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The Efficacy of Intra-Articular Hyaluronan Injection After the Microfracture Technique for the Treatment of Articular Cartilage Lesions

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Background: Although the exact mechanism of action has yet to be elucidated, recent animal studies have demonstrated chondroprotective and anti-inflammatory properties of hyaluronic acid viscosupplementation.

Hypothesis: Intra-articular hyaluronic acid after microfracture improves the quality of the repair leading to a more hyaline-like repair tissue with better defect fill and adjacent area integration.

Study Design: Controlled laboratory study.

Methods: Full-thickness cartilage defects were created in the weightbearing area of the medial femoral condyle in 36 female New Zealand White rabbits. The defects were then treated with surgical microfracture. Eighteen rabbits formed the 3-month cohort and the other 18 formed the 6-month cohort. Within each cohort, 6 rabbits were randomly assigned to receive 3 weekly injections of hyaluronic acid (group A), 5 weekly injections (group B), or control injections of normal saline (group C). At 3 and 6 months postmicrofracture, the animals were sacrificed and the operative knee harvested. Repair tissue was assessed blinded—both grossly, using a modified component of the International Cartilage Repair Society (ICRS) Cartilage Repair Assessment scoring scale, and histologically, using the modified O'Driscoll histological cartilage scoring system. Comparisons were made with respect to gross and histologic findings between treatment groups at each time point. Effects of each treatment type were also evaluated longitudinally by comparing the 3-month results with the 6-month results. Statistical analysis was performed using unpaired Student *t* tests with significance defined as $P < .05$.

Results: At 3 months, gross and histologic evaluation of the repair tissue demonstrated that the 3-injection group had significantly better fill of the defects and more normal appearing, hyaline-like tissue than controls (a mean ICRS score of 1.92 vs 1.26; $P < .05$ and a mean modified O'Driscoll score of 10.3 vs 7.6; $P < .02$). Specimens treated with 5 weekly injections were not significantly improved compared with controls. At 6 months, the mean gross appearance and histologic scores between the 3 specimen cohorts were not significantly different. However, examination of the entire operative knee demonstrated a significantly greater extent of degenerative changes (synovial inflammation and osteophyte formation) in the control group than in both hyaluronic acid treatment groups ($P < .05$).

Conclusion: Supplementing the microfracture technique with 3 weekly injections of intra-articular hyaluronic acid had a positive effect on the repair tissue that formed within the chondral defect at the early follow-up time point. This improvement was not found for the 3-injection group at 6 months or for the 5-injection group at either time point. Additionally, hyaluronic acid supplementation had a possible chondroprotective and anti-inflammatory effect, limiting the development of degenerative changes within the knee joint.

Clinical Relevance: The adjunctive use of hyaluronic acid appears to hold promise in the treatment of chondral injuries and warrants further investigation.

Keywords: hyaluronic acid; viscosupplementation; microfracture; cartilage

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Focal, full-thickness chondral defects are commonly seen after injuries sustained during athletic activities.[3,6] These lesions have been shown to have poor intrinsic potential for spontaneous healing, and may predispose patients to the development of future joint degeneration.[15,16] Current treatment options used in the management of articular cartilage injuries include articular surface debridement with chondral shaving, abrasion chondroplasty, microfracture

techniques, soft tissue arthroplasties such as periosteal and perichondrial grafts, and chondrocyte or osteochondral transplantation.[3,4,11,17]

Microfracture is a frequently used technique to attempt repair of symptomatic articular cartilage lesions.[18,24-26] Penetration of the subchondral bone plate within the chondral defect leads to bleeding and subsequent fibrin clot formation, filling the defect and covering the exposed bony surface. Pluripotent, marrow-derived mesenchymal stem cells then migrate into the clot and promote the formation of a fibrocartilaginous repair tissue.[3,21] By filling the defect with repair tissue, a more congruent joint surface is obtained, leading to symptomatic improvement in the majority of published reports.[3,5]

Hyaluronic acid, the mucopolysaccharide component of synovial fluid responsible for its viscoelastic properties, has been used with increased frequency in the nonoperative management of osteoarthritis.[27] Studies have shown that during the progression of osteoarthritic degeneration, the concentration and molecular weight of hyaluronic acid are reduced.[8] In a recent animal model, intra-articular injection of hyaluronic acid was shown to reduce arthritic lesions of articular cartilage by inhibiting degenerative changes within chondrocytes and the cartilage matrix, decreasing the extent of synovial inflammation, and enhancing the cartilage proteoglycan content.[19] In another in vitro study, hyaluronic acid was shown to induce chondrogenic differentiation of embryonic mesenchymal cells.[12] These potential chondroprotective and anti-inflammatory properties have led to interest in the use of hyaluronic acid viscosupplementation as an augment to cartilage defect repair strategies.

The current pilot investigation was performed to evaluate the impact of hyaluronic acid viscosupplementation on the quality of repair tissue after surgical microfracture in a rabbit chondral defect model. We hypothesized that intra-articular injection of hyaluronic acid after the microfracture technique would improve the quality of the repair in a rabbit chondral defect model, resulting in a more hyaline-like repair tissue with better defect fill and adjacent area integration.

MATERIALS AND METHODS

In this Institutional Animal Care and Use Committee–approved pilot study, 36 female New Zealand White rabbits weighing between 3.5 and 4.5 kg had a full-thickness cartilage defect created in the weightbearing area of the medial femoral condyle. With the animal under general anesthesia, and with use of a standard aseptic technique, the right knee was approached through a medial parapatellar incision with the patella dislocated laterally. A 3.0-mm full-thickness cartilage defect was created in the central portion of the weightbearing area of the medial femoral condyle with a dermal biopsy punch and manual debridement. All calcified cartilage was carefully removed with a curette, exposing the subchondral bone plate. Each specimen then underwent microfracture using a 0.35-in (0.9-mm) Kirschner wire tapped into the subchondral bone with a mallet to a depth of approximately 3 mm, until bleeding from the hole was apparent. Three microfracture holes were created within each full-thickness chondral defect in a triangular configuration. Once the microfracture was completed, the patella was reduced, the joint capsule was closed with interrupted sutures, and the wound was closed in anatomical layers. Postoperatively the animals were allowed to move freely within their cages.

Seven days after surgery, 18 rabbits were randomly selected to form the 3-month cohort and the other 18 rabbits formed the 6-month cohort. Within each cohort, 6 rabbits were randomly assigned to each of 3 study groups. The first group of six rabbits (group A) received a weekly injection of hyaluronic acid (5 mg/0.50 mL) for 3 weeks postmicrofracture, 6 rabbits received a weekly hyaluronic acid injection (5 mg/0.50 mL) for 5 weeks postmicrofracture (group B), and 6 rabbits received a control injection (0.50 mL of normal saline) weekly for 5 weeks postmicrofracture (group C).

At 3 months after microfracture, the specimens in the 3-month cohort were sacrificed and the operative knee harvested. At the time of harvest, the knee was approached with a medial parapatellar incision with a lateral patellar dislocation. Gross assessment of the microfractured areas was performed by a blinded observer, using a modified component of the International Cartilage Repair Society (ICRS) Cartilage Repair Assessment scoring scale (macroscopic appearance subcategory).[22] After gross inspection, the operative knee was harvested and fixed in neutral-buffered formalin until preparation for histologic examination. Histologic analysis of the repair tissue was performed for each specimen by a blinded observer, with attention paid to the overall appearance of the repair tissue, cell shape, the extent of defect filling, and the integration with the defect edges. Additionally, the surrounding cartilage immediately outside the repaired defect (adjacent articular cartilage) was assessed histologically. All histologic specimens were scored according the modified O'Driscoll histological cartilage scoring system.[20] At 6 months after microfracture, this process was repeated for the specimens in the 6-month cohort.

Comparisons were made with respect to gross and histologic findings between treatment groups at each time point. Effects of each treatment type were also evaluated longitudinally by comparing the 3-month results and the 6-month results. Statistical analysis was performed using unpaired Student t tests with significance defined as $P < .05$. The Tukey test was used for all post hoc comparisons.

RESULTS

None of the animals demonstrated any external evidence of injection reaction to the hyaluronic acid treatment at any point during the experiment.

At the 3-month time point, gross evaluation of the repair tissue demonstrated that the group receiving 3 weekly injections of hyaluronic acid after microfracture had significantly better fill of the defects than controls (Figure 1). The mean gross ICRS appearance score for the 3-injection cohort was 1.92 (±0.61) compared with a mean score of 1.26 (±0.51) for the specimens receiving saline injections ($P < .05$). Specimens treated with 5 weekly injections of hyaluronic acid after microfracture had a mean gross score of 1.85 (±0.67), which was not significantly different than either the 3-injection specimens or the controls (Figure

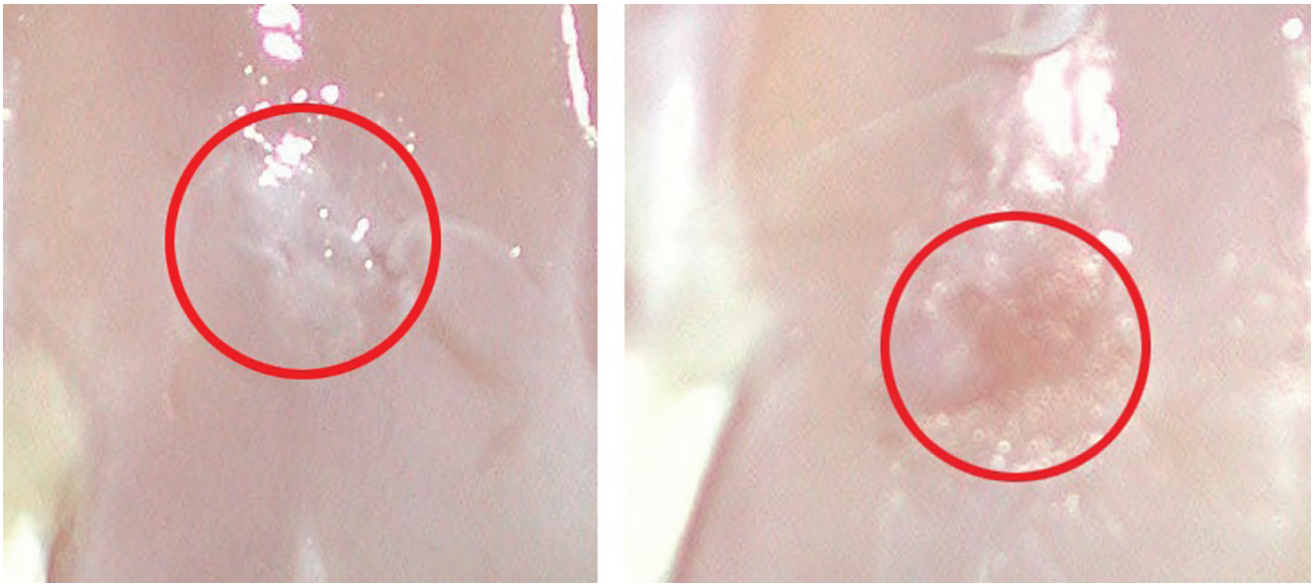

Figure 1. Repair specimens 3 months after microfracture procedure (40× magnification). Circles enclose the repaired chondral defect area. Left panel, knee treated with 3 once-weekly injections of hyaluronic acid. Note the microfracture holes filled with white repair tissue; the debrided area is also covered with white repair tissue. Right panel, control knee (saline injections). Note the filled microfracture holes, but incomplete defect fill.

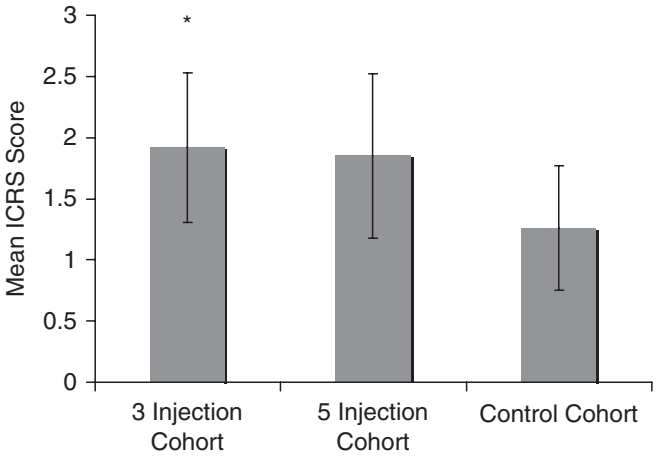

Figure 2. At the 3-month time point, the group receiving 3 weekly hyaluronic acid injections had better defect fill and higher gross appearance scores than controls. *Indicates a statistically significant difference between groups; error bars represent standard deviation; ICRS, International Cartilage Repair Society.

2, Table 1). The greatest difference in appearance of the groups was the significant reduction in fissures in the repair surface seen in the group treated with 3 hyaluronic acid injections (1.81 ± 0.22; 5 hyaluronic acid injections, 1.33 ± 0.23; controls, 1.15 ± 0.15).

At the 6-month time point, the mean gross ICRS appearance score for the 3-injection cohort was 1.5 (±1.1), which was lower than that seen at 3 months; the difference was not statistically significant. The mean scores for both the 5-injection cohort (2.13 ± 1.17) and the controls (1.57 ± 0.45) were improved over their 3-month scores, but the differences were not significant.

Comparison of the repair tissue between treatment groups at 6 months after treatment failed to demonstrate any significant differences in mean gross score (Figure 3).

Gross examination of the entire operative knee at 6 months demonstrated a greater extent of degenerative changes in the control group than in both hyaluronic acid treatment groups. Among the specimens receiving weekly saline injections, 5 of 6 (83%) had evidence of osteophyte formation and synovial inflammation. This incidence of degenerative, osteoarthritis-type changes in the control group was significantly higher than that seen in the 3-injection group (no evidence of synovial inflammation in any specimens and 1 of 6 [17%] with osteophyte formation; $P < .04$). Compared with controls, the 5-injection group had a lower incidence of postoperative degenerative change (2 of 6 [33%] with synovial inflammation and osteophyte formation), but this difference was not statistically significant (Figure 4).

Histologic analysis of the repair tissue at 3 months using the modified O'Driscoll histological cartilage scoring system demonstrated significantly better scores for the repair tissue within the chondral defect in the 3-injection cohort (10.3 ± 0.52) than that seen in the control group (7.6 ± 2.3; $P < .02$) (Figures 5 and 6). Specimens in the 5-injection group had a mean O'Driscoll score of 8.5 (±2.6), which was not significantly different from the scores in the control group or the 3-injection group (Figure 6). Histological features that showed significant improvement with 3 hyaluronic acid injections were the structural integrity of

TABLE 1
Gross and Histologic Evaluation of Repair Tissue[a]

	3 HA Injection Cohort	5 HA Injection Cohort	Control (Saline Injection) Cohort
Mean gross ICRS appearance score at 3 months	1.92 ± 0.61[b]	1.85 ± 0.67	1.26 ± 0.51
Mean gross ICRS appearance score at 6 months	1.50 ± 1.1	2.13 ± 1.17	1.57 ± 0.45
Mean modified O'Driscoll histologic score at 3 months	10.3 ± 0.52[b]	8.5 ± 2.6	7.6 ± 2.3
Mean modified O'Driscoll histologic score at 6 months	8.8 ± 3.1	8.6 ± 2.5	6.5 ± 2.4

[a]HA, hyaluronic acid; ICRS, International Cartilage Repair Society.
[b]Significant difference between the 3 HA injection cohort and controls.

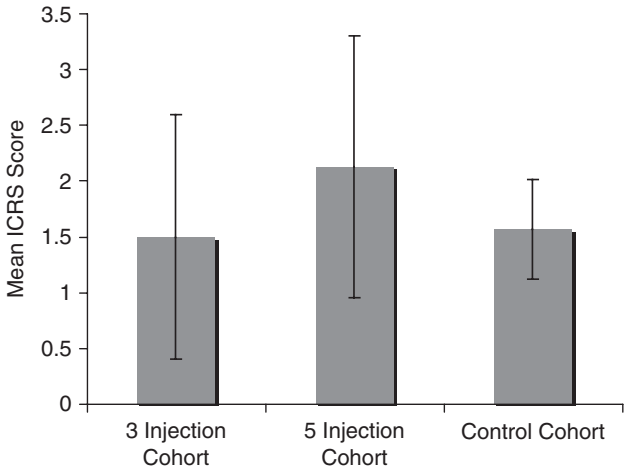

Figure 3. At 6 months, there was no longer a significant difference in gross appearance scores between the treatment groups. Error bars represent standard deviation; ICRS, International Cartilage Repair Society.

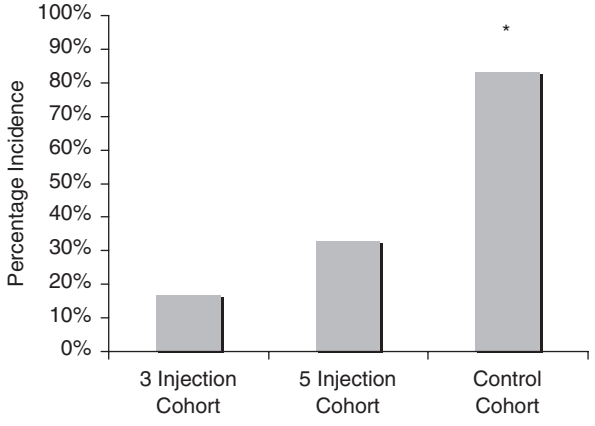

Figure 4. A higher incidence of degenerative changes was noted in control specimens than in either hyaluronic acid treatment group with evidence of synovial inflammation and osteophyte formation. *Indicates a statistically significant difference between groups.

the repair (3 hyaluronic acid injections, 1.33 ± 0.52; 5 injections, 0.5 ± 0.55; controls, 1.2 ± 0.44) and freedom from degenerative changes of osteoarthritis (3 hyaluronic acid injections, 1.01 ± 0.02; 5 injections, 1.04 ± 0.16; controls, 0.6 ± 0.55). Repair tissue thickness and the degree of subchondral bone reconstitution showed an improving trend, but not at the level of statistical significance. At 6 months, repair tissue specimens from the 3-injection cohort had a mean histologic score of 8.8 ± 3.1, which was similar to that seen in the 5-injection cohort (8.6 ± 2.5). Both treatment groups had mean histologic scores that were higher than that seen in controls (6.5 ± 2.4); however, these differences did not reach statistical significance (Figure 7).

Examination of the articular cartilage adjacent to the chondral defects did not demonstrate significant differences in histologic scores between the 3 cohorts at 3 months. However, at 6 months, the adjacent tissue in the 3-injection group had significantly higher histologic scores than that seen in the control group ($P < .02$). No significant difference was seen between specimens from the 5-injection cohort and controls. Comparing the 3-month and 6-month groups, the 3-injection group maintained surface quality over time, while the other 2 groups showed a small but significant deterioration (7% worse for 5 hyaluronic acid injections, $P < .02$; 9% worse for controls, $P < .04$).

DISCUSSION

In the current rabbit chondral defect model, gross and histologic evaluation of control specimens treated with microfracture alone demonstrated incomplete defect fill, with a thin repair tissue characterized by surface irregularity and poor adjacent area integration. Analysis of specimens in which the microfracture technique was augmented with intra-articular hyaluronic acid demonstrated a positive effect of hyaluronic acid viscosupplementation on the appearance of the repair tissue within the defect, both grossly and histologically, without having an adverse effect on the surrounding cartilage. Compared with control specimens, those treated with 3 weekly injections after microfracture had significantly improved gross appearance scores and a more normal-appearing repair tissue histologically at the early follow-up time point. There was also evidence of protection against the development of degenerative changes within the overall knee joint, with hyaluronic acid viscosupplementation appearing

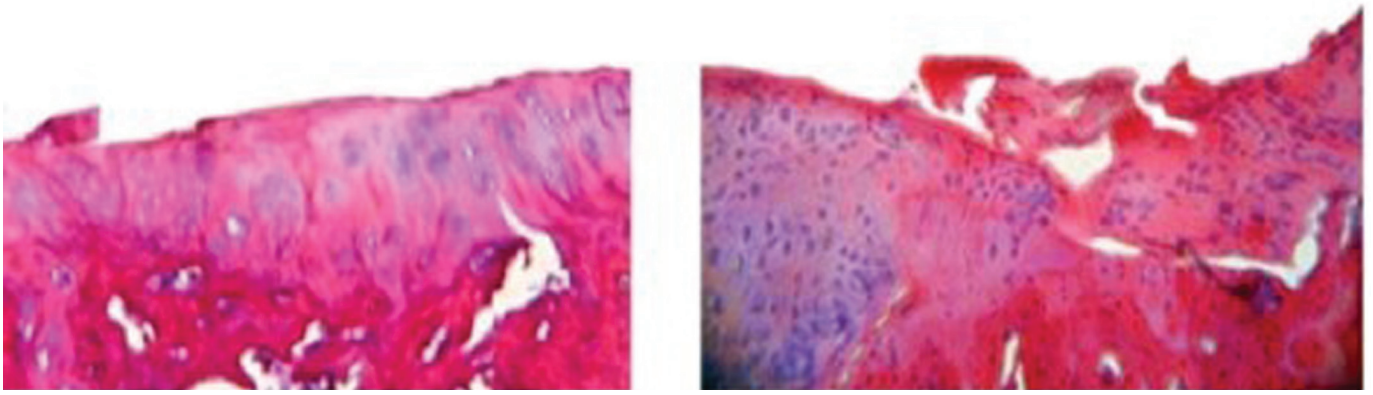

Figure 5. Repair specimens 3 months after microfracture procedure (100× magnification). Left panel, knee treated with 3 once-weekly injections of hyaluronic acid. Note integration of host and new tissue with a smooth tissue surface. Right panel, control (saline injections). Note islands of cartilage lacking integration, with an irregular surface and persistent cartilage in bone region.

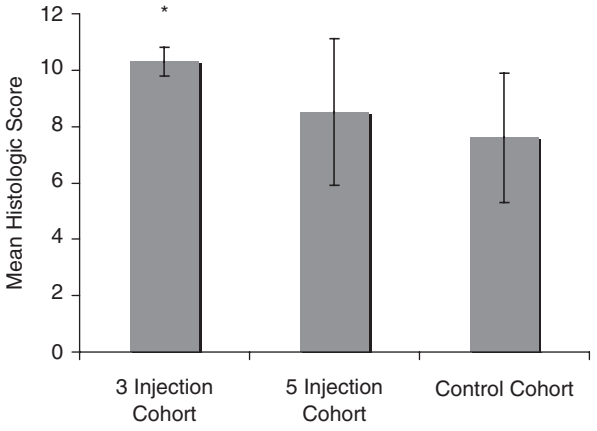

Figure 6. Histologic evaluation of the repair tissue at 3 months after microfracture demonstrated higher scores in the 3-injection cohort than in controls. *Indicates a statistically significant difference between groups; error bars represent standard deviation.

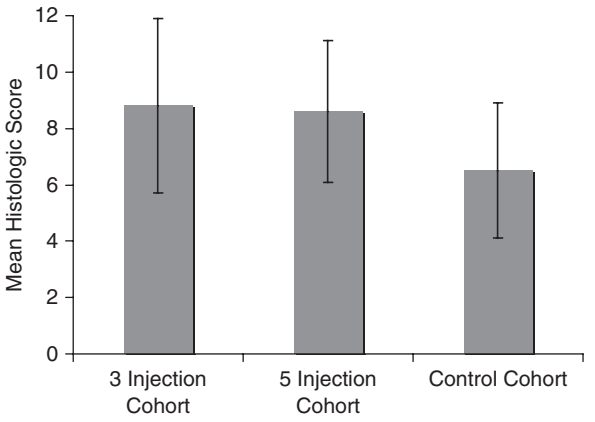

Figure 7. At 6 months, there was no longer a significant difference in the histologic scores between treatment groups. Error bars represent standard deviation.

to have an anti-inflammatory effect, at least in the 3-injection group.

The poor intrinsic healing potential of chondral defects and the risk of the subsequent development of joint degeneration make these injuries difficult for the orthopaedic surgeon to manage successfully. A number of different operative procedures have been developed, with the goal of filling the articular cartilage defect with repair tissue to obtain a more congruent joint surface. The microfracture technique is one such procedure in which the subchondral bone plate is penetrated, creating bleeding, fibrin clot formation within the defect, and subsequent fibrocartilage formation, covering the exposed bony surface. Studies in the orthopaedic literature have demonstrated variable outcomes after microfracture in the management of symptomatic articular cartilage defects, with most reporting improvement in knee function in 70% to 90% of treated patients.[28] Although recent long-term studies with follow-up of 6 to 11 years have reported little decline in the functional and symptomatic improvement seen after microfracture,[7,23] the durability and longevity of the fibrocartilaginous repair tissue is a concern. Many authors believe that the inferior biochemical and biomechanical properties of fibrocartilage in comparison with normal articular cartilage will predispose patients to the development of degenerative arthritis.[13,28] Research is ongoing

in an attempt to use adjuvant treatments to improve the quality of the repair tissue after the microfracture procedure, with the goal of producing a more hyaline-like repair capable of stable, long-term function.

Hyaluronic acid, the mucopolysaccharide component of synovial fluid that is responsible for its viscoelastic properties, has been increasingly used in the nonoperative management of osteoarthritis.[1,2,9,14,27,29] Studies have shown that during the progression of osteoarthritic degeneration, the concentration and molecular weight of hyaluronic acid are reduced.[8] In rabbits, intra-articular injection of hyaluronic acid has been shown to reduce arthritic lesions of articular cartilage through inhibition of degenerative changes within chondrocytes and the cartilage matrix, decrease the extent of synovial inflammation, and enhance the cartilage proteoglycan content.[19] Additionally, hyaluronic acid has been shown to induce chondrogenic differentiation of embryonic mesenchymal cells in cell-culture experiments.[12] These chondroprotective and anti-inflammatory properties have led to the use of hyaluronic acid viscosupplementation to augment cartilage defect repair strategies.

Miyakoshi et al[19] evaluated the effect of intra-articular administration of basic fibroblast growth factor (b-FGF) with hyaluronic acid in a rabbit osteochondral defect model. The authors found that when administered alone, b-FGF induced poor repair tissue coupled with undesirable side effects. The addition of hyaluronic acid to the b-FGF injection resulted in significantly better repair tissue as evaluated grossly and with histology, with minimal side effects. Tytherleigh-Strong et al[27] examined the effect of hyaluronic acid viscosupplementation after mosaic arthroplasty in an ovine osteochondral defect model. They found that the aggregate moduli of specimens from the articular surface was significantly higher in the hyaluronic acid treatment group than in specimens harvested from the control group (that received postoperative buffer injections). Additionally, histologic evaluation demonstrated more articular cartilage flow in the hyaluronic acid–treated group, with the control group showing more persistent interstitial tissue in the interstices of the grafts. In a recent rabbit model, Jansen et al[10] reported that a single intra-articular injection of hyaluronic acid after a partial-thickness chondral injury had chondroprotective effects, preventing apoptosis in the cartilage immediately adjacent to the lesion and improving chondrocyte metabolism in areas remote to the injury. At the present time, research on the mechanism of action and in vivo properties of hyaluronic acid is relatively new, with the majority of studies reported based on animal models. Whether the beneficial effects of hyaluronic acid viscosupplementation seen in these models translate into improved repair tissue and clinical outcomes in human patients has yet to be determined.

In the current pilot study, combining the chondroprotective and anti-inflammatory properties of hyaluronic acid viscosupplementation with the microfracture technique improved the gross and histologic appearance of the repair tissue within the chondral defect at the early follow-up time point. This was coupled with what appeared to be a protective effect against the inflammation and osteophyte formation associated with degeneration of the overall knee joint. None of the treated specimens demonstrated evidence of adverse effects of the hyaluronic acid supplementation. Weekly hyaluronic acid injection for 3 weeks after operative treatment appeared to be more effective than extending the supplementation for 5 weeks. With a more complete coverage of the debrided area surrounding the microfracture drill holes, hyaluronic acid treatment appears to provide an early advantage. At 6 months, repair surfaces without treatment were qualitatively similar to those with HA treatment.

Limitations of the current pilot study include those inherent to the use of an animal model of a chondral defect, including interanimal variability. The animals were allowed to move freely about their cages after the microfracture procedure, which placed weightbearing forces across the repair tissue immediately postoperatively. It is possible that avoiding weightbearing after microfracture may alter the quality of the repair tissue compared with what we observed. Additionally, the number of specimens per group used in our pilot study was small. Larger studies are needed to confirm the reproducibility of our findings and may also reveal additional significant differences. Future studies may address some of these issues in addition to evaluating the effect of varying the dose or frequency of supplementation.

CONCLUSION

Articular cartilage injury remains a complex entity, the optimal management of which has yet to be resolved. Supplementing the microfracture technique with intra-articular hyaluronic acid injections had a positive effect on the repair tissue that formed within the chondral defect at the early follow-up time point. Additionally, hyaluronic acid supplementation appeared to have a putative chondroprotective and anti-inflammatory effect, limiting the development of degenerative changes within the knee joint. The adjunctive use of hyaluronic acid appears to hold promise in the treatment of chondral injuries and warrants further investigation.

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REFERENCES

1. Adams ME, Atkinson MH, Lussier AJ, et al. The role of viscosupplementation with hylan G-F 20 (Synvisc) in the treatment of osteoarthritis of the knee: a Canadian multicenter trial comparing hylan G-F 20 alone, hylan G-F 20 with non-steroidal anti-inflammatory drugs (NSAIDs) and NSAIDs alone. *Osteoarthritis Cartilage.* 1995;3: 213-225.
2. Altman RD. Intra-articular sodium hyaluronate in osteoarthritis of the knee. *Semin Arthritis Rheum.* 2000;30(2 Suppl 1):11-18.
3. Buckwalter JA. Articular cartilage injuries. *Clin Orthop Relat Res.* 2002;402:21-37.
4. Chen FS, Frenkel SR, Di Cesare PE. Repair of articular cartilage defects: part II, treatment options. *Am J Orthop.* 1999;28:88-96.

5. Frisbie DD, Trotter GW, Powers BE, et al. Arthroscopic subchondral bone plate microfracture technique augments healing of large chondral defects in the radial carpal bone and medial femoral condyle of horses. *Vet Surg.* 1999;28:242-255.
6. Gill TJ, McCulloch PC, Glasson SS, Blanchet T, Morris EA. Chondral defect repair after the microfracture procedure: a nonhuman primate model. *Am J Sports Med.* 2005;33:680-685.
7. Gobbi A, Nunag P, Malinowski K. Treatment of full thickness chondral lesions of the knee with microfracture in a group of athletes. *Knee Surg Sports Traumatol Arthrosc.* 2005;13:213-221.
8. Greenwald RA. Oxygen radicals, inflammation, and arthritis: pathophysiological considerations and implications for treatment. *Semin Arthritis Rheum.* 1991;20:219-240.
9. Hempfling H. Intra-articular hyaluronic acid after knee arthroscopy: a two-year study. *Knee Surg Sports Traumatol Arthrosc.* 2007;15:537-546.
10. Jansen EJ, Emans PJ, Douw CM, et al. One intra-articular injection of hyaluronan prevents cell death and improves cell metabolism in a model of injured articular cartilage in the rabbit. *J Orthop Res.* 2008;26:624-630.
11. Knutsen G, Engebretsen L, Ludvigsen TC, et al. Autologous chondrocyte implantation compared with microfracture in the knee: a randomized trial. *J Bone Joint Surg Am.* 2004;86:455-464.
12. Kujawa MJ, Caplan AI. Hyaluronic acid bonded to cell-culture surfaces stimulates chondrogenesis in stage 24 limb mesenchyme cell cultures. *Dev Biol.* 1986;114:504-518.
13. Linden B. Osteochondritis dissecans of the femoral condyles: a long-term follow-up study. *J Bone Joint Surg Am.* 1977;59:769-776.
14. Lussier A, Cividino AA, McFarlane CA, Olszynski WP, Potashner WJ, De Medicis R. Viscosupplementation with hylan for the treatment of osteoarthritis: findings from clinical practice in Canada. *J Rheumatol.* 1996;23:1579-1585.
15. Mankin HJ. The response of articular cartilage to mechanical injury. *J Bone Joint Surg Am.* 1982;64:460-466.
16. Marder RA, Hopkins GJ, Timmerman LA. Arthroscopic microfracture of chondral defects of the knee: a comparison of two postoperative treatments. *Arthroscopy.* 2005;21:152-158.
17. Minas T, Nehrer S. Current concepts in the treatment of articular cartilage defects. *Orthopedics.* 1997;20:525-538.
18. Mithoefer K, Williams RJ 3rd, Warren RF, et al. The microfracture technique for the treatment of articular cartilage lesions in the knee: a prospective cohort study. *J Bone Joint Surg Am.* 2005;87:1911-1920.
19. Miyakoshi N, Kobayashi M, Nozaka K, Okada K, Shimada Y, Itoi E. Effects of intraarticular administration of basic fibroblast growth factor with hyaluronic acid on osteochondral defects of the knee in rabbits. *Arch Orthop Trauma Surg.* 2005;125:683-692.
20. O'Driscoll SW, Marx RG, Beaton DE, Miura Y, Gallay SH, Fitzsimmons JS. Validation of a simple histological-histochemical cartilage scoring system. *Tissue Eng.* 2001;7:313-320.
21. Shapiro F, Koide S, Glimcher MJ. Cell origin and differentiation in the repair of full-thickness defects of articular cartilage. *J Bone Joint Surg Am.* 1993;75:532-553.
22. Smith GD, Taylor J, Almqvist KF, et al. Arthroscopic assessment of cartilage repair: a validation study of 2 scoring systems. *Arthroscopy.* 2005;21:1462-1467.
23. Steadman JR, Briggs KK, Rodrigo JJ, Kocher MS, Gill TJ, Rodkey WG. Outcomes of microfracture for traumatic chondral defects of the knee: average 11-year follow-up. *Arthroscopy.* 2003;19:477-484.
24. Steadman JR, Miller BS, Karas SG, Schlegel TF, Briggs KK, Hawkins RJ. The microfracture technique in the treatment of full-thickness chondral lesions of the knee in National Football League players. *J Knee Surg.* 2003;16:83-86.
25. Steadman JR, Rodkey WG, Briggs KK. Microfracture to treat full-thickness chondral defects: surgical technique, rehabilitation, and outcomes. *J Knee Surg.* 2002;15:170-176.
26. Steadman JR, Rodkey WG, Rodrigo JJ. Microfracture: surgical technique and rehabilitation to treat chondral defects. *Clin Orthop Relat Res.* 2001;(391 Suppl):S362-S369.
27. Tytherleigh-Strong G, Hurtig M, Miniaci A. Intra-articular hyaluronan following autogenous osteochondral grafting of the knee. *Arthroscopy.* 2005;21:999-1005.
28. Williams RJ 3rd, Harnly HW. Microfracture: indications, technique, and results. *Instr Course Lect.* 2007;56:419-428.
29. Wobig M, Dickhut A, Maier R, Vetter G. Viscosupplementation with hylan G-F 20: a 26-week controlled trial of efficacy and safety in the osteoarthritic knee. *Clin Ther.* 1998;20:410-423.