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Efficacy and Safety of Bone Marrow Concentrate for Osteoarthritis of the Hip; Treatment Registry Results for 196 Patients

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Abstract

Introduction: We investigated the efficacy and safety of autologous bone marrow concentrate (BMC) for the treatment of symptomatic hip osteoarthritis.

Methods: Treatment registry data for 216 hips treated among 196 patients who underwent a BMC procedure for hip osteoarthritis (OA) were analyzed. Data regarding adverse events (AEs), subjective percentage improvement, Oxford Hip Scores (OHS), and numeric pain scale (NPS) scores were assessed and compared to baseline at 1, 3, 6 months, and annually after treatment.

Results: The mean reported subjective percentage improvement across all 216 treated hips was 30.2%. The mean OHS change was 6.4 points improved (p<0.001). The NPS scores from baseline to post treatment decreased from 4.5 to 3.3 (p<0.001). Twelve AEs were reported, none of which were serious or persisting. Patients ≤ 55 years old were substantially more likely to report improvement on the OHS [OR: 11.1 (1.6-77.8)] and also more likely to report greater than 50% improvement on the subjective percentage improvement scale [OR: 2.8 (1.2-6.7)].

Conclusion: The present study of BMC injections for hip OA demonstrated encouraging results for improved outcomes with no significant complications. We found that patients younger than 55 years old were more likely to report improvement on the OHS and subjective percentage improvement scales. Further study with randomized trials is warranted to confirm the reported results.

Keywords: Bone marrow concentrate; Stem cells; Autologous stem cells; Mesenchymal stem cells; Hip osteoarthritis; Non-surgical hip pain treatment

Introduction

Osteoarthritis of the hip is a significant cause of pain and disability in the adult population in the United States [1]. In its end stage the condition is most commonly treated with partial or total joint replacement. The number of total hip arthroplasties (THR) performed in 2010 in the U.S. was approximately 332,000 [2], an increase of roughly 30% from the number of THRs in 2000 [3]. THR is a highly invasive and expensive surgery that is associated with significantly increased perioperative morbidity, including a 25.5 fold increased risk of myocardial infarction [4] and a 4.7 times increased risk for ischemic stroke [5]. Moreover, although most patients obtain improved function after THR, the procedure is not universally successful; approximately two thirds of hip replacement patients continue to experience pain after the surgery [6].

Non-surgical options to THR are few. Corticosteroid injections are effective at temporarily reducing pain [7,8] and hyaluronic acid injections into the joint can also decrease pain, as well as possibly delay the need for THR [9]. Autologous platelet rich plasma (PRP) injection has been evaluated as a potential hip OA therapy, with early studies showing efficacy approximately equal to that of hyaluronic acid injection [10]. A common characteristic of these therapies is that while they can temporarily ameliorate symptoms of OA they don't significantly alter the natural history of the disease such that joint replacement can be substantially delayed, much less avoided.

One technique with such potential is adult autologous stem cell therapy. Mesenchymal stem cells (MSCs), a cell type found in bone marrow as well as other tissue, are capable of cartilage and bone repair in animal models and early human clinical trials [11-14]. Bone marrow

aspirate concentrate (BMC) is rich in MSCs, and has been used to treat early stage avascular necrosis of the femoral head for nearly 2 decades [15-17]. Although the adaptation of the technique for OA of the hip joint has been previously described in a case study [18], the procedure has not been widely adopted for clinical application. Currently there are no large scale studies describing the safety or efficacy of intra-articular BMC in the treatment of hip OA.

In the present study we report on the results of a prospective treatment registry analysis of hip OA patients treated with BMC. As is common with such analyses, outcome and safety data are patient reported, and include percentage improvement, function, and pain scores.

Methods

Setting and participants

Data were accessed from a private autologous cellular treatment registry. The database is the result of an ongoing prospective survey system that was designed to follow the safety and efficacy of various

orthopedic treatment protocols utilizing autologous MSC, BMC, and PRP injectate. Registry data for all patients who underwent a BMC procedure for hip OA from April 2010 to December 2013 were included in the study. Only patients who had responded to the outcome questionnaires at 1, 3, 6, 12 months, and annual follow-up points following the procedure were included in the outcomes analysis. There were 17 outpatient facilities that contributed patients to the registry; however the majority of cases (67.7%) were performed at a single center at which the primary author (CJC) is affiliated. Following enrollment in the registry patients were tracked via an electronic database system using Clin Capture software (Clinovo Clinical Data Solutions, Sunnyvale, California; http://www.clinovo.com/clincapture). The program includes an automated emailing system to send patients clinical outcome questionnaires at a pre-determined post-treatment frequency. Complications were monitored by e-mail or during clinic visit preoperatively and at 1, 3, 6 months, and annually after the procedure by a dedicated registry staff. Non-responders were contacted by phone and/or e-mail. Several studies using data from this ongoing registry have been published previously [14,19-23].

Procedure descriptions

Pre-Injection: The first step of the treatment was a pre-injection of a hypertonic dextrose solution into the hip joint intra-articular with the target area being the upper portion of the femoral head (weight bearing portion of the joint). Other painful extra-articular structures were also injected. These injections took place two to five days prior to injection of the bone marrow concentrate. The purpose of the pre-injection was to introduce a hyper-osmolar irritant to the joint in order to prompt a brief inflammatory healing response. Intra-articular femoroacetabular joint (FAJ) needle placement was guided via direct ultrasound visualization and confirmed on fluoroscopy. Iodixanol (Visipaque, NDC# 0407-2223-06) radiographic contrast was first slowly injected to confirm a joint arthrogram and then this was followed by injection of 3-5ccs of 12.5% dextrose (NDC# 0409-6648-02) and 0.1% lidocaine (NDC# 0409-4276-02) in normal saline (NDC# 0409-4888-50).

Bone marrow harvest: All patents underwent a bone marrow aspirate procedure. Prior to the procedure, patients were restricted from taking all corticosteroids and nonsteroidal anti-inflammatory drugs (NSAIDs) for a minimum of 2 weeks as these medications may reduce bone and soft tissue healing [24-28]. Whole bone marrow aspirate (BMA) was harvested from the patients' iliac crest (posterior-superior area) under ultrasound or fluoroscopic guidance. Approximately 10-15 cc of BMA was withdrawn from 6-8 sites (approximately 3-4 on each side) into syringes containing heparin. One thousand units of heparin (NDC# 25021-403-01 and 25021-404-01) were used per 1cc of BMA volume in syringe. The aspirate was processed by lab staff in a sterile ISO-7 class clean room and in ISO-5 class laminar flow cabinets to isolate the buffy coat portion through multiple centrifugation steps. This isolation produced 1-7 ccs of BMC which was then taken via sterile transport the short distance back to the operating room. The nucleated cell count of the injectate was counted and recorded by lab staff with a Cell counter (TC10 manufactured by BioRad) via light microscopy. This data was only recorded at the site of the principal investigators but all sites follow the same standard operating procedures for processing. Coincident with this BMA, approximately 60ccs of heparinized intra-venous blood was drawn to be used for isolating platelet rich plasma (PRP) and platelet lysate (PL). To prepare the PRP, the plasma layer was separated via centrifugation at 200 g which produced plasma and buffy coat layers from the whole blood. The resultant supernatant lying above the concentrated solids was red cell/white cell poor. To prepare

the PL, PRP was pipetted off and stored at -20°; platelet bodies were then removed via re-centrifugation, and the supernatant was drawn off.

Reinjection of the bone marrow concentrate: Cannulation of the intra-articular hip joint was confirmed by fluoroscopy or ultrasound. The injectate consisted of 1-4 ccs of bone marrow concentrate, 1cc of PRP, and 1cc of PL. The volume of the bone marrow concentrate depending on the size of the buffy coat layer and the entire volume were used for all patients but no more than 4ccs injected intra-articular. The primary target was the weight bearing area of the hip via the technique described above for the pre-injection. Additional injectate was also injected into painful or otherwise damaged structures (i.e. psoas tendon or the trochanteric area if painful).

In the immediate post-op period, patients were discharged with instructions to be light weight bearing for several days if there was significant post-op pain, but then to return to full weight bearing as soon as was comfortable. Post-operative instruction sheets regarding activity were provided to all patients, describing a gradual return to full activities over approximately 6 weeks. Patients were encouraged to participate in appropriate physical therapy, but this was not required nor was it controlled.

Outcome predictive factors examined: We analyzed the effect on outcomes of four putative predictive factors: age, gender, BMI; and baseline severity of osteoarthritis as determined by radiographs or Magnetic Resonance Imaging (MRI) [29-32]. The Kellgren-Lawrence (KL) scale [33] was used to grade the severity of OA observed in the patients' pre procedure radiographic imaging. Good status (mild severity) was assigned for KL1 grade, fair status (moderate severity) was assigned for KL2 and KL3, while poor status (severe disease) was assigned for KL4. Due to the small number of cases in the KL4 grade, these procedures were grouped in one category with the moderate cases (KL2-4, reference group for severity grade). Age was divided into ≤55 and >55 years. BMI was also dichotomized as below 25 and 25 or higher. Older age and higher BMI were considered as the reference groups for age and BMI. Males were the reference group for gender.

Outcome assessment: The outcomes of interest were function and pain levels, and subject-reported symptomatic improvement rating after treatment. Patients were also asked to rate their improvement after treatment using the following question: "Compared to your condition prior to the procedure, what percent difference have you seen in your condition?" The response could range from -100% worse to 100% better with zero indicating no change. A change of 50% or greater was selected as the threshold for "significant" improvement. The results of this question are referred to hereafter as the "percentage improvement scale" in this paper. Functional level was measured using the Oxford Hip Scale (OHS) (Questionnaire). OHS is a self-administered questionnaire which is designed specifically for the hip joint and usually used to assess the outcomes of total hip replacement [34]. The questionnaire includes 12 items with a maximum total score of 48 indicating maximum function. The minimal important difference or change in the scale has been previously reported at 4.9 points, which was used as the improvement threshold for the present study [35]. Pain severity was assessed using the Numeric Pain Scale (NPS). NPS has eleven levels of pain ranging from 0 for no pain, to 10, indicating worst possible pain. The minimal important difference or change in the NPS has been previously reported at 2 points, which was the threshold improvement value used in the present study [36]. The analysis of the outcome scale results was based on a comparison between baseline and the most current assessment, with the average duration of baseline to current assessment reported in months for each outcome scale.

1. During the past 4 weeks…				
How would you describe the pain you usually have from your hip?				
None	Very mild	Mild	Moderate	Severe
☐	☐	☐	☐	☐
2. During the past 4 weeks…				
Have you had any trouble with washing and drying yourself (all over) because of your hip?				
No trouble at all	Very little trouble	Moderate trouble	Extreme difficulty	Impossible to do
☐	☐	☐	☐	☐
3. During the past 4 weeks…				
Have you had any trouble getting in and out of a car or using public transport because of your hip? (whichever you tend to use)				
No trouble at all	Very little trouble	Moderate trouble	Extreme difficulty	Impossible to do
☐	☐	☐	☐	☐
4. During the past 4 weeks…				
Have you been able to put on a pair of socks, stockings or tights?				
Yes, easily	With little difficulty	With moderate difficulty	With extreme difficulty	No, impossible
☐	☐	☐	☐	☐
5. During the past 4 weeks…				
Could you do the household shopping on your own?				
Yes, easily	With little difficulty	With moderate difficulty	With extreme difficulty	No, impossible
☐	☐	☐	☐	☐
6. During the past 4 weeks…				
For how long have you been able to walk before pain from your hip becomes severe? (with or without a stick)				
No pain/More than 30 minutes	16 to 30 minutes	5 to 15 minutes	Around the house only	Not at all/pain severe on walking
☐	☐	☐	☐	☐
7. During the past 4 weeks…				
Have you been able to climb a flight of stairs?				
Yes, easily	With little difficulty	With moderate difficulty	With extreme difficulty	No, impossible
☐	☐	☐	☐	☐
8. During the past 4 weeks…				
After a meal (sat at a table), how painful has it been for you to stand up from a chair because of your hip?				
Not at all painful	Slightly painful	Moderately painful	Very Painful	Unbearable
☐	☐	☐	☐	☐
9. During the past 4 weeks…				
Have you been limping when walking, because of your hip?				
Rarely/ never	Sometimes, or just at first	Often, not just at first	Most of the time	All of the time
☐	☐	☐	☐	☐
10. During the past 4 weeks…				
Have you had any sudden, severe pain - 'shooting', 'stabbing' or 'spasms' - from the affected hip?				
No days	Only 1 or 2 days	Some days	Most Days	Every day
☐	☐	☐	☐	☐
11. During the past 4 weeks…				
How much has pain from your hip interfered with your usual work (including housework)?				
Not at all	A little bit	Moderately	Greatly	Totally
☐	☐	☐	☐	☐
12. During the past 4 weeks…				
Have you been troubled by pain from your hip in bed at night?				
No nights	Only 1 or 2 nights	Some nights	Most Nights	Every night
☐	☐	☐	☐	☐

Questionnaire: Oxford Hip Score.

Assessment of adverse events: Patients were sent questionnaires to survey for adverse events at 1, 3, 6 months and annually thereafter. The questionnaire included the following questions: "Did you experience any complications you believe may be due to the procedure (i.e. infection, illness, etc.)? If 'Yes', please explain" and "Have you been diagnosed with any new illness since the procedure? If 'Yes', please explain." Any untoward or unfavorable medical occurrence that was reported was sent to the treating physician for assessment of causality and severity. Either the treating physician or one of the authors then determined through patient interview or chart review, based on the U.S. Department of Health and Human Services (DHHS) guidelines [37] whether the condition was pre-existing, unexpected, mild/moderate/severe, related to the therapeutic agent or procedure, or resolved/ongoing/fatal.

Statistical analysis

Baseline characteristics were described using the mean and standard deviation for continuous variables and frequency and proportion for categorical variables. Frequencies of adverse events were reported per category. Changes in the OHS and NPS were assessed using the Wilcoxon signed-rank test, a non-parametric test for dependent samples. Predictive covariates for functional and symptomatic improvement were examined with multivariate logistic regression. Models were constructed for each outcome assessment variable (OHS, NPS, and the percentage improvement scale), with the results reported in Odds Ratios (OR). Subjects with missing observations were removed from the analysis. To determine if missing outcome data was associated with the demographic factors, we analyzed the demographical differences between responders and non-responders using t-test and chi square test as appropriate. Analyses included only patients with available baseline data of the respective clinical scale.

All analyses were performed retrospectively utilizing SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA). Figures of means and standard deviations were created using Microsoft Excel software version 14.0 (Microsoft, Redmond, WA, USA).

Results

There were 216 treated hips among 196 patients, with 40 bilateral procedures (18.5%) performed on 20 patients. The mean age and BMI of the study population were 57 years and 26.2 respectively. One hundred twenty four (57.4%) procedures were performed on males. Radiological data was available for 174 (80.5%) joints. Based on the radiological classification; 118 (67.8%) joints were potential THA candidates (KL 2-4 grade) (Table 1). The mean nucleated cell counts and volume of the bone marrow concentration was 527 million and 2.5 ccs (Table 2).

OHS data were available for 57 procedures (26.4% of all treated hips). The mean OHS increased by 6.4 points, from 26.6 at the baseline to 33 at the last follow-up over a mean follow up time of 4.9 months (P<0.001). NPS data were available for 81 procedures (37.5% of all treated hips). The mean NPS decreased from 4.5 to 3.3 from baseline to last follow-up over an average of 5.9 months follow up (a 26.7% decrease (P<0.001). At an average of 9 months post-treatment follow-up, percentage improvement scaledata were available for 135 joints (62.5% of the total), with an average rating of 31.2% improved (Table 3 and Figure 1).

The multivariate analysis results were as follows: for the OHS, patients in the younger age group (≤ 55 years) were substantially

more likely to report improvement of at least 4.9 points than patients >55 years, with an odds ratio (OR) of 11.1 (1.6-77.8). The effects of gender, BMI and KL grade on the OHS outcomes were not statistically significant. Similarly, patients in the younger age group were more likely to report 50% or higher score on the percentage improvement scale, with an odds ratio of 2.8 (1.2-6.7). Age did not have a significant effect on the NPS outcomes. None of the other predictive factors (BMI, gender and KL grade) had a significant effect on the NPS outcomes (Table 4).

The number of the joints meeting the improvement thresholds for each outcome variable, as described in the methods section, were as follows: 28 out of 44 available cases in the OHS model (64%), 35 out of 59 available cases in the NPS model (59%), and 43 out of 100 total available cases in the improvement rating model (43%). Analysis of the missing outcome data showed that demographical characteristics were not statistically different between patients who responded to the follow-up surveys (responders) and these who failed to respond (non-responders) (Table 5).

Twelve patients reported adverse events (AEs) that included six events of pain/swelling, two skin events, one blood work event, and three others. Eight of these events were classified as mild and four were deemed moderate. There were no severe or serious AEs. Based on the DHHS guideline, 1 AE was assessed as likely related to the procedure, 8 were possibly related, and 3 were unlikely to be related. At the time of

	N	Mean (SD)
Age	216	57 (10.6)
BMI	184	26.2 (4.3)
Gender	216	-
Male	124 (57.41%)	
Female	92 (42.59%)	
Grade	174	-
KL1	56 (32.2%)	
KL2-3	80 (46.0%)	
KL4	38 (21.8%)	

SD: Standard Deviation, BMI: Body Mass Index, KL: Kellgren-Lawrence scale

Table 1: Baseline characteristics and follow-up scores of the functional and symptomatic scales.

	N	Mean	SD	Minimum	Maximum
NC Count (in millions)	127	527.4	265.2	108	1518.9
Volume Injected (ml)	127	2.5	1.4	0.6	7

NC: Nucleate Cells, SD: Standard Deviation

Table 2: Nucleated Cell count and volume of bone marrow concentrate.

		N	Mean (SD)	P-value
Oxford Hip Score	Baseline	57	26.6 (8.8)	
	Follow-up	57	33.0 (8.7)	<0.001
	Follow-up duration	57	4.9 (4.9)	
Numerical pain scale	Baseline	81	4.5 (2.0)	
	Follow-up	81	3.3 (2.3)	<0.001
	Follow-up duration	81	5.9 (5.7)	
Percentage improvement scale	Follow-up	135	31.2 (38.6)	-
	Follow-up duration	135	9.0 (7.7)	

SD: Standard Deviation. Follow-up durations are in months. P-values are for intra-group differences (changes from the baseline)

Table 3: Clinical outcomes as measured by the Oxford hip, numeric pain scale and percentage improvement scale.
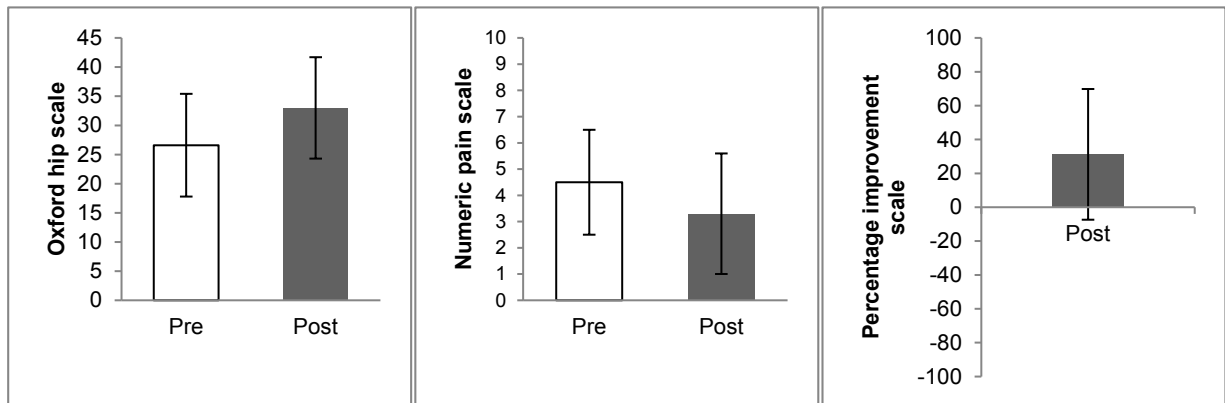
Figure 1: Pre- and post-treatment means (+/- 1 standard deviation) of the Oxford hip and numeric pain scales and post-treatment mean of the percentage improvement scale.

	Functional improvement measured by the OHS	Pain improvement measured by the NPS	Reporting ≥50% improvement
Age			
≤55 Yr.	11.1 (1.6-77.8)	0.8 (0.3-2.5)	2.8 (1.2-6.7)
>55 Yr.	1 (Reference)	1 (Reference)	1 (Reference)
BMI			
<25	1.8 (0.4-9)	0.9 (0.3-2.7)	1.4 (0.5-3.5)
≥25	1 (Reference)	1 (Reference)	1 (Reference)
Gender			
Female	0.9 (0.2-4.8)	0.7 (0.2-2.3)	1.7 (0.7-4.5)
Male	1 (Reference)	1 (Reference)	1 (Reference)
Severity Grade			
KL1 (mild)	0.2 (0.0-1.4)	0.6 (0.2-1.9)	1.8 (0.7-4.4)
KL2-4 (moderate/severe)	1 (Reference)	1 (Reference)	1 (Reference)

OHS model included patients who had OHS baseline score of 40 or below, NPS model included patient who had NPS baseline score of 2 or higher, BMI: body mass index, KL: Kellgren-Lawrence scale. Ns in each model were the following: 44 (OHS), 59 (NPS) and 100 (percentage improvement rating)

Table 4: Odds ratios (and 95% confidence intervals) of improvement reported on the functional and symptomatic scales by predictive factors*

Follow-up survey		Non-responders			Responders			P-value
		N	Mean (or %)	SD	N	Mean (or %)	SD	
Oxford hip scale	Age	52	57	11.3	57	56.5	10.3	0.792
	BMI	46	25.9	4.6	53	26.1	4.8	0.839
	Male %	31	59.6	-	26	45.6	-	0.143
	KL1 %	18	52.9	-	36	72	-	0.07
Numeric pain scale	Age	51	56.8	11.6	81	57.1	9.1	0.876
	BMI	46	26.3	4.3	76	26	4.4	0.685
	Male %	31	60.8	-	42	51.9	-	0.314
	KL1 %	26	70.3	-	46	64.8	-	0.566
Percentage improvement scale	Age	81	57.1	11.2	135	56.9	10.2	0.853
	BMI	69	26.2	4.1	115	26.2	4.5	0.999
	Male %	46	56.8	-	78	57.8	-	0.887
	KL1 %	37	61.7	-	81	71.1	-	0.207

P-values are for the differences between patients who responded and these who failed to respond to the surveys. For gender and severity, table presents the frequency (N) and percentage (%) of males and KL1 grade respectively (Control groups are females and KL2-4 grade). Frequencies and percentages are not presented for the control groups. SD: standard deviation. KL: Kellgren-Lawrence scale.

Table 5: Demographical characteristics of patients who responded and these failed to respond to the follow-up surveys (patients with available baseline data).

reporting, 10 AEs were resolved/recovered and two were ongoing. No AE resulted in significant disability.

Discussion

In the present study, the use of BMC for symptomatic hip OA was both safe and effective, by patient report. The mean change in the OHS was 6.4, which met the minimal clinically important difference of 4.9 points [38]. NPS scores decreased by 26.7%, which also met the threshold for a clinically important difference for this metric [36].

Younger hip OA patients (under age 55) were significantly more

likely to report functional changes on the OHS and percentage improvement scale. These findings are consistent with those of prior authors who have described better outcomes for surgical treatment of chronic problems of the hip in younger patients, including arthroscopic hip labrum debridement and femoroacetabular impingement surgery [39].

The finding that KL grade did not predict subjective or functional outcomes was consistent with the reports of earlier authors. Prior studies have demonstrated that KL grade is more reliable for predicting symptom severity and need for THA [40,41], than it is for predicting outcomes from treatment with biologics. Other authors have observed an inverse relationship between KL grade and treatment success with growth factors [42], whereas some authors have reported the best results with PRP therapy for hip OA in patients with KL grade 4, versus lower grades [10]. A reasonable explanation for the findings in the present study is that the grouping of the small number of KL grade 4 subjects with the lesser grades served to obscure real differences between the grades.

Pain/swelling was the most commonly reported AE (6 of 12). These symptoms were generally self-limited and resolved without treatment. The skin reactions consisted of one self-limited rash and persistent redness at the injection site when cold, without evidence of infection. Two of the other reported complications included a patient who complained of persistent popping/cracking in the joint, which was thought to be secondary to continued degenerative disease, and a case of reported boney growth at the joint, which was later determined to be continued osteophyte formation due to advancing degenerative joint changes. There was one patient in whom a mild transitory drop in WBC count was noted post-procedure. Overall, these post-procedural complications were quite mild, and/or unrelated to the treatment. In comparison, the AEs with THA are far more serious and common; myocardial infarction, pulmonary embolism, and deep venous thrombosis are reported in 2.1%, 0.5%, 0.6%, and 1.3% surgeries, respectively [43].

The major limitations of the present study, as with any registry study, were the lack of a control group, the lack of randomization, and low survey response rates. Because of the lack of a randomized control group we could not exclude a placebo effect as an explanation for the observed improvements. Non-response can be attributed to the demographic differences between responders and non-responders and it may result in biased outcomes [44-47]. In the present study, the low response rate wasn't a likely source of non-response bias. The missing outcome analysis demonstrated that the response status was not related to the baseline factors. Another potential limitation was the low number of events per predictor variable included in the logistic regression analysis. This limitation might increase the risk of statistical errors, however, emerging studies are encouraging to accept lower numbers of observations per predictor [48,49]. Our population size met the minimum requirement specified in these studies. In spite of these limitations, we are encouraged by the result we report here. A randomized controlled trial of the therapy is warranted as a next step in the investigation of BMC therapy for hip OA. Another way to improve upon future studies would be to utilize objective measures such as functional tests performed by a blinded party.

Conclusions

This report of registry data from patients receiving BMC for symptomatic hip OA yielded encouraging results. The reported complications for the tracked patients were minimal, and far less serious and common than for THA. Younger patients were significantly more likely to reporting positive results. Further study is warranted using a randomized controlled study design.

Acknowledgement

Conflict of Interest

Dr. Centeno is a shareholder and director of Regenerative Sciences, LLC. Al-Sayegh is employed by Regenerative Sciences, LLC.

References

1. Nho SJ, Kymes SM, Callaghan JJ, Felson DT (2013) The burden of hip osteoarthritis in the United States: epidemiologic and economic considerations. J Am Acad Orthop Surg 21: S1-6. [PubMed]

2. CDC/NCHS National hospital Discharge Survey.

3. OECD Indicators (2013) OECD, Hip and knee replacement.

4. Lalmohamed A, Vestergaard P, Klop C, Lerkevang Grove E, De Boer A, et al. (2012) Timing of acute myocardial infarction in patients undergoing total hip or knee replacement: a nationwide cohort study. Arch Intern Med 172: 1229-1235. [PubMed]

5. Lalmohamed A, Vestergaard P, Cooper C, de Boer A, Leufkens HG, et al. (2012) Timing of stroke in patients undergoing total hip replacement and matched controls: a nationwide cohort study. Stroke 43: 3225-3229. [PubMed]

6. Pinto PR, McIntyre T, Ferrero R, Araújo-Soares V, Almeida A, et al. (2013) Persistent pain after total knee or hip arthroplasty: differential study of prevalence, nature, and impact. J Pain Res 6: 691-703. [PubMed]

7. Deshmukh AJ, Panagopoulos G, Alizadeh A, Rodriquez JA, Klein DA (2011) Intra-articular hip injection: does pain relief correlate with radiographic severity of osteoarthritis? Skeletal Radiol 40: 1449-1454. [PubMed]

8. Kruse DW (2008) Intraarticular cortisone injection for osteoarthritis of the hip. Is it effective? Is it safe? Curr Rev Musculoskelet Med 1: 227-233. [PubMed]

9. Migliore A, Bella A, Bisignani M, Calderaro M, De Amicis, et al. (2012) Total hip replacement rate in a cohort of patients affected by symptomatic hip osteoarthritis following intra-articular sodium hyaluronate (MW 1,500-2,000 kDa) ORTOBRIX study. Clin Rheumatol 31: 1187-1196. [PubMed]

10. Battaglia M, Guaraldi F, Vannini F, Rossi G, Timoncini A, et al. (2013) Efficacy of ultrasound-guided intra-articular injections of platelet-rich plasma versus hyaluronic acid for hip osteoarthritis. Orthopedics 36: e1501-1508. [PubMed]

11. Pittenger MF, Mackay AM, Beck SC, Jaiswal RK, Douglas R, et al. (1999) Multi lineage potential of adult human mesenchymal stem cells. Science 284: 143-147. [PubMed]

12. Lange C (2013) High-potential human mesenchymal stem cells. Stem Cells Dev 14: 70-80. [PubMed]

13. (2013) Autologousmesenchymal stem cells for treating knee osteoarthritis. Manag Care 22: 15-16. [PubMed]

14. Centeno CJ, Busse D, Kisiday J, Keohan C, Freeman M, et al. (2008) Increased knee cartilage volume in degenerative joint disease using percutaneously implanted, autologous mesenchymal stem cells. Pain Physician 11: 343-353. [PubMed]

15. Hernigou P, Beaujean F (2002) Treatment of osteonecrosis with autologous bone marrow grafting. Clin Orthop Relat Res. [PubMed]

16. Gangji V, Hauzeur JP (2005) Treatment of osteonecrosis of the femoral head with implantation of autologous bone-marrow cells. Surgical technique. J Bone Joint Surg Am 87: 106-112. [PubMed]

17. Gangji V, Toungouz M, Hauzeur JP (2005) Stem cell therapy for osteonecrosis of the femoral head. Expert Opin Biol Ther 5: 437-442. [PubMed]

18. Centeno CJ, Kisiday J, Freeman M, Schultz JR (2006) Partial regeneration of the human hip via autologous bone marrow nucleated cell transfer: A case study. Pain Physician 9: 253-256. [PubMed]

19. Centeno CJ, Busse D, Kisiday J, Keohan C, Freeman M, et al. (2008) Regeneration of meniscus cartilage in a knee treated with percutaneously

implanted autologous mesenchymal stem cells. Med Hypotheses 71: 900-908. [PubMed]

20. Centeno CJ, Schultz JR, Cheever M, Freeman M, Faulkner S, et al. (2011) Safety and complications reporting update on the re-implantation of culture-expanded mesenchymal stem cells using autologous platelet lysate technique. Curr Stem Cell Res Ther 6: 368-378. [PubMed]

21. Centeno CJ, Schultz JR, Cheever M, Robinson B, Freeman M, et al. (2010) Safety and complications reporting on the re-implantation of culture-expanded mesenchymal stem cells using autologous platelet lysate technique. Curr Stem Cell Res Ther 5: 81-93. [PubMed]

22. Centeno CJ, Schultz JR, Cheever M, Freeman M, Robinson B, et al. (2011) A Case Series of Percutaneous Treatment of Non-Union Fractures with Autologous, Culture Expanded, Bone Marrow Derived, Mesenchymal Stem Cells and Platelet Lysate. J Bioengineer & Biomedical Sci S2: 007.

23. Centeno JC, Freeman MD (2013) Percutaneous injection of autologous, culture-expanded mesenchymal stem cells into carpometacarpal hand joints: a case series with an untreated comparison group. Wiener MedizinischeWochenschriff 164: 83-87. [PubMed]

24. Chen MR, Dragoo JL (2013) The effect of nonsteroidal anti-inflammatory drugs on tissue healing. Knee Surg Sports Traumatol Arthrosc 21: 540-549. [PubMed]

25. Wiggins ME, Fadale PD, Barrach H, Ehrlich MG, Walsh WR (1994) Healing characteristics of a type I collagenous structure treated with corticosteroids. Am J Sports Med 22: 279-288. [PubMed]

26. Tsai WC, Hsu CC, Chen CP, Chen MJ, Lin MS, et al. (2006) Ibuprofen inhibition of tendon cell migration and down-regulation of paxillin expression. J Orthop Res 24: 551-558. [PubMed]

27. Tsai WC, Tang FT, Wong MK, Pang JH (2003) Inhibition of tendon cell migration by dexamethasone is correlated with reduced alpha-smooth muscle actin gene expression: a potential mechanism of delayed tendon healing. J Orthop Res 21: 265-271. [PubMed]

28. Randelli P, Randelli F, Cabitza P, Vaienti L (2010) The effects of COX-2 anti-inflammatory drugs on soft tissue healing: a review of the literature. J Biol Regul Homeost Agents 24: 107-114. [PubMed]

29. Gold SL, Burge AJ, Potter HG (2012) MRI of hip cartilage: joint morphology, structure, and composition. Clin Orthop Relat Res 470: 3321-3331. [PubMed]

30. Mamisch TC, Zilkens C, Siebenrock KA, Bittersohl B, Kim YJ, et al. (2009) Hip MRI and its implications for surgery in osteoarthritis patients. Rheum Dis Clin North Am 35: 591-604. [PubMed]

31. Mamisch TC, Zilkens C, Siebenrock KA, Bittersohl B, Kim YJ, et al. (2009) MRI of hip osteoarthritis and implications for surgery. Radiol Clin North Am 47: 713-722. [PubMed]

32. Santaguida PL, Hawker GA, Hudak PL, Glazier R, Mahomed NN, et al. (2008) Patient characteristics affecting the prognosis of total hip and knee joint arthroplasty: a systematic review. Can J Surg 51: 428-436. [PubMed]

33. Kellgren JH, Lawrence JS (1957) Radiological assessment of osteo-arthrosis. Ann Rheum Dis 16: 494-502. [PubMed]

34. Nilsdotter A, Bremander A (2011) Measures of hip function and symptoms: Harris Hip Score (HHS), Hip Disability and Osteoarthritis Outcome Score (HOOS), Oxford Hip Score (OHS), Lequesne Index of Severity for Osteoarthritis of the Hip (LISOH), and American Academy of Orthopedic Surgeons (AAOS) Hip and Knee Questionnaire. Arthritis Care Res (Hoboken) 63: S200-207. [PubMed]

35. Harris KP, Dawson J, Jill D, David M, Andrew C, et al. (2013) Minimal important change or difference for the oxford hip and knee scores following joint replacement surgery.

36. Kelly AM (2001) The minimum clinically significant difference in visual analogue scale pain score does not differ with severity of pain. Emerg Med J 18: 205-207. [PubMed]

37. Guidance for Clinical Investigators, Sponsors, and IRBs Adverse Event Reporting to IRBs - Improving Human Subject Protection, U.S.D.o.H.a.H. Services (2009) Office of the Commissioner, the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research (CBER), the Center for Devices and Radiological health (CDRH), and the Good CLinical Practice Program (GCPP) at the Food and Drug Administration.

38. Bohm ER (2012) Determining Minimum Clinically Important Difference and Targeted Clinical Improvement Values for the Oxford.

39. Wilkin G, March G, Beaule PE (2014) Arthroscopic acetabularlabral debridement in patients forty-five years of age or older has minimal benefit for pain and function. J Bone Joint Surg Am 96: 113-118. [PubMed]

40. Philippon MJ, Briggs KK, Carlisle JC, Patterson DC (2013) Joint space predicts THA after hip arthroscopy in patients 50 years and older. Clin Orthop Relat Res 471: 2492-2496. [PubMed]

41. Jordan JM, Helmick CG, Renner JB, Luta G, Dragomir AD, et al. (2009) Prevalence of hip symptoms and radiographic and symptomatic hip osteoarthritis in African Americans and Caucasians: the Johnston County Osteoarthritis Project. J Rheumatol 36: 809-815. [PubMed]

42. Civinini R, Nistri L, Martini C, Redl B, Ristori G, et al. (2013) Growth factors in the treatment of early osteoarthritis. Clin Cases Miner Bone Metab 10: 26-29. [PubMed]

43. Mantilla CB, Horlocker TT, Schroeder DR, Berry DJ, Brown DL (2002) Frequency of myocardial infarction, pulmonary embolism, deep venous thrombosis, and death following primary hip or knee arthroplasty. Anesthesiology 96: 1140-1146. [PubMed]

44. Delgado-Rodriguez M, Llorca J (2004) Bias. J Epidemiol Community Health 58: 635-641. [PubMed]

45. Melton LJ, Dyck PJ, Karnes JL, O'Brien PC, Service FJ (1993) Non-response bias in studies of diabetic complications: the Rochester Diabetic Neuropathy Study. J Clin Epidemiol 46: 341-348. [PubMed]

46. De Winter AF, Oldehinkel AJ, Veenstra R, Brunnekreef JA, Verhulst FC, et al. (2005) Evaluation of non-response bias in mental health determinants and outcomes in a large sample of pre-adolescents. Eur J Epidemiol 20: 173-181. [PubMed]

47. Korkeila K, Suominen S, Ahvenainen J, Ojanlatva A, Rautava P, et al. (2001) Non-response and related factors in a nation-wide health survey. Eur J Epidemiol 17: 991-999. [PubMed]

48. Vittinghoff E, McCulloch CE (2007) Relaxing the rule of ten events per variable in logistic and Cox regression. Am J Epidemiol 165: 710-718. [PubMed]

49. Cepeda MS, Boston R, Farrar JT, Strom BL (2003) Comparison of logistic regression versus propensity scores when the number of events is low and there are multiple confounders. Am J Epidemiol 158: 280-287. [PubMed]