

## Comparison of the effects of intraarticular hyaluronic acid and antiinflammatory drug treatments on the surgical intervention rates in patients with gonarthrosis

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**Aim:** The aim of this study was to compare the frequencies of surgical interventions between patients receiving intraarticular hyaluronic acid (IAHA) injection and those receiving only oral antiinflammatory drug treatment at the end of a 1-year follow-up period.

**Materials and methods:** A total of 705 patients diagnosed with knee osteoarthritis (OA) between 2007 and 2009 were included in this study. Their records were investigated retrospectively. We divided 218 of the patients into 3 groups according to the Kellgren–Lawrence criteria, and they received sodium hyaluronate once a week for 3 weeks. Another 487 patients with gonarthrosis served as group 2 and were treated with nonsteroidal oral antiinflammatory drugs and exercises. The surgical rates between the IAHA groups and the control groups were compared. The groups with the 2 different treatment modalities were compared according to the surgical operation rates at the end of a 1-year period.

**Results:** While 9 of the 68 IAHA-treated patients with grade 2 OA had a surgical intervention within the year, 22 of the 172 patients with grade 2 OA in group 2 were operated on (13.2% versus 12.8%,  $P = 0.927$ ). A surgical intervention was performed in 7 of the 78 IAHA-treated patients with grade 3 OA at the end of 1 year, and in 18 of the 164 patients with grade 3 OA (group 2) (8.9% versus 10.9%,  $P = 0.629$ ). Of the 51 IAHA-treated patients with grade 4 OA, 4 underwent a surgical intervention within the year, whereas 22 of the 151 patients in group 2 were operated on (7.8% versus 14.6%,  $P = 0.222$ ).

**Conclusion:** Although there was no statistically significant difference between the groups, a lower percentage of IAHA-treated patients with grade 4 OA underwent surgical interventions. At the end of 1 year, the rates of surgical operations between the patients receiving IAHA and antiinflammatory treatment in the other 2 groups (knee grades 2 and 3 OA) showed no statistically significant difference.

**Key words:** Hyaluronic acid, intraarticular injections, osteoarthritis, knee surgery

### 1. Introduction

Osteoarthritis (OA) is the most common form of arthritis (1). Approximately one-third of all adults have radiological signs of OA (2). However, clinically significant OA of the knees, hands, and hips was reported in 8.9% of the adult population (3). It is most commonly seen in the knee joint. Obesity, anatomic abnormalities, and loss of joint stability set abnormal stresses on the joint and can lead to cartilage changes and degradation. Aging, genetic predisposition, inflammation, and immune system activity can also play a role in abnormal cartilage changes (4).

Patients suffering from OA might complain of pain, muscle weakness, a limited range of motion, and increasing disability (5). The aim of treatment is to reduce pain, stop

damage to the cartilage, and increase the range of motion. Patient education, weight loss, physiotherapy and exercise, assisting devices, pharmacological therapies, and surgery are the treatment modalities used in gonarthrosis (6). OA is often treated with nonsteroidal antiinflammatory drugs (NSAIDs) (7,8). Diclofenac sodium is the most frequently used NSAID in the treatment of OA. The efficacy of diclofenac sodium is largely unchallenged in that it remains as effective as newer pain relief medications employed in OA (9).

One conservative treatment modality in gonarthrosis is hyaluronic acid (HA) injection. The surfaces of the cartilage and synovial membrane are coated with HA (10). HA also plays a particular role in synovial fluid,

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giving it its shock-absorbing and viscoelastic properties (11). Incomplete synthesis and increased production of incompletely polymerized HA have been postulated as possible explanations of OA (12). Initially, repeated courses of intraarticular hyaluronic acid (IAHA) injection had been accepted as effective and safe in the treatment of gonarthrosis and other diseases (13–17). However, in recent years, studies found that IAHA had no effect in the treatment of OA (18,19). In another study, IAHA treatment could prolong the time to surgery in patients with gonarthrosis that did not respond to conservative treatment (20).

This study aimed to compare the frequencies of surgical interventions between patients receiving IAHA injections and those receiving only oral antiinflammatory drug treatment at the end of a 1-year follow-up period. The relationship between the surgical operation rates and grade of OA was investigated.

## 2. Materials and methods

A total of 705 patients with knee pain, diagnosed between January 2007 and June 2009, were included in the study. All of them had a diagnosis of knee OA according to the American College of Rheumatology (ACR) criteria (21). Standing radiographic images of the knee joint from anteroposterior and lateral aspects were performed and the patients were divided into 3 groups according to the Kellgren–Lawrence criteria (KLC) (22) (Table 1). Exclusion criteria were as follows: a) intraarticular injection history in the previous 3 months, b) arthroscopic intervention in the previous year, and c) history of pain occurrence related to intraarticular injection.

Group 1 initially consisted of 218 patients who received 25 mg of sodium hyaluronate (Adant<sup>®</sup>, 25 mg of sodium hyaluronate dissolved in 2.5 mL of physiological saline, Meiji-Seika Kaisha, Japan) once a week for 3 weeks. Due to pain or swelling and effusion occurrence after the first IAHA injection, 21 patients (9.6%) were excluded from the study. Therefore, group 1 finally comprised 197 patients.

According to ACR criteria, group 2 consisted of 487 patients with gonarthrosis. These patients received only medical treatment with NSAID oral drugs (diclofenac sodium in doses of 75 mg twice daily for 10 days) and exercise. These participants were also divided into 3 groups according to the KLC (Table 1).

In all groups, surgical decisions were made based on the conditions of persisting pain, limitation of movements in the knees, and unresponsiveness to given medical treatment. The operation rates between IAHA groups and NSAID groups were compared statistically.

SPSS 15.0 was used for statistical analysis and the variables were compared by using chi-square and Friedman tests. Values less than 0.05 were considered significant.

## 3. Results

Demographic data of the patients in all groups are shown in Table 2

Of the 68 patients (13.2%) with grade 2 OA (group 1), 9 had a surgical intervention after 1 year (1 meniscal tear, 8 cartilage-related problems), whereas 22 of 172 patients (12.8%) with grade 2 OA in group 2 were operated on within the year (6 meniscal tears, 16 cartilage-related problems). There was no significant difference between the groups ( $P = 0.926$ ). All operations were performed arthroscopically with debridement and washing (Table 3).

A surgical intervention was done in 7 (8.9%) of 78 patients from group 1 with grade 3 OA at the end of 1 year (4 cartilage-related problems with arthroscopic debridement and washing, 3 total knee prostheses). In the NSAID group, 18 (10.9%) of 164 patients with grade 3 OA were operated on (2 meniscal tears, 12 cartilage-related problems, and 4 total knee prostheses). The difference was not statistically significant ( $P = 0.629$ ). Arthroscopy was performed on patients not responding to conservative treatment. The patients who had severe cartilage defects in arthroscopy and were not satisfied with the operation underwent knee prosthesis operation within 3 months (Table 3).

In group 1, 4 of 51 patients with grade 4 OA (7.8%) underwent a surgical intervention within the year, whereas 22 of 151 patients (14.6%) with grade 4 OA from group 2 were operated on. Although the observed operation frequency in patients with grade 4 OA was 6.8% less than that in grade 4 OA patients of the control group, the difference was not statistically significant ( $P = 0.222$ ). In all of these patients, a total knee prosthesis operation was performed (Table 3). The decision to perform a surgical intervention was made for patients with night pain, walking pain, and limited walking distances.

**Table 1.** Kellgren–Lawrence criteria.

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Grade 1: Doubtful narrowing of joint space and possible osteophytic lipping.

Grade 2: Definite osteophytes, definite narrowing of joint space.

Grade 3: Moderate multiple osteophytes, definite narrowing of joints space, some sclerosis and possible deformity of bone contour.

Grade 4: Large osteophytes, marked narrowing of joint space, severe sclerosis and definite deformity of bone contour.

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**Table 2.** Demographic data of study groups. SD: Standard deviation, Grade: according to Kellgren–Lawrence criteria.

	Group 1			Group 2		
	Grade 2	Grade 3	Grade 4	Grade 2	Grade 3	Grade 4
	n = 68	n = 78	n = 51	n = 172	n = 164	n = 151
Age, mean (SD), years	52 (11.8)	56 (10.2)	68 (13.3)	49 (11.8)	53 (10.6)	61 (12.2)
<b>Sex</b>						
Female, n (%)	61 (92.8)	67 (85.8)	33 (64.7)	159 (92.4)	143 (87.1)	109 (72.1)
Male, n (%)	7 (7.2)	11 (14.2)	18 (35.3)	13 (7.6)	21 (12.9)	42 (27.9)

**Table 3.** Treatment results of study groups. IAHA: intraarticular hyaluronic acid injection. NSAID: nonsteroidal antiinflammatory drugs. Grade: according to Kellgren–Lawrence criteria.

	Treatment				Surgical treatment					
	IAHA		NSAID		Arthroscopy		Total knee replacement		Total	
	n	%	n	%	n	%	n	%	n	%
<b>Group 1 grade</b>										
2	59	86.8	0	0	9	13.2	0	0.0	68	100
3	71	91.0	0	0	4	5.2	3	3.8	78	100
4	47	92.2	0	0	0	0.0	4	7.8	51	100
Total	177	89.8	0	0	13	6.6	7	3.6	197	100
<b>Group 2 grade</b>										
2	0	0	150	87.2	22	12.8	0	0.0	172	100
3	0	0	146	89.0	14	8.5	4	2.5	164	100
4	0	0	129	85.4	0	0.0	22	14.6	151	100
Total	0	0	425	97.3	36	7.4	26	5.3	487	100

#### 4. Discussion

According to international guidelines for knee symptoms, NSAIDs should be the first choice of medication for pain relief in osteoarthritis. Of all prescribed pain medication in general practice, 90% consists of nonsteroidal antiinflammatory drugs (23). Diclofenac is a commonly prescribed NSAID for pain relief in OA. A review of the available data demonstrates that diclofenac continues to provide physicians with a benchmark pharmacological treatment for OA (9). However, long-term use of NSAIDs is also directly related to many side effects, including gastrointestinal bleeding, hypertension, congestive heart failure, hyperkalemia, and renal insufficiency (24).

Although IAHA treatment has been used for years with promising results, there are conflicting results concerning this treatment in patients with OA. Altman et al. (25) compared HA injections to a placebo or oral naproxen in 495 patients with idiopathic osteoarthritis in a 26-week, double-blind masked trial. Patients receiving IAHA treatment achieved better results than the placebo group ( $P < 0.05$ ). At the end of 26 weeks, 47.6% of patients treated with IAHA had slight pain or were pain-free, compared to the placebo group or naproxen patients. A metaanalysis and additional studies also reported on the effectiveness of IAHA treatment (16,26–28).

However, another study concluded that IAHA offers no significant benefit over a placebo during the treatment period but leads to a significantly higher morbidity, and therefore has no place in the routine treatment of OA (29). A study by Jorgenson et al. (18) showed that intraarticular injections of hyaluronan did not improve pain, function, paracetamol consumption, or other efficacy parameters in the following 12-month period.

To our knowledge, there is only one prospective study that claimed that IAHA treatment could be effective in delaying the time to total knee replacement in patients with knee OA that did not respond to conservative treatment. However, this prospective study by Turajane et al. did not include a control group (20). In the present study, IAHA treatment did not reduce the need for surgical intervention in patients with knee OA. Although the difference between

the operation frequencies of all groups was not statistically significant, it was 6.8% less in patients with grade 4 OA than in the controls. This difference was obvious, although not significant (7.8% versus 14.6% in grade 4 OA and controls respectively,  $P = 0.222$ ). IAHA treatment could prolong the time to surgery, especially in patients with grade 4 OA, but this effect should be investigated in prospective studies with more patients.

In conclusion, although not statistically significant, a lower percentage of IAHA-treated patients with grade 4 OA underwent surgical intervention. At the end of 1 year, the rates of surgical operations as compared between the patients receiving IAHA injections and those receiving antiinflammatory treatment in the other 2 groups (knee grades 2 and 3 OA) showed no statistically significant difference.

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