Subchondroplasty for Treating Bone Marrow Lesions

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Abstract

Bone marrow lesions (BMLs), also referred to as bone marrow edemas (BMEs), are a commonly described magnetic resonance imaging (MRI) finding associated with stress injuries, trauma, or fractures. Osteoarthritis (OA)-related BMLs represent histologically and mechanically altered subchondral bone, and have been shown to correlate with accelerated joint deterioration.1 Subchondral BMLs have been demonstrated in the knee, hip, clavicle, foot, and ankle of patients with OA.2–5 These osseous defects are unrecognized by standard radiographs, but in fat-suppressed MRI sequences they appear as diffuse water-consistent signals in the marrow space.1,6,7 BMLs occur in association with OA when physiologic subchondral remodeling fails due to ongoing joint forces, increased focalization of stress, and/or reduced healing capacity of subchondral bone.8,9 BML development is associated with localized inflammation, increased subchondral vascularization, high bone turnover,1 subchondral bone attrition,8 and progression of cartilage loss.10,11 Clinically, the presence of a BML closely correlates with pain (presence and severity)12 and rapid joint deterioration.8,10,11 Bone retrieval analysis of a BML reveals altered subchondral bone with loss of mechanical integrity in the region of the BML and a histologic appearance consistent with a nonhealing chronic stress fracture.13

Arthroscopic debridement generally does not provide lasting relief for patients with moderate to severe knee OA. In one prospective trial of 180 patients randomized to receive arthroscopic debridement, arthroscopic lavage, or placebo, and followed over a 24-month period, “At no point did either of the intervention groups report less pain or better function than the placebo group.”14 In another prospective trial of 172 patients randomized to receive either arthroscopic debridement/lavage
Subchondroplasty (SCP), developed in 2007, is a procedure that utilizes an orthobiologic to treat a chronic nonhealing BML defect. It is performed under fluoroscopic guidance by injecting a flowable, synthetic, calcium phosphate (CaP) bone void filler into the region of a BML defect. SCP is often performed in conjunction with arthroscopy to improve accuracy of the desired injection location and to correct associated intra-articular pathologies (i.e., degenerative meniscus tears, loose bodies, chondral flaps, synovitis), if present. The goal of SCP is to improve the structural integrity of damaged subchondral bone and create the potential for subchondral bone remodeling.

Methods

Inclusion and exclusion criteria are listed in Table 1.

Between May 2008 and May 2012, approximately 3,000 patients presented to the authors with indications for knee arthroplasty (i.e., moderate to severe symptoms > 2 months and unsatisfactory response to nonoperative care) to consult with a fellowship-trained arthroplasty surgeon to discuss unicompartmental or TKA surgery. After clinical evaluation, appropriate patients were informed about SCP, including a description of the procedure and evidence limitations. Patients were considered eligible for SCP if, after MRI evaluation, they were determined to have BML in the tibia and/or femur (Fig. 1A,B); had pain generally localized to the same compartment as the BML(s); and met the indications for arthroplasty, including failure of weight loss, corticosteroid injections, hyaluronic acid injections, nonsteroidal anti-inflammatory drugs (NSAIDs), physical therapy, and/or unloader bracing. Patients with a BML who were excluded

Table 1 Inclusion/exclusion criteria

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<th>Inclusion criterion</th>
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<tr>
<td>• Moderate to severe pain &gt; 2 mo</td>
<td>• Primary cause of patient pain and loss of function due to</td>
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<td>• Failure of symptom relief with corticosteroid injections, hyaluronic acid</td>
<td>pathology other than BML, by patient history and clinical</td>
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<tr>
<td>injections, NSAIDs, physical therapy, and/or unloader bracing</td>
<td>evaluation</td>
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<tr>
<td>• Presence of BML(s) on MRI in a weight-bearing region of the knee (medial/lateral</td>
<td>• Presence of gross instability</td>
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<td>femoral condyle or tibial plateau)</td>
<td>• &gt; 8 degrees of varus or valgus</td>
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<tr>
<td>• Patient pain confined to the same compartment as the BML</td>
<td>• Tricompartamental radiographic grade 4 OA</td>
</tr>
<tr>
<td>• Pain in compartment of BML at least 4/10</td>
<td></td>
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<tr>
<td>• Moderate to severe joint disease confined to the same compartment as the BML</td>
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Abbreviations: BML, bone marrow lesion; MRI, magnetic resonance imaging; NSAIDs, nonsteroidal anti-inflammatory drugs; OA, osteoarthritis.
had greater than 8 degrees of varus or valgus alignment or tricompartmental radiographic Kellgren-Lawrence (K-L) grade 4 OA. Informed consent was obtained for all patients.

Patients meeting inclusion/exclusion criteria for treatment were given the option of arthroscopy combined with SCP as an alternative to arthroplasty. Of the approximately 3,000 patients entering the clinic during the study period, 69 met procedure criteria and chose SCP instead of arthroplasty.

At the outset of this retrospective study, Institutional Review Board (IRB) approval was granted by a local IRB to contact 66 of the 69 patients to review prospectively-collected data and gather additional follow-up information. Of the three patients excluded from analysis, one patient received SCP from a surgeon not participating in the study, one received SCP treatment to the patella, and one additional patient passed away approximately 1 year following surgery of causes unrelated to their knee surgery. Thus, this cohort comprises 66 patients.

The SCP procedure was performed as described in prior publications.\textsuperscript{6,9,30} Preoperative MRI was used to determine the extent and location(s) of the BML. Intraoperative anteroposterior and lateral fluoroscopic views were used to guide the injection of the bone substitute into the desired region of the lesion (\textsuperscript{\textbullet} \textbf{Fig. 1C,D}). Arthroscopy was performed to aid in the accurate placement of the bone substitute, ensure that no intra-articular extravasation of the injected material occurred, evaluate intra-articular pathology, and address correctable problems (e.g., chondral flaps, loose bodies, degenerative meniscus tears, osteophytes, and synovitis). Patients with gross knee instability, or whose primary cause of pain and loss of function was due to pathology other than a BML, were excluded from the study to limit confounding factors.

Following SCP, patients were allowed to resume weight-bearing activities as tolerated, with crutch assistance if needed for up to 1 week. Physical therapy was initiated 10 to 14 days after surgery, and a return to full unrestricted activities was allowed 4 to 8 weeks postoperatively. Any patient who utilized a preoperative unloader brace was given the option of using it for 4 to 8 weeks postoperatively during recovery.

Following the initial postoperative period, patients were encouraged to follow up regularly, as per standard clinical practice. When possible, patients returning for follow-up visits participated in formal clinical assessment via the visual analog scale (VAS) for pain (VAS, 10.0 representing the “worst pain ever”) and/or the International Knee Documentation Committee (IKDC) Subjective Knee Evaluation Form.\textsuperscript{32} It was also determined if and when a patient later “converted” to knee arthroplasty. No VAS or IKDC scores were considered after a patient underwent arthroplasty.

For each patient, all dates were indexed to the date of the SCP. Baseline measures for both VAS and IKDC were obtained prior to SCP. Because we are primarily interested in long-term results, the “postoperative” measure used was the final measurement available in the chart for each instrument and patient. Because of variable patient participation per visit, the final IKDC measure may have been obtained at a different follow-up interval than the final VAS measure. VAS and IKDC were analyzed independently. For each, the null hypothesis was that scores were equally likely to worsen as they were to improve. We tested this null hypothesis using the binomial test (Minitab v16.1.1, Minitab Inc., State College, PA). We applied this test to the entire cohort, to patients with outcomes collected at least 6 months posttreatment, and to those with outcomes collected at least 2 years posttreatment.

\textbf{Results}

\textbf{Characteristics of the Cohort}

As summarized in \textsuperscript{\textbullet} \textbf{Table 2}, 52% of patients were female (34 of 66), the average age was 55.9 years (range 35.0–76.0), and the average body mass index (BMI) was 30.1 kg/m\textsuperscript{2} (range 20.3–53.2 kg/m\textsuperscript{2}). Prior to surgery, patients had an average of 22.4 months duration of symptoms (range 2.0–180.0 months). The modified Outerbridge grade of the chondral surface was determined during intraoperative diagnostic arthroscopy.\textsuperscript{33} Ninety-six percent (96%) of subjects had grade 3 or 4 changes in the SCP-treated compartment, and 71% had grade 2 or less in the contralateral tibial-femoral compartment. Only two patients had less than grade 3 changes in the SCP-treated compartment (one patient with grade 0 changes, one with grade 2 changes). Sixty-two percent had grade 3 or 4 changes in the patellofemoral compartment. Patients
Described mean preoperative pain as a 7.6 out of 10 (range 4–10). Mean IKDC score at baseline was 30.5 (range 14.9–55.2).

Durable Improvement in Pain Scores after Subchondroplasty with Arthroscopy
Preoperative (baseline) VAS scores were available for 59 out of the 66 patients (89%), and at least one postoperative VAS score was available for 57 of these 59 (median postoperative time of final follow-up VAS = 27.2 months). As illustrated in ❄ Fig. 2A, 50 of these 57 patients exhibited pain improvement on final follow-up, 3 had worse pain scores, and 4 were unchanged. Notably, even those patients who ultimately elected to receive arthroplasty (15 out of these 57 patients) typically showed improved pain scores (see Discussion). ❄ Fig. 2B illustrates that improvements in pain scores were observed at all durations post-SCP.

The binomial test rejected the null hypothesis that pain was not improved after SCP, both across all patients (< 0.001), or considering only those whose last follow-up VAS was at least 6 months postoperative (n = 44, 38 improved, p < 0.001), or at least 2 years postoperative follow-up (n = 34, 29 improved, p < 0.001). Thus, patients experienced durable pain relief after SCP.

The magnitude of improvement in VAS pain scores was clinically meaningful. Across the three groupings (all patients, those with at least 6-month follow-up VAS and those with at least 2-year follow-up VAS), the mean improvements in VAS scores were 4.2, 4.3, and 4.5 points, respectively. For VAS pain

| Table 2 Demographic characteristics of patients with bone marrow lesion treated with subchondroplasty (n = 66) |
|---|---|
| Mean age, y (range) | 55.9 (35.0–76.0) |
| Sex (% female) | 52% |
| Mean height, in (range)a | 67.0 (59.0–74.0) |
| Mean weight, lb (range)a | 195.0 (115.0–350.0) |
| Mean BMI, kg/m² (range)b | 30.1 (20.3–53.2) |
| Mean length of symptoms before subchondroplasty, mo (range)a | 22.4 (2.0–180.0) |
| Side of knee, n (%) | Left = 40 (61%), Right = 26 (39%) |
| Alignment, degrees varus, rangeb | –8 to 8 |
| Treated area Outerbridge gradeb | Grade 0: 1 (2%), Grade 1: 0 (0%), Grade 2: 1 (2%), Grade 3: 17 (27%), Grade 4: 43 (69%) |
| Contralateral area Outerbridge grade | Grade 0: 16 (27%), Grade 1: 4 (7%), Grade 2: 22 (37%), Grade 3: 13 (22%), Grade 4: 4 (7%) |
| Patellofemoral Outerbridge grade | Grade 0: 7 (12%), Grade 1: 1 (2%), Grade 2: 15 (25%), Grade 3: 28 (47%), Grade 4: 9 (15%) |
| Preoperative ROM, rangea | Extension: 0–5 degrees, Flexion: 100–135 degrees |
| Prior treatments, n (%) | Arthroscopy 19 (29%), Bracing 14 (21%), Cortisone 41 (62%), Hyaluronic acid 48 (73%), NSAID 30 (45%), Partial medial meniscectomy 18 (27%), Physical therapy 8 (12%) |
| Baseline VAS scores, mean (SD, range)c | 7.6 (1.5, 4–10) |
| Baseline IKDC scores, mean (SD, range)c | 30.5 (10, 14.9–55.2) |

Abbreviations: BMI, body mass index; IKDC, International Knee Documentation Committee; NSAID, nonsteroidal anti-inflammatory drug; OA, osteoarthritis; ROM, range of motion; SD, standard deviation; VAS, visual analog scale.

a < 5% missing data points.
b < 10% missing data points.
c < 15% missing data points.
scores, an improvement of 2 points (20 mm on the 100-mm scale) is considered clinically important (minimal clinically important differences [MCID]).

Fig. 2C shows all three dimensions of the data (baseline VAS, final VAS, and postoperative duration at final follow-up) for all patients with at least 6 months of VAS follow-up. Fig. 2D shows the distributions of scores in this patient group.

Durable Improvement in IKDC (symptom/function) Scores after Subchondroplasty with Arthroscopy

Preoperative (baseline) IKDC scores were available for 48 patients, all of whom also had at least one postoperative score. As illustrated in Fig. 3A, 38 of these 48 patients exhibited improvement (higher IKDC scores indicate improved symptoms and function) on final follow-up, 9 had worse scores, and 1 was unchanged. Fig. 2B illustrates that improvements in IKDC scores were observed at all durations post-SCP.

The binomial test rejected the null hypothesis that function was not improved after SCP, both across all patients ($p < 0.001$), or considering only those whose last follow-up IKDC was at least 6 months postsurgery ($n = 35$, 28 improved, $p < 0.001$), or at least 2 years postoperative ($n = 26$, 21 improved, $p < 0.002$). Thus, patients experienced durable functional/symptomatic improvement after SCP.

The magnitude of improvement in IKDC scores was clinically meaningful. Across the three groupings (all patients, those with at least 6 months follow-up IKDC, those with at least 2-year follow-up IKDC), the mean improvements in IKDC scores were 18.3, 17.2, and 17.8 points, respectively. For IKDC pain scores, an improvement of 11.5 points is considered clinically important (MCID).

Fig. 3C shows all three dimensions of the data (baseline IKDC, final IKDC, and postoperative duration at final follow-up) for all patients with at least 6 months of IKDC follow-up. Fig. 3D shows the distributions of IKDC scores in this patient group.

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Fig. 3C shows all three dimensions of the data (baseline IKDC, final IKDC, and postoperative duration at final follow-up) for all patients with at least 6 months of IKDC follow-up. Fig. 3D shows the distributions of IKDC scores in this patient group.
Conversion to Arthroplasty
Sixty of the 66 patients (91%) were available for 2-year follow-up that allowed a determination of whether and when patients elected to undergo arthroplasty. Of the six patients not available, only one had 1-year follow-up data, and five were lost to follow-up. Kaplan-Meier analysis (Fig. 4), demonstrated 2-year joint preservation survivorship of 70% (42 out of 60) for study patients. Because patients in this study initially presented for arthroplasty consultation, this survival rate seems promising.

Variables potentially associated with conversion to arthroplasty were assessed using logistic regression and included: patient age, BMI, length of symptoms, joint alignment, preoperative VAS scores, treated area grade, previous partial meniscectomy, and the presence of kissing lesions (adjacent BMLs of the tibia and femur). Older age and a history of prior meniscectomy were both positively associated with subsequent conversion to arthroplasty, with or without controlling

Fig. 3 Improvement of International Knee Documentation Committee (IKDC) function/pain scores after subchondroplasty. (A) Change in IKDC scores (final minus baseline) for all 57 patients who had both a presurgical score and at least one follow-up score. (B) Change in IKDC score, plotted versus the number of years after subchondroplasty at which the final follow-up IKDC score was obtained, for each patient. (C) Baseline and final IKDC scores, for all patients whose final follow-up IKDC score was at least 6 months postsurgery (n = 44). (D) Box-and-whiskers plots of baseline and final IKDC scores, showing median, interquartiles, and range (whiskers).

Fig. 4 Kaplan-Meier plot of conversion to total knee arthroplasty (TKA). At 2 years after subchondroplasty, 70% of patients (42/60) did not still elect to receive arthroplasty on the affected knee.
for length of symptoms and BMI (p < 0.05). The mean age of patients who converted to arthroplasty was 58.2 years (range 47.0–76.0), compared with a mean of 55.1 years (range 35.0–73.0) among patients who did not. Thirty-nine percent (39%) of patients who had subsequent arthroplasty also had a previous partial meniscectomy, compared with 23% of patients who did not. Other variables analyzed showed no significant association with the probability of conversion.

Adverse Events. The observed number of adverse events following the SCP procedure included one patient who experienced postoperative drainage at the CaP injection site, which resolved with surgical irrigation and debridement, and one patient diagnosed postoperatively with a deep vein thrombosis, which required treatment with oral anticoagulation.

Discussion

The natural history of OA is slow but progressive joint degeneration. Knee OA patients with BMLs have a poor prognosis, with accelerated progression to the need for total knee replacement.8,10,11 Considering these facts, the magnitude and durability of the pain relief and functional improvement observed in this retrospective study is noteworthy. For patients with at least 2 years of follow-up, mean pain improvement was 4.5 points on the VAS scale (corresponding to “good to excellent” pain relief36), and mean functional/symptomatic improvement was 17.8 points on the IKDC scale (relative to the MCID of 11.5). Our results suggest that SCP may be a promising treatment for BMLs associated with OA.

Several limitations of this study warrant discussion. First, with any nonrandomized study, selection bias is possible. For example, qualifying patients were allowed to select between arthroplasty and the alternative treatment under study (SCP). It is possible that an unidentified personal trait could predispose someone to both (1) choose SCP over arthroplasty and (2) exhibit sustained improvement in knee pain for reasons unrelated to SCP. Mitigating this concern is the poor prognosis of patients entering this study, who were all originally indicated for arthroplasty. A second limitation is a lack of standardization in the collection of follow-up data. Not all subjects completed the patient reported outcomes measures at all time points, and the final follow-up data were collected at varying time points. This makes it difficult to evaluate the progression of pain and function outcomes for patients treated with SCP from this dataset. A third limitation is a lack of postoperative imaging to assess changes in the BML. Future studies that include a series of MR images postoperatively may provide valuable insight into the remodeling of the CaP material and potential relationships between the status of the BML and patient outcome. A fourth limitation is the absence of control cohorts: there was no placebo cohort, and because SCP was always performed along with arthroscopy, the relative contributions of these two procedures were not empirically separated. Future study with an arthroscopy-matched control group may be useful in further evaluating efficacy. However, several studies of subjects with pathology and symptoms similar to the present patient population indicate that arthroscopic debridement alone provides no durable relief of OA symptoms.12-14 The lack of durable pain relief in these studies may have been due to the presence of BMLs. BMLs are commonly present in this patient population and are not treated by traditional arthroscopy.

Another recent study evaluated the effect of SCP on outcomes in patients with knee BMLs,37 in a nonmatched cohort of 22 patients with knee OA. They reported that both the Knee Injury and Osteoarthritis Outcome Score (KOOS) and the Tegner-Lysholm Knee Scoring Scale scores significantly improved (p < 0.001) at greater than 6 months posttreatment. Surprisingly, despite these improvements, the authors

Table 3 Review of studies quantifying the effects of knee arthroscopy on pain and function outcomes at 24 months

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<th>Study</th>
<th>Patients</th>
<th>Design</th>
<th>Outcome</th>
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<tr>
<td>Moseley et al, New Engl J Med, 2002</td>
<td>n = 180 patients * VAS pain ≥ 4 * No severe joint deformity</td>
<td>Prospective, randomized to 1. Arthroscopic debride-ment 2. Arthroscopic lavage 3. Placebo • Follow-up through 24 mo</td>
<td>No differences in pain or function (6 different score metrics) in any groups at any time point</td>
</tr>
<tr>
<td>Kirkley et al, New Engl J Med, 2008</td>
<td>n = 172 patients * Kellgren-Lawrence grade 2, 3, or 4</td>
<td>Prospective, randomized to 1. Arthroscopic debride-ment and lavage to-gether with optimized physical and medical therapy 2. Physical and medical therapy alone • Follow-up through 24 mo</td>
<td>No differences in WOMAC or SF-36 scores between groups</td>
</tr>
<tr>
<td>Thorlund et al, BMJ, 2015</td>
<td>n = 1,270 patients across 9 studies</td>
<td>Meta-analysis • Follow up through 24 mo</td>
<td>Small improvements at 3 and 6 mo in pain No improvement in pain or function at 12 and 24 mo</td>
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concluded that the treatment was “ineffective.” However, the authors defined “clinical failure” based on a categorization of postoperative Tegner-Lysholm scores historically used to evaluate success of anterior cruciate ligament (ACL) reconstruction, a scoring method likely inappropriate for evaluating the success rate of this treatment.\textsuperscript{38,39}

The present study is the largest series to date evaluating the effectiveness of SCP. Interestingly, although most patients (70%) did not convert to arthroplasty, a majority of the patients who \textit{did} progress to arthroplasty actually had shown improvements in both VAS and IKDC scores prior to their decision to undergo a total knee replacement. Factors such as patient expectations (both with SCP and total knee replacement) and patient satisfaction were not evaluated in this study. This highlights the complexity of the personal decision to undergo surgery and thus the difficulty of using revision to an elective surgery for assessing efficacy.

It is important to consider biologic options for subchondral bone lesion treatment, such as calcium-phosphate SCP, in the context of other treatment options. TKA provides predictable pain relief; however, functionality is typically reduced.\textsuperscript{22,23,25,30} Additionally, TKA is costly, invasive, and requires substantial recovery time (typically, 6–12 months).\textsuperscript{24,40} SCP, on the other hand, represents a minimally invasive approach that provides fairly reliable pain relief while preserving the native joint, and enables patients to resume some normal activities as soon as 1 week postprocedure.\textsuperscript{30} These factors may be particularly important for younger, active patients who wish to reduce pain and avoid arthroplasty, but retain function and delay the productivity losses associated with major surgery.

\section*{Conclusion}

Patients with severe knee OA have limited options, usually requiring arthroplasty to regain mobility and relieve pain. For patients who also have BMLs, the prognosis is poor and joint deterioration usually progresses rapidly. In this study we evaluated the efficacy of using SCP—a technique for applying a CaP bone substitute to the BML defect—with arthroscopy, as a less invasive, joint-preserving option in patients with BMLs associated with advanced OA. We observed clinically significant and durable improvements in pain and function in most patients in our investigation. Understanding the limitations of retrospective case studies, this first patient series shows potential for treating patients with pain due to presence of BMLs.

\section*{References}

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24 Browne JP, Bastaki H, Dawson J. What is the optimal time point to assess patient-reported recovery after hip and knee replacement? A systematic review and analysis of routinely reported outcome data from the English patient-reported outcome measures programme. Health Qual Life Outcomes 2013;11:128


