Chapter 7

BioCartilage®: new frontiers in cartilage restoration

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INTRODUCTION

Tissue engineering techniques are being refined with the intent of promoting the regeneration of hyaline-like cartilage within chondral defects; these techniques include enhanced or augmented microfracture techniques (1).

The efficacy of microfracture depends in part upon bleeding from small holes created within the defect and the subsequent formation of clots, the constituents of which are growth factors and mesenchymal stem cells (MSCs) originating from the subchondral bone (2). Levels of type II collagen mRNA expression increase in the repair tissue within six weeks of the microfracture procedure, although varying degrees of a fibrocartilage/hyaline-like cartilage repair tissue is generated (3).

Bae et al. (4) reported that in their cohort of patients who underwent microfracture, quantitative collagen formation was 44% greater compared to that found in the normal control group. Nevertheless, microfracture alone is limited by incomplete defect filling with repair tissue and by total type II collagen and aggrecan contents that are lower than those seen in native cartilage tissue (3, 5).

Arthrex BioCartilage® (Arthrex, Naples, Fl, USA) is a micronized allograft cartilage extracellular matrix (ECM) consisting of type II collagen, proteoglycans and additional cartilaginous growth factors; placed in/over the microfractured defect, it is intended to provide a scaffold that may signal autologous cellular interactions within the defect.

The procedure can be enhanced through concomitant hydration using Platelet-Rich Plasma (PRP) creating a mechanically stable paste when covered with fibrin glue. BioCartilage® is intended to improve chondral regeneration and tissue quality after microfracture surgery.

It is:

- hypothermically dehydrated
- lyophilized
- micronized with particle sizes ranging from 100-300 microns.

It has a five-year shelf life at ambient storage temperature. The small particle size is designed to improve delivery of the product to the defect site and also increases its relative surface area, and thus its potential sites of attachment to host subchondral bone. Its use is proposed as a means of improving the often limited, short-lived clinical outcomes of an isolated microfracture procedure and to expand the indications for the use of microfracture.

OUTCOMES OF ISOLATED MICROFRACTURE

When well performed, the microfracture procedure has good potential in the treatment of small- to medium-sized chondral defects (Table 7.2).

Short-term results of microfracture for isolated, full-thickness chondral defects of the glenohumeral joint have demonstrated significant improvement in pain relief and function (6, 7).

Similar early results have been reported with osteochondral lesion treatment by microfracture in the talus (8, 9).

The differences in opinion between orthopedic surgeons regarding the practice of microfracture were highlighted in a survey study by Theodoropoulos et al. (10).

They surveyed 299 Canadian orthopedic surgeons on the practice of microfracture for knee chondral defects and reported that there was widespread variation of responses among the cohort as to the particular indications for the surgery, surgical technique, postoperative rehabilitation and patient outcome assessment.

Ultimately, the results of isolated microfracture surgery, which is performed almost 125,000 times annually in the United States, remain mixed and often short-lived.

TABLE 7.2 Clinical outcomes after isolated microfracture procedure for the treatment of full-thickness cartilage defects of the knee.

Reference	Study Design	Results	Conclusions
Bae et al. (4)	49 knees in 46 patients with moderate osteoarthritic changes Mean age, 57 years Mean lesion size, 3.9 cm^2 Retrospective case series Level of evidence: IV	Significant improvements in parameters of daily living activity and pain ($p < 0.05$) Significant joint space widening on AP (1.06 mm) and standing lateral (1.37 mm) films ($p < 0.05$) Type II collagen formation identified on IHC staining 44% growth of quantitative collagen vs control	Patients with full-thickness chondral defects of knee improve function and increase joint space after microfracture. After the procedure, cartilaginous tissue is formed which contains type II collagen in mix of fibrocartilage and hyaline-like cartilage.
Cerynik et al. (49)	24 professional NBA players Mean age, 26 years Case-control study Level of evidence: IV	Mean 30 weeks to return to NBA game from surgery, PER decreased by 3.5 ($p < 0.01$) in first season back, mpg decreased by 4.9 min ($p < 0.05$) in first season back Power rating during 2 years post-procedure decreased by 3.1 ($p < 0.01$) and mpg decreased by 5.2 ($p < 0.001$) 21% did not return to competition	The performance of professional basketball players diminishes for those who undergo microfracture and return to competition. On return to play, performance and mpg are diminished.
Gobbi et al. (39)	53 athletes Mean lesion size, 4.0 cm^2 Mean age, 38 years Prospective cohort study Level of evidence: IV	Knee pain, swelling improved in 70%. Tibiofemoral crepitus improved in 60%. Subjective evaluation improved, 40/100 → 70/100. Lysholm score improved, 56.8 → 87.2. IKDC score improved, final follow-up 70% scored A/B. Tegner score improved at 2 years, 3.2 → 6. 80% showed decline in sports activity. level at final follow-up.	Microfracture offers functional, clinical and subjective improvement in athletes. It may not be the definitive procedure, however, for an athlete's knee given the decline in sports participation over time.
Gobbi et al. (40)	61 athletes Mean lesion size, 4.01 cm^2 Mean age, 15.1 years Prospective cohort study Level of evidence: IV	IKDC, Lysholm, Tegner scores increased significantly at 2 years. Outcome scores were declining at long term (still significantly above baseline). 11% failures 9 players reported pain, swelling after strenuous activities. Smaller lesions, younger age were associated with significantly better KOOS, VAS and Marx scores.	Microfracture in younger patients with smaller lesions has good clinical results at both short- and long-term follow-up. Lesion size is more of a prognostic factor than age in determining outcome. Clinical outcomes deteriorate 2 to 5 years postoperatively. Degenerative changes are present at long-term follow-up.
Goyal et al. (41)	15 studies, comparing outcomes of microfracture to other treatments Systematic review Level of evidence: II	Majority of studies reported poor clinical outcomes. Small-sized lesions and younger patients showed good results in the short term. Later post-operative periods showed osteoarthritis and treatment failures, 5 to 10 years postoperatively.	Microfracture use in small lesions and patients with low demands resultd in good short-term clinical outcomes. Younger patients fare better. Failure can occur 5 years postoperatively regardless of lesion size.

OUTCOMES OF MICROFRACTURE WITH CONCOMITANT PROCEDURES

Given the mixed results and limitations in patient selection with the microfracture procedure performed in isolation, numerous procedures have been evaluated as concomitant treatment options to enhance the results of microfracture (Table 7.3).

Like BioCartilage®, these concurrent interventions take advantage of the access granted by microfracture to MSCs within the subchondral bone and subsequently enhance the effects of the procedure from a biochemical and physiological standpoint. Intra-articular injection of bone marrow-derived MSCs have been used along with microfracture in the knee joint to attempt to enhance the cartilage healing response.

While no clinical or histological differences have been reported in comparison to microfracture alone, McIlwraith et al. (11) found enhanced cartilage repair with firmer tissue and increased aggrecan content.

PRP has been injected as an adjunct to arthroscopically performed microfracture in the treatment of early knee osteoarthritis and demonstrated improved results in 40-50 year olds as compared to microfracture alone (12).

Similar functional improvements were seen at mid-term follow-up with its use in patients with osteochondral talus lesions (13, 14).

A combination of microfracture and a cell-free polymer-based matrix has been shown to produce a gradual clinical improvement in patients at two-year follow-up with adequate filling of defects (15), while combining microfracture with the use of a cartilage ECM biomembrane to prevent washout of the clot at the defect site demonstrated superior outcomes in the degree

TABLE 7.3 Clinical outcomes after microfracture with concurrent enhancement procedure for the treatment of full-thickness focal cartilage defects of the knee.

Reference	Study Design	Results	Conclusions
Kreuz et al. (42)	85 patients with full- thickness chondral lesions Divided into 6 groups based on age, lesion location Prospective compariso study Level of evidence: II	Scores improved in all groups over 3-year study period ($p < 0.05$). Patients under 40 years had better results ($p < 0.01$). ICRS scores deteriorated ($p < 0.05$) between 18 and 36 months postoperatively in patients > 40 years old. Younger patients had better overall scores and MRI defect filling at 3 years postoperatively.	Clinical results are age dependent. Deterioration begins 18 months postoperatively, particularly in patients > 40 years old. Defects on femoral condyles and patient age < 40 years were most prognostic factors for good results.
Mithoefer et al. (43)	32 high-impact athletes Mean age, 38 years Mean lesion size, 4.92 cm^2 Prospective case series Level of evidence: IV	66% reported good or excellent results Significant increases in ADL, Marx activity rating, and Tegner scores. Scores decreased in 47% after initial improvement. 44% returned to high-impact sports, with 57% at preoperative level.	Microfracture is an effective first-line treatment in young athletes (< 40 years old), with short symptomatic intervals (< 12 months), small lesions (< 200 mm^2).
Mithoefer et al. (44)	48 patients Mean age, 41 years Mean lesion size, 4.82 cm^2 Prospective cohort study Level of evidence: IV	67% rated good or excellent knee function at final follow-up. Significant increases in ADL, IKDC, SF-36 physical scores ($p < 0.05$). Worst results for patients with BMI > 30 kg/m^2. Improved ADL score correlated with <12 months preoperative symptom duration.	Microfracture results in significant functional improvement at a minimum 2 years of follow-up. Best short-term results are with low BMI, short duration of preoperative symptoms. High BMI adversely affects short-term outcome.
Negrin et al. (45)	Meta-analysis of before/after-data of controlled studies Level of evidence: II	Calculated overall best estimate of 1.106, with (0.566; .646) as 95% CI of the mean standardized treatment effect.	Clinically relevant improvement is seen following the microfracture surgery comparing preoperative to postoperative clinical status. As a rough estimate, an increase of 22 overall KOOS points can be expected.
Salzmann et al. (46)	145 patients Mean age, 48 years Mean lesion size, 2.7 cm^2 Retrospective case series Level of evidence: IV	At mean 4.2 years post-procedure, 40.6% had persistent improvement in subjective symptoms, 8.2% reported symptom deterioration. 47.5% were very satisfied, 10.3% not satisfied. 12.4% had reoperation related to symptoms. Male patients had significantly better clinical outcomes than female patients.	Microfracture gives good clinical outcomes but not full recovery in patients with isolated lesions.

of cartilage repair when compared to isolated microfracture at two-year follow-up (16).
Stanish et al. (17) evaluated BST-CarGel, a chitosan-based medical device mixed with autologous whole blood, used to stabilize the initial clot and enhance marrow-derived repair.
The authors used the adjunctive treatment in combination with microfracture and compared the results to those obtained in patients who had microfracture alone.
They found greater lesion fill and superior quality of repair tissue with equivalent clinical benefit at 12 months post-surgery.
A case report by Gigante et al. (18) showed excellent clinical results at 24 months with the use of autologous Bone Marrow Concentrate (BMC) and a protective scaffold within the microfracture defect to augment the rate of defect fill and hyaline-like cartilage regeneration.
Autologous Matrix-Induced Chondrogenesis (AMIC) has been performed arthroscopically in combination with microfracture; the aim is to capture MSCs and growth factors released from the bone marrow during the microfracture within the collagen I/III matrix membrane in order to improve local chondral healing – particularly in the setting of larger lesions not amendable to other cartilage procedures.
This technique has been described in the hip and talus, as well as the knee (5, 19, 20, 21, 22, 23). Results following AMIC with microfracture have shown it to be an efficacious and safe procedure with the potential for regenerative defect fill in full-thickness chondral and osteochondral lesions of the knee in the short-term (~ 2 years), particularly retropatellar lesions (2, 5, 24, 25). AMIC with PRP, termed AMIC plus, was reported to produce clinical improvements in a small cohort of patients (26) at two-year follow-up.
Furthermore, AMIC with BMC (27, 28), perforated decalcified cortical bone matrix with adenovirus-bone morphogenetic proein-4 (29), and MSCs with hyaluronic acid (30), each of which has given encouraging early results, continue to be evaluated as potential options for enhancement of microfracture surgery.

PRINCIPLES BEHIND THE USE OF BIOCARTILAGE®

The basic science rationale behind BioCartilage® has been studied and is, as a result, supported by scientific literature demonstrating that dehydrated allograft cartilage scaffolds can be used with microfracture to enhance chondral defect healing.
In vitro evidence (31) was collected to examine whether a porous scaffold derived from articular cartilage had the ability to induce chondrogenesis of adipose-derived adult stem cells (ASCs).
Quantitative RT-PCR analysis determined the presence of chondrogenesis (particularly type II collagen) of ASCs in cultures in which ASCs had been seeded onto lyophilized cartilaginous scaffolds without exogenous growth factors, and the chondrogenic tissue was found to show mechanical properties nearing those of native cartilage.
A similar cartilage-derived porous matrix scaffold, used to enhance microfracture treatment of chondral defects in a preclinical rabbit model, showed significant upregulation of type II collagen and aggrecan and persistent proteoglycan content in comparison to microfracture alone (32).
Finally, a preclinical in vivo model in baboons demonstrated induced better formation of chondrogenic, hyaline-like reparative tissue in small osteochondral lesions filled with BioCartilage® in comparison with isolated microfracture control group

(33). These novel studies give credence to the potential for using cartilage ECM such as BioCartilage® as scaffolding in therapeutic chondral procedures.

The purpose of adding PRP to this injected mixture at the time of microfracture is to take advantage of the anti-catabolic and pro-anabolic growth factors it harnesses within the granules of platelets, and the pro-hyaline-like tissue formation it supports at the site of microfracture, in order to enhance cartilage healing in chronic focal chondral defects (26, 34).

It relies on evidence that human PRP may stimulate chondrogenic differentiation and migration of subchondral progenitor cells that are produced by microfracture (35).

Other studies, as noted in the above section, have demonstrated, clinically and radiologically, the ability of scaffolds to enhance cartilage healing during microfracture treatment of isolated chondral lesions in the knee through stabilization of the clot and, as a result, the attraction of marrow-derived stem cells to the defect site (5, 16-23, 36).

Scaffolds are useful in osteochondral repair as they are biodegradable, biocompatible, reproducible, permeable, non-cytotoxic, mechanically stable, and provide temporary support to local cells (37).

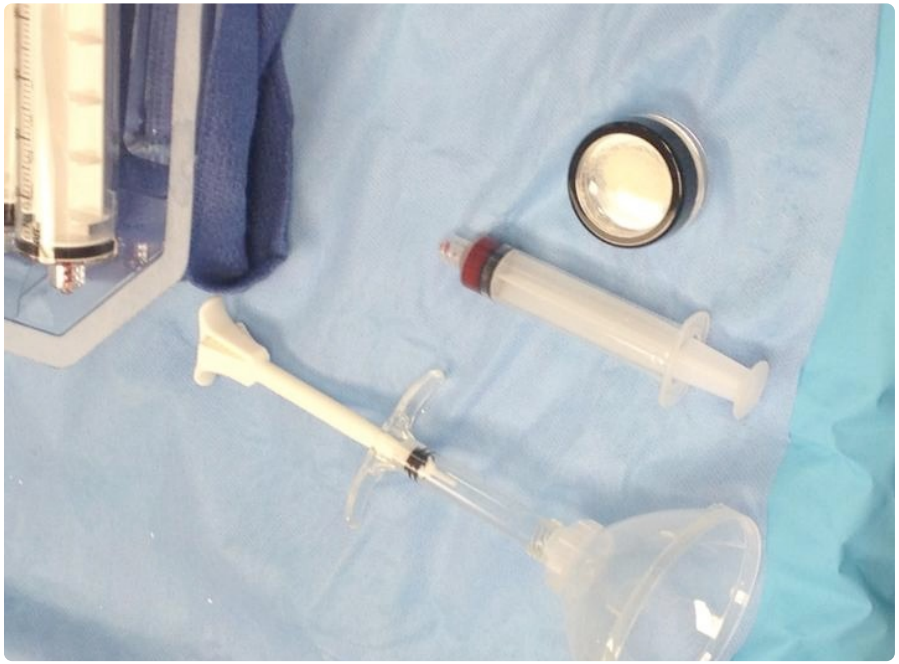
A variety of scaffolds have been used with some success in osteochondral lesion treatment in the knee, including protein-based scaffolds (fibrin, collagen, gelatin), carbohydrate-based scaffolds (agarose, poly-L-lactic acid and polyglycolic acid, hyaluron, alginate, chitosan and chitin), synthetic or artificial polymer-based scaffolds (hydroxyapatite, polyethylene glycol), and combined scaffolds (MaloRegen, TruFit, Bilayered Collagen I/III Scaffolds, Cartipatch, Chondrotissue, Gelrin C, Bioseed C, BST-CarGel, ChonDux, Cartilage Autograft Implantation System).

OPERATIVE TECHNIQUE

Preparation of BioCartilage®

The syringe cap from the mixing and delivery syringe should be removed and a funnel is firmly placed onto the end of the syringe (Figure 7.17). BioCartilage® is then emptied from its container into the funnel and PRP is then introduced into the syringe in a 1:1 ratio to the BioCartilage® scaffold. The syringe cap and luer cap are then put back on the syringe. The pushrod on the mixing syringe is then removed from the mixing element and the BioCartilage® and PRP are mixed by pushing and pulling the mixing element back and forth while rotating the syringe. Once the solution has been thoroughly

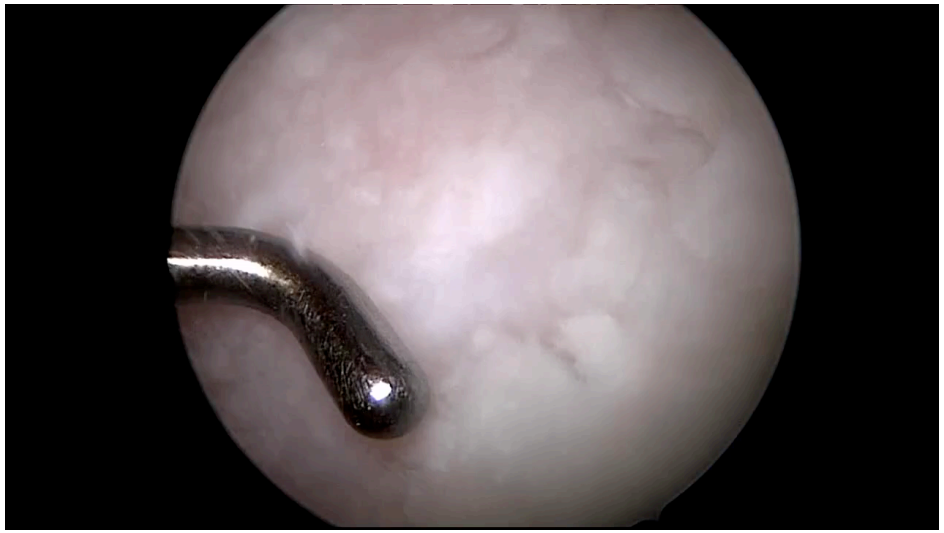
FIGURE 7.17 The mixing and delivery syringe and funnel required to prepare the BioCartilage® mixture.



mixed, the mixing element is pulled back to its starting position and the pushrod is put back into the mixing element converting the construct to a standard syringe mechanism. A delivery needle is then applied to the end of the syringe and the BioCartilage® mixture is dispensed into a clean dry and meticulously prepared defect with an obturator.

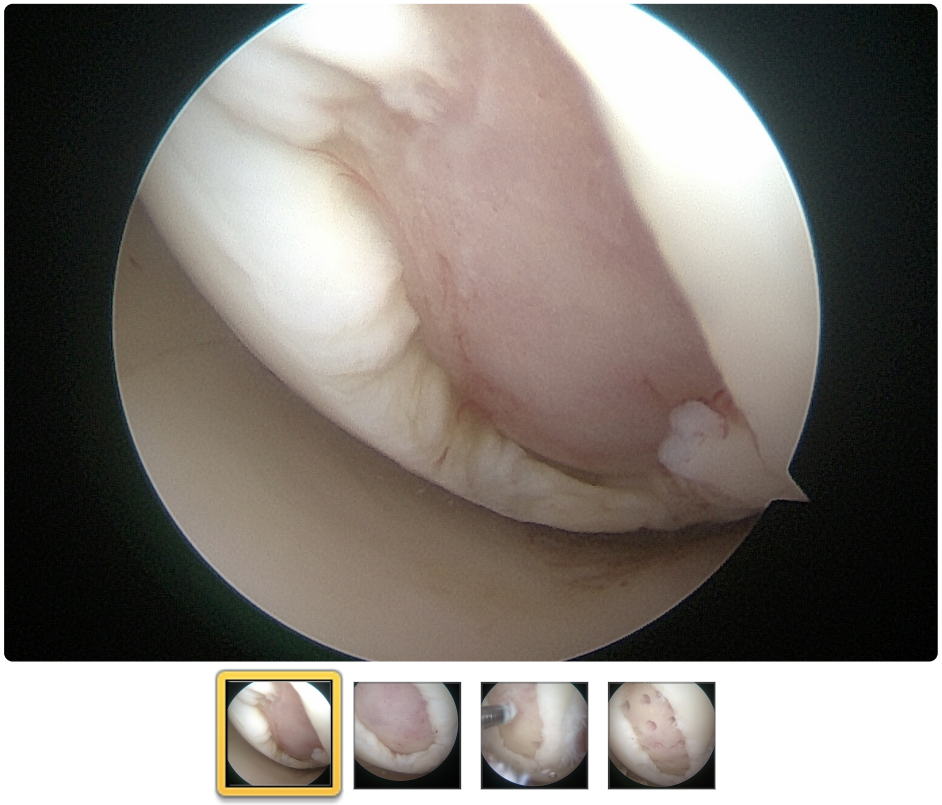
Surgical technique (Video 7.8)
Preoperative antibiotics are administered and standard sterile prepping and draping are performed. Limb exanguination is performed with an Esmarch bandage and the tourniquet is inflated before diagnostic knee arthroscopy is performed. Any concomitant pathology is treated and the defect is visualized. An arthroscopic shaver is used to debride the articular cartilage defect to obtain a stable border with vertical margins. A ring curette is then used to achieve vertical margins and to debride the calcified cartilage layer at the base of the defect. Marrow stimulation is performed via standard microfracture techniques using either a standard microfractue awl or a PowerPick (Arthrex, Naples, Fl, USA). The preference of the senior author (BJC) is to use power to perform the microfracture technique given the reduced impact on the subchondral bone and subsequent reduction in the "fracture" response within the defect (Gallery 7.14).
If the lesion is easily accessible arthroscopically, the BioCartilage® mixture may be administered via arthroscopic means. In this case, all arthroscopic fluid should be aspirated and the defect should be debrided with pledgets.
The inflow on the scope should be turned off at this point to ensure that the knee stays dry. A Gemini cannula (Arthrex, Naples, Fl, USA) is placed through the portal overlying the lesion and the scope is inserted through the cannula before applying distraction to the soft tissues to improve visualization.
BioCartilage® can then be delivered to the defect using a Tuohy delivery needle (Arthrex, Naples, Fl, USA) through another portal.
An Articulating Paddle Elevator (Arthrex, Naples, Fl, USA) is used to smooth the BioCartilage® inside the defect so that it is slightly recessed below the surface of the surrounding cartilage. A dual lumen applicator is then introduced through the same portal via which BioCartilage® was applied to facilitate placement of fibrin glue over the defect.
A single lumen needle should not be used as this will result in premature activation of the fibrin before application is complete. Care should also be taken to apply only a thin layer of fibrin glue in order to avoid making the overall construct proud. The knee should then be kept still for five minutes while waiting for the fibrin glue seal to set.

VIDEO 7.8 Surgical techinique



Gallery 7.14

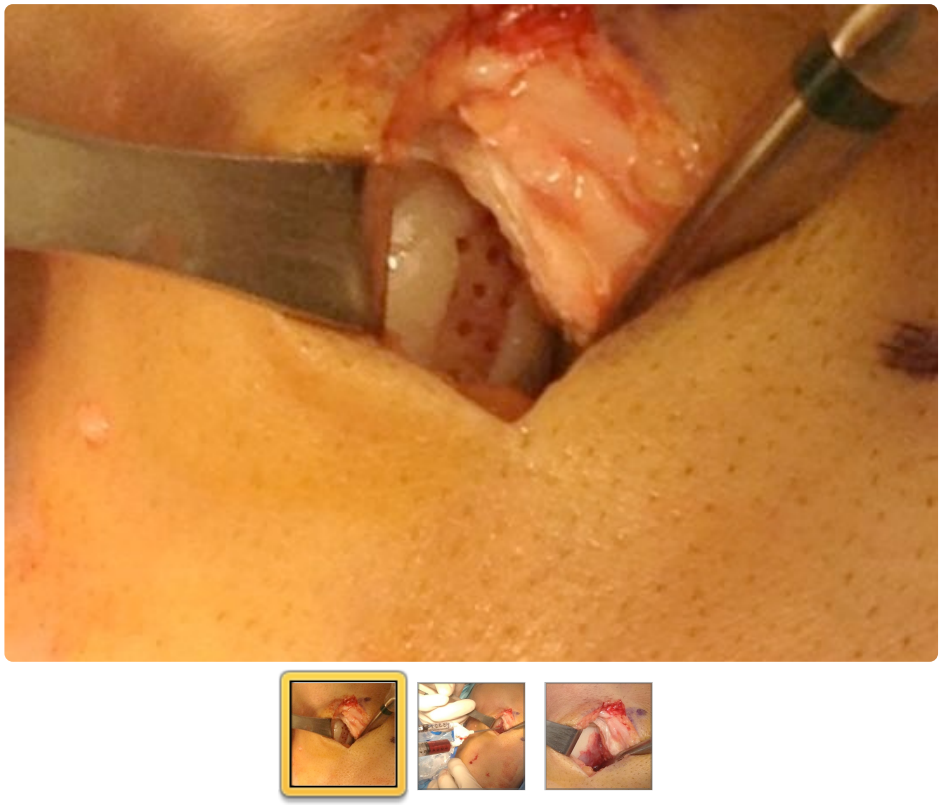
A) View of an 18 mm x 18 mm chondral defect on the medial femoral condyle of the left knee.



If defects are not accessible arthroscopically, a limited arthrotomy may be made overlying the defect once microfracture is complete. The defect is thoroughly dried and the BioCartilage® mixture can be placed into the defect using either the syringe or an obturator. As mentioned above, the mixture is smoothed so that it sits recessed compared to the surrounding cartilage and fibrin glue is placed over the top of the scaffold complex using a dual lumen applicator (Gallery 7.15).

Gallery 7.15

A) A limited medial arthrotomy is performed to provide direct access to the defect on the medial femoral condyle for BioCartilage® implantation.



ALTERATIONS TO THE NORMAL POSTOPERATIVEREHABILITATION PROTOCOL

In general, standard postoperative protocols can be followed, as per post-microfracture knee surgery. Expert opinion recommends that the postoperative patient be kept non-weight bearing in a knee immobilizer locked in extension for several days in order to allow the stimulated bone marrow elements and MSCs to fully saturate the BioCartilage® mixture and form a stable clot. Subsequently, the use of the brace in tibiofemoral lesions is dictated by the surgeon's experience and choices, however protected weight bearing should continue for at least six weeks. For patellofemoral lesions, the brace is maintained with restricted knee flexion with full weight bearing allowed initially in extension for two weeks followed by unlocking of the brace to 45-60 degrees, for ambulation, for an additional four weeks. When possible, the senior author (BJC) utilizes continuous passive motion (CPM) for up to six hours per day at one cycle per minute. The total initial postoperative protection phase lasts for six to eight weeks, at which point full weight bearing (tibiofemoral) is allowed and the brace and CPM are discontinued (38).

TAKE-HOME MESSAGES

- BioCartilage®, which has an extended shelf life (five years), offers a relatively low-cost arthroscopic option for the treatment of chondral lesions for which microfracture alone is unlikely to provide a definitive long-term treatment.
- Early ongoing in vivo equine studies comparing isolated microfracture to the BioCartilage® procedure have found the latter to produce statistically significant improvements in chondral defect fill and macroscopic appearance at up to 13 months post-procedure, but definitive results are pending.
- Like the aforementioned microfracture augmentation procedures, BioCartilage® can potentially be used in lesions within virtually any diarthrodial joint.
- It is possible that, due to the improved structural properties and similarity to hyaline cartilage of the repair tissue generated as a result of its use, the indications for BioCartilage® may in the future expand to include larger lesion sizes in older patients, and may hopefully provide longer-lasting benefits (38).
- Further high-level studies with longer follow-up are ongoing to better characterize the use of this novel cartilage repair technique.

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