Comparison of Different Hyaluronates

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ÖZET

Çift-Kör- Randomize Olarak İki Farklı Moleküler Ağırlıktaki İntraartiküler Hyaluronik Asit Tedavisinin Bilateral Diz Osteoartriti Teşhisi Almış Hastaların Farklı Dizlerinde Karşılaştırılması

Giriş: *Hyaluronik asit (HA), sağlıklı eklem matriksinin ana komponentidir. HA; sinoviyal sıvının viskozite ve elastisitesini sağlayarak eklem lubrikasyonu ve homeostazına katkıda bulunur. Osteoartritli (OA) hastaların sinoviyumlarında HA azalması sonucu sinoviyal sıvı viskoelastisitesini kaybeder ve eklem harabiyetine yol açar. Bu sebeple, intraartriküler HA enjeksiyonu, osteoartritli hastalarda sinoviyal sıvıya akışkanlık özelliklerini tekrar kazandırmak amacıyla günümüzde bir tedavi yöntemi olarak kullanılmaktadır. In vitro yapılan çalışmalarda, farklı molekül ağırlıklı HA preparatlarının kondrositler üzerinde farklı biyolojik etkileri olduğu gösterilmiştir; fakat kullanımda olan farklı molekül ağırlıklı HA preparatlarının klinik etkilerini kıyaslayan çalışmalar oldukça azdır. Bu çalışmamızdaki amacımız, molekül ağırlığı farklı iki HA preparatının diz OA tedavisindeki klinik etkinliğini kıyaslamaktı. Hasta popülasyonundaki klinik cevap değişkenliğini azaltmak için hastaları randomize etmektense her hastanın iki dizini randomize etmeyi tercih ettik.*

Materyal-Metod: *Her iki diz ağrısı ile Nisan-Eylül 2006 tarihleri arasında S.B. İstanbul Eğitim ve Araştırma Hastanesi Fiziksel Tıp ve Rehabilitasyon Kliniği polikliniklerine başvuran, ACR (American College of Rheumatology) radyolojik ve klinik kriterlerine göre (4) bilateral diz osteoartriti tanısı alan 40 hasta, randomize kontrollü çift-kör olarak planladığımız çalışmamıza dahil edildi. Çalışmaya dahil edilen hastaların bilgisayar ortamında SPSS programı ile randomize olarak belirlediğimiz bir dizine düşük moleküler ağırlıklı hyaluronik asit (hyalgan), diğer dizine ise yüksek moleküler ağırlıklı hyaluronik asit (adant) intraartiküler enjeksiyonla haftada bir kez toplamda üç enjeksiyon olacak şekilde bağımsız bir doktor tarafından aynı teknikle uygulandı.Değerlendirmeler tedavi öncesi, tedavi sonrası, tedavi sonrası 1.ay ve tedavı sonrası 3. ayda kör (bağımsız) bir doktor tarafından her iki diz için ayrı ayrı yapıldı. Değerlendirme parametreleri: Eklem hareket açıklığı,ağrı derecesi ve WOMAC indeksiydi.*

Bulgular: *ACR kriterlerine göre OA tanısı olan 40 hasta çalışmaya dahil edildi. 8 hasta kontrol muayenelerine gelmediği için, 6 hasta da tedavi süresınce non-steroidal antiinflamatuar ilaç kullandığı için çalışmadan çıkarıldı. 26 hasta çalışmaya alındı. 21'İ kadın, 5'i erkekti. Hastaların yaş ortalaması 58.9 ± 8 yıl (46-73). Ortalama WOMAC ve VAS skorları, eklem hareket açıklığı ölçümleri Adant ve Hyalgan uygulanan dizler arasında benzerdi. WOMAC skorları ortalama 17 puan her 2 grupta da azaldı. Bu azalma her 2 grup için istatiksel olarak anlamlıydı. ($p<0.001$) Bu etki tedavi bitirildikten sonraki 1. ve 3. ayda korunmuştur. İki grup arasında WOMAC skorları benzer şekilde kaldı.*

SUMMARY

Similar Efficacy of Different Molecular Weight Hyaluronic Acid Preparations in the Treatment of Osteoarthritis of the Knee

Objective: *To investigate the clinical efficacy of two HA preparations with different molecular weights in the treatment of bilateral knee osteoarthritis.*

Design: *Randomized, double-blinded study.*

Setting: *The study was conducted during a six-month period extending from April 1st to September 30th of 2006 at the Physical Therapy and Rehabilitation Clinic of the Istanbul Training and Research Hospital.*

Participants: Subjects were recruited from patients who had clinical evidence of osteoarthritis based on the criteria of American College of Rheumatology and radiographic evidence of osteoarthritis, stage II and above according to Kellgren-Lawrence.

Interventions: *. Patients received three weekly intra-articular injections of low molecular weight preparation of hyaluronic acid (Hyalgan®) to one knee and high molecular weight preparation of hyaluronic acid (Adant®) to the other knee. All injections were given by a single physician (EA) with an anterolateral approach, keeping the knee in the 90° flexion position.*

Main Outcome Measures: *Clinical evaluations were conducted prior to treatment (baseline), immediately at the end of the therapy period, 1 month and 3 months after therapy. Outcome parameters included (i) measurement of range of motion (ROM) of the knee, measured at prone position using a goniometer; (ii) Visual Analog Scale (VAS) scored from 1 to 10 for pain at rest; and (iii) total scores of Western Ontario McMaster Universities Index (WOMAC) of global measurement of pain, stiffness, and disability.*

Results: *Forty patients with knee osteoarthritis were enrolled in the trial; however, only 26 of the subjects completed the trial and were included in the analyses. The study population consisted of 21 female and 5 male patients. The mean ± standard deviation (SD) age of the subjects was 58.9 ± 8.0 years (range 46-73). The mean body mass index was 32.5 ± 4.0 kg/m2. Mean scores for WOMAC and VAS assessments and mean ROM measurements were similar between the Adant®-receiving and Hyalgan®-receiving knees. The results of our study show an overall improvement in disease activity parameters of knee osteoarthritis in both treatment groups. A difference in therapeutic efficacy did not emerge, however, between Adant®-receiving and Hyalgan®-receiving knees.*

VAS skorları tedavi sonunda her 2 grupta düşmüştü. Her 2 grup kıyaslandığında etkinlik açısından anlamlı bir fark yoktu. Adant grubunda ortalama 1 puan (p=0.004), Hyalgan grubundan ortalama 2 puan (p<0.001) azalmıştı. Bu etki enjeksiyondan 1 ve 3 ay sonrada korunmuştur.Diz eklem hareket açıklığı Adant grubunda 5.2°, Hyalgan grubunda ortalama 5.7° artmış olup (p<0.001) 3 aya kadar bu etki korunmuştur. Gruplar arasında anlamlı bir fark yoktu.

Sonuç: *Bizim çalışmamız HA etkinliği yönünden diğer çalışmalarla uyumlu idi. Biz molekül ağırlıktaki faklılığın herhangi bir terapötik avantaj sağlamadığını gözlememize rağmen yüksek veya düşük molekül ağırlıklı hangi HA seçileceği hala tam cevaplanmamış bir konudur.*

Anahtar kelimeler: *Diz osteoartriti, intraartiküler hyaluronik asid, farklı molekül ağırlığı*

Conclusions: *Our study corroborates previous trials of HA derivatives in the treatment of knee osteoarthritis in demonstrating their efficacy. Whether HA preparations with high or low molecular weight should be preferred remains a yet unanswered question as we did not observe a therapeutic advantage in either of the study preparations.*

Keywords: *knee osteoarthritis, intra-articular hyaluronic acid, different molecular weights*

INTRODUCTION

Hyaluronic acid (HA), a linear chain of repeating disaccharide units, is the major component of the matrix of healthy joints. The high viscosity of this substance endows it with hydrodynamic properties that are essential for the physiologic functioning of the joints. HA not only acts as a lubricant for the articular surfaces, but also as a shock absorber during rapid movement of the joint.

The synovial fluid concentrations of HA are decreased in joints afflicted with osteoarthritis as a result of the depolymerization of the HA molecule, induced by reactive radicals produced during the inflammatory process (1). Lower concentrations of HA reduce the viscoelasticity of the synovial fluid and exacerbate the destructive process in the osteoarthritic joint. Synthetic HA derivatives, administered intra-articularly, replenish the low concentrations of endogenous HA and thus restore the disturbed rheological properties of the synovial fluid in the osteoarthritic joint (2). The clinical effect derived from HA derivatives probably are caused by other biologic effects as the half-life of these products is shorter than 2 days (3). One such biologic effect is believed to be enhancement of synthesis of endogenous HA (2). HA may also ameliorate the joint damage by reducing chondrocyte apoptosis (4).

Intra-articular injections of HA have been used in the treatment of osteoarthritis of the knee in an effort to modify the disease process, with some success, and most experts believe that further trials are needed to define the exact role of HA derivatives in the treatment of knee osteoarthritis (5). A recent retrospective study suggests that therapy with intra-articular HA may delay total knee replacement in patients with knee osteoarthritis (6).

The molecular weight (MW) of synthetic HA preparations used in previous studies vary considerably; such a structural difference possibly imparts different biomechanical and biologic properties to the treated joints. Although in vitro studies have suggested that different MWs have different biological effects on chondrocytes, a therapeutic difference has not been readily detected in most clinical trials.

In this randomized, double-blinded study, we sought to investigate the clinical efficacy of two HA preparations with different MWs in the treatment of bilateral knee osteoarthritis. In an effort to thwart variability in patient population as a confounding factor, we randomized the two knees of each individual patient rather than the patients themselves.

METHODS

The study was conducted during a six-month period extending from April 1st to September 30th of 2006 at the Physical Therapy and Rehabilitation Clinic of the Istanbul Training and Research Hospital. Patients presenting with bilateral knee pain underwent clinical and radiological evaluation for knee osteoarthritis. Subjects were recruited from patients who had clinical evidence of osteoarthritis based on the criteria of American College of

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Rheumatology and radiographic evidence of osteoarthritis, stage II and above according to Kellgren-Lawrence. Exclusion criteria were physical therapy or intra-articular injection in the preceding year and arthritis secondary to inflammatory-infectious causes or trauma. The study was approved by the institutional ethics committee. Subjects were enrolled to trial after provision of written informed consent.

Patients were told to discontinue all current medications for osteoarthritis, including non-steroidal anti-inflammatory drugs (NSAIDs), two weeks prior to HA therapy. Using a computer software, the left-sided knees of each subject was randomized to receive either of the two HA preparations, while the right-sided knee received the other preparation.

The study medications were Hyalgan® (distributed by Sanofi Aventis, manufactured by Fidia Farmaceutici S.p.A. Padua, Italy) and Adant® (distributed by Er-Kim, manufactured by Meiji Seiki Kaisha, Ltd., Tokyo, Japan). Hyalgan® contains a solution of sodium HA of 500 to 750 kDa molecular weight. The molecular weight of the HA in Adant® is 900 to 1000 kDa. Patients received three weekly intra-articular injections of low MW preparation of hyaluronic acid (Hyalgan®) to one knee and high MW preparation of hyaluronic acid (Adant®) to the other knee. All injections were administered by a single physician (EA), using an anterolateral approach, keeping the knee in the flexion position at 90°.

Clinical evaluations were conducted prior to treatment (baseline), immediately at the end of the therapy period, 1 and 3 months after therapy. Patients and physicians carrying out the evaluations were blinded to the treatment drug.

Outcome parameters included (i) measurement of range of motion (ROM) of the knee, measured at prone position using a goniometer; (ii) Visual Analog Scale (VAS) scored from 1 to 10 for pain at rest; and (iii) total scores of Western Ontario McMaster Universities Index (WOMAC) of global measurement of pain, stiffness, and disability.

Statistical analyses were performed using the SPSS 11.5 and Microsoft Excel software programs. For non-parametric variables, i.e. WOMAC and VAS scores, Mann-Whitney U test was employed to compare outcome scores among treatment groups and Wilcoxon signed-rank test was used to compare post-therapy scores to baseline. The improvement in WOMAC scores was also assessed as percent change from baseline and compared between treatment groups using one-way Analysis of Variance. For parametric variables, i.e. knee ROM measurements, paired t-test was employed to compare outcome scores among treatment groups and to compare post-therapy scores to baseline.

RESULTS

Forty patients were diagnosed with knee osteoarthritis according to American College of Rheumatology criteria and were enrolled in the trial; however, only 26 of the subjects completed the trial and were included in the analyses. The study population consisted of 21 female and 5 male patients. The mean ± standard deviation (SD) age of the subjects was 58.9 ± 8.0 years (range 46-73). The mean body mass index was 32.5 ± 4.0 kg/m2. Twenty (77%) of the subjects were homemakers, 5 were retired white-collar workers, and 1 patient was a retired carpenter.

Mean scores for WOMAC and VAS assessments and mean ROM measurements were similar between the Adant®-receiving and Hyalgan®-receiving knees, as shown in Tables 1, 3 and 4.

WOMAC scores were reduced by a mean of 17 points both in the Adant®-receiving knees and in the Hyalgan®-receiving knees by the end of the therapy period. This reduction was statistically significant for both groups ($p< 0.001$ for both of these groups). This effect was sustained at 1 month and 3 months after the therapy was terminated, as shown in Table 1. WOMAC scores remained similar between groups at all periods of assessment.

Table 2 shows the improvement in WOMAC scores as calculated percentage change compared to baseline. Although there was a higher level of improvement in the Adant®-receiving knees compared to the Hyalgan®-receiving knees at the end of the treatment period (43.3 ± 28.9 vs. 34.0 ± 35.2, respectively); this did not reach statistical significance ($p=0.339$). Level of improvement remained stable at 1 and 3 months after end of therapy.

VAS scores similarly had improved in both Adant®-receiving and Hyalgan®-receiving knees by the end of the therapy period. VAS score was reduced by a mean of

Table 1. Mean WOMAC scores obtained at baseline, immediately at the end, and 1 and 3 months after end of therapy. Post-therapy scores were compared to baseline in each treatment group, as well as among groups.

	Baseline	At the end of the therapy	1 month after end of therapy	3 months after end of therapy
WOMAC scores for Adant® group (mean ± standard deviation and significance level as compared to baseline mean score)	47 ± 18	30 ± 19 p<0.001	29 ± 22 p<0.001	30 ± 21 p<0.001
WOMAC scores for Hyalgan® group (mean ± standard deviation and significance level as compared to baseline mean score)	44 ± 20	27 ± 19 p<0.001	26 ± 20 p<0.001	29 ± 19 p<0.001
Significance level of comparison between groups	**p=0.673**	**p=0.601**	**p=0.876**	**p=0.905**

Table 2. Improvement in WOMAC scores, expressed as percent change from baseline. These values were compared between treatment groups, as indicated in the third row.

	At the end of the treatment period	At 1 month after therapy	At 3 months after therapy
Adant® group (mean ± standard deviation and 95% Confidence Interval)	43.3 ± 28.9 % (95% CI 31.7 - 55.0 %)	44.3 ± 33.7 % (95% CI 30.7 - 57.9 %)	34.0 ± 35.2 % (95% CI 19.8 - 48.3 %)
Hyalgan® group (mean ± standard deviation and 95% Confidence Interval)	34.4 ± 37.3 % (95% CI 19.3 - 49.5 %)	36.3 ± 37.5 % (95% CI 21.1 - 51.4 %)	35.1 ± 38.3 % (95% CI 19.7 - 50.6 %)
Significance level of comparison between two groups	p=0.339	p=0.421	p=0.915

Table 3. Mean VAS scores obtained at baseline, immediately at the end, and 1 and 3 months after end of therapy. Post-therapy scores were compared to baseline in each treatment group, as well as among groups.

	Baseline	At the end of the therapy	1 month after end of therapy	3 months after end of therapy
VAS scores for Adant® group (mean ± standard deviation and significance level as compared to baseline mean score)	6 ± 2	5 ± 3 p=0.004	5 ± 3 p=0.002	5 ± 3 p=0.004
VAS scores for Hyalgan® group (mean ± standard deviation and significance level as compared to baseline mean score)	6 ± 2	4 ± 3 p<0.001	4 ± 3 p<0.001	5 ± 3 p=0.002
Significance level of comparison between groups	p=0.493	p=0.754	p=0.523	p=0.825

Table 4. Mean ROM scores obtained at baseline, immediately at the end, and 1 and 3 months after end of therapy. Post-therapy scores were compared to baseline in each treatment group, as well as among groups.

	Baseline	At the end of the therapy	1 month after end of therapy	3 months after end of therapy
Knee ROM measurements for Adant® group (mean ± standard deviation and significance level as compared to baseline mean score)	108.6° ± 8.8°	113.8° ± 8.5° p<0.001	115.5° ± 7.5° p<0.001	114.0° ± 9.4° p=0.001
Knee ROM measurements for Hyalgan® group (mean ± standard deviation and significance level as compared to baseline mean score)	108.7° ± 11.6°	114.4° ± 10.7° p<0.001	114.8° ± 9.8° p<0.001	114.4° ± 10.3° p<0.001
Significance level of comparison between groups	p=0.993	p=0.824	p=0.773	p=0.872

1 points in the Adant® group (p=0.004) and by 2 points in the Hyalgan® group (p< 0.001). This effect was also sustained 1 month and 3 months after the therapy was terminated, as shown in Table 3. VAS scores of the two treatment groups were not significantly different from each other at any of the therapy stages.

Knee ROM measurements increased by a mean of 5.2° in the Adant®-receiving knees and by a mean of 5.7° in the Hyalgan®-receiving knees at the end of the therapy period (p< 0.001 for both groups). This improvement persisted at 1 month and 3 month follow-up assessment, as shown in Table 4. Post-therapy ROM measurements were not different among treatment groups at any time.

No side effects were reported in either the Adant®-receiving knees or the Hyalgan®-receiving knees.

DISCUSSION

Despite the continued use of HA derivatives in the treatment of osteoarthritis, it is still not known whether derivatives with higher or lower MW would show a superior therapeutic effect. Laboratory studies have shown that derivatives with lower MW penetrate better through the extracellular matrix of the synovium and reduce synovial inflammation more effectively (7).

The results of our study show an overall improvement in disease activity parameters of knee osteoarthritis with both lower and higher MW preparations of HA, when given intra-articularly to either knee of the same patient. A difference in therapeutic effectiveness was not observed with either agent. The fact that we used both HA derivatives on the same patient eliminated subjective variations as a confounding factor in our study. Both the patients and the evaluators were blinded to the therapy, so bias to-

wards one of the preparations was successfully eliminated.

Several researchers have compared the clinical effects of different HA products (8). Román et al. compared the efficacy of Hyalgan® and Adant® in 49 patients with knee osteoarthritis (9). They found that more excellent or good responses were obtained at three months with Adant® than with Hyalgan® (50% vs. 21.1%). This result was ascribed to the higher viscosity, hence longer intra-articular half-life of the former preparation.

In conclusion, our study corroborates previous trials of HA derivatives in the treatment of knee osteoarthritis in demonstrating their efficacy (10). Whether HA preparations with high or low molecular weight should be preferred remains a yet unanswered question, as we did not observe a therapeutic advantage in either of the study preparations.

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