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

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Conflict of Interest: Patrick Reischling was a paid employee of Zimmer Biomet at the time of the study and Jennifer Woodell-May is a current paid employee of Zimmer Biomet.

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Trial registration: NCT01621893, ClinicalTrials.gov (http://www.clinicaltrials.gov/), Level II Prospective Cohort Therapeutic Study

Abstract:
Introduction: 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.
Methods: This observational, prospective, multicenter, cohort study evaluated the effect of the SCP Procedure at two-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 images (MRI) were performed at baseline and up to 24 months post-operatively. Patient selection was not limited based on degree of osteoarthritis (OA) as determined radiologically by Kellgren-Lawrence (K-L) grade. For a subset of subjects, patient reported outcomes were collected up to five years including pain evaluation, patient knee global assessment, and satisfaction with the procedure.
Results: Pre-operative radiographs indicated moderate to severe osteoarthritis (K-L grades 2-4) in 65 subjects (92.8%). Significant improvements ($p<0.0001$) 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 two years. The subset of subjects followed for five years demonstrated low pain scores and high procedure satisfaction.
Conclusion: This study presents statistically significant and clinically meaningful evidence of improvement in clinical outcomes following SCP for BMLs of the knee after two years. The survivorship rate from arthroplasty at two years was 76.2%. SCP for BMLs can relieve pain with a minimally invasive procedure and may delay the need for knee arthroplasty.

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Registration: NCT01621893 (ClinicalTrials.gov)

Level of evidence: Level II Prospective Cohort Therapeutic Study

KEYWORDS: Bone marrow lesion, Subchondral defect, Bone substitute material, AccuFill, Subchondroplasty

ABBREVIATIONS:

ADL Activities of daily living

AP Anteroposterior

BMI Body Mass Index

BMLs Bone Marrow Lesions

CaP Calcium phosphate

IKDC International Knee Documentation Committee

IRB Institutional Review Board

K-L Kellgren-Lawrence

KOOS Knee Injury and Osteoarthritis Outcome Score

LTF Lost to follow up

mKSS modified Knee Society Score

MRI magnetic resonance images

mITT modified intent-to-treat

NPRS Numeric Pain Rating Scale

OA Osteoarthritis

QOL Quality of life

SCP Subchondroplasty®

SEM Standard error of the mean

TKA Total Knee Arthroplasty

UKA unicompartmental knee arthroplasty

VAS Visual Analog Scale

INTRODUCTION

While the loss of articular cartilage is the hallmark pathological change in OA, there is evidence to suggest an important role of abnormal subchondral bone, such as bone marrow lesions, in the early stages of disease. Bone marrow lesions (BMLs) were initially described as bone marrow edema due to the appearance of bright signal on fluid sensitive 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 which preserves the native joint.[5]

AccuFill bone graft 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). Subjects requiring concomitant procedures were not excluded as long as they met the inclusion/exclusion criteria.

Patient reported outcomes were completed pre-operatively and again at two weeks, six weeks, three months, six months, twelve months, and twenty-four months including KOOS, IKDC, VAS, and modified Knee Society Score. 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 two-year follow-up, a subset of subjects was followed out to five years (three years (n=33), four years (n=24), five 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 pre-operatively and at six weeks, three months, six months, 12 months, and 24 months post-operatively. MRI examinations were conducted using 1.5 Tesla systems pre-operatively and at six months, 12 months, and 24 months post-operatively. K-L Grading and BML volume was performed by each 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 exam with orthogonal fluoroscopy during the procedure. Once localized, an AccuPort® Delivery Cannula (Blinded) was drilled directly into the defect under fluoroscopic and arthroscopic guidance and the inner stylet removed to create an access portal into the lesion. AccuFill® calcium phosphate bone substitute material (BSM) (Blinded) 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 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 four to six 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 exited 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. Subjects undergoing revision surgery were withdrawn from the study at the time of the revision surgery and no further data was collected; however, data collected up to the point of revision was included in the analysis.

Statistical Methods

The sample size of this study was based on an expected clinical success rate of 80% at 12-month follow-up. Clinically meaningful success was defined as an improvement of at least 10 points on the KOOS pain sub score. Sixty-two patients were determined to be a sufficient sample size with 95% confidence. Seventy subjects 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 that signed an informed consent and were treated with the SCP Procedure. Continuous outcomes were summarized using traditional point estimates, along with Inter-Quartile 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 Sign Rank tests (non-parametric data) were performed to compare to 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 (70) patients were enrolled and treated with the Subchondroplasty procedure between 2012 and 2017. Three (3) patients were lost to follow up (LTF) before the 12-months visit and four (4) others before the 24-months visit (Figure 1).

At baseline, most patients (92.8%) had moderate to severe osteoarthritis (K-L grade 2 to 4). Thirty-four patients (49%) had a previous procedure on the index knee. Demographics of the enrolled subjects is provided in Table 2.

The medial compartment (88.6%) was most frequently treated. All patients also underwent arthroscopy of the knee to check for post injection extravasation of AccuFill into the joint space and to treat intra-articular pathology. The average volume of Accufill in the tibia was 4.2 cc (0.5 to 9) and in the femur was 3.8 cc (1 to 8). 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 two-

week visit. Improvement in Quality of life (QOL) was statistically significant ($p<0.0001$) at all follow-up intervals (Figure 2). Clinically meaningful improvement (10 points on KOOS pain scale) was achieved in 48 subjects enrolled at 12 months (71.6% of 12-month mITT population (n=67)) and 38 subjects enrolled at 24 months (60.3% of 24-month mITT population (n=63)).

IKDC score improved and average of 24.9 points (96.2% improvement) at 24 months. Improvement in IKDC score was statistically significant at all follow-up intervals ($p=0.008$ at two weeks, $p<0.0001$ remaining timepoints). VAS pain score (100 mm) improved an average of 31.0 points (39.9% improvement) at 24 months. Improvement in 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 mKSS Function score was statistically significant ($p<0.0001$) at all follow-up intervals after the six-week visit (Table 4).

The volume of BSM injected during the SCP procedure was sufficient for visualization on most radiographs and MRI images. The appearance of the injectate was consistent with the descriptions in two publications of case reports [12,15]. For example, in a 56-year-old male with K-L grade 3, BSM appeared as a radiopaque region on radiographs at the first post-operative visit (Figure 3). BSM appeared as a hypointense region relative to the surrounding bone marrow on T1-weighted MRI, whereas on T2-weighted MRI, 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 (63) patients were included in the survivorship analysis at 24 months. Seven (7) enrolled subjects were not included at 24 months due to one death (unrelated) and 6 subjects withdrew consent or were lost to follow-up. Fifteen procedures were converted to arthroplasty including 3 UKA and 12 TKA. Kaplan-Meier analysis demonstrated survivorship of 76.2% at 24 months (Figure 4). A subset of subjects had long term follow-up out to 5 years (Table 5).

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 BMI (Table 6). While not contributing significantly to conversion rates, the average baseline BML volume between subjects that converted to TKA/UKA was 6.27 ± 3.24 cm^3 compared to 4.93 ± 3.03 cm^3 for those that did not. Significant differences in TKA/UKA conversion rates at 24 months was only found for meniscus extrusion status with a 10.0% conversion rate for patients with <3mm of extrusion and 40.0% for patients with ≥3mm of extrusion (p=0.007). Clinical success by KOOS pain was negatively correlated to number of BML (unipolar versus bipolar BML defects) (p=0.010), BML size (p=0.020), and the presence of a meniscal extrusion ≥ 3mm (p=0.034). The size of BML did significantly influence clinical meaningful improvements with successful subjects having an average BML size of 4.43 ± 2.51 cm^3 while those failing to meet the clinical success pain improvement were 6.56 ± 3.53 cm^3.

One hundred thirteen (113) 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 post-operative visit. Intra-articular extravasation identified during the procedure was removed using arthroscopic irrigation. None of the extravasation events identified post-operatively required medical intervention and all resolved radiographically with no material identified outside the bone at 12 months. Serious adverse events were reported in 4 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 outcomes scores through 24 months in a prospective study. Survivorship rate from arthroplasty was 76.2% after 2 years, which is similar to 77.1% report by Randelli et al.[14] and 70% by Cohen[10]. Wood et al.[11] and Levy et al.[16] found long term survivorship rates of 73% at 5 years and 76% at 7 years, respectively. It was observed that studies enrolling subjects that excluded K-L grade 4 tend to have higher survivorship rates at 24 months or longer. [13,17,18]

For patients with progressive osteoarthritis disease after Subchondroplasty, 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 instances

where material was seen on x-ray after the procedure, the 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 post-operative period. [18,20,21]

In this study, conversion rates for K-L 1-3 compared to K-L 4 at the two-year primary endpoint was not statistically different (p=0.3027). In addition, the difference in conversion rates for unipolar defects (20.0%) vs bipolar BML (30.4%) was not statistically significant (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 extrusion of the meniscus $\geq$3mm as measured on MRI were four times more likely to convert to arthroplasty than those with <3mm of extrusion in 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 Subchondroplasty procedure, were predominately in their middle age (57 +/-7), 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]

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 Subchondroplasty 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 three months reported by Kirkley et al. for arthroscopy compared with physical therapy for treatment of osteoarthritis.[24] These results also appear to exceed the short-term placebo effect associated with arthroscopic surgery both in magnitude and duration of effect.[25] It is also important to note the difference in presentation of bone marrow lesion 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 significant correlation to treatment success, the sample numbers are low and larger studies may be needed to confirm these findings.

Farr et al. [21] reported that approximately a quarter of patients continued to experience pain following the SCP procedure. Subchondroplasty 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 follow-up maintained low NPSR 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 three years) was reported by Krebs et al.[17] Levy et al. observed a maintenance of favorable pain relief through VAS pain score measurements at seven years post-SCP.[16]

CONCLUSION

This study presents statistically significant and clinically meaningful improvement in outcomes following Subchondroplasty 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 Subchondroplasty procedure can provide an additional tool in the arsenal of early intervention strategies that may help treat arthritis related knee pain.

FUNDING

Funding for the study visits and post-operative imaging was provided by Blinded.

CONFLICT OF INTEREST

Blinded was a paid employee of Blinded at the time of the study and Blinded is a current paid employee of Blinded.

REFERENCES

1. Zanetti M, Bruder E, Romero J et al. Bone marrow edema pattern in osteoarthritic knees: correlation between MR imaging and histologic findings. Radiology 2000; 215: 835-840
2. Felson DT, Chaisson CE, Hill CL et al. The association of bone marrow lesions with pain in knee osteoarthritis. Ann Intern Med 2001; 134: 541-549

3. Felson DT, McLaughlin S, Goggins J et al. Bone marrow edema and its relation to progression of knee osteoarthritis. Ann Intern Med 2003; 139: 330-336
4. Hunter DJ, Zhang Y, Niu J et al. Increase in bone marrow lesions associated with cartilage loss: a longitudinal magnetic resonance imaging study of knee osteoarthritis. Arthritis Rheum 2006; 54: 1529-1535
5. Sharkey PF, Cohen SB, Leinberry CF et al. Subchondral bone marrow lesions associated with knee osteoarthritis. Am J Orthop (Belle Mead NJ) 2012; 41: 413-417
6. Colon DA, Yoon BV, Russell TA et al. Assessment of the injection behavior of commercially available bone BSMs for Subchondroplasty® procedures. Knee 2015; 22: 597-603
7. Lee DD, Tofighi A, Aiolova M et al. alpha-BSM: a biomimetic bone substitute and drug delivery vehicle. Clin Orthop Relat Res 1999: S396-405
8. Murphy CM, O'Brien FJ. Understanding the effect of mean pore size on cell activity in collagen-glycosaminoglycan scaffolds. Cell adhesion & migration 2010; 4: 377-381
9. Tofighi A, Chakravarthy P, Lee D et al. Setting reactions involved in injectable cements based on amorphous calcium phosphate. Key Engineering Materials 2001; 192:
10. Cohen SB, Sharkey PF. Subchondroplasty for Treating Bone Marrow Lesions. J Knee Surg 2016; 29: 555-563
11. Wood DS, Paulson S, Nolan JR et al. What Factors are Associated With Conversion to Knee Arthroplasty After Subchondroplasty? Clin Orthop Relat Res 2023; 481: 1543-1550
12. Nevalainen MT, Sharkey PF, Cohen SB et al. MRI findings of subchondroplasty of the knee: a two-case report. Clin Imaging 2016; 40: 241-243
13. Stratton A, Wanless M, Abidi N. Total Knee Conversion Rates and Functional Outcome After Calcium Phosphate Injection for Bone Marrow Lesions of the Knee. J Knee Surg 2023:
14. Randelli P, Compagnoni R, Ferrua P et al. Efficacy of Subchondroplasty in the Treatment of Pain Associated With Bone Marrow Lesions in the Osteoarthritic Knee. Orthop J Sports Med 2023; 11: 23259671231163528
15. Agten CA, Kaplan DJ, Jazrawi LM et al. Subchondroplasty: What the Radiologist Needs to Know. AJR Am J Roentgenol 2016; 207: 1257-1262
16. Levy AS, Cousins K. The rational for and efficacy of subchondroplasty in the injured worker. J Orthop 2020; 22: 48-52
17. Krebs NM, Kehoe JL, Van Wagner MJ et al. The Efficacy of Subchondroplasty for the Treatment of Knee Pain Associated with Bone Marrow Lesions. Spartan medical research journal 2020; 4: 11767
18. DeBernardis D, Stark M, Ford E et al. Percutaneous Skeletal Fixation of Painful Subchondral Bone Marrow Edema of the Knee. Arthrosc Sports Med Rehabil 2020; 2: e583-e590
19. Yoo JY, O'Malley MJ, Matsen Ko LJ et al. Knee Arthroplasty After Subchondroplasty: Early Results, Complications, and Technical Challenges. J Arthroplasty 2016; 31: 2188-2192
20. Rebolledo BJ, Smith KM, Dragoo JL. Hitting the Mark: Optimizing the Use of Calcium Phosphate Injections for the Treatment of Bone Marrow Lesions of the Proximal Tibia and Distal Femur. Arthrosc Tech 2018; 7: e1013-e1018
21. Farr II J, Cohen SB. Expanding applications of the subchondroplasty procedure for the treatment of bone marrow lesions observed on magnetic resonance imaging. Operative Techniques in Sports Medicine 2013; 21: 138-143
22. Chatterjee D, McGee A, Strauss E et al. Subchondral Calcium Phosphate is Ineffective for Bone Marrow Edema Lesions in Adults With Advanced Osteoarthritis. Clin Orthop Relat Res 2015; 473: 2334-2342

23. Allaire R, Muriuki M, Gilbertson L et al. Biomechanical consequences of a tear of the posterior root of the medial meniscus. Similar to total meniscectomy. J Bone Joint Surg Am 2008; 90: 1922-1931
24. Kirkley A, Birmingham TB, Litchfield RB et al. A randomized trial of arthroscopic surgery for osteoarthritis of the knee. N Engl J Med 2008; 359: 1097-1107
25. Moseley JB, O'Malley K, Petersen NJ et al. A controlled trial of arthroscopic surgery for osteoarthritis of the knee. N Engl J Med 2002; 347: 81-88

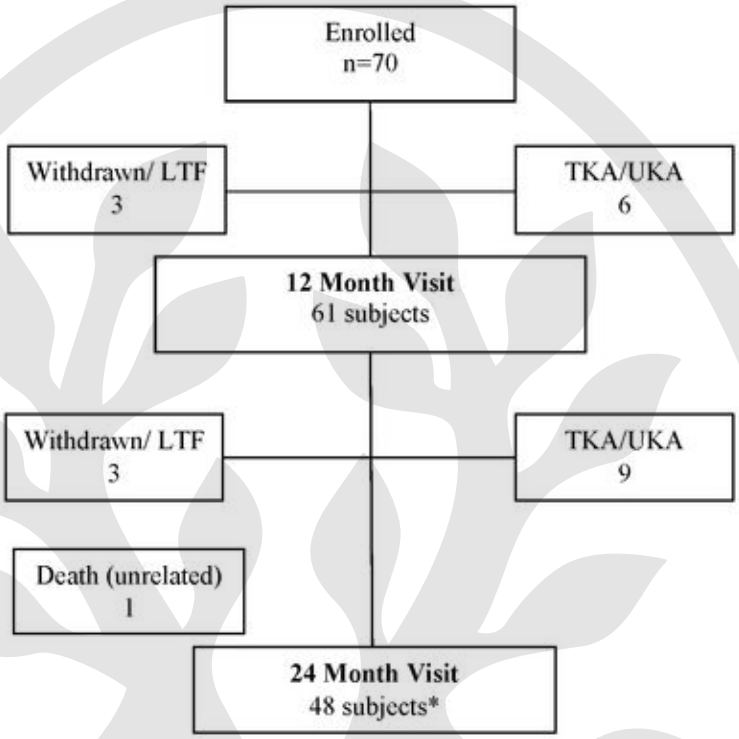

Figure 1. Study CONSORT diagram. (LTF, lost to follow up; TKA, total knee arthroplasty; UKA, unicompartmental knee arthroplasty). *At 24-month follow-up, 2 subjects competed 24-month follow-up but then elected to receive TKA and are accounted as TKA-converted subjects. Their data is included in the 24-month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

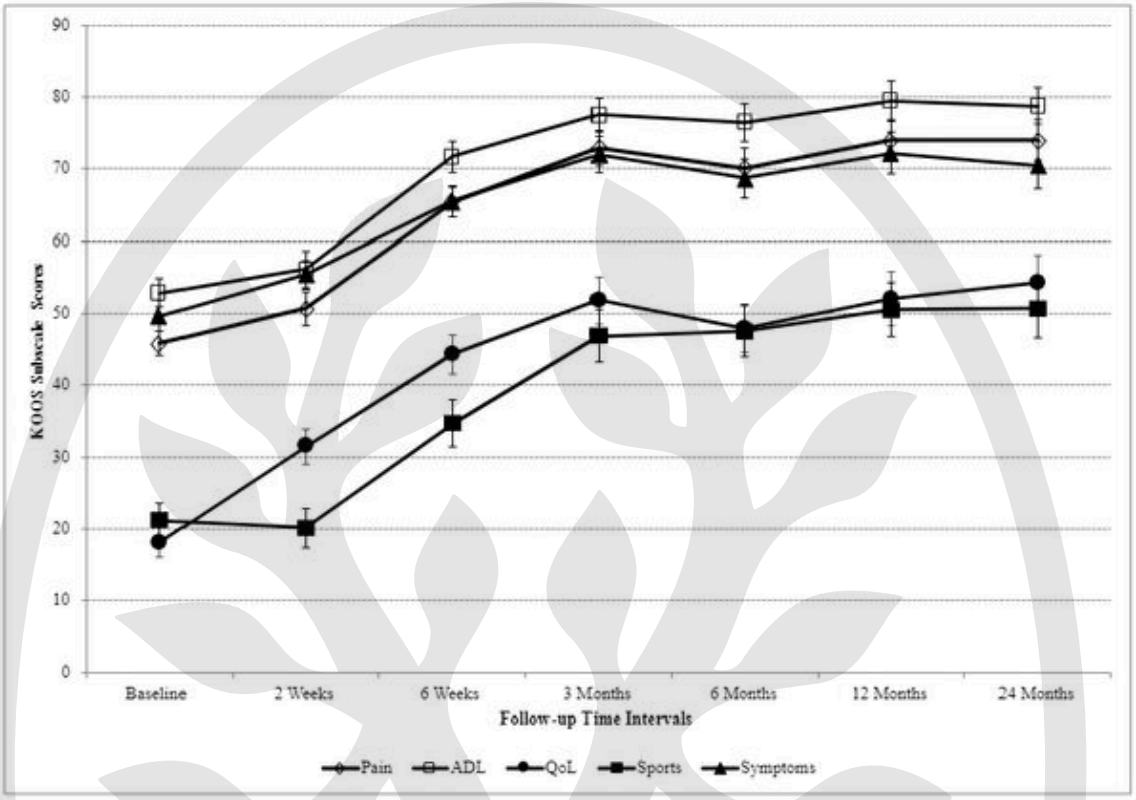

Figure 2. Mean KOOS subscales scores from baseline through 24 months (mean ± SEM). All groups significantly improved from baseline at 24 weeks $p<0.0001$).

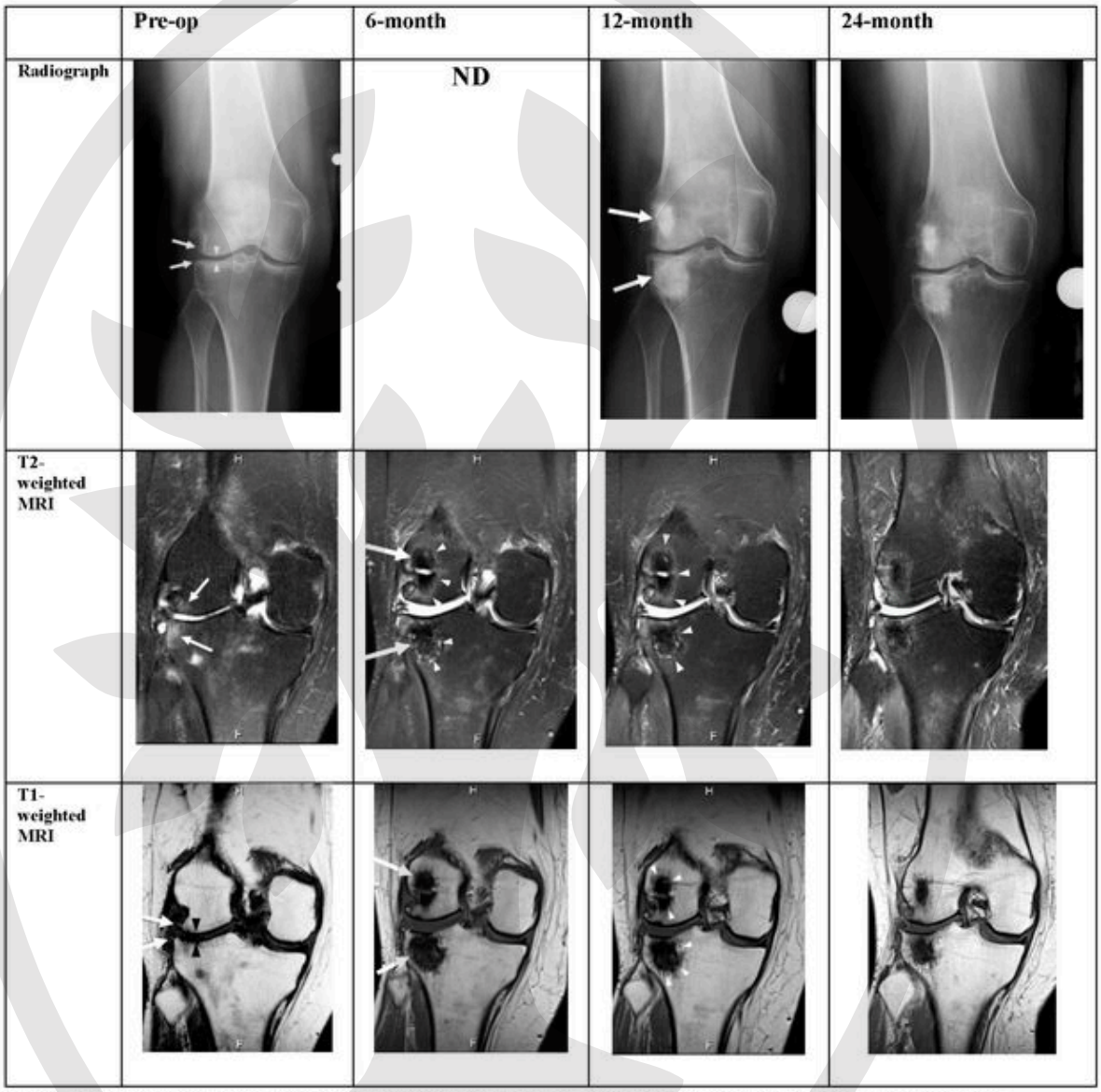

Figure 3. 56-year-old male right knee with BMLs and K-L grade 3 at pre-op and corresponding 6, 12 and 24-month post-op MRI images after SCP Procedure. (ND = not done)

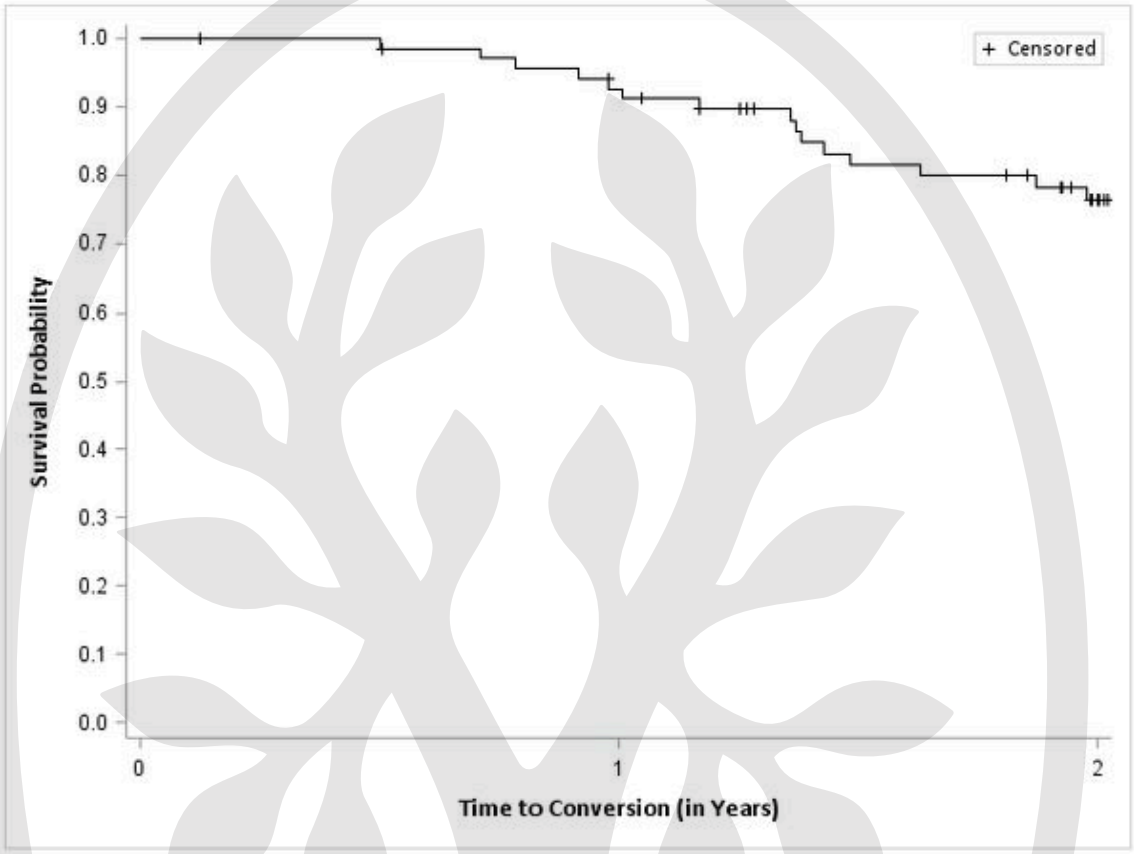

Figure 4. Kaplan-Meier Survivorship Curve (conversion to arthroplasty)

Table 1 Inclusion and Exclusion Criteria

Inclusion Criteria	• Age 40-70 • Body Mass Index (BMI) is < 40 • Knee pain ≥ 3 months • BML confirmed on T2 weighted MR Imaging • Single BML of tibia, single BML of femur, or adjoining BML of tibia & femur • Baseline KOOS pain subscore is ≤ 65 • Knee alignment defined as one of the following: Neutral, ≤ to 7° mechanical varus or < 7.5° mechanical valgus • Intact anterior and posterior cruciate ligaments • No more than one failed operative treatment on treatment knee; none within 6 months prior to enrollment • 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 years • 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 days • Pregnant or planning on becoming pregnant during the study period • Subject is accepting workers' compensation

Table 2. Baseline Demographics

Characteristic	N=70
Mean age	57 +/-7
Mean 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%)

Table 3. 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 cc (0.5 to 9)
Femur	3.8 cc (1 to 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%)

Table 4. Mean Patient Reported Outcomes Scores (mean ± SEM).

	Follow-up							
Measure	**Baseline** (n = 69)	**2 weeks** (n = 68)	**6 weeks** (n = 69)	**3 months** (n = 63)	**6 months** (n = 63)	**12 months** (n = 57)	**24 months** (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	p<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	p<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	p<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	p<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	p<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	p<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	p<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	p<0.0001

P values for comparison between the baseline 24 weeks scores using the paired t test or the Wilcoxon Signed Rank tests.

Table 5. Subset of subjects enrolled past two-year primary endpoint.

Timepoint	Subjects (n)	Mean Numeric Pain Rating Scale	Mean Procedure Satisfaction (0-10)	Would do procedure again (%)	Patient assessment "stayed same or improved" (%)
3 years	33	2.4 (62.7% improvement from baseline)	8.5	87.9%	84.9%
4 years	24	2.2 (67.4% improvement from baseline)	9.1	87.5%	91.7%
5 years	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 months	
	n/N	**p-value**	**n/N**	**p-value**
Overall	15/63		38/61	
Age				
<55	3/25		16/23	
≥55	12/38	p=0.074	22/38	p=0.362
Sex				
Male	4/30		19/28	
Female	11/33	p=0.063	19/33	p=0.409
K-L Grade*				
K-L 1-3	14/57		35/57	
K-L 4	0/4	p=0.237	2/4	p=0.652
Number of BML				
Unipolar	8/40		29/39	
Bipolar	7/23	p=0.349	9/22	**p=0.010**
BML size**				
(cm^3)	15/58	p=0.130	35/58	**p=0.020**
Meniscal Extrusion***				
< 3mm	3/30		21/29	
≥ 3mm	12/30	**p=0.007**	13/29	**p=0.034**
BMI				
	15/63	p=0.961	38/61	p=0.848

*2 subjects x-ray score missing (1 with converted TKA)
**5 subjects MOAKS BML score missing
***3 subjects meniscal grade missing (only n=58 with associated KOOS scores)

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 BML	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**