


Microfracture: Dead or the Future?

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The Birth of Microfracture—A Promising Beginning

It is well-known that, given the complex intra-articular environment within a diseased joint, articular cartilage defects lack the ability to spontaneously heal. However, penetration of the subchondral bone, allowing access to pluripotent mesenchymal stem cells (MSCs), may improve the ability for tissue to regenerate beyond creeping substitution from chondrocytes alone. Popularized by Steadman et al[1] in 1997, the microfracture procedure has become a mainstay in the cartilage restoration armamentarium. The clinical outcomes following microfracture, as published by Steadman et al,[2] remain promising, including improved symptoms in patients regardless of age, lesion size, and defect chronicity at up to 17 years following surgery. Then why, in the opinion of many, do surgeons strive for a better surgical procedure than microfracture for patients with symptomatic cartilage defects?

Microfracture Undergoes an Awkward Puberty

As the microfracture technique achieved broader clinical adoption, results published by others failed to support the initial panacea. A recent systematic review by Goyal et al[3] highlighted that while short-term improvements are present, these deteriorate after 2 to 5 years, even in smaller defects. Critically evaluating the microfracture technique leads to several observations related to its "simplicity." The procedure, even when performed with exact technique, is not particularly demanding, can be performed largely arthroscopically for most defect locations, requires little in the way of specialized equipment or capital investment, and can be implemented as a "point-of-care" procedure with little planning other than patient education related to the demands of postoperative rehabilitation. What is most troublesome related to these procedural characteristics is that the indications can inadvertently become lax and the willingness to address comorbidities (ie, malalignment, meniscal deficiency, and ligament instability) in order to achieve an excellent durable result is lacking.

The benefit of any first-line treatment is that it has a reasonable chance of providing a satisfying outcome without burning any bridges to future procedures. As more attention is being paid to the role of the subchondral bone in cartilage restoration, Minas et al[4] investigated the outcomes of first-generation autologous chondrocyte implantation in the setting of prior marrow stimulation treatment. Similar to the findings of Pestka et al,[5] outcomes were inferior in this setting. Furthermore, there is evidence at our institution that some patients with incidental defects treated with microfracture may subsequently become symptomatic. Therefore, one of the major tenants of microfracture, that it does not burn any bridges, is now being challenged. Contemporary thinking suggests that surgeons should only choose microfracture for patients in whom they believe it will work as a relatively definitive treatment, because they should, not simply because they can.

In a similar vein, beyond proper indications, microfracture has specific technique and postoperative requirements, including removal of the calcified cartilage layer (CCL), use of continuous

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passive motion (CPM) in the absence of applied load,[6] and strict protected weight bearing. Extensive technique heterogeneity as seen in the Canadian orthopedic community was highlighted in a recent survey study by Theodoropoulos et al[7] where 45% did not remove the CCL, 59% did not limit weight bearing, and 98% did not use CPM postoperatively. Guidance from the literature would suggest that optimal results require the following: age younger than 40 years,[8] defect less than 4 cm^2, body mass index less than 30 kg/m^2, Tegner score greater than 4, microfracture as primary surgery, CCL removal, stable cartilage margin after debridement, at least 66% cartilage fill, minimal presurgical symptom duration, and location on the femoral condyle. In a meta-analysis published by Negrin et al,[9] the clear benefits of adhering to strict indications were evidenced by the results of the study by Gudas et al,[10] as this was a positive outlier among many series with moderate results.

Microfracture Is Alienated and Reduced to a Comparison Group

Despite varied outcomes, microfracture became the standard by which all new techniques would be judged. Many hopeful scientists and enterprising venture capital firms looked to create the ultimate solution for cartilage restoration using stem cells, printed scaffolds, and complex tissue engineering techniques. However, the regulatory burden as promulgated by the Food and Drug Administration (FDA) has stifled even the best-laid plans.

In 1997, the FDA formed the Tissue Reference Group (TRG) governing the criteria for human cells, tissue, and cellular and tissue-based products (HCT/Ps) under section 361 of the Public Health Service Act. These guidelines indicate that in order to avoid performing an FDA-monitored clinical trial, cells or tissue can be considered "minimally manipulated" when "not combined with a drug or device, except for water, crystalloids, or a...storage agent," and one cannot "alter the original relevant characteristics" of structural tissue. Specific to cells, the primary function of the HCT/P cannot be "dependent upon the metabolic activity of living cells...unless intended for autologous use or allogeneic use in a first or second degree blood relative." Tissue use must also be of a homologous nature. For example, in 2011, the use of a demineralized bone matrix as a cartilage restoration scaffold was denied because this was not the original intent of the bone matrix. A more recent example, from 2013, was the exclusion of bone marrow-derived MSCs expanded in culture because they were considered to be more than minimally manipulated. The expansion of MSCs categorized this technology as a "biologic product," triggering the complex FDA market approval pathway. Although these requirements are in place for a perceived common good, they have greatly limited the rate of biologic innovation in the United States.

Microfracture Endures and Rises Like the Phoenix

Largely because of the regulatory hurdles and associated economic burden, which is not fortified by the market size or socioeconomic factors associated with the incidence and impairment related to isolated cartilage defects, industry has returned to microfracture as the basis of many new treatment modalities. Therefore, the literature is becoming populated with methods to improve on the existing microfracture technique. Some evolutionary considerations include the following: marrow elements are easier to access in the lateral vs medial compartment,[11] drilling to a depth of 6 mm increases percent fill compared with 2 mm,[12] increased chondrogenesis was noted in the trochlear vs femoral condyles,[13] and drilling causes less thermal necrosis than Kirschner wires.[14] Many of these findings suggest that the pendulum will swing back to work similar to that of Pridie[15] regarding the use of a drill over an awl. Continuing to improve on the technique should increase both the cellular yield and the quality of tissue integration, and possibly maintenance of the subchondral bone following surgical violation.

As the main tenants of tissue engineering are the triumvirate of a scaffold, growth factors, and cellular components, significant focus is now directed to harnessing the potential benefits of microfracture by "augmenting" these tenants. The goal at this stage has been to offer improved ability to maintain the clot (the role of a scaffold) or to improve the environment to which the cells are exposed (the role of growth factors and cellular elements). Clot stabilization could allow for increased cellular presence in the defect, potentially stabilize the subchondral bone and allow for earlier weight bearing, and ultimately improve defect fill. This has been achieved with hyaluronic acid, chitosan, fibrin glue, and various polymers. Clinical application has included use of autologous matrix-induced chondrogenesis with a type I/III collagen membrane,[16,17] a polyglycolic acid-hyaluronan scaffold with platelet rich plasma (PRP),[18] a cell free polymer-based matrix,[19] non-woven polyglycolic acid fleece with hyaluronic acid, gelrin C (Regentis, Or-Akiva, Israel) biodegradable photopolymerized hydrogel of polyethylene glycol diacrylate bound to fibrinogen, BST-CarGel chitosan (Piramal, Laval, Quebec, Canada) with autologous blood,[20] and micronized allograft articular cartilage combined with PRP.[21] Most notably, the work by Stanish et al[20] was the first "microfracture plus" randomized clinical trial with a microfracture alone treatment group. Although no difference was found clinically at 12 months, the improved lesion fill and hyaline-like nature on magnetic resonance imaging may suggest that results will endure beyond microfracture alone.

One reason microfracture does not form hyaline cartilage is because of the lack of growth and anti-inflammatory factors in the extracellular environment. This has been addressed through different applications of thrombospondin-1, bone morphogenic protein (BMP) 2, BMP-4, BMP-7 (osteogenic protein-1), and

insulin-like growth factor-1. These specific proteins can be administered via injection, but concern exists regarding the half-life and rate of degradation leading to only a transient improvement of the biologic milieu. Klinger et al[22] and Morisset et al[23] have attempted to overcome this with viral vectors producing chondromodulin-1 or interleukin-1 receptor antagonist, respectively. Beyond application of specific growth factors, use of a biologic milieu such as PRP or autologous conditioned plasma may be beneficial in a series of injections, as demonstrated by Milano et al.[24] Use of these augmentations is important in providing an environment conducive to production of hyaline cartilage.

Moving forward, the space most conducive for innovation in cartilage regeneration is likely the "microfracture plus" category. Clearly, cellular access alone is not sufficient. Through a combination of maintained environmental augmentation, improved clot adherence, and optimal postoperative protocol with CPM use and restricted weight bearing, microfracture will continue to evolve and remain a viable option. Further research needs to maintain strict indications for microfracture implementation and focus on randomized clinical trials when possible to increase the likelihood of valid clinical effectiveness.

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