Intra-articular injection of hyaluronic acid for treatment of osteoarthritis knee: comparative study to intra-articular corticosteroids

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Objective
Osteoarthritis (OA) is a chronic degenerative joint disease characterized by pain and progressive functional limitation. Although both corticosteroid and hyaluronic acid (HA) injections are widely used to palliate the symptoms of knee OA, few researches involving a comparison of two interventions have been conducted.

The objective of the study was to compare the efficacy and safety of HA to corticosteroid injections for the treatment of knee OA.

Patients and methods
We enrolled 60 patients with knee OA who were randomized to receive intra-articular injection of either HA or the corticosteroid. The therapy was followed for 6 months. The patients treated with HA received one course of injections per week for 3 weeks and the other group received single injection of corticosteroid. The two groups were compared as regards pain and functional improvement using the Western Ontario and McMaster University Osteoarthritis Index and visual analog scale.

Results
The study included 60 patients, with age ranging from 36 to 65 years with a mean of 51.8 years. All of them were diagnosed with knee OA using ACR clinical classification criteria. Patients were recruited between May and December 2015.

After 6 months of the treatment, both groups showed functional improvement. HA group showed significant improvement compared with the corticosteroid group as regards the Western Ontario and McMaster University Osteoarthritis Index and visual analog scale (P=0.01).

Conclusion
Both HA and corticosteroid groups showed improvement in pain and knee function, but the intra-articular HA was superior to corticosteroid on long-term follow-up. This supports the potential rate of intra-articular HA as an effective long-term therapeutic option for patients with OA of the knee.

Keywords:
hyaluronic acid, intra-articular injection, osteoarthritis

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Introduction

Osteoarthritis (OA) is a very common complaint of the elderly and imparts physical and mental stress to the patient. It is a joint degenerative disorder affecting the joint cartilage leading to joint pain, stiffness, swelling, and disability [1]. This disease commonly involves hip, knee, spine, and fingers. OA is the second cause of living disability and includes 3% of total disabilities. The knee is the most common joint that is affected with OA and plays an important role in weight bearing and mobility [2]. Treatment of OA of the knee includes reducing pain, improving knee function, and quality of life. The medical treatment is directed mainly for reducing pain and inflammation and maintaining performance and normal movement of the joints [3]. As part of the overall management of patients with OA, it is important to use a therapeutic strategy including physical therapy and rehabilitation, NSAIDs, analgesics, chondroprotective agents, and intra-articular treatment with infiltrative substances such as steroids and hyaluronates [4]. Intra-articular injections of hyaluronic acid (HA) have been well established for the treatment of knee OA [5].

HA is a nonsulfated naturally occurring glycosaminoglycan with distinct physicochemical properties,

consisting of alternately repeating d-glucouronic acid and *N*-acetylglucosamine units. Hyaluronan possesses chondroprotective effects, which make it useful for the treatment of OA and RA. The cell surface reception of hyaluronan is involved in (i) the inhibition of catabolic actions exerted by proinflammatory cytokines and matrikines (matrix degradation products, which are known to be increased in OA and RA joints) and (ii) the inductor of catabolic enzyme (e.g. collagens and aggrecanase) that cause cartilage degradation [6].

Patients with OA have been shown to have a variable degree of synovitis, and it is thought that several cytokines and other mediators, particularly tumor necrosis factor and interleukin, may play a role in both synovial inflammation and in activation of chondrocytes and synovial fibroblasts [7].

Injection of exogenous HA into a joint may restore the articular viscoelastic properties [8]. HA exerts a beneficial effect on the cartilage integrities and responds to OA damage, which may be related to a primary effect of HA on the cartilage surface. HA may also act on the synovial membrane by limiting the synovial reaction [9].

The effects of HA on human OA chondrocytes are also related to its molecular weight, and thus the 500–730 kDa HA at 200 mg/ml reduces the synthesis of both interleukin and prostaglandin E2 by 70 and 45%, respectively, whereas the 6000 kDa HA does not [10].

Corticosteroids are most extensively used over the years by many researchers for intra-articular injection. Data regarding the comparison between HA with corticosteroids have revealed that intra-articular administration of the former drugs causes better and long-term pain relief in patients with knee OA [11].

The objective of the study was to compare the efficacy and safety of HA to corticosteroid injections for the treatment of knee OA.

Patients and methods

In this study, 60 patients with knee OA were included, with age ranging from 36 to 65 years old. They were diagnosed with primary OA according to ACR clinical classification criteria. Patients with radiological grades 2 and 3 according to Kellgren–Lawrence classification were included. Patients who reported that they had pain for more than 3 months and pain score of more than 40 mm on 100-mm visual analog scale (VAS) were included in this study. We excluded the patients with secondary OA, history of knee injections such as cortisone, pregnant patients, and patients suffering from diabetes mellitus, rheumatic diseases, and coagulation disorder.

In all, 60 women and men were randomly divided into two groups. One group included 30 patients who were treated with intra-articular HA by brand Sinovial Forte (IBSA Biochimque Institute SA, Switzerland, Lugano) 1.6% at an amount of 32 g/2 ml three times 1 week apart. The other group included 30 patients who were treated with intra-articular 2 ml of betamethasone sodium phosphate–betamethasone dipropionate mixed in 1 ml of lidocaine, one injection.

The Western Ontario and McMaster University Osteoarthritis Index (WOMAC) and the 100-mm visual analog pain scale were the outcomes instruments used to assess the response to treatment. The WOMAC was used as a self-administered questionnaire in accordance with the developer's instructions. With the use of WOMAC, a lower score represented a better outcome; the possible values range from 0 (best score) to 96 (worst score) based on the three subdomains of pain, stiffness, and difficulty in performing daily activities [12]. The VAS, which also was administrated by the patient, ranged from 0 to 100 mm, with lower numbers representing less pain and higher numbers representing more pain. Both instruments were used at the time of enrollment in the study before any injection and then again at three and 6 months after initial injection.

Intra-articular injections

Sinovial Forte 1.6% was administered in accordance with the manufacturer's recommendations as a course of three weekly injections. Each injection was given with the use of manufacture's prefilled syringes (32.0 mg of HA sodium salt in 2 ml of buffered physiological solution of sodium chloride). Before the administration of HA, knee effusions were aspirated into a separated syringe; the same needle was left in place and the syringe that had been prefilled with Sinovial Forte was used for injection.

The corticosteroid was given as a single injection of 2 ml of betamethasone sodium phosphate–betamethasone dipropionate mixed in 1 ml of lidocaine.

The injection was made via the anterolateral portal, and after injection the patient was advised to take 1 day of rest and apply ice to the area. Informed consent was obtained from patients before treatment, and none of the patients were excluded from the study.

Statistical analysis of data from this study was done using Student's *t*-test.

Results

In this study, we enrolled 60 patients with mild and moderate knee OA, with a mean age of 51.8 years. In all, 48 (70%) patients were female and 18 (30%) patients were male. The patients were divided randomly into two groups of 30 and were treated with intra-articular corticosteroid and sodium HA in knee joints. All patients participated until the end of the study and no specific medical complication occurred for the patients during this period.

No significant difference between the treatment groups was found with respect to age, weight (kg), and BMI, as shown in Tables 1 and 2.

Statistical analysis of data from this study was done using Student's *t*-test. The WOMAC score improved from baseline for patients treated with HA (median, 68–42 points; $P<0.01$) but not for those treated with corticosteroid (median, 65–58 points; $P=0.15$). The score on the VAS improved for the patients in the HA group (median, 72–54 mm; $P<0.010$) but not for those in the corticosteroid group (median, 71–66 mm; $P=0.4$). The difference between the improvements of the two groups was significantly different, with respect to the results on The WOMAC Index and the VAS at the 6-month follow-up evaluation. Thus, the patients receiving HA had greater improvements in the WOMAC and VAS than patients receiving corticosteroid.

Discussion

The study showed that in both HA and corticosteroid groups, the function of the knee was associated with an improvement, but intra-articular HA is superior to corticosteroid in improving pain, stiffness, and functional state.

The benefits of intra-articular hyaluronans have been shown in multiple randomized trials, but their onset of benefit is sometimes gradual, taking up to 2 months after the injections to achieve the optimal response. As an example, a 2011 meta-analysis of 54 randomized trials involving 7545 patients with knee OA examined the time course of benefit from intra-articular HA injection compared with placebo over a 6-month period [13]. Statistically and clinically significant improvement in joint pain was detectable by week 4, which peaked at week 8 and then trended downward, with some clinically relevant benefit still evident at week 24. The peak degree of benefit at week 8 was greater than that reported in most trials of acetaminophen and comparable to that of NSAIDs for knee OA. An analysis restricted to the high-quality trials failed to demonstrate statistically significant functional benefit, although the reduction in pain and the trajectory of the response was similar to that seen in the larger analysis.

Comparison with intra-articular glucocorticoids: intra-articular HA injections may provide benefits similar to those of intra-articular glucocorticoids, but the time courses of the responses to the agents may differ [14]. The following studies illustrate the range of findings:

(1) A systematic review of 28 randomized trials of intra-articular glucocorticoid injections for knee OA, involving 1973 patients, compared glucocorticoid injection with HA products, joint lavage, and placebo [15]. There were no significant differences between glucocorticoid injections and hyaluronate during the first month; greater benefit of hyaluronate appeared between 5 and 13 weeks postinjection, but was not sustained.
(2) A 2009 meta-analysis of seven randomized trials involving 606 patients with knee OA compared the time course of benefit (over 6 months) from intra-articular injection in the knee of either HA or glucocorticoid [16]. During the first 4 weeks following injections, comparisons favored intra-articular glucocorticoids; the agents were comparable in efficacy from week 4 to 8;

Table 1 Baseline demographic and clinical parameters

Treatments	Age (years)	BMI (kg/m^2)	% patients using NSAID
Hyaluronic acid	40–63 (52.5±12.5)	21–38 (28.5±10.6)	52
Corticosteroid	36–65 (50.2±11.4)	19–39 (28.3±11.4)	65
P value	0.42	0.9	

Table 2 Change in median outcomes score over time

Treatments	Total WOMAC (points)	Visual analog scale (mm)
Hyaluronic acid		
Before treatment	68±19.7	72±22.4
After 3 months	42±17.6	52±19.6
After 6 months	47±19.3	54±19.3
P value	<0.01	<0.01
Corticosteroid		
Before treatment	66±22.4	71±23.4
After 3 months	53±19.5	56±17.9
After 6 months	58±19.3	66±18.9
P value	0.15	0.4

WOMAC, Western Ontario and McMaster University Osteoarthritis Index.

and the comparisons favored intra-articular HA beyond 8 weeks.

(3) A larger 2014 network meta-analysis of 137 trials involving more than 33,000 patients with knee OA compared the relative efficacy of available treatments of knee OA, including intra-articular HA and glucocorticoids [17]. For pain reduction, the efficacy of intra-articular HA was not superior to that of intra-articular glucocorticoids at 3 months of follow-up.

In a prospective, randomized study, Jones *et al.* [18] reported that patients who have received HA injections for the treatment of inflammatory knee arthritis had less pain at 6 months of follow-up than did patients who received the corticosteroid triamcinolone hexacetonide. Only 63 patients were enrolled in that study, and 43 (68.3%) of them withdrew most commonly because of worsening of the symptoms – before the 6-month final follow-up evaluation. In addition, when those authors applied an intent-to-treat analysis that included all of the patients who had withdrawn, no significant differences were detected between the group treated with HA and that treated with the corticosteroid. Outcomes assessment in that report was limited to the VAS.

Conclusion

According to results, both HA and corticosteroid showed improvement in pain and knee function, but the intra-articular HA was superior to corticosteroid. This supports the potential rate of intra-articular HA as an effective long therapeutic option for patients with OA of the knee.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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