Rate of Adverse Reactions to More Than 1 Series of Viscosupplementation

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abstract

Viscosupplementation, hyaluronic acid treatment, is an ancillary method for treating patients with symptomatic stage I or II osteoarthritis. Previous studies reported that local reactions occurred more frequently in patients receiving >1 course of treatment compared with patients receiving their first course of treatment. One (2%) of 42 first series patients and 4 (21%) of 19 of repeated series patients had adverse reactions severe enough to seek unscheduled care.

This study was performed to determine whether patients receiving >1 series of viscosupplementation had an increased adverse reaction rate. A retrospective chart review was performed on all patients who received >1 series of viscosupplementation during the study. A local adverse reaction was defined as acute swelling and pain in the knee, with no injury or trauma within 72 hours after hyaluronic acid injection.

Twenty-eight knees received >1 series of viscosupplementation. The adverse reaction rate to second series injections was 1.28% (3.57% of knees). The adverse reaction rate to >3 series was 0.9% (6.67% of knees). This adverse reaction rate was significantly less than the 21% reported in previous studies for multiple series injections ($z = -1.90; P < .05$) and is not significantly different than the 2% rate of adverse reactions reported for first series injections. No significant difference existed in the adverse reaction rates between 2 series and >3 series of viscosupplementation.

The current study suggests that the rate of adverse reaction was low at 1.28% of second series viscosupplementation.

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Viscosupplementation, a hyaluronic acid treatment, is an ancillary method for treating patients with symptomatic stage I or II osteoarthritis, as demonstrated by radiographs. As articular degeneration occurs, the level of hyaluronic acid in the joint decreases, leading to knee pain. Hyaluronic acid derivatives injected intra-articularly increase the elasticity and viscosity of the synovial fluid to the density of healthy synovial fluid, leading to a decrease in osteoarthritic pain and an improvement in mobility.1-2

Viscosupplementation temporarily relieves the symptoms of mild osteoarthritis based on the Visual Analog Score (VAS) and Western Ontario and McMaster University Osteoarthritis Index (WOMAC) scores.1-4 Viscosupplementation can significantly improve pain during load, pain at rest, and duration of walking activity vs baseline and can significantly increase patients’ activity levels.4 Higher-molecular-weight products, such as Hylan G-F 20 (Synvisc; Genzyme Biosurgery, Ridgefield, New Jersey), are superior to other formulations of hyaluronic acid viscosupplementation because they require fewer injections and have a decreased risk of infection compared with lower-molecular-weight hyaluronic products.5 When the efficacy of Hylan G-F 20 was compared with sodium hyaluronate, the clinical effectiveness and patient satisfaction was significantly better in patients who received Hylan G-F 20.6

In addition, treating osteoarthritis with Hylan G-F 20 can prolong the time before total knee arthroplasty (TKA) is necessary by 2 years.7 It has decreased pain and improved stiffness and physical functioning in patients who have previously undergone arthroscopic surgeries and partial meniscectomies.8,9 Hylan G-F 20 is a commonly used. Treatment involves 3 weekly intra-articular injections. Recently, single-injection hyaluronic acid therapy has been approved and is available for use (Synvisc-One; Genzyme Biosurgery). If results are beneficial, patients are able to receive another series of injections after a 6-month latency period, which is the time required by most insurance plans between treatments.

Previous studies, most notably that conducted by Leopold et al,10 reported that local reactions occurred more often in patients who received more >1 course of treatment compared with patients receiving their first course of treatment. One of 42 (2%) first series patients and 4 of 19 (21%) repeated series patients had adverse reactions severe enough to seek unscheduled care. An acute local reaction was defined as an acute onset of pain and swelling in the knee that occurred within 72 hours after the Hylan G-F 20 injection in the absence of another cause, such as acute trauma. These acute local reactions caused severe pain and limitation of activity and were treated with aspiration and corticosteroid injections that relieved the symptoms.10

The purpose of this study was to determine the risk of adverse reactions in patients receiving more >1 series of treatment with viscosupplementation.

**MATERIALS AND METHODS**

After Institutional Review Board approval, all patients who received >1 series of treatment with viscosupplementation from the orthopedic departments at Tufts Medical Center and Orthopaedic Associates at the Faulkner Hospital between July 2004 and July 2009 were identified. A retrospective chart review was performed, and data were collected, including: patients’ ages, sexes, arthritic knee compartments (medial, lateral, patellofemoral), which knees were injected with hyaluronic acid viscosupplementation, the number of series of hyaluronic acid viscosupplementation patients underwent, and adverse reactions. In addition, information was collected on whether the patients previously received steroid injections or whether they underwent arthroscopic surgery or TKAs since completing treatment with viscosupplementation.

Local adverse reactions were identified using the same guidelines that Leopold et al10 established. A local adverse reaction was defined as acute swelling and pain in the knee, with no injury or trauma within 72 hours after viscosupplementation. Painless effusions identified clinically at routine follow-up were not considered reactions.10

All intra-articular injections were performed using an aseptic technique with a 22-gauge needle by the orthopedic surgeons (A.W., E.M.) in these 2 practices. If an effusion existed, the fluid was drained using a straight-leg superolateral approach, and the viscosupplement was injected using the same needle but a separate syringe, as recommended by the manufacturers. If no effusion existed, the injection was administered using a flexed-knee anteromedial or anterolateral approach. Of the 28 knees injected with Hylan G-F 20, 28 of the first series knees and 25 of the second series knees were injected with Synvisc-One, which is 1 injection of 6 mL of Hylan G-F 20. The other 3 second series knees were injected with Synvisc-One, which is 1 injection of 6 mL of Hylan G-F 20. Conrozier et al11 demonstrated that one 6-mL injection is as efficacious as three 2-mL injections 1 week apart. After patients received injections, they were instructed to ice their knees and to not participate in strenuous activities for 1 to 2 days. Patients who had adverse reactions were asked about the circumstances of their symptoms to determine possible causation.

Excel 2004 for Mac version 11.5.8 (Microsoft, Redmond, Washington) was used for data management and statistical analysis. The percentage comparison function was used to calculate z scores to test for significant differences in proportions between pooled local adverse reactions in the current study and in the previous study by Leopold et al.10 The rate of adverse reactions between our first series and their first series, our second series and their first series, and our second series and their multiple series were compared.
A .05 significance level was used for all statistical tests. Significance levels are for 1-tailed tests.

RESULTS

Twenty-two patients (28 knees) received >1 series of Hylan G-F 20. Eleven (15 knees) patients were women and 11 (13 knees) patients were men. Mean age was 61.3 years (range, 38-86 years). Fourteen knees were left knees and 14 were right knees; 6 patients received bilateral injections. Radiographs revealed osteoarthritic changes on 25 medial, 12 lateral, and 23 patellofemoral compartments. Radiographs showed that 4 patients were affected in 1 compartment (all medial), and 8 patients had tricompartmental osteoarthritis (Table).

Of the 28 knees, 28 completed 2 series, 15 completed 3 series, 10 completed 4 series, 7 completed 5 series, 3 completed 6 series, and 1 completed 9 series of treatment with viscosupplementation. Mean total number of series completed was 3.36. All first and second series injections were with Synvisc. One patient underwent 2 series of Synvisc followed by 3 series of Orthovisc (Anika Therapeutics, Woburn, Massachusetts), and another patient received 5 series of Synvisc followed by 1 series of Hyalgan (Sanofi-Aventis, Bridgewater, New Jersey). During a fourth series injection with Synvisc, 1 patient had an adverse reaction and discontinued treatment with Synvisc. She finished her fourth series with Orthovisc. All other injections were with Synvisc. Mean time between the first and second series of treatment was 8.8 months (Table).

One patient had a local adverse reaction to a second series injection. The frequency of adverse reactions to second series injections was 1.28% (3.57% of knees and 4.54% of patients). This rate of adverse reactions to second series injections is significantly less than the 21% reported in by Leopold et al. for multiple series injections (z = -1.90; P < .05). No difference existed in the rate of adverse reactions to first series injections reported by Waddell et al and our second series injections. This adverse reaction was in a 78-year-old woman who placed heat on her knee following the first injection of her second series, resulting in increased pain and swelling. Treatment consisted of ice, elevation, and nonsteroidal anti-inflammatory drugs (NSAIDs), with resolution of the symptoms the following day. The second series was completed the following week, and the patient subsequently had 3 more Synvisc treatments, with no further adverse reactions.

No local adverse reactions to third series injections occurred, but 1 local adverse reaction to a fourth series injection occurred. The frequency of local adverse reactions to a fourth series was 3.57% of injections (10% of knees, and 12.5% of patients). A 53-year-old woman called the day after her first injection of the fourth series and reported that her knee was painful and swollen, with no redness or fever. It was presumed to be an allergic pseudoseptic reaction, and the patient did not complete the rest of the series. Treatment consisted of rest, ice, elevation, and NSAIDs, with resolution of the symptoms over the next few days. She began another fourth series with Orthovisc a month later. The rate of adverse reactions to fourth series Synvisc injections is similar to that accepted in the literature for first series adverse reactions and to our rate for second series adverse reactions. No adverse reactions occurred after fifth, sixth, or ninth series injections. In addition to determining the rate of adverse reactions to multiple series of viscosupplementation, previous and subsequent knee treatments of each patient were investigated. Twenty-one of 28 (75%) knees had received steroid injections prior to their first series of Synvisc. Both patients who experienced local adverse reactions received steroid injections previously. In addition, 12 (42.9%) of 28 knees had undergone arthroscopic surgery prior to their first series of Synvisc. Average time from arthroscopic surgery to beginning Synvisc was 29.8 months (range, 5 months-13 years). Of the 28 knees, 5 (17.9%) underwent TKA after Synvisc. Average time was 3.8 months after completing 4.8 series of Synvisc treatment. Fifty percent of the patients who had adverse reactions had previous arthroscopic surgeries, and neither patient had a TKA.

DISCUSSION

Acute local reactions following injections of viscosupplementation have been reported following first and multiple series of injections. However, a definition of a local adverse reaction has not been used consistently in the literature. For instance, a study looking at the tolerability and effectiveness of Hylan G-F 20 included 4253 patients and reported that treatment-related adverse events occurred in 4.2% of patients (2.4% of injections), but they defined an adverse event as joint effusion, joint swelling, arthralgia, joint warmth, and injection-site erythema. This is a broader definition in which the reactions could be from the injection or osteoarthritis itself, not the nature of the injected product.

This is similar to the low-threshold definition of “pain, warmth, and swelling lasting up to 3 weeks” that Puttick et al. used when they reported the rate of adverse events for first series injections to be 27% of patients and 11% of injections. These milder symptoms do not hinder the treatment or prognosis of patients.

When a product safety review reported that the most common adverse events with hyaluronic acid were mild injection site pain and swelling. Rare accounts were reported of severe acute inflammatory reactions and pseudoseptic knees with Synvisc. This was believed to be caused by antibodies to chicken proteins found in Hylan G-F 20. However, Synvisc demonstrated a favorable safety protocol in clinical trials and practice when compared with other standard therapies for managing osteoarthritic knee pain.
Table

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Abbreviations: F, women; L, left; Lat, lateral; M, men; Med, medial; N, no; PF, patellofemoral; R, right; Y, yes.

* First and second series Synvisc, third, fourth and fifth series Orthovisc (Anika Therapeutics, Woburn, Massachusetts).

**Patient had knee pain and swelling after heating it postinjection. This was the first injection of her second series. Patient finished her second series and had 3 subsequent series with Synvisc and no other reactions.

* First series Synvisc (Genzyme Biosurgery, Ridgefield, New Jersey), second series Synvisc-One (Genzyme Biosurgery).

* First to fourth series Synvisc, fifth series Synvisc-One.

* First to fifth series Synvisc, sixth series Hyalgan (Sanofi-Aventis, Bridgewater, New Jersey).

* Patient had an adverse reaction to the first injection of her fourth series of Synvisc; she discontinued the series and began a new fourth series with Orthovisc 7 weeks later.

* Patient had an allergic pseudoseptic reaction to the first injection of her fourth series. She did not complete the series and was treated with a fourth series of Orthovisc.
Many studies reported the rate of local adverse events to second series injections to be lower than the 21% of patients reported by Leopold et al.10 In a study of 71 patients with a mean time of 19.6 months between first and second series, Waddell et al.11 reported the incidence of local adverse reactions to second series was 1 (1.4%) of 71 patients. This patient did not discontinue the study due to this adverse event, supporting the repeated use of Synvisc if the patient has had a previous favorable clinical response. This study is consistent with the data collected in the current study, supporting the theory that multiple courses of Synvisc are well tolerated. Waddell et al.12 later reported that the incidence of treatment-related adverse events was 3.4% of patients (0.8% of injections) in the first series, 13.1% of patients (4.3% of injections) in the second series, and 17.3% of patients (5.4% of injections) in the third series.

The current study documented the adverse reaction rate to second series injections to be less than the incidence found by Leopold et al.10 and Waddell et al.12. The frequency of adverse events was similar to the incidence of first series adverse reactions reported by the manufacturer. Waddell et al.16 reported that 7.2% patients (2.2% of injections) experience adverse events in the first series. Therefore, the data from the current study support the hypothesis that no increased chance exists of experiencing an adverse event if one continues with multiple series of injections. No difference exists in the rate of adverse reactions to first vs repeated series of Hylan G-F 20 injections.

Raynauld et al.18 conducted a randomized controlled trial, in which 255 patients were randomized to an appropriate care group and an appropriate care with Hylan G-F 20 group, to determine the effectiveness of Synvisc. The group receiving Synvisc was subdivided into patients who received 1 course of treatment and patients who received ≥2 courses of treatment. Using the WOMAC pain scale, the single series subgroup improved by 41%, the repeat series subgroup improved by 35%, and the appropriate care group improved by 14%. Both subgroups improved significantly over the appropriate care group, and no significant differences existed in the number of adverse events between the single and repeat course groups.18 This study supports the hypothesis of the current study that Synvisc should be used for the treatment of osteoarthritis and that multiple courses can be given if pain continues. Repeat series continue to reduce pain, prolonging the time until TKA is needed.

The literature has also looked at a 12-month follow-up on patients treated with a second course of Hylan G-F 20. Patients improved significantly from baseline on the WOMAC and VAS index at 26 weeks and 52 weeks after injection, supporting the repeated use of Hylan G-F 20 with patients who previously had successful results with Synvisc.16 Synvisc continues to relieve pain with repeated series, and injections should continue to be given if a patient has done well with previous series.

Most patients avoid TKA if nonoperative treatments are available for the treatment of osteoarthritis. After activity modification, physical therapy, and the use of NSAIDs, choices for treating osteoarthritis are corticosteroid injections and viscosupplementation injections. Leopold et al.19 reported no significant difference with respect to pain relief at 6-month follow-up when comparing these fundamentally different intra-articular injections. Two randomized controlled trials found that viscosupplementation was superior to corticosteroids when evaluating the duration of pain relief.20,21 Seventy-five percent of the patients in the current study received steroid injections prior to the start of their treatment with Hylan G-F 20. Time to TKA is delayed when patients are treated with Synvisc.7

Local adverse reactions are a potential side effect of viscosupplementation. In one study, Synvisc, Hylan, and Supartz were injected into the air pouches of mouse knees to histologically examine the local inflammatory reactions. All showed a significant increase in total membrane cellularity, but an antibody response only occurred with Synvisc. Ottavini et al.22 concluded that this antibody response could be directed against a nonhyaluronic part of Synvisc, a possible reason why adverse reactions occur in Synvisc patients more often than with other viscosupplements.

Another study observed granulomatous inflammation after Hylan G-F 20 in 6 patients and concluded that Synvisc may be responsible for synovitis.23 However, Marino et al.24 rebutted by stating that this inflammation could be from miniscule levels of contaminants in the Hylan G-F 20 injection. The synovial fluid analysis of a patient with a large knee effusion after injection with viscosupplementation revealed intracellular rhomboid crystals typical of pseudogout.2

Another possible cause of local adverse reactions from Hylan G- F20 injections could be injection technique. If the viscosupplements are not properly administered into the joints and are instead injected into the fat pads of knees, local inflammatory reactions occur.23 Viscosupplements must be delivered into the joints and not into the anterior fat pads or subsynovial tissues. Looking at the accuracy of needle placement into the intra-articular space of the knee using fluoroscopic imaging on 240 consecutive injections by 1 orthopedic surgeon in the absence of knee effusions, 71% of anterolateral, 75% of anteromedial, and 93% of lateral midpatellar injections entered the knee joint space.26 This supports the theory that needle placement is correlated with adverse reactions rates. Lussier et al.4 concluded that the incidence of adverse reactions is significantly influenced by injection technique, although 69% of their patients who experienced adverse events still improved clinically. If an adverse event occurred, one cannot as-
sume that the treatment with Hylan G-F 20 was not successful.

This study demonstrated that the risk of adverse reaction after multiple series of hyaluronic acid treatment is 1.28%. Limitations of this study include biases involved in a retrospective review. In addition, 28 patients received multiple series of Synvisc injections. A larger sample size could have provided more confidence in the data. Also, multiple surgeons were involved, and thus injection technique was not standardized. All surgeons used a sterile technique and followed the manufacturer’s recommendations. Now that Synvisc One is available, adverse reactions may differ due to the increased volume of the injection and the decreased number of injections required for each series.

If patients experience positive results with a first series of viscosupplementation, then a second series can be considered with no increased risk compared with a first series of hiviscosupplementation. Patients in this study received up to 9 series of injections with positive results, with 1 patient discontinuing treatment because of an adverse reaction to a fourth series injection. Patients should be aware of the low risks of adverse reactions to viscosupplementation and that this risk does not increase with multiple series. A prospective follow-up study is currently being performed to evaluate the incidence of local adverse reactions to multiple series of Synvisc-One.

REFERENCES


