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HIP

Hip decompression combined with bone marrow concentrate and platelet-rich plasma for corticosteroid-induced osteonecrosis of the femoral head

MID-TERM UPDATE FROM A PROSPECTIVE STUDY

M. T. Houdek,
C. C. Wyles,
J-R. H. Smith,
A. Terzic,
A. Behfar,
R. J. Sierra

From Mayo Clinic, Rochester, Minnesota, USA

Aims

Bone marrow-derived mesenchymal stem cells obtained from bone marrow aspirate concentrate (BMAC) with platelet-rich plasma (PRP), has been used as an adjuvant to hip decompression. Early results have shown promise for hip preservation in patients with osteonecrosis (ON) of the femoral head. The purpose of the current study is to examine the mid-term outcome of this treatment in patients with precollapse corticosteroid-induced ON of the femoral head.

Methods

In all, 22 patients (35 hips; 11 males and 11 females) with precollapse corticosteroid-induced ON of the femoral head underwent hip decompression combined with BMAC and PRP. Mean age and BMI were 43 years (SD 12) and 31 kg/m^2 (SD 6), respectively, at the time of surgery. Survivorship free from femoral head collapse and total hip arthroplasty (THA) and risk factors for progression were evaluated at minimum five-years of clinical follow-up with a mean follow-up of seven years (5 to 8).

Results

Survivorship free from femoral head collapse and THA for any reason was 84% and 67% at seven years postoperatively, respectively. Risk factors for conversion to THA included a high preoperative modified Kerboul angle (grade 3 or 4) based on preoperative MRI (hazard ratio (HR) 3.96; p = 0.047) and corticosteroid use at the time of decompression (HR 4.15; p = 0.039). The seven-year survivorship for patients with grade 1 or 2 Kerboul angles for conversion to THA for articular collapse, and THA for any reason, were 96% and 72%, respectively, versus THA for articular collapse and THA for any reason in patients with grade 3 or 4 Kerboul angles of 40% (p = 0.003) and 40% (p = 0.032).

Conclusion

At seven years, hip decompression augmented with BMAC and PRP provided a 67% survivorship free from THA in patients with corticosteroid-induced ON. Ideal candidates for this procedure are patients with low preoperative Kerboul angles and can stop corticosteroid treatment prior to decompression.

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Correspondence should be sent to Rafael J Sierra; email: sierra.rafael@mayo.edu

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Introduction

Osteonecrosis (ON) of the femoral head is a progressive disease commonly seen in patients aged younger than 40 years.[1-3] The disease is a multifatorial process characterized by an insult to the blood supply, leading to trabecular and subchondral bone death, ultimately progressing to fracture and collapse of the joint surface.[4-9] Treatments for the disease process are based on integrity of the

Table I. Characteristics of patients undergoing hip decompression augmented with bone marrow aspirate concentrate and platelet-rich plasma for femoral head for corticosteroid-induced osteonecrosis.

Demographic	Patients (n = 22)	Hips treated (n = 35)	p-value
Mean patient age, yrs (SD)	43 (12)	42 (12)	0.882*
Males, n (%)	11 (50)	16 (46)	0.791†
Females, n (%)	11 (50)	19 (54)	0.791†
Mean BMI, kg/m² (SD)	31 (6)	30 (6)	0.899*
Continued corticosteroid use, n (%)	8 (36)	14 (40)	1.000†
Low preoperative kerboul grade 1 or 2, n (%)	N/A	30 (86)	N/A
High preoperative grade 3 or 4, n (%)	N/A	5 (14)	N/A

*Student's *t*-test.
†Fisher's exact test.
N/A, not applicable; SD, standard deviation.

femoral head, with total hip arthroplasty (THA) being the standard of care following collapse when the joint cannot be salvaged.[6,10-15]

In patients where the femoral head has not collapsed, hip decompression has become a preferred means of treatment, with a femoral head preservation rate of 96% with early precollapse disease, specifically Ficat stage I.[7,16-26] As the disease progresses, decompression failure rate increases, with patients with advanced precollapse disease (Ficat or University of Pennsylvania Stage II) having failure rates of up to 77%.[25,26] In order to improve the outcome of patients with advanced precollapse disease, bone marrow aspirate concentrate (BMAC) has been injected into the femoral head at the time of decompression, with or without platelet-rich plasma (PRP).[19-23,27,28] We previously reported on the early outcomes (up to three years of follow-up) of a group of patients with corticosteroid-induced precollapse ON of the femoral head undergoing hip decompression augmented with BMAC and PRP, showing a 93% rate of preventing femoral head collapse, with 84% free of conversion to THA.[28] The purpose of the current study is to investigate the mid-term follow-up of these patients at a minimum of five years.

Methods. Following approval from our institutional review board, we reviewed a prospectively collected patient population who underwent hip decompression of the femoral head augmented with autologous BMAC and PRP.[28] The cohort was composed of 22 patients (11 males and 11 females) who had a mean age of 43 years (22 to 66), and a mean BMI of 31 kg/m² (22 to 41) at the time of surgery. In all, 13 patients (59%) had bilateral disease treated concurrently under a single anaesthetic, and nine had unilateral disease, for a total of 35 hips (Table I). All patients had painful precollapse ON, rated either University of Pennsylvania stage 1 (four hips; 11%) or stage 2 (31 hips; 89%).[29] All patients had at least five years of clinical follow-up, with a mean follow-up of seven years (5 to 8) (Table I).

At the time of decompression, all patients had a history of corticosteroid use, with 14 patients taking oral corticosteroids at the time of decompression. In addition to ON of the femoral head, a labral tear was present on MRI in 20 hips (57%) (Table I). Overall, 13 hips (37%) had acetabular degenerative changes which were related to impingement. Prior to surgery, all patients had an MRI of the hip to assess the size of the necrotic lesion using the modified Kerboul angle.[30] Lesions were graded as 1 (< 200°; n = 14), 2 (200° to 249°; n = 16), 3 (250° to 299°; n = 3), and 4 (≥ 300°; n = 2).[30] A high Kerboul angle was defined as grade 3 or 4.

All patients underwent a hip decompression with injection of 12 cc of BMAC and 6 cc of PRP.[28] For analysis of the BMAC, three additional cc was taken to the laboratory to assess the MSC content through total nucleated cell count and fibroblast colony-forming unit assays (CFU), as previously described.[28]

Clinical evaluation

The Harris Hip Score (HHS)[31] was used to assess functional outcome. In addition, progression of ON with subsequent collapse and additional procedures including THA and repeat decompression were also captured. Failure of the procedure was defined as progressing to THA.

Statistical analysis. Student's *t*-tests were used to compare continuous variables, and Fisher's exact tests were used to compare categorical variables. The Kaplan-Meier method was used to analyze survivorship free from conversion to THA, any procedure, and femoral head collapse. In patients with bilateral disease, each hip was analyzed independently. Univariate cox proportional hazard regression was used to identify risk factors for failure and reoperation. Statistical significance was set at a p-value < 0.05.

Results

Conversion to total hip arthroplasty. Over the course of follow-up, ten hips (six patients) underwent THA (Table II). Indication for THA included articular collapse (n = 5), continued pain without articular collapse (n = 3), and pain with radiological and clinical progression in osteoarthritis (OA) of the acetabulum (n = 2). The mean

Table II. Preoperative characteristics of patients undergoing reoperation.

Sex	Age, yrs	Kerboul angle, °	Kerboul grade	Still taking corticosteroids	Indication for steroids	Reoperation	Reason for reoperation	Time to THA, yrs
Female	44	223	2	Yes	Peripheral neuropathy	THA	Pain	Three
		160	1	Yes		THA	Pain	Five
Female	43	230	2	Yes	Polyarthralgia	Decompression	Pain	
		200	2	Yes		Decompression, THA	OA acetabulum	Seven
Female	41	183	1	Yes	Asthma	THA	Collapse	Five
		173	1	Yes		THA	Collapse	Six
Male	51	320	4	No	Psoriasis	THA	Collapse	Two months
Female	54	278	3	No	Adrenal insufficiency	Decompression	Pain	
		230	2	No		Decompression	Pain	
Female	23	199	2	Yes	Solid organ transplant	THA	Collapse	Five
		178	1	Yes		THA	OA acetabulum	Six
Female	57	300°	4	No	Asthma	THA	Collapse	Two
		270	3	No		THA	Collapse	Four

OA, osteoarthritis; THA, total hip arthroplasty.

Table III. Cox proportional hazard analysis for failure of hipdecompression augmented with bone marrow aspirate concentrate and platelet-rich plasma or corticosteroid induced osteonecrosis of the femoral head.

Risk factor at time of decompression	Conversion to THA, HR (95% CI)	p-value*	Conversion to THA for femoral head collapse, HR (95% CI)	p-value*	Repeat surgical procedure, HR (95% CI)	p-value*
Males	0.14 (0.01 to 1.12)	0.064	0.32 (0.03 to 2.89)	0.312	0.09 (0.01 to 0.70)	0.022
Females	7.04 (0.89 to 55.66)	0.064	3.09 (0.34 to 27.71)	0.312	10.98 (1.42 to 84.71)	0.022
High preoperative Kerboul angle	3.96 (1.02 to 15.47)	0.047	13.34 (2.19 to 81.31)	0.004	5.35 (1.63 to 17.86)	0.006
Obesity	0.63 (0.16 to 2.45)	0.509	0.39 (0.04 to 3.52)	0.404	1.02 (0.33 to 3.13)	0.967
Smoking	1.10 (0.23 to 5.20)	0.901	N/A	0.999	1.72 (0.38 to 7.79)	0.479
Steroids use	4.15 (1.07 to 16.10)	0.039	1.11 (0.18 to 6.69)	0.904	2.82 (0.92 to 8.64)	0.069

*Cox proportional hazard regression.
CI, confidence interval; HR, hazard ratio; N/A, not applicable; THA, total hip arthroplasty.

time to THA was four years (two months to seven years). The overall survival free of femoral head collapse leading to THA at the two-year, five-years, and seven-year time points was 97%, 87%, and 84%, respectively. Survivorship free from THA for all causes at the two-year, five-year, and seven-year time points was 97%, 85%, and 67%, respectively.

Hips with a high preoperative Kerboul angle (grade 3 or 4) were at increased risk of conversion to THA compared to patients with a low (grade 1 or 2) Kerboul angle (hazard ratio (HR) 3.96, 95% confidence interval (CI) 1.02 to 15.41; p = 0.047, Cox proportional hazard regression (Table III)) for any reason and for collapse of the femoral head (HR 13.34, 95% CI 2.19 to 81.31; p = 0.004, Cox proportional hazard regression). The seven-year survivorship for patients with grade 1 or 2 Kerboul angles for conversion to THA for articular collapse and THA for any cause were 96% and 72%, respectively. The survivorship free of conversion to THA in these patients was improved compared to patients with grade 3 or 4 Kerboul angles where the seven-year survivorship free of conversion to THA for articular collapse and THA for any cause was 40% (p = 0.003, Kaplan-Meir method with log-rank test) and 40% (p = 0.032, Kaplan-Meir method with log-rank test), respectively.

Patients who required continued corticosteroids at the time of the decompression were at increased risk of failure (HR 4.15, 95% CI 1.07 to 16.10; p = 0.039, Cox proportional hazard regression). All hips that progressed to THA had Steinberg Stage II disease at the time of decompression (n = 10 (32%) vs n = 0 (0%); p = 0.300). Female sex trended towards an increased risk of conversion to THA (HR 7.04, 95% CI 0.89 to 55.66; p = 0.064, Cox proportional hazard regression); however, this failed to reach statistical significance.

Repeat decompression. Overall, two patients (four hips) underwent repeat decompression with BMAC and PRP injection for pain. One patient (two hips) had relief of pain at eight years of follow-up following the repeat decompression. The other patient had one hip in which the pain improved and on a postoperative MRI the area of ON had improved. However, in the same patient, the contralateral hip progressed to THA at six years due to continued pain, without collapse, and noted to have OA of the acetabulum at the time of THA. A high (grade 3 or 4) preoperative Kerboul angle (HR 5.35, 95% CI 1.63

to 17.86; p = 0.006, cox proportional hazard regression) was associated with a repeat surgical procedure. In addition, females were more likely to undergo a repeat surgical procedure (HR 10.98, 95% CI 1.42 to 84.71; p = 0.022, Cox proportional hazard regression).

Cellular concentration analysis. At the time of index decompression, the mean CFU was 19 (standard deviation (SD) 6) and the mean concentration of nucleated cells per millilitre of BMAC was 1.93×10^7 (SD 2.08) x 10^7 cells/ml. Patients undergoing an additional surgical procedure (THA or repeat core decompression) had lower mean CFUs compared with those who did not (14 (SD 6) vs 20 (SD 7); p = 0.021, Student's *t*-test), but there was no difference in the mean concentration of nucleated cells per millilitre of BMAC between these groups (1.23×10^7 (SD 1.56) x 10^7 cells/ml vs 2.34×10^7 (SD 2.26) x 10^7 cells/ml; p = 0.129, Student's *t*-test).

Compared to our previous analysis,[28] at mid-term follow-up there was no difference in the mean CFU between patients who were converted to a THA for femoral head collapse compared to patients who did not undergo conversion to THA (15 (SD 7) vs 18 (SD 7); p = 0.475, Student's t-test). When examining THA for all causes, there was no difference in the mean CFU between patients who underwent THA for any reason compared to patients who did not undergo conversion to THA (16 (SD 5) vs 18 (SD 8); p = 0.369, Student's t-test). There was no difference in mean concentration of nucleated cells per millilitre of BMAC in patients undergoing a THA for femoral head collapse compared to patients who did not have a THA for collapse (5.19 x 10^6 (SD 2.88) x 10^5 cells/ml vs 2.17 x 10^7 (SD 2.16) x 10^7 cells/ml; p = 0.101, Student's t-test). There was no difference in the mean concentration of nucleated cells per millilitre of BMAC in patients who underwent a THA for any reason compared to patients who were not converted to a THA (1.46 x 10^7 (SD 1.73) x 10^7 cells/ml vs 2.12 x 10^7 (SD 2.20) x 10^7 cells/ml; p = 0.409, Student's t-test).

Functional outcomes. Prior to surgery, the mean HHS was 57 (SD 12), improving to 85 (SD 15) at short-term (two to three years), and 76 (SD 19) at mid-term (five to seven years) follow-up. There was improvement between the preoperative and short-term mean HSS (p < 0.001, Student's *t*-test) and mid-term HHS (p < 0.001, Student's t-test); however, there was a reduction in the mean HSS between the mean short-term and mid-term HHS (p = 0.02, Student's *t*-test).

Discussion

ON of the femoral head is a progressive disease that often impacts young patients and required THA for definitive management. Early results on the use of core decompression combined BMAC and PRP for precollapse disease showed hip preservation to be 84% to 93% at three years postoperatively, with risk factors for failure being a high preoperative modified Kerboul grade and a low BMAC concentration.[28] Further follow-up of this group of patients showed the failure rate in terms of conversion to THA for all causes and articular collapse to be 67% and 84%. Patients requiring THA were more likely on corticosteroids at the time of decompression and had a higher Kerboul angle. In addition, the initial association between cell counts and success of the procedure are not apparent at seven-year follow-up.

Core decompression of the femoral head has been shown to adequately treat patients with precollapse disease without changes on radiographs (Steinberg stage I); however, when the areas of ON become visible on radiographs (Steinberg stage II), core decompression alone has been associated with disease progression.[7,16-26] In order to improve the rate of hip preservation, Hernigou et al[19] began combining hip decompression with BMACs, recently reporting a mean 25 -year follow-up showing core decompression combined with BMAC yielded 72% survivorship as compared to decompression alone at 28%.[32] In the long-term follow-up study by Hernigou et al,[32] the authors noted that patients with advanced disease (Steinberg stage II) were at increased risk of progression to THA. This is like the results of the current study, with all patients who advance to THA having Steinberg stage II disease at the time of hip preservation surgery. In the present series, the success of the decompression surgery is highly dependent on size of the lesion and continued use of steroid treatment.

Patients with a grade 3 or 4 Kerboul angle have been found to have an increased risk of femoral head collapse.[30] In a study by Ha et al the authors noted that 100% with a grade 3 or 4 Kerboul angle eventually developed collapse of the femoral head compared to 29% of patients with a Kerboul grade 1 or 2.[30] The results of the current study are similar, with a high preoperative Kerboul angle having the greatest risk for progression to THA (HR 3.96; p = 0.047, Cox proportional hazard regression) in addition into to an even greater risk of needing a THA for femoral head collapse (HR 13.34; p = 0.004, Cox proportional hazard regression). In our study, two hips with high preoperative Kerboul angles are free of collapse and THA at seven and eight years postoperatively. That is the exception, not the norm. As such, a high preoperative Kerboul angle could be indicated if a less invasive procedure is entertained by patient and surgeon but has a 60% risk of failure at seven years. Patients with a high preoperative angle should be cautioned on the high risk of failure of this procedure.

Although ON of the femoral head is progressive in a majority of patients, it should also be noted that not all patients with ON of the femoral head require surgical intervention, with up to 41% of patients known to not progress to joint collapse.[6] For patients with asymptomatic medial based, small lesions (< 25% of the femoral

head), a period of initial observation is warranted as < 10% of patients will progress.[6] However, if the lesion is located in weightbearing lateral portion of the femoral head, even small lesions are noted to progress to symptomatic disease, and, as such, hip preservation procedures are warranted.[13]

Recently, disruption in the peroxisome proliferator-activated receptor-γ (PPARγ) has been linked to an increased risk of ON of the femoral head.[33] PPARγ is a known "master regulator" for adipocyte differentiation and has been shown to have important roles in lipid metabolism. In addition, it has been previously shown that females have a greater sensitivity to PPARγ ligands,[34,35] showing potential sex-based differences in these receptors. In the current series, female sex seemed to be closely associated with progression of disease, namely conversion to THA and the need for additional procedures. It is possible that sex-based difference in the PPARγ receptors could account for this progression, however future studies are warranted to investigate this association.

The deficient concentration of BMAC in the proximal femur in patients with ON was one of the reasons for augmenting core decompression with BMAC.[36,37] It has been shown a majority of the cells remain in the femoral head 24 hours after injection,[27] leading to a paracrine effect in the environment orchestrating the healing response. Recently, Hernigou et al[32] showed new bone formation in the necrotic lesions of the femoral head when decompression is augmented by BMACs. The mean number of CFUs injected in the femoral head has been shown to be 24; however, this is variable based on the aetiology of the ON.[38] There is also a decrease in the CFU of cells injected into the femoral head to be associated with progression to THA in patients with corticosteroid induced ON.[19] In our early follow-up, we observed that patients with a higher cell count and CFU at the time of surgery reduced the risk of progression to THA at early follow-up.[28] However, with longer follow-up there was no difference in the mean CFU between patients who progressed to THA and those who did not indicating that there are extrinsic and more important factors, such as the size of the lesion and the continued steroid treatment that are predictors of THA.

All patients undergoing surgery had pain. Core decompression has been associated with improvements primarily in pain, but also in function with or without the addition of BMAC.[19,21,27,28,39] In our previous series, we noted improvements in pain and function based on the Harris hip score regardless of the Kerboul angle.[28] In the current series, we noted that compared to baseline, in patients who did not progress to a THA, HHS remained improved at mid-term follow-up compared to baseline with mild interval regression. Improvements in pain and function alone, even if progression occurs, should be considered an indication to perform this procedure.

Limitations. The results of the current series should be interpreted with acknowledging certain limitations. All patients were treated with hip decompression augmented with autologous BMAC and PRP with no control or comparison group. This study only included patients with a history of corticosteroid induced ON and, as such, may not be representative for ON due to other etiologies. Indeed, corticosteroid-induced ON is thought to be one of the more recalcitrant forms of disease, especially when ongoing corticosteroid use is required following diagnosis. Although this series reports a concise mid-term follow-up, it is likely that with continued follow-up there may be an increased rate of conversion to THA. Due to the limited number of patients, our analysis of variables associated with failure was limited and we were unable to perform multivariant analysis.

The results of the current series show approximately 10% need for THA per year of follow-up. Increased risk of THA is seen in patients with high preoperative Kerboul angles, or those who continued to use steroids at the time of the decompression. In the authors opinion, the close to 70% survivorship from THA and 84% survivorship from head collapse, in the entire group, makes hip decompression with injection of BMAC and PRP an option for patients with hip pain secondary to early stage ON. The procedure carries minimal risk, is done on an outpatient basis, and patients can weightbear as tolerated with crutches immediately after the procedure. The ideal candidate for this procedure, however, is one with a low preoperative Kerboul angle and those that can stop their corticosteroids prior to surgery. In the latter patients, articular collapse is observed in less than 10% of at mid-term follow-up.

Take home message

- Hip decompression with injection of bone marrow concetrate and platelet-rich plasma is a viable joint presevation strategy best for patients with smaller osteonecrosis lesions of the femoral head without collapse and if the patient is no longer taking steroids for underlying conditions.

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Author information:
- M. T. Houdek, MD, Associate Professor Orthopaedic Surgery
- J-R. H. Smith, MS, Medical Student
- A. Terzic, MD, PhD, Professor Medicine and Pharmacology
- A. Behfar, MD, PhD, Associate Professor of Medicine
  Orthopaedic Surgery, Mayo Clinic, Rochester, Minnesota, USA.
- C. C. Wyles, MD, Orthopaedic Surgery Resident
- R. J. Sierra, MD, Professor Orthopaedic Surgery
  Ortho Surgery, Mayo Clinic College of Medicine, Rochester, Minnesota, USA.

Author contributions:
- M. T. Houdek: Formal analysis, Project administration, Investigation, Writing – original draft, Writing – review & editing.
- C. C. Wyles: Investigation, Formal analysis, Writing – review & editing.
- J-R. H. Smith: Investigation, Writing – review & editing.
- A. Terzic: Writing – review & editing.
- A. Behfar: Writing – review & editing.
- R. J. Sierra: Supervision, Funding acquisition, Writing – review & editing.

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