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Biologic Augmented Microdrilling Surgery for Multiple and Large Full-Thickness Cartilage Lesions in the Knee: Early Clinical and Radiological Results

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Abstract

Background: Various biologic treatments are available for articular cartilage lesions in the knee, but no one exists that is applicable to the full range of chondral disease and that is compliant with United States Food and Drug Administration regulations. The aim of this study was to evaluate outcomes following microdrilling surgery augmented with postoperative injections of bone marrow aspirate concentrate (BMAC), platelet rich plasma (PRP) and hyaluronic acid (HA). **Methods:** Eighteen patients with at least one symptomatic, full-thickness chondral lesion underwent arthroscopic microdrilling surgery. Immediately following surgery, patients received an intra-articular injection of fresh BMAC, PRP, and HA. This injection was repeated once per week for 5 consecutive weeks. At 4 and 12 months postoperatively, patients received 3 additional weekly injections for a total of 12 injections. **Outcome Measures:** IKDC (International Knee Documentation Committee) scores, KS (Knee Society) scores and plain radiographs. **Results:** The mean treated area was 6.2 ± 4.5 (range, 0.6 - 14.7) cm^2. The mean preoperative IKDC and KS scores (±SE) were 43.0 ± 3.2 and 68.3 ± 3.6 respectively. At 24 months postoperatively, IKDC and KS scores improved to 85.3 ± 4.2 and 94.7 ± 4.4, respectively; both changes from baseline were significant ($p < 0.001$). Radiographic analysis revealed that 9 of 18 patients in this series had joint space (JS) narrowing preoperatively. At 24 months, there was a 0.7 ± 0.3 mm overall increase in JS ($p = 0.05$). This change was greater in patients with preoperative JS < 2 mm, with an increase of 1.4 ± 0.5 mm (p for the difference between groups = 0.1). **Conclusions:** Microdrilling of cartilage lesions augmented with BMAC, PRP, and HA may be a viable treatment for a range of chondral disease with good early clinical and radiological results.

Keywords

Cartilage, Microdrilling, Stem Cells, Joint Space

1. Introduction

Articular cartilage disease spans a wide range of pathology. At one end of the spectrum are small localized lesions, typically resulting from trauma. These lesions do not spontaneously heal and may become larger over time [1]. At the other end of the spectrum is the absence of cartilage over two large opposing surfaces (kissing lesions), as seen in advanced osteoarthritis. The ideal treatment of cartilage lesions in the knee has yet to be determined.

Various treatments of knee cartilage lesions have been proposed including microfracture, autologous chondrocyte implantation (ACI), osteochondral autografts, osteochondral allografts, and scaffold-based chondrocyte transplants; all of these treatments generally perform more poorly in patients with bipolar (kissing) lesions [1] [2]. Microfracture yields good defect fill, but the repair tissue formed is usually fibrocartilage, which is known to be inferior to hyaline cartilage. Also, microfracture does not perform as well with larger lesions, and as such, has not been recommended for lesions larger than 2 cm^2 or 4 cm^2 [3] [4]. While ACI has been used to successfully treat larger lesions, most authors consider osteoarthritis to be a contraindication [5]. Furthermore, the repair tissue with ACI may be no different than the fibrocartilage formed with microfracture [6]. ACI is expensive, requires two surgeries, and does not perform as well in patients with a previous history of microfracture [7]. Osteochondral autografts may also be used to treat large lesions; however, this procedure is limited by donor site morbidity. Arthroplasty is a viable option in older patients, but its limited lifespan limits the suitability for young, active patients.

Regenerative medicine with the use of stem cells holds great theoretical promise in the treatment of a wide range of chondral disease [8] [9]. Saw and colleagues showed that intraarticular (IA) injections of cryopreserved peripheral blood progenitor cells (PBPCs) and hyaluronic acid (HA) following microdrilling surgery in the knee produced repair tissue that is substantially better than the repair tissue generated after microfracture with injections of hyaluronic acid alone [10]. That same group has used this technique to treat large areas of bipolar cartilage damage [10] [11]. Currently, United States law does not allow the use of cryopreserved PBPCs in the knee, because the Food and Drug Administration (FDA) bans tissue transfers from one part of the body (peripheral blood) to another (knee), unless the transfer occurs during the same procedure ("same surgery exclusion") [12].

Fresh bone marrow aspirate concentrate may provide a source of stem cells to augment microdrilling surgery that complies with current FDA regulations. Several animal studies have demonstrated that bone marrow stem cell injections following microfracture improve the repair tissue quality [13] [14] [15]. Platelet

rich plasma (PRP) injection following microfracture has also improved quality of repair cartilage and clinical outcomes in patients over age 40 with cartilage lesions <4 cm^2 [16]. Additionally, PRP has been shown to promote differentiation of bone marrow mesenchymal stem cells into chondrocytes and to act as a bioactive scaffold in cartilage regeneration [17]. Intra-articular HA after microfracture in rabbits has been shown to inhibit degenerative changes and promote better defect fill than microfracture alone [18]. Consequently, microdrilling surgery of the knee followed by injections of fresh bone marrow aspirate concentrate (BMAC), PRP, and HA is a treatment protocol that complies with current FDA regulations and may potentially produce similar outcomes as treatment with PBPCs and HA. The goal of the current study, therefore, was to evaluate feasibility and early clinical and radiological outcomes in a series of patients who received a novel therapeutic regimen that complies with FDA regulations. Our hypothesis was that we would see improvement in clinical outcome measures and an increase in joint space among patients with joint space narrowing.

2. Methods

Nineteen patients underwent microdrilling surgery with up to 12 postoperative supplemental injections for treatment of symptomatic cartilage defects at a private practice orthopedic surgery center and clinic. Eighteen patients have at least 2 years of follow-up data. One patient was lost to follow-up 17 months postoperatively.

The first author assessed all patients as part of his orthopedic practice, and discussed this procedure as an option for eligible patients. All data were collected prospectively. Inclusion criteria were as follows: being 18 - 64 years of age and having one or more symptomatic cartilage defects, which were either unipolar (<9 cm^2) or bipolar (<18 cm^2). Defects were MRI confirmed and had to be classified as grade III or IV according to International Cartilage Repair Society (ICRS) classification [19]. Exclusion criteria were inflammatory arthritis, BMI > 35, and a mechanical axis deviation >50% across either plateau. Long leg alignment views were obtained in all patients with joint space narrowing or clinical/radiological evidence of malalignment. Patients with a significant mechanical axis deviation were offered the option of staged osteotomy followed by microdrilling surgery. Previous surgery, including microfracture surgery, was not exclusionary for the study.

Institutional review board approval was granted for this study and written informed consent was obtained from all patients prior to enrollment. ClinicalTrials.gov Identifier: NCT02285725.

2.1. Microdrilling Surgery

All surgeries were performed by the same surgeon (1st author). The details of the surgical procedure and postoperative PRP and BMAC processing and injection have been previously described [20]. In a standard arthroscopic procedure, the knee was thoroughly inspected and microdrilling and abrasion chondroplas-

ty was performed over each lesion. Drill holes were 2 mm in diameter, 7 mm deep and placed approximately 3 mm apart. The calcified cartilage was removed in grade III lesions. A 2.9 mm mini burr (3530, Smith and Nephew, London, UK) was used to perform the drilling. A portion of the 2.9 mm outer sleeve was removed to allow drilling to a depth of 7 mm. Intraoperative measurements were taken of each lesion after debridement and drilling using a standard probe with 1 mm markings.

2.2. Intra-Articular Injections

At the conclusion of the surgical procedure, and weekly for 5 weeks postoperatively, the knee was injected with a mixture of PRP, BMAC and 25 mg of hyaluronic acid (Supartz, Bioventus, Durham, NC). Patients also received 3 weekly injections at 4 months and 12 months postoperatively for a total of 12 injections over a 1 year period, similar to the protocol of Saw, *et al.* [10]. Collection protocols for PRP and BMAC follow.

2.2.1. PRP

At the time of each injection, 55 ml of peripheral blood was collected from a peripheral vein. Approximately 7 ml platelet rich plasma was prepared from the blood using the Biomet GPS III Platelet Separation System (Biomet Biologics, Warsaw, IN).

2.2.2. BMAC

Before the start of the microdrilling procedure, each patient had 15 - 20 ml bone marrow aspirated from the ipsilateral posterior superior iliac spine using an 11 gauge Jamshidi® bone marrow aspiration needle (CareFusion, McGaw Park, IL) affixed to a 20 ml syringe containing 100 units heparin. The resulting mixture was run through a 210 micron filter (11141-48, Hospira, Lake Forest, IL) in a sterile closed system to remove any bone particulates and divided into two 10 ml serum tubes (366441, BD Vacutainer, Becton Dickinson, Franklin Lakes, NJ). The tubes were centrifuged for 10 minutes at 1300 g. The resulting buffy coat and some plasma were aspirated from both tubes using a sterile 18 gauge spinal needle, yielding a total of 3 - 5 ml of BMAC per patient.

When patients presented to the office for postoperative injections, the same technique was utilized under aseptic conditions and with 1% lidocaine (buffered to physiologic pH with sodium bicarbonate 8.4%) used as local anesthesia. Also, when permitted by appropriate body habitus, a smaller 15 gauge Illinois® (CareFusion, McGaw Park, IL) bone marrow aspiration needle was used to maximize patient comfort.

2.3. Postoperative Rehabilitation

Two days after surgery, patients began using a continuous passive motion (CPM) machine for 2 hours daily and continued this for 4 weeks. Patients with drilling on the femoral condyle or tibial plateau were restricted to partial weight bearing for 6 weeks postoperatively. Those who had only patellofemoral drilling

were allowed to bear full weight as tolerated. This protocol was established in accordance with previously-published recommendations [11].

Supervised physical therapy was initiated on day 2 postoperatively and continued 5 days per week for 4 weeks, after which the frequency of formal therapy sessions decreased gradually. Early on, there was a focus on isometric exercises in varying degrees of flexion in order to properly load all areas of the knee that were treated with microdrilling. However, early dynamic loading was not recommended in order to prevent a possible shearing injury to new tissue.

2.4. Imaging

Patients had digital radiographs taken preoperatively and at 6, 12 and 24 months and yearly intervals thereafter. Views taken include merchant view, anteroposterior (AP) standing and posteroanterior (PA) standing with 30˚ of flexion. When joint space narrowing was noted on both the AP and PA, the view with the greater degree of narrowing was selected as the baseline measurement. Multiple angles of each view were obtained to ensure that joint space could be properly evaluated and compared to baseline images. A 25.4 mm metallic sphere was placed in the mid-coronal plane of the knee to allow for standardized joint space measurements [21]. Joint space measurements were taken in the medial and lateral tibiofemoral joint and in the patellofemoral joint using Echoes software version 3.0.21.1 (Medstrat, Inc., Downers Grove, IL). Patients were considered to have joint space narrowing if they were grade 1, 2 or 3 according to the OARSI Radiographic Atlas [22].

2.5. Outcome Measures

Patients were assessed using the subjective International Knee Documentation Committee (IKDC) score and Knee Society Score (KSS). In an effort to determine the clinical significance of the change in IKDC score from baseline, individual scores and group means were compared to the minimum clinically important change (MCIC), 11.5 points. This benchmark has been previously determined to optimally distinguish patients who are improved from those who are not [23].

2.6. Statistical Analysis

Statistical analyses were conducted using PASW Statistics for Windows, version 18.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics including mean, standard deviation and proportions were calculated where appropriate. All data were evaluated for normality. Student's t test was used to compare the observed change in IKDC with the previously established MCIC. Repeated-measures regression models were used to evaluate changes in clinical scores from baseline overall and among patients with ≤4 cm^2 and >4 cm^2 treated, as well as changes in joint space from baseline. For correlations between outcomes and patient characteristics, the Pearson coefficient was calculated. All tests were two-sided unless otherwise stated. The significance level was defined at $p < 0.05$.

3. Results

Mean (±standard deviation) age at surgery was 35.4 ± 13.7, (range, 18 - 64) years. Five patients had previous microfracture surgery. All previous surgeries were performed at least 8 months prior to entering the study. The chief preoperative complaint for all patients was knee pain. Patients had a mean total area treated of 5.8 ± 4.4 cm^2 (range, 0.6 - 14.7 cm^2). Twelve patients had bipolar chondral disease, and 9 of those 12 had radiographic evidence of joint space narrowing preoperatively (Table 1).

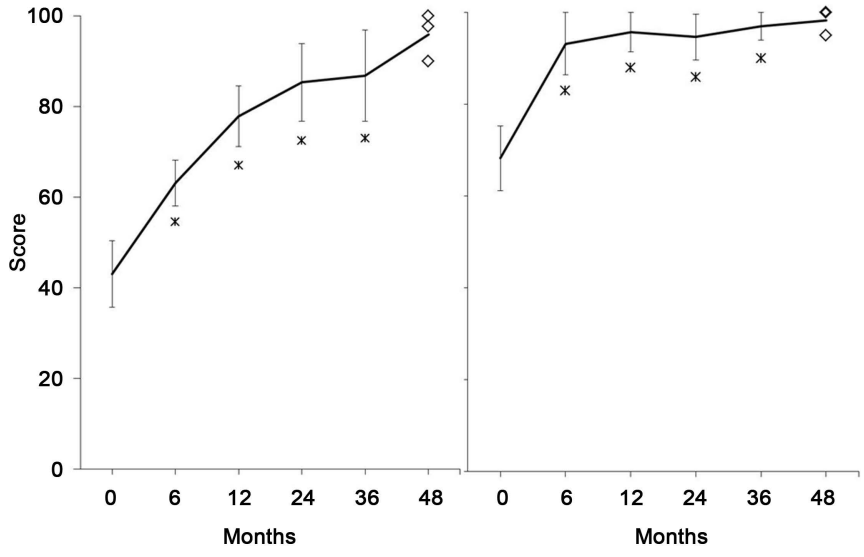
Clinical scores improved significantly from baseline to 24 months postoperatively. The mean IKDC and KS scores (±standard error) before surgery were 43.0 ± 3.2 and 68.3 ± 3.6, respectively. After 24 months, IKDC and KS scores improved to 85.3 ± 4.2 and 94.7 ± 4.4, respectively; both changes from baseline were significant ($p < 0.001$) (Figure 1).

At 12 months, the mean IKDC change from baseline, 34.7 ± 3.9, was significantly higher than the MCIC of 11.5 points (one sided test, $p < 0.001$). At 24

Table 1. Patient and lesion characteristics.

Patient Characteristics[a,b]	Values
Demographics	
Sex, male/female, n	8/10
Age at surgery, mean ± SD (range), y	35.4 ± 13.7 (18 - 64)
Duration of Symptoms, mean (range), m	62 (8 - 243)
BMI, mean ± SD (range)	27.2 ± 4.1 (21.8 - 34.5)
Follow-up, mean ± SD (range), m	32.7 ± 9.0 (24 - 48)
Baseline data	
Knee, right/left, n	8/10
Chondral disease classification, bipolar/unipolar, n	12/6
Joint space narrowing, yes/no, n	9/9
Total area treated, mean ± SD (range), cm^2	5.8 ± 4.4 (0.6 - 14.7)
Patients with area treated ≤4 cm^2/>4 cm^2, n	6/12
Lesions treated, mean ± SD (range), n	3.1 ± 1.7 (1 - 6)
Lesion characteristics[c]	
Lesion size, mean ± SD (range), cm^2	1.9 ± 2.1 (0.2 - 9.1)
ICRS grade, III/IV, n	30/25
Lesion location, n	
Femoral condyle	25
Tibia plateau	12
Patella	9
Trochlea	9

[a]BMI, Body Mass Index; [b]Joint space narrowing grades I, II or III according to OARSI radiographic atlas; [c]ICRS, International Cartilage Repair Society.



(a) (b)

Figure 1. Mean (a) IKDC and (b) KSS scores over the follow-up period. Error bars show 95% confidence intervals. At 48 months (n = 3), markers (◊) represent individual data points. The significance of the change from baseline is denoted by *, $p < 0.001$.

months postoperatively, 17 of 18 patients' IKDC scores exceeded the MCIC (**Table 2**).

After 24 months, mean IKDC scores for patients with ≤4 cm^2 treated improved 49.7 ± 6.1 points, and patients with >4 cm^2 treated improved 43.7 ± 4.3 points; both groups' changes from baseline were significant ($p < 0.001$) (**Figure 2**). At their last follow-up, on the KS score form, 8 patients reported no pain, 9 had mild or occasional pain and 1 patient reported severe pain.

Clinical scores showed agreement with a positive correlation between IKDC and KSS scores (Pearson coefficient = 0.81, $p < 0.001$). Higher patient age was associated with larger total area treated (Pearson coefficient = 0.8, $p < 0.001$). In addition, higher patient age was associated with a lower final IKDC score (Pearson coefficient = −0.62, $p = 0.007$). However, when adjusted for age, there was no significant correlation found between size of the treated area and final IKDC score (partial correlation coefficient = −0.18, $p = 0.49$).

Two patients had a second arthroscopic procedure during the follow up period that allowed for examination of the repair tissue. Defect fill was noted as full and well integrated 14 months postoperatively for a patient with bipolar chondral disease (**Figure 3**). In both patients, ICRS macroscopic scores were grade II (nearly normal) for the principal chondral lesion repair tissue [19].

Radiographic joint space analysis revealed that 9 of the 18 patients in this series had medial or lateral tibiofemoral joint space (JS) narrowing preoperatively. No patients had patellofemoral JS narrowing. There was a significant overall increase of JS ($p = 0.03$), which was more pronounced in the patients with JS < 2 mm at baseline. Overall, JS narrow patients gained an average 0.7 mm (95%CI, 0.0 - 1.4) JS at 24 months postoperatively. Among patients with <2 mm preoperatively, mean JS increase was 1.4 mm (95% CI, 0.4 - 2.3) at 24 months. **Figure 4**

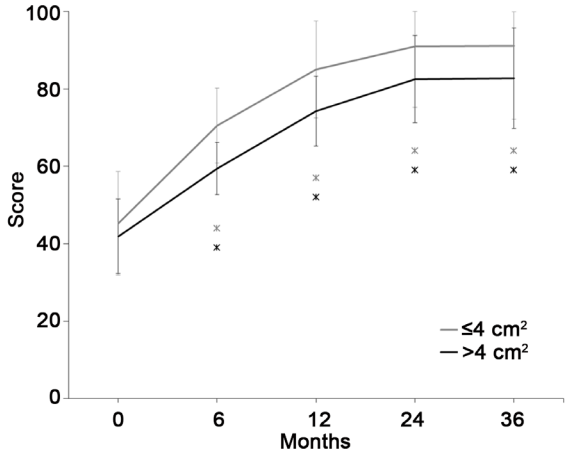


Figure 2. Mean IKDC scores for patients with ≤4 cm² treated (n = 6) and >4 cm² treated (n = 12). Error bars show 95% confidence intervals. The significance of the change from baseline for each group is denoted by *, $p < 0.001$.

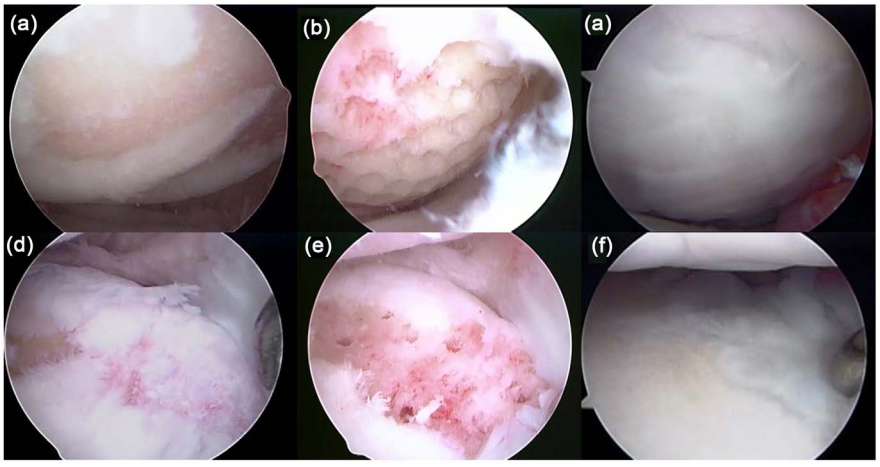


Figure 3. Intraoperative and second-look arthroscopic images for a 28-year-old male with bipolar lateral compartment chondral disease. (a) Lateral femoral condyle (LFC) lesion; (b) LFC lesion after microdrilling; (c) LFC repair cartilage at 14 months postoperatively is smooth and well integrated with surrounding normal cartilage. ICRS repair assessment grade II: defect repair level = 3, integration = 4, appearance = 4, total= 11/12; (d) Lateral tibial plateau (LTP) lesion; (e) LTP lesion after microdrilling; (f) LTP repair cartilage at 14 months postoperatively. ICRS repair assessment grade II: defect repair level = 4, integration = 4, appearance = 3, total = 11/12.

Table 2. IKDC score improvements exceed the minimal clinically important change (MCIC) of 11.5[a].

Month	n	Change from Baseline	% >MCIC	*p* value[b]
6	18	20.1 ± 3.2	78%	0.02
12	18	34.7 ± 3.9	94%	<0.001
24	18	42.3 ± 4.2	94%	<0.001
36	10	37.7 ± 4.8*	100%	<0.001
48	3	50.7 ± 8.1	100%	0.04

[a]Values are expressed as mean ± standard error; [b]P value denotes the significance of the difference between the change from baseline and the MCIC. *Baseline mean IKDC score for the reduced n at 36 months was much higher than at earlier time points, resulting in a depressed change from baseline.

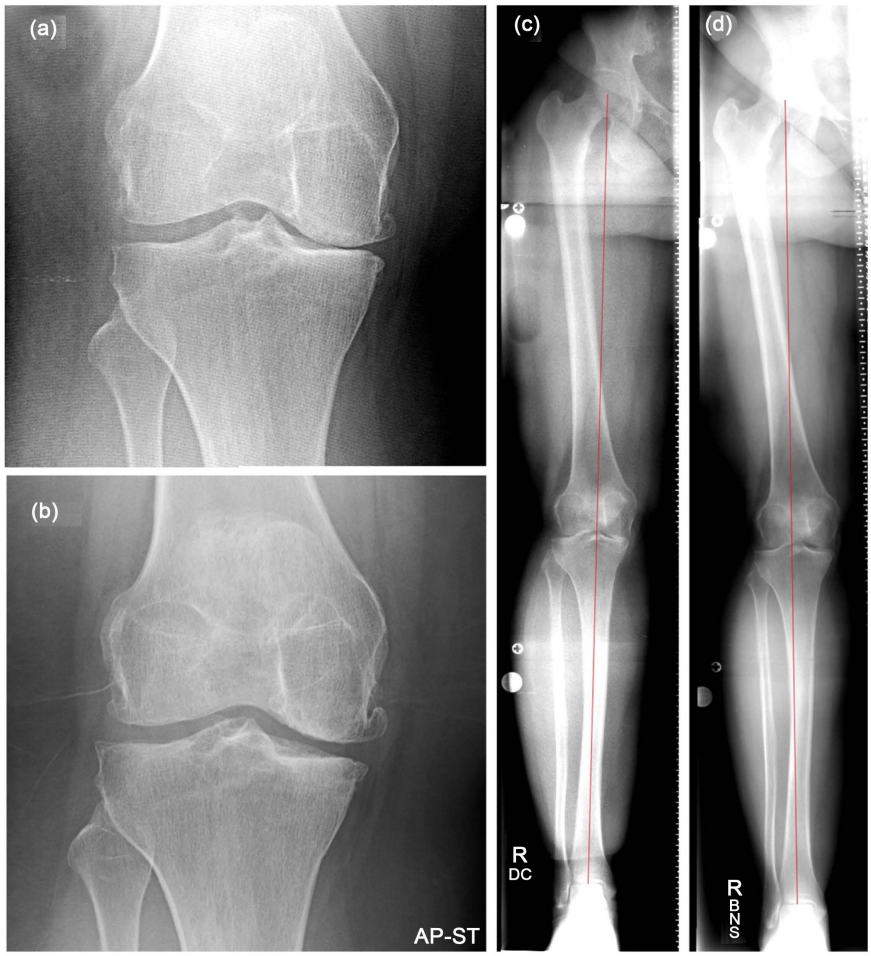


Figure 4. (A-D) Weight-bearing anterior-posterior radiographs for a 50 year-old female (BMI = 28.6). (a) Preoperative radiograph shows severe medial joint space narrowing with 0.5 mm joint space; (b) Three years postoperatively, medial joint space is nearly normal at 3.7 mm; (c) Standing hip-to-ankle radiographs show the knee in slight varus preoperatively and (d) improvement in alignment 3 years postoperatively.

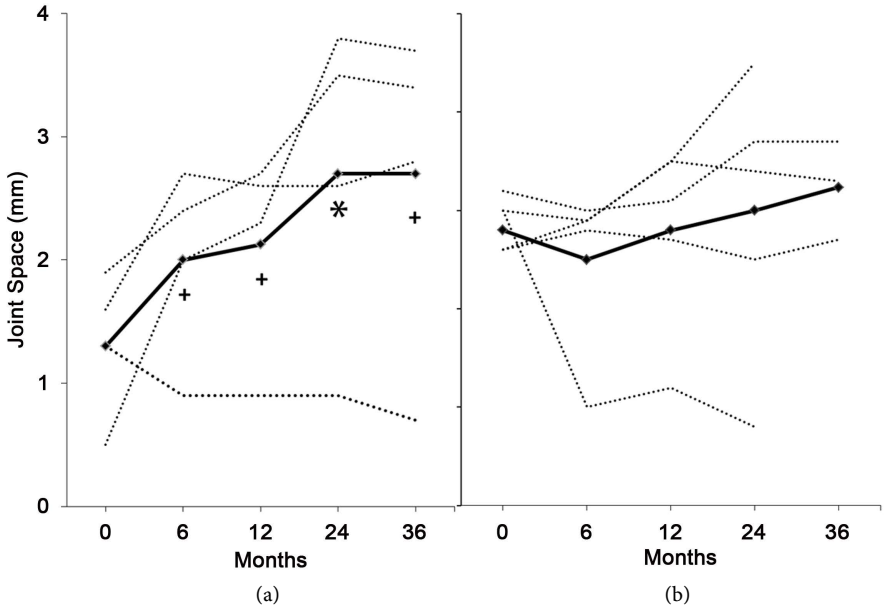
presents the radiographic JS change of a patient in this group. Among patients with ≥2 mm preoperatively, mean JS increase was 0.1 mm (95% CI, −0.7 - 1.0) at 24 months. **Table 3** and **Figure 5** show the individual and mean JS changes over the study period.

Protocol Deviations and Adverse Events

Two patients declined the final series of 3 injections at 12 months postoperatively and therefore received a total of 9 injections. No serious adverse events related to the procedure were encountered. A list of adverse events reported by patients is presented in **Table 4**.

4. Discussion

Microdrilling surgery augmented with serial injections of BMAC, PRP and HA resulted in improvements in clinical outcome measures and increased joint space among patients with joint space narrowing. Under this treatment regimen,



(a) (b)

Figure 5. Joint space (JS) changes for 9 patients with baseline JS narrowing (dashed lines). (a) Patients with preoperative JS ≤ 2 mm (n = 4); (b) Patients with preoperative JS > 2 mm (n = 5). Group means are denoted by solid lines. Significance of the mean change from baseline is indicated by +, $p \leq 0.05$ or *, $p = 0.01$.

Table 3. Joint space change from baseline in mm[a].

Month	All JS Narrow Knees, n = 9		Baseline JS < 2, n = 4		Baseline JS ≥ 2, n = 5[b]	
	Mean Change (95% CI)	*P* value	Mean Change (95% CI)	*P* value	Mean Change (95% CI)	*P* value
6	0.1 (−0.3 - 0.5)	0.60	0.7 (0.1 - 1.3)	0.03	−0.3 (−0.9 - 0.2)	0.21
12	0.3 (−0.3 - 0.9)	0.26	0.8 (0.0 - 2.6)	0.05	−0.1 (−0.8 - 0.7)	0.87
24	0.7 (0.0 - 1.4)	0.05	1.4 (0.4 - 2.3)	0.01	0.1 (−0.7 - 1.0)	0.78
36	0.7 (−0.1 - 1.5)	0.09	1.3 (0.2 - 2.4)	0.02	0.2 (−0.8 - 1.2)	0.71

[a]*p* value denotes the significance of the joint space (JS) change from baseline; [b]At 36 months, n = 3.

Table 4. Adverse events.

Patients (N)	Event	Intervention
1	Immediate postoperative urinary retention	Treated in emergency room with complete resolution
2	Knee pain after injection*	Resolved without intervention
2	Painful catching over capsule on pre-existing osteophyte	Arthroscopic osteophyte excision + 3 weekly injections of HA

*The injectables may have gone into the fat pad instead of the joint space. The injection was repeated 1 week later.

mean IKDC and KS scores significantly improved ($p < 0.001$), with 17 of 18 patients exceeding the minimum clinically important change (MCIC) for IKDC at 24 months postoperatively. Importantly, even patients with multiple lesions and large areas treated (>4 cm^2) reported significant improvements in IKDC ($p <$

0.001). Several case series reporting good short-term outcomes on surgical cartilage repair procedures augmented with a stem cell component have been published in recent years [11] [24] [25] [26]. Few of these studies, however, included patients with large areas of cartilage damage and fewer included patients with osteoarthritic changes and bipolar lesions. In contrast, the current study included patients with an average treated area of 5.8 cm^2 up to a maximum of 14.7 cm^2. A larger treated area was not associated with a worse clinical outcome. This finding contrasts sharply to a study of 110 knees treated with microfracture alone which found that patients with one lesion treated had significantly better clinical outcomes than those who had 2 or 3 lesions treated [3].

IKDC scores improved from a mean baseline score of 43.0 to a 2 year score of 85.3. A large systematic review reported IKDC scores for 106 patients treated with traditional microfracture. The pooled patient population was similar to the present study with a mean age of 32.9 and a mean baseline IKDC score of 45.6. Also, 90% of the studies included in the review reported a detailed postoperative rehabilitation protocol with progressive weight bearing and use of CPM. However, the mean area treated in our study was larger than in this microfracture review (5.8 cm^2 vs. 3.3 cm^2). Also, 2 year postoperative mean IKDC scores were higher in our study (85.3 vs. 72.6).

KS scores in the present study improved from a mean baseline score of 68.2 to a two year score of 94.7. Although KS scores are usually used as an outcome measurement following knee arthroplasty, we chose to include this outcome because some of our patients had extensive disease that would otherwise have been amenable to unicondylar or total knee replacement.

Nine of 18 patients had radiographic evidence of joint space narrowing preoperatively. A significant overall mean improvement of 0.7 mm in standing radiographic joint space was noted at 2 years postoperatively. Among the subset of patients with <2 mm joint space preoperatively, the mean increase in joint space was 1.4 mm at 2 years. We are aware of only 1 other study that demonstrated increased joint space 2 years after a cartilage repair procedure. In that study, the authors performed conventional microfracture in osteoarthritic knees and noted an average joint space improvement of 1.06 mm on weight bearing AP radiographs taken at a mean of 27 months postoperatively [27]. This improvement in joint space, however, did not persist after 10 years of follow-up [28]. The longevity of the joint space restoration in our patients is of course unknown.

In the present study, although there was a significant overall improvement in joint space, 2 patients experienced a decrease in joint space, and 1 patient had no change. These were 3 of the 4 oldest patients in the study. Two of these patients required a large area to be treated on the tibia plateau. Microdrilling was used universally for lesions of the femoral condyle, trochlea, and patella. The tibia plateau is difficult to access with perpendicular drilling, so a microfracture awl was often used instead. The authors speculate that, compared to microfracture, the increased density and depth of drill holes with the microdrilling technique results in increased bony surface area and encourages more mesenchymal stem

cells (MSCs) from BMAC to be recruited into the defects. Over time, cartilage regrowth in the densely populated drill holes generates greater hydrostatic pressure than in microfractured holes and results in increased joint space. Our hypothesis is aligned with the theory generated by Saw and colleagues [11].

Microdrilling was used on the tibial plateau of the patient who gained 3.2 mm JS, shown in **Figure 4**. She was also one of the 4 oldest patients in the study. Although the other 3 oldest patients did not appreciate an increase in joint space, the results of this patient demonstrate that age alone may not be a contraindication for biologic augmented microdrilling.

The joint space analysis has led the lead author to change his technique slightly since this patient series, performing a percutaneous release of the medial collateral ligament, when necessary, in the method described by Fakioglu, *et al.* [29]. The improved access allows medial tibia lesions to be more easily drilled. Although this technique was not used in this original patient cohort, it is now the practice of the first author to perform a percutaneous MCL release for patients requiring drilling of the tibia plateau instead of resorting to a microfracture awl.

As this study investigated a novel approach to articular cartilage repair in the knee, feasibility of the treatment protocol was an important study endpoint. Minimally manipulated, fresh BMAC was obtained at the time of each injection in accordance with the FDA's "same procedure" statute. BMAC was prepared using readily available materials to avoid the high cost associated with commercially available bone marrow concentrate kits, and injections were performed in an outpatient clinic setting. Although this protocol required 11 of the 12 bone marrow aspirations under only local anesthesia, patients rated the aspiration procedure as causing only minimal discomfort, and no patient has refused further injections due to pain from the procedure. We believe this is due to the appropriate use of local anesthesia buffered to physiologic pH, use of a smaller aspiration needle, and efficient technique.

We recognize the complexity of our current approach which includes microdrilling surgery and 12 postoperative bone marrow aspirations, peripheral blood draws and IA knee injections over the course of 1 year. However, we feel that in the absence of knowing what the floor of treatment is, we would rather err on the side of over treating to ensure success. Saw and colleagues use the same number and timing of injections in their treatment protocol. Also, dose response studies have found that patients with osteoarthritis who received an IA injection with a higher concentration of MSCs experienced better clinical and histological results than patients who received a lower concentration of cells [30] [31].

Limitations

There are several limitations of our results. One patient was lost to follow-up 17 months post-operatively. This patient had a 16˚ flexion contracture preoperatively which persisted after surgery. Had this patient's outcomes been included in this series, based on their trajectory, they likely would have weakened the

study results. The lead author now feels that a significant flexion contracture is a contraindication to this procedure.

Another limitation is the lack of a second-look biopsy to evaluate the composition of the repair tissue. Two patients did undergo a second arthroscopy 14 months postoperatively because of late development of mechanical snapping of tissue over a pre-existing femoral condyle osteophyte. These osteophytes had not been removed at the time of the index procedure, as they were asymptomatic. In both patients, nearly the entire femoral condyle had been drilled at the initial procedure. Second-look arthroscopy revealed repair tissue, in both patients, that grossly resembled hyaline cartilage, with a smooth firm white surface, and no surface fibrous membrane typically seen in fibrocartilage (**Figure 3**). Biopsy was not performed, as the lead author and the patients preferred not to violate the newly formed repair tissue. Longer follow-up is needed to assess the durability of the repair tissue. Also, because we used a manual method of BMAC collection, there may have been some variation in BMAC characteristics both from week to week in the same patient and also between patients.

Other study limitations include the lack of a control group and small sample size. The fact that clinically- and statistically-significant changes were detected within this small sample is noteworthy, however.

5. Conclusion

Microdrilling of full thickness chondral lesions in the knee augmented with BMAC, PRP, and HA may have a role in the treatment of a wide range of disease, especially for those patients with advanced osteoarthritis who are too young to consider arthroplasty. Furthermore, the technique complies with current United States FDA regulations.

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