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Enhanced Marrow-Stimulation Techniques

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CURRENT PROCEDURAL TERMINOLOGY CODE	
29879	Microfracture, drilling, abrasion

Articular cartilage defects of the knee are challenging clinical treatment problems. Articular cartilage lesions are common,[1-3] with one report identifying chondral lesions in more than 60% of 30,000 adults undergoing knee arthroscopy, 40% of which were Outerbridge grade III or IV.[4] Although the natural history of these lesions is not entirely understood, these defects may lead to degenerative osteoarthritis, knee pain, and ultimately loss of function.[5] This issue is complicated because not all articular cartilage lesions generate symptoms. Even full-thickness defects found incidentally on advanced imaging studies, during diagnostic arthroscopy, or during surgery for other pathology (ie, anterior cruciate ligament reconstruction[3,6]) may be asymptomatic. It is critical for the surgeon to distinguish between those lesions that are symptomatic and those that are simply incidental. As noted recently by McCormick et al,[7] articular cartilage surgical procedures in the knee are being performed at a growing rate, with an annual incidence growth of 5% in the past 5 years. Of these procedures, microfracture remains the most common articular cartilage repair technique performed in the United States.[8] As such, understanding the indications for cartilage surgery and selecting the appropriate patient for the appropriate procedure are critical.

Once deemed a lesion that requires surgical treatment, the articular cartilage lesion now faces various options. Currently, evidence supporting any single "best" option is limited.[9,10] For appropriate patients, marrow-stimulation techniques, such as microfracture (or subchondral Pridie drilling or abrasion arthroplasty), have historically produced reliable short-term clinical outcomes with improvement in pain control and return to function.[8,11-15] However, the durability of sustained clinical improvement beyond 2 years after microfracture is variable.[16,17] Recent technological advances have attempted to improve standard techniques by using matrices and scaffolds to stabilize the mesenchymal clot produced by marrow stimulation, and to improve mesenchymal stem cell (MSC) differentiation into more hyaline-like articular cartilage. These procedures fall into either single-stage or 2-stage procedures. Single-stage techniques include autologous matrix-induced chondrogenesis (AMIC)[18-21] and enhanced marrow-stimulation products such as Biocartilage[17] (Arthrex Inc), BST-CarGel[22,23] (Piramal Life Sciences, Bio-Orthopaedics Division), and GelrinC[24,25] (Regentis Biomaterials Ltd).

The aim of traditional marrow stimulation in the treatment of full-thickness articular defects is to "fill" the chondral

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defect with an MSC superclot.[26] Following penetration of the subchondral bone using an awl, pick, or drill, mesenchymal elements enter the bed of the lesion and form a clot. Although unable to recreate the normal hyaline cartilage structure of native articular cartilage, the marrow-derived clot ultimately forms a primarily fibrocartilage repair tissue. This tissue ideally remains within the lesion's vertical walls, "filling" the defect. Augmentation to traditional microfracture may use matrices and scaffolds to stabilize the mesenchymal clot produced by marrow stimulation, as well as to improve MSC differentiation into more hyaline-like articular cartilage. Unlike 2-stage cartilage restoration procedures such as autologous chondrocyte implantation, enhanced microfracture techniques are performed in the same general way as traditional microfracture, using a single-stage, minimally invasive approach.

AMIC was first described by Behrens and colleagues,[18-21] and combines microfracture with fixation of a commercially available porcine collagen (type I/III) matrix (Chondro-Gide, Geistlich Pharma AG). An aluminum template can be used to create the appropriate matrix size. The actual matrix is created by centrifuging the patient's own blood and mixing the thrombin produced by centrifugation with allogeneic fibrinogen from commercially available fibrin glue. The purpose of the matrix is to cover the mesenchymal clot, while allowing the MSCs to differentiate into chondrocytes.

BST-CarGel[22,23] is a bioscaffold composed of a soluble biopolymer containing chitosan. Chitosan is a glucosamine polysaccharide derived from the exoskeleton of crustaceans, and is an ideal scaffold owing to its availability, biocompatibility, biodegradability, adhesive properties, and low toxicity. As described by Stanish and colleagues,[22] BST-CarGel is made by dissolving chitosan into an aqueous glycerophosphate buffer and combining the product with fresh, autologous whole blood, which is then inserted via a separate arthrotomy into the lesion bed following microfracture.

GelrinC[24,25] is an investigational device not available for sale in the United States or Israel, where it is manufactured. The product itself is a biosynthetic hydrogel composed of polyethylene glycol diacrylate and fibrinogen that, after exposure to ultraviolet light, becomes a semisolid material that integrates tightly with the surrounding tissue. Unlike the previous technique, GelrinC does not require a fibrin glue following application. After approximately 6 to 12 months following implantation, GelrinC degrades "in synchronization" with the development of "hyaline-like" cartilage tissue.

Indications and Contraindications

Enhanced microfracture techniques, including AMIC, BioCartilage, BST-CarGel, and GelrinC, can be used in the same patient population that would be indicated for traditional microfracture surgery. Patients with symptomatic, isolated, unipolar chondral or osteochondral defects (International Cartilage Repair Society [ICRS] grade 3) of the knee may be treated with advanced microfracture techniques. Lesions with subchondral bone involvement (ICRS grade 4) must be carefully evaluated, as significant bone defects may best be treated with a reconstructive technique such as osteochondral autograft transfer or osteochondral allograft transplantation. Patients with pain localized to the lesion; mechanical symptoms including clicking, popping, catching, and/or locking of the knee; and swelling in the joint both at rest and with activity can be considered for cartilage repair and restoration procedures. Defects most appropriate for microfracture are those that are less than 2 to 4 cm^2 in size,[27-29] with normal surrounding articular cartilage. Patients with concomitant meniscal deficiency, ligamentous insufficiency, coronal plane malalignment, and/or patellofemoral maltracking should be counseled on the need for possible concomitant procedures (meniscal transplantation, ligamentous reconstruction, and osteotomy).[30]

Contraindications for advanced microfracture techniques are similar to contraindications for traditional microfracture and include bipolar, or "kissing," lesions underlying inflammatory arthritis, diffuse degenerative osteoarthritis, and untreated soft tissue (meniscus, ligamentous) deficiency as well as uncorrected malalignment. Bipolar lesions in particular, or those that occur on both surfaces within an articulation, should not undergo advanced microfracture, as these lesions are best treated with reconstructive procedures including osteoarticular transplantation in some cases, or more often, arthroplasty. A complete evaluation of the patient's symptoms, including the location and severity of symptoms as well as the functional demands and goals of the patient, should occur prior to deeming someone a candidate for advanced microfracture surgery. Patients who are unwilling to comply with the postoperative rehabilitation procedures and potential activity limitations should not undergo microfracture.

Preference Card and Instrumentation

- 30-degree knee arthroscope system with 5-mm scope and arthroscopic pump
- Arthroscopic probe with calibrated 3-mm tip
- Arthroscopic instrument tray: biters, graspers
- Arthroscopic microfracture awls (power if using PowerPick)
- Motorized arthroscopic shaver: 3.5 mm
- Arthroscopic radiofrequency ablation device (optional)
- Trays/implants specific to the product being used

Pearls and Pitfalls

- Must appropriately indicate patients for procedure: isolated, full-thickness, unipolar defects (and correct concurrent pathology as needed: alignment, meniscus, ligament)
- Prepare defect adequately by removal of calcified cartilage layer and creation of surrounding vertical walls
- Be diligent with microfracture technique regarding hole depth and placement
- Follow manufacturer instructions regarding product preparation, including drawing peripheral blood if needed at the start of the case
- Allow the product to "sit" in the defect bed for the specific duration of time prior to moving the knee and closing the wounds

Surgical Technique

Diagnostic Knee Arthroscopy

The patient is positioned in the supine position on a standard operating table. Pending surgeon preference and any concomitant procedures to be performed (eg, osteotomy, ligament reconstruction, meniscal transplantation), the leg is placed in a leg holder with the foot of the bed dropped, or, alternatively, a lateral post is used with the foot of the bed intact. A tourniquet is placed on the thigh and is used at the discretion of the surgeon. This procedure can be performed under regional anesthesia (with or without sedation) or general anesthesia. The operative site is confirmed with a time-out procedure, the leg is prepared and draped in standard fashion, and diagnostic arthroscopy performed. Identification and characterization of the defect is performed to confirm the appropriateness of the lesion to perform advanced microfracture; this includes the ability to obtain vertical walls circumferentially after removal of all unhealthy articular cartilage, the integrity of the subchondral bone, and the ability to remove the calcified cartilage layer.

Defect Preparation

Preparation of the articular defect involves identification and removal of all loose, frayed, and degenerative surrounding articular cartilage with the use of arthroscopic shavers and curettes. Within the defect, the calcified cartilage layer should be removed, without disrupting the subchondral bone plate. Vertical walls of normal hyaline articular cartilage should be created using a curette as well as a no. 15 scalpel blade. Both the removal of the calcified cartilage layer and the creation of vertical walls surrounding the defect are absolutely critical. It can be difficult to visualize the difference between the calcified cartilage layer and the subchondral bone, and as such, tactile differences between the layer and the bone guide the dissection.[23] Next, the dimensions of the articular cartilage defect should be measured and documented. Based on the specific system used, the product is prepared, microfracture is performed, and the product is placed into the defect. The following sections will describe in detail how the above-mentioned techniques are employed. All techniques use 4 general steps, including (1) lesion preparation, (2) microfracture, (3) product/mixture preparation, and (4) product/mixture delivery. The microfracture technique has been discussed in more detail in Chapter 14.

Product Preparation and Application

Autologous Matrix-Induced Chondrogenesis[18-21]

Based on the template, the membrane is sized appropriately, taking care to avoid overstuffing and dislocation of

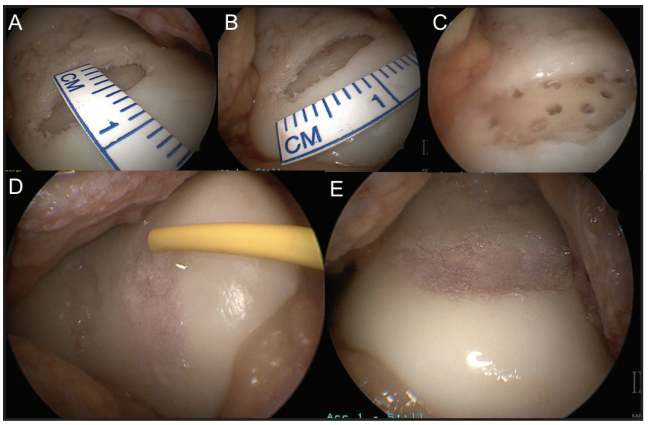

Figure 15-1. Intraoperative photographs of the right knee with a trochlear defect, demonstrating placement of BioCartilage into defect: (A) measurement of width of defect, (B) measurement of length of defect, (C) preprocedure microfracture preparation, (D) injection of BioCartilage, (E) implant in situ.

the product with postoperative movement. Microfracture is performed with awls or a 1.1-mm K-wire. Microfracture holes should be placed in standard fashion, 3 to 4 mm deep and 3 to 4 mm apart. If the K-wire technique is used, cold irrigation should be constantly applied to minimize heat injury to the bone and surrounding articular cartilage. Following microfracture, fibrin glue is applied with the collagen type I/III membrane attached. The fibrin glue can either be a commercially available, off-the-shelf (allogenic fibrin glue) product, or can be combined with the thrombin component of a sample of the patient's centrifuged blood (partially autologous fibrin glue). The collagen membrane must be placed slightly recessed within the defect, so that it does not displace with patient movement postoperatively.

BioCartilage[17]

For the BioCartilage technique, platelet-rich plasma (PRP) is placed into the defect, and as such, the surgeon's preferred PRP system should be available in the operating room at the time of surgery. Similarly, the surgeon should request that the anesthesia team draw the patient's peripheral blood for the PRP preparation early into the case to avoid untimely delays. Following defect preparation as described above, microfracture is performed using a mechanical awl, drill, or PowerPick (Arthrex Inc). If performed arthroscopically, the pump is turned off following microfracture to permit fat droplets to exude from the subchondral bone.

The prepackaged BioCartilage (1 mL) is placed into the designated mixing and delivery syringe, and 1 mL of PRP is added to the syringe to create a homogenous mixture. BioCartilage is allograft cartilage extracellular matrix, containing type II collagen and proteoglycans. After acquisition of the cartilage, it is dehydrated and micronized (100 to 300 μ) prior to sterile packaging and storage (5-year shelf-life). A Tuohy needle is inserted into the joint, sometimes via an accessory portal pending the location of the cartilage defect. Suction tubing is connected to the Tuohy needle to keep the defect bed as dry as possible. The syringe containing the BioCartilage-PRP mixture is then attached to the Tuohy needle, product is injected into the needle, and the needle is used to deliver the product into the microfractured defect (Figure 15-1). One must be careful to not overhydrate the BioCartilage with too much PRP (~1 mL). An elevator can be used to smooth the mixture over the defect. Finally, fibrin glue is dripped over the defect, effectively sealing it off, and is allowed to dry for at least 10 minutes. The knee is next taken through a range of motion to ensure implant stability.

BST-CarGel[22,23]

For the BST-CarGel technique, peripheral whole blood from the patient is mixed with the BST-CarGel; as such, the surgeon should request that the anesthesia team draw the patient's peripheral blood for preparation early in the case to avoid untimely delays. While the defect is being prepared, a surgical assistant simultaneously prepares the BST-CarGel/blood mixture so the mixture can be delivered to the defect immediately after it is prepared. At least 5 mL of peripheral blood is drawn into a 5-mL syringe. A prepackaged, sterile vented dispensing pin is then inserted into the prepackaged BST-CarGel mixing vial's rubber septum. A nonsterile assistant (eg, circulating nurse) then attaches the syringe with the peripheral blood to the pin and injects 4.5 mL of blood. The mixing vial is then shaken vigorously. A new, prepackaged sterile vented dispensing pin (this time attached to a 3-mL sterile syringe) is then inserted into the vial, and 2 mL of the BST-CarGel/blood mixture is withdrawn.

Following diagnostic arthroscopy and defect preparation, the leg is positioned so the defect is horizontal in order to "hold" the product for at least 15 minutes and prevent it from falling out of the defect bed. Similar to all of the techniques discussed, BST-CarGel can be delivered either arthroscopically or via a mini-open approach, pending surgeon preference and defect size/location. After microfracture is performed, the lesion bed is dabbed with gauze to maintain a dry bed prior to application of the BST-CarGel/blood mixture. The 3-mL syringe containing the 2-mL BST-CarGel/blood mixture is injected into the lesion bed in a drop-wise manner over each microfracture hole, and then over the entire lesion, without overfilling. Prior to closing the surgical wounds, the BST-CarGel/blood mixture must sit in the lesion bed for 15 minutes without any movement of the leg to allow for solidification (Figure 15-2).

GelrinC[24,25]

Following defect preparation, microfracture, and lesion bed drying, the GelrinC delivery device is placed into the defect bed, and GelrinC liquid is injected into the resurfaced lesion, allowing for complete fill of the defect (Figure 15-3). Next, the defect is exposed to ultraviolet light

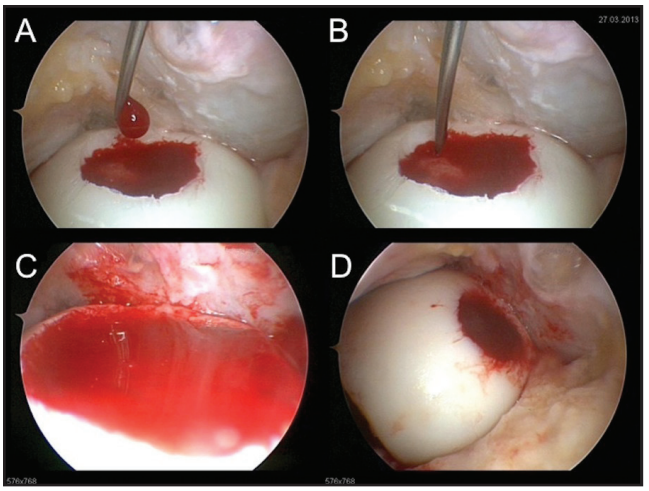

Figure 15-2. Arthroscopic photographs of the left knee with a lateral femoral condyle defect demonstrating placement of BST-CarGel into defect: (A) product injection, (B) smoothing of product into defect, (C) solidification of product, (D) final appearance in situ. (Reprinted with permission from Prof. Matthias Steinwachs, SportClinic Zurich.)

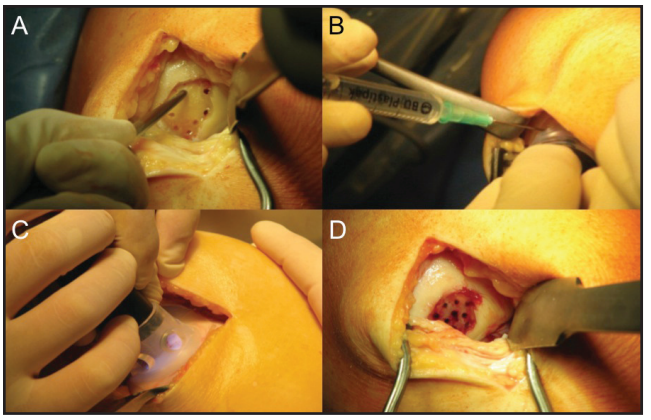

Figure 15-3. Intraoperative photographs of the left knee with a medial femoral condyle defect, demonstrating placement of GelrinC into defect: (A) preprocedure microfracture preparation, (B) injection as a liquid, (C) curing to elastomeric solid implant, (D) implant in situ. (Reprinted with permission from Regentis Biomaterials Ltd.)

with the prepackaged light device for 90 seconds, which converts the liquid into a soft, elastomeric hydrogel implant (Figure 15-4). Once the curing process is complete, the hydrogel implant fits tightly to the surrounding articular cartilage and underlying bone. The joint is then flexed to secure the GelrinC implant into place.

Wound Closure

The wounds are closed using standard knee closure techniques per surgeon preference. Intra-articular drains should not be used to avoid disrupting the product fixation.

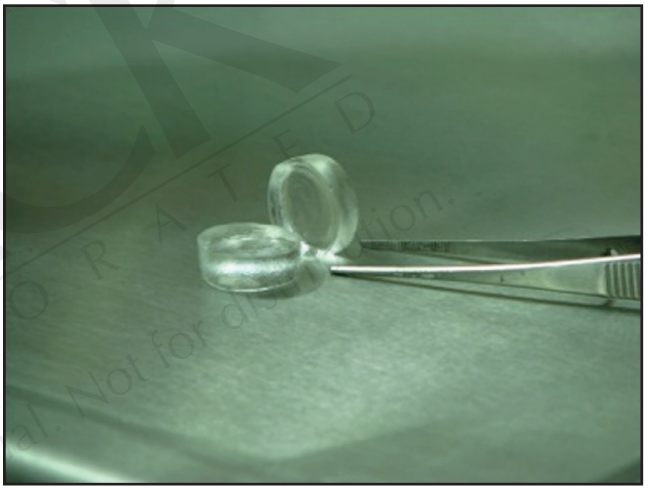

Figure 15-4. Intraoperative photograph demonstrating GelrinC hydrogel product in solidified form. (Reprinted with permission from Regentis Biomaterials Ltd.)

Postoperative Rehabilitation

Standard tibiofemoral and patellofemoral microfracture rehabilitation protocols should ensue immediately post-surgery. For tibiofemoral defects, a 4- to 6-week period of toe-touch protected weight bearing is required, while using continuous passive motion (CPM) for up to 6 hours per day. Pending surgeon preference, the use of CPM may be delayed for 2 to 5 days postoperatively to allow for full infiltration of the product's bone marrow element and stable clot formation. For patellofemoral defects, immediate weight bearing is permitted while the knee is in extension, with limits in flexion during the first 4 to 6 weeks while using CPM. Of note, if patellofemoral-enhanced microfracture is performed in association with a tibial tubercle realignment procedure, protected weight bearing will be required for 6 weeks.

Clinical Outcomes

Reports of clinical outcomes for patients undergoing enhanced microfracture techniques for articular cartilage defects are limited. All of the techniques described in this chapter are relatively new, and thus long-term outcomes are unavailable. As shown on the following page, all available studies do show promising clinical results in patients with appropriate indications; however, additional studies with larger cohorts and longer follow-up durations are necessary before any conclusions can be drawn regarding the short- and long-term effectiveness of these procedures.

Enhanced Marrow-Stimulation Techniques—Clinical Outcome Investigations								
AUTHORS	**STUDY DESIGN**	**TECHNIQUE**	**NUMBER OF PARTICIPANTS**	**AVERAGE AGE (YEARS)**	**AVERAGE BMI (KG/M^2)**	**AVERAGE DEFECT SIZE (CM^2)**	**AVERAGE FOLLOW-UP**	**NOTABLE OUTCOMES**
Gille et al[21] (2013)	Level IV prognostic	AMIC	57	37.3	Not provided (weight ranged 40 to 118 kg)	3.4	24 months	Significantly improved VAS, Lysholm scores
Gille et al[19] (2010)	Level IV Prospective	AMIC	27	37	26	4.2	37 months (minimum 24)	87% highly satisfied; significant improvements in Meyer, Tegner, Lysholm, ICRS, and Cincinnati scores
Stanish et al[22] (2013)	Level I RCT (compared to standard MFX)	BST-CarGel	41 BST-CarGel 39 MFX		27 BST-CarGel 25 MFX	2.32 BST-CarGel 1.95 MFX	12 months	Significantly greater lesion filling and more hyaline cartilage-like T2 values on MRI in BST-CarGel group; equivalent clinical outcomes and safety in both groups
Almqvist et al[25] (2013)	Pilot study (assessing safety primarily), single arm, multicenter	GelrinC	21		26.7	2.64	24 months	Significant improvements in KOOS, IKDC, VAS, SF-36; serious adverse events in 3 (not related to implant or procedure)

AMIC, autologous matrix-induced chondrogenesis; BMI, body mass index; ICRS, International Cartilage Repair Society; IKDC, International Knee Documentation Committee; KOOS, Knee Injury and Osteoarthritis Outcome Score; MFX, microfracture; MRI, magnetic resonance imaging; RCT, randomized clinical trial; SF-36, Short Form 36; VAS, visual analog scale.

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