

# Long-term efficacy and safety of intra-articular sodium hyaluronate (Hyalgan®) in patients with osteoarthritis of the knee

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## **Abstract**

### **Objective**

*This prospective cohort study evaluated the long-term efficacy and safety of 5 weekly intra-articular (i.a.) injections of sodium hyaluronate (Hyalgan®) in 76 patients (92 knees) with moderate to severe osteoarthritis (OA) of the knee whose pain was not controlled by conventional measures.*

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### **Results**

*Thirteen patients had a repeat treatment course. A total of 72% of patients achieved >50% improvement (defined by physical examination and assessment of pain using a visual analog scale [VAS]) for 1 year or longer; 9% of patients failed to achieve >50% improvement for any period of time. The duration of response exceeded 2 years in some patients. Total knee replacement surgery was avoided or significantly delayed in 15 of 19 patients who were considering surgery prior to the injections. Ten of 15 (67%) knees improved after a repeat treatment course. Local adverse events were minor and infrequent.*

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### **Conclusion**

*Intra-articular sodium hyaluronate was an effective and safe treatment for pain in difficult-to-treat patients with moderate to severe OA of the knee.*

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### **Key words**

Osteoarthritis of the knee, sodium hyaluronate, Hyalgan®.

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### Introduction and rationale

Hyaluronan (hyaluronate, hyaluronic acid) is a glycosaminoglycan produced by chondrocytes and synovial cells, and it is found in the synovial fluid and cartilage of the knee and other synovial joints. Its viscous nature plays an important role in regulating the rheologic properties and homeostasis in the joint (1,2). This biological matrix within the articular space is altered in osteoarthritis (OA) of the knee, and can progress to the eventual destruction of the articular cartilage. The pathologic changes include a decrease in total concentration and average molecular weight of the hyaluronans (hyaluronic acid) in the synovial fluid (3).

The clinical use of intra-articular (i.a.) injections of high-molecular weight hyaluronans, so called "viscosupplementation", in patients with OA of the knee was introduced 10 years ago in Europe, and more than 7 years ago in Canada. In 1997, this form of treatment was approved for marketing by the US Food and Drug Administration (FDA) for the relief of pain due to OA of the knee in patients who have not responded to conventional measures (4-8). Current American College of Rheumatology (ACR) guidelines for the treatment of OA of the knee include the use of i.a. hyaluronans as an alternative or adjunct therapy to other nonpharmacologic and pharmacologic approaches (9). Hyalgan® (sodium hyaluronate, FIDIA S.p.A., Padua, Italy) is a naturally-derived 500-730 kDa molecular weight fraction of purified hyaluronan that is FDA approved for administration in a course of three to five i.a. injections at weekly intervals (7).

Randomized, controlled clinical trials have demonstrated that the majority of patients experience clinical benefit for periods up to 26 weeks, and sometimes longer, from a single series of i.a. sodium hyaluronate therapy (10-12). Moreover, unlike another hyaluronan preparation marketed in the United States, sodium hyaluronate (Hyalgan®) has no safety restrictions in its label related to an acute reaction occurring as an aftermath of the injection (6, 7).

The objective of this study was to eval-

uate the long-term efficacy and safety (1 to 2 years) of a course of 5 i.a. injections of sodium hyaluronate administered in a clinical office setting in patients with moderate to severe OA of the knee (Kellgren-Lawrence grades 2 to 4), and whose pain was inadequately controlled by conventional therapies. The efficacy and safety of a repeat treatment course of sodium hyaluronate was also evaluated in a small subgroup of patients.

### Patients and methods

#### Patients

Seventy-six patients (92 knees) with moderate to severe osteoarthritis (OA) of the knee whose pain was not controlled by conventional measures were studied. All patients, male and female, ranging in age from 40 to 80 years, had OA of the knee for more than 3 years, with a Kellgren-Lawrence class of grades 2 to 4, and chronic knee pain with difficulty on prolonged standing and walking. No patient was excluded because of age or any other reason and all patients who received sodium hyaluronate for OA of the knee during the study period were included in the data analysis.

#### Study design

Five i.a. injections of 20 mg of sodium hyaluronate were administered at weekly intervals. All injections were carried out by the same injector. This was an "open" study and there was no placebo control. Clinical assessment was carried out at baseline, weekly at the time of injections, at the end of the series, at 6 months, 12 months, and 24 months, by physical examination and outcome measures of pain, night pain, and pain on walking, using categorical assessment and a visual analog scale (VAS) of 1 to 10. Quality of life was assessed by measuring Activities of Daily Living (ADL) before and after therapy. Each subject served as his or her own control. Standing anteroposterior radiographs of the knees were performed at baseline, and 1 and 2 years after completion of therapy.

#### Safety

Monitoring was carried out at each visit

for any possible treatment-related undesirable or adverse effects.

*Baseline patient characteristics*

Demographic characteristics, baseline radiologic class, and previous i.a. steroid therapeutic status are shown in Table I. Male and female patients with a mean age of 64 ± 7.4 years were included in the study; 60% of the patients were > 65 years of age. All patients had OA of the knee for more than 3 years. The duration of OA was over 7 years in the majority of patients with mean duration of 15.3 years. The majority of patients (73%) had previously received i.a. steroid injections. Other previous drugs or treatments included agents commonly used in the treatment of OA, such as a variety of nonsteroidal anti-inflammatory drugs and non-narcotic analgesics (i.e., acetaminophen and/or Darvocet N100). A total of 92 injections of hyaluronate were administered to 76 patients with OA of the knee. Ten patients (3%) had bilateral injections, and 13 patients (17%) had a repeat course of treatment administered to the same knee because of inadequate response or early recurrence of pain. The majority of knees were rated as Kellgren grade 3 (54/92 knees [58.7%]).

**Results**

*Efficacy*

The results for overall assessment of pain at baseline, at 5 weeks (after completion of therapy), and at 6, 12, and 24 months are shown in Table II. A total of 72% of patients achieved a >50% improvement (reduction in VAS score) for 1 year or longer. Only 3 patients (3.8%) did not demonstrate any clinical benefit. Twelve of 15 patients who had been scheduled for total knee replacement (TKR) surgery (based on history) no longer considered the procedure necessary.

Quality of life effects measured by ADL, such as effects on walking, rising from a low seat, climbing steps, and getting in and out of a car, frequently showed improvement.

*Duration of response/clinical benefit*

The duration of clinical benefit was

**Table I.** Baseline patient characteristics.

Characteristic	Patients (N = 76)
Sex, n (%)	
Male	60 (79)
Female	16 (21)
Mean age (± SD)	64 (± 7.4)
Patients > 65 years, n (%)	46 (60)
Ethnicity, %	
White	88
Black	11
Other	1
Mean duration of disease, years	15.59 ± 3.7
> 5 years, %	95
> 10 years, %	68
Radiologic class, n (%)	(n = 92 knees)
Kellgren grade 2	26 (28)
Kellgren grade 3	54 (59)
Kellgren grade 4	12 (13)
Previous i.a. steroid therapy, n (%)	67 (73)

**Table II.** Overall assessment of pain (VAS) (N = 92 knees).

Pain	VAS rating	Baseline	End of series	6 months	12 months	24 months
None	0	0	0	6	5	4
Slight	1-3	0	50 (55%)	32 (35%)	25 (28%)	12 (13%)
Moderate	4-6	28 (31%)	38 (42%)	16 (18%)	9	7
Severe	7-9	54 (59%)	3	4	3	1
Extreme	9 or >	10 (11%)	1	0	0	0
Lost to FU or TKR				34 (37%)	50 (55%)	68 (74%)

FU: follow-up; TKR: total knee replacement; VAS: visual analog scale.

ascertained by looking at the patients' categorical assessment of pain over time. As shown in Table III, some patients continued to experience no pain or slight pain for up to 2 years. The mean duration of response was 9 ± 0.5 months.

*Efficacy of sodium hyaluronate according to OA grade*

Clinical improvement correlated somewhat with the stage of disease severity, as related to radiologic joint space narrowing. As shown in Figure 1, sodium hyaluronate was effective in the majority of patients with Kellgren grade 2 and 3 OA, resulting in clinical improvement in 71% and 62% of those patients, respectively; slightly less than half of the patients with grade 4 OA (42%) exhibited clinical improvement as well. Reduced analgesic intake or use of assistive walking devices was noted in 64%, 49%, and 27% of patients with

grades 2, 3, and 4 OA, respectively; overall, 50% of patients reduced their analgesic intake. Moreover, no additional loss of radiologic joint space was noted in any radiographs taken 1 year after completion of therapy.

*Repeat treatment with sodium hyaluronate*

A total of 13 patients (15 knees) received a repeat course of treatment with sodium hyaluronate in the same knee for either an inadequate initial response or early recurrence of pain. Ten of 15 knees (67%) exhibited clinical improvement after a repeat treatment course when assessed 6 weeks after the completion of therapy.

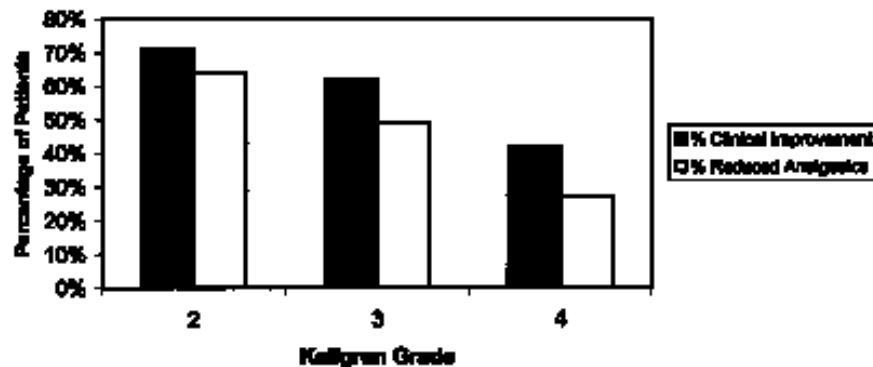
*Safety*

No systemic adverse effects were noted during the 1- to 2-year follow-up period (Table IV). Adverse events were

**Table III.** Duration of response/clinical benefit (N = 92 knees).

Degree of pain*	Baseline	End of series	6 weeks	6 months	12 months	24 months ++
None	0	4	7	5	6	3
Slight 1+	0	31 (34%)	34 (37%)	29 (32%)	21 (23%)	11 (12%)
Moderate 2+	13 (14%)	50 (55%)	32 (35%)	20 (22%)	12 (13%)	7
Severe 3+	73 (80%)	6	5	3	3	1
Extreme 4+	6	1	0	0	1	0
Lost to FU or TKR	0	0	14 (15%)	35 (38%)	49 (54%)	70 (76%)

\* Categorical assessment of pain



**Fig. 1.** Effectiveness of sodium hyaluronate in Kellgren-Lawrence (radiologic) categories. The percentage of patients (N = 76 patients, 92 knees) with Kellgren-Lawrence grade 2, 3, or 4 who showed clinical improvement (defined as a > 50% reduction in the VAS score for pain at rest, night pain, and pain on walking) or reduced analgesic consumption and/or use of assistive walking devices (considering only patients who showed improvement for > 1 year).

**Table IV.** Adverse effects reported during the 1- to 2-year follow-up period (N = 92 knees)\*.

Adverse effects	Percentage of patients
Injection-site pain	20%
1-2 hours after injection	12%
24 hours after injection	2%
Injection-site bruising	9%
24 hours after injection	4.7%
Headache, 24 hours after injection	7.5%
Nausea	3%

\* No systemic adverse events, no "dropouts"

minor and infrequent, and included brief post-injection pain, minor bruising at the injection site, rare headache, and nausea. Injection-site reactions were generally transient and required only reassurance of the patient and the application of ice. No pseudoseptic reactions were encountered, and no patient withdrew from the series of injections before completion because of adverse effects.

**Discussion**

The efficacy and safety for up to 26 weeks of a 5-injection course of sodium hyaluronate for treatment of OA of the knee has been demonstrated in a number of randomized controlled clinical trials (10-13). In the United States, a randomized, saline- and naproxen-controlled, multicenter trial of 5 i.a. injections of sodium hyaluronate was carried out in 495 patients with OA of

the knee (10). Sodium hyaluronate-treated patients demonstrated significantly greater beneficial effects compared with patients in the saline control group, and similar pain relief compared with the patients receiving naproxen 500 mg twice daily. Adverse events were generally minimal and limited to injection-site pain or bruising, as opposed to the significantly higher rate of gastrointestinal complaints in the group receiving naproxen. These results were confirmed in a similar large placebo-controlled trial carried out in the United Kingdom (12).

Despite the efficacy observed in clinical trials, it is important to evaluate effectiveness in a less controlled clinical setting. Controlled clinical trials are somewhat artificial with constraints, such as generally restricting enrollment to patients with Kellgren grade 2 or 3, and excluding patients with more advanced disease (Kellgren grade 4). Many of the latter OA patients are candidates for TKR surgery, which is a last resort for patients whose pain is not controlled by the usual comprehensive therapeutic approaches. The majority of patients in the present study had OA of grades 3 or 4 (72%) and most had received i.a. steroids without obtaining significant duration of benefit. Moreover, although 26-week studies have indicated that efficacy does not appear to wane significantly within that period, longer-term studies are necessary to establish the duration of pain relief that can be obtained with a single course of sodium hyaluronate. A 12-month, open-label, uncontrolled multicenter study conducted in Austria evaluated the long-term efficacy and safety of i.a. sodium hyaluronate in 108 patients with OA of the knee, and also examined in a small subset of patients the efficacy and safety of a repeat course of injections for the recurrence of pain (14). After a single course of treatment, significant pain relief was observed in more than 80% of patients and this was maintained in over 90% of these patients at a 12-month follow-up. Significant benefit in a number of efficacy parameters was also obtained in a group of 14 patients who received a repeat treatment course. The safety and effica-

cy of up to 5 repeat courses of i.a. sodium hyaluronate over 25 months (regardless of whether pain recurred) was also demonstrated in a study involving 75 patients reported by Scali (15).

The data from our study augments observations from controlled and uncontrolled clinical trials, providing evidence for the ameliorative effect and safety of a 5-injection course of sodium hyaluronate in difficult-to-treat patients whose pain has not been controlled by other approaches, including those with advanced OA who may have been considered as candidates for joint replacement. Although patients with Kellgren grades 2 or 3 OA experienced somewhat greater benefit than did patients with more severe OA (71% and 62% improvement in patients with grades 2 and 3, respectively), nearly half (42%) of patients with advanced OA derived clinical improvement.

#### *The power of the needle*

In the absence of blinding or control group, it is relevant to comment on the confounding factor of the "Power of the Needle". It is important to point out that sham knee injections provide transient relief of symptoms in a certain percentage of patients. However, almost all of the patients in this data base were long-term "veterans" of severe OA, who had endured a variety of forms of therapy in the past without obtaining significant benefit. In addition, it was unusual for patients to report any improvement until after the third injection, and in many instances, not until after the fourth or fifth injection. Thus, the occurrence of a strong placebo effect in this group of patients

is considered to be highly unlikely.

#### **Conclusion**

In conclusion, this clinical report of patients with moderate to severe OA of the knee indicated that treatment with i.a. sodium hyaluronate was effective in the majority of patients, and may have prevented or delayed TKR in some patients with end-stage (Kellgren grade 4) disease. Twelve patients were able to avoid scheduled TKR surgery, and additional patients were able to delay the surgery. Significant pain relief was noted up to 2 years after completion of therapy in many patients. Repeat radiographs of the injected knee demonstrated no new or progressive changes. Sodium hyaluronate demonstrated an excellent safety profile, and was associated with only minor and infrequent local adverse reactions. The findings also confirm the efficacy and safety of a repeat course of sodium hyaluronate treatment for the recurrence of pain. These results indicate that i.a. sodium hyaluronate, as either a single course or in repeated courses of treatment, is a worthwhile treatment option in difficult-to-treat patients with moderate to severe OA whose pain has not been controlled by usual conventional treatment options.

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