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Hyaluronan Injections Show No Histologic Evidence of Adverse Tissue Effects

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Abstract

Background: The safety of hyaluronan intra-articular injections is mostly based on animal studies and clinical evidence rather than histologic studies from human administration. **Objective:** This study analyzed the histologic effects of viscosupplementation with sodium hyaluronate on the synovium and articular cartilage of human knee specimen status post total knee arthroplasty within 3 years of viscosupplementation. **Methods:** Twenty-four specimens from total knee arthroplasties from April 2012 to August 2016 at NYU Winthrop Hospital were selected for microscopic analysis. All cases had a diagnosis of end-stage osteoarthritis at the time of surgery. Thirteen of the cases had 3 viscosupplementation injections of the knee with Euflexxa, a hyaluronate-based viscosupplementation agent, within 3 years preceding a total knee replacement. The remaining 11 did not receive viscosupplementation and were incorporated as controls. Upon histologic review, synovium was categorized by degree of hyperplasia and inflammation and the presence or absence of foreign material and giant cell reactions. Residual articular cartilage was categorized by staining intensity, and the presence or absence of crystals, foreign material, and giant cell reactions. **Results:** No significant difference was found between these groups for degree of synovial hyperplasia ($P = .33$) or for cartilage staining density ($P = .42$). None of the samples displayed evidence of foreign material, crystals, or giant cell reactions. **Conclusion:** In this cohort of patients, we demonstrated that Euflexxa was administered without any discernible microscopic adverse tissue effects.

Keywords

hyaluronan, hyaluronic acid, viscosupplementation, cartilage, synovium, osteoarthritis

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Introduction

Osteoarthritis (OA) is one of the most prevalent diseases diagnosed in the aging population.[1] A pathology of multifactorial influences, it can be a debilitating and painful manifestation of changes at the articular surface of joints, acting as a progressive condition with no true cure. In the early stages of OA, treatment may consist of rest, activity modification, and pain control with nonsteroidal anti-inflammatory drugs (NSAIDs) for exacerbations of symptoms. At the end stages of OA, after all conservative measures have failed to provide significant relief, joint arthroplasty becomes the optimal option for pain relief and joint motion restoration. However, prior to joint arthroplasty and following the most conservative measures, many patients and treating physicians advocate for intra-articular injections of various constitutes.[2] Steroid injections have demonstrated some relief in selective patients, acting as anti-inflammatory agents to decrease pain.[3] Other common injections for symptomatic OA relief include "gel" viscosupplementation utilizing substitutes of hyaluronic acid (HA). High-molecular-weight hyaluronan is a major component of synovial fluid; the molecular weight of the hyaluronan decreases by an order of magnitude in arthropathies secondary to the accumulation of fluid from localized inflammation.[4] It is the purpose of such gels to restore the natural hyaluronic acid that is lost in OA.

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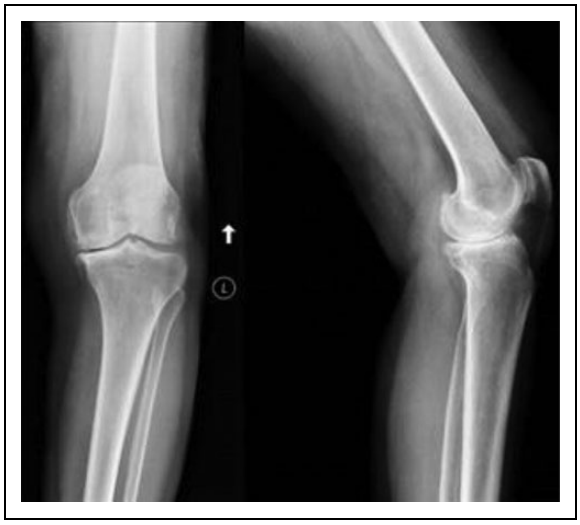

Figure 1. Preoperative left knee radiographs.

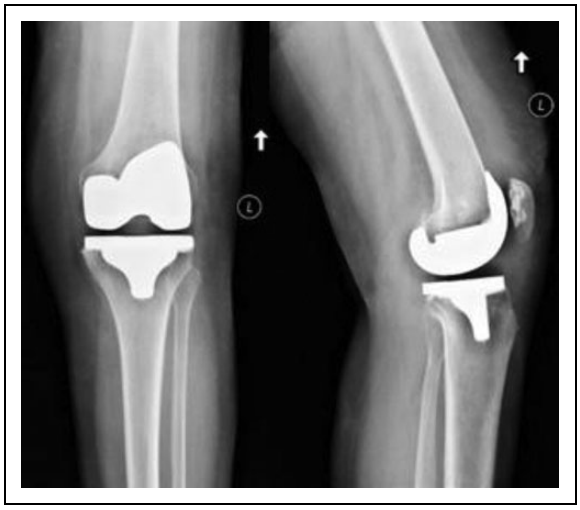

Figure 2. Postoperative left knee radiographs.

The synovial membrane is essential for both lubrication and nutrition of the articular cartilage. The synovium is made up of 2 layers—a thin intima with synoviocytes and a subintima layer composed of fibroblasts, macrophages, immune cells, nerves, and vascular structures.[5] Osteoarthritis increases the intimal cellularity, fibrosis, and vascularity of the synovium. The increased synovial fibrosis was correlated with knee pain in patients who underwent anterior cruciate ligament (ACL) reconstructive surgery.[6] The mechanism of HA injections is controversial considering its half-life in the joint is less than 1 day; however, it may act as a disease-modifying OA drug, decreasing the inflammation, fibrosis, and cellularity of the synovium.[6,7] HA appears to decrease inflammation by suppressing arachidonic acid and prostaglandin E2 release from fibroblasts and synovial cells, respectively.[4,7] Conversely, Ronchetti et al found HA treatment to increase fibroblasts and thus fibrosis, acting as a reparative mechanism, while decreasing the inflammation.[4] It is worth noting that the updated American Academy of Orthopaedic Surgeons (AAOS) clinical practice guidelines now strongly recommend against hyaluronic acid injections due to a number of studies showing a low likelihood of achieving a meaningfully important difference over placebo.[8]

The evasiveness of a definitive mechanism is in part due to the limited number of histological studies on the effects of HA injection on human synovium. Furthermore, without fully understanding this mechanism, the safety of the injections cannot be truly known.[9,10] The purpose of this study is to analyze the long-term histologic effects of viscosupplementation with sodium hyaluronate on the synovium and articular cartilage of human knee specimens status post knee arthroplasty within 3 years of viscosupplementation.

Methods

Twenty-four distal femur specimens from total knee arthroplasties from April 2012 to August 2016 at NYU Winthrop University Hospital were selected for microscopic analysis. All cases selected had a diagnosis of end-stage primary OA as exemplified in a preoperative radiograph shown in Figure 1. All patients with a history of inflammatory arthropathies were excluded. Any patients who received any other type of intra-articular injection during the 3 years preoperatively were also excluded. An example postoperative radiograph is shown in Figure 2. Thirteen of the specimens were from patients who received 3 viscosupplementation injections of the knee with Euflexxa (1% sodium hyaluronate; Ferring Pharmaceuticals Inc, Parsippany, NJ), a hyaluronate-based viscosupplementation agent, within 3 years, and at least 1 year, preceding a total knee arthroplasty . The remaining 11 did not receive viscosupplementation and were incorporated as controls. The area of maximal wear was selected for each specimen and underwent standard hematoxylin and eosin staining. A board-certified orthopedic pathologist reviewed these specimens in a blinded fashion. Synovium was categorized by degree of hyperplasia and inflammation as well as the presence or absence of foreign material and giant cell reactions. Residual articular cartilage was categorized by staining intensity as well as the presence or absence of crystals, foreign material, and giant cell reactions. Degree of hyperplasia and staining intensity were graded on a 0 to 3 scale, with zero indicating no hyperplasia/staining, 1 indicating minimal/focal hyperplasia/staining, 2 indicating moderate hyperplasia/staining, and 3 indicating diffuse hyperplasia/staining. Mann-Whitney U tests were run to determine the significance of differences between the groups. All statistics were performed in Microsoft Excel utilizing the Real Statistics add-in.

Results

Of the 13 viscosupplementation samples analyzed, 4 (31%) were classified as minimal hyperplasia and 9 (69%) were classified as moderate hyperplasia. Two (15%) of these samples did not have any staining for cartilage, 6 (46%) were classified as moderate staining density and 5 (38%) as diffuse staining

Table 1. Synovial Hyperplasia and Cartilage Staining Intensity of Viscosupplementation Samples.

Sample	Synovial Hyperplasia	Cartilage Staining
Viscosupplementation Data		
1	1	2
2	1	3
3	2	2
4	2	3
5	2	3
6	2	3
7	2	2
8	1	2
9	2	2
10	2	0
11	1	2
12	2	3
13	2	0

Table 2. Synovial Hyperplasia and Cartilage Staining Intensity of Control Samples.

Sample	Synovial Hyperplasia	Cartilage Staining
Control Data		
1	2	2
2	1	3
3	2	3
4	1	3
5	2	0
6	1	1
7	1	2
8	1	2
9	1	2
10	2	2
11	2	2

(Table 1). None of the samples displayed evidence of foreign material, crystals, or giant cell reactions.

Of the 11 control samples analyzed, 6 (55%) were classified as minimal synovial hyperplasia and 5 (45%) were classified as moderate synovial hyperplasia. One (9%) sample did not have any staining for cartilage, 1 (9%) was classified as minimal cartilage staining density, 6 (55%) as moderate cartilage staining density, and 3 (27%) with diffuse cartilage staining (Table 2). None of the samples displayed evidence of foreign material, crystals, or giant cell reactions. Utilizing Mann-Whitney U tests, no significant difference was found between these groups for degree of synovial hyperplasia ($P = .33$) or for cartilage staining density ($P = .42$; Table 3).

Table 3. Summary of Hyperplasia and Staining Intensity of Controls versus Viscosupplementation Samples.

Hyperplasia			Staining		
Control summary					
None	0	0%	None	1	9%
Minimal	6	55%	Minimal	1	9%
Moderate	5	45%	Moderate	6	55%
Diffuse	0	0%	Diffuse	3	27%
Viscosupplementation summary					
None	0	0%	None	2	15%
Minimal	4	31%	Minimal	0	0%
Moderate	9	69%	Moderate	6	46%
Diffuse	0	0%	Diffuse	5	38%
P value	.33		*P* value	.42	

Discussion

Our study provided a retrospective, histological review of articular cartilage and synovial pathology of knee specimens following total knee arthroplasty in the setting of prior viscosupplementation with Euflexxa within 3 years of surgery. We theorized that synovium would likely demonstrate the most notable physiologic changes, categorized for review by degree of hyperplasia and inflammation, as well as presence or absence of foreign material and giant cell reactions. Similarly, from our clinical understanding, it was theorized that articular cartilage would ideally benefit from such viscosupplementation, and residual findings were categorized by staining intensity as well as presence or absence crystals, foreign material, and giant cell reactions. Viscosupplementation should increase the amount of cartilage staining if it was successful in helping to preserve the cartilage of the specimen. Following a blinded review, there was no significant identifiable difference between the viscosupplementation group and the control group, with no histological evidence to demonstrate which patients did or did not receive viscosupplementation.

A limited number of histologic studies have been performed with regard to HA injections. One study by Schumacher et al showed no deleterious effect from these injections, but these samples were taken via arthroscopy, confounding the effects of lavage on the synovium. One meta-analysis concluded HA injections were safe; however, this was based on clinical adverse events with no histologic support.[1] On the contrary, a large meta-analysis by Rutjes et al recommended against HA injections due to an increased risk of adverse events.[11] There also remains concern that HA may counterintuitively increase synovitis based on reports of acute pseudo-septic flares.[12] This study, however, illustrates that there were no appreciable histologic adverse effects of prearthroplasty viscosupplementation with Euflexxa in synovium or articular cartilage of the knee over a period of 1 to 3 years.

This study does elicit some inherent subjective qualities that affect its strength. Despite a qualitative measuring system for staining characteristics, the attributing of such grades is at the discretion of a single pathologist and is not quantitative. Additionally, not all sample sizes were the same nor included the same amount of bone or tissue components relevant to histological review. Detailed demographic information of each patient and exact timing of HA injections was unfortunately unavailable for the analysis. Finally, while this study provides for insight utilizing its investigative techniques, a larger sample size may prove of variable statistical significance.

While the exact mechanism of HA injections remains elusive, these injections appear to be safe both clinically and histologically.[13] In this cohort of patients, we demonstrated that Euflexxa was administered without any discernible microscopic adverse tissue effects.

Declaration of Conflicting Interests

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