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ORIGINAL ARTICLE

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# Efficacy of intra-articular sodium hyaluronate in the treatment of knee osteoarthritis

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**Abstract** To assess the efficacy of intra-articular hyaluronic acid in patients with knee osteoarthritis, sixty female patients with knee osteoarthritis were randomised to three weekly intra-articular injections of 30 mg sodium hyaluronate (Na HA) with a high molecular weight (1.0 to 2.9 million Da) or 40 mg 6-methylprednisolone acetate (6-MPA). The clinical assessments included pain at rest, at weight-bearing and on walking, Lequesne Index and active range of knee flexion. Assessments were done at baseline, at week 4, and at months 3 and 6. A significant decrease in VAS scores for pain at rest, at weight-bearing and pain on walking, and in Lequesne index was found in both groups at week 4 when compared to baseline and there was no significant differences between the two groups. However, at 3$^{rd}$ month improvement in all pain scores and Lequesne index was found in favour of hyaluronic acid. At 6$^{th}$, no significant difference was found between the treatment groups. Improvement in pain was accompanied by an increase in joint flexion at week 4 and at month 3 in both groups. Both treatments were well-tolerated. The results showed that both intra-articular hyaluronic acid and 6-MPA treatments provide clinically significant improvement and demonstrated that Na HA has a long-term beneficial effect in patients with knee osteoarthritis.

**Keywords** Corticosteroid · Hyaluronic acid · Intra-articular injection · Knee osteoarthritis

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## Introduction

Osteoarthritis (OA) is the most common joint disease in the elderly and it causes a high health care expense [1–3]. Traditional treatments for OA include weight loss, muscle-strengthening exercises, simple analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), intra-articular corticosteroids, and surgery [4] . NSAIDs are commonly used in the treatment of osteoarthritis but they can lead to important gastrointestinal adverse effects [5, 6].

Intra-articular corticosteroids are also widely used in the treatment of knee osteoarthritis and they provide rapid relief of pain [7]. Although they produce rapid improvement, their benefit appears to be short-lived [8]. Intra-articular hyaluronic acid (HA) injection is another treatment approach for osteoarthritis of the knee. HA is an important component of synovial fluid and normal cartilage and this viscoelastic polymer, is responsible for some of the protective functions of the synovial fluid, including shock absorption, traumatic energy dissipation, protective coating of the articular cartilage surface and lubrication [9]. It has been shown that HA has a variety of effects on cells in vitro. For example, it reduces the leukocyte count and prostaglandin synthesis induced by interleukin-1 [10]. It stabilises lysosomal membranes, inhibits the phagocytosis and chemotaxis of inflammatory cells, removes free radicals and other reactive oxygen species [11, 12]. It has been shown that monoclonal antibodies against the HA receptor, CD44, blocks the effect of HA on expression of IL-1$\beta$, TNF $\alpha$, and IGF-1, indicating direct interaction of HA with the cell [13].

The concentration of HA in the synovial fluid of patients with knee OA is lower than that of normal synovial fluid and the molecular weight is reduced [14, 15]. These alterations may result in decreased physiological protective functions of the synovial fluid [16]. The principle of the intra-articular HA treatment is to restore the normal viscoelastic properties of SF to relieve the signs and symptoms of OA [9].

The treatment of OA using HA has been investigated in clinical studies. Randomised, blinded, controlled trials of intra-articular hyaluronic acid for the treatment of OA of the knee reported to date have shown variable results. Some authors have failed to show a difference between HA and placebo or intra-articular corticosteroid injections [17,18,19]. In contrast, a large number of studies have reported a significant decrease in pain and an improvement of mobility and function that can persist up to 6 months in OA patients treated with intraarticular HA [20–25]. The exact duration of improvement is not clear, but these effects may last for months, even though injected HA has a half-life of less than 24 hour in the joint [26].

In many studies, HA has proven to be safe in the treatment of knee osteoarthritis, resulting in minimal adverse effects [27].

The aim of this study was to assess the efficacy and safety of intra-articular sodium hyaluronate (Na HA) for the treatment of patients with knee osteoarthritis and to compare the results with the results obtained from the patients treated with intra-articular corticosteroid.

## Patients and methods

### Patients

Sixty-nine female ambulant patients who had idiopathic osteoarthritis according to American College of Rheumatology criteria were recruited for the study [28]. All patients had Grade II to III knee osteoarthritis confirmed radiologically according to the Kellgren – Lawrence grading system [29]. In all patients pain under weight-bearing was more than 40 mm on a horizontal visual analogue scale.

Exclusion criteria included Kellgren–Lawrence Grade IV radiological changes; knee joint disease other than osteoarthritis, osteoarthritis of the hip joint, osteoarthritic involvement of the foot joints, serious concomitant systemic diseases; intra-articular injections within the 3 months prior to study, skin infections overlying the joint; intra-articular fluid effusion; history of allergy or hypersensitivity to drugs; treatment with anticoagulants. None of the patients had previously undergone knee surgery.

The patients were briefed about the study and written consent was obtained from all patients.

### Study design

This study was an open-label, prospective, randomised, parallel group, controlled study with a 6 month follow-up period. Because of the differences in viscosity between hyaluronic acid and 6-MPA, we chose an open design.

This study was approved by the ethics committee of the Osmangazi University Medical School.

### Drug administration

Intra-articular HA treatment consisted of 3 weekly injections of 2 ml sodium hyaluronate with a high molecular weight of 1.0 to 2.9 million Da (15 mg/ml, Orthovisc®, Anika Therapeutics, Inc, Woburn, MA). In the control group, 1 ml 6-methylprednisolone acetate (40 mg/ml, Depo-Medrol®, Eczacıbaşı, Istanbul, Turkey) was administered by intra-articular injection. This treatment was also given weekly for 3 weeks.

The patients were allowed to use paracetamol (to a maximum of 3 gr daily) during the study period as considered appropriate by the physician. However, no paracetamol use was permitted for at least 48 hours before each injection and clinical assessment.

### Clinical assessment

The clinical assessment was made by the same investigator for each patient at baseline, at weeks 1, 2, 3, 4, and at months 3 and 6.

This assessment included pain levels at rest, at weight-bearing, and on walking and knee function. The level of knee pain was evaluated by the use of a 100 mm VAS (visual analog scale). In order to estimate functional impairment, Lequesne Functional index was used [30]. In addition active range of knee flexion was assessed in degrees on each visit.

The occurrence of adverse events was also reported at each visit.

### Laboratory assessment

Laboratory assessment (according to standard methods) was performed only at baseline and included the routine haematological and blood biochemistry tests.

### Statistical analysis

The efficacy parameters were statistically analysed using the values measured at baseline and at week 4, and at months 3 and 6.

Paired *t*-test was performed to groups with regard to age, disease duration and body mass index. For categorical analysis, chi-squared test was used. The mean efficacy criteria values for each treatment group at each session were compared using repeated measures analysis of variance (ANOVA) to determine any statistically significant differences between the groups and within the groups at any time. Fisher's exact test was used to compare the number of adverse events between the groups.

Statistical significance for comparisons was set at $P < 0.05$.

## Results

Sixty female patients were included in the trial and were assigned to two group, 30 patients in each group. Table 1 summarises their characteristics at the start of the trial. There were no statistically significant differences in demographic data measured between the two groups.

One patient in the 6-MPA group and one patient in the Na HA group discontinued after the second injection due to increased pain. One patient in the Na HA group and two patients in the 6-MPA group were not available for follow-up. At the end of the trial, a clinical

**Table 1** Baseline characteristics of the patients

| | Na HA ($n$ = 30) | 6-MPA ($n$ = 30) | $P$ value |
|---|---|---|---|
| Age (years) (mean ± SD) | 57.40 ± 6.54 | 60.10 ± 8.65 | NS |
| Disease duration (years) (mean ± SD) | 5.90 ± 4.59 | 6.8 ± 4.12 | NS |
| Body mass index (kg/m$^2$) (mean ± SD) | 32.65 ± 4.12 | 33.30 ± 4.48 | NS |
| KL Grade (II/III) | 12/18 | 14/16 | NS |

Na HA: Sodium hyaluronate, 6-MPA: 6-methyl prednisolone acetate, KL: Kellgren-Lawrence

**Table 2** Pain at rest by VAS

| | Na HA ($n$ = 28) (mean ± SD) | 6-MPA ($n$ = 27) (mean ± SD) | $P$ value |
|---|---|---|---|
| Baseline | 30.43 ± 9.78 | 29.90 ± 10.15 | NS |
| Week 4 | 11.83 ± 11.47* | 8.30 ± 9.76‡ | NS |
| Month 3 | 12.00 ± 10.15† | 19.70 ± 11.72§ | 0.030 |
| Month 6 | 23.56 ± 10.11 | 26.46 ± 14.30 | NS |

*$P < 0.001$ (one way anova; baseline versus week 4, in Na HA group)
†$P < 0.001$ (one way anova; baseline versus month 3, in Na Ha group)
‡$P < 0.001$ (one way anova; baseline versus week 4, in 6-MPA group)
§$P < 0.001$ (one way anova; baseline versus month 3, in 6-MPA group)

**Table 3** Weight-bearing pain by VAS

| | Na HA ($n$ = 28) (mean ± SD) | 6-MPA ($n$ = 27) (mean ± SD) | $P$ value |
|---|---|---|---|
| Baseline | 54.26 ± 22.65 | 53.10 ± 18.30 | NS |
| Week 4 | 31.83 ± 21.57* | 26.80 ± 15.83‡ | NS |
| Month 3 | 22.86 ± 17.05† | 38.50 ± 16.53§ | 0.033 |
| Month 6 | 40.96 ± 23.15 | 56.36 ± 16.10 | NS |

*$P < 0.001$ (one way anova; baseline versus week 4, in Na HA group)
†$P < 0.001$ (one way anova; baseline versus month 3, in Na Ha group)
‡$P < 0.001$ (one way anova; baseline versus week 4, in 6-MPA group)

assessment was obtained in 55 patients (28 patients in the Na HA group and 27 patients in the 6-MPA group).

## Pain

As shown in table 2, compared to baseline at week 4 and at month 3, a significant decrease was found in the VAS score for rest pain in both treatment groups ($P < 0.001$). There was no significant difference between the groups at week 4, but at month 3 the decrease in VAS score for pain rest was in favour of Na HA treated patients ($P = 0.030$). At month 6, the pain intensity returned to baseline values in both groups ($P < 0.001$). The difference between the groups at month 6 was not statistically significant.

The intensity of weight-bearing pain showed a parallel reduction in both groups at week 4 ($P < 0.001$). Three months later, the difference was statistically significant in Na HA group when compared to the baseline ($P < 0.001$). When the groups were compared with each other, a significant decrease was found in favor of the Na HA group ($P = 0.033$). At month 6, the difference between groups was not statistically important.

At week 4, both treatments were associated with decreased pain on walking ($P < 0.001$), and the difference between the groups was not statistically significant. A significant difference was found in the VAS score for pain on walking between the two treatment groups in favour of Na HA at months 3 ($P = 0.015$). At month 6, Na HA administration was associated with decreased pain while walking ($P < 0.05$), although the differences between treatment groups were not statistically significant (Table 4).

## Lequesne index

The improvement in the functional impairment assessed by the Lequesne functional index was statistically significant in both groups at week 4 ($P < 0.001$), and there was no significant difference between groups. Whereas, at month 3, there was a significant difference in this efficacy parameter between the two treatment groups in favor of Na HA ($P = 0.045$), but the difference was not significant at month 6.

## Active knee flexion

Improvement in pain was accompanied in Na HA group by an increase in joint flexion at week 4 and at month 3 ($P = 0.027$ and $P = 0.003$, respectively). No significant difference was observed in 6-MPA treated group. However, the difference between treatment groups for

**Table 4** Pain on walking by VAS

| | Na HA ($n$ = 28) (mean ± SD) | 6-MPA ($n$ = 27) (mean ± SD) | $P$ value |
|---|---|---|---|
| Baseline | 67.60 ± 21.03 | 69.00 ± 21.96 | NS |
| Week 4 | 37.60 ± 25.00* | 38.00 ± 16.01§ | NS |
| Month 3 | 32.03 ± 22.15† | 50.46 ± 18.46** | 0.015 |
| Month 6 | 51.16 ± 20.81‡ | 66.06 ± 20.83 | NS |

*$P < 0.001$ (one way anova; baseline versus week 4, in Na HA group)
†$P < 0.001$ (one way anova; baseline versus month 3, in Na HA group)
‡$P < 0.05$ (one way anova; baseline versus month 6, in Na HA group)
§$P < 0.001$ (one way anova; baseline versus week 4, in 6-MPA group)
**$P < 0.05$ (one way anova; baseline versus month 3, in 6-MPA group)

**Table 5** Lequesne functional index

| | Na HA ($n$ = 28) (mean ± SD) | 6-MPA ($n$ = 27) (mean ± SD) | $P$ value |
|---|---|---|---|
| Baseline | 10.23 ± 1.88 | 9.86 ± 1.88 | NS |
| Week 4 | 7.86 ± 1.47* | 7.96 ± 1.58‡ | NS |
| Month 3 | 7.66 ± 1.60† | 9.06 ± 1.13§ | 0.042 |
| Month 6 | 8.46 ± 2.04 | 9.60 ± 1.83 | NS |

*$P < 0.001$ (one way anova; baseline versus week 4, in Na HA group)
†$P < 0.01$ (one way anova; baseline versus month 3, in Na HA group)
‡$P < 0.001$ (one way anova; baseline versus week 4, in 6-MPA group)
§$P < 0.05$ (one way anova; baseline versus month 3, in 6-MPA group)

**Table 6** Active range of knee flexion (degrees)

| | Na HA ($n$ = 28) (mean ± SD) | 6-MPA ($n$ = 27) (mean ± SD) | $P$ value |
|---|---|---|---|
| Baseline | 108.70 ± 10.79 | 108.06 ± 10.27 | NS |
| Week 4 | 116.36 ± 7.79* | 114.20 ± 9.98 | NS |
| Month 3 | 115.76 ± 7.72† | 113.40 ± 8.10 | NS |
| Month 6 | 114.60 ± 8.19 | 109.60 ± 9.91 | NS |

*$P < 0.05$ (one way anova; baseline versus week 4, in Na HA group)
†$P < 0.01$ (one way anova; baseline versus month 3, in Na HA group)

this parameter was not statistically significant at any time.

### Concomitant medications

At the beginning of the study paracetamol consumption was similar in both groups (58% in the Na HA group; 54% in the 6-MPA group). The percentages of the patients using paracetamol during the injection period (18% in the Na HA group; 15% in the 6-MPA group) and during the 6 month follow-up (21% in the Na HA group; 22% in the 6-MPA group) were also very similar in both groups and there was no significant difference between the groups.

### Safety

No serious systemic adverse event was reported which could be related to the treatment. Six patients treated with Na HA (21%) and five patients treated with 6-MPA (18%) reported knee pain after the injection. One patient in the Na HA treated group experienced knee pain and swelling, which resolved 4 days later. No significant difference between groups was observed with respect to adverse events (Table 7). Any clinically significant modifications in body weight and blood pressure were observed during the study period.

## Discussion

This study confirms that both Na HA and 6-MPA injections provide beneficial effects for patients with knee OA on a short term basis. But in the long-term assessment, pain relief and improvement in function were better in the Na HA treated group. Although there was a trend in favour of the Na HA treated group, the differences between treatment groups were not statistically significant at month 6. Our results were in consistence with many other studies which have demonstrated similar effects.

**Table 7** Adverse events reported by the patients

| | Number of adverse events | |
|---|---|---|
| | Na HA ($n$ = 28) | 6 = MPA ($n$ = 27) |
| Musculoskeletal | 7 | 5 |
| Skin | 2 | 1 |
| Gastrointestinal | 3 | 2 |
| General | 4 | 5 |

Na HA: Sodium hyaluronate, 6-MPA: 6-methyl prednisolone acetate

The safety and efficacy of different hyaluronic acid formulations have been investigated in many studies. In most of these studies, the investigators have compared hyaluronic acid to saline placebo. Studies by Huskisson [20], Dougados [23], Wobig [31], and Petrella [32] have shown symptomatic improvement in knee OA after treatment with HA. In another study, Adams [33] showed that the combination of HA and NSAIDs resulted in lower visual analogue pain and Lequesne functional index scores at 26 weeks compared with those taking NSAIDs alone.

Recently, a three arm study was conducted by Altman [34]. In this study, patients were treated with 5 weekly intra-articular injections of HA, saline or naproxen (500 mg twice a day). The results demonstrated that HA was superior to placebo. Findings in the HA group were similar to those in the naproxen group.

In a double-blind, multicenter, randomised, placebo controlled trial, Lohmander [35] has found a significant difference only in patients 60 years or older and a Lequesne index greater than 10 at baseline.

In contrast to the above studies, in a very recent placebo-controlled, open-label, single-blinded study, Tamir [17] was unable to show any significant difference between the HA and placebo groups.

The sodium hyaluronate preparation that we used in this study, like other preparations, is derived from rooster combs. It is a purified, high molecular weight, high concentrated, non-crosslinked, stable hyaluronic acid preparation. There are only one publication from which to assess its efficacy and safety. A double-blind, multicenter, placebo-controlled study which was conducted by Brandt [36] and colleagues has recently been published. The results of this study showed that Na HA treatment produced statistically and clinically significant improvement in patients with mild to moderate knee OA.

Comparative studies with intra-articular steroid injections have also been done. An open study comparing HA and 6-MPA suggested that the efficacy of hyaluronic acid was comparable to that of the steroid on a short term basis, while at the end of the follow-up all the pain monitoring parameters presented significant difference in favour of the HA treated group [8]. In another study, Jones [19] compared hyaluronic acid with triamcinolone and found no significant clinical differences.

In the present study, three-weekly injections of Na HA produced pain relief and improvement in function which continued for 3 months. Although there was

a trend in favour of the Na HA treated group, the differences between treatment groups were not statistically significant at month 6. The improvement in joint pain and function may persist for months, even though injected HA is cleared rapidly from the joint. The basis for this long-term effect on symptoms in some patients after intra-articular HA injections, is difficult to explain. In animal models, studies attempting to ascertain whether IA injections of HA significantly modifies structural damage in OA joint have produced conflicting results. In some experimental models of OA, HA has been reported to exert a disease-modifying OA drug effect [37]. In other cases, no effect has been observed [38]. It has been suggested that injected HA may trigger the synthesis of endogenous HA in the OA joint and lead to an increase in the viscosity of the synovial fluid [9, 39].

Osteoarthritis is a chronic disease that often requires systemic or local therapies. Because of this reason economic evaluation is an evolving field that will become increasingly important in the treatment of osteoarthritis. The cost-effectiveness and cost-utility of intraarticular HA treatment were determined in a very recent study and the results of this multicenter trial provided strong evidence for adoption of treatment with HA in patients with knee OA [40]. In our study the beneficial effects of Na HA and 6-MPA tend to persist several months after the cessation of therapy. In addition, unlike NSAIDs, any important adverse event has been reported and both treatments appeared to be well tolerated. Based on these data, it can be suggested that these advantages should have an overall cost lowering effect.

Until today many double-blind studies comparing the efficacy of different hyaluronic acid preparations with either placebo or corticosteroids have been done. However, there is just one trial comparing the efficacy of hyaluronic acid preparation that we used in this study with placebo. Also there is no study that compares the efficacy of this preparation with intra-articular corticosteroids so far. With the assumption that the analysed topic is a new one, we planned this trial. However, the results that we obtained were similar to the results of the previous studies. The open-label protocol was the main limitation of our study. Because of the differences in the viscosity of Na HA and 6-MPA we had to use this protocol. We admit that this protocol may lead biases about the objectivity of both the patients and the clinical observer. In order to eliminate the risk of bias we used an observer blinded to the nature of the injected medication.

In conclusion, this study suggests that intra-articular injections of Na HA is well-tolerated, provide pain relief and improved function and have a long-term beneficial effect in patients with knee osteoarthritis and gives further support to previous literature about the efficacy of HA. We believe that additional long-term studies are needed to assess the prolonged pain-relieving effect of hyaluronic acid.

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