

Prospective Study

e The Treatment of Bone Marrow Lesions Associated with Advanced Knee Osteoarthritis: Comparing Intraosseous and Intraarticular Injections with Bone Marrow Concentrate and Platelet Products

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Background: Bone marrow lesions are a radiographic indication of bony pathology closely associated with advanced osteoarthritis of the adjacent joint. Injection of autologous orthobiologic products, including bone marrow concentrate and platelet-rich plasma, have demonstrated safety and efficacy in treating both advanced osteoarthritis (via intraarticular injection) and associated bone marrow lesions (via intraosseous injection). The relative efficacy of intraarticular versus intraosseous injection of orthobiologics has not been evaluated at the present time.

Objectives: The objective was to evaluate differences in orthobiologic bone marrow lesions treatment, either as a collateral result of intraarticular injection with bone marrow concentrate and platelet products alone, or intraosseous plus intraarticular injection as measured by patient reported outcomes.

Study Design: This study employed a prospective case-matched cohort design.

Setting: This study took place at a single outpatient interventional orthopedic pain clinic.

Methods: Using data from a prospective orthobiologic treatment registry of knee patients, a population of knee osteoarthritis with bone marrow lesions patients who had undergone only intraarticular knee injections of bone marrow concentrate and platelets (for symptomatic advanced osteoarthritis) were age, gender, and disease severity case-matched to a series of advanced osteoarthritis and bone marrow lesions patients who underwent intraosseous plus intraarticular injections. Self-reported patient outcomes for Numeric Pain Scale, International Knee Documentation Committee, lower extremity functional scale, and a modified single assessment numeric evaluation were compared between the 2 treatment groups.

Results: Eighty patients were included, 40 in each group. Although pain and functional outcome scores were significantly improved in both treatment groups, there was no statistically significant differences in patient reported outcomes based on the type of treatment.

Limitations: There are several limitations to this study, including multiple providers performing the injections, varying onset of symptoms to treatment, and additional injections after their initial treatment, that were not controlled. In addition, increasing the sample size may be beneficial as well, particularly with the large bone marrow lesions group, which did suggest possible improvement with intraosseous plus intraarticular over the intraarticular, although was not statistically significant in our sample. Limited data availability for this cohort as well as some missing data are other limitations to consider.

Conclusion: Treating knee bone marrow lesions with intraosseous bone marrow concentrate and platelet products did not affect patient reported outcomes.

Key words: Intraosseous, intraarticular, bone marrow concentrate, bone marrow lesion, bone marrow edema, knee osteoarthritis, platelet-rich plasma, injection

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A gradual increase in the average age of the US population has contributed to an increase in the prevalence of osteoarthritis (OA) (1). Knee OA is the most common form of arthritis, affecting the integrity of subchondral bone, hyaline cartilage, synovium, menisci, and ligaments, which in turn is associated with a wide range of pain and disability (2,3). There are multiple pharmacologic, nonpharmacologic, and surgical modalities for the treatment of OA. Partial or total joint replacement surgery (arthroplasty) is the most common (2) for advanced stage OA.

Bone marrow lesions (BMLs) are a pathological feature of knee OA which is associated with knee pain, meniscal tears, subchondral cyst formation, and progression of OA (3,4). BMLs are diagnosed via magnetic resonance imaging (MRI) findings of hypo-intense signals on T1 weighted images and hyper-intense signals on T2 weighted images (5). The pathogenesis of BMLs includes microfractures of compromised trabecular bone, medullary fat necrosis, decreased venous clearance of the marrow space, and capillary leakage caused by increased blood flow that increases intravascular pressure and affects capillary wall permeability (5).

A variety of treatments for symptomatic BMLs have been proposed, including bisphosphonate therapy, extracorporeal shock wave therapy, and subchondroplasty via injection of bone substitute cement, each with varying results and several possible side effects (5,6). A potentially promising alternative treatment of BMLs involves the use of autologous biologic products (i.e., orthobiologics). Bone marrow concentrate (BMC) is a source of mesenchymal stem cells (MSCs), and MSC therapy has been shown to decrease inflammation and apoptosis in bone (7). MSCs are multipotent cells that can differentiate into multiple cell types including osteoblasts and chondrocytes, and thus the therapy has the potential to restore degraded bone and cartilage for patients with knee OA (8,9). Another type of orthobiologic therapy utilizes platelet rich plasma (PRP), which contains growth factors that can prevent cartilage loss and have anti-inflammatory effects in the joint space (10). A commonly used form of PRP in clinical practice is platelet lysate (PL), which contains the growth factor rich supernatant portion of lysed PRP (11). There is accumulating evidence of safety and efficacy for the intraarticular use of orthobiologic (MSC and PRP) therapy for symptomatic degenerative knee OA (12-14), and more recently, the therapy has been described for intraosseous treatment of BMLs (10,15). At the present time, there are no published investiga-

tions of whether the 2 therapeutic targets (i.e., both intraarticular and intraosseous) provide a synergistic benefit when treated together.

Based on the premise that 1) many patients with symptomatic OA have both intraarticular pathology and BMLs, and 2) there is evidence of efficacy of BMC therapy directed at symptomatic OA pathology in the joint and bone, an important clinical question is whether there is a benefit in combining intraarticular and intraosseous orthobiologic therapies in symptomatic knee OA patients with both joint disease and BMLs.

In an effort to address this question, the present study was designed to compare the efficacy of intraarticular (IA) biologic therapy to a combined intraosseous and intraarticular (IO+IA) biologic therapy for patients with advanced knee OA with BMLs. The IA group will be referred to as the control group and the combined IO+IA injection patients will be referred to as the treatment group. We believe this to be the first direct comparison of these 2 types of treatments using case-matched controls.

METHODS

This study took place at a single outpatient interventional orthopedic pain clinic where patients are invited to voluntarily participate in a prospective tracking registry related to orthobiologic treatments. The registry study protocol underwent review and approval through the International Cellular Medicine Society IRB (OHRP #IRB00002637). Upon completing informed consent, patients are prospectively followed with outcome questionnaires at baseline (pretreatment) and post-treatment at months one, 3, 6, 12, 18, and 24 and every year thereafter using ClinCapture software (Clinovo Clinical D Solutions, Sunnyvale, CA). Registry data for patients who underwent treatment for knee OA, and who received IA vs IA+IO protocols between November 2013 and December 2017 were reviewed for study inclusion. See Fig. 1. Once these patients were identified, they were matched algorithmically.

MRI Grading

All patient MRIs were reviewed for BML presence, OA grade and severity, and the presence or absence of meniscus extrusion with or without osteophyte formation on the side corresponding to the BML. The BML was confirmed on both T2 and T1 images in multiple planes. BML diameter size was determined as either small (< 1 cm), medium (1 – 2 cm), or large (> 2 cm). Knee OA grade was assessed using the method described by

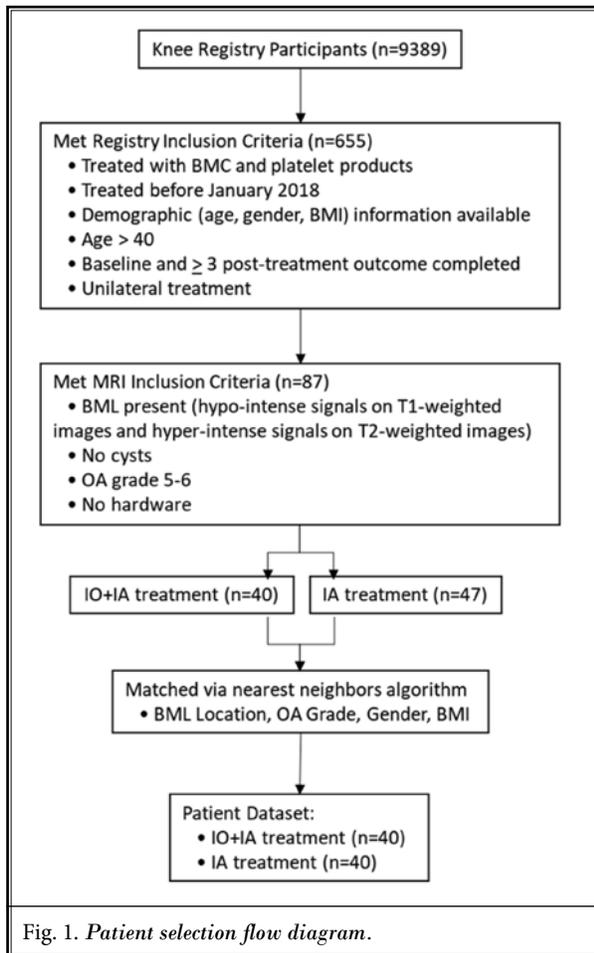


Table 1. Knee OA scoring method by Yamabe et al. (16).

Grade	Cartilage Morphology	Severity Rating
0	normal	mild
1	signal heterogeneity	
2	fraying	
3	fissuring	moderate
4	thinning < 50%	
5	thinning > 50%	moderate-severe
6	full thickness loss	severe

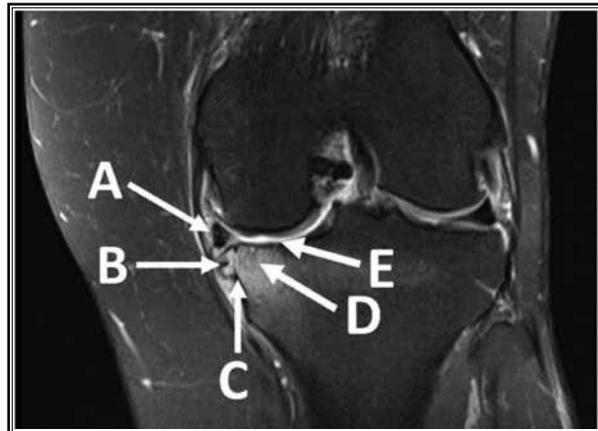


Fig. 2. Magnetic resonance imaging of a knee, coronal section, T2-weighted. Demonstration of (A) an extruded meniscus, (B) a tibial osteophyte, (C) the native border of the tibia from which the extruded meniscus is measured, (D) hyper-intense signal indicating BML, (E) grade 5 chondral loss.

Yamabe et al (16) (Table 1). Medial or lateral meniscus extrusion and osteophyte formation was classified as present or absent using the edge of the tibial plateau as a reference. See Fig. 2.

After MRI grading was complete, the patient population was selected using the following criteria:

- Grade 5 – 6 knee OA
- Unilateral knee treatment
- BML observed on MRI (hypo-intense signal on T1 and hyper-intense signal on T2)
- Pre- and post-treatment outcome data available, along with gender, age, body mass index (BMI), and treatment laterality
- No obvious signs of past surgery on MRI including presence of implanted hardware
- Absence of subchondral intraosseous cysts

Case Matching

A nearest neighbor algorithm was employed

to match IA (control group) patients to IO+IA patients (treatment group). The algorithm most heavily weighted BML location (i.e., medial femoral condyle, lateral tibial plateau, etc.) followed by OA grade, gender, and then BMI. If a duplicate IA patient most closely matched more than one IO+IA patient, the duplicate was replaced with the next closest IA patient. This resulted in equally sized patient populations.

Outcome Metrics

A numeric pain scale, 2 orthopedic functional surveys, and a subjective assessment of improvement were used to quantify post treatment changes in knee pain and function relative to baseline, as follows. The numeric pain scale (NPS) is a 0– 10 scale quantifying weekly average pain. The International Knee Documentation Committee (IKDC) is a patient-reported questionnaire used to measure knee symptoms and function (17). The lower extremity functional scale (LEFS) assesses a

patient's ability to perform everyday tasks (18). The single assessment numeric evaluation (SANE) evaluates patient reported percentage of improvement (19), ranging from 0% to 100%. The question administered to patients allowed responses to range between 100% improved to -100% worsened, with 0% indicating no change. Therefore, we calculated a modified-SANE score by truncating negative scores to 0% to remain consistent with the commonly reported SANE score. Patients were also asked about adverse events and additional treatments and/or surgeries at each follow-up time point.

Procedure Description

Two weeks prior to the IA or IO+IA procedure patients were asked to stop taking all corticosteroid and nonsteroidal anti-inflammatory medications (20,21). Ultrasound and fluoroscopy were used for injections

to confirm correct placement. Under fluoroscopic guidance, lohexol (Omnipaque, NDC # 0407-1413-61) radiographic contrast was injected to confirm exact needle placement, to rule out venous and arterial intraosseous injections, and to ensure that the injection was on target with respect to the BML location on MRI. Figure 3 shows an example of BML on MRI and micro-trocar placements under fluoroscopy. Figure 4 shows the results of the contrast injected into these locations, noting that in panel A, regardless of volume injected, the contrast does not reach the subchondral area target. Panel B shows improved placements to inject into the target zone. Internal data on the effects of contrast on bone marrow MSCs has shown minimal impact on MSC viability at or under 40 mg/mL of lohexol (unpublished data). Our protocol used small volumes of contrast diluted to approximately 30 mg/mL to minimize its impact on MSC viability.

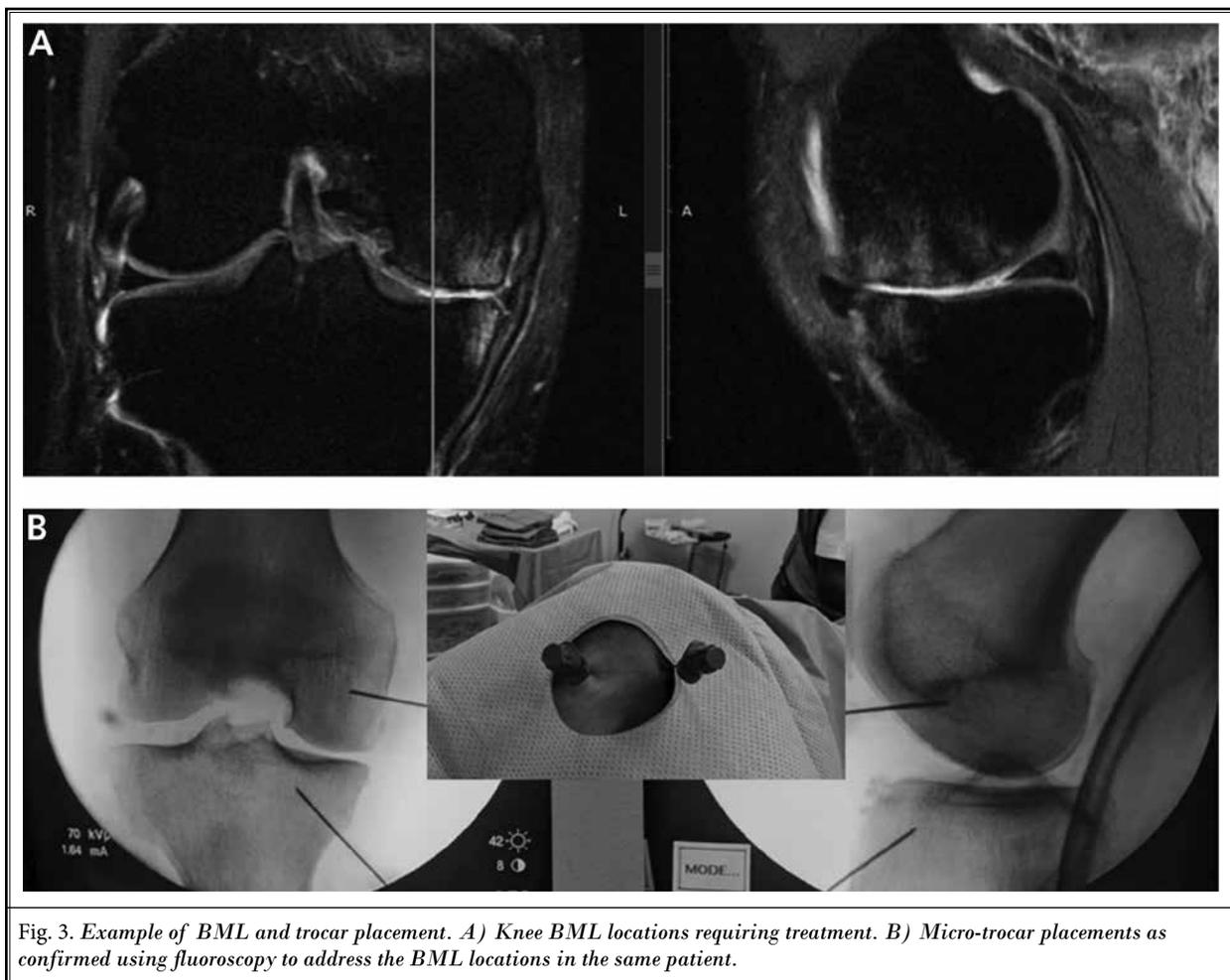


Fig. 3. Example of BML and trocar placement. A) Knee BML locations requiring treatment. B) Micro-trocar placements as confirmed using fluoroscopy to address the BML locations in the same patient.

Pre-Injection

All patients received intraarticular knee injections 2 to 5 days before injection of the BMC. This injection consisted of a solution of 3 – 4 mL 12.5% dextrose, 0.125% ropivacaine, and normal saline with the purpose of causing a brief inflammatory response (22).

Bone-Marrow Aspiration and Concentration

A detailed description of the bone marrow aspiration (BMA) and platelet concentration procedures has been previously described in detail (14). In brief, a

total of 60 – 120 mL bone marrow was aspirated from the posterior superior iliac spine under ultrasound or fluoroscopic guidance. The bone marrow concentrate was then processed manually under sterile conditions and the nucleated cells contained within the buffy coat were isolated for re-injection.

Total Nucleated Cell Count

Total nucleated cell count (TNCC), or the number of nucleated cells contained in the BMC, was determined by lysing red blood cells (RBCs) from the

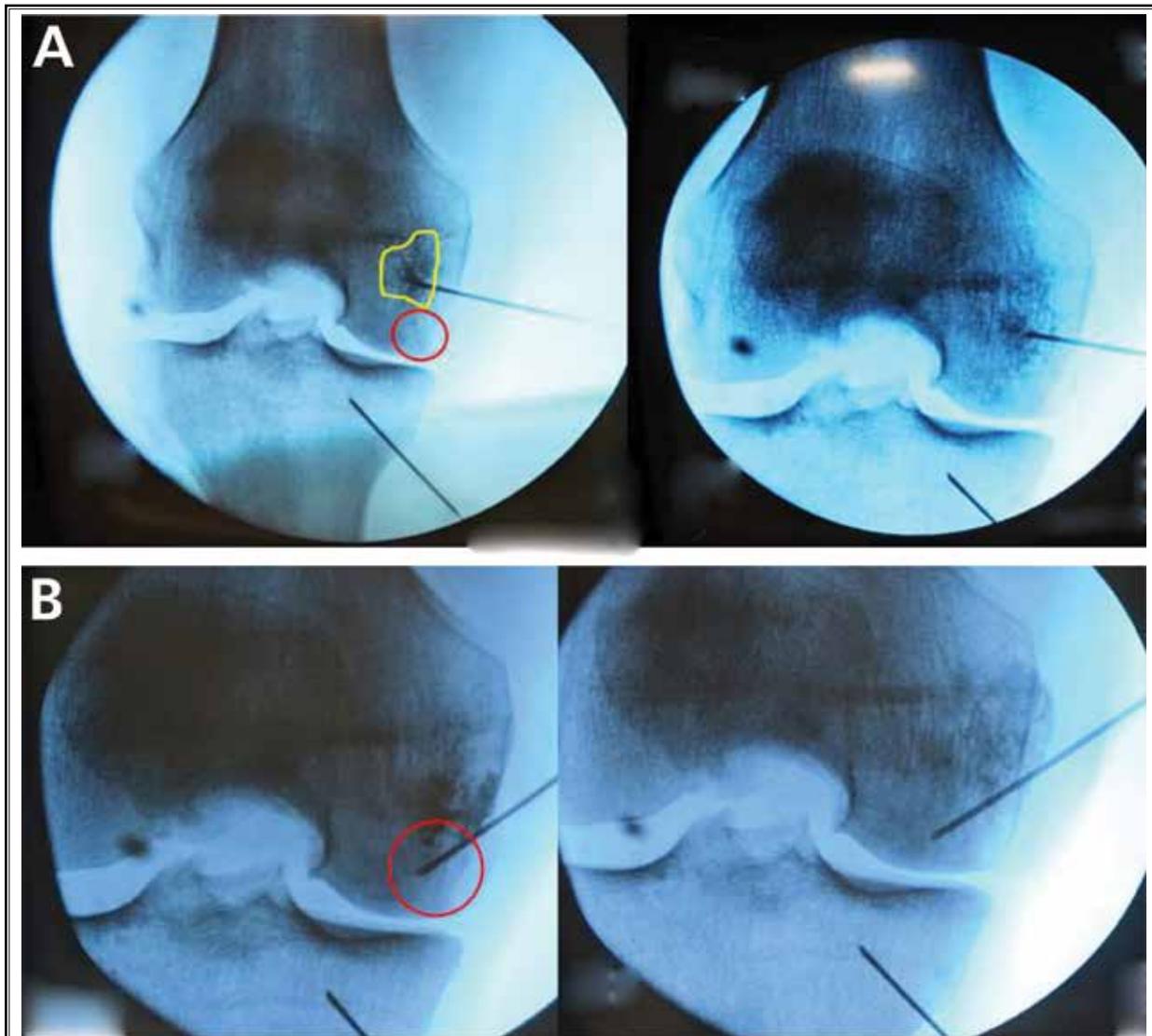


Fig. 4. Using contrast for needle placement. A) Initial contrast flow (yellow outline) which is not near target subchondral BMLs (red circle). B) Reposition of trocar inferior to cover BML target area (red circle).

samples and counting the remaining nucleated cells (23).

IA Injection Procedure – Control Group

Under sterile conditions, ultrasound and/or fluoroscopic guidance was used to identify the intraarticular space. Following this, 4 – 5 mL of the injectate consisting of a mixture of approximately 75% by volume BMC, 12.5% by volume PL, and 12.5% by volume PRP was injected into the intraarticular space.

IO+IA Injection Procedure – Treatment Group

In addition to the IA procedure, an Arrow OnControl Bone Lesion Biopsy 15-gauge 2.7 – 3.5 inch needle was either hand threaded or advanced with the Power Driver (#IPN033774) towards the BML using fluoroscopic guidance. Once needle position was confirmed, 2 – 3 mL of injectate solution consisting of approximately 75% BMC with 12.5% by volume PL and 12.5% by volume PRP by volume was injected directly into the BML.

Post-Injection

Two to 4 days after the BMC procedure, all patients returned for a 4 mL post-injection into the intraarticular space consisting of 25% by total volume of each of the following: concentrated PRP, concentrated PL, doxycycline (20 µg/mL) to inhibit metalloproteases, and dexamethasone (400 ng/mL) to stimulate chondrogenesis (24). Patients were given standard rehab protocols and specific knee braces designed to unload the most symptomatic compartment for approximately 6 weeks.

Statistical Analysis

Independent 2-group Wilcoxon rank-sum tests and chi-squared tests were used to assess baseline differences between IO+IA and IA patients for continuous (age, BMI, TNCC, cell viability, and tibial angle) and categorical (gender, OA grade, osteophyte presence, meniscus extrusion, and BML size) variables, respectively. Linear mixed-effects models were employed to assess differences from baseline in NPS, LEFS, and IKDC outcome metrics, and differences from one-month scores for modified-SANE, for each group. If significant differences were found, post-hoc Tukey was applied to determine which time points differed from baseline (or one month).

To test for differences in IO+IA group outcomes versus IA group outcomes, linear mixed-effects models were created for each outcome metric versus time. Potential confounding variables (i.e., age, gender, BMI,

OA Grade, BML size, osteophyte presence, and meniscus extrusion) were assessed by dividing the IO+IA and IA groups on the following factors: age (older than or equal to the median versus younger than the median), gender (male versus female), OA grade (5 versus 6), BML size (< 1 cm versus 1 – 2 cm versus > 2 cm), osteophyte(s) (present versus absent), and meniscus extrusion (present versus absent). Because the interval of months between assessments was not consistent (i.e., one, 3, 6, and 12 months, etc.) time was scaled using a log transformation, based on AIC (Akaike Information Criteria) results for the best fit. Optimal models were selected via Likelihood Ratio tests, thereby determining if confounders significantly affected outcomes. *P*-values of 0.05 were considered significant. All analyses were performed using R version 3.3.3 and RStudio version 1.0.136.

RESULTS

Forty IO+IA patients matched the inclusion criteria, along with 47 IA patients, of which 40 were isolated using the nearest neighbor matching algorithm. Ages ranged from 42 to 90 years of age. No significant differences were observed between the 2 groups for any baseline variable (*P* > .05) (Table 2).

For both groups, models showed time was a significant predictor of NPS, LEFS, and IKDC outcome scores. Post-hoc analysis showed NPS, LEFS, and IKDC scores significantly improved compared to baseline at all post-treatment time points (*P* < 0.05). Modified-SANE scores did not differ significantly between time points (Fig. 5). The IO+IA and IA groups did not differ significantly across any metric (modified-SANE, NPS, LEFS, IKDC) over time (*P* > .05).

In all cases, models incorporating treatment group and confounding variables were not significant (*P* > .05), and therefore conclude that no confounding variable contributed significantly to outcome differences between groups. See Fig. 6 for an example output of a model testing for IKDC outcome differences relative to BML size (*P* = 0.24).

No serious adverse events related to the procedure were reported in the registry. One patient from the IO+IA group reported undergoing a knee replacement at 24 months, and one patient from the IA group reported receiving a partial knee replacement at 12 months. Twelve point five percent of IO+IA patients received an additional intraarticular PRP injection; one at 4 months, 2 at 8 months, one at 12 months, and one at 24 months. Thirty percent of IA patients received ad-

ditional intraarticular PRP injections; one at 3 months, 5 at 6 months, 4 at 12 months, and 2 at 18 months.

DISCUSSION

As described above, both groups showed significant improvement per NPS, LEFS, and IKDC scores, but neither outperformed the other. These results were unexpected, considering that prior studies have demonstrated promising results following intraosseous BMC for the hip (10,25).

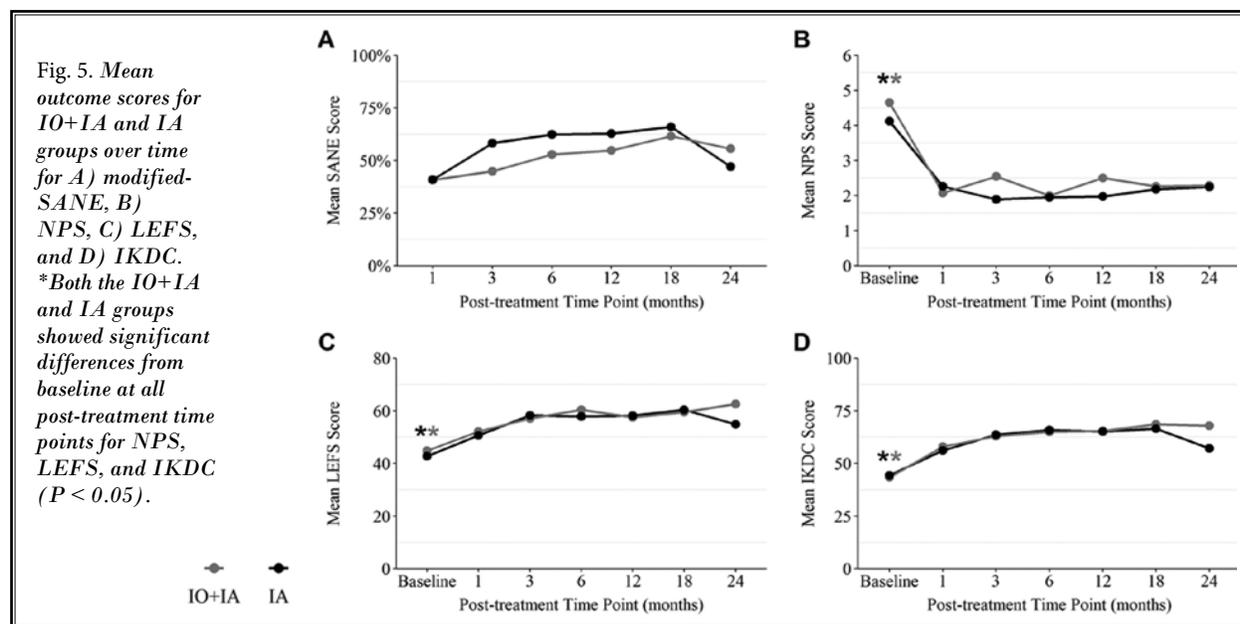
There are several potential explanations for these results. The first credible interpretation is that there are truly no differences in the efficacy of these 2 treatments. Second, we offer the possibility that differences do exist, but not enough volume was injected for the intraosseous treatment. Third, differences may not have been detected due to our study population being different than others investigating intraosseous treatment for BML. Fourth, it is plausible that the use of imaging guidance to focus on targeting the BML may be hampering our results by limiting the area injected. Lastly, there may be other unknown variables that are impacting our results, other than those we have considered.

There is a chance that there truly are no differences between the IA and the IA+IO treatments. It is possible that treating this one characteristic of advanced OA, a BML, does not significantly impact how a patient responds to treatment, in terms of pain and function. There could be other characteristics of advanced knee

Table 2. Patient demographics and characteristic variables by treatment group.

	n	IO+IA	IA Only
		40	40
BML Location	Lat-Fem	2	2
	Lat-Tib	4	5
	Med-Fem	9	5
	Med-Tib	6	8
	Med-Tib/Fib	19	20
OA Grad	5	9	16
	6	31	24
Osteophyte(s)	Yes	33	38
	No	7	2
Extruded	Yes	39	36
Meniscus	No	1	4
BML Size	Small (< 1cm)	8	18
	Medium (1-2cm)	19	10
	Large (> 2cm)	13	12
Gender	Male	24	20
	Female	16	20
Mean (SD)			
Tibial Angle (degrees)		173 (4.5)	174 (3.1)
Age (years)		61 (8)	62 (11)
BMI (lbs/in ²)		28.2 (4.5)	27.2 (6.1)
TNCC (million)		739*	728 (380)
Viability (%)		93%* (4%)	94% ^s (3%)

*n = 39; #n = 24; ⁿ = 32; Lat = lateral; Med = medial; Fem = femoral; Tib = tibial; BML = bone marrow lesion



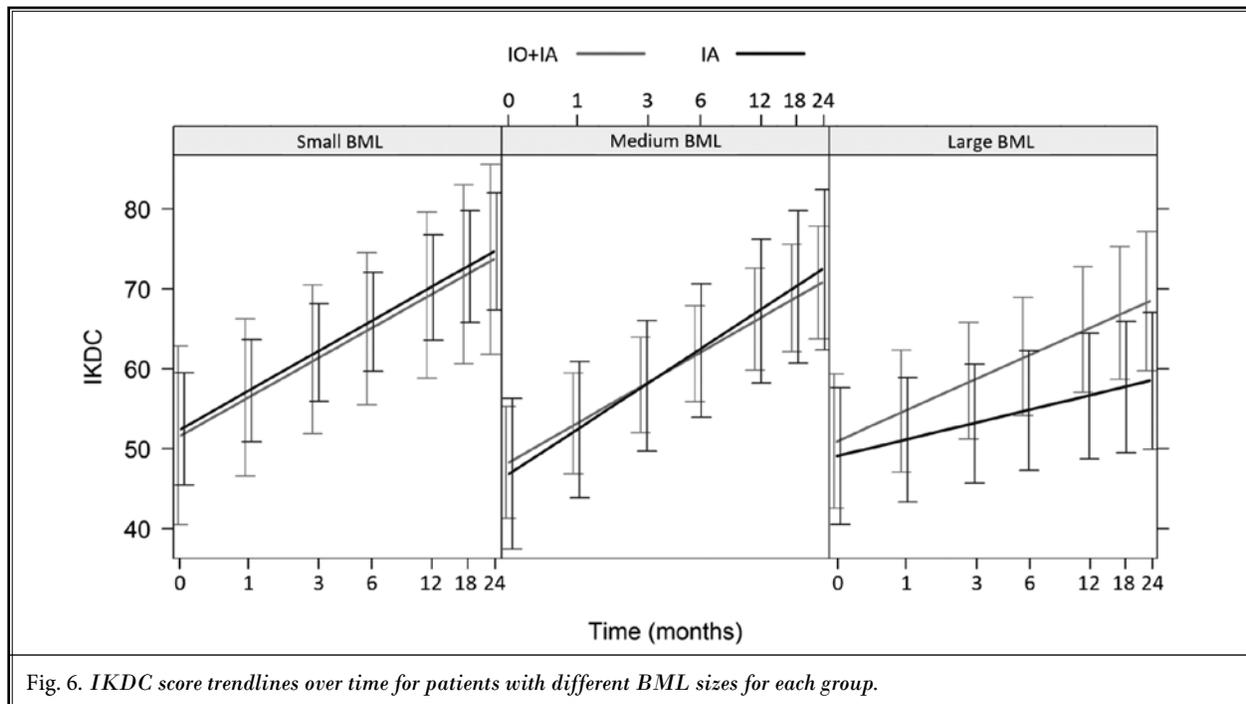


Fig. 6. IKDC score trendlines over time for patients with different BML sizes for each group.

OA that would be worth investigating and treating other than BMLs.

It is also possible that the amount of the intraosseous injectate volume was insufficient to impact symptoms stemming from the BML. Hernigou et al (26) injected 20 mL of BMC when treating non-union fractures of the tibia under a general anesthetic. Fiz et al (10) injected 5 mL BMC into the acetabular and femoral bone marrow lesions with the use of IV sedation. In the present study, intraosseous injectate volumes were 2 – 3 mL of BMC on average. This was due to the treatment goal of covering the lesion with contrast, which was often accomplished with a lower volume of BMC injectate.

The population we compared in the current study may be different from others in the literature. For example, our inclusion criteria included patients over the age of 40 for investigating treatment for advanced knee OA. However, other published studies involving subchondral injections of bone marrow concentrate have been on very different populations. A study by Hernigou et al (27) comparing TKA to contralateral subchondral BMC reported patients' mean age as 28 years (ranging from 18 to 41), which may have impacted their results in a way very different from our older sample.

Another explanation is that there are differences in the IA and the IA+IO treatments, but that our meth-

odology of imaging guidance is impeding our results. Our use of fluoroscopy to target the injection into the exact site of the BML as seen on the MRI, may be limiting the treatment area. It may be that once a BML is seen on MRI, that the tissue damage is too advanced to respond to an orthobiologic injection, while the actual lesions are elsewhere and not visible on MRI. In turn, this effect may be mitigated by injecting larger volumes of BMC without guidance. It has been previously suggested that large volume injections into the center of the bone would allow for the BMC to disseminate into both the living and the dead parts of the bone (28).

It must also be considered that other unknown variables may be impacting our results. Although our case-matching methodology was performed on a random sample of patients meeting specific inclusion criteria in an effort to create similar groups, there may be other variables that were not examined in the dataset that would better stratify these groups or may be driving the current findings.

It should be noted that our results did not show age playing a significant role in how patients responded to either treatment. Some sources in the literature do show an age dependent decrease in colony forming cells (26,29,30), yet other conflicting evidence shows no relationship between colony forming cells and age (31-33). Further, Oreffo et al (34,35) found that although colony forming frequency showed no relationship,

proliferation did decrease with age. Although this type of analysis was not completed in the present study, we did not find TNCC to significantly impact outcomes for either BMC treatment. This is in line with previous work that did not show age impacting outcomes for knee OA treated with BMC (14).

There are several limitations to the interpretation of these results. Factors to consider include but are not limited to the following: multiple providers performing the injections, small sample size, and incomplete registry data. Patients included in the sample were treated by multiple providers, although we do not believe this made a significant difference between groups since they treated patients in both groups. Increasing the sample size may have helped detect statistical differences with the large BML group, which did suggest possible improvement with IO+IA over the IA, although was not statistically, possibly due to the small sample once groups were subdivided into smaller groups for each factor. However, data availability was limited due there being fewer patients receiving the newer IO+IA treatment comparative to IA treated patients. Additionally, to limit the impact of missing data, only patients who responded at multiple time points including baseline and at least 3 post-treatment time points were eligible for inclusion in analysis. The argument can be made that the multiple injection protocol used would make it more difficult to interpret which part of the treatment may be impacting the results, however, the only difference in treatment between these 2 groups of patients is the addition of the intraosseous injection. The rationale behind this injection series protocol has been previously described (36).

In brief, the pre-injection was performed to commence the inflammatory process to activate local MSCs, essentially prepping the knee to receive the BMC. The post-injection, comprised of PRP, PL, and dexamethasone, helps stimulate the proliferation of MSCs. Although corticosteroids in the milligram dose range are toxic to MSCs, dexamethasone has been found to be the least toxic to MSCs compared to other corticosteroids (37). Additionally, in the nanogram dose range, in vitro, it plays a role in the mesenchymal stem cell chondrogenic differentiation protocol (38,39).

Overall, the incidence of serious adverse events reported with bone marrow concentrate is low, approximately 0.01% (40). Our study patients also reported no SAE, in line with these findings.

Although there were various limitations in this registry-based matched-groups analysis, it does provide a foundation for future randomized-controlled trials in the study of treating BMLs in knee OA patients. Variables that should be considered include increasing the volume of concentrate BMC used in treatment, standardization of treatment protocol, increasing sample size, as well as other treatment modalities worth comparing to, such as bracing only or zoledronic acid, to name a few.

CONCLUSION

The results from this case-matched control study determined that both the IO+IA and IA groups demonstrated improved pain and functional outcomes compared to baseline. However, there were no significant differences in self-reported outcomes between the 2 groups.

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