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Role of Intra-Articular Hyaluronic Acid in the Medical Treatment of Osteoarthritis: A Prospective Study

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Abstract
The aim of this study was to determine the effectiveness of intra-articular hyaluronic acid in the patients with knee osteoarthritis. This study being a prospective controlled study included 86 patients with osteoarthritis of knee (Kellegren II & III). The effect of intraarticular hyaluronic acid (hyalgan 500-730kda) on the clinical parameters was noted. A total of 40 males and 46 females fulfilled the inclusion criteria with an age between 55–76 years .Of them 44 received five injections of hyaluronic acid (one injection per week) and 42 received intraarticular saline injection and served as control. A reduction in lequesne score from 13.68±1.25 to 7.85±3.63 was observed (P<0.01).The pain was recorded with the help of visual analog scale of 0-100. The VAS scores were reduced at rest from 43±3 to 16±2 and during weight beaing from 73±1 to 38±2 (P<0.01). This study concluded that hyaluronic acid is effective and well tolerated in the management of chronic primary osteoarthritis.
Keywords: *osteoarthritis, viscosupplementation, hyaluronan, hyaluronic acid.*

Introduction

Osteoarthritis (OA), which eventually results in the destruction and loss of articular cartilage, is the most prevalent disorder of the musculoskeletal system. The disease process leads to limitation of joint movement, joint deformity, tenderness, inflammation, and severe pain. 10% of the population over the age of 55 years has troublesome knee pain and, of those, 25% are severely disabled. OA is the leading cause of physical disability in people age over 65 years[1]. It also directly affects the quality of life with physical and/or mental co-morbidity[2]. Osteoarthritis is poorly understood because of its vast complexity and interplay of various biological factors such as: genetic alterations, sex hormone deficit, and aging[3]. Once the diagnosis of OA of the knee is confirmed, treatment is directed predominantly at relieving symptoms, maintaining and improving joint function, and minimizing disability and handicap. The Guidelines specify two major treatment modalities: nonpharmacological therapy and pharmacological therapy. Non pharmacological therapy includes changes in lifestyle, exercise, weight reduction, and other measures to unload the damaged joint. The pharmacological modalities vary from prescription of acetaminophen, non-selective NSAIDs (Non steroidal anti-inflammatory drugs) and selective COX-2 inhibitors agents and even opioid prescription. NSAIDs are the most prescribed agents for OA[4]. However their long term use is associated with potential harmful adverse effects. The other potential non-operative

therapeutic methods are chondroitin sulfate, glucosamine, and intraarticular injections of visco-supplements, corticosteroids, or blood-derived products.

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[5].

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. Hyaluronicacid contributes to the elasticity and viscosity of synovial fluid, and thus hyaluronans are used for the viscosupplementation of joints[6]. Hyaluronic acid is produced by chondrocytes and fibroblasts in the synovial lining (type Bcells)[7]. 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[8-10]. A number of controlled studies have documented the therapeutic value of intraarticular applications of hyaluronic acid[11-16]. The present trial was designed to assess the effectiveness of 5, weekly intra-articular injections of hyaluronate in chronic idiopathic OA of the knee.

Material and Methods

Patient Selection

Inclusion Criteria

- Men and women over 50 years of age were eligible for study if they had chronic primary OA of the knee
- Radiographic changes equivalent to Kellgren stage II–III
- Patients must also have had daily pain on activity and persistent pain despite the use of other anti-inflammatory or analgesic treatments.
- an erythrocyte sedimentation rate <40 mm/h

Exclusion Criteria

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

Trial Design

The study was a prospective, randomized controlled study carried out in accordance with the principles of the Declaration of Helsinki. Only patients with radiographically documented degenerative OA of the knee were included in this study.

The treatment group received an intraarticular injection of hyaluronic acid (Hyalgan®, supplied by Fidia S.p.A., a concentrated (20 mg/2 ml) solution with 500-730 kDa molecular weight) weekly up to a total number of five injections in the knee. The control group received intra-articular buffered saline solution.

An intake of analgesics or non-steroidal anti-inflammatory drugs was to be avoided starting 2 weeks prior to the administration of the injection. Only paracetamol (500 mg) was permitted as pain medication. Administration of paracetamol8 h before control assessment was prohibited. Physical therapy was not carried out during the study period.

Patients were masked by a screen placed so that it obscured their view of the procedure. The

administering physician was masked to treatment. Further, separate evaluator who was not present at the time of treatment performed the patient assessment which was documented for every patient prior to the first administration of hyaluronic acid and one week after the last injection (after 6 weeks).

The clinical assessment included the following criteria:

- Evaluation of knee function: The Lequesne score was used which takes pain, maximal walking distance and the activitie sof daily living into account[17] (maximum point score is 26).
- Pain intensity (visual analog scale). The patients were asked to document their pain on a 100mm horizontal visual analogue scale (VAS), on which 0 equaled no pain or normal activity and 100 equaled unbearable pain or complete cessation of activity[18].

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

Table 1. Demographic characteristics

	Hyaluronan (n=42)	Saline (n=44)	Total (n=86)
Sex(%)			
Male	20(48)	20(45)	40(47)
Female	22(52)	24(55)	46(53)
Age(yrs)*	63±1	67±1	65±1
Height(cm)*	164±8	160±4	162±6
Weight(kg)*	76±7	80±3	78±5

*Values expressed as mean± SEM

Statistical Analysis

All the retrieved data was subjected to a descriptive statistical analysis. The data of all patients entering the study was considered to be randomized. The intent-to-treat population, defined as all knees that were randomized to receive at least one intra-articular injection, was considered. 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 α=0.05. The statistic program SAS 6.10 (SAS Institute, Inc., Cary, North Carolina) was used in the data analysis.

Results

A total of 86 patients (40 men; 46 women) fulfilled the inclusion criteria and consented to take part in this study. Of this 42(20 men and 22 women) received hyalgan and 44 received saline (20 men and 24 women). The average age was documented as 65.0 years (range 55–76). The average height and weight of the patients was found to be 162±6 cm and 78±5 kg.In the hyaluronic acid treatment group 22 knees were classified as Kellgren II and 20 as Kellgren III.

In comparison, the control group included 26 knees documented as Kellgren II and 18 as Kellgren III.

The joints treated with the hyaluronic acid showed a reduction in the Lequesne score from 13.68±1.25 to7.85±3.63 (P<0.01) at final follow-up. The control group showed no significant change in the point score.

The values for pain at rest prior to treatment documented via VAS were found to be for the controls 43±3 and42±2for the treatment group. During weight bearing, the pain levels increased to 73±1and 74±2, respectively. Upon conclusion of the treatment protocol, pain at rest had decreased to 16±2, while the VAS level for pain upon weight bearing was found to be 38±2. 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.

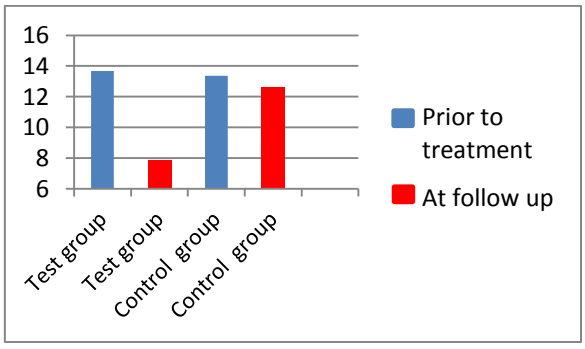

Fig. 1 . The Lequesne score

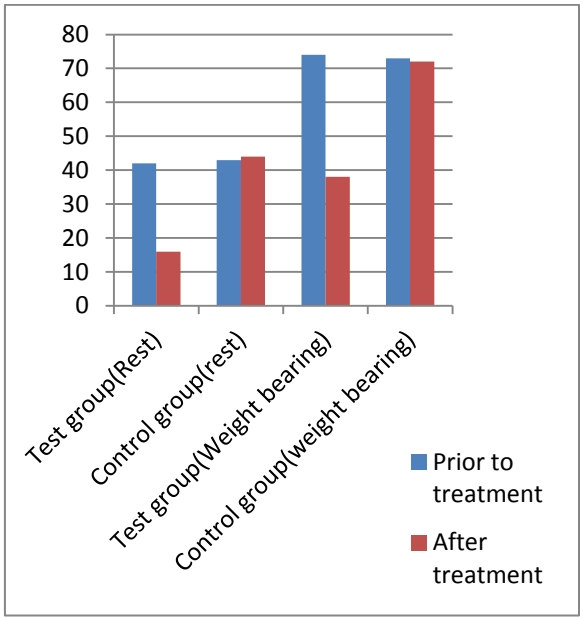

Fig. 2. Pain at rest/weight bearing (VAS)

Discussion

The goal of this study was to evaluate the effectiveness of intraarticular hyaluronic acid with the help of clinical parameters (Lequesne score, VAS pain levels) in patients with OA of the knee. This study supports existing data concerning the beneficial symptomatic effects of intra-articular injections of hyaluronic acid in osteoarthritis of the knee.

The choice of the number of injections (five) and the interval between each injection(1 week) was based on data previously reported in different clinical studies suggesting that at least five weekly injections help to improve the clinical manifestations of osteoarthritis, and that this improvement persists several months after cessation of treatment[19,20,21].

The intra-articular injections were performed in the hyaluronan treatment group even though the patients were painless and a good acceptability was seen among patients.

The reduction of the Lequesne Index score points indicates an improvement in the treatment group. This is in consistency with the functional analysis as defined by Lequesne has in past studies[12, 22, 23]. According to Lequesne, the effective treatment should lead to a score improvement of 30–40% at the time offollow-up[24]. In his study, he described the average patient with degenerative joint disease as presenting with score values between 9–11 points. In our trial, the treatment and control groups scored 13.68±1.25 and 13.36±1.28, respectively, at the time of the initial examination. This means that only patients with a more severe level of disability were included in this study. Lequesne score showed a reduction following treatment to 7.85±3.63 points which represents an improvement of 40%, which significantly points towards the 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.

Wobig in his study was able to demonstrate VAS score reduction in pain on weight bearing from 80 to 20 at 26 weeks followup[25]. Miltner recorded VAS values reduction at rest from 3.8cmto 1.3cm and during weight bearing from 7.5cm to 3.7cm[26]. Similar significant improvement in pain at rest and weight bearing was also seen in our study which is in accordance with the previous studies.

No local adverse reaction was observed in our study.

It is concluded that intraarticular hyaluronic acid injection offers a significant advantage over placebo injection in terms of pain and quality of living improvement in patients of chronic idiopathic osteoarthritis.

References

1. Cross M, Smith E, Hoy D, et al. The global burden of hip and knee osteoarthritis: estimates from the global burden of disease 2010 study. Ann Rheum Dis 2014;73:1323–30.
2. Moskowitz RW (2009) The burden of osteoarthritis: clinical and qualityof- life issues. Am J Manag Care 15(8 Suppl):S223–S229
3. Herrero-Beaumont G et al (2017) Clinical settings in knee osteoarthritis: pathop-hysiology guides treatment. Maturitas 96:54–57

4. Brosseau L et al (2017) The Ottawa panel clinical practice guidelines for the management of knee osteoarthritis. Part two: strengthening exercise programs. Clin Rehabil 31(5):596–611
5. Creamer P, Hochberg MC. Osteoarthritis. Lancet 1997;350:503–8.
6. Bothner H, Wik O. Rheology of hyaluronate. Acta Otolaryngol 1987; 442:25–30.
7. Fraser JR, Clarris BJ, Baxter E. Patterns of induced variation in the morphology, hyaluronic acid secretion, and lysosomal enzyme activity of cultured human synovial cells. Ann Rheum Dis 1979;38:287–94.
8. Dahl LB, Dahl IM, Engstrom-Laurent A, Granath K. Concentration and molecular weight of sodium hyaluronate in synovial fluid from patients with rheumatoid arthritis and other arthropathies. Ann Rheum Dis 1985;44:817–22.
9. Smith MM, Ghosh P. The synthesis of hyaluronic acid by human synovial fibroblasts is influenced by the nature of the hyaluronate in the extracellular environment. Rheumatol Int 1987;7:113–22. Engstrom-Laurent A. Hyaluronan in joint disease. J Intern Med 1997;242:57–60.
10. Pietrogrande V, Melanotte PL, D'Agnolo B, Ulivi M, Benigni GA, Turchetto L, et al. Hyaluronic acid versus Methylprednisolone intrarticularly injected for treatment of osteoarthritis of the knee. Current therapeutic research 1991;5: 691–700.
11. Carrabba M, Paresce E, Angelini M, Zamboni AM, Bragantini A, Paissan A, et al. The intraarticular treatment of the osteoarthritis of the knee: a comparative study between hyaluronic acid (Hyalgan®) and orgotein. Eur J Rheumatol Inflamm 1992; 12:47–57.
12. Dougados M, Nguyen M, Listrat V, Amor B. High molecular weight sodium hyaluronate (hyalectin) in osteoarthritis of the knee: a 1 year placebo-controlled trial. Osteoarthritis Cart 1993;1:97–103.
13. Graf J, Neusel E, Schneider E, Niethard FU. Intraarticular treatment with hyaluronic acid in osteoarthritis of the knee joint: a controlled clinical trial versus mucopolysaccharide polysulfuric acid ester. Clin Exper Rheumatol 1993;11:367–72.
14. Jones AC, Pattrick M, Doherty S, Doherty M. Intraarticular hyaluronic acid compared to intraarticular triamcinolone hexacetonide in inflammatory knee osteoarthritis. Osteoarthritis Cart 1995;3:269–73.
15. Listrat V, Ayral X, Patarnello F, Bonvarlet JP, Simonnet J, Amor B, et al. Arthroscopic evaluation of potential structure modifying activity of hyaluronan (Hyalgan) in osteoarthritis of the knee. Osteoarthritis Cart 1997;5:153–60.
16. Altman RD, Moskowitz R. Intraarticular sodium hyaluronat (Hyalgan) in the treatment of patients with osteoarthritis of the knee: a randomized clinical trial. J Rheumatol 1998;25:2203–11.
17. Lequesne MG, Mery C, Samson M, Gerard P. Indexes of severity for osteoarthritis of the hip and knee.Validation. Value in comparison with other assessment tests. Scand J Rheumatol 1987;65:85–9.
18. Price DD, Harkins SW. Combined use of experimental pain and visual analogue scales in providing standardized measurement of clinical pain. Clin J Pain. 1987; 3:1-8.
19. Shichikawa K, Maeda A, Ogawa N. [Clinical evaluation of sodium hyaluronate in the treatment of osteoarthritis of the knee]. Ryumachi 1983;23:280–90.

20. Puhl W, Bernau A, Greiling H, et al. Intra-articular sodium hyaluronate in osteoarthritis of the knee: a multicenter, double-blind study. Osteoarthritis Cartilage 1993;1:233–41.
21. Navarro-Sarabia F, Coronel P, Collantes E, et al. A 40-month multicentre, randomised placebo-controlled study to assess the efficacy and carry-over effect of repeated intra-articular injections of hyaluronic acid in knee osteoarthritis: the AMELIA project. Ann Rheum Dis 2011;70:1957–62.
22. Huskisson EC, Donnelly S. Hyaluronic acid in the treatment of osteoarthritis of the knee. Rheumatology 1999;38:602–7.
23. Lohmander LS, Dalen N, Englund G, Haemaelaeinen M, Jensen EM, Karlson K, et al. Intraarticular hyaluronan injections in the treatment of osteoarthritis of the knee: A randomised, double blind, placebo controlled multicentre trial. Ann Rheum Dis 1996;55: 424–431.
24. Lequesne MG. The algofunctional indices for hip and knee osteoarthritis. J Rheumatol 1997;24:779–81.
25. Manfred Wobig, Adalbert Dickhut, Raimund Maier,and Georg Vetter; Viscosupplementation with Hylan G-F 20: A 26-Week Controlled trail of Efficacy and Safety in the Osteoarthritic Knee; CLINICAL THERAPEUTICS/VOL. 20, NO. 3, 1998.
26. O. Miltner, U. Schneider, C. H. Siebert, C. Niedhart and F. Uwe Niethard; Efficacy of intraarticular hyaluronic acid in patients with osteoarthritis—a prospective clinical trial ;Osteoarthritis and Cartilage (2002) 10, 680–686 ; 2002