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Original Research

Prospective Evaluation of Intra-Articular Sodium Hyaluronate Injection in the Ankle

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ABSTRACT

Viscosupplementation by injection of hyaluronic acid into the ankle can be used to provide pain relief and to delay the need for surgery in patients with osteoarthritis of the ankle. In the present investigation, we prospectively evaluated 50 consecutive patients (25 males and 25 females) undergoing a 3-injection protocol of sodium hyaluronate viscosupplementation in the ankle from January 2014 to January 2015. The Foot and Ankle Outcomes Score was used to compare the patients' pre- and post-treatment opinions about their ankle problems. The mean pretreatment Foot and Ankle Outcomes Score was 48 ± 6.3 (range 25 to 84) and the 6-month post-treatment score was 78 ± 5.8 (range 48 to 100). This difference was statistically significant ($p = .003$). From our findings in the present prospective cohort study, we have concluded that intra-articular injection of sodium hyaluronate viscosupplementation is a useful conservative therapy for osteoarthritis of the ankle.

Symptomatic ankle arthritis affects 1% to 4% of the population, although it is less prevalent than hip and knee arthritis (1). Generally, a younger cohort is affected by ankle arthritis, and the etiology differs from that of primary hip or knee osteoarthritis (OA). The etiology underpinning ankle arthritis is primary idiopathic in 7% of cases, inflammatory arthritis such as rheumatoid arthritis or gout in 12%, and post-traumatic in 70% (2). The prevalence of OA is increasing in older adults and is expected to increase by 7% by 2030. Also, it is thought that approximately 20% of the U.S. population will have developed OA by 2030 (3). In the United States, a substantial number of primary care visits (approximately 36 million) and hospitalizations (approximately 750,000) were attributable to OA in 1997, revealing the important economic burden this disease imposes (3). Because ankle arthritis appears to affect younger patients (compared with knee and hip OA), useful conservative therapies that forestall or prevent the need for surgery are important. Conservative treatments include symptom control with analgesics, intra-articular corticosteroid injections, physiotherapy, and offloading and restriction of motion with bracing, shoe modifications, orthoses, assistive devices such as canes and crutches, and weight reduction. Recent recommendations from the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (4), the European League Against Rheumatism (5), the American College of Rheumatology (6), and the Osteoarthritis Research Society International (7,8) have suggested the use of intra-articular hyaluronic acid (HA) as a treatment option for patients with OA of the knees whose symptoms continue despite alternative treatments. Viscosupplementation (VS) appears to be increasing in popularity as a conservative treatment option for the management of symptomatic ankle OA, because it can effect analgesia and often delay the need for surgery.

Since its discovery, HA has been widely used in the treatment of OA of the knee. Although systematic reviews and randomized control trials pertaining to ankle arthritis are lacking in this area, a number of meta-analyses have evaluated the use of HA in the treatment of knee OA. In 2006, Bellamy et al (9) conducted a Cochrane review that included different HA products and 76 trials. In that review, HA was compared with placebo, intra-articular (IA) corticosteroid injections, and nonsteroidal anti-inflammatory drugs (NSAIDs). The pooled analyses showed a benefit associated with HA VS in terms of pain and function, and the benefit was sustained for 5 to 13 weeks after injection. Improvements from baseline of 28% to 54% for pain and 9% to 32% for function were observed. A similar benefit was noted when VS was

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compared with the use of NSAIDs, but the former had a safer side effect profile in elderly patients. Moreover, they also noted a longer duration of benefit with VS compared with IA steroid injections.

Bannuru et al (10) performed a meta-analysis of 137 studies comparing conservative treatment interventions for knee OA and found that HA had a significant effect size of 0.63 (95% Bayesian central credible interval). VS was superior to placebo and paracetamol and resulted in a greater sustained effect on pain for ≤3 months. They noted that trials that compared continuous NSAIDs directly with IA HA did not show significant short-term differences in terms of pain or stiffness; however, a greater side effect and adverse outcomes profile was seen in association with continuous use of NSAIDs.

VS has also been found to have a sustained effect on pain relief in patients with OA (10). Studies comparing IA HA and IA steroid injections found that for the first 4 weeks both were equivalent; however, from 4 to 26 weeks, IA HA resulted in greater pain relief (11).

A number of retrospective studies have evaluated VS as a method to delay the need for joint replacement. Altman et al (12) evaluated an administrative claims database of ~79 million patients to identify all patients with knee OA, who during a 6-year period underwent total knee replacement (TKR). The mean time to TKR in patients who did not receive HA was 0.7 year. In contrast, for patients who had received a single IA HA injection, the average duration to TKR was 1.4 years, and patients who had undergone ≥5 courses of VS succeeded in delaying TKR by 3.6 years ($p < .001$).

Despite the evidence supporting the use of VS in the knee, good-quality randomized controlled trials investigating its efficacy in ankle arthritis are lacking. HA is contained within the endogenous synovial fluid, and it acts as a fluid shock absorber. It also helps to maintain the structural and functional characteristics of the cartilage matrix. However, degradation of HA has been associated with increased susceptibility to articular cartilage damage (13–15). Further studies are needed to add to the existing data of HA to treat ankle arthritis. Differing protocols of low-molecular-weight (LMW) and high-molecular-weight (HMW) hyaluronic acid and injection techniques have been reported throughout the published data, making direct comparisons between trials challenging.

The aims of the present investigation were to prospectively evaluate consecutive patients receiving HA VS for the treatment of symptomatic ankle arthritis. The hypothesis was that injection of HA into ankles with OA could reduce joint pain and overall function as measured using a patient self-reported outcomes instrument.

Patients and Methods

The institutional review board of Galway University Hospital, Saolta Hospital Group (Galway, Ireland), provided ethical approval for the present investigation.

Study Population

The patients were recruited prospectively from a single surgeon's (S.R.K.) practice. The senior author (S.R.K.) injected all eligible patients if they had met the inclusion criteria. Two of us (E.M., M.C.) were involved in data extraction, outcome assessments, and 1 of us (G.T.) performed the statistical analyses. Two of us (E.M., N.P.M.) wrote the report. We decided a priori to consecutively enroll eligible patients during a 12-month period from the senior author's (S.K.) practice. A total of 50 patients (25 females and 25 males) were recruited during a 12-month period. We decided to perform the study for a 12-month period and to re-evaluate the patients during the following 12 months.

Patients with OA or post-traumatic ankle arthritis were included. Eligible patients were aged 18 to 70 years and had OA or post-traumatic arthrosis of the ankle diagnosed by the senior author (S.R.K.). Ankle OA or post-traumatic arthrosis was diagnosed from the clinical, history, and imaging results, including the following: *(1)* joint space narrowing, *(2)* osteophyte formation, and *(3)* obliteration of the joint space.

Inclusion Criteria

Patients aged 18 to 70 years were included. Both males and females were eligible for inclusion. Patients with a previous injury to the ankle without magnetic resonance imaging evidence of osteochondral lesions or sprains were included. Finally, patients who were able to participate voluntarily were recruited.

Exclusion Criteria

Patients who had received previous steroid injections or platelet-rich plasma injections were excluded. Patients taking anticoagulants, including novel oral anticoagulants and warfarin equivalents, that could not be discontinued were excluded. Patients with a peripheral neurologic degenerative condition were also excluded. Patients with a documented allergy to HA were excluded. Patients with a hypersensitivity to hyaluronate preparations, avian proteins, and feather and egg products were also excluded. Finally, patients with active skin disease or infections in the area of the injection site, and those with relative contraindications such as substantial venous and/or lymphatic stasis were excluded.

Intervention

For the purposes of the present investigation, VS was performed by a series of three 2-mL IA injections of sodium hyaluronate solution. Each injection was administered at 2-week intervals using an aseptic technique and delivered through the anteromedial portal typically used for ankle arthroscopy. The specific viscosupplement used in the present investigation was Suplasyn® (Mylan Pharma Group Ltd., Casla, Ireland). The sodium hyaluronate in Suplasyn® is considered to be a LMW polysaccharide preparation. The series of 3 articular injections has been shown to be more readily tolerated than a single injection. This was determined by the previous experience of the senior author (S.R.K.). It was observed that patients tolerated large volumes of VS injection to the ankle poorly. In general, the indications for IA injection of HA are an inadequate response to standard pharmacologic and nonpharmacologic treatment options, the desire to postpone surgery, and patients who are poor surgical candidates. The contraindications to receiving HA articular injections are hypersensitivity to hyaluronate preparations, avian proteins, feather and egg products, and active skin disease or infections in the area of the injection site. The relative contraindications include substantial venous and/or lymphatic stasis and the concomitant use of anticoagulants.

Outcomes Assessment

All the patients who participated in the present investigation completed the Foot and Ankle Outcomes Score (FAOS), which has been shown to provide valid information regarding patients' subjective opinion of the influence that their foot and/or ankle has on their activities (16). The FAOS consists of 42 questions, and it evolved out of the Knee Injury and Osteoarthritis Outcome Score. The FAOS addresses 5 domains: *(1)* overall burden of symptoms, *(2)* pain, *(3)* daily function (activities of daily living), *(4)* function in sports and recreation, and *(5)* foot- and ankle-related quality of life. The patients are instructed to answer the questions in regard to the previous week, using Likert-type responses that are tallied and normalized such that a score of 100 indicates no symptoms and 0 indicates severe symptoms and disability.

For the purposes of the present investigation, the FAOS questionnaire was administered before the patients received the VS injection and at 6-month intervals ≤12 months after injection. Adverse reactions and complications were monitored. The FAOS questionnaire considers stiffness, weakness, range of motion, and difficulty with ambulating; thus, these factors were not specifically analyzed individually.

Statistical Analysis

The data were considered in terms of the type and distribution, and the cohort was described in statistical terms (Tables 1 and 2). Student's paired *t* tests were used to compare the FAOSs before and after the intervention, and statistical significance was defined at the 5% ($p \leq .05$) level.

Results

Our cohort consisted of 50 patients with either primary or post-traumatic OA of the ankle. Of the 50 patients, 25 were male (50%). A statistical description of the cohort is provided in Table 1. The mean average age of these patients was 49 ± 8 (range 30 to 70) years. The etiology of ankle OA was primary in 14 patients (28%), post-traumatic in 34 (68%), and postinflammatory in 2 patients (4%). The mean duration of ankle arthritis symptoms was 36 ± 10 (range 8 to 48) months, and the mean follow-up duration was 12 ± 4 (range 8 to 16) months.

The statistical comparisons for the FAOS, by domain, for the baseline and follow-up scores are listed in Table 2. The mean baseline overall symptom burden domain score was 54 ± 8 (range 22 to 70),