Case Series

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Regenerative Medicine

Intra-articular bone marrow concentrate injection protocol: short-term efficacy in osteoarthritis

Aim: Evaluate intra-articular injection of bone marrow concentrate (BMC), followed by platelet-rich plasma (PRP) injection at 8 weeks follow-up in moderate/severe osteoarthritis. **Design:** Single center, retrospective Case Series (n = 125). **Methods:** Bone marrow was aspirated/concentrated using a standardized technique. Patients received a single intra-articular injection of BMC, with follow-up injection of PRP at 8 weeks. **Results:** Median absolute pain reduction in all joints was five points (71.4%) on visual analog scale. Median patient satisfaction was 9.0/10, while 91.7% indicated that they would repeat the procedure and 94% said that they would recommend the procedure to a friend. **Conclusion:** Intra-articular injection of BMC, followed by a PRP injection, can provide short-term benefits in moderate-to-severe osteoarthritis.

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Keywords: bone marrow concentrate • orthobiologics • osteoarthritis • platelet-rich plasma

Steven Sampson[1,2,3,4], Jay Smith[5], Hunter Vincent*[,6], Danielle Aufiero[1,2,3,4], Mona Zall[7] & Angie Botto-van-Bemden[8]

[1]David Geffen School of Medicine at UCLA; 10833 Le Conte Ave, Los Angeles, CA 90095, USA

[2]Western University of Health Sciences; 309 E 2nd St, Pomona, CA 91766, USA

[3]Touro College of Osteopathic Medicine, 230 W 125th St #1, NY 10027, USA

[4]The Orthobiologic Institute (TOBI), Woodland Hills, CA 91365, USA

[5]Departments of PM&R, Radiology & Anatomy, Mayo Clinic Sports Medicine Center, Mayo Clinic College of Medicine; 200 1st St SW, Rochester, MN 55905, USA

[6]UC Davis Medical Center, Department of Physical Medicine & Rehabilitation; 4860 Y St, Med Center, Sacramento, CA 95817, USA

[7]Greater Los Angeles VA Medical Center, Department of Physical Medicine & Rehabilitation; 11301 Wilshire Blvd, Los Angeles, CA 90073, USA

[8]Musculoskeletal Research International, Clinical Research Experts; 1004 Avocado Isle, Ft. Lauderdale, FL 33315, USA

*Author for correspondence: huntervincent35@gmail.com

Osteoarthritis (OA) has traditionally been considered to be a chronic, degenerative process of the hyaline cartilage resulting from aging, repetitive activity and in some cases prior trauma. However, contemporary research indicates that histologic, radiographic and clinical OA represents the end-result of complex inflammatory, cellular and molecular processes affecting all joint tissues [1,2]. More specifically, an imbalance between intra-articular anabolic, anti-inflammatory cytokines, as well as catabolic, pro-inflammatory cytokines leads to cartilage loss, synovial inflammation and hypertrophy, subchondral bone changes, osteophytosis and damage to surrounding peri-articular structures such as the capsule and ligaments. This may explain why OA often occurs post traumatically, such as following anterior cruciate ligament tears or meniscal injuries [3]. Although generally considered to be a disease of older individuals, an increasing number of young individuals are presenting with symptomatic arthritis as a results of prior injuries such as anterior cruciate ligament tear or meniscal tears [4]. In patients refractory to nonoperative management, joint arthroplasty remains the gold standard treatment for severe joint OA. However, the limited 'lifespan' of current implants remains problematic, particularly among young individuals. Consequently, there is a continued need to investigate nonoperative, minimally invasive interventions to reduce pain and improve function in patients with refractory symptoms.

For several decades, research has continued to grow in the area of minimally invasive biologic treatments, known as orthobiologics, such as platelet-rich plasma (PRP) and bone marrow concentrate (BMC). BMC is an autologous bone marrow-derived product containing a heterogenous mixture of cells including, but not limited to, mesenchymal stem cells (MSCs), hematopoietic cells and platelets, as well as bioactive molecules such as cytokines. Bone marrow-derived MSCs have been demonstrated to possess anti-inflammatory, immunomodulatory, anti-apoptotic, antibacterial and chondrogenic properties [5]. Due

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to the potential therapeutic benefits of bone marrow-derived MSCs, multiple researchers have begun to explore the safety and efficacy of MSCs to treat a variety of joint disorders, including OA [5–8], osteochondral lesions [9–14], meniscus tears [15], nonunion fractures and spine-mediated pain [16,17]. In addition, autologous BMC has demonstrated promise when utilized intraoperatively as an adjunct to debridement or microfracture surgery for cartilage defects [13,18–22]. Based on these experiences, intra-articular application of MSCs appear to be safe and has resulted in pain reduction, functional improvement and/or tissue regeneration in some patients. Although, to date, the majority of published studies have utilized culture-expanded MSCs, which are not currently available for use in the USA outside of an approved clinical trial. However, BMC can provide both MSCs as well as a variety of other potentially therapeutic cells, growth factors and cytokines [5].

In addition, as one of the first generations of orthobiologic, PRP and its dense mileau of growth factors have accrued substantially more research than BMC, demonstrating potential pain and symptom relieving qualities in a variety of musculoskeletal disorders, most notably chronic tendinopathies [23] and joint OA [24]. In addition, PRP and its growth factors, namely TGF-β, have also exhibited potential chondrogenesis in cartilage repair [25]. Furthermore, studies have shown that PRP and its PDGF may potentially act as a recruiter for MSCs [26], and potentially enhance the osteogenic potential of MSCs and BMC. Provided the potential benefits of both PRP and BMC treatments alone for pain and symptoms with joint OA, combined with the theorized additive effects of PRP on MSCs, we proposed an intra-articular injection protocol involving BMC and PRP for the treatment of OA.

We hypothesized that intra-articular administration of autologous, nonculture expanded BMC with subsequent follow-up injection of PRP at 8 weeks post BMC injection, could effectively reduce pain in patients with OA without significant adverse effects and thereby serve as a point-of-care therapeutic option. Consequently, autologous BMC and PRP injections were implemented into our practice in January 2012 to September 2013. Here we report on 125 patients who were retrospectively followed after receiving a single, ultrasound guided, intra-articular injection of BMC, followed by a PRP injection to the affected joint at approximately 8 weeks in the setting of moderate-to-severe OA.

Methods

Setting

All procedures were performed in an outpatient setting at the senior author's practice between January 2012 and September 2013.

Subjects

All patients meeting the following inclusion criteria were eligible for participation: aged ≥18 years, fluent in English, >3 months of symptomatic OA unresponsive to at least two of the following: activity modification, physical therapy, bracing, assistive devices, acupuncture, nonsteroidal anti-inflammatory medications, local steroid injections, hyaluronic acid injections or arthroscopy, Kellgren–Lawrence [27] grade III or higher radiographic OA and treated with our intra-articular BMC injection protocol for symptomatic OA between January 2012 and September 2013. Patients meeting any of the following exclusion criteria were not included in the analysis: pregnancy or breastfeeding at the time of treatment, participating or planning to participate in a worker's compensation program at the time of the treatment or follow-up period, pending or planned legal action pertaining to knee pain, intolerance to acetaminophen or Vicodin®, history of drug abuse, cortisone injection into the affected joint within 6 weeks of intra-articular BMC injection, use of a nonsteroidal anti-inflammatory medication <1 week prior to BMC, history of anemia, bleeding disorders or inflammatory joint disease, surgical intervention of the affected or contralateral joint <3 months prior to BMC injection, infection of the joint scheduled for treatment within 6 months of BMC injection, active infection, active malignancy.

The study was reviewed and determined to be exempt by the Western Institutional Review Board. Prior to treatment, each patient completed an informed consent process during which the risks and benefits of the procedure were reviewed and patients were given ample time to ask questions.

Procedures

A total of 45 min prior to bone marrow aspiration, patients were given 1 mg of oral lorazepam and 50 mg of tramadol, which have been shown to decrease procedural anxiety and pain [28]. For bone marrow extraction, the patient was placed in a prone position and the posterior superior iliac spine (PSIS) was palpated and marked with a standard surgical marker. Afterward, the PSIS and posterior pelvic regions were prepared and draped in normal sterile fashion. A 15–6 MHz linear array transducer (Sonosite Edge, Bothell, WA, USA) was used to locate the extraction site on the posterior iliac crest. (Figure 1) [29]. Under ultrasound guidance and utilizing an out of plane technique, the periosteum of the PSIS and overlying skin was initially anesthetized using a 1:4 cc ratio of ropivacaine to sterile normal saline, followed by periosteal local anesthesia with 2% lidocaine. Needle size and length varied with body habitus; however, in most patients a 25-gauge

1.5 inch needle was used for initial subcutaneous anesthesia, followed by a 22-gauge 3.5 inch needle for periosteal anesthesia. An automated power driver (Arrow OnControl Powered Bone Marrow Biopsy System, NC, USA) (Figure 2) was used to access the marrow cavity with an 11 gauge needle, in order to decrease procedural time and reduce patient discomfort [28].

Prior to aspiration, a 20 cc syringe was flushed with heparin (1000 μ/cc) and then filled with 2 cc heparin, of which 0.5 cc was injected into the marrow cavity. Following this, three 20 cc syringes were used to aspirate 60 cc of bone marrow. Marrow was collected from one to two different sites within the marrow cavity at one to two different depths. More specifically, the bone marrow aspiration needle was repositioned between syringes within the marrow cavity, without completely withdrawing the aspiration needle out of the bone. For patients scheduled to receive a single joint injection, bone marrow was extracted from a single PSIS, whereas patients scheduled for two joint injections had 60 cc of marrow aspirated from bilateral PSIS regions. The procedure time was recorded for each case. Following bone marrow aspiration, pressure was applied to the skin entry site, followed by placement of triple antibiotic ointment and a sterile dressing. This standard aspiration protocol was performed by each of the three physicians whose patients has complete data to be included in this investigation (physician A: 66; physician B: 19; physician C: 2).

Following extraction, the bone marrow aspirate was concentrated utilizing a double-spin centrifugation technique (10 min at 2800 RPMs and 6 min at 3400 RPMs; Thermo Scientific CL2 centrifuge, MA, USA) yielding approximately 6 cc of BMC for every 60 cc of bone marrow aspirate. Cell cytometry was not available at the time of the procedures, and specific cell types, cell count and concentrations were not obtained for each BMC sample. The BMC was injected into the target joint(s) using standard injection techniques and image guidance: ultrasound for peripheral joints and contrast-controlled fluoroscopy for spinal procedures [29]. During the injection, precautions were taken to avoid intra-articular local anesthetic, because of potential detrimental effects to progenitor cells [30]. Following injection of peripheral joints (i.e., excluding spine injections), the joint was passively moved through flexion and extension, and the patient received Game Ready cryotherapy (Game Ready cold hydrotherapy, CA, USA) for 10 min. After 24–48 hrs following the procedure, patients were contacted via telephone to inquire about adverse reactions to the injection.

All patients received a single intra-articular BMC injection. For patients receiving bilateral joint injections, both joint injections were performed on the same day for patient convenience. All patients that received either unilateral or bilateral joint injections received a follow-up injection of PRP at approximately 8 weeks.

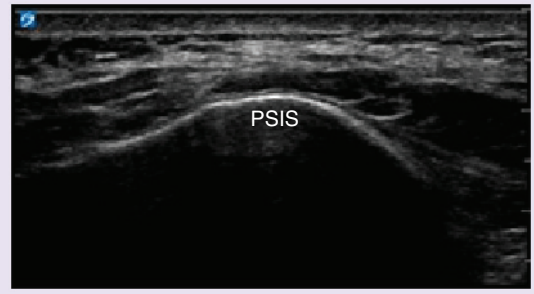

Figure 1. Ultrasound image of posterior superior iliac spine in anatomic transverse view (similar to the ultrasound view used for marrow aspiration). Image orientation = medial = left, lateral = right, superficial = top, deep = bottom.
PSIS: Posterior superior iliac spine.

Approximately 8 weeks post BMC injections, patients returned to clinic for an additional 'booster' injection with PRP to the same affected joint(s). Studies have shown that PRP and its PDGF may potentially act as a recruiter for MSCs [26], and potentially enhance its osteogenic potential. The PRP was prepared in the same manner as the BMC using the Thermo Scientific CL2 centrifugation system and a double-spin technique. Whole venous blood was drawn from a peripheral vein of the patient, and spun for 10 min at 2800 RPMs. Following the first centrifugation, the platelet-poor plasma (PPP) and buffy coat were isolated. The PPP and buffy coat layers were centrifuged for an additional 6 min at 3400 RPMs. The PPP layer was then removed. A small sample of the remaining fluid, PRP, was placed in an Act 5 Diff Plus cell cytometer (Beckman Coulter, Inc., CA, USA) for cellular analysis.

The PRP was standardized using the following Platelets, Leukocytes, Red Blood Cells, Activation (PLRA) classification: platelets between 1 million and

Figure 2. Automated power driver for bone marrow aspiration (see 'Procedures' section).

1.5 million, low leukocytes, low red blood cells and nonactivated [17]. BMC did not undergo the same cellular analysis and we recognize that no similar classification exists for BMC. However, the BMC used consisted primarily of the buffy coat layer, similar to PRP, which is composed of a cellular milieu with concentrated platelets, monocytes and leukocytes. The volume of BMC and PRP injected into each joint varied by location and patient. Larger joints were injected with larger volumes, approximately 5 cc, while smaller joints were injected with approximately 1–2 cc. The same injection protocol was used for PRP injections as was used for the BMC injections, including ultrasound guidance and sterile techniques.

For both BMC and PRP injections, patients were given tramadol for postoperative pain management [31] and instructed to limit the use of their affected joint for 48 h. After 48 h of relative rest, patients were instructed to be weight bearing as tolerated (if a lower body joint was treated) with progression of daily activities as tolerated (for all patients). No specific bracing protocol was followed. Most patients performed postprocedure physical therapy or a home exercise program, but no standardized protocol was followed.

Outcome measurements

Outcome was assessed using standard Brittberg–Peterson visual analog scale (VAS; 0–10) [32] and a global patient satisfaction survey (0–10 scale). The patient satisfaction survey included the following questions: "How satisfied were you with the procedure?" (graded on a scale from 1 to 10); "would you repeat the procedure?" (answer choices included 'yes' or 'no') and "would you refer a friend?" (answer choices included 'yes' or 'no'). Subjective pain measurement of marrow aspiration procedure was recorded in person immediately following the aspiration. Adverse reactions to the marrow aspiration or intra-articular injection were recorded via a phone conversation completed within the first 24–48 h of the procedure. Patient survey data and postprocedure VAS scores were recorded in varying time periods (mean follow-up time: 148 days; minimum: 56 days) via phone calls and direct patient evaluations. Due to the retrospective design of the study, data were not collected at designated intervals and data collection varied on a patient-to-patient basis.

Data analysis

Statistical methods

Descriptive statistics were generated for all variables. Continuous data following a normal (Gaussian) distribution (e.g., age and BMI) were summarized with means and standard deviations (SDs). Continuous data such as VAS scores not following a normal distribution were summarized with medians and ranges and/or interquartile (25th percentile, 75th percentile) ranges. The injected joint location variable was collapsed into eight exclusive categories: ankle, bilateral knees, cervical spine (C-spine), hip, unilateral knee, shoulder and other. If there were three or fewer observations in the original joint location category, the observation was put in the 'other' category.

The student's *t*-test was used to compare means when the data followed the normal distribution (age, height, weight, BMI). The Wilcoxon rank sum test/Kruskal–Wallis test was used to compare medians for follow-up days, continuous scores or other continuous data that did not follow the normal distribution. Normal quartile plots were used to determine whether continuous data distribution follows a normal distribution. The association between changes in median pain scores and BMI, and changes in median pain scores and age, were assessed by fitting a spline curve to assess monotonicity and by computing the Pearson or Spearman (rank) correlation coefficients.

Patients were considered to have complete data if they had both pretreatment pain levels assessed on the procedural day, as well as post treatment pain levels recorded in the medical record based on phone call or in person assessments. BMI data, VAS scores for procedural pain and patient satisfaction surveys were not considered part of the 'complete' data analysis and were analyzed separately.

Comparisons were completed between those 87 patients with complete data versus those 38 patients without complete data to determine if the 38 patients with missing data were missing completely at random. Formal documentation of similarity between the complete and incomplete data suggests that the missing data can be considered as missing completely at random, indicating that the 38 patients are not a biased subset of the 125 total patients.

Results

The initial study group consisted of 125 patients ages 23–79 years (mean: 57 years) with an average BMI of 26.8 kg/m^2 (SD: 5.1 kg/m^2) at the time of injection. The distribution of BMC injections was as follows: ankle (n = 6), bilateral knees (n = 27), C-spine (n = 5), hip (n = 14), unilateral knee (n = 46), shoulder joint (n = 18), other (n = 9). The median bone marrow aspiration procedural pain was 2.0 out of 10 among the 103 patients with available data (range: 0–9; 25th percentile: 1.0; 75th percentile: 3.0).

All 125 patients were contacted via telephone within 24 h to screen for acute adverse events, and none were reported. A total of 87 of 125 patients had complete data as previously defined, with a median follow-up

duration from the time of bone marrow injection (i.e., time of last post-treatment assessment) of 148 days (range: 56–673; 25th percentile: 89 days; 75th percentile: 222 days). With respect to these 87 patients, no adverse effects were reported during the follow-up period, median pre-injection absolute pain scores were 7.0 (range: 2–10; 25th percentile: 5.0; 75th percentile: 9.0; Figure 3) and median postinjection absolute pain scores were 2.0 (range: 0–10; 25th percentile: 1.0; 75th percentile: 3.0; Figure 4). In summary, patients reported a median pain reduction of -5.0 (range: -9.0 to +6.0; 25th percentile: -7.0; 75th percentile: -3.0) and an average pain reduction of 71.4% compared with pretreatment values ($p < 0.0001$).

Median pain change (absolute; percentage) varied with treated joint and data is presented in Table 1. Of note, there was less pain reduction in the hip (median: -3.0; -50%) and ankle (-3.0; -43.8%), compared with the knee (-5.0; -66.7%), bilateral knees (-6.0; -80.0%) and shoulder (-5.0; -62.5%). Table 1 illustrates the absolute median pain change by joint (overall p-value = 0.0230), as well as the percentage change in median pain (overall p-value = 0.0885).

Patients with higher BMIs reported slightly greater reductions in pain post-treatment (Spearman correlation: –0.22; p = 0.05). In comparison, there was no correlation between age and pain reduction.

Minimal differences were shown in provider, follow-up, and age at treatment. However the analysis suggests no evidence of selection bias.

In total, 84 patients completed a follow-up patient satisfaction form with respect to the BMC injection protocol. Median patient satisfaction was 9.0 out of 10 (25th percentile: 7.0; 75th percentile: 10.0; Figure 5), 91.7% (77/84) of patients indicated that they would repeat the procedure, and 94% (79/84) indicated that they would recommend the procedure to a friend.

Discussion

The most important finding of the current investigation was that a single, image-guided intra-articular injection of BMC followed by a supplementary intra-articular injection with PRP at 8 weeks follow-up, was well-tolerated and significantly improved pain at short-term follow-up among patients with moderate-to-severe OA. Although we do not fully understand the mechanism of pain relief, we can theorize that the presence of the IL-1Rα cytokine in BMC, which has exhibited anti-inflammatory characteristics, may alter the inflammatory cytokine environment and concomitantly decrease pain [33]. In addition, BMC contains a high concentration of platelets, which have been shown to decrease pain via a peripheral endocannibinoid-related pathway [34], the NF-κB pathway and enhancing production of endogenous hyaluronic acid production [35]. Understanding the relationship between cytokines and pain, is an area that holds much potential for future research. It can provide much insight into the potential pain relieving mechanisms and mechanisms of cartilage degeneration, as well as potentially leading to a more individualized joint injections based on a patient's cellular environment.

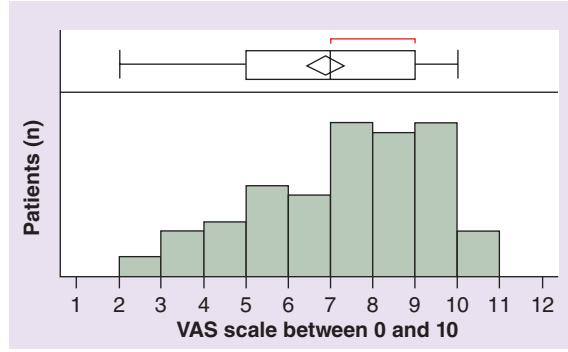

Figure 3. Pre-injection median Brittberg–Peterson visual analog scale between 0 and 10 (n = 87).
VAS: Visual analog scale.

Among our 125 patients, no patient reported a significant side effect from the treatment, and the median pain reduction among the 87 patients with complete data at a median follow-up of 148 days was 71.4%. Furthermore, median patient satisfaction for the 84 patients that completed the postprocedure satisfaction survey was 9.0 out of 10. While 77 of 84 patients (91.7%) indicated that they would repeat the procedure, 79 of 84 (94%) patients indicated that they would recommend the procedure to a friend. These preliminary findings support further exploration of our BMC protocol as a potential treatment for patients with refractory OA.

As the field of Orthobiologics continues to develop, documenting the safety of newly introduced therapies is crucial. None of our patients experienced a signifi-

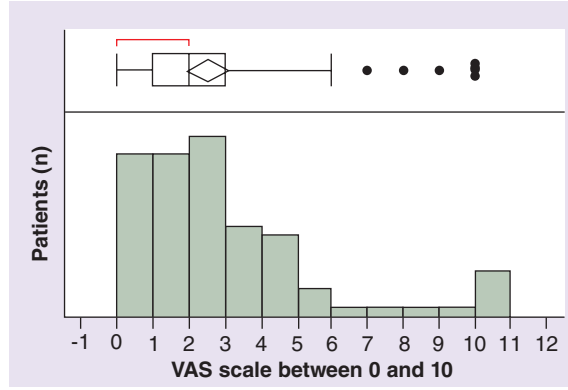

Figure 4. Post-injection median Brittberg–Peterson visual analog scale between 0 and 10 (n = 87).
VAS: Visual analog scale.

Table 1. Median absolute and percentage change by region with interquartile ranges.

Region	n†	Median absolute change (IQR)	Median percentage change (IQR‡) (%)
Knee	31	-5.0 (-6.0, -2.0)	-67 (-89, -44)
Bilateral knees	21	-6.0 (-8.0, -4.5)	-80 (-100, -69)
Shoulder	13	-5.0 (-8.0, -3.5)	-63 (-94, -53)
Hip	10	-3.0 (-4.0, -0.8)	-50 (-80, -15)
Ankle	6	-3.0 (-4.0, +1.8)	-44 (-68, +25)
Other	4	-3.5 (-6.3, +.8)	-70 (-95, +4)
Cervical spine	2	-7.0 (-7.0, -7.0)	-89 (-100, -78)
Overall	87	-5.0 (-7.0, -3.0)	-71 (-100, -50)

†n = 87 is total number of patients with complete data as defined in the methods.
‡IQR, 25th to 75th percentile.
IQR: Interquartile range.

cant treatment-related side effect during our short-term follow-up period, including infection. Utilization of sterile technique is paramount for infection control. However, the natural antibiotic LL-37 released by MSCs may also mitigate infection risk following BMC injections [36]. In addition, PRP has also shown potential to exhibit antibacterial effects [37]. Although our safety data are limited by lack of long-term follow-up, prior research has documented the long-term safety of BMC, including the lack of tumorgenicity [38].

The bone marrow aspiration procedure was also well tolerated with a median VAS pain score of 2.0 out of 10 for procedural pain. Thus, our data correlate with previous research illustrating that pharmacologic (i.e., tramadol and lorazepam) and nonpharmacologic (i.e., automated power driver) techniques can decrease patient anxiety and procedural pain with bone marrow biopsy and aspiration [28,31,39,40].

The logic for the specific timing of the injection protocol, including intra-articular BMC injection with an 8-week follow-up injection with PRP, is based in the physiological principles of wound healing. According to recent data presented by Kenneth Mautner at The Orthobiologic Institute 7th annual symposium (Las Vegas, NV, USA, 10–12 June 2016), the normal inflammatory response follows three phases: inflammation, involving increased blood flow and platelet activation, lasting approximately 3 days; repair, lasting until approximately the tenth day, in which angiogenesis and cell proliferation are started; and remodeling, in which collagen formation begins and can last for several months. At approximately 8 weeks post-BMC injection, phase 1 and phase 2 of the inflammatory response have subsided, and the patient is theoretically undergoing collagen remodeling at the site of injury and injection. By re-instituting PRP into the joint during the remodeling phase, we can potentially reset the inflammatory cascade, once again increasing platelet activation and blood flow while promoting angiogenesis. This in turn, can increase the amount of growth factors in the area, leading to increased fibroblasts in the local environment and potentially propagate the collagen formation that is occurring from the initial injection with BMC. By providing a supplemental PRP injection during the third phase of the inflammatory response, we are in theory elongating the supraphysiologic inflammatory process, resulting in increased cellular proliferation and collagen formation [41].

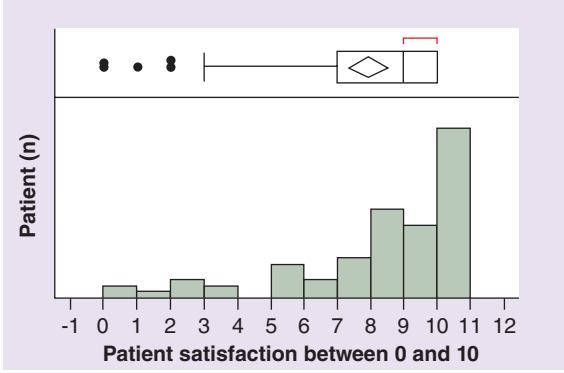

Figure 5. Patient satisfaction (n = 84): scale between 0 and 10. A total of 84 of 125 patients completed the postprocedure satisfaction survey.

Several of our findings warrant further discussion. First, although the overall study group reported significant improvement in pain, not all patients responded and the response varied with body region treated (Table 1). The results varied by body region, with patients receiving hip and ankle injections experiencing the least favorable outcomes. Although the reason for the reduced response among hips and ankles cannot be determined from the current study, these findings may reflect the limitations of our BMC protocol in highly constrained weight bearing joints. Compared with the hip and ankle patients, those patients with unilateral knee OA generally exhibited a good response to our BMC injection protocol.

This differentially better response in the weightbearing knee may reflect the less constrained nature of the knee when compared with a joint like the hip and ankle, which is significantly more constrained. Second, patients who received bilateral knee injections exhibited the most significant improvements. Once again, the reason for this improved response cannot be determined based on the current methodology. However, we do recognize that the overall dose of BMC (and presumably MSCs) was greater in this group than the other patients who received only a single joint injection. Further research is needed to clarify the relationship between BMC/MSC dose and efficacy in the treatment of OA. Third, patients with higher BMIs at the time of treatment reported greater pain reductions at final follow-up. These findings are consistent with unpublished data reported by Centeno *et al.*, although the reason for this observation is unclear [42,43]. In our population, the greater response among high BMI patients may be a consequence of the higher baseline pain scores among this group, providing a larger degree of potential change post-treatment. Alternatively, patients with higher BMIs may potentially benefit more from our BMC protocol due to independent effects of increases in mobility associated with their response to the injections. Further research is warranted to confirm and clarify any interaction between BMI and response to BMC injections for OA.

Although not all patients responded to our BMC protocol, no patients reported worsening of symptoms following the BMC or PRP procedures. The nature of our methodology precludes identification of specific risk factors for lack of response to our protocol. However, we hypothesize that OA severity, baseline pain and functional limitations, BMC dose, PRP dose and interindividual biologic factors can all influence treatment efficacy. Clearly, additional clinical experience and formal investigation is necessary in this regard.

Overall, our patient population reported a median satisfaction of 9.0 out of a possible 10-point scale, while 91.7% (77/84 patients) indicated that they would repeat the procedure and 94% (79/84 patients) indicated that they would recommend the procedure to a friend. These results indicate a high degree of patient satisfaction.

Several study limitations should be considered when interpreting the results of the current investigation. First, this is a preliminary, uncontrolled investigation of a relatively novel treatment performed in an office-based setting. The uncontrolled nature of the study did not allow for exclusion of placebo effects. Although our short-term results are promising, we recognize the need to perform additional prospective, controlled studies using standardized functional outcome tools (e.g., Knee Injury and Osteoarthritis Outcome Score, Oswestry Disability Index) with longer-term follow-up to confirm and expand upon our findings. Second, because our research examined a variety of joints affected by OA, the n value for each individual joint is significantly smaller than would be needed for a high-powered study. However, the diversity of our participants serves to illustrate the many potential applications of a BMC and PRP protocol in short-term pain relief for OA. In addition, we do not report the cellular contents, specific cell counts and cellular concentrations of the BMC. Although the PLRA classification system was used for the PRP preparation, no such classification existed for BMC at the time of injections and cellular analysis was not performed. We now obtain point of care cellular analysis on both BMC and PRP, and recognize the importance of reporting the cellular components, cytokines such as IL-1Rα [33], platelet concentrations and volume of injected BMC for future research, as has been recently emphasized for PRP [17,44].

At last, it is important to note that the addition of a supplementary PRP injection to the BMC treatment protocol can potentially influence the results of an isolated BMC injection for OA. While PRP has been shown to have therapeutic efficacy in mild joint OA [45], it appears to be less effective for moderate-to-severe OA (grade 3–4), as treated in the current investigation. Consequently, we do not believe that the positive effects observed in our investigation can be attributed solely to PRP. The potential benefits of a follow-up booster injection with PRP after receiving BMC is yet to be fully examined, and significant research is needed to illustrate the potentiating effects.

Conclusion

A single ultrasound-guided intra-articular injection of autologous, nonculture expanded BMC followed by a supplemental PRP booster injection at approximately 8 weeks appears to be safe and provide short-term benefits in patients with moderate-to-severe OA. Future research will focus not only on maximizing MSC content and concentration, but improving delivery of cells including high definition visualization of the intra-articular environment and intraosseous infiltration to subchondral bone. Furthermore, much research is needed to evaluate the potential mechanisms of pain relief, histological changes in joint tissue as well as correlations with joint cytokine environment.

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No writing assistance was utilized in the production of this manuscript.

Informed consent disclosure

The study was reviewed and determined to be exempt from review board approval by the Western Institutional Review Board. Prior to treatment, each patient completed an informed consent process during which the risks and benefits of the procedure were reviewed and patients were given ample time to ask questions.

Open access

Executive summary

- A single ultrasound-guided intra-articular injection of autologous, nonculture expanded bone marrow concentrate followed by a supplemental platelet-rich plasma booster injection at approximately 8 weeks appears to be a safe and provide short-term benefits in patients with moderate-to-severe osteoarthritis.
- No adverse effects were reported in all participants who received intra-articular bone marrow concentrate and platelet-rich plasma injections.
- The bone marrow aspiration procedure was well tolerated with a median visual analog scale pain score of 2.0 out of 10.0.
- Median pain reduction among the 87 patients with complete data at a median follow-up of 148 days was 71.4%.
- Our patient population reported a median satisfaction of 9.0 out of a possible 10-point scale.
- A total of 91.7% (77/84 patients) of patients indicated that they would repeat the procedure.
- A total of 94% (79/84 patients) indicated that they would recommend the procedure to a friend.

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