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Original Article

Prospective Evaluation of Clinical Outcomes of the Subchondroplasty Procedure for Treatment of Symptomatic Bone Marrow Lesions of the Knee

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Abstract

Bone marrow lesions (BMLs) have a strong correlation to patient-reported pain, functional limitations, joint deterioration, and rapid progression to total knee arthroplasty. The Subchondroplasty (SCP) procedure uses AccuFill, a calcium phosphate bone substitute material (BSM), to treat bone defects such as microtrabecular fractures and BML. This observational, prospective, multicenter, cohort study evaluated the effect of the SCP procedure at the 2-year follow-up for 70 patients with knee BML. Under arthroscopic and fluoroscopic guidance, the BML was injected with AccuFill. Patient-reported outcomes, including Visual Analog Scale (VAS) pain, Knee Injury and Osteoarthritis Outcome Score (KOOS), International Knee Documentation Committee (IKDC), and modified Knee Society Score (mKSS) were collected through 24 months postoperatively. Radiographs and magnetic resonance imaging (MRI) were performed at baseline and up to 24 months postoperatively. Patient selection was not limited based on the degree of osteoarthritis (OA) as determined radiologically by the Kellgren–Lawrence (K-L) grade. For a subset of patients, patient-reported outcomes were collected up to 5 years including pain evaluation, patient knee global assessment, and satisfaction with the procedure. Preoperative radiographs indicated moderate to severe OA (K-L grades 2–4) in 65 patients (92.8%). Significant improvements

Keywords
- bone marrow lesion
- subchondral defect
- bone substitute material
- AccuFill
- Subchondroplasty

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($p < 0.0001$) in mean VAS pain, IKDC, mKSS, and KOOS scores were observed compared with baseline. Kaplan–Meier survivorship free from conversion to knee arthroplasty was 76.2% at 2 years. The subset of patients followed for 5 years demonstrated low pain scores and high procedure satisfaction. This study presents statistically significant and clinically meaningful evidence of improvement in clinical outcomes following SCP for BMLs of the knee after 2 years. The survivorship rate from arthroplasty at 2 years was 76.2%. SCP for BMLs can relieve pain with a minimally invasive procedure and may delay the need for knee arthroplasty.

Registration NCT01621893 (ClinicalTrials.gov).

Level of Evidence Level II, Prospective Cohort Therapeutic Study.

While the loss of articular cartilage is the hallmark pathological change in osteoarthritis (OA), there is evidence to suggest an important role of abnormal subchondral bone, such as bone marrow lesions (BMLs), in the early stages of disease. BMLs were initially described as bone marrow edema due to the appearance of bright signal on fluid sensitive magnetic resonance imaging (MRI) sequences. However, histopathology of BMLs suggests that there is minimal true edema. Instead, findings show abnormal bone spicules with excessive fibrosis and extensive bony remodeling, essentially the pattern often seen after fatigue fractures in bone.[1] Felson et al found a significant correlation between patients with BML and those requiring knee arthroplasty.[2] Subchondral BML may be a clinically important contributor to OA symptoms because there is a correlation with knee pain,[3] increased cartilage defect scores,[4] and progression of knee OA as measured by joint space narrowing.[2]

The Subchondroplasty (SCP) procedure was first described by Sharkey et al in 2012 as a minimally invasive treatment option for painful BMLs that preserves the native joint.[5] AccuFill bone substitute material (BSM), an engineered calcium phosphate (CaP), was selected as the material for the SCP procedure because it is injectable and flows through the native trabecular bone,[6] is self-setting, provides a scaffold that is the same chemically as the inorganic component of natural bone, is structurally similar both in compressive strength and porosity to trabecular bone, and is capable of undergoing cell-mediated remodeling over time during the healing process.[7–9] To date, several retrospective case studies[10–13] and one prospective study[14] have been published on this procedure. We hypothesized that patients undergoing the SCP procedure for subchondral BMLs would obtain pain relief and low conversion to knee arthroplasty. The purpose of this study was to prospectively evaluate patients for 24 months following an SCP procedure of the knee.

Methods

Between 2012 and 2017, 70 patients across seven centers with moderate to severe knee pain who met the inclusion/exclusion criteria (►**Table 1**) and signed an Institutional Review Board (IRB) approved informed consent were prospectively and consecutively enrolled in the study (ClinicalTrials.gov NCT01621893). Patients requiring concomitant procedures were not excluded as long as they met the inclusion/exclusion criteria.

Patient-reported outcomes were completed preoperatively and again at 2 weeks, 6 weeks, 3 months, 6 months, 12 months, and 24 months including Knee Injury and Osteoarthritis Outcome Score (KOOS), International Knee Documentation Committee (IKDC), Visual Analog Scale (VAS), and modified Knee Society Score (mKSS). The primary outcome of the study was the KOOS pain subscale at 24 months with an improvement of 10 points being considered clinically significant. While the study was designed for a 2-year follow-up, a subset of patients was followed out to 5 years (3 years [$n = 33$], 4 years [$n = 24$], 5 years [$n = 10$]). Numeric pain rating scale (NPRS), patient global assessment, and procedure satisfaction were additionally collected for the subset of patients tracked beyond 24 months.

Neutral anteroposterior (AP) and lateral radiographs were acquired preoperatively and at 6 weeks, 3 months, 6 months, 12 months, and 24 months postoperatively. MRI examinations were conducted using 1.5-T systems preoperatively and at 6, 12, and 24 months postoperatively. K-L grading and BML volume were each performed by an independent radiologist.

The SCP procedure was performed on the subchondral bone of the knee using a fluoroscopically assisted percutaneous approach. Skin incisions were made for the insertion of arthroscopic instrumentation. Debridement of any meniscal/chondral pathology was performed as necessary. The BML was localized by cross-referencing the MRI examination with orthogonal fluoroscopy during the procedure. Once localized, an AccuPort Delivery Cannula (Zimmer Biomet, Warsaw, IN) was drilled directly into the defect under fluoroscopic and arthroscopic guidance and the inner stylet was removed to create an access portal into the lesion. AccuFill CaP BSM (Zimmer Biomet, Warsaw, IN) was injected into the BML and/or the surrounding area until the region of the BML was filled. Care was taken to not overfill the defect as over-pressurizing the device may lead to extrusion beyond the site of intended application and damage to surrounding tissues. Debridement of the meniscal/chondral area is performed as necessary. Once the BSM hardened, the cannula was removed and the joint was arthroscopically inspected to ensure there was no extravasation of the material. Any detected extravasated material was removed with irrigation

Table 1 Inclusion and exclusion criteria

Inclusion criteria	• Age 40–70 y • Body mass index (BMI) <40 • Knee pain ≥3 mo • BML confirmed on T2-weighted MR imaging • Single BML of the tibia, single BML of the femur, or adjoining BML of the tibia and femur • Baseline KOOS pain subscore ≤65 • Knee alignment defined as one of the following: neutral, ≤7 degrees of mechanical varus or <7.5 degrees of mechanical valgus • Intact anterior and posterior cruciate ligaments • No more than one failed operative treatment on treatment knee; none within 6 mo prior to enrollment • The subject is willing and able to sign a written consent form • The subject has the mental capacity and the willingness to comply with the specified follow-up evaluations, and can be contacted by telephone by the site personnel
Exclusion criteria	• Knee pain is primarily related to an alternate condition such as a baker cyst, synovitis, meniscal pathology, or other • BML caused by acute trauma • Sensory, motor, and reflex neurological deficit • Insulin dependent • History of invasive malignancy, unless no recurrence for 5 y • Primary bone tumor in the knee area • Lower extremity surgery other than the investigational surgery during the course of the study • History of substance abuse • Involved in another study or have received investigational product or treatment within the last 30 d • Pregnant or planning on becoming pregnant during the study period • The subject is accepting workers' compensation

Abbreviations: BML, bone marrow lesion; KOOS, Knee Injury and Osteoarthritis Outcome Score; MR, magnetic resonance.

and a shaver during the joint arthroscopy. Postoperative rehabilitation was typical of standard knee arthroscopy with immediate weight bearing as tolerated and return to full activity within 4 to 6 weeks.

Adverse events were recorded from the start of the surgical approach to the final follow-up visit. Patients were asked at each follow-up visit whether they sought any rescue therapy or intervention for their knee pain including pharmaceuticals, injections, surgical interventions, and total or unicompartmental knee replacement. Data were categorized by type and timing of the intervention. Rates of secondary procedures were assessed. Patients were excluded from the study if a revision surgery was performed on the index knee. Revision surgery was defined as a procedure that adjusts or in any way modifies or removes part of the original implant configuration, which included total or unicompartmental knee arthroplasty. Patients undergoing revision surgery were withdrawn from the study at the time of the revision surgery and no further data were collected; however, data collected up to the point of revision were included in the analysis.

Statistical Methods

The sample size of this study was based on an expected clinical success rate of 80% at 12 months of follow-up. Clinically meaningful success was defined as an improvement of at least 10 points on the KOOS pain subscore. Sixty-two patients were determined to be a sufficient sample size with 95% confidence interval. Seventy patients were selected to account for patients lost to follow-up at 12 months.

Analysis was performed using a modified intent-to-treat (mITT) population without imputation for missing data and was defined as all patients who signed an informed consent and were treated with the SCP procedure. Continuous outcomes were summarized using traditional point estimates, along with interquartile range and 95% confidence intervals. Anderson–Darling tests were performed on patient-reported outcomes to determine normality and subsequent paired *t*-tests (normal) and Wilcoxon signed-rank tests (nonparametric data) were performed to compare with baseline data.

Conversion was defined as a patient undergoing total or unicompartmental arthroplasty. Chi-squared tests were used to compare conversion rates in subgroup analyses. Statistical significance was evaluated at 0.05. Kaplan–Meier estimates were provided for the survival analysis (rate of conversion to arthroplasty).

Results

Seventy patients were enrolled and treated with the SCP procedure between 2012 and 2017. Three patients were lost to follow-up before the 12-month visit and four others before the 24-month visit (►**Fig. 1**).

At baseline, most patients (92.8%) had moderate to severe OA (K-L grade 2–4). Thirty-four patients (49%) had a previous procedure on the index knee. The demographics of the enrolled patients are provided in ►**Table 2**.

The medial compartment (88.6%) was most frequently treated. All patients also underwent arthroscopy of the knee to check for postinjection extravasation of AccuFill into the

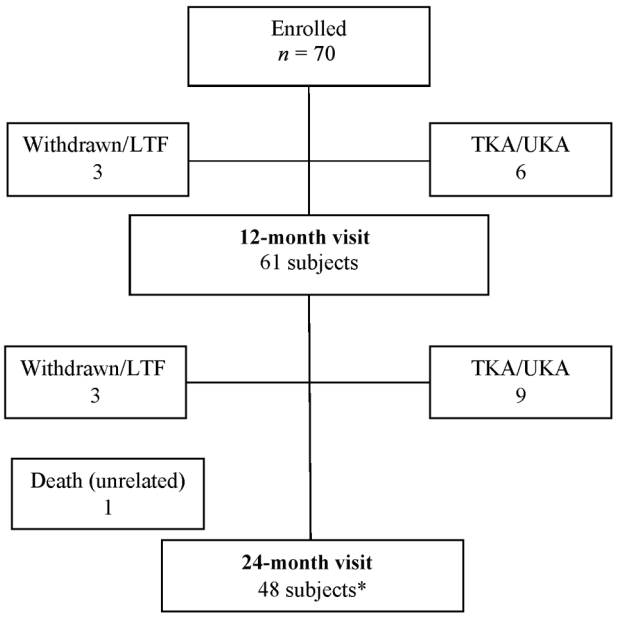

Fig. 1 Study CONSORT diagram. LTF, lost to follow-up; TKA, total knee arthroplasty; UKA, unicompartmental knee arthroplasty. *At the 24-month follow-up, two patients completed the 24-month follow-up but then elected to receive TKA and are accounted as TKA-converted patients. Their data are included in the 24-month follow-up visits. Two (2) more patients have missing 24-month data.

joint space and to treat intra-articular pathology. The average volume of AccuFill in the tibia was 4.2 mL (range: 0.5–9) and it was 3.8 mL (range: 1–8) in the femur. The most common concomitant procedures included partial medial meniscectomy (62.9%), partial lateral meniscectomy (47%), debridement chondroplasty (41%), and synovectomy/plica excision (20%). A summary of lesion location and concomitant procedures is listed in ►**Table 3**.

KOOS pain improved an average of 27.7 points (86.7% improvement) at 24 months. Improvements from baseline in pain, activities of daily living (ADL), symptoms, and sports and recreation were statistically significant ($p < 0.0001$) at all follow-up intervals except the 2-week visit. Improvement in quality of life (QOL) was statistically significant ($p < 0.0001$) at all follow-up intervals (►**Fig. 2**). Clinically meaningful improvement (10 points on KOOS pain scale) was achieved in 48 patients enrolled at 12 months (71.6% of 12-month mITT population, $n = 67$) and 38 patients enrolled at 24 months (60.3% of 24-month mITT population, $n = 63$).

The IKDC score improved by an average of 24.9 points (96.2% improvement) at 24 months. Improvement in the IKDC score was statistically significant at all follow-up intervals ($p = 0.008$ at 2 weeks, $p < 0.0001$ in the remaining time points). The VAS pain score (100 mm) improved by an average of 31.0 points (39.9% improvement) at 24 months. Improvement in the VAS pain score was statistically significant at all follow-up intervals ($p < 0.0001$; ►**Table 4**). The modified KSS function score improved an average of 19.1 points (63.9% improvement) at 24 months. Improvement in the mKSS function score was statistically significant ($p < 0.0001$) at all follow-up intervals after the 6-week visit (►**Table 4**).

Table 2 Baseline demographics

Characteristic	$N = 70$
Mean age	57 ± 7
Mean body mass index (BMI)	30.3 ± 4.4
Sex	
Male	36 (51.4%)
Female	34 (48.6%)
Race	
Asian	2 (2.9%)
African American	2 (2.9%)
White	65 (92.9%)
Unknown	1 (1.4%)
Ethnicity	
Hispanic or Latino	1 (1.4%)
Not Hispanic or Latino	68 (97.1%)
Missing	1 (1.4%)
Employment	
Full-time	44 (62.9%)
Part-time	10 (14.3%)
Not employed	4 (5.7%)
Retired	12 (17.1%)
Work type	
Heavy labor	6 (8.6%)
Moderate labor	27 (38.6%)
Sedentary labor	20 (28.6%)
Missing	17 (24.3%)
Index knee	
Left	30 (42.9%)
Right	40 (57.1%)
Kellgren–Lawrence grade	
Grade 0	1 (1.4%)
Grade 1	2 (2.9%)
Grade 2	21 (30.0%)
Grade 3	39 (55.7%)
Grade 4	5 (7.1%)
Missing	2 (2.9%)

The volume of BSM injected during the SCP procedure was sufficient for visualization on most radiographs and MR images. The appearance of the injectate was consistent with the descriptions in two case reports.[12,15] For example, in a 56-year-old man with K-L grade 3, the BSM appeared as a radiopaque region on radiographs at the first postoperative visit (►**Fig. 3**). The BSM appeared as a hypointense region relative to the surrounding bone marrow on T1-weighted

Table 3 Bone marrow lesion (BML) location and concomitant procedures

Characteristic	$N = 70$
BML location	
Medial tibial plateau	54 (77.1%)
Lateral tibial plateau	7 (10%)
Medial femoral condyle	33 (47.1%)
Lateral femoral condyle	4 (5.7%)
Bipolar (femur and tibia)	28 (40%)
Injection volumes	
Tibia	4.2 mL (0.5–9)
Femur	3.8 mL (1–8)
Concomitant procedure	
Arthroscopy	70 (100.0%)
Partial medial meniscectomy	44 (62.9%)
Partial lateral meniscectomy	33 (47.1%)
Chondroplasty	29 (41.4%)
Abrasion arthroplasty	1 (1.4%)
Synovectomy/plica excision	14 (20.0%)
Medial meniscectomy	1 (1.4%)
Lateral release	3 (4.3%)
Meniscal root repair	1 (1.4%)
Lateral/peripatellar release	4 (5.7%)
Loose body removal	4 (5.7%)
Microfracture	1 (1.4%)

MRI, whereas on T2-weighted MRI, the BSM appeared as a hypointense region surrounded by a rim of hyperintensity at the edges of the injectate. The hyperintense rim may be due to active remodeling on the edge of the material. The T1-weighted images were preferred to the T2-weighted images for visualizing the BSM since the contrast between bone marrow and BSM was greater. Overall, while there was MRI evidence of remodeling of the AccuFill material, all patients appeared to have some amount of material remaining in the bone through 24 months.

Sixty-three patients were included in the survivorship analysis at 24 months. Seven enrolled patients were not included at 24 months due to one death (unrelated) and six patients withdrew consent or were lost to follow-up. Fifteen procedures were converted to arthroplasty including 3 unicompartmental knee arthroplasties (UKA) and 12 total knee arthroplasties (TKAs). Kaplan–Meier analysis demonstrated survivorship of 76.2% at 24 months (►**Fig. 4**). A subset of patients had long-term follow-up out to 5 years (►**Table 5**).

A correlation analysis of conversion to arthroplasty and clinically meaningful improvement (≥10 points improvement on KOOS pain score) at 24 months was performed to evaluate the effects of age, sex, K-L grade, number and size of BML treated, preoperative meniscus extrusion status, and patient body mass index (BMI; ►**Table 6**). While not contributing significantly to conversion rates, the average baseline BML volume between patients who converted to TKA/UKA was $6.27 \pm 3.24\ cm^3$ compared with $4.93 \pm 3.03\ cm^3$ for those who did not. Significant differences in TKA/UKA conversion rates at 24 months were only found for meniscus extrusion status with a 10.0% conversion rate for patients with less than 3 mm of extrusion and 40.0% for patients with ≥3 mm of extrusion ($p = 0.007$). Clinical success by KOOS pain was negatively correlated to the number of BML (unipolar vs. bipolar BML defects; $p = 0.010$), BML size ($p = 0.020$), and the presence of a meniscal extrusion ≥3 mm ($p = 0.034$). The size of BML did significantly influence clinical meaningful improvements with successful patients having an average BML size of $4.43 \pm 2.51\ cm^3$, while those failing to meet the clinical success pain improvement were $6.56 \pm 3.53\ cm^3$.

One hundred and thirteen adverse events were reported in 61 patients. Thirty-five (38%) events were related to the procedure and/or the device (►**Table 7**). The most common device-/procedure-related adverse event was extravasation of the AccuFill material occurring in 18 patients. This was identified either during the procedure or during the first postoperative visit. Intra-articular extravasation identified during the procedure was removed using arthroscopic irrigation. None of the extravasation events identified postoperatively required medical intervention and all resolved radiographically with no material identified outside the bone at 12 months. Serious adverse events were reported in four patients and were unrelated to the device or procedure. There was one death reported between the 12- and 24-month visits. The cause of death is unknown.

Discussion

This study provides statistically and clinically meaningful improvement in pain and function outcome scores through 24 months in a prospective study. Survivorship rate from arthroplasty was 76.2% after 2 years, which is similar to 77.1% reported by Randelli et al[14] and 70% by Cohen and Sharkey.[10] Wood et al[11] and Levy and Cousins[16] found long-term survivorship rates of 73% at 5 years and 76% at 7 years, respectively. It was observed that studies that excluded patients with K-L grade 4 tend to have higher survivorship rates at ≥24 months.[13,17,18]

For patients with progressive OA disease after SCP, preliminary results indicate that they can be successfully converted to a partial or total joint replacement without detrimental effects on the procedure or short-term outcome due to the presence of AccuFill BSM in the bone. Additionally, it is notable that other SCP studies reporting on survivorship rates did not propose any contraindications for conversion to UKA/TKA.[14,19]

The most common adverse event reported in this study was extravasation of the BSM into the joint or surrounding tissues. This was seen as a short-term event as the AccuFill BSM is hydrophilic and easily irrigated out of the joint or expressed out of the soft tissues. In the instances where material was seen on X-ray after the procedure, the

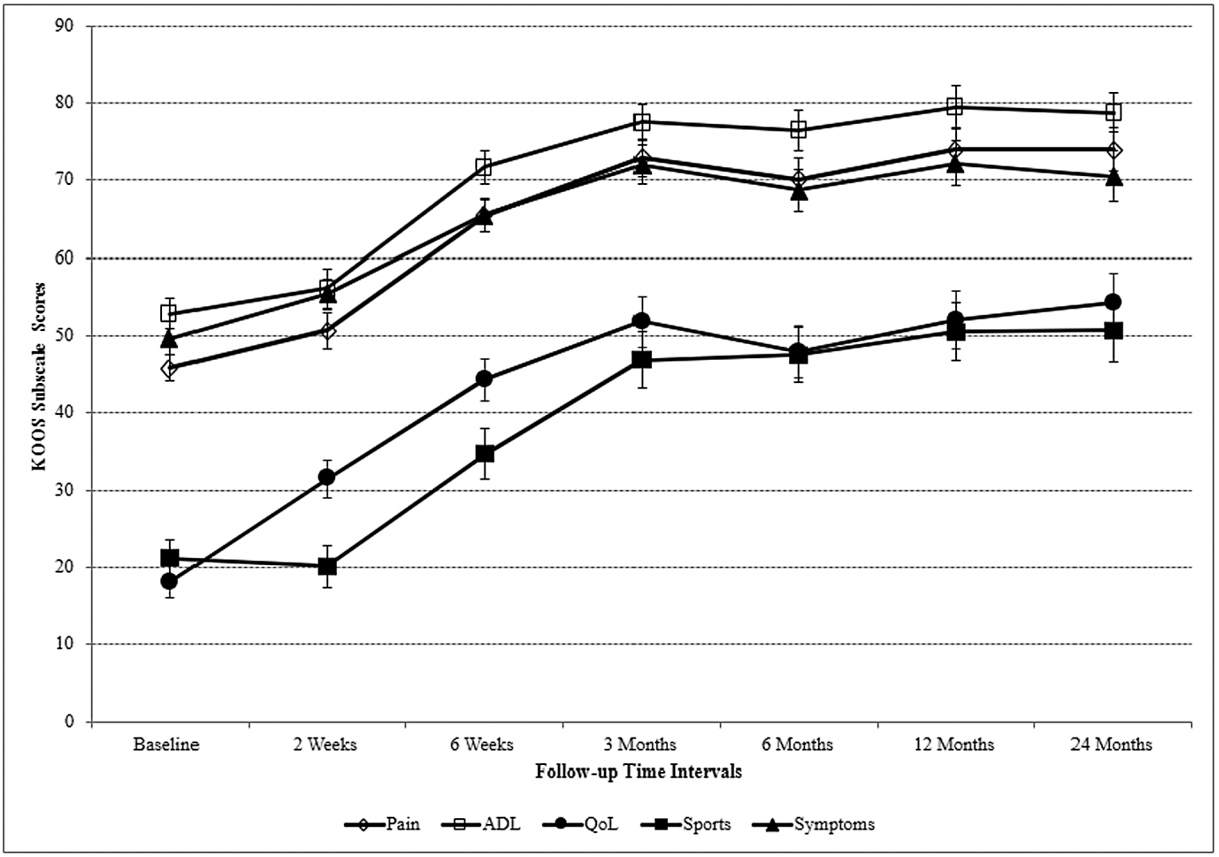

Fig. 2 Mean Knee Injury and Osteoarthritis Outcome Score (KOOS) subscales scores from baseline through 24 months (mean ± standard error of the mean [SEM]). All groups significantly improved from baseline at 24 weeks ($p < 0.0001$). ADL, activities of daily living; QoL, quality of life.

Table 4 Mean patient-reported outcomes scores (mean ± SEM)

		Follow-up						
Measure	Baseline ($n = 69$)	2 wk ($n = 68$)	6 wk ($n = 69$)	3 mo ($n = 63$)	6 mo ($n = 63$)	12 mo ($n = 57$)	24 mo ($n = 48$)	p value
KOOS								
Pain	45.8 ± 1.7	50.7 ± 2.4	65.4 ± 2.1	72.9 ± 2.4	70.1 ± 2.6	73.9 ± 2.7	74 ± 2.8	< 0.0001
ADL	52.9 ± 1.9	56.1 ± 2.4	71.7 ± 2.2	77.5 ± 2.3	76.5 ± 2.6	79.5 ± 2.8	78.7 ± 2.5	< 0.0001
QOL	18.1 ± 2.1	31.5 ± 2.4	44.3 ± 2.8	51.8 ± 3.3	47.9 ± 3.4	52.1 ± 3.7	54.3 ± 3.8	< 0.0001
Symptoms	49.7 ± 2.1	55.4 ± 2.0	65.5 ± 2.1	72 ± 2.5	68.7 ± 2.7	72.2 ± 3.0	70.5 ± 3.2	< 0.0001
Sports and recreation	21.2 ± 2.5	20.1 ± 2.7	34.7 ± 3.3	46.9 ± 3.6	47.6 ± 3.6	50.6 ± 3.8	50.8 ± 4.1	< 0.0001
IKDC	33.9 ± 1.4	38.3 ± 1.8	50.6 ± 2.0	57.6 ± 2.4	56.9 ± 2.5	61.0 ± 2.6	59.1 ± 3.0	< 0.0001
VAS pain	62.4 ± 0.2	47.7 ± 0.3	34.6 ± 0.3	31.5 ± 0.3	31.5 ± 0.3	29.0 ± 0.4	32.9 ± 0.4	< 0.0001
mKSS function	59.2 ± 2.4	37.7 ± 2.6	64.2 ± 2.6	73.1 ± 2.4	73.5 ± 2.4	77.4 ± 2.4	76.0 ± 2.6	< 0.0001

Abbreviations: ADL, activities of daily living; IKDC, International Knee Documentation Committee score; KOOS, Knee Injury and Osteoarthritis Outcome Score; mKSS, modified Knee Society Score; QOL, quality of life; SEM, standard error of the mean; VAS, Visual Analog Scale.
Note: *p*-values are for comparison between the baseline 24-week scores using the paired *t*-test or the Wilcoxon signed-rank tests.

extravasated material appeared to resolve by 12 months. Since the initial enrollment for this study, improvements have been made to both the design of the delivery cannula and the targeting techniques to improve the accuracy of BSM placement and reduce the likelihood of extravasation. In addition, the recommended volumes of BSM to use for a given BML size and location have been reduced with successful clinical outcomes.[14,17,18,20] In addition, surgeons now refrain from overfilling and forced pressurization during delivery[11,18,20,21] as overfilling a defect may lead to more pain in the immediate postoperative period.[18,20,21]

In this study, conversion rates for K-L grades 1 to 3 compared with K-L grade 4 at the 2-year primary endpoint were not statistically different ($p = 0.3027$). In addition, the difference in conversion rates for unipolar defects (20.0%) versus bipolar BML (30.4%) was not statistically significant

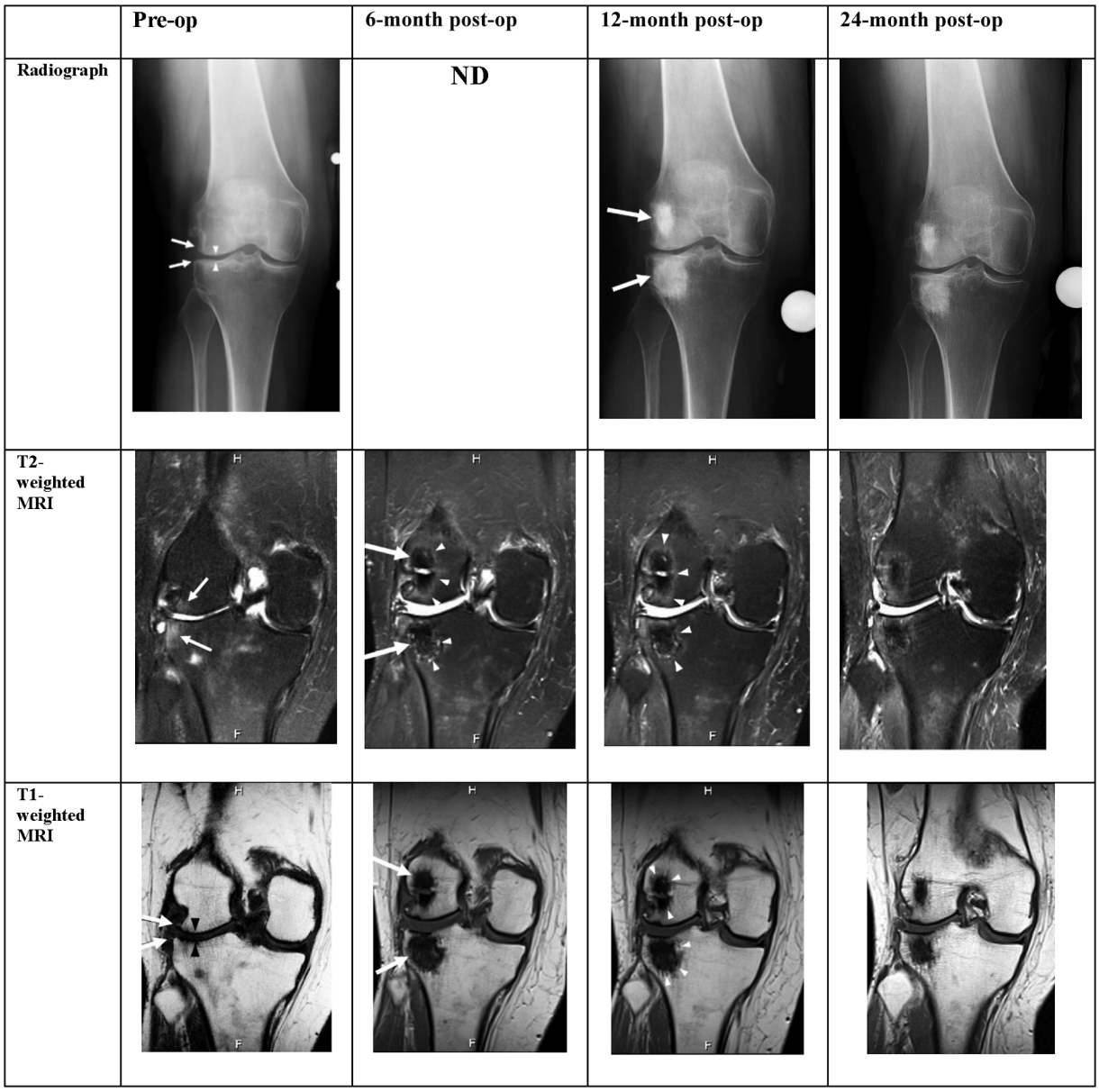

Fig. 3 A 56-year-old man's right knee with bone marrow lesions (BMLs) and Kellgren–Lawrence (K-L) grade 3 at pre-op and corresponding 6-, 12-, and 24-month post-op magnetic resonance images after the Subchondroplasty (SCP) procedure. ND, not done.

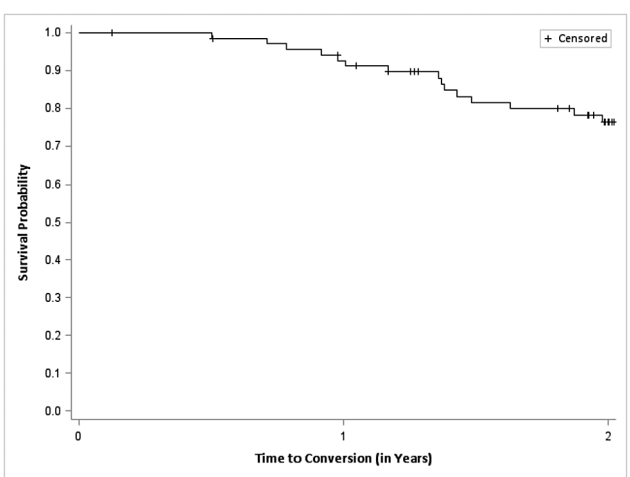

Fig. 4 Kaplan–Meier survivorship curve (conversion to arthroplasty).

($p = 0.3545$). Chatterjee et al previously reported a moderate and inverse relationship between preoperative K-L grade and Tegner–Lysholm scores in a study of 22 SCP patients.[22] Wood et al demonstrated that patients older than 50 years with grade 4 chondral lesions were more likely to convert to knee arthroplasty.[11] Cohen and Sharkey found increased age and previous meniscectomy were associated with conversion to knee arthroplasty.[10] DeBernardis et al observed a significantly greater average BMI within patients who required an additional intervention compared with that of the success group and indicated that it could represent a possible correlation between increasing BMI and failure of SCP.[18] In this study, preoperative meniscal status appeared to be a predictor of conversion to arthroplasty. In particular, patients with an extrusion of the meniscus of $\geq$3 mm as measured on MRI were four times more likely to convert to arthroplasty than those with less than 3 mm of extrusion in

Table 5 Subset of patients enrolled past the 2-year primary endpoint

Time point	Patients (*n*)	Mean numeric pain rating scale	Mean procedure satisfaction (0–10)	Would do procedure again (%)	Patient assessment "stayed same or improved" (%)
3 y	33	2.4 (62.7% improvement from baseline)	8.5	87.9	84.9
4 y	24	2.2 (67.4% improvement from baseline)	9.1	87.5	91.7
5 y	10	2.4 (41.2% improvement from baseline)	9.4	100	90

Table 6 Correlations between TKA/UKA conversion rates (15 out of 61 converted by 24 months) and clinical success (≥10-point improvement on KOOS pain scale; 38 of 61 met clinical meaningful difference at 24 months)

	Conversion to UKA/TKA		Success at 24 mo	
	n/*N*	*p*-value	*n*/*N*	*p*-value
Overall	15/63		38/61	
Age (y)				
<55	3/25	0.074	16/23	0.362
≥55	12/38		22/38	
Sex				
Male	4/30	0.063	19/28	0.409
Female	11/33		19/33	
K-L grade[a]				
K-L 1–3	14/57	0.237	35/57	0.652
K-L 4	0/4		2/4	
Number of BML				
Unipolar	8/40	0.349	29/39	0.010
Bipolar	7/23		9/22	
BML size[b] (cm^3)	15/58	0.130	35/58	0.020
Meniscal extrusion[c]				
<3 mm	3/30	0.007	21/29	0.034
≥3 mm	12/30		13/29	
BMI	15/63	0.961	38/61	0.848

Abbreviations: BMI, body mass index; BML, bone marrow lesion; K-L, Kellgren–Lawrence grade; KOOS, Knee Injury and Osteoarthritis Outcome Score; TKA, total knee arthroplasty; UKA, unicompartmental knee arthroplasty.
[a]Two patients' X-ray score is missing (1 with converted TKA).
[b]Five patients' MRI Osteoarthritis Knee Score (MOAKS) for BMLs is missing.
[c]Three patients' meniscal grade is missing (only $n = 58$ with associated KOOS scores).

this study. This is likely attributed to the significant increases in tibiofemoral contact pressures in a meniscal-deficient knee as demonstrated in previous studies.[23] Along with meniscal extrusion, number and size of BMLs negatively correlated with clinically meaningful success at 24 months. The demographics in this study, which could help define the patient population most appropriate for the SCP procedure, were predominately in their middle age (57 ± 7 years), not severely obese (BMI: 30.3 ± 4.4), not heavy laborers (91.4% of the population), and K-L grade ≤3 (92.6% of population).

In this study, an independent radiologist reviewed all radiographs and MRI scans. While there was MRI evidence of remodeling of the AccuFill material, all patients appeared to have some amount of material remaining in the bone through 24 months, as seen in previous studies.[12,15]

The limitations of this study include a lack of a comparative control group, blinding, or randomization. Concomitant arthroscopic procedures, such as partial meniscectomy, are another limitation as the contribution of the SCP to patient outcomes is difficult to distinguish from the arthroscopic procedure. However, the maintenance of favorable patient-reported outcomes through 24 months appears to be an improvement over the maximum effectiveness at 3 months reported by Kirkley et al for arthroscopy compared with physical therapy for treatment of OA.[24] These results also appear to exceed the short-term placebo effect associated with arthroscopic surgery both in magnitude

Table 7 Device-/procedure-related adverse events

Device- or procedure-related adverse event description	*n*	% of device and/or procedure ($n = 35$)
Deep vein thrombosis	1	2.9
Ecchymosis	1	2.9
Edema, numbness	1	2.9
Infection, lower extremity	2	5.7
Extravasation bone substitute material	18	51.4
Knee pain	2	5.7
Knee pain, edema	1	2.9
New imaging finding—new bone marrow lesion	4	11.4
Pes anserine bursitis	2	5.7
Shortness of breath	1	2.9
Superficial infection	1	2.9
Syncope	1	2.9
Total	35	100.0

and duration of effect.[25] It is also important to note the difference in presentation of BML-related knee pain versus intra-articular symptoms. Additionally, while some patient factors like number of lesions treated, BML size, and meniscal extrusion were found to be a significant correlation to treatment success, the sample numbers are low and larger studies may be needed to confirm these findings.

Farr and Cohen[21] reported that approximately a quarter of patients continued to experience pain following the SCP procedure. SCP does not address the intra-articular environment where most OA changes occur and where pain could also arise. Overall, a majority of patients who were contacted annually until the fifth year of follow-up maintained low NPRS pain scores, were satisfied with the procedure, would do the procedure again, and graded their knee as the same or improved. Consistent with this study, a satisfaction rate of 92% (11 of 12 patients enrolled after 3 years) was reported by Krebs et al.[17] Levy and Cousins observed a maintenance of favorable pain relief through VAS pain score measurements at 7 years post-SCP.[16]

Conclusion

This study presents a statistically significant and clinically meaningful improvement in outcomes following SCP for BMLs of the knee up to 24 months. The overall conversion rate of patients in this study suggests this minimally invasive procedure may delay the need for knee arthroplasty. The SCP procedure can provide an additional tool in the arsenal of early intervention strategies that may help treat arthritis-related knee pain.

Ethical Approval

This study was approved by the WCG IRB Connexus, Princeton, NJ review board (WIRB HRP-2002 protocol number 20120493).

Informed Consent

Each subject enrolled in the study signed an informed consent.

Authors' Contributions

S.B.C., C.H., G.L.L., S.A., P.J.D., D.J.W., T.Y., L.M.J., R.J.D., and J.F. all reviewed and approved the manuscript. P.R. designed the study, drafted, and reviewed the manuscript. J.E.W.M. drafted and reviewed the manuscript.

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Conflict of Interest

S.B.C. was a consultant for Zimmer Biomet during the conduct of the study. He receives royalties from Slack Inc and receives research support from Major League baseball. C.H. is currently a consultant for Corin, MaxxOrtho, and Medacta. G.L.L. has no disclosures. S.A. is a paid consultant for Arthrex, Inc. P.J.D. has nothing to disclose. D.J.W. was a consultant for Zimmer Biomet during the conduct of the study. T.Y. is a paid consultant for Arthrex. L.M.J. is on the editorial board for *Bulletin for the Hospital for Joint Diseases*, editorial board for *JBJS Reviews*, has stock or stock options in Lazurite, received research support from Mitek, Arthrex, Inc., and Smith and Nephew, and receives royalties, financial or material support by Wolters Kluwer Health - Lippincott Williams & Wilkins: Publishing. R.J.D. is an independent contractor for a surgeon consulting group "Chicagoland Joint Replacement Specialists LLC. J.F.'s disclosures are for Elute: Data Safety Monitoring Committee; Lumiheal: Medical advisory board; Medipost Consultant; Med Market Consulting; Moximed: Design surgeon for product and clinical study of the "knee unloader": MISHA knee system;

Organogenesis: Consultant; Vericel Consultant; and ZKR Orthopedics Consultant/Medical Board. P.R. was a paid employee of Zimmer Biomet during the conduct of the study. J.E.W.M. is a paid employee of Zimmer Biomet.

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