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Operative Techniques in

Sports Medicine

BioCartilage: Background and Operative Technique

Geoffrey D. Abrams, MD,[*] Nathan A. Mall, MD,[†] Lisa A. Fortier, PhD,[‡] Brandon L. Roller, MD,[§] and Brian J. Cole, MD, MBA[*]

Damage to articular cartilage is prevalent and causes significant morbidity. A common initial treatment for focal, full-thickness articular cartilage defects is microfracture, which has been shown to have good to excellent short-term outcomes in appropriately indicated patients. Unfortunately, microfracture leads to the growth of fibrocartilage repair tissue rather than native hyaline-like cartilage and is less durable at longer-term follow-up. Efforts to augment repair and restore hyaline-like cartilage have led to the use of 2-stage procedures, such as autologous chondrocyte implantation, allografts, harvesting of autograft tissue, or complex scaffolds. An effective and reliable simple, single-stage method of cartilage restoration is needed. BioCartilageTM is a new product containing dehydrated, micronized allogeneic cartilage and is implanted with the addition of platelet rich plasma over a microfractured defect. Platelet rich plasma is shown to potentiate the cartilage repair process and is chemotactic for mesenchymal stem cells introduced following the microfracture procedure. BioCartilageTM is also an appropriate allogeneic cartilage scaffold with the proper biochemical makeup, including Collagen Type II and cartilage matrix elements. The procedure can be performed as a single-stage procedure with instrumentation and skill level consistent with standard microfracture techniques. The use of BioCartilage may create more hyaline-like tissue at the repair site vs microfracture alone.

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Damage to articular cartilage is a common problem.[1-3] In one investigation, chondral lesions were identified in more than 60% of approximately 30,000 knee arthroscopies with more than 40% judged as Outerbridge grade III or greater.[4] Unfortunately, adult cartilage has little to no regenerative capacity because it is aneural, avascular, and hypocellular.[5,6]

Current treatment options for injured articular cartilage fall into 2 broad categories: (1) interventions aimed at stimulating native cells to differentiate and proliferate, and (2) procedures focusing on direct replacement of lost or damaged tissue.[7] Surgical resurfacing techniques such as subchondral drilling,[8] abrasion arthroplasty,[9] and microfracture[10,11] are undertaken to access mesenchymal cells that are present within the subchondral bone. The most utilized of these techniques currently is microfracture, which was initially reported in the veterinary literature[12] and then introduced soon thereafter by Steadman et al. in the orthopaedic realm.[13]

Microfracture is popular as it is a single-stage, relatively straightforward procedure that can be utilized for the treatment of cartilage defects. Unfortunately, the repair tissue achieved with this technique alone remains nonhyaline in nature and lacks the overall structure, mechanical properties, and durability of a normal articular cartilage.[14] Xing et al. reported that fibrocartilage-like tissue was mostly seen in their microfracture group with poor Safranin-O and collagen type II staining, both markers for hyaline cartilage.[14]

This difference in structure, and therefore function, between the fibrocartilage-like regrowth following microfracture and native hyaline cartilage likely accounts for the clinical results following microfracture procedures. In a study involving players in the National Basketball Association, Namdari et al. found that 8 of 24 (33%) were not able to return to play following microfracture for symptomatic chondral defects of the knee.[15] Of those players that were able to return to play following microfracture, a significant decline in points per game was noted. Another investigation in high-impact athletics

*Rush University, Department of Orthopaedic Surgery, Chicago, IL.
†St. Louis Center for Cartilage Restoration and Repair, Regeneration Orthopedics, St. Louis, MO.
‡Department of Orthobiologics, Arthrex, Inc, Naples, FL.
§Department of Clinical Sciences, Cornell University, College of Veterinary Medicine, Ithaca, NY.
Address reprint requests to Geoffrey D. Abrams, MD, Rush University, Department of Orthopaedic Surgery, 1611 W. Harrison St, Suite 300, Chicago, IL 60612. E-mail: gabrams@gmail.com

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found that only 66% of athletes reported good or excellent results following microfracture in the knee. After an initial improvement following surgery, clinical outcome score decreases were observed in 47% of athletes and only 44% of patients were able to regularly participate in high-impact, pivoting sports.[16] In general, despite the variable initial and long-term success following microfracture, because it is a relatively safe, low-cost option, it remains the most common cartilage-repair procedure performed in the United States.[17]

Because of these mixed results, alternative approaches aimed at directly replacing damaged cartilage or bone or both have been investigated. These techniques include the use of scaffolds with or without growth factor impregnation or stem cells or both,[18] periosteal and perichondral grafts,[19,20] autologous chondrocyte implantation (ACI),[21] characterized chondrocyte implantation,[22] autologous osteochondral transplantation,[23] and allograft transplantation.[24] These techniques vary in their implementation, from use of natural or synthetic polymer scaffolds seeded with stem cells or growth factors or both and relying on in vivo chondrocyte differentiation to replacement of entire segments of diseased cartilage or bone or both with autograft or allograft transplantation.

Cartilage restoration techniques that aim to stimulate native cells to differentiate and proliferate fall into either single-stage or two-stage procedures. Among the single-stage procedures, Autologous Matrix-Induced Chondrogenesis has been used as a type of "enhanced" microfracture for larger defects. This technique involves standard microfracture with the use of a type I or III porcine collagen matrix (Chondro-Gide, Geistlich Pharma), which is able to contain the blood clot emanating from the subchondral bone.[25] BST-Cargel (Piramal Life Sciences, Laval, Quebec, Canada) is another single-stage enhanced microfracture product approved in Europe that contains a chitosan-based liquid scaffold intended to promote hyaline cartilage regeneration.

Two-stage procedures include ACI, characterized chondrocyte implantation, and autologous-seeded scaffolds. The first procedure involves an assessment of cartilage damage as well as a biopsy of cartilage from a non–weight-bearing area of the knee. These chondrocytes are then cultured for 4-5 weeks, generating between 5 and 10 million cells.[26] The cells are then placed in a liquid medium and, during the second procedure, placed within the cartilage defect, typically using a mini-open arthrotomy of the joint. The initial description by Brittberg et al. called for containment of the cells with a patch of periosteum harvested from the proximal tibia and was known as first-generation ACI.[21] Second-generation and third-generation ACI soon followed with the use of type I or III collagen membranes and then scaffolds (matrix-associated ACI), respectively, instead of a periosteal patch.[27-29]

Even with the use of autologous cells, the clinical results of ACI have been mixed. At 2-year follow-up, Knutsen et al. reported a lack of superiority for ACI over microfracture.[30] A report at 5 years for the same population of patients found no significant differences in clinical outcome between ACI and microfracture patients.[31] Others have reported improved results with the use of second-generation and third-generation techniques as compared with the periosteal patch.[32] Problems persist with ACI however, and include a low mechanical stability environment for chondrocyte growth,[33] uneven distribution of the cells,[34] and overgrowth.[35]

To ameliorate some of these problems, some clinicians utilize autograft osteochondral transfers or allograft osteochondral transfers or both. Recently, Krych et al. reported return to sport in 88% of recreational athletes and full return to preinjury level in 79% of those receiving a fresh osteochondral graft for femoral condyle cartilage defects.[24] In comparing ACI with autograft transfers for cartilage defects of the knee, Dozin et al. found no significant differences in the clinical outcomes of the 2 groups at final follow-up.[36] In addition to these results, downsides of these techniques include the need to wait for a size-appropriate donor graft to become available (allograft) or the requirement for a second-site osteochondral harvest (autograft) and its associated morbidity.[37]

As each of the aforementioned techniques has its limitations, there exists a clear need for the development of a minimally invasive, single-stage cartilage-restoration technique. There have been early reports on techniques and products that meet this description. The Cartilage Autograft Implantation System (CAIS) was a single-stage surgical procedure for the primary treatment of chondral lesions in the knee that was previously under a phase III clinical trial comparing it with microfracture. The technique calls for autologous hyaline cartilage to be harvested arthroscopically and then mechanically minced and placed on a synthetic, absorbable scaffold using fibrin glue. The lesion site is then prepared (without microfracture) and the implant, loaded with minced cartilage fragments, is placed into the lesion and fixed with synthetic, absorbable staples. Phase I and II clinical trials showed promising results compared with microfracture[38] but the FDA trial process was recently discontinued owing to challenges with enrollment and concerns that the cost of further investigation was in excess of the product's market potential.

Another single-stage cartilage-restoration technique involves the use of particulated (allograft) juvenile articular cartilage (DeNovo NT, Zimmer Inc, Warsaw, Indiana/ISTO Technologies Inc, St Louis, Missouri). This product is based upon the findings that human allogeneic juvenile chondrocytes have greater growth potential than adult chondrocytes.[39] As with CAIS, no microfracture is utilized in preparation of the defect. According to the manufacturer, DeNovo NT has shown promising results for treatment of chondral defects of the knee,[40] but peer-reviewed literature is not yet available as investigational studies are currently ongoing. The same company is also developing DeNovo ET currently, an investigational product consisting of a scaffold-free engineered tissue graft, which also contains juvenile chondrocytes.[41] However, this trial, much like the CAIS trial, has recently been suspended owing to concerns related to enrollment. No human clinical data is available yet on this product. Both CAIS and DeNovo ET require at least 3-5 years to navigate the regulatory process and would only be terminally approved if superiority is demonstrated compared with microfracture. In addition, the procedures would be performed through an open approach and likely be associated with relatively high resource intensity and financial burden.

Rationale for BioCartilage

The currently available cartilage-restoration techniques have mixed results in the literature (microfracture), require separate staged procedures (ACI), call for autograft harvesting and its associated morbidity (osteochondral transplantation), require a wait time for donor availability (osteochondral allograft), or do not take advantage of all potential autologous biological sources of regeneration through the use of platelet-rich plasma (PRP) or microfracture or both (CAIS, DeNovo).

BioCartilage (Arthrex, Naples, FL) is a unique new product containing dehydrated, micronized allogeneic cartilage and is implanted with the addition of PRP over a microfractured defect. Microfracture provides access channels for mesenchymal stem cells (MSCs) present within the subchondral bone to populate a scaffold that has been implanted over the prepared defect.[42] These mesenchymal cells are essential for the stimulation and propagation of chondrogenesis.[43] In addition, the use of PRP is beneficial owing to its anabolic, anticatabolic, and antiinflammatory factors.[44] When PRP is used in conjunction with microfracture in articular cartilage defects, potentiation effects with regard to chondral regeneration is seen.[45] Furthermore, when PRP combined with a collagen membrane or matrix was placed in the presence of a microfractured area, hyaline-like tissue formation was enhanced.[46] This supports previous findings of the ability of dehydrated, micronized allograft cartilage tissue to serve as a scaffold to promote chondrogenesis.[47,48]

In a 14-month preclinical feasibility animal study, International Cartilage Repair Society grade 3 cartilage defects 1.5 cm in diameter and 10 mm in depth were created on the femoral condyle of baboons. The control group included no treatment for the cartilage defect, whereas the experimental group received BioCartilage. Complete macroscopic regeneration of the cartilage over the chondral lesion was found at 9 weeks and beyond in 90% of experimental subjects while all control subjects maintained an open osteochondral lesion (data on file, University of Miami Tissue Bank, Miami, FL). No adverse events or immunologic reactions were noted. In addition, an equine study is currently underway to examine the macroscopic and histologic outcomes in surgically created defect treated with microfracture with and without the addition of BioCartilage.

It should be noted that there are no human clinical outcomes data available for the use of BioCartilage at this time. Data regarding results of BioCartilage use in human subjects are limited to expert opinion, but an overall beneficial effect has been observed in more than 100 patients implanted with BioCartilage with no adverse events related to this adjunct. Controlled trials examining outcome differences between standard microfracture vs BioCartilage (with its corresponding application technique) are currently underway.

Potential Uses

BioCartilage can be used in any situation where microfracture is indicated. Current indications for microfracture vary slightly,

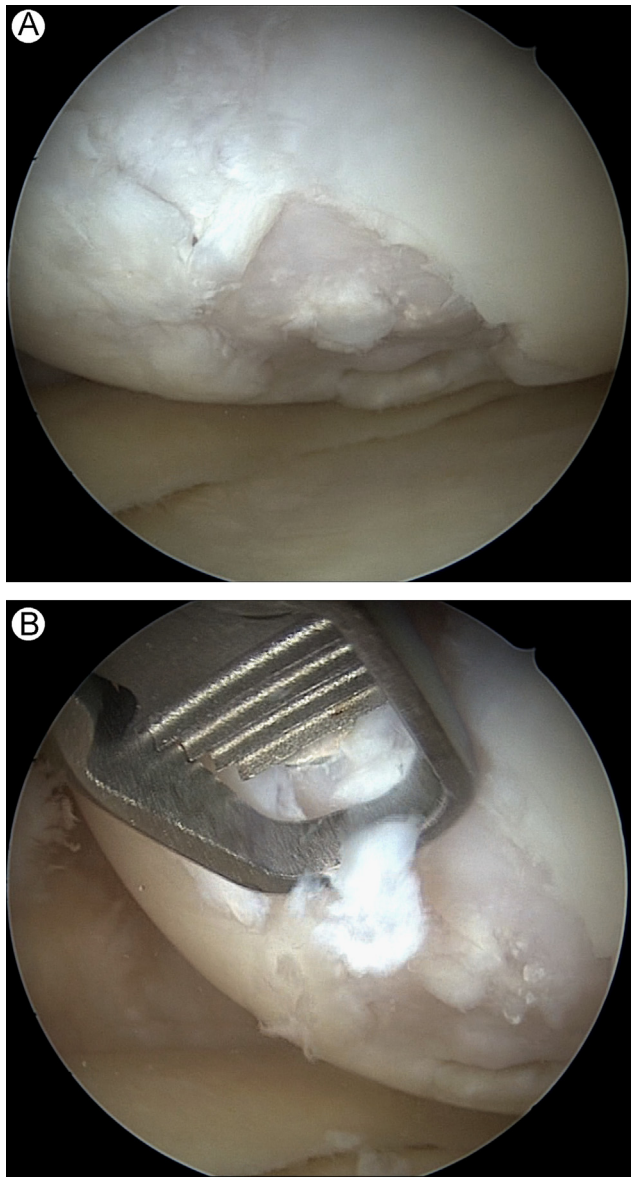

Figure 1 (A) Arthroscopic picture of a full-thickness cartilage defect of the medial femoral condyle before defect preparation and treatment with BioCartilage. (B) Arthroscopic picture of the medial femoral condyle lesion in (A) undergoing defect preparation with an arthroscopic biter to establish vertical walls around the defect.

but current literature suggests improved results in patients with body mass index less than 30 kg/m^2,[49] dimensions less than 2-4 cm^2,[31,50,51] symptoms for less than a year,[50,52] and when used as a primary or index procedure.[16,50] Lesions that are not contained are not appropriate for microfracture or microfracture with BioCartilage. With improved structural properties that more closely resemble hyaline cartilage, microfracture indications may be expanded when combined with BioCartilage. However, without clinical data to support this, BioCartilage currently should only be used in patients in whom microfracture is indicated until this hypothesis is proved or disproved with clinical studies.

BioCartilage can be used arthroscopically when visualization is possible with dry arthroscopy. Notably, as with any cartilage

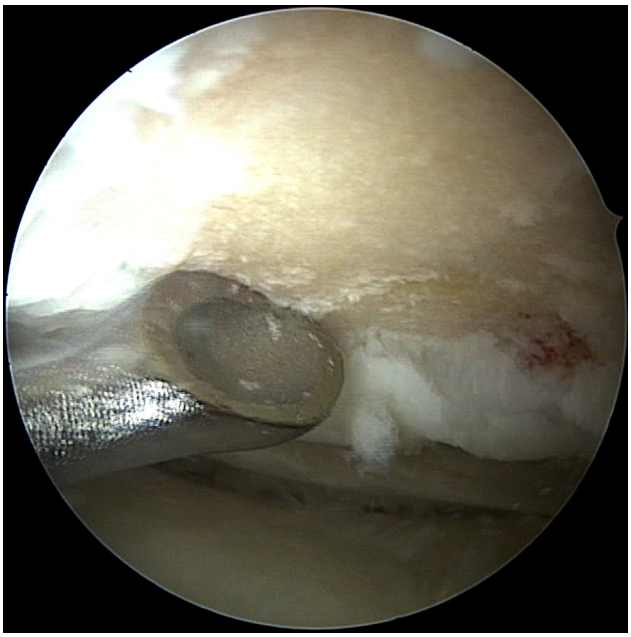

Figure 2 Picture demonstrating removal of the calcified cartilage layer within the defect with the use of a curette. (Color version of figure is available online.)

repair technique, recognizing and treating co-morbidities such as malalignment, meniscal deficiency and ligament disruption is paramount to achieving a successful outcome. However, this is only possible in areas that would allow gravity to keep the BioCartilage in the defect until fibrin glue can be applied. Areas amenable to this include the tibial plateau, talus, distal radius, and some femoral condyle defects. If a thicker mixture is desired by using less of the liquid portion (PRP, bone marrow aspirate, whole blood, etc.), treatment of other defects with arthroscopic techniques may become more feasible in areas such as the humeral head or glenoid defects, femoral head and acetabular defects, most femoral condyle lesions, and some radial head or capitellar defects. This greatly improves the treatment options for many of these defects, as cartilage defects in some of these areas can more easily be addressed arthroscopically. For example, when treating lesions of the acetabulum and most femoral head lesions, a surgical hip dislocation may be required to access the defect. Glenoid cartilage defects, if treated open, either require violation of the subscapularis through a subscapularis split approach or complete takedown of the tendon to gain access to the glenoid. Similarly, access to talar lesions often requires a medial or lateral malleolus osteotomy, which can lead to nonhealing wounds or nonunions of the osteotomy site.[53] Some posterior capitellar defects must be addressed open through an olecranon osteotomy. Distal radial defects often are difficult to access as well, requiring extreme flexion or extension of the radiocarpal joint to be able to visualize the defect. This may still not afford the needed angle to access the joint when treating the lesion with various cartilage restoration techniques.

Microfracture in the hip has had some success, with several studies noting improved outcomes,[54] higher postoperative activity level,[55] and a mean 91% fill of the defects at second-look arthroscopy.[56] Capitellar microfracture has achieved good results as well, but in case reports and small case series.[57,58] Microfracture used in the glenoid produced a reduction in pain and improvement in functional outcome scores at a mean of 28 months.[59] A recent systematic review of results following microfracture for osteochondral lesions of the talus yielded an improvement in functional scores and good to excellent results in 80% of patients.[53] Despite good results in 80%, there is certainly room for improvement, which may occur with more normal hyaline-like cartilage formation in the presence of a scaffold made from dehydrated, micronized allograft cartilage and PRP.

Surgical Technique

A tourniquet should be placed on the operative leg prior to prepping and draping. Standard diagnostic knee arthroscopy is performed to identify or confirm, or both, the presence of

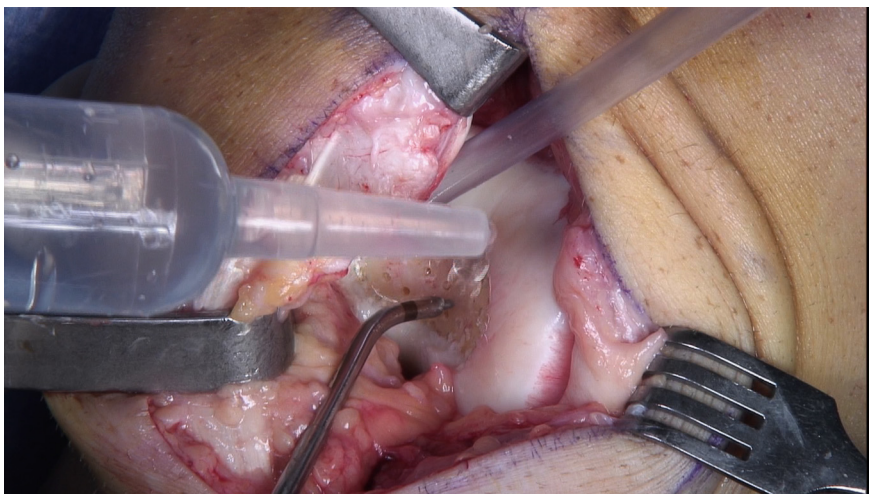

Figure 3 Image demonstrating the use of the PowerPick (Arthrex, Inc., Naples, FL) to create microfracture holes within the defect. Use of irrigation during this step of the procedure reduces thermal injury to the bone. (Color version of figure is available online.)

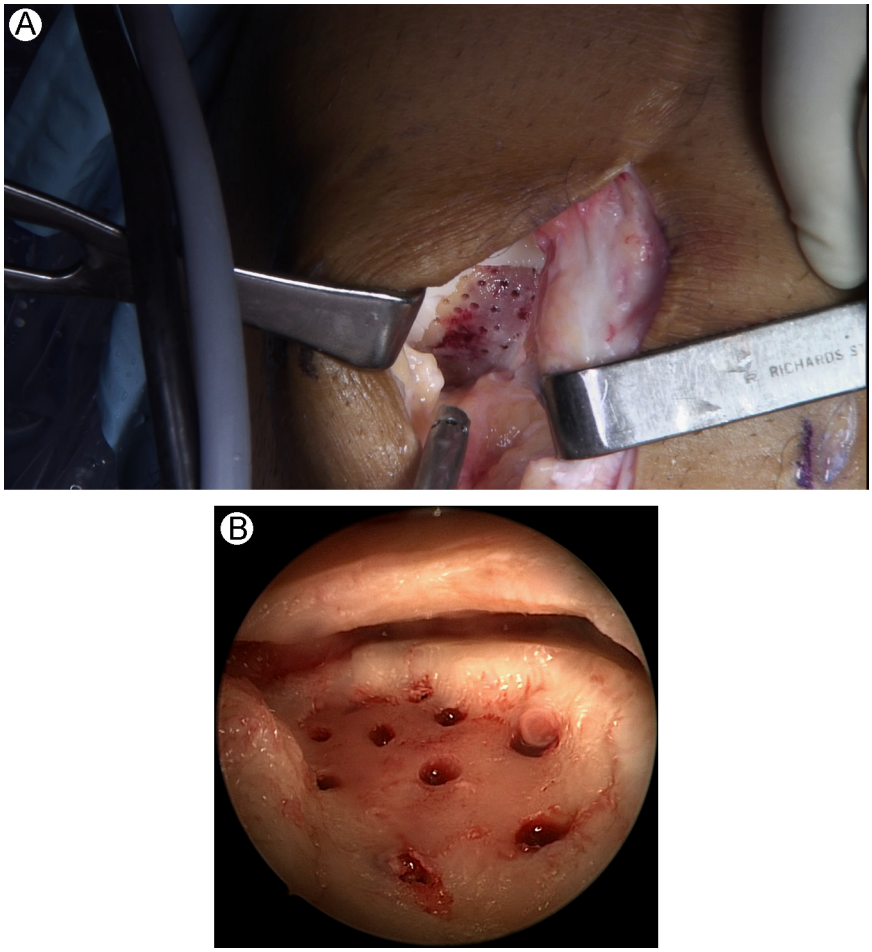

Figure 4 Image demonstrating defect following debridement and microfracture procedure performed through (A) mini-parapatellar arthrotomy to access the medial femoral condyle and (B) arthroscopic technique for treatment of a lateral tibial plateau lesion.

lesions that may be amenable to treatment with BioCartilage. If the decision to use BioCartilage is confirmed, PRP would be needed. It is advisable to have the PRP system of choice available in the room at the time of surgery and to request anesthesia to draw blood on the patient as early as possible.

Defect Preparation

First, use a shaver or biter to debride the defect (Fig. 1 A and B), and then a curette to remove the calcified cartilage layer and establish 90° margins around the periphery of the defect (Fig. 2). Defect wall preparation can also be facilitated with the use of a no. 15 blade to trim loose cartilage edges. The vertical walls are important as they serve to contain the BioCartilage following placement. This step may be done arthroscopically or through a mini medial or lateral parapatellar arthrotomy depending on surgeon preference and size of the lesion. Next, microfracture the defect using a mechanical awl or a PowerPick (Arthrex, Inc, Naples, FL) to minimize the consequences of subsequent fracture biology (Fig. 3). Irrigation should be utilized during this process to minimize heat injury to the bone. Microfracture holes should be approximately 2-3 mm apart and care should be taken so that one hole does not break into another and damage the subchondral plate (Fig. 4). After

Figure 5 Picture demonstrating the process of mixing the BioCartilage (bottom) with the previously prepared PRP.

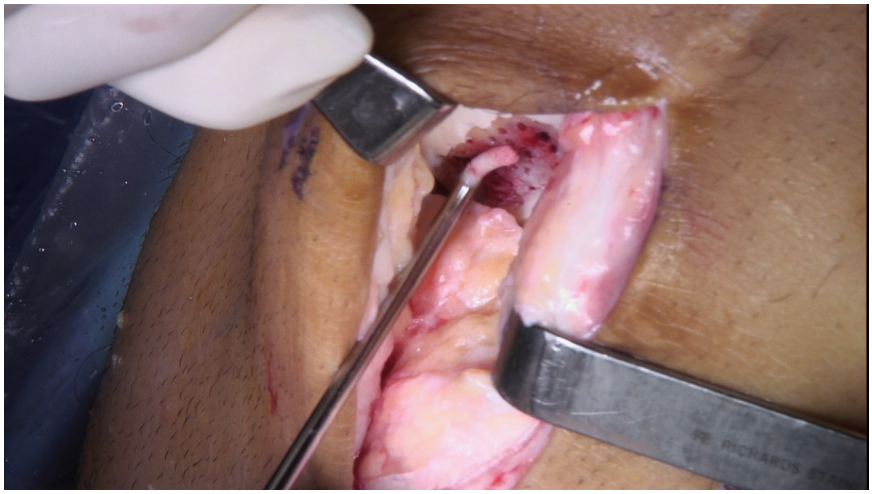

Figure 6 Picture showing injection of the BioCartilage and PRP mixture onto a microfracture prepared defect of the medial femoral condyle.

microfracture has been completed, turn off the pump and use suction to removed fluid from the joint if the procedure is being performed arthroscopically.

BioCartilage Preparation

Place the 1 mL of prepackaged BioCartilage into the Arthrex Mixing and Delivery Syringe. Next add 1 mL of previously prepared PRP. The syringe has a mixing element that allows the allograft powder and PRP liquid to be mixed together into a homogeneous mixture. The syringe can then be used to assist with delivery (Fig. 5).

BioCartilage Paste Application

We recommend inflation of the tourniquet for the BioCartilage application as a dry defect bed is critical. The defect should also be dried of any previous arthroscopic fluid which may still be present. If an arthroscopic technique would be utilized for application, a cannula (Arthrex Gemini cannula, Arthrex, Naples, FL) is placed into the viewing portal. The wings on the cannula function to distract the synovium away from the defect. This is helpful as there is no joint distraction via fluid pressure at this stage of the procedure. A Tuohy needle is then introduced into the joint. Sometimes it may be necessary to create an accessory portal with the Tuohy needle to achieve the proper orientation with respect to the cartilage defect. Place one of the suction tubings on the end of the Tuohy needle and use this to help dry the defect bed of any excess fluid. Next, insert a pledget to help further dry the defect bed.

The mixing and delivery syringe containing the BioCartilage-PRP mixture is attached to the Tuohy needle after the defect is thoroughly dried. The mixture is injected into the Tuohy needle and then the needle is removed from the syringe and the obturator is inserted into the back end of the needle. Using the portal with the Gemini cannula as the viewing portal, place the Tuohy needle in the previously identified portal and guide the needle over the defect. Inject the BioCartilage paste material into the microfractured defect (Fig. 6). The amount injected should be just enough to fill the defect to a point just

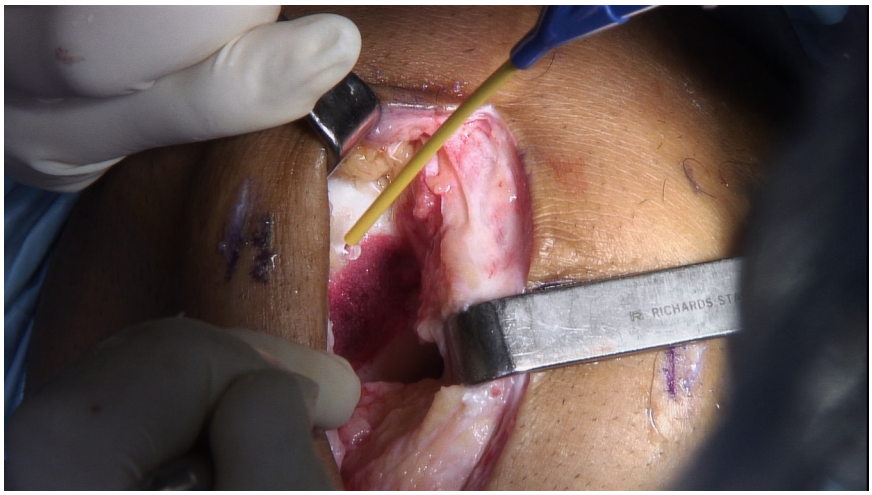

Figure 7 Image demonstrating the application of fibrin glue sealant following placement of the BioCartilage and PRP mixture to a defect on the medial femoral condyle.

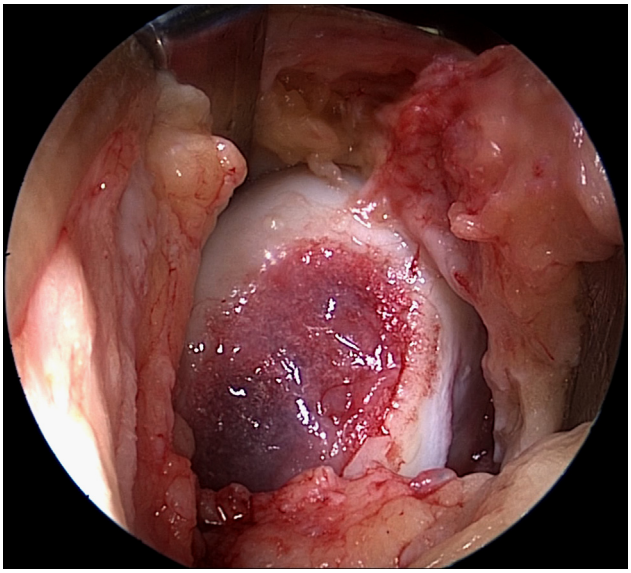

Figure 8 Final image of a prepared defect of the medial femoral condyle using BioCartilage after drying of the fibrin glue.

underneath the surrounding cartilage margin. A Freer elevator should be used to smooth out the BioCartilage over the defect. Fibrin glue is then dripped over the defect and neighboring cartilage to create a seal (Fig. 7). Allow the fibrin glue to dry for 5 minutes (Fig. 8). Lastly, remove all instrumentation and cannulas and apply a compressive force to the knee so that the defect may be contoured against the opposing articular surface.

Postoperative Protocol

A postmicrofracture protocol is utilized. Patients are kept to strict toe-touch weight bearing for 6 weeks with the use of crutches. For patellofemoral lesions, we allow full weight bearing in extension with limits in flexion for the first 6 weeks to avoid overload of the healing defect. Notably, most patella lesions are treated with a concomitant tibial tubercle osteotomy and thus, protected weight bearing for 6 weeks is advised to avoid a tibia fracture. It is common practice to delay motion for approximately 2-5 days depending upon surgeon preference to allow the bone marrow elements to fully infiltrate the BioCartilage mixture and form a stable, resilient clot. When available, we utilize continuous passive motion for 6 weeks for up to 6 hours per day.

Common Questions Regarding BioCartilage

- Q: Why do you feel it is important to augment the microfracture procedure?
- A: Several new technologies have focused on improving the outcomes of microfracture beyond what we have seen in the literature. Unfortunately, the regulatory burden that nonallograft and biologic therapies must overcome has virtually halted the emergence of new solutions for cartilage repair. There are more than 125,000 microfracture procedures performed annually, yet the results remain mixed and often, short lived. Thus, harnessing the relative simplicity of microfracture and promoting stem cell recruitment with the addition of a bioactive scaffold provides a legitimate opportunity to improve outcomes for our patients.
- Q: What intrigued you about utilizing a technology that does not contain live cells and instead functions purely as a scaffold?
- A: Microfracture, when technically well performed, has profound potential. The technique requires that we create vertical walls surrounding the defect in an effort to help the defect better "shoulder the load." Completely eliminating the calcified layer is also critical to promote the development of adherent, robust fibrocartilagenous repair tissue. Atraumatic perforations created by the Power Pick minimize the "fracture" component (and the associated negative effect that otherwise occurs with the biology of fracture healing with stiffening of the subchondral plate) provide anchor points for fibrocartilage repair tissue and access to MSCs within the bone marrow. BioCartilage is a conductive scaffold with natural cartilage proteins native to articular cartilage with the added advantage of an inductive effect through active proteins and the addition of PRP. Ample in vitro and early in vivo evidence exists supporting the positive effects of these substrates both individually and collectively.
- Q: When would you utilize BioCartilage over other types of cartilage procedures?
- A: The optimal-sized defect treated first-line with microfracture typically includes small to medium-sized defects. BioCartilage as an adjunct to microfracture makes intuitive sense given the variable results of microfracture alone. Osteochondral allograft transplantation remains an excellent option when the subchondral bone is involved especially for larger defects.
- Q: Do you come across lesions that you did not expect to treat where BioCartilage has been utilized?
- A: Clinicians should always be aware of the possibility that a cartilage defect would be appreciated at the time of arthroscopy and that it might be determined to be the source of the patient's symptoms, despite it not being objectively appreciated from preoperative assessments (magnetic resonance imaging, prior surgical findings, etc.). Thus, having a relatively low-cost arthroscopic option with an extended shelf life (5 years) is appealing as long as the patient is adequately consented preoperatively.
- Q: When performing a BioCartilage procedure, are there any technique pearls you really focus on?
- A: Our experience in large animal studies and initial clinical utilization of BioCartilage has helped to identify several pearls. A no. 15 scalpel is used to delineate the defect in the initial preparation of the vertical wall. A small ring curette and arthroscopic basket is useful for further delineation. It is critical to violate and remove the

calcified layer without macroscopically disrupting the subchondral plate. The objective is to get the bone to "pink up" following complete preparation. An arthroscopic shaver on forward or reverse is also useful for this purpose. Switching portals to better access different portions of the lesion is important. I prefer the Power Pick over standard arthroscopic awls as it creates a short, uniform diameter hole that is less atraumatic and minimizes crack propagation at the edges of the hole. When mixing the micronized allograft cartilage with PRP, we recommend a 1:1 ratio. However, if the paste is too dry or difficult to eject from the catheter, it is occasionally helpful to add a very small amount of additional PRP to improve the handling properties. The bed of the defect should be as dry as possible and using a cannula to pass neuropatties or Q tip–type swabs along the base of the defect to dry it is helpful. Placing the patient in some degree of Trendelenburg during positioning can eliminate the effects of gravity. It is best to underfill the defect slightly to avoid contact with opposing surfaces. Prior to fibrin glue placement, it is helpful to dry the surrounding native articular cartilage edges. Finally, when applying the fibrin glue, only add enough to the construct to make it flush with the surrounding articular surface rather than leaving it proud. Wait a full 5-7 minutes before ranging the joint. Use a sharp instrument (scalpel, basket hand instrument) to get rid of excess fibrin that is not relevant to the final construct.

- Q: When you use BioCartilage, does your postop rehab protocol change?
- A: Standard protocols described for microfracture surgery are followed. Occasionally, the patient is placed in a knee immobilizer locked in extension for at least 48 hours before beginning continuous passive motion to allow MSCs and bone marrow elements to fully infiltrate the BioCartilage mixture and form a stable, resilient clot. Notably, heel-touch weight bearing may be used for most tibiofemoral lesions without the use of a brace. For patellofemoral lesions, full weight bearing may be allowed in a brace. Continuous passive motion use is encouraged for a total of 6 h/d for at least 6 weeks. Higher degrees of flexion are initially prohibited for patellofemoral lesions, but full range of motion is allowed for tibiofemoral lesions. Total weight-bearing protection for tibiofemoral lesions ranges from 6-8 weeks.

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