Novel Scaffold-Based BST-CarGel Treatment Results in Superior Cartilage Repair Compared with Microfracture in a Randomized Controlled Trial

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Investigation performed at twenty-six clinical sites in Canada, Spain, and South Korea

Background: Microfracture, the standard of care, is recognized to be an incomplete solution for cartilage damage. BST-CarGel, a chitosan-based medical device, is mixed with autologous whole blood and is applied to a microfractured cartilage lesion in which it physically stabilizes the clot and guides and enhances marrow-derived repair. An international, multicenter, randomized controlled trial was conducted to evaluate BST-CarGel treatment compared with microfracture alone in the repair of cartilage lesions in the knee.

Methods: Eighty patients between the ages of eighteen and fifty-five years with a single, symptomatic focal lesion on the femoral condyles were randomized to BST-CarGel and microfracture treatment (n = 41) or microfracture treatment alone (n = 39). The primary end points of repair tissue quantity and quality at twelve months were assessed by quantitative three-dimensional magnetic resonance imaging measuring the degree of lesion filling and T2 relaxation time with use of standardized one and twelve-month posttreatment scans. The secondary end point at twelve months was clinical benefit determined with the Western Ontario and McMaster Universities Osteoarthritis Index. The tertiary end point was quality of life determined by the Short Form-36. Safety was assessed through the recording of adverse events.

Results: Patient baseline characteristics were similar in the two groups, although baseline lesion areas were slightly larger on quantitative magnetic resonance imaging for the BST-CarGel group compared with the microfracture group. Blinded quantitative magnetic resonance imaging analysis demonstrated that, at twelve months, when compared with microfracture treatment alone, BST-CarGel treatment met both primary end points by achieving statistical superiority for greater lesion filling (p = 0.011) and more hyaline cartilage-like T2 values (p = 0.033). The lesion filling values were 92.8% ± 2.0% for the BST-CarGel treatment group and 85.2% ± 2.1% for the microfracture treatment group, and the mean T2 values were 70.5 ± 4.5 ms for the BST-CarGel treatment group and 85.0 ± 4.9 ms for the microfracture treatment group. Western Ontario and McMaster Universities Osteoarthritis Index subscales for pain, stiffness, and function yielded equivalent improvement for both groups at twelve months, which were significant (p < 0.0001) from baseline. Treatment safety profiles were considered comparable.

Conclusions: At twelve months, BST-CarGel treatment resulted in greater lesion filling and superior repair tissue quality compared with microfracture treatment alone. Clinical benefit was equivalent between groups at twelve months, and safety was similar.

Level of Evidence: Therapeutic Level I. See Instructions for Authors for a complete description of levels of evidence.
Articular cartilage damage remains an unresolved orthopaedic challenge. The full-thickness cartilage lesions found in >60% of adult knees during arthroscopy 4-7 can seriously affect knee-related quality of life. If left untreated, these lesions are believed to progress to degenerative osteoarthritis and thus represent a compelling target for new regenerative technologies.

The goal of any cartilage repair treatment is to achieve a repair tissue with structural characteristics comparable with native hyaline cartilage, which may result in long-term durability, joint function, and pain relief. Unfortunately, the low methodological quality of most published clinical studies 4-10 has produced ambiguous or contradictory conclusions regarding individual surgical options, and consequently there are very few evidence-based surgical algorithms for this pathology.

The current standard of care is microfracture, the most commonly used first-line surgical treatment 10. Microfracture is the straightforward, deliberate penetration of the subchondral bone below a cartilage lesion to elicit bleeding. The bone marrow stimulation initiates a repair response that essentially follows the traditional wound-healing sequence 2. Although microfracture has demonstrated minor success in filling lesions, it does so inconsistently and with a fibrocartilaginous tissue that lacks hyaline articular structure 4. This poor tissue quality and the highly variable clinical outcomes frequently observed in animals and humans are not surprising, considering the instability of the marrow-derived blood clots formed in the lesion 4-8, 11, which shrink and detach as a consequence of platelet-driven clot retraction 4-12. That the critical component for bone marrow-derived cartilage repair is the quantity of the initial blood clot present in the cartilage lesion is demonstrated by studies showing that improved repair can be achieved with a more adherent, voluminous clot that modulates repair events 4,13.

BST-CarGel (Piramal Life Sciences, Bio-Orthopaedic Division) was developed to stabilize the blood clot in the cartilage lesion by dispersing a soluble polymer scaffold containing chitosan throughout the blood. Chitosan is an abundant glucosamine polysaccharide derived from the exoskeleton of crustaceans whose many desirable biomaterial properties, such as low toxicity and biocompatibility, biodegradability, and adhesivity to tissues, have motivated extensive research into its use in biomedical applications 16-18. By dissolving chitosan in an aqueous glycerophosphate buffer 16, BST-CarGel is obtained as a liquid chitosan solution having physiological pH, cytocompatibility, and biodegradability. When mixed with fresh, autologous whole blood, BST-CarGel does not interfere with normal coagulation, but reinforces the resulting clot by impeding its retraction 16. Furthermore, increased clot adhesivity within the lesion due to chitosan’s cationic nature ensures prolonged activation of tissue repair processes by maintaining critical blood components above marrow access holes 7,9,14.

This randomized controlled trial (RCT) was designed to determine whether BST-CarGel treatment of symptomatic cartilage lesions of the femoral condyle could result in superior repair cartilage quantity and quality compared with microfracture treatment alone. The primary end points were repair cartilage quantity defined by the degree of lesion filling and the quality of the new repair cartilage at twelve months. The secondary end point of the trial was to demonstrate that the clinical benefit at twelve months was at least comparable in both treatment groups.

Materials and Methods

Study Design and Participants

This trial was performed in accordance with the Declaration of Helsinki, the International Conference on Harmonisation Guidelines for Good Clinical Practice, and standards from the International Organization for Standardization (ISO). The protocol and any amendments were implemented only after approval by clinical site research ethics boards and national competent authorities. All eligible subjects received standardized information about the trial and provided written informed consent. The trial was registered with ClinicalTrials.gov (NCT00314236).

This RCT was conducted at twenty-six international clinical sites. Eligible male and female patients were eighteen to fifty-five years of age with a single, focal cartilage lesion on the femoral condyles and moderate knee pain (>4 cm on a 10-cm visual analog scale [VAS]). All patients agreed to posttreatment rehabilitation. Additional inclusion and exclusion criteria are referenced in the Appendix.

This study was a single-blind trial as the independent center carrying out the analyses of primary end points was unaware of patient treatment. Investigators and patients were not blinded because of differences in incision size related to treatment. Consequently, self-administered questionnaires were not blinded.

Randomization Process

There were three distinct screening phases prior to patient randomization: (1) initial screening after informed consent, (2) trial-specific diagnostic magnetic resonance imaging (MRI), and (3) diagnostic arthroscopy for final eligibility. Randomization was completed immediately following the diagnostic arthroscopy, via telephone interactive voice response system with use of a central, computer-generated randomization schedule. Patients were randomized to microfracture and BST-CarGel treatment or microfracture treatment alone (Fig. 1), and were stratified by site to avoid data bias and site-specific effects and by lesion chronicity (acute or chronic) to address possible repair differences related to etiology.

Study Treatments

All procedures were performed under general anesthesia. The microfracture surgical procedure for all eighty patients was performed arthroscopically as published 20,21 and was closely monitored by a sponsor representative (A.R. and/or M.S.S.) to ensure standardization. The arthroscopic portals were then closed for patients randomized to microfracture alone, or patients received BST-CarGel treatment as previously described through a mini-arthrotomy 22. BST-CarGel was prepared and was manually mixed with fresh, autologous whole peripheral blood at a ratio of 3:1 (blood:BST-CarGel). The microfractured lesion was swabbed with gauze to create a “dry field” before the application of the BST-CarGel and blood mixture with a syringe in a drop-wise manner. The mixture volume used per patient naturally varied according to lesion size. After delivery, the BST-CarGel and blood implant clotted in place during the required fifteen-minute waiting period, prior to incision closure. The use of a tourniquet was not standardized and was left to standard practice. As a general rule, when used with BST-CarGel treatment, the tourniquet was released only after the fifteen-minute waiting period.

Patients in both groups followed an identical twelve-week physiotherapy program that included six weeks of non-weight-bearing that progressed to 100% at eight weeks and assisted passive motion manually applied during frequent physiotherapy sessions (thirty-two sessions maximum during twelve weeks). No full-impact activities involving jumping or pivoting were permitted for twelve months. Each participating physiotherapist received training on the...
clinical trial and the rehabilitation guidelines. Patient compliance and progression data were collected by the interactive voice response system activated by physiotherapists.

**Outcome Measures**

Patients were clinically evaluated at pretreatment and at one, three, six, and twelve months posttreatment by investigators. At pretreatment and at one and twelve months posttreatment, patients underwent MRI scanning. At pretreatment and at three, six, and twelve months posttreatment, patients completed questionnaires.

**Structural Outcomes**

The primary end points were repair tissue quantity (lesion % Fill) and quality (T2 relaxation time) at twelve months as measured by three-dimensional quantitative MRI (Fig. 2). MRI scan acquisition was standardized at fifteen MRI clinics local to clinical sites. On-site technician training and 1.5-T MRI scanner magnet qualification were conducted prior to trial activities. All blinded scans were sent to an imaging core lab (VirtualScopics, Rochester, New York), were reviewed for scan quality, were approved, and were stored. Uniformity and linearity phantom scans were performed monthly for quality control at each MRI clinic. Imaging phantoms within the field of view served as internal controls.

The primary end-point analyses were centralized and were conducted at a blinded imaging core lab (Qmetrics Technologies, Rochester, New York) with use of validated techniques. See the process in Figure 2. Scans with use of customized high-spatial-resolution pulse sequences were acquired from each patient from one and twelve months posttreatment. Standardized, 1.5-mm-thick, coronal and sagittal three-dimensional, fat-suppressed spoiled gradient echo and sagittal three-dimensional, gradient echo sequences were used for morphological analyses of cartilage, cartilage lesions, and bone. Standardized, 2-mm-thick, sagittal, fat-suppressed, dual-echo, fast-spin-echo sequences were used for T2 relaxation time analyses. For each scan, automatic (unsupervised) definition of the different anatomical knee regions was carried out on the basis of programmed atlas segmentation. With use of the pre-registered spoiled gradient echo and gradient echo series, a musculoskeletal radiologist with expertise in cartilage repair manually traced the lesion boundaries on the one-month posttreatment scan. The one-month structural segmentation was then co-registered with the twelve-month scan and the tissue boundaries were adjusted by the expert radiologist if needed. Quantitative measurements of unique knee-related biomarkers from the prespecified regions of interest were automatically calculated from the edited follow-up, three-dimensional segmentations. From one-month posttreatment scans, debrided lesion surface areas and cartilage lesion (and missing bone, if applicable) volumes were extracted. From twelve-month scans, the segmented three-dimensional volume of new tissue within the lesion was used to obtain: the degree of lesion filling (lesion % Fill), calculated from the ratio of the new tissue volume at twelve months to the baseline cartilage lesion volume at one month posttreatment, and the mean T2 relaxation time from the entire repair tissue volume at twelve months. A radiologist-selected region on the posterior medial femoral condyle in the same knee was analyzed for each patient as a native cartilage control.

**Clinical Outcomes**

The secondary outcome was clinical benefit at twelve months as measured by the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) VAS version, consisting of three subscales: pain, stiffness, and physical function. The tertiary outcome was quality of life as measured by the 36-Item Short-Form Health Survey version 2 (SF-36), an eight-scale profile
of functional health and well-being scores, as well as summary components of physical and mental health. The 95% confidence intervals (95% CI) for the WOMAC minimal clinically important difference from baseline were determined with use of the anchor method and scores from patients whose rating of global change was "somewhat better" on the SF-36 Reported Health Transition item.

**Statistical Analysis**

Sample size was determined on the basis of large animal study data of cartilage repair. Assuming a treatment effect size of 15% for both the quantity and quality of repair end points and using a two-sided test, a 5% Type-I error rate (alpha level), and a Type-II error rate of 10% (i.e., 90% power), a sample size of forty-six patients (twenty-three per group) was calculated. To account for a 20% dropout rate and lack of human data, the sample size was increased to eighty patients (forty per group). All analyses were performed according to the intention-to-treat principle and followed a preapproved statistical analysis plan. Between-group comparisons were made for the primary end points of lesion %Fill and repair tissue T2 with use of analysis of covariance (ANCOVA) models adjusted for the prespecified covariate of baseline lesion volume. WOMAC and SF-36 questionnaire comparisons were adjusted for baseline. Parametric tests were used and were supported in some cases by non-parametric sensitivity analyses. Interactions were examined for treatment, site, treatment by site, and lesion chronicity (acute or chronic). All reported p values were two-sided. P values of <0.05 were considered significant.
TABLE I Baseline Characteristics of Trial Participants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>BST-CarGel (N = 41)</th>
<th>Microfracture (N = 39)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age † (yr)</td>
<td>35.1 ± 9.6</td>
<td>37.2 ± 10.6</td>
<td>0.36</td>
</tr>
<tr>
<td>Sex †</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>23 (56.1)</td>
<td>25 (64.1)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>18 (43.9)</td>
<td>14 (35.9)</td>
<td></td>
</tr>
<tr>
<td>Body mass index † (kg/m²)</td>
<td>27.0 ± 3.3</td>
<td>25.2 ± 3.0</td>
<td>0.92</td>
</tr>
<tr>
<td>Activity level †</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>High</td>
<td>20 (48.8)</td>
<td>19 (48.7)</td>
<td></td>
</tr>
<tr>
<td>Medium</td>
<td>19 (46.3)</td>
<td>19 (48.7)</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>2 (4.9)</td>
<td>1 (2.6)</td>
<td></td>
</tr>
<tr>
<td>Smoking status †</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoked</td>
<td>22 (53.7)</td>
<td>19 (48.7)</td>
<td></td>
</tr>
<tr>
<td>Former smoker</td>
<td>8 (19.5)</td>
<td>9 (23.1)</td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>11 (26.8)</td>
<td>11 (28.2)</td>
<td></td>
</tr>
<tr>
<td>Time since symptom onset ‡ (yr)</td>
<td>1.25 (0.1 to 25.2)</td>
<td>2.17 (0.2 to 27.1)</td>
<td>0.52</td>
</tr>
<tr>
<td>VAS # at screening ‡ (cm)</td>
<td>6.6 ± 1.2</td>
<td>7.0 ± 1.2</td>
<td>0.18</td>
</tr>
<tr>
<td>WOMAC subscale scores †** (baseline)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>22.4 ± 10.3</td>
<td>22.9 ± 9.1</td>
<td>0.79</td>
</tr>
<tr>
<td>Stiffness</td>
<td>10.5 ± 4.4</td>
<td>9.4 ± 4.9</td>
<td>0.26</td>
</tr>
<tr>
<td>Function</td>
<td>80.3 ± 38.5</td>
<td>75.9 ± 38.0</td>
<td>0.60</td>
</tr>
<tr>
<td>Index knee synovitis ††</td>
<td>13 (31.7)</td>
<td>8 (20.5)</td>
<td></td>
</tr>
<tr>
<td>Index lesion †</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medial femoral condyle</td>
<td>40 (97.6)</td>
<td>38 (97.4)</td>
<td></td>
</tr>
<tr>
<td>Lateral femoral condyle</td>
<td>1 (2.4)</td>
<td>1 (2.6)</td>
<td></td>
</tr>
<tr>
<td>Area ‡‡§§## (cm²)</td>
<td>2.32 ± 1.43 (6.77)</td>
<td>1.95 ± 1.35 (4.46)</td>
<td>0.20</td>
</tr>
<tr>
<td>Volume including missing bone ‡‡§§## (cm³)</td>
<td>0.95 ± 0.82</td>
<td>0.70 ± 0.53</td>
<td>0.12</td>
</tr>
<tr>
<td>No. of rehabilitation sessions per patient over a twelve-week period †§§</td>
<td>28.4 ± 7.4</td>
<td>27.0 ± 7.6</td>
<td>0.41</td>
</tr>
</tbody>
</table>

*The p values were obtained by a two-sample Student t test. †The values are given as the mean and the standard deviation. ‡The values are given as the number of patients, with the percentage in parentheses. §The values are given as the median, with the range in parentheses. #The VAS was 10 cm in length. **WOMAC includes three subscales (pain, stiffness, and function) in the VAS format of 0 to 10 cm in length. Scores have a maximum value of 50 points for pain, 20 points for stiffness, and 170 points for function. ††The values are given as the mean and the standard deviation, with the maximum in parentheses. §§Two patients in the microfracture group were lost to follow-up, resulting in thirty-seven patients in the microfracture group evaluated in these categories. ‡‡Lesion area and volume were determined post-debridement with use of quantitative MRI at one month posttreatment.

Safety

The safety definitions used during this trial conformed to international regulatory norms for clinical trials investigating medical devices. All adverse events were recorded up to twelve months posttreatment.

Source of Funding

The trial was conducted by Piramal Life Sciences, Bio-Orthopaedic Division (formerly BioSyntech Canada Inc.), which makes the product BST-CarGel that was tested and was reported on in this study. Piramal Life Sciences, Bio-Orthopaedic Division, provided funds that were used to pay for clinical service fees, third-party MRI-related activities and analyses, trial-related expenses, and patient travel expenses. Two authors (W.D.S. and F.F.) have received consulting fees from Piramal Life Sciences, Bio-Orthopaedic Division. One author (A.R.) is an employee of Piramal Life Sciences, Bio-Orthopaedic Division. One author (M.S.S.) was an employee and is now a senior advisor to Piramal Life Sciences, Bio-Orthopaedic Division.

Results

Enrollment and Patient Baseline Characteristics

Screening and enrollment took place from May 2006 to January 2009. Follow-up was concluded in February 2010. The patient disposition and the numbers of patients who contributed to end-point analyses are shown in Figure 1. Of the 228 patients screened for eligibility, 133 advanced to diagnostic arthroscopy, from which eighty were randomized: forty-one to the BST-CarGel group and thirty-nine to the microfracture group. Forty-one patients in the BST-CarGel group and thirty-seven patients in the microfracture group completed the twelve-month follow-up. Baseline demographic characteristics of the patients were similar in the two groups and there were no significant differences (Table I). The baseline post-debridement lesion areas and areas...
## TABLE II Primary, Secondary, and Tertiary Outcomes at Twelve Months

<table>
<thead>
<tr>
<th>Variable</th>
<th>BST-CarGel (N = 41)</th>
<th>Microfracture (N = 39)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Co-primary end points*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Degree of lesion fill† (%)</td>
<td>92.81 ± 1.98</td>
<td>85.22 ± 2.08</td>
<td>0.011</td>
</tr>
<tr>
<td>Repair cartilage T2 relaxation time† (ms)</td>
<td>70.46 ± 4.49</td>
<td>85.04 ± 4.89</td>
<td>0.033</td>
</tr>
<tr>
<td>Secondary end point§#</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WOMAC subscale scores** (change from baseline) (points)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>-16.16 ± 1.16 (–22.4 to –10.6)</td>
<td>-16.91 ± 1.21 (–25.2 to –18.7)</td>
<td>0.646</td>
</tr>
<tr>
<td>Stiffness</td>
<td>-5.97 ± 0.68 (–9.8 to –4.7)</td>
<td>-6.56 ± 0.71 (–11.3 to –6.7)</td>
<td>0.543</td>
</tr>
<tr>
<td>Function</td>
<td>-55.96 ± 4.24 (–89.2 to –34.3)</td>
<td>-60.59 ± 4.41 (–97.7 to –56.9)</td>
<td>0.443</td>
</tr>
<tr>
<td>Tertiary end point††</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SF-36 version 2 score (change from baseline)††§§ (points)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical component</td>
<td>13.02 ± 1.50</td>
<td>14.76 ± 1.52</td>
<td>0.416</td>
</tr>
<tr>
<td>Mental component</td>
<td>3.54 ± 1.56</td>
<td>0.84 ± 1.58</td>
<td>0.229</td>
</tr>
</tbody>
</table>

*The values are given as the least squares means, adjusted for the baseline defect volume, and the standard error. †Two patients in the microfracture group were lost to follow-up, resulting in thirty-seven patients in this category. ††Because of aberrant data points (>200 ms), two patients in the BST-CarGel group and four patients in the microfracture group were removed, resulting in thirty-nine patients in the BST-CarGel group and, with two more patients lost to follow-up, thirty-three patients in the microfracture group. §The values are given as the least squares means, adjusted for baseline, and the standard error, with the 95% CI for the minimally clinical important difference in parentheses. The 95% CI were determined with use of scores from patients whose rating of global change was “somewhat better” on the SF-36 Reported Health Transition item (the minimal clinically important difference). #Data were missing for one patient in the BST-CarGel group. **These three subscales are in VAS format of 0 to 10 cm. Scores have a maximum change of 50 points for pain, 20 points for stiffness, and 170 points for function. Greater negative scores indicate better results. †††The values are given as the least squares means, adjusted for the baseline, and the standard error. ††SF-36 includes two aggregate measures (physical and mental components) derived from eight subscales, and one Reported Health Transition item. Higher positive scores indicate better results. §§Thirty-six patients in the BST-CarGel group and thirty-four patients in the microfracture group were evaluated in this category.

Volumes were both numerically larger for the BST-CarGel group than for the microfracture group. The largest lesions in the trial measured by MRI were 6.77 cm² in the BST-CarGel group and 4.46 cm² in the microfracture group.

### Primary End Points

The co-primary end points of this RCT were statistically achieved. Quantitative MRI demonstrated that, at twelve months, the BST-CarGel-treated lesions were filled with significantly more repair tissue (92.8% ± 2.0%) than microfracture-treated lesions (85.2% ± 2.1%) (p = 0.011) (Table II, Fig. 3-A). The frequency distribution of adjusted lesion %Fill values in Figure 4 shows that BST-CarGel treatment was more consistent than microfracture treatment alone in producing a greater degree of filling.

In addition, the repair tissue demonstrated significantly lower (p = 0.033) adjusted T2 relaxation times when the BST-CarGel treatment group (70.5 ± 4.5 ms) was compared with the microfracture treatment group (85.0 ± 4.9 ms) (Table II, Fig. 3-B). These values were also closer to the internal cartilage control values.

Statistical analysis found no effects from lesion chronicity (acute versus chronic lesions), geographic region, clinical site, or site-by-treatment interactions on the primary end points.

### Secondary and Tertiary End Points

When adjusted for baseline, there were no significant differences between the groups for any of the WOMAC subscales at twelve months (Table II). Both treatment groups showed significant improvement from baseline in all three subscales (p < 0.0001).

For the SF-36 score, there were no significant differences between BST-CarGel and microfracture treatment groups for any of the subscales at twelve months (data not shown). The SF-36 physical and mental component summaries were also similar (Table II). However, the single-question Reported Health Transition item found that 75% of patients in the BST-CarGel group reported feeling “better than one year ago” compared with 60% of patients in the microfracture group (p = 0.22).

### Safety

Overall, both trial treatments were well tolerated and the safety profiles were considered to be comparable. A similar percentage of patients in both groups reported adverse events: 97.6% of BST-CarGel patients (forty patients) and 92.3% of microfracture patients (thirty-six patients). Most adverse events (>95%) were of mild to moderate intensity. The most frequently observed adverse events in the groups were arthralgia (68.3% in the BST-CarGel group and 64.1% in the microfracture group), procedural pain (31.7% in the BST-CarGel group and 30.8% in the microfracture group), and nausea.
(17.1% in the BST-CarGel group and 0.0% in the microfracture group). Procedure-related adverse events were experienced by thirty-eight patients (92.7%) in the BST-CarGel group compared with thirty patients (76.9%) in the microfracture group.

In the BST-CarGel group, unanticipated device-related adverse events occurred with five patients (12.2%), and anticipated device-related adverse events occurred with four patients (9.8%). These adverse events were mild to moderate in intensity.

In the BST-CarGel group, unanticipated device-related adverse events occurred with five patients (12.2%), and anticipated device-related adverse events occurred with four patients (9.8%). These adverse events were mild to moderate in intensity.
except for three cascading unanticipated device-related adverse events (deep vein thrombosis, pulmonary embolism, and pleurisy) in a single patient, which were categorized as severe. All patients who experienced device-related adverse events recovered, except for one patient with arthralgia, which was still ongoing at trial end. Serious adverse events were reported for five patients (12.2%) in the BST-CarGel group (four of which were procedure-related and one of which was device-related) and for one patient (2.6%) in the microfracture group (which was not procedure-related). There were no discontinuations from the trial or deaths due to an adverse event in either group.

Discussion

The level of evidence in the literature for cartilage repair is generally low, and only two other prospective randomized studies have been published similarly under good clinical practice guidelines. The current trial design incorporated novel modalities not previously used, which increased the level of validity and reproducibility of the comparisons, in addition to decreasing potential bias. Specifically, the use of validated three-dimensional quantitative MRI to non-invasively assess the primary outcomes of repair tissue quality and quantity in a blinded fashion with a high level of standardization and precision has never before, to our knowledge, been achieved in an articular cartilage repair trial.

This RCT demonstrated that treatment with BST-CarGel significantly improves both the quantity and the quality of repair cartilage at twelve months in patients with full-thickness cartilage lesions compared with microfracture treatment alone. These superior structural outcomes associated with BST-CarGel have been demonstrated previously across other species. Initially observed in sheep and rabbits, and now in humans, these outcomes are believed to be a result of specific modifications in the repair sequence compared with bone marrow stimulation alone. Both orthopaedic experience and clinical evidence support the notion that improved repair cartilage tissue quality is predictive of improved clinical symptoms and longer-term durability.

The baseline characteristics of the treatment groups were generally well balanced in this trial. The median time to symptom onset prior to surgery in the BST-CarGel group (1.25 years) was less than that of the microfracture group (2.17 years), but both were less than the three-year cutoff identified in predicting clinical outcomes following treatment with microfracture or characterized chondrocyte implantation. Although the overall mean lesion size (approximately 2 cm$^2$) fell within the generally accepted algorithm for microfracture, the slightly larger lesion area and volume in the BST-CarGel group could be considered a bias against BST-CarGel outcomes. Interestingly, sensitivity analyses showed that %Fill following BST-CarGel treatment was unaffected by lesion area compared with microfracture treatment alone, which resulted in lower %Fill with increasing lesion area.

In this trial, BST-CarGel treatment resulted in significantly more repair tissue by lesion %Fill, an outcome that appears related to increased consistency and enhanced repair compared with microfracture treatment alone (Fig. 4), and further supports the role of BST-CarGel in stabilizing the initial blood clot. No correlation was found between %Fill and WOMAC scores, possibly because of the shorter-term follow-up of twelve months. In studies with at least twenty-four months of follow-up, the importance of the degree of lesion filling becomes more evident because it correlates with several clinical outcomes and can deteriorate over the long term (thirty to sixty months).

The quality of cartilage repair tissue can also be examined with biochemical MRI biomarkers such as T2 relaxation time. T2 is well known to be sensitive to, and highly dependent on, the extracellular cartilage matrix, particularly the collagen network structure and orientation, as well as macromolecular concentration and tissue hydration. As such, either cartilage degeneration or maturation of repair tissue can be longitudinally observed as T2 values deviate from native cartilage T2 values, respectively. Thus, it has become generally accepted that the quality of articular tissue can be assessed by the closeness of measured T2 values to that found in normal articular cartilage for the same joint compartment.

In the present trial, the repair cartilage T2 for the BST-CarGel treatment group was significantly different and lower than that of the microfracture treatment group, indicating an improved level of tissue quality, albeit not yet at the level of native cartilage after only twelve months. No correlation was found between T2 and WOMAC scores, but similarly to lesion %Fill, longer-term follow-up (twenty-nine months) may be required to correlate T2 to clinical outcomes. This result is not unexpected, knowing that remodeling and maturation of repair tissue is a continuous process that occurs over time.

Both treatment groups demonstrated comparable improvements in clinical benefit on the WOMAC scale, which is similar to other RCTs using subjective questionnaires at twelve months posttreatment, which showed acceptable but equivalent clinical outcomes regardless of treatment. Interestingly, subgroup analysis identified that male patients less than thirty-five years of age with a high activity level in the BST-CarGel group demonstrated greater improvement over those in the microfracture group in subscales of pain (44% [p = 0.02]), stiffness (90% [p = 0.37]), and function (56% [p = 0.02]).

Similar safety profiles were observed for both groups, as anticipated, considering the similarity in the treatments, which differed only by the mini-arthrotomy, the fifteen-minute waiting period required for the BST-CarGel and blood mixture to clot, and the BST-CarGel product itself. The difference in observed incidence of adverse events between the BST-CarGel group (92.7%) and the microfracture group (76.9%) is directly attributed to postoperative nausea and vomiting, probably secondary to the longer period of anesthesia.

The major strengths of this trial were the level of conformance to good clinical practice regulations, the careful
supervision of every microfracture procedure by a sponsor representative (A.R. and/or M.S.S.) ensuring its standardization, tracking of the same rehabilitation program for all patients, semiautomated, blinded MRI quantitative analyses to assess primary outcomes, and use of a preapproved statistical analysis plan. A limitation of the trial was the short, twelve-month follow-up, as current regulatory guidance suggests a twenty-four-month follow-up for such trials, particularly those with a clinical end point, in which differences may not be observed even after five years. However, twelve months can be appropriate for a structural end point when using highly accurate quantitative measures that are sensitive to early changes in cartilage structure. Another limitation was that the trial was single-blind; double-blinding was not possible because of procedural differences such as the mini-arthroscopy for patients in the BST-CarGel group. However, all primary end-point analyses were centralised and were blinded.

In conclusion, as a single-step cartilage repair surgical option, at twelve months BST-CarGel treatment results in a superior cartilage tissue with increased quantity and improved structural characteristics shown by quantitative MRI compared with microfracture treatment alone. Improvements in clinical benefit were equivalent for both groups and were significant over baseline. Safety was considered comparable for both groups. Whether the advantage of cartilage repair tissue with superior structural properties will correlate with improved long-term clinical benefit requires further study.

Appendix

A table showing inclusion and exclusion criteria is available with the online version of this article as a data supplement at jbjs.org.

Note: The BST-CarGel Clinical Trial Group, including the critical efforts of the research coordinators who tirelessly contributed to the trial’s success and more than sixty dedicated physiotherapists, are warmly acknowledged. We are indebted to Professors Michael Buschmann and Caroline Hoemann, the inventors of BST-CarGel, along with the Biomatériaux and Cartilage Laboratory at École Polytechnique de Montréal, which, over the period of more than a decade, established the scientific foundation for BST-CarGel. Trial and data management, including site monitoring and statistical analysis, were performed by Cato Canada (Montreal); additional statistical input and oversight was provided by D. Ar van Renshaw (San Andreas, California). MRI site qualification and management was carried out by VirtualScopics (Rochester, New York) and MRI quantitative analyses were performed by Cato Canada (Montreal); additional statistical input and oversight was provided by Dr. Alex Yaroshinsky (San Andreas, California). MRI site qualification and management was carried out by VirtualScopics (Rochester, New York) and MRI quantitative analyses were performed by Cato Canada (Montreal); additional statistical input and oversight was provided by D. Ar van Renshaw (San Andreas, California). MRI site qualification and management was carried out by VirtualScopics (Rochester, New York) and MRI quantitative analyses were performed by Cato Canada (Montreal); additional statistical input and oversight was provided by D. Ar van Renshaw (San Andreas, California). MRI site qualification and management was carried out by VirtualScopics (Rochester, New York) and MRI quantitative analyses were performed by Cato Canada (Montreal); additional statistical input and oversight was provided by D. Ar van Renshaw (San Andreas, California). MRI site qualification and management was carried out by VirtualScopics (Rochester, New York) and MRI quantitative analyses were performed by Cato Canada (Montreal); additional statistical input and oversight was provided by D. Ar van Renshaw (San Andreas, California). MRI site qualification and management was carried out by VirtualScopics (Rochester, New York) and MRI quantitative analyses were performed by Cato Canada (Montreal); additional statistical input and oversight was provided by D. Ar van Renshaw (San Andreas, California).

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References


