. The use of alendronate in the treatment of avascular necrosis of the femoral head: follow-up to 8 years. *J Bone Joint Surg (Br)*. 2009; 91(8): 1013-1018.
3. Aigner N, Schneider W, Eberl V, Knahr K. Core decompression in early stages of femoral head avascular necrosis—an MRI-controlled study. *Int Orthop*. 2002; 26: 31.
4. Belmar CJ, Steinberg ME, Hartman-Sloan KM. Does pain predict outcome in hips with osteonecrosis? *Clin Orthop Relat Res*. 2004; 425: 158-162.
5. Bozic KJ, Zurakowski D, Thornhill TS. Survivorship analysis of hips treated with core decompression for nontraumatic osteonecrosis of the femoral head. *J Bone Joint Surg Am*. 1999; 81(2): 200-209.
6. Chen C, Chang J, Lai K, Hou S, Chang C, Wang G. Alendronate in the prevention of collapse of the femoral head in nontraumatic osteonecrosis: a two-year multicenter, prospective, randomized, double-blind, placebo-controlled study. *Arthritis Rheumatol*. 2012; 64(5): 1572-1578.
7. Colwell CW Jr, Robinson CA, Stevenson DD, Vint VC, Morris BA. Osteonecrosis of the femoral head in patients with inflammatory arthritis or asthma receiving corticosteroid therapy. *Orthopedics*. 1996; 19(11): 941-946.
8. Ficat R, Arlet J. Necrosis of the femoral head. In: *Ischemia and necrosis of bone*. Baltimore: Williams & Wilkins; 1980: 171-182.
9. Gangji V, De Maertelaer V, Hauzeur J. Autologous bone marrow cell implantation in the treatment of non-traumatic osteonecrosis of the femoral head: five year follow-up of a prospective controlled study. *Bone*. 2011; 49(5): 1005-1009.
10. Hashimoto M. The distribution of active marrow in the bones of normal adult. *Kyushu J Med Sci*. 1960; 11(3): 103-105.
11. Hernigou P, Beaujean F. Treatment of osteonecrosis with autologous bone marrow grafting. *Clin Orthop Relat Res*. 2002; 405: 14-23.
12. Hernigou P, Beaujean F, Lambotte JC. Decrease in the mesenchymal stem-cell pool in the proximal femur in corticosteroid-induced osteonecrosis. *J Bone Joint Surg (Br)*. 1999; 81(2): 349-355.
13. Hernigou P, Poignard A, Zilber S, Rouard H. Cell therapy of hip osteonecrosis with autologous bone marrow grafting. *Indian J Orthop*. 2009; 43(1): 40-45.
14. Johannson HR, Zywiel MG, Marker DR, Jones LC, McGrath MS, Mont MA. Osteonecrosis is not a predictor of poor outcomes in primary total hip arthroplasty: a systematic literature review. *Int Orthop*. 2011; 35(4): 465-473.
15. Kang P, Pei F, Shen B, Zhou Z, Yang J. Are the results of multiple drilling and alendronate for osteonecrosis of the femoral head better than those of multiple drilling? A pilot study. *Joint Bone Spine*. 2012; 79(1): 67-72.
16. Koo KH, Kim R, Ko GH, Song HR, Jeong ST, Cho SH. Preventing collapse in early osteonecrosis of the femoral head. A randomised clinical trial of core decompression. *J Bone Joint Surg (Br)*. 1995; 77(6): 870-874.
17. Lai KA, Shen WJ, Yang CY, Shao CJ, Hsu JT, Lin RM. The use of alendronate to prevent early collapse of the femoral head in patients with nontraumatic osteonecrosis. A randomized clinical study. *J Bone Joint Surg Am*. 2005; 87(10): 2155-2159.
18. Mont MA, Carbone JJ, Fairbank AC. Core decompression versus nonoperative management for osteonecrosis of the hip. *Clin Orthop Relat Res*. 1996; 324(324): 169-178.
19. Neumayr LD, Aguilar C, Earles AN, et al. Physical therapy alone compared with core decompression and physical therapy for femoral head osteonecrosis in sickle cell disease. *J Bone Joint Surg Am*. 2006; 88(12): 2573-2582.
20. Sen RK. Management of avascular necrosis of femoral head at pre-collapse stage. *Indian J Orthop*. 2009; 43(1): 6-16.
21. Sen RK, Tripathy SK, Aggarwal S, Marwaha N, Sharma RR, Khandelwal N. Early results of core decompression and autologous bone marrow mononuclear cells instillation in femoral head osteonecrosis: a randomized control study. *J Arthroplasty.* 2012; 27(5): 679-686.
22. Steinberg ME, Bands RE, Parry S, Hoffman E, Chan T, Hartman K. Does lesion size affect the outcome in avascular necrosis? *Clin Orthop Relat Res*. 1999; 367: 262-271.
23. Steinberg ME, Hayken GD, Steinberg DR. A quantitative system for staging avascular necrosis. *J Bone Joint Surg (Br)*. 1995; 77(1): 34-41.
24. Stulberg BN, Davis AW, Bauer TW, Levine M, Easley K. Osteonecrosis of the femoral head: a prospective randomized treatment protocol. *Clin Orthop Relat Res*. 1991; 268: 140-151.
25. Wang GJ, Cui Q, Balian G. The Nicolas andry award. The pathogenesis and prevention of steroid-induced osteonecrosis. *Clin Orthop Relat Res*. 2000; 370(370): 295-310.
26. Wang C, Peng J, Lu S. Summary of the various treatments for osteonecrosis of the femoral head by mechanism: a review. *Exp Ther Med*. 2014; 8(3): 700-706.
27. Yang S, Halim AY, Werner BC, Gwathmey FW, Cui Q. Does osteonecrosis of the femoral head increase surgical andmedical complication rates after total hip arthroplasty? A comprehensive analysis in the United States. *Hip Int*. 2015; 25(3): 237-244.
28. Zalavras CG, Lieberman JR. Osteonecrosis of the femoral head: evaluation and treatment. *J Am Acad Orthop Surg*. 2014; 22(7): 455-464.
29. Zhao D, Cui D, Wang B, et al. Treatment of early stage osteoecrosis of the femoral head with autologous implantation of bone marrow-derived and cultured mesenchymal stem cells. *Bone*. 2012; 50(1): 325-330.