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Efficacy of intraarticular hyaluronic acid in patients with osteoarthritis—a prospective clinical trial

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Summary

Aim: The goal of this study was to determine whether or not the intraarticular administration of hyaluronic acid can improve functional parameters, such as isokinetic muscle strength or total work and clinical test results in patients with osteoarthritis (OA) of the knee.

Method: As part of a prospective, controlled study 43 patients with osteoarthritic changes of both knees (radiographic Kellgren stage II–III) were followed in a right/left comparison. The influence of intraarticularly injected hyaluronic acid (20 mg hyaluronic acid/2 ml Hyalart®) on functional and clinical parameters was analysed. We used the isokinetic system Cybex 600 for measuring maximal isokinetic muscle strength and total work. A total of 20 males and 23 females fulfilled the inclusion criteria with an age between 55–78 years and underwent five injections of hyaluronic acid (one injection per week). The injected knee represented the treatment group, while the contralateral knee served as the control.

Results: The maximum peak torque of the knee extensors in the treatment group was measured between 57±26.15/32.33±19.63 Nm prior to the injections and 77.17±32.54/47.83±21.43 Nm following the hyaluronic acid therapy ($P<0.01$). The analysis of the knee flexors at angular velocities of 60°/s and 180°/s revealed values of 40.44±21.58/22.89±16.64 Nm and 53.55±24.26/34.05±17.37 Nm ($P<0.01$) respectively. The evaluation of the total work of the knee flexors and extensors revealed a significant difference ($P<0.01$) between the treatment and control group. The Lequesne score was reduced from 13.57±1.88 prior to the injections to 7.94±2.53 after the treatment ($P<0.01$). The pain score was documented with the help of a visual analog scale. The VAS values were reduced at rest from 3.83±1.72 cm to 1.36±1.42 cm and during weight bearing from 7.57±1.34 cm to 3.75±1.32 cm in the treatment group ($P<0.01$).

Conclusions: This controlled prospective clinical trial confirmed that 5 weekly intraarticular injections of HA (Hyalart®) in patients with OA of the knee provide pain relief and functional improvements. © 2002 OsteoArthritis Research Society International. Published by Elsevier Science Ltd. All rights reserved.

Key words: Hyaluronic acid, Isokinetic testing, Maximal isokinetic muscle strength, Total work, Osteoarthritis, Knee joint.

Introduction

Osteoarthritis (OA) or degenerative joint disease is the most frequent joint disease known to man[1]. The treatment of OA consists of pain reduction, modification of activities of daily living and improvement of joint function[2]. Prior to surgical management of the disease, which is expensive and not risk-free, all other treatment options such as medication and physical therapy should be fully exploited. In the treatment protocol presented by Creamer and Hochberg in *Lancet* 1997, hyaluronic acid plays an important role[3].

Hyaluronic acid represents one of the main components of synovial fluid and is a polysaccharide consisting of N-acetyl-D glucosamine and D-glucuronic acid. Hyaluronic acid contributes to the elasticity and viscosity of synovial fluid, and thus hyaluronans are used for the viscosupplementation of joints[4]. Hyaluronic acid is produced by chondrocytes and fibroblasts in the synovial lining (type-B-cells)[5].

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Changes documented as part of OA include the reduction of viscoelastic properties of the hyaluronic acid secondary to reduced molecular weight, as well as a reduction of its intraarticular concentration[6–8]. A number of controlled studies have documented the therapeutic value of intraarticular applicatoins of hyaluronic acid[9–15]. These studies relied on pain relief (visual analog scale), knee function (Lequesne or WOMAC score) as well as range of motion of the affected joint as parameters for the effectiveness of such a treatment.

The pain and consequent modification of activities frequently lead to a reduced activity level. This can lead to a weakening of the quadriceps and hamstring muscles with a secondary increase of instability and joint degeneration. To measure muscle strength, the use of isokinetic testing has become widespread[16,17]. These tests are frequently used as a diagnostic tool, as well as to document disease progression and treatment effect in patients with muscle or joint disorders[18,19].

The aim of this study was to determine the efficacy of a series of five intraarticular applications of hyaluronic acid (Hyalart®) in patients with bilateral OA of the knee. Functional parameters including isokinetic muscle strength or total work, pain as documented via visual analog scale and Lequesne score were evaluated.

Material and methods

PATIENTS

Inclusion criteria

- Adults of both genders with a minimum age of 50 years.
- OA of both knees.
- Radiographic changes equivalent to Kellgren stage II–III bilaterally.
- Symptomatic gonarthrosis for a minimum of 12 months.
- Pain level during weight bearing on the VAS of a minimum of 4 cm bilaterally.
- To avoid larger differences between both affected knee joints, the Lequesne score during the initial evaluation may not differ by more than ±2 points in the total value.

Exclusion criteria

- Patients who do not meet all inclusion criteria.
- Neurological deficits in the lower extremities.
- The following underlying diseases were excluded:
  - primary inflammatory joint disease
  - joint infections
  - crystalline arthritis
  - intraarticular tumors
  - axis deviation of >15° varus or valgus malalignment
  - ligamentous instability
  - previous fractures of the joint
  - arthroscopic surgery on the knee in the previous 12 months.
- Intraarticular injections of the knee joint in the 3 months prior to the study.

TRIAL DESIGN

The study was a prospective clinical trial carried out in accordance with the principles of the Declaration of Helsinki. Only patients with radiographically documented bilateral degenerative joint disease of the knee were included in this study[20].

The treatment group had to receive an intraarticular injection of 20 mg hyaluronic acid (Hyalart®, Bayer AG, Leverkusen, Germany) weekly up to a total number of five injections in the knee, which was randomized to treatment. The control group received no treatment.

An intake of analgesics or non-steroidal antiinflammatory drugs was to be avoided. Only paracetamol (500 mg) was permitted as pain medication. Administration of paracetamol 8 h before control assessment was prohibited. Physical therapy was not carried out during the study period.

The patients that fulfilled the inclusion criteria without presenting with an exclusion criteria were entered into a randomization scheme for the administration of hyaluronic acid into the right or left knee. A stratification was carried out regarding the more impaired knee (right stratum 1; left stratum 2). The injected knee was entered into the treatment group, while the contralateral, untreated knee was included in the control group. The stratification was carried out based on the results of the primary evaluation of both knees. In case a more impaired knee could not be defined via objective criteria, the patient's subjective view was taken into account.

CLINICAL ASSESSMENT

The clinical assessment was documented by the same investigator for every patient prior to the first administration of hyaluronic acid and after 5 weeks. A different physician carried out the actual intraarticular injection of the hyaluronic acid.

The clinical assessment included the following criteria:

(1) Evaluation of knee function. The Lequesne score takes pain, maximal walking distance and the activities of daily living into account[21]. An independent evaluation of each knee is possible, maximum point score is 26.
(2) Isokinetic test. The evaluation was carried out with a Cybex 6000 system (Cybex, Ronkonkoma, U.S.A.) utilizing various velocities and repetitions (60°/s/5R, 90°/s/10R, 120°/s/12R, 150°/s/15R, 180°/s/20R). The patient was placed in a seated position with 90° of hip flexion. The degree of freedom of the knee was restricted to extension/flexoion of 0–0–90°. A break of 2 min was granted between sets. From the retrieved data the maximum work load (J) of all sets and the maximum peak torque (Nm) at 60°/s and 180°/s were determined. The maximum peak torque (Nm) was defined as the maximum force produced by the tested musculature at the various velocities.
(3) Pain intensity (visual analog scale). The patients were asked to document their pain levels at rest, as well as during weight bearing in accordance with the Huskisson scale of 0 to 10 cm[22].

The clinical data, isokinetic test, Lequesne score, and VAS were obtained 1 day prior to the first injection. In the following weeks, the next four intraarticular administraitons were carried out. One week after the final injection, the complete clinical assessment was repeated.

STATISTICAL ANALYSIS

All the retrieved data was subjected to a descriptive statistical analysis. The primary evaluation analysed the treatment efficacy in accordance with the original intention-to-treat. The data of all patients entering the study was considered to be randomized. The comparison was carried out between the treatment and non-treatment groups. A paired *t*-test was applied. The level of significance was fixed as $\alpha=0.05$. The statistic program SAS 6.10 (SAS Institute, Inc., Cary, North Carolina) was used in the data analysis.

Results

A total of 43 patients (20 men; 23 women) fulfilled the inclusion criteria and consented to take part in this study. The average age was documented as 67.0 years (range 55–78). The average height and weight of the patients was found to be 170±8 cm and 79±17 kg.

In the treatment group 24 knees were classified as the more impaired knees and 19 knees as less impaired knees by the patients. Naturally, in the control group the reversed distribution was found (19 more; 24 less impaired knees). In the hyaluronic acid treatment group 20 knees were classified as Kellgren II and 23 as Kellgren III. In comparison, the control group included 26 knees documented as Kellgren II and 17 as Kellgren III.

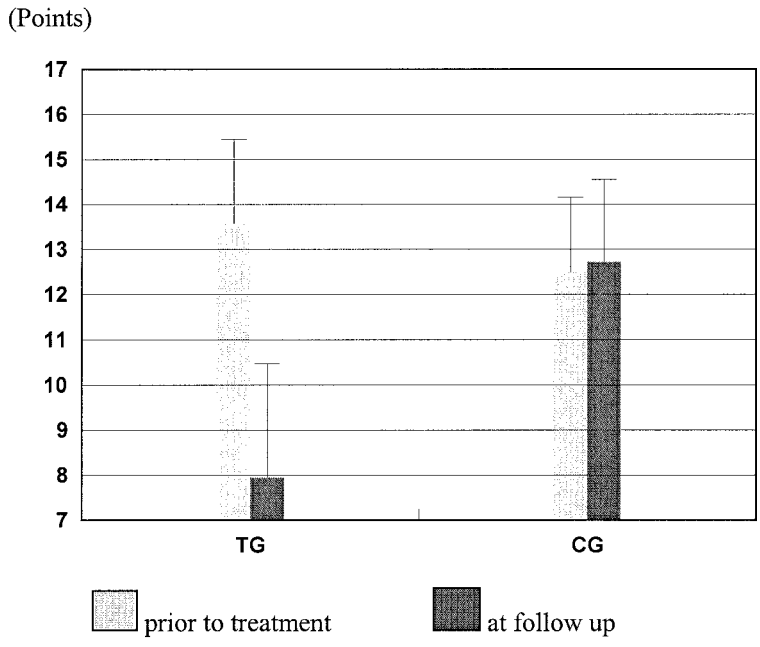

Fig. 1. Lequesne score (points).

Table I
Peak torque (Nm)/angular velocities 60°/s and 180°/s (extension/flexion)

	Treatment group		Control group	
	60°/s	180°/s	60°/s	180°/s
Flexion				
Before treatment	40.44±21.58	22.89±16.64	51.06±25.76	29.33±17.45
At follow-up	53.33±24.26	34.05±17.37	46.58±24.93	27.11±14.02
Extension				
Before treatment	57±26.15	32.33±19.63	73.38±32.88	48.83±23.65
At follow-up	77.17±32.54	47.83±21.43	71.55±30.67	42.05±21.30

The joints treated with the hyaluronic acid showed a reduction in the Lequesne score from 13.57±1.88 to 7.94±2.53 (P<0.01) at final follow-up. The untreated control group showed no significant change in the point score (Fig. 1).

The isokinetic data of the present study is summarized in Table I. The initial values for the maximum peak torque for the extensors at angular velocities of 60°/s and 180°/s were 57±26.15 Nm and 32.33±19.63 Nm, respectively, in the treatment group and 73.38±32.88/43.83±23.65 Nm in the control group. The initial values for the maximum peak of the flexor revealed a similar baseline difference between treatment and control group (Table I).

The isokinetic peak torque (Nm) of the extensors and flexors improved significantly (P<0.01) in the treatment group (Figs 2 and 3). In the control group no change in the isokinetic peak torque was found upon final evaluation.

Total work was defined as the work load at various angular velocities (60°/s, 90°/s, 120°/s, 150°/s and 180°/s). The initial values for the total work of the knee flexor and extensor demonstrated a baseline difference between treatment and control group.

The total work load documented in knee extension, as well as knee flexion improved significantly following the treatment with hyaluronic acid (P<0.01). Especially in knee extension an increase of the total work (J) was noted. The preliminary value of 2046.28±1311.28 J improved to 3044.61±1539.23 J at the time of the follow-up evaluation. In contrast, the parameters of the control group did not improve during the evaluation period. The testing of the knee flexors prior to treatment revealed values of 1310.39±1134.5 J and increased to 2034.22±1247.13 J following the treatment with hyaluronic acid (Fig. 4).

The values for pain at rest prior to treatment documented via VAS were found to be 3.67±1.53 cm for the controls and 3.83±1.72 cm for the treatment group. During weight bearing, the pain levels increased to 7.43±1.41 and 7.57±1.34, respectively. Upon conclusion of the treatment protocol, pain at rest had decreased to 1.36±1.42 cm, while the VAS level for pain upon weight bearing was found to be 3.75±1.32 cm. These changes were found to be significant (P<0.01) for the treated knees. The scores for the control group did not change compared to the preliminary results (Fig. 5).

Discussion

The goal of this study was to evaluate the effectiveness of intraarticular hyaluronic acid with the help of functional (isokinetic tests) and clinical parameters (Lequesne score, pain levels) in patients with bilateral OA of the knee. In the

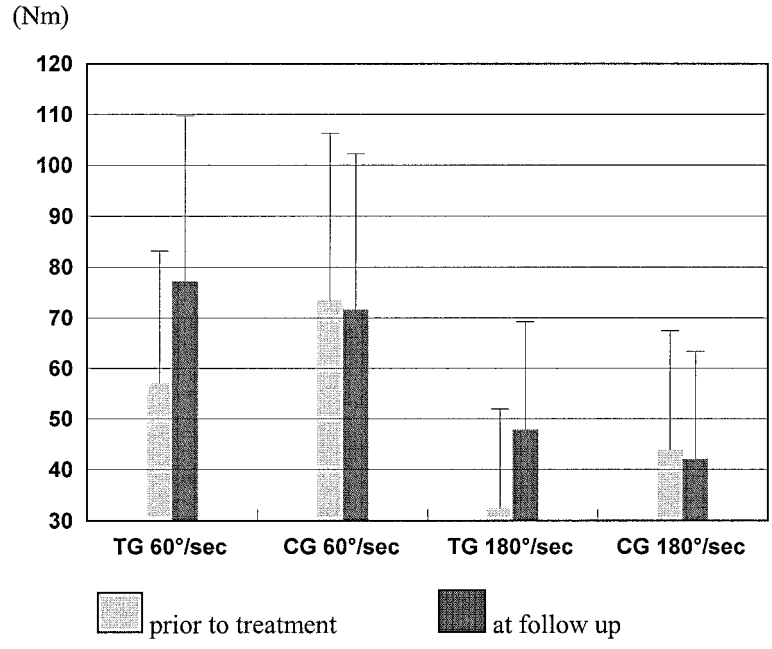

Fig. 2. Maximum peak torque/extension (60°/s/180°/s).

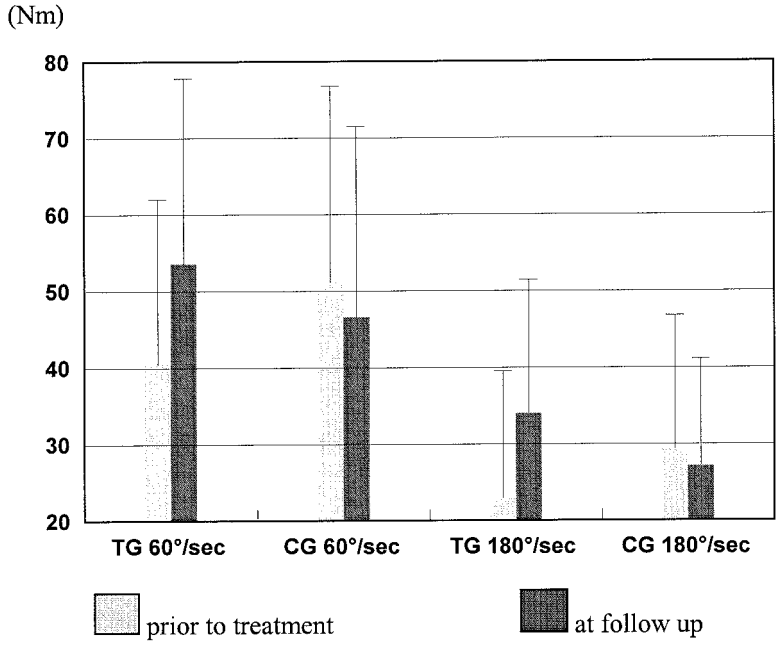

Fig. 3. Maximum peak torque/flexion (60°/s/180°/s).

past, various studies with hyaluronic acid have also used the Lequesne score to quantify joint function, while visual analog scales (VAS) have proven to supply reliable data in the documentation of pain levels[21,22].

Pietrogrande was able to show a pain reduction 60 days after the intraarticular administration of hyaluronic acid from VAS values of 6 cm down to 2 cm[9]. The comparison of pain upon weight bearing to that of the control groups showed a significant difference after a period of 5 weeks[23]. Di Marco and Letizia analysed pain upon weight bearing following treatment with hyaluronic acid in 1995. They found a reduction of the pain level from 6.7 cm to 4.7 cm[24]. The described improvement regarding pain at rest and during weight bearing was also documented in our study.

The functional analysis as defined by Lequesne has in past studies with hyaluronic documented improved scores by about 4 points with a follow-up of one year[11,23,25]. Lequesne defined effective treatment forms as those leading to a score improvement of 30–40% at the time of follow-up[26]. In his study, the average patient with degenerative joint disease was described as presenting with score values between 9–11 points. In our evaluation, the treatment and control groups scored 13.57±1.88 and 12.48±1.68, respectively, at the time of the initial

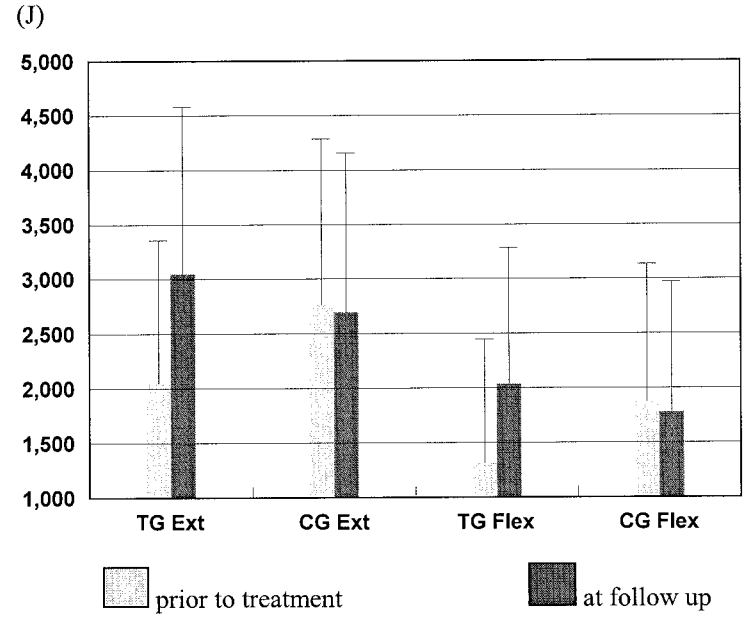

Fig. 4. Total work/extension/flexion.

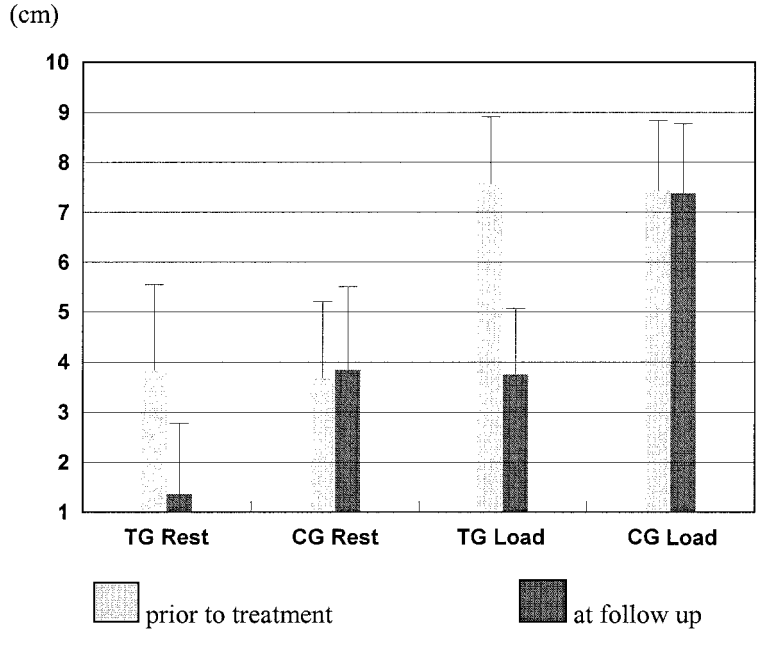

Fig. 5. Pain at rest/during weight bearing (VAS).

examination. This documents that only patients with a high level of disability were included in this study. The reduction of the Lequesne score following treatment to 7.94±2.53 points represents an improvement of 40%, which is at the upper end of the values used to define treatment effectiveness. Therefore, using the Lequesne criteria, the intraarticular administration of hyaluronic acid can be defined as an effective therapeutic measure in the treatment of OA.

Isokinetic testing is frequently used to quantify muscle weakness and dysbalances, as well as for the documentation of therapeutic effects[27–30]. The comparison to the untreated contralateral extremity represents a standardized and well researched evaluation modus for such tests[31–33]. Total work (J) and peak torque (Nm) have proven to be reliable parameters for the evaluation joint and muscle function[34]. As part of a preliminary evaluation of 18 patients, it was possible to document the value of such isokinetic testing. The study showed a significant improvement of the total work in knee flexion, as well as knee extension, following the treatment with hyaluronic acid[35].

The fact that the more impaired knee was entered in the treatment group more often than in the control group is believed to be responsible for the difference of the baseline values for total work (J) as well as peak torque (Nm) found in this study. It must also be taken into account that more patients with advanced radiographically documented joint destruction (Kellgren III) are found in the treatment group than in the control. In a previous study, Brandt described

a similar correlation between radiographic changes and muscle strength[36].

In the present study, the total work load of the knee flexors and extensors improved in the treatment group, while the controls demonstrated a slight further muscle weakening. Our study showed a significant improvement of the maximum peak torque in extension and flexion at low (60°/s), as well as high angular velocities (180°/s) ($P<0.01$) following the injections. The application of hyaluronic acid lead to an improvement of the parameters total work and peak torque in the knees treated in this study.

The viscoelastic properties of the degenerative joint are greatly reduced compared to normal conditions[37]. In an *in vitro* study, Rainer described an increase in viscosity in such pathological joint fluid by a factor of 8–10 following the application of high molecular hyaluronic acid. An improvement of the elastic qualities of the synovial fluid was also documented, in turn leading to an improvement of the biomechanics of the joint[38].

The knee joint is supplied by three structurally and functionally different afferent fibers[39,40]. These fibers receive their signals from four different receptors (Pacinian, Ruffini's and Golgi-Mazzoni corpuscles; muscle spindles) found in the tissues surrounding the joint. These receptors vary in number and location[41]. The degenerative changes in a joint lead to an increased release of a variety of mediators resulting in a secondary stimulation of nociceptors[43,44]. The interaction between the mechanoreceptors and these nociceptors can lead to changes in coordinative and muscular function of the affected extremity. The administration of intraarticular hyaluronic acid seems to reduce this disabling effect, as evidenced by the increased work load and peak torque secondary to the improved neuromuscular function of the treated knees[44,45].

One of the major factors leading to the improved joint and muscle parameters is the reduction of pain both at rest and during weight bearing. In 1992, Hayes and Falconer evaluated 43 patients with OA and were able to show an apparent weakening of the extensor, as well as flexor, muscle groups[46]. Pain was defined as one of the major causes of this muscle weakness[47,48].

In conclusion it can be pointed out that the improvement of the joint parameters can be explained by the improved joint mechanics and muscular function, as well as the reduced pain levels at rest and upon weight bearing.

With this pilot study, it was possible to demonstrate the effectiveness of intraarticular administration of hyaluronic acid with regard to functional (total work, peak torque) and clinical parameters (Lequesne score, pain) in patients suffering from OA. To evaluate the long-term effects of hyaluronic acid, studies with longer follow-up periods will be required.

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