

OUR RESULTS OF DRUG APPLICATIONS IN PATIENTS WITH GONARTHROSİS

GONARTROZLU HASTALARDAKİ İLAÇ UYGULAMA SONUÇLARIMIZ

Tolga Atay, MD

Suleyman Demirel University, School of Medicine, Department of Orthopaedics

Barbaros Baykal, MD

Suleyman Demirel University, School of Medicine, Department of Orthopaedics

Metin L. Baydar, MD

Suleyman Demirel University, School of Medicine, Department of Orthopaedics

Vecihi Kirdemir, MD

Yeditepe University, Faculty of Medicine Department of Radiology

Corresponding Author

Tolga Atay, MD

Suleyman Demirel University, School of Medicine, Department of Orthopaedics Isparta/Turkey
E-mail: ataytolga@gmail.com

ABSTRACT

Background: The purpose of this study was to evaluate the effect of intra-articular injections (high and low molecular weight Hyaluronic Acid, NSAID) in patients with mild-to-moderate knee osteoarthritis.

Patients and Methods: One hundred twenty patients (34 men, 86 women; mean age 56.55 years; range 40 to 78 years) who were primary knee osteoarthritis of Kellgren-Lawrence grade II-III, divided four groups consisting of randomly. High molecular weight hyaluronic acid content was administered intraarticularly to patients in Group-I, Low molecular weight hyaluronic acid content was administered intraarticularly to patients in Group-II, Group-III were administered Tenoxicam intraarticularly and 0.9 % saline were given to the fourth group as a control group. WOMAC Pain Scale values were applied to patients before treatment and after 3. month treatment. Student's t-test was used in statistical analysis of the data.

Results: We have found statistically significant difference between the data picked before and after the treatment between administration of high and low molecular weight hyaluronic acid.

Conclusion: Intra-articular HA injections provide additional short-term benefits, but this therapy should be justified by further controlled studies with longer follow-up and larger patient groups.

Key words: Hyaluronic acid/therapeutic use, injections, intra-articular, steoarthritis, knee/therapy

ÖZET

Amaç: Hafif ve orta derece diz osteoartriti olan hastalarda eklem içi enjeksiyonların (yüksek ve düşük molekül ağırlıklı Hyalüronik Asit, NSAİ) etkisi araştırıldı.

Hastalar ve Yöntemler: Kellgren-Lawrence sınıflandırmasına göre evre II-III primer diz osteoartriti olan 120 hasta (34 erkek, 86 kadın; ort. yaş 56.55; dağılım 40-78) rastgele 4 gruba ayrıldı. Birinci gruba eklem içi yüksek molekül ağırlıklı hyaluronik asit, ikinci gruba düşük molekül ağırlıklı hyaluronik asit, üçüncü gruba tenoxicam uygulandı. Dördüncü grup kontrol grubu olup, eklem içine %0.9'luk SF uygulandı. WOMAC ağrı indeksi değerleri hastalara uygulanarak, tedavi öncesi ve tedavi sonrası 3. ay verileri student T testi ile istatistiksel olarak analiz edildi.

Bulgular: Tedavi öncesi ve tedavi sonrası yüksek ve düşük molekül ağırlıklı hyalüronik asit enjeksiyonları arasında analiz edilen veriler anlamlı bulundu.

Sonuç: Eklem içi HA tedavisinin erken dönemde ek yararı olsa da, bu tedavinin önerilebilmesi için daha uzun takip süresi olan daha geniş kontrollü çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: *Hyalüronik asit/terapötik kullanım, enjeksiyon, eklemiçi, osteoartrit, diz/tedavi.*

INTRODUCTION

Osteoarthritis (OA) is the most common disease of the musculoskeletal system after 50 years of age. Although its ethiological background has not been fully elucidated yet, it is supposed that some traumatic, biomechanical or genetical factors may account for the mechanism of occurrence and progression of osteoarthritis (1). Knee joint is one of the most affected sites in OA. During the course of disease, various pathological alterations including degenerative changes in joints and bones, anatomical and / or

physiological functional disorders and pain modalities may be encountered (2). There is a progressive loss in joint cartilages, which is accompanied by insufficient repair and recovery of tissues, subchondral sclerosis and frequently osteophytosis (3-4). The most important factor involved in the pathogenesis of OA is chondrocytic activity disorder. It is estimated that numerous ethiological factors lead to damage in chondrocyte cells, thereby cause an imbalance in extracellular matrix synthesis and metabolism (5). Hence, it is impossible to restore or stop the tissue damage caused by OA via using the current treatment approaches to the OA patients with big joint involvement. Thus, the primary aims of these treatment modalities are to relieve symptoms, to increase the mean life quality and to delay the big joint arthroplasty operations, which are major surgical interventions to be applied in the latter stages of disease (6-7). Various drugs are prescribed to patients with OA at mild or moderate degrees. In our study, we aimed to compare different intraarticular agent injection therapies applied to the patients diagnosed as having gonarthrosis, who have not undergone surgical operation and to report clinical outcomes.

MATERIALS AND METHODS

A total of 120 patients clinically diagnosed as having osteoarthritis according to the criteria of ACR (American College of Rheumatology) (8), who were in stage II or III according to Kellgren-Lawrence classification (9) during diagnosis, were included in this study. Some additional criteria for this study were also applied as follows: To be older than 40 years of age, not having any previous surgical intervention to knee joint and no intraarticular injection treatment before. Whereas, there were some exclusion criteria: Previous intraarticular injection treatment history, surgical arthroscopic intervention, patients who have serious systematic disease, individuals who have different disorders that may affect the knee joint, previous infective conditions

localized in knee joint, pregnancy or pregnancy suspect, hypersensitivity to some drugs and patients who do not want to participate in the study.

Detailed history was recorded for each patient. X-ray images of the knee joints were taken from antero-posterior and lateral aspects for whole participants and patients were randomly and equally divided into four groups: Group-I (n=30, High Molecular Weight Hyaluronic Acid, Hylan G-F20 (Synvisc®) injected at 2 ml intraarticularly once for a week for three weeks), Group-II (n=30, Na-Hyaluronate-Hyaluronan (Hyalgan®) injected at 2 ml intraarticularly once for a week for five weeks), Group-III (n=30, Tenoxicam-(Tilcotil®) was intraarticularly injected at a dose of 20 mg once) and Controls (n=30, saline was intraarticularly injected at a dose of 2 ml once).

All patients were evaluated according to the WOMAC (Western Ontario and McMaster Universities) index at the beginning of the study and at 12th week follow-up (15). In WOMAC index, 24 questions were used to evaluate the pain, articular stiffness and physical function parameters. Each answer was graded as follows: None (0), Mild (1), Moderate (2), Heavy (3) and Serious (4). In this evaluation system, higher total point results suggest worse signs and symptoms. In statistical analysis, Student's t-test was used to compare the groups and p values under 0.05 were considered as statistically significant.

RESULTS

Of the whole participants, 86 (72 %) were female and 34 (% 28) male. The youngest patient was 40 years old, whereas the oldest one was 78. The mean age was 56.55. Mean age values and gender distribution of the groups were given in Table-1.

When the initial WOAMC scores were compared, there was a statistically

significant difference between the study groups and controls ($p < 0.05$). the WOMAC scores were given in Table-2. There was no statistically significant difference between the groups by means of WOMAC values measured at the beginning of the study. When WOMAC index values of the groups measured at 12th week were compared, there was a significant difference between groups ($p < 0,05$).

DISCUSSION

Pain is the main clinical manifestation of the patients diagnosed as having osteoarthritis. Pain can occur as a result of various conditions including metabolic residual accumulation in tissues, strain in adjacent tissues such as ligament, tendon, fascia, spasm and contracture in periarticular muscles, exposure of the subchondral bone to high pressure and excessive stimulation of the adjacent nerves. For this reason, treatment modalities are mostly focused on relieving pain and numerous drugs including analgesics, non-steroidal antiinflammatory agents and intraarticular injections are used. At present, hyaluronic acid injection treatment is one of the most widespread methods (10).

Hyaluronan treatment was firstly introduced and developed by Balazs in 1960s. Preliminary implementational trials of hyaluronan took place in the mid 1970s in animals and humans. In 1987, it was firstly manufactured as an approved agent to be used in osteoarthritis treatment (11). It has been reported that intraarticular hyaluronan injection treatment have some several favorable outcomes such as improvement in viscoelasticity of synovial fluid, formation of a protective layer on cartilage tissue, increment in the synthesis of endogeneous high molecular weight HA and absorption of the energy of traumatic force affecting the articular surface (12, 13). Viscosupplementation is a new treatment approach.

Table-1: Mean age values and gender distribution of the groups

	Number	Male	Female	Mean Age
Group – I	30	23 (77 %)	7 (23 %)	54.6
Group – II	30	21 (70 %)	9 (30 %)	59.6
Group – III	30	23 (77 %)	7 (23 %)	56.4
Controls	30	19 (63 %)	11 (37 %)	55.6

Table-2: The WOMAC scores of groups were given in the table.

	Drugs	Patients (n)	Before Treatment WOMAC Mean	Before Treatment WOMAC SD	After Treatment 3. month WOMAC Mean	After Treatment 3. month WOMAC SD
Group-1	Hylan G-F 20	30	14.3	2.140	4.3	1.749
Group-2	Na-Hyaluronate	30	13.2	2.210	4.42	1.747
Group-3	Tenoxicam	30	12.7	2.251	5.6	2.367
Controls	saline	30	13.9	3.23.6	13.01	3.113

In our study, we aimed to determine the various responses of the patients to different treatment modalities and to compare these results with other intraarticular treatment approaches applied in our clinic. We have considered that this treatment method is reliable, as we have not observed any local or systemic adverse effect during the application and follow-up periods. In numerous animal studies conducted about the effect of intraarticular HA injection, it has been reported that synovial cell proliferation decreased, chondrocyte protection was established, lesion progression was slowed down and analgesia occurred against pain, following the treatment of experimental osteoarthritis models with weekly injection of HA, which has an approximately 7×10^5 Daltons of molecular weight (14, 15). There are so many studies about the intraarticular injection of hyaluronic acid preparations in osteoarthritis. In almost all of these studies, it has been reported that pain was relieved in knee joints (16-18). In

similar studies, it has also been reported that there has been a slight and / or moderate improvement in general symptoms. In a multicentric study by Brandt et al, it has been reported that there has been a recovery at slight to moderate degrees in symptoms (19). During the follow-up visits of our study at 12th week, we have observed that pain was significantly relieved in especially in group treated with hyaluronic acid injection, when compared with the group who were given intraarticular anti-inflammatory agent treatment. Whereas, there was no recovery in pain symptom in control group, which may suggest that intraarticular injection treatment methods are effective on decreasing pain symptoms. There was no statistically significant difference between the groups treated with high and low molecular weight hyaluronic acid ($p > 0,05$). Thus, it may be considered that these two methods have no superiority to each other in pain relief. In another placebo-controlled study conducted by Bragantini et al. on 55 patients with

gonarthrosis, it has been reported that there has been a significant difference in spontaneous, motional and enforced pain scores in favor of the group treated with hyaluronic acid at 21st day, lasting up to the end of two months of observation period. It has been estimated that hyaluronic acid can be effective on the pathophysiological mechanism of osteoarthritis via ameliorating the articular functionality and establishing the normalization of synovial fluid. Moreover, it has also been stated that the favorable outcomes of hyaluronic acid can last for long periods (21-23). Corrado et al. have reported that clinical improvement observed in patients following hyaluronic acid treatment may be due to the biological activity and especially the inflammatory process controlling capacity of hyaluronic acid, rather than its mechanical contribution to the viscoelasticity of synovial fluid (14). Carraba has reported that the therapeutical effect is dose-dependent during the first four months and the longest effectiveness duration was achieved after the administration of hyaluronic acid for five times, whereas the maximum pick effect was observed following the third injection (23). Peyron et al. have stated that at least three times of injection treatment was required to gain considerable therapeutic effectiveness. Peyron has observed that patients under 50 years of age who have symptoms for one year or less, having mild to moderate radiological level without any effusion have had better response to the applied treatment (24).

As a result, we have statistically determined that intraarticular low and high molecular weight hyaluronic acid injection treatments have decreased the symptoms in patients with osteoarthritis at slight to moderate degrees. Whereas, there was no statistically significant difference between the two study groups. In group treated with Tenoxicam, we have observed that the effectiveness of treatment was less than the hyaluronic acid treatment, although there has been a

significant difference before and after Tenoxicam treatment by means of improvement in symptoms. It can be concluded that it is important to plan more comprehensive studies on hyaluronic acid injection treatment to prevent further interventions, to avoid labour force loss and to improve life quality.

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