The Knee xxx (xxxx) xxx

Contents lists available at ScienceDirect

The Knee

Arthroscopic and open treatment of cartilage lesions with BST-CARGEL scaffold and microfracture: A cohort study of consecutive patients

Matthias Steinwachs [a,*], Nicola Cavalcanti [a], Santhosh Mauuva Venkatesh Reddy [b], Clement Werner [c], Daniel Tschopp [d], Hema N. Choudur [b]

[a] Facharzt für Orthopädische Chirurgie und Traumatologie des Bewegungsapparates SportClinic Zürich, Klinik Hirslanden, Zürich, Switzerland
[b] Division of MSK Imaging, McMaster University, Hamilton, Ontario, Canada
[c] Ortho Clinic Zürich, Hirslanden Klinik Im Park, Zürich, Switzerland
[d] Hirslanden AG, Klinik Hirslanden, Zürich, Switzerland

ARTICLE INFO

Article history:
Received 14 March 2018
Received in revised form 18 October 2018
Accepted 9 November 2018
Available online xxxx

Keywords:
CARGEL
Cartilage repair
Microfracture
Pain
Postoperative complications
Reoperation

ABSTRACT

Background: CARGEL (Smith & Nephew Inc.), a chitosan-based polymer scaffolding biomaterial, has been used since 2012 for treating articular cartilage lesions. Limited data are available on patient outcomes following CARGEL treatment. This study aimed to describe short-term clinical and radiographic outcomes in a cohort of patients treated with CARGEL and microfracture surgery for articular cartilage defects in the knee.
Methods: A retrospective cohort study was conducted of consecutive patients with articular cartilage defects who had undergone microfracture surgery with CARGEL, or in patellar lesions microfracture and CARGEL plus Chondro-Gide (at SportsClinic Zurich). Study outcomes included reoperations, infections, allergic reactions, pain, swelling, range of motion, and tissue quality and quantity. Ethics approval was obtained from the local ethics committee on 05/09/2017 (Basec. Nr: 2017-01441).
Results: A total of 91 participants, with 93 treated lesions, consenting to chart review were included. No participants required reoperation due to complications on the index lesion. Fifteen participants had second-look surgery on the index knee for other reasons, allowing for visual confirmation of cartilage repair. No study participants experienced a post-surgical infection or suffered an allergic reaction. No significant changes in range of motion or T2 values were observed from pre-treatment to post-treatment follow-up. However, significant decreases were found in pain ($P < 0.001$) and swelling ($P < 0.001$), along with significant increases in MOCART II scores ($P < 0.001$). Similar results were found in a subgroup of patients with patellar lesions.
Conclusions: Patients treated with CARGEL experienced few postoperative complications and reported promising reductions in pain and swelling after treatment.
Level of evidence: IV

1. Introduction

Articular cartilage lesions are characterized by the degeneration or injury of flexible cartilage over the articulating ends of bones [1]. While articular cartilage injuries can occur in any joint, they often develop and become problematic in the knee. Prev-

* Corresponding author at: Facharzt für Orthopädische Chirurgie und Traumatologie des Bewegungsapparates, SportClinic Zürich, Klinik Hirslanden, Witellikerstrasse 40, CH-8032 Zürich, Switzerland.
E-mail address: msteinwachs@sportclinic.ch (M. Steinwachs).

https://doi.org/10.1016/j.knee.2018.11.015
0968-0160/

alence studies indicate that cartilage lesions of varying severity are found in 60–63% of knee arthroscopies [2–4]. They are commonly seen in younger active patients and the optimal treatment remains unknown [5,6].

Treatment of articular cartilage lesions can prove to be challenging, as the joint cartilage is hypocellular with poor vasculature and lymphatic drainage [1,7]. When conservative approaches such as weight loss and physiotherapy fail to provide relief, a surgical approach is used to restore the cartilage. The most frequently used bone marrow-based cartilage restoration technique is microfracture surgery [8]. In this procedure, an arthroscopic awl is used to make multiple holes in the subchondral bone to promote formation of a pluripotent, stem-cell-rich blood clot from the marrow that covers and stabilizes the injury while the tissue heals [9]. The success of this procedure is contingent on achieving stable perpendicular edges of healthy cartilage around the exposed subchondral lesion [8], and on the stability of the newly formed clot. The stability of the marrow-derived clot can be enhanced by applying CARGEL, a natural bioscaffold, to the microfracture site [10].

CARGEL (developed by BioSyntech Canada Inc. until 2010, Piramal from 2010 to 2015, and recently acquired by Smith & Nephew Inc.) was developed to stabilize the microfracture-based blood clot by mixing a buffer, a chitosan solution, and the patient's whole blood to create a liquid bioscaffold. The mixture is implanted over marrow access holes in a cartilage lesion. CARGEL is prepared as a cytocompatible liquid chitosan solution with physiological pH that does not interfere with normal whole blood coagulation, but quantifiably reinforces the implanted clot by impeding its retraction [11]. This allows the ingrowth of mesenchymal progenitor cells from the subchondral bone and, thereby, formation of repair cartilage of improved quality that is structurally similar to hyaline cartilage [12]. As a result, the application of CARGEL during microfracture maintains critical blood components above marrow holes, which enhances early healing processes, including cell recruitment, vascularization of repair tissue, and subchondral bone remodeling [13].

CARGEL is applied in combination with microfracture to treat cartilage lesions in a single-stage procedure with five key steps. First, the defect is exposed arthroscopically, and protruding synovial tissue is removed. Proper visualization of the defect in a horizontal position is necessary and indicated for an arthroscopic knee cartilage repair approach. Second, the damaged cartilage is debrided down to the subchondral bone, with removal of the calcified layer, and to a stable rim of healthy cartilage. Microfractures are performed with an awl, picking holes of three to four millimeters in depth and apart. The prepared defect is dried with small swabs to ensure secure adherence of CARGEL. Third, the defect is arranged in a horizontal position, and the arthroscopy liquid is drained. Fourth, CARGEL is injected and the entire defect is filled and forms a stable clot in the defect after 15 min. Finally, intra-articular drainage (without suction) is inserted, and the arthroscopy portals are closed in standard fashion. The leg is immobilized in extension for 24 h [10].

It is recommended that patients receive a physiotherapy program following surgery for six to 12 weeks that includes partial weight-bearing and progresses to full weight-bearing by eight weeks. On the first postoperative day, patients are mobilized for the first time during physiotherapy with a partial load of five kilograms and F/E 30/0/0°. Partial weight-bearing is recommended for six weeks, with progression to full weight-bearing thereafter. Range of motion (ROM) is limited by a brace for six weeks (weeks 0 to two: 30°/0°/0°; weeks three to four: 60°/0°/0°, and weeks five to six: 90°/0°/0°). Continuous passive motion treatment is advised within the allowed angle for two hours daily for six weeks. Assisted passive motion is manually applied during physiotherapy sessions twice per week. No full-impact activities involving jumping or pivoting are recommended for 12 months [12].

Prior research has found that treatment with CARGEL scaffold with microfracture promotes greater lesion filling, increased clot stability, and the growth of repair tissue that is superior in quality compared with microfracture surgery alone [13–16]. A randomized controlled trial of 80 patients treated with CARGEL or microfracture alone showed significantly greater lesion fill and an increase in hyaline cartilage-like repair tissue (magnetic resonance imaging (MRI) findings of lower T2 relaxation times) in patients who received CARGEL scaffold at 12 months after surgery [12]. A follow-up study found that superior repair tissue quality and quantity is sustained at five years after surgery [16].

Early detection of cartilage lesions and postoperative evaluation of repair techniques have been improved with increasing access to MRI, thus cartilage lesions are routinely assessed using MRI of cartilage morphology of the knee joint [17]. This approach is limiting because it has low sensitivity to early cartilage degeneration and slight changes in morphology [18]. In 2009, the improved 3D magnetic resonance observation of cartilage repair tissue (MOCART) score-based system was proposed to improve assessment of high-resolution macroscopic MRI of cartilage repair based on nine parameters [19,20]. Subsequently, it has been shown that evaluating T2 relaxation times of native, lesion, and repair cartilage using high-resolution imaging increases value by adding a quantitative measure of cartilage health as short as six months after treatment [18]. Healthy native cartilage produces lower mean T2 values, suggesting decreased water content in tissue. Patients with articular cartilage lesions produce higher mean T2 values, suggesting increased water content and disruption of collagen matrix ultrastructure [21]. Therefore, repairing cartilage with hyaline-like qualities that resemble healthy cartilage should result in lower mean T2 values.

Limited data are published on the patient outcomes following treatment with CARGEL. Therefore, this retrospective cohort study was conducted to report on patient outcomes following management with CARGEL and microfracture surgery.

2. Methods

2.1. Study summary

A retrospective cohort study was conducted on consecutive patients with articular cartilage defects who had undergone microfracture surgery with CARGEL, or in patellar lesions microfracture and CARGEL plus ChondroGide®, at SportsClinic Zurich

Please cite this article as: M. Steinwachs, N. Cavalcanti, S. Mauuva Venkatesh Reddy, et al., Arthroscopic and open treatment of cartilage lesions with BST-CARGEL scaffold and microfracture: A cohort..., The Knee, https://doi.org/10.1016/j.knee.2018.11.015

between September 2014 and September 2017. Local ethics board approval was obtained from the Kantonale Ethikkommission, Zurich prior to starting this study. This study addresses the following clinical questions:

1. How often do patients who are treated with CARGEL require reoperations on the lesion that was treated with the microfracture and CARGEL?
2. What is the incidence of infection following treatment with CARGEL?
3. What is the incidence of allergic reactions following treatment with CARGEL?
4. What is the change in ROM from pre-surgery to post-surgery for patients treated with CARGEL?
5. What is the change in pain score from pre-surgery to post-surgery for patients treated with CARGEL?
6. What is the change in knee swelling from pre-surgery to post-surgery for patients treated with CARGEL?
7. What is the short-term quantity and quality of lesion repair tissue following treatment with CARGEL?

2.2. Eligibility criteria and consent process

All patients with articular cartilage defects treated with CARGEL scaffold and microfracture surgery between September 2014 to September 2017 and who had at least three months of follow-up were invited, by mail and telephone follow-up, to participate in the study. The indications for arthroscopic CARGEL scaffold and microfracture surgery included: symptomatic cartilage defect in femoral condyle, trochlea or patella; intact corresponding cartilage; Kellgren–Lawrence classification of osteoarthritis <grade 3; a stable knee; defect size <2 cm^2; and age < 50 years. Axis correction was indicated for axis deviation of >5°, which was confirmed by long leg X-rays. In cases where a varus deviation >5° was confirmed and the defect was located in the medial femoral condyle, an open-wedged high tibia osteotomy (HTO) was recommended. In the case where the patient had cartilage damage to the lateral femoral condyle and valgus malalignment, a distal femoral osteotomy (DFO) was performed in the form of a medial closed-wedge osteotomy with a TomoFix™ plate.

Patients with cartilage damage to the patella were clinically and radiologically screened prior to surgery. All patients with cartilage damage to the patella received a medial arthrotomy, the patella was inverted and the defect treated in the same way as defects in other sites. To prevent unwanted shearing of CARGEL from the defect, the defect in patella cases was additionally covered by stitching of a ChondroGide® collagen membrane (Geistlich, Wolhusen, Switzerland). Treated patellofemoral instabilities in this study were trochlear dysplasia < Dejour type B. The study only included patients who did not have high-grade varus, valgus, or rotational defects. There were no corrections on the tibial tuberosity (Caton-Deschamps index <1.2, TT-TG distance <20 mm) performed. Patellofemoral instability was treated by reconstruction of the medial patellofemoral ligament according to the technique by Fink et al. [22,23] Soft-tissue correction of active maltracking was performed by medial shortening of the retinaculum and capsule, and, if necessary, by additional covered lateral release.

Patients who agreed to participate provided written informed consent. Once informed consent was obtained, eligibility was confirmed by reviewing the participants' medical records.

2.3. Data collection

A medical student abstracted patient demographics, baseline characteristics, lesion characteristics, surgical details, and outcome data from the participants' medical records. Outcome data included rates of reoperation and second-look surgery, incidence of infection, ROM in degrees of flexion, and pain and swelling scores using a four-point Likert scale.

Baseline and post-treatment MRIs were anonymized and sent to independent musculoskeletal radiologists, who are not associated with the study participants' care, for review. To be included, the post-treatment MRIs must have been taken at least three months from the index procedure. The radiologists assessed coronal and sagittal fat saturated sequences and axial images, and determined the short-term quantity and quality of the lesion repair according to the Magnetic Resonance Observation of Cartilage Repair Tissue (MOCART) II scoring system and using T2 relaxation time [20]. They assessed the index lesion on the pre-treatment MRI and on the post-treatment MRI. The pre-treatment values were compared with the post-treatment values.

2.4. Definition of the subgroup

A subgroup of patients with patellar lesions treated with CARGEL and microfracture plus ChondroGide membrane were identified. The analyses (see below) were repeated for this subgroup due to differences in surgical procedures (e.g. mechanical support and open technique).

2.5. Data analysis

Categorical variables were summarized using frequencies and proportions. The Wilcoxon signed-rank test was used to test differences in endpoints measured at baseline and at post-treatment follow-up visit. Continuous variables were evaluated using measures of central tendency (means, medians), mean difference, and spread (95% confidence intervals, standard deviations). The analyses were repeated on a subgroup of patients with patellar lesions treated with microfracture and CARGEL plus ChondroGide. All statistical analyses were performed using IBM® SPSS® Statistics Version 25.

Please cite this article as: M. Steinwachs, N. Cavalcanti, S. Mauuva Venkatesh Reddy, et al., Arthroscopic and open treatment of cartilage lesions with BST-CARGEL scaffold and microfracture: A cohort..., The Knee, https://doi.org/10.1016/j.knee.2018.11.015

3. Results

3.1. Participant characteristics

One hundred and eleven patients were invited to participate in the study and 91 provided informed consent for 93 index lesions to be included. No patients were excluded after the review of their medical records. The mean age of study participants was 42.2 years and the majority were male (72.5%) (Table 1). Fifty-two percent (51.6%) of patients were affected in the right knee, 46.2% in the left knee, and 2.2% in both knees. Eighty-one knee cartilage lesions were classified using the International Cartilage Repair Society (ICRS) evaluation system [24]. Overall index defects were classified as ICRS class II (3.2%), ICRS class III (50.5%) or ICRS class IV (33.3%). Localization of index lesions was identified among patients in the following regions: medial femoral condyle (40.9%), trochlea (32.3%), patella (16.1%), lateral femoral condyle (7.5%), and lateral tibial plateau (4.3%). In addition to the treatment of cartilage damage with CARGEL, 33.3% of lesions were treated by partial resection of the meniscus; 22.6% by bone drilling; 21.5% by cartilage debridement; 19.4% by arthrotomy; 16.1% by meniscal suture; 11.8% by arthroscopic anterior cruciate ligament reconstruction; 6.5% by reconstruction of the medial patellofemoral ligament, with five out of six of these patients treated by arthrotomy and cartilage repair with a combination of CARGEL and ChondroGide® membrane; and 12.9% by patellar balancing. Furthermore, 3.2% of patients were treated by open-wedged high tibial osteotomy to correct varus deformity, performed medially and on the proximal tibia in all cases, and stabilized with a TomoFix™ plate. A total of 1.1% of patients were treated by medial closed wedge distal femoral osteotomy to treat valgus malformation and stabilized with a distal femur plate (TomoFix™). Figure 1 depicts the femoral condyle in a 27-year-old male competitive athlete showing (a) debridement of lesion and microfracture and (b) filling with CARGEL plus autologous blood.

Table 1
Baseline characteristics of study participants and lesions.

Characteristic	Participants (n = 91), lesions (n = 93)
Age, years, mean (SD)	42.2 (±9.8)
Sex, male, n (%)	66 (72.5)
Affected knee, n (%)	
Left	42 (46.2)
Right	47 (51.6)
Both	2 (2.2)
Additional diagnosis(es), n (%)	
Meniscus tear	37 (39.8)
Anterior cruciate ligament injury	18 (19.4)
Cysts	5 (5.4)
ICRS Grade, n (%)	
2	3 (3.2)
3	47 (50.5)
4	31 (33.3)
Missing	12 (12.9)
Location of index lesion, n (%)	
Medial femoral condyle	38 (40.9)
Trochlea	30 (32.3)
Patella	15 (16.1)
Lateral femoral condyle	7 (7.5)
Lateral tibial plateau	4 (4.3)
Number of surgical procedures prior to CARGEL surgery, n (%)	
0	38 (40.9)
1	32 (34.4)
2	11 (11.8)
3	7 (7.5)
> 3	2 (2.2)
Missing	3 (3.2)
Surgical management alongside CARGEL treatment, n (%)	
Partial resection of meniscus	
Bone drilling	31 (33.3)
Cartilage debridement	21 (22.6)
Arthrotomy	20 (21.5)
Meniscal suture	18 (19.4)
Anterior cruciate ligament reconstruction	15 (16.1)
Medial patellofemoral ligament reconstruction	11 (11.8)
Patellar balancing	6 (6.5)
Lateral retinacular release	8 (8.6)
Medial retinacular reefing	4 (4.3)
Associated realignment procedures performed in combination with CARGEL treatment, n (%)	
High tibial osteotomy	3 (3.2)
Distal femoral osteotomy	1 (1.1)

Please cite this article as: M. Steinwachs, N. Cavalcanti, S. Mauuva Venkatesh Reddy, et al., Arthroscopic and open treatment of cartilage lesions with BST-CARGEL scaffold and microfracture: A cohort..., The Knee, https://doi.org/10.1016/j.knee.2018.11.015

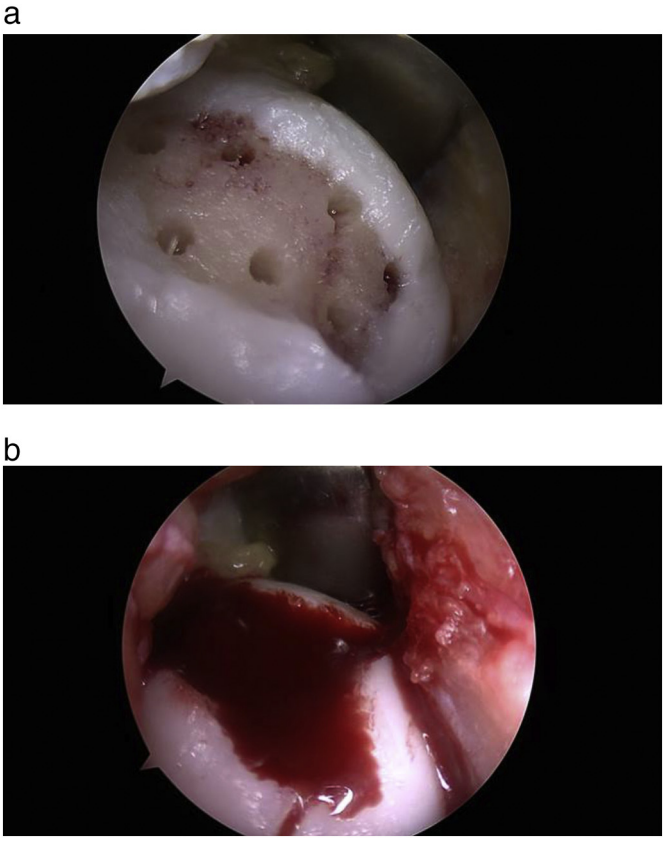

Figure 1. The femoral condyle of a 27-year-old male competitive athlete showing (a) debridement of lesion and microfracture, and (b) filling with CARGEL plus autologous blood.

Thirteen participants had index patellar lesions (14 index lesions in total) that were treated with microfracture and CARGEL plus ChondroGide collagen membrane for mechanical support in an open technique. Participants who had patellar lesions were slightly younger than the rest of the study population (mean 39.5 years) with a similar sex distribution (61.5% male) (Table 2). All participants who had patellar lesions had an arthrotomy. A third of lesions treated in this group involved medial patellofemoral ligament reconstruction. Patellar lesions were classified with an ICRS grading distribution similar to lesions in other regions. All patellar lesions were treated alongside CARGEL with arthrotomy and more than half were treated with patellar balancing techniques. No lesions in this group were treated with partial resection of meniscus, cartilage debridement or meniscal suture.

3.2. Study outcomes

The mean length of participant follow-up was six months ±1.7 months, with a range of three to 12 months. No participants had a reoperation due to a complication at the index lesion. Fifteen participants had subsequent surgery on their index knee for other reasons. Six (6.6%) participants underwent second-look surgery for arthroscopic arthrolysis, four (4.4%) had manipulations under anesthesia, and the remaining five who required reoperation were operated on the same knee, but for defects other than the target lesion treated with CARGEL. The second-look surgery allowed for visual confirmation of the cartilage repair in all cases. Figure 2 shows the lesion from the patient in Figure 1 at a second-look procedure approximately six months from the index procedure. No second-look surgeries were due to complications for lesions that were treated with microfracture and CARGEL. None of the study participants experienced a post-surgical infection and none suffered an allergic reaction following treatment with CARGEL.

ROM pre-surgery and at follow-up was documented in the medical records of 67 patients (73.6%). The mean ROM prior to treatment with CARGEL was 135.5° ±10.9. At post-surgery follow-up, the mean ROM was 136.9° ± 6.1. The mean difference in ROM between baseline and post-surgery was 1.34° ± 12.0, which was not statistically significant (Table 3). For patients with patellar lesions, the mean ROM prior to treatment with CARGEL was 134.5° ± 15.7. At post-surgery follow-up, the mean ROM was 136.5° ± 5.3. The mean difference in ROM between baseline and post-surgery was 2.0° ± 17.8, which was not statistically significant.

Please cite this article as: M. Steinwachs, N. Cavalcanti, S. Mauuva Venkatesh Reddy, et al., Arthroscopic and open treatment of cartilage lesions with BST-CARGEL scaffold and microfracture: A cohort..., The Knee, https://doi.org/10.1016/j.knee.2018.11.015

Table 2
Baseline characteristics of patellar subgroup participants and lesions.

Characteristic	Participants (n = 13), lesions (n = 14)
Age, years, mean (SD)	39.5 (±9.8)
Sex, male, n (%)	8 (61.5)
Affected knee, n (%)	
Left	8 (61.5)
Right	4 (30.8)
Both	1 (7.7)
Additional diagnosis(es), n (%)	
Meniscus tear	1 (7.1)
Anterior cruciate ligament injury	1 (7.1)
Cysts	1 (7.1)
ICRS Grade, n (%)	
2	0 (0.0)
3	6 (42.9)
4	6 (42.9)
Missing	2 (14.3)
Number of surgical procedures prior to CARGEL surgery, n (%)	
0	10 (71.4)
1	4 (28.6)
2	0 (0.0)
3	0 (0.0)
> 3	0 (0.0)
Surgical management alongside CARGEL treatment, n (%)	
Bone drilling	
Arthrotomy	6 (42.9)
Anterior cruciate ligament reconstruction	14 (100.0)
Medial patellofemoral ligament reconstruction	1 (7.1)
Patellar balancing	5 (35.7)
Lateral retinacular release	7 (50.0)
Medial retinacular reefing	3 (21.4)
Associated realignment procedures performed in combination with CARGEL treatment, n (%)	
High tibial osteotomy	0 (0.0)
Distal femoral osteotomy	0 (0.0)

Pain scores were available for 73 (80.2%) participants. The median pain score was 2.0 pre-surgery and decreased significantly to 1.0 at six months' post-treatment ($Z = -6.117$, $P < 0.001$) (Table 4). Swelling scores were available for 73 (80.2%) participants and the median swelling score was 1.0 pre-treatment and decreased significantly to 0.0 at six months' post-treatment ($Z = -5.552$, $P < 0.001$). For participants with patellar lesions, the median pain score was 2.0 pre-surgery and decreased significantly to 1.0 at six months' post-treatment ($Z = -2.585$, $P = 0.010$) (Table 5). The median swelling score for participants with patellar lesions was 0.5 pre-treatment and remained 0.0 at six months' post-treatment ($Z = -1.414$, $P = 0.157$).

MOCART II scores increased significantly from pre-treatment (mean, 38.89 ± 19.6) to post-treatment (mean, 56.90 ± 27.2) ($P < 0.001$). T2 relaxation times for repair tissue were measured and mapped for participants. Figure 3 shows the resulting T2 scores six months' post-treatment of the same patient depicted in Figures 1 and 2, including the corresponding T2 map identifying scores for each layer and control cartilage, and an MRI image of the defect. The short-term T2 relaxation times increased slightly from pre-treatment (mean, 41.62 ms ± 22.6) to post-treatment (mean, 45.73 ms ± 18.5) ($P = 0.241$) (Table 6). In the patellar

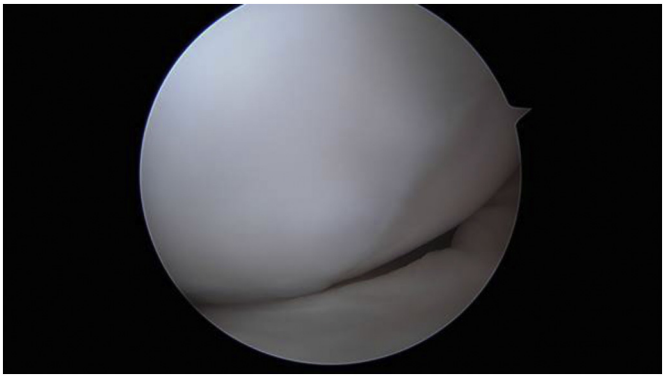

Figure 2. Second-look arthroscopy of the same patient depicted in Figure 1, six months' post-treatment.

Please cite this article as: M. Steinwachs, N. Cavalcanti, S. Mauuva Venkatesh Reddy, et al., Arthroscopic and open treatment of cartilage lesions with BST-CARGEL scaffold and microfracture: A cohort..., The Knee, https://doi.org/10.1016/j.knee.2018.11.015

Table 3
Changes in ROM[a] for study population and subgroup with patellar lesions.

Population	Pre-treatment, mean (SD)	Post-treatment, mean (SD)	Mean difference	95% CI
Study population (n = 67)	135.5 (±10.9)	136.9 (±6.1)	1.34	(−1.6, 4.3)
Subgroup with patellar lesions (n = 10)	134.5 (±15.7)	136.5 (±5.3)	2.00	(−10.8, 14.8)

[a] Range of motion measured in change from pre-treatment, with mean, standard deviation, and confidence interval.

Table 4
Changes in pain and swelling for the study population.

	Pre-treatment, median	Post-treatment, median	Z	*P*
Pain[a] (n = 73)	2.00	1.00	−6.117	<0.001
Swelling[a] (n = 73)	1.00	0.00	−5.552	<0.001

[a] Wilcoxon signed-rank test used with reported Z statistic, *P*-value, and median for pre-treatment and post-treatment endpoint.

subgroup, MOCART II scores increased significantly from pre-treatment (mean, 38.64 ± 25.3) to post-treatment (mean, 59.55 ± 19.4) ($P = 0.016$). The short-term T2 relaxation times remained unchanged from pre-treatment (mean, 37.20 ms ± 26.3) to post-treatment (mean, 36.50 ms ± 13.4) ($P = 0.936$) (Table 7). Figure 4 shows an MRI of the same location at 12 months after treatment.

4. Discussion

In this cohort study of 91 patients and 93 index knee cartilage lesions treated with microfracture and CARGEL, no patients underwent reoperation due to complications at the index lesion. However, six (6.6%) participants underwent surgery for arthroscopic arthrolysis and four (4.4%) had manipulations under anesthesia. These procedures allowed for a second-look and visual confirmation of the cartilage repair in all cases. There were no infections or allergic reactions. Additionally, there was no change in ROM from pre-surgery to post-treatment follow-up, and significant decreases in pain and swelling from pre-treatment to post-treatment follow-up. Reviews of MRIs found significant improvements in MOCART II score assessing lesion quality and quantity, but no significant difference in the T2 relaxation times, which were likely due to the physiological healing process.

The rate of reoperation in this study is similar to those reported in the literature for cartilage regenerative techniques [25]. Consistent with the current cohort study, prior clinical studies that evaluated CARGEL did not report any postoperative infections or allergic reactions following treatment [12,16]. CARGEL is contraindicated for use in patients with hypersensitivities to shellfish, active blood clotting disorders, receiving anti-coagulant therapy that cannot be interrupted, rheumatoid arthritis, or advanced musculoskeletal diseases. The absence of allergic reactions in this study reinforces findings that CARGEL is safe for use in patients outside of these vulnerable groups. Knee arthroscopy is one of the most commonly performed orthopedic procedures in the world [26–28], and studies have shown that postoperative infection rates after knee arthroscopy are extremely low [29,30].

While the current study did not find any significant improvements in ROM from pre-treatment to post-treatment follow-up, it did find significant decreases in pain and swelling from pre-treatment to post-treatment. Prior studies did not report on ROM. Stanish et al. reported statistically significant improvements in pain from pre-treatment to 12 months' post-treatment on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) [12], and Shive et al. reported that these reductions in pain remained at five years' post-treatment [16]. Results in the current cohort study confirm the pain reductions found by Stanish et al. [12] and Shive et al. [16], but the use of a Likert scale internal to the study clinic and not validated by others limited ability to make comparisons about the magnitude of the reductions that were found. The two previous clinical studies did not report on changes in swelling [12,16]. The age distribution in the study population in these studies also differs from the current cohort study population. The mean age at the time of treatment in the previous clinical trial was 34.3 years ±9.7, while the mean age at treatment in the current cohort was 42.2 years ±9.8. This suggests that improvements in pain and swelling reported in the current cohort study demonstrate efficacy in an older population.

Table 5
Changes in pain and swelling for the patellar subgroup.

	Pre-treatment, median	Post-treatment, median	Z	*P*
Pain[a] (n = 11)	2.00	1.00	−2.585	0.010
Swelling[a] (n = 10)	0.50	0.00	−1.414	0.157

[a] Wilcoxon signed-rank test used with reported Z statistic, *P*-value, and median for pre-treatment and post-treatment endpoint.

Please cite this article as: M. Steinwachs, N. Cavalcanti, S. Mauuva Venkatesh Reddy, et al., Arthroscopic and open treatment of cartilage lesions with BST-CARGEL scaffold and microfracture: A cohort..., The Knee, https://doi.org/10.1016/j.knee.2018.11.015

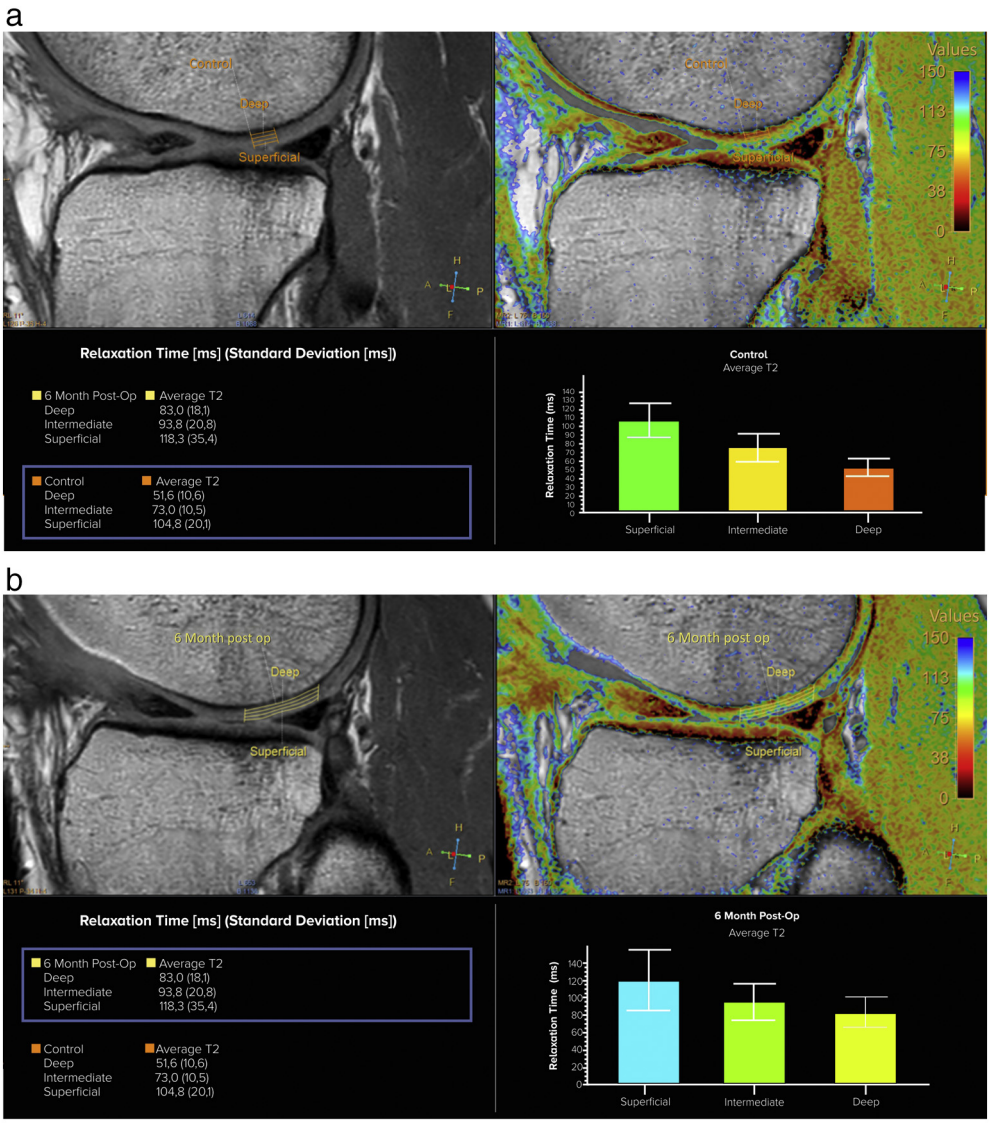

Figure 3. The T2 scores of the same patient at six months' post-treatment. A and B: the corresponding T2 map showing deep and superficial layers of the adjacent tissue and control cartilage. C. the defect 6 months' after CARGEL treatment.

Please cite this article as: M. Steinwachs, N. Cavalcanti, S. Mauuva Venkatesh Reddy, et al., Arthroscopic and open treatment of cartilage lesions with BST-CARGEL scaffold and microfracture: A cohort..., The Knee, https://doi.org/10.1016/j.knee.2018.11.015

Table 6
Changes in T2 relaxation time and MOCART II score.

	Pre-treatment, mean (SD)	Post-treatment, mean (SD)	Mean difference	*P*
Cartilage T2 relaxation time[a]	41.62 (22.6)	45.73 (18.5)	4.11	0.241
MOCART II score[b]	38.89 (19.6)	56.90 (27.2)	18.02	<0.001

[a] T2 relaxation time measures tissue quality in milliseconds (ms).
[b] Magnetic resonance observation of cartilage repair tissue (MOCART) II score based on high-field MRI macroscopic assessments of knee cartilage for the following parameters: defect fill, cartilage interface, surface, adhesions, structure, signal intensity, subchondral lamina, subchondral bone, and effusion.

Table 7
Changes in T2 relaxation time and MOCART II score for the patellar subgroup.

	Pre-treatment, mean (SD)	Post-treatment, mean (SD)	Mean difference	*P*
Cartilage T2 relaxation time[a]	37.20 (26.3)	36.50 (13.4)	−0.70	0.936
MOCART II score[b]	38.64 (25.3)	59.55 (19.4)	20.91	0.016

[a] T2 relaxation time measures tissue quality in milliseconds (ms).
[b] Magnetic resonance observation of cartilage repair tissue (MOCART) II score based on high-field MRI macroscopic assessments of knee cartilage for the following parameters: defect fill, cartilage interface, surface, adhesions, structure, signal intensity, subchondral lamina, subchondral bone, and effusion.

There is evidence that patients with patellar lesions treated with bone-marrow stimulating techniques exhibit differences in clinical outcome compared to patients treated for cartilage defects in other locations of the knee [31,32]. Mean filling of the patellar defects in animal models can be twice that of other areas of the knee in short-term follow-up [16]. In patients treated for cartilage lesions of the patella, larger defects were significantly associated with poor clinical outcomes, and defects located on the lateral patellar facet were correlated with improved clinical outcomes [17]. In this study, a subgroup of participants who had patellar lesions demonstrated significant decreases in pain consistent with the study population but did not demonstrate significant decreases in swelling. This is likely due to the small sample size. It could also be due to grouping patients with patellar defects rather than categorizing based on defect location within the patella.

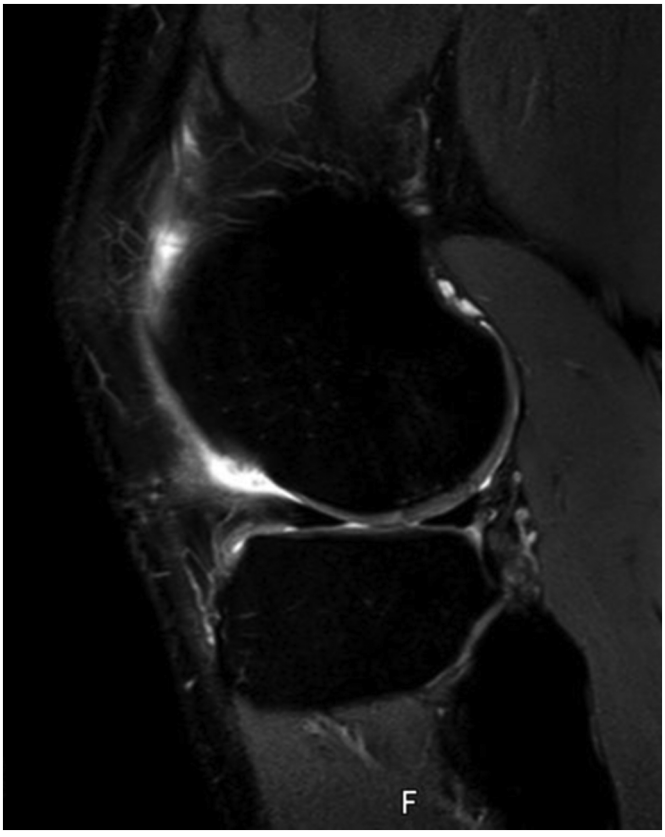

Figure 4. An MRI of the same location 12 months after treatment.

Please cite this article as: M. Steinwachs, N. Cavalcanti, S. Mauuva Venkatesh Reddy, et al., Arthroscopic and open treatment of cartilage lesions with BST-CARGEL scaffold and microfracture: A cohort..., The Knee, https://doi.org/10.1016/j.knee.2018.11.015

This cohort study found that treatment with CARGEL significantly improved quality and quantity of repair cartilage at short-term follow-up in patients with articular cartilage lesions when compared to pre-surgery cartilage. Magnetic resonance imaging evaluation showed that treatment with CARGEL for articular damage in the knee resulted in good quantity and quality short tissue repair integrated into the surrounding tissue. The mean MOCART II score was 56.9 at follow-up, which was significantly higher than MOCART II scores pre-treatment. A significant increase in MOCART II scoring was also observed in the subgroup of patients with patellar defects, where the mean MOCART II score was 59.5 at follow-up. MOCART II increases observed in this study confirm early radiological results from other articular cartilage treatment studies that showed total MOCART II scores ranging from 41 to 75 at follow-up ranging from three to 12 months, when CARGEL was used for the treatment of articular cartilage defects of the knee [33,34]. These increases also affirm recent findings that CARGEL treatment results in the improvement of several structural and cellular characteristics of repair tissue over microfracture [35]. This was demonstrated through visual assessments made during second-look arthroscopy to apply ICRS macroscopic scoring and histological assessments that showed significant improvement in surface architecture, surface/superficial assessment, cell viability, and cell distribution.

Overall, T2 relaxation time measurements increased slightly after CARGEL treatment for the study population and remained unchanged for the subgroup of patients with patellar defects, which is likely related to the ongoing physiological healing process and earlier timing of MRI. Previous studies evaluating T2 relaxation times in CARGEL reported significant decreases in T2 relaxation times for hyaline-like repair cartilage. In those studies, baseline MRI reference points were collected one month after treatment and follow-up was ≥2 years [11]. In contrast, in the current study, baseline MRI reference points were collected prior to treatment and post-treatment MRIs were taken at a mean of six months after surgery. Post-treatment reference points and a lengthier follow-up may yield different findings as the healing process progresses.

This cohort study was strengthened by the use of scoring systems for many of the outcomes, including the assessment of ROM, scores for pain, and scores for swelling. Another strength of the study was that the MRI review was conducted by independent experienced musculoskeletal radiologists, and that repair tissue quantity and quality were assessed using three-dimensional quantitative MRI imaging. This study was limited by its retrospective design. Additionally, follow-up was limited to a mean of six months' post-treatment, with a range from three to 12 months. Based on the literature, six months of follow-up is appropriate for assessing early post-surgical infection [36,37], and pain and swelling [27]. However, longer follow-up is necessary to adequately assess structural outcomes, including the quality and quantity of cartilage repair tissue, after the tissue has fully healed. Another limitation of this study was that all participants were operated on and assessed by the same orthopedic surgeon, thus limiting the generalizability of the results. However, this aspect also eliminated any inter-surgeon variability and ensured standardized treatment and follow-up.

The results of this retrospective cohort study found that patients treated with CARGEL did not require any reoperations due to complications related to CARGEL, experienced no infections or allergic reactions, and reported promising improvements in pain and swelling outcomes after treatment. Moreover, this study also showed that lesions treated with CARGEL had improved short-term cartilage tissue quantity and quality, as per the MOCART II score, when compared to pre-surgery lesions. This cohort study suggests that microfracture treatment with CARGEL is safe and effective for the management of articular cartilage lesions in the knee.

Statement of funding

This work was funded by Smith & Nephew Inc., USA.

Declaration of conflicts of interest

None of the authors have any conflicts of interest to declare.

References

[1] Lories RJ, Luyten FP. The bone–cartilage unit in osteoarthritis. Nat Rev Rheumatol 2011;7:43–9.
[2] Curl WW, Krome J, Gordon ES, Rushing J, Smith BP, Poehling GG, Stat M, Ph D. Cartilage injuries: a review of 31,516 knee arthroscopies. Arthroscopy 1997;13:456–60.
[3] Hjelle K, Solheim E, Strand T, Muri R, Brittberg M. Articular cartilage defects in 1,000 knee arthroscopies. Art Ther 2002;18:730–4.
[4] Widuchowski W, Widuchowski J, Trzaska T. Articular cartilage defects: study of 25,124 knee arthroscopies. Knee 2007;14:177–82.
[5] Mithoefer K, Hambly K, Logerstedt D, Ricci M, Silvers H, Villa SD. Current concepts for rehabilitation and return to sport after knee articular cartilage repair in the athlete. J Orthop Sports Phys Ther 2012;42:254–73.
[6] Mithoefer K, Peterson L, Zenobi-Wong M, Mandelbaum BR. Cartilage issues in football-today's problems and tomorrow's solutions. Br J Sports Med 2015;49:590–6.
[7] Orth P, Rey-Rico A, Venkatesan JK, Madry H, Cucchiarini M. Current perspectives in stem cell research for knee cartilage repair. Stem Cells Cloning 2014;7:1–17.
[8] Bhosale AM, Richardson JB. Articular cartilage: structure, injuries and review of management. Br Med Bull 2008;87:77–95.
[9] Steadman JR, Rodkey WG, Singleton SB, Briggs KK. Microfracture technique forfull-thickness chondral defects: technique and clinical results. Oper Tech Orthop 1997;7(4):300–4.
[10] Steinwachs MR, Waibl B, Mumme M. Arthroscopic treatment of cartilage lesions with microfracture and BST-CarGel. Arthrosc Tech 2014;3(3):e399–402.
[11] Hoemann CD, Sun J, McKee MD, Chevrier A, Rossomacha E, Rivard G-E, Hurtig M, Buschmann MD. Chitosan-glycerol phosphate/blood implants elicit hyaline cartilage repair integrated with porous subchondral bone in microdrilled rabbit defects. Osteoarthr Cartil 2007;15:78–89.
[12] Stanish WD, McCormack R, Forriol F, Mohtadi N, Pelet S, Desnoyers J, Restrepo A, Shive MS. Novel scaffold-based BST-CarGel treatment results in superior cartilage repair compared with microfracture in a randomized controlled trial. J Bone Joint Surg 2013;95:1640–50.

Please cite this article as: M. Steinwachs, N. Cavalcanti, S. Mauuva Venkatesh Reddy, et al., Arthroscopic and open treatment of cartilage lesions with BST-CARGEL scaffold and microfracture: A cohort..., The Knee, https://doi.org/10.1016/j.knee.2018.11.015

[13] Chevrier A, Hoemann CD, Sun J, Buschmann MD. Chitosan-glycerol phosphate/blood implants increase cell recruitment, transient vascularization and subchondral bone remodeling in drilled cartilage defects. Osteoarthr Cartil 2007;15:316–27.
[14] Cheung RCF, Ng TB, Wong JH, Chan WY. Chitosan: An update on potential biomedical and pharmaceutical applications. Mar Drugs 2015;13:5156–86.
[15] Hoemann CD, Hurtig M, Rossomacha E, Sun J, Chevrier A, Shive MS, Buschmann MD. Chitosan-glycerol phosphate/blood implants improve hyaline cartilage repair in ovine microfracture defects. J Bone Joint Surg Am 2005;87:2671–86.
[16] Shive MS, Stanish WD, McCormack R, Forriol F, Mohtadi N, Pelet S, Desnoyers J, Méthot S,, Vehik K, Restrepo A. BST-CarGel® treatment maintains cartilage repair superiority over microfracture at 5 years in a multicenter randomized controlled trial. Cartilage 2015;6:62–72.
[17] Forney MC, Gupta A, Minas T, Winalski CS. Magnetic resonance imaging of cartilage repair procedures. Magn Reson Imaging Clin N Am 2014;22:671–701.
[18] Kijowski R, Blankenbaker DG, Munoz Del Rio A, Baer GS, Graf BK. Evaluation of the articular cartilage of the knee joint: value of adding a T2 mapping sequence to a routine MR imaging protocol. Radiology 2013;267:503–13.
[19] Goebel L, Orth P, Müller A, Zurakowski D, Bücker A, Cucchiarini M, Pape D, Madry H. Experimental scoring systems for macroscopic articular cartilage repair correlate with the MOCART score assessed by a high-field MRI at 9.4 T—comparative evaluation of five macroscopic scoring systems in a large animal cartilage defect model. Osteoarthr Cartil 2012;20:1046–55.
[20] Welsch GH, Zak L, Mamisch TC, Resinger C, Marlovits S, Trattnig S. Three-dimensional magnetic resonance observation of cartilage repair tissue (MOCART) score assessed with an isotropic three-dimensional true fast imaging with steady-state precession sequence at 3.0 Tesla. Invest Radiol 2009;44:603–12.
[21] Dunn TC, Lu Y, Jin H, Ries MD, Majumdar S. T2 relaxation time of cartilage at MR imaging: comparison with severity of knee osteoarthritis. Radiology 2004;232:592–8.
[22] Fink C, Veselko M, Herbort M, Hoser C. Minimally invasive reconstruction of the medial patellofemoral ligament using quadriceps tendon. Arthrosc Tech 2014;3(3):e325–9.
[23] Fink C, Veselko M, Herbort M, Hoser C. MPFL reconstruction using a quadriceps tendon graft: part 2: operative technique and short term clinical results. Knee 2014;21(6):1175–9.
[24] Brittberg M, Winalski CS. Evaluation of cartilage injuries and repair. J Bone Joint Surg Am 2003;85-A(Suppl. 2):58–69.
[25] Devitt BM, Bell SW, Webster KE, Feller JA, Whitehead TS. Surgical treatments of cartilage defects of the knee: systematic review of randomised controlled trials. Knee 2017;24:508–17.
[26] Kim S, Bosque J, Meehan JP, Jamali A, Marder R. Increase in outpatient knee arthroscopy in the united states: a comparison of national surveys of ambulatory surgery, 1996 and 2006. J Bone Joint Surg Am 2011;93:994–1000.
[27] Mithoefer K, McAdams T, Williams RJ, Kreuz PC, Mandelbaum BR. Clinical efficacy of the microfracture technique for articular cartilage repair in the knee: an evidence-based systematic analysis. Am J Sports Med 2009;37:2053–63.
[28] Montgomery SR, Foster BD, Ngo SS, Terrell RD, Wang JC, Petrigliano FA, McAllister DR. Trends in the surgical treatment of articular cartilage defects of the knee in the United States. Knee Surg Sports Traumatol Arthrosc 2014;22:2070–5.
[29] Bert JM, Giannini D, Nace L. Antibiotic prophylaxis for arthroscopy of the knee: is it necessary? Art Ther 2007;23:4–6.
[30] Peel TN, Cheng AC, Buising KL, Choong PFM. Microbiological aetiology, epidemiology, and clinical profile of prosthetic joint infections: are current antibiotic prophylaxis guidelines effective? Antimicrob Agents Chemother 2012;56:2386–91.
[31] Heir S, Årøen A, Løken S, Sulheim S, Engebretsen L, Reinholt FP. Intraarticular location predicts cartilage filling and subchondral bone changes in a chondral defect. Acta Orthop 2010;81:619–27.
[32] Niemeyer P, Steinwachs M, Erggelet C, Kreuz PC, Kraft N, Köstler W, Mehlhorn A, Südkamp NP. Autologous chondrocyte implantation for the treatment of retropatellar cartilage defects: clinical results referred to defect localisation. Arch Orthop Trauma Surg 2008;128:1223–31.
[33] Christensen BB, Foldager CB, Jensen J, Lind M. Autologous dual-tissue transplantation for osteochondral repair: early clinical and radiological results. Cartilage 2015;6:166–73.
[34] Trattnig S, Ohel K, Mlynarik V, Juras V, Zbyn S, Korner A. Morphological and compositional monitoring of a new cell-free cartilage repair hydrogel technology — GelrinC by MR using semi-quantitative MOCART scoring and quantitative T2 index and new zonal T2 index calculation. Osteoarthr Cartil 2015;23:2224–32.
[35] Methot S, Changoor A, Tran-Khanh N, Hoemann CD, Stanish WD, Restrepo A, Shive MS, Buschmann MD. Osteochondral biopsy analysis demonstrates That BST-CarGel treatment improves structural and cellular characteristics of cartilage repair tissue compared with microfracture. Cartilage 2016;7:16–28.
[36] Arshi A, Cohen JR, Wang JC, Hame SL, McAllister DR, Jones KJ. Operative management of patellar instability in the United States: an evaluation of national practice patterns, surgical trends, and complications. Orthop J Sports Med 2016;4 [2325967116662873].
[37] Wyatt RWB, Maletis GB, Lyon LL, Schwalbe J, Avins AL. Efficacy of prophylactic antibiotics in simple knee arthroscopy. Art Ther 2017;33:157–62.

Please cite this article as: M. Steinwachs, N. Cavalcanti, S. Mauuva Venkatesh Reddy, et al., Arthroscopic and open treatment of cartilage lesions with BST-CARGEL scaffold and microfracture: A cohort..., The Knee, https://doi.org/10.1016/j.knee.2018.11.015