Short-Term Outcomes in Treatment of Knee Osteoarthritis With 4 Bone Marrow Concentrate Injections

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ABSTRACT

BACKGROUND: Preliminary research suggests that bone marrow concentrate (BMC), which contains mesenchymal stem cells and platelets, is a promising treatment for knee osteoarthritis. The aim of this study was to build on this preliminary research by reporting the short-term progress of 15 patients (20 knees) with knee osteoarthritis through 4 BMC treatments.

METHODS: Patients underwent four sequential BMC treatments with mean injection times of 13.80 days after the first treatment, 21.40 days after the second treatment, and 33.50 days after the third treatment. The last follow-up was conducted a mean 86 days after the first treatment. Baseline and posttreatment outcomes of resting pain, active pain, lower functionality scale, and overall improvement percentage were compared after each treatment.

RESULTS: Patients experienced statistically significant improvements in active pain and functionality score after the first treatment. Additionally, patients experienced a mean decrease in resting pain after the first treatment, yet outcomes were not statistically significant until after the second treatment. On average, patients experienced an 84.31% decrease in resting pain, a 61.95% decrease in active pain, and a 55.68% increase in functionality score at the final follow-up. Patients also reported a mean 67% total overall improvement at study conclusion. Outcomes at the final follow-up after the fourth treatment were statistically significant compared to outcomes at baseline, after first treatment, after second treatment, and after third treatment.

CONCLUSIONS: These results are promising, and additional research with a larger sample size and longer follow-up is needed to further examine the treatment effectiveness of multiple BMC injections for knee osteoarthritis.

KEYWORDS: Stem cells, knee osteoarthritis, bone marrow concentrate, nonoperative therapy

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Introduction

Osteoarthritis (OA) is the most prevalent joint disease in the United States.[1] Knee OA affects more than 13% of men and 10% of women over the age of 60,[2] and these prevalences are expected to increase with increasing population age and prevalence of obesity. As a degenerative joint disease, OA causes significant pain, limits function, and adversely affects patient livelihood due to overspending on treatments of limited efficacy.[1] Many patients choose to treat knee OA with surgery or total joint replacement, which is invasive and may cause adverse complications such as increased morbidity or even death.[3] A recent systematic review of chronic pain following total knee arthroplasty showed that at least 10% to 34% of patients reported unfavorable levels of long-term pain.[4] These complication rates in addition to expense have prompted increasing numbers of patients to choose lower risk, nonsurgical, regenerative treatments.

Two regenerative therapies that have been shown to improve patient symptoms related to knee OA are dextrose prolotherapy and platelet-rich plasma (PRP) therapy. Dextrose prolotherapy uses irritant solution injection into painful muscles, ligaments, and joints to stimulate growth factor secretion and soft tissue healing.[5] Studies have shown positive effects of dextrose prolotherapy on OA.[6,7] A second therapy shown to improve pain and function in patients with knee OA is PRP,[8,9] which uses autologous platelets concentrated in a small plasma volume.[10] Platelets, the first cells to arrive at the site of tissue injury, function in early inflammation[11] through the secretion of protein growth factors that enhance cell proliferation, migration, differentiation, matrix synthesis, chondrocyte metabolism, chondrogenesis, and cartilage healing.[12]

A newer regenerative treatment for OA is bone marrow concentrate (BMC) injection. This solution contains many cell types and biofactors such as cytokines, growth factors, and hematopoietic stem cells, but most notably contain mesenchymal stem cells (MSCs) and platelets.[13] Mesenchymal stem cells are adult multipotent stem cells with self-renewal and differentiation capacity that are present within a broad range of tissues.[14] Mesenchymal stem cells can be isolated from bone marrow, adipose tissue, synovial tissue, lung tissue, umbilical cord blood, and peripheral blood.[15] For clinical use, MSCs are most commonly isolated from BMC and adipose tissue. However, previous studies show that MSCs from BMC have more chondrogenic potential to treat OA compared with

MSCs from adipose tissue.[16,17] One pioneering animal study showed that MSCs influence cell differentiation and protein expression in rabbit tendon repair.[18] Another study by Chinese researchers showed that MSCs injected into bone fracture sites promoted rapid and accelerated bone healing in rats.[19] Recent studies in patients with knee OA showed that BMC treatment improved pain and quality of life.[20–23]

Although BMC treatment has demonstrated clinical benefits for patients with OA, evidence is lacking regarding patient response to multiple BMC treatments. If a patient at our clinic requires multiple injections, we advise them to receive injections approximately 14 days apart. This 14-day time period is when there is growth factor secretion from various cell types that participate in the late phases of wound healing. [24,25] TGF-*B* is one of these growth factors and has been shown to enhance MSC growth and osteogenic differentiation.[25,26] Similar studies[20,21] injected PRP simultaneously with the BMC because growth factors secreted by platelets have also been shown to increase MSC proliferation.[27] We hypothesize that receiving multiple BMC injections may result in greater symptomatic relief than single injection.

The purpose of this study was to analyze patient short-term progress with respect to pain, function, and total overall improvement percentage over the course of 4 BMC treatments for knee OA.

Methods

Patients

This is a report of clinical practice outcomes in which variables were accessed prospectively and data were analyzed retrospectively. Patients included in this study underwent 4 BMC treatments for knee OA at a solo practitioner private practice from July 2016 to June 2017. All other patients with knee OA who underwent 1, 2, or 3 treatments were excluded and will be reported in a separate study. The diagnosis of knee OA was based on radiographic findings. The patients were classified as moderate to severe OA as stated on the radiographic findings; however, the severity of OA based on the Kellgren-Lawrence scale was not taken into consideration. Patients underwent 4 sequential BMC treatments with mean times between treatments of 13.80, 21.40, and 33.50 days. All patients were directed to have injections approximately 14 days apart; however, scheduling conflicts between patients and physician resulted in average follow-up injections greater than 14 days. All treatments were prescribed on an individual basis, as recommended by a physician. Written informed consent was obtained prior to each treatment. Patients were instructed not to use anti-inflammatory drugs during treatment, as they hinder MSC potential to differentiate into osteogenic cells.[28] For patients who underwent bilateral knee treatment, each knee was considered independent and given a separate survey for statistical analysis.

Procedure

Patients were in the prone position and sterilized with 10% povidone-iodine on the skin above the posterior superior iliac spine (PSIS). Next, 4% chlorhexidine gluconate (Hibiclens) was administered with sterile gauze in a circular motion starting at the PSIS. Patients were then anesthetized with 10-cc of 1% lidocaine and 2-cc of 8.4% sodium bicarbonate, injected locally on and around the patient's PSIS. After sufficient local anesthesia was achieved, a fenestrated 11-gauge, 4-inch disposable needle was drilled to penetrate PSIS and extract BMC. A 20-cc syringe prepared with 1-cc of heparin (1000 USP units/mL) was used to extract BMC for a total yield of 19-cc. To maximize stem cell yield and avoid an excess of peripheral blood, the needle was rotated slowly within the ilium cavity and penetrated deeper as required. The BMC was then spun in a centrifuge, and the upper portion without visible red cells was isolated from the centrifuged BMC. 1-cc of Ropivicaine was added to every 5-cc of centrifuged BMC to ensure that the treated area was less painful after the injection. Ropivacaine has shown limited toxicity to MSCs.[29] Various 25-gauge needle lengths were used to inject the 6-cc mixture, depending on the depth of the joint capsule. The knee was sterilized with 10% povidone-iodine followed by 4% Hibiclens. The 6-cc injection was performed under ultrasound guidance into the knee joint capsule. If an effusion was noted, after local anesthesia it was aspirated with an 18-gauge needle prior to the injection of cells via the same needle.

Outcomes

The outcomes of interest for this study were changes to resting pain and active pain (numerical pain scale [NPS]), overall improvement (percentage scale), and joint function (scored questionnaire). Variables were chosen for ease of comparison with similar variables reported by other studies of BMC for knee OA treatment.[20,21] Data were collected at baseline and preceding each subsequent treatment (Figure 1). The last data collection occurred at a mean time of 24.30 days after the fourth treatment. The functionality portion of the questionnaire, which assessed degree of difficulty in performing daily activities, was not only based on 10 of 20 activities assessed in the Lower Extremity Functional Scale[30] but also included a "not applicable (N/A)" response option. This scale has been reported to be a reliable functionality questionnaire for knee OA in addition to an alternative to the Western Ontario and McMaster Universities Arthritis Index.[30] The NPS to assess resting and active pain used a scale of 0 (no pain) to 10 (extreme pain).[31] Finally, the form included a subjective measure of how much overall improvement the patient experienced following treatment on a scale of 0% to 100%.

Statistical analysis

Baseline and postintervention data were compared using means and standard deviations. Each follow-up response was compared

Lower Extremity Functionality Questions

Please describe the deg ree of difficulty you have performing these activities with your injured lower body part

	Activities	Extreme Difficulty	Quite a Bit of Difficulty	Moderate Difficulty	A Little Bit of Difficulty	No Difficulty	N/A
1	Job, housework, or school activities	0	1	2	3	4	N/A
2	Hobbies, recreational, or sport activities	0	1	2	3	4	N/A
3	Squatting	0	1	2	3	4	N/A
4	Walking two blocks	0	1	2	3	4	N/A
5	Going up stairs	0	1	2	3	4	N/A
6	Rolling over in bed	0	1	2	3	4	N/A
7	Standing for an extended period of time	0	1	2	3	4	N/A
8	Lifting a heavy objecting	0	1	2	3	4	N/A
9	Getting in and out of your car	0	1	2	3	4	N/A
10	Bending to the floor	0	1	2	3	4	N/A

Total:_____

Resting Pain Level: 0 (No pain) 1 2 3 4 5 6 7 8 9 10 (Extreme pain)

Active Pain Level: 0 (No pain) 1 2 3 4 5 6 7 8 9 10 (Extreme pain)

Improvement Since Date of First Treatment (%) 0 10 20 30 40 50 60 70 80 90 100

Figure 1. Patient questionnaire.

with its corresponding baseline response using the Wilcoxon signed rank test. Responses per knee within and between patients were assumed independent for analytic purposes. Due to the limited sample size, covariates were not accessed in this report. Statistical significance was set at P less than .05 and statistical analysis was performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

In total, 80 treatments were performed on 15 patients (20 knees). There was 100% questionnaire completion prior to treatment and after each successive treatment. The last follow-up showed a mean of 86 days (range: 28-185 days) after the first treatment. In all, 2 out of 5 male patients and 3 of 10 female patients underwent bilateral knee treatment. Patient characteristics and results are shown in Tables 1 to 3.

Compared with baseline, patients experienced reduced resting pain after the second and subsequent treatments (1.55, 1.65, and 2.15). After 2 treatments, the 1.55 reduction in resting pain was 60.78% decrease to baseline (P=.008); after 3 treatments, the 1.65 reduction was a 64.71% decrease to baseline (P=.005); and after 4 treatments, the 2.15 reduction was an 84.31% decrease to baseline (P=.001). In all, 17 out of 20 knees reported a resting pain level of zero following the fourth treatment.

Table 1. Baseline patient characteristics.

	N	MEAN (SD)
Age	15	67.67 (7.90)
Body mass index (BMI)	15	24.87 (2.71)
Gender, %		
Male	5	33.33
Female	10	66.67

Table 2. Resting pain, active pain, overall improvement percentage, and functionality outcomes by bone marrow concentrate injections received, N = 20 knees.

	TREATMENT NUMBER				
	0	1	2	3	4
Resting pain (0-10)	2.55	1.45	1.00	0.90	0.40
Mean (SD)	(2.65)	(1.64)	(1.41)	(1.26)	(0.99)
Active pain (0-10)	5.65	3.80	3.25	2.75	2.15
Mean (SD)	(2.32)	(1.96)	(1.97)	(1.71)	(1.31)
Total improvement (0%-100%)	—	43.15%	51.00%	58.75%	67.00%
Mean (SD)		(25.7)	(24.63)	(20.32)	(18.02)
Functionality score (0-40)	17.60	20.35	23.75	25.50	27.40
Mean (SD)	(8.12)	(7.37)	(7.16)	(5.74)	(4.66)

Table 3. Changes in resting pain, active pain, overall improvement percentage, and functionality outcomes compared with baseline, N = 20 knees.

	TREATMENT NUMBER			
	1	2	3	4
Change in resting NPS	–1.10	–1.55[0]	–1.65[0,1]	–2.15*
Mean (SD)	(2.40)	(2.65)	(2.58)	(2.64)
Change in active NPS	–1.85[0]	–2.40[0]	–2.90[0,1]	–3.50*
Mean (SD)	(2.08)	(2.52)	(1.77)	(1.67)
Total improvement (0%-100%)	43.15%	51.00%[1]	58.75%[1]	67.00%[1,2,3]
Mean (SD)	(25.7)	(24.63)	(20.32)	(18.02)
Change in functionality score	2.75[0]	6.15[0,1]	7.90[0,1]	9.80*
Mean (SD)	(3.31)	(5.17)	(6.03)	(6.7)

[0]Statistically significant ($P < .05$) compared with baseline outcomes.
[1]Statistically significant ($P < .05$) compared with outcomes after first injection.
[2]Statistically significant ($P < .05$) compared with outcome after second injection.
[3]Statistically significant ($P < .05$) compared with outcome after third injection.
*Statistically significant ($P < .05$) compared with outcomes to baseline, first injection, second injection, and third injection.

Of the 20 knees, 9 reported a baseline active pain level of 7 or more on a 10-point scale. After the fourth treatment, all the 20 knees reported an active pain level of 5 or less. Active pain was decreased from baseline following each treatment (1.85, 2.4, 2.9, and 3.5). Reported active pain decreased compared with baseline by 32.74% ($P = .002$), 42.48% ($P = .001$), 51.33% ($P < .001$), and 61.95% ($P < .001$), respectively, after each treatment.

With respect to subjective overall improvement, the largest improvement (43.8%) occurred after the first treatment. The next 3 treatments were associated with a 7.95% mean improvement compared with the immediately preceding treatment, resulting in a mean 67% total overall improvement after 4 treatments. In addition, 7 knees reported 80% or more overall improvement.

Although most variables showed the greatest change between baseline and first treatment, the Lower Extremity Functionality score changed the most between the second and third treatments. Per patient report, functionality increased following each treatment: 2.75 points after the first ($P = .002$), 6.15 points after the second ($P < .001$), 7.9 points after the third ($P < .001$), and 9.8 points after the fourth ($P < .001$).

Discussion

We found that in the short-term, receiving multiple injections may be more effective than receiving a single BMC injection. Outcomes at the final follow-up after the fourth treatment were statistically significant compared with outcomes at baseline, after first treatment, after second treatment, and after third treatment. Functionality score increased from baseline to first treatment, illustrating that patients experienced an immediate benefit in performing everyday activities with less difficulty. At the same time, although patients reported a mean

decrease in resting pain after the first treatment, they did not report a resting pain that was statistically significant to baseline until after the second injection. Patients then experienced additional decreases in resting pain with each treatment thereafter. The increase in mean functionality score with successive BMC treatments shows that increasing the number of BMC treatments improves patient performance in daily activities. The active NPS results mirrored those of the functionality scores. Patients experienced less pain during activity following the first treatment, and that active pain continued to decrease with increasing number of treatments.

The present findings may provide new clinical insights into treating OA with BMC. If BMC treatments become more affordable or covered by insurance companies, there could be an increase in the number of patients receiving multiple BMC treatments for OA. If patients who reported improvement to a single injection received multiple, they may experience increased symptomatic relief such as the patients in our study. An additional finding illustrated that patients experienced a greater pain relief when injected with a high-nucleated cell count compared to a lower dose.[21] Our study demonstrates that gradual increase in BMC injections in a short time period may be more effective than a single injection.

A recent study involved patients with knee, hip, or wrist OA who were treated with unspun whole bone marrow injections. All 7 patients who participated reported symptomatic improvements and increased quality of life.[32] Because the authors in this study did not remove any cells from the BMC, they attributed the improvements to the microenvironment of the MSCs, not the concentration process.[32] We hypothesize that receiving 4 sequential BMC treatments 14 days apart provides a more favorable microenvironment due to the prevalence of growth factors. Further research is needed to determine the ideal number of BMC injections before a plateau effect is reached.

When patients were asked whether they experienced adverse side effects at each follow-up, the most common complaints were pain at the extraction site and inflammation at the injection site. Grinding, popping, and snapping sensations in the knee joint were common with specific movements, as was joint stiffness, especially 1 to 2 days following BMC treatment. However, the stiffness generally resolved by the next follow-up visit. Although one patient reported having fallen (which could have hindered healing), there were no other reported incidents that would have negatively influenced the results.

The results from this study are limited because of the absence of a control group, short follow-up times, and possible self-report bias for the subjective response variables. The absence of treatment randomization, lack of nucleated cell count, and small sample size limit the external validity. Additional studies that compared patients who received one injection to patients who received multiple injections are needed to validate these results.

Conclusions

The short-term outcomes of our report demonstrate that patients experienced less pain and were able to perform daily activities with less difficulty after the first BMC injection and reported additional benefit with each subsequent treatment. Further investigation is warranted to determine if receiving multiple BMC injection is superior to a single injection.

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