



Intra-articular sodium hyaluronate injections after arthroscopic debridement for osteoarthritis of the knee: a prospective, randomized, controlled study

Diz osteoartriti tedavisinde artroskopik debridman sonrası eklemiçi sodyum hiyalüronat enjeksiyonu: Prospektif, randomize, kontrollü çalışma

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Amaç: Hafif ve orta derece diz osteoartriti olan hastalarda artroskopik debridman sonrası eklemiçi hiyalüronik asit (HA) enjeksiyonlarının ağrı ve fonksiyon parametreleri üzerindeki etkisi araştırıldı.

Çalışma planı: Kellgren-Lawrence sınıflandırmasına göre evre II-III primer diz osteoartriti olan 67 hasta (21 erkek, 46 kadın; ort. yaş 56; dağılım 40-65) standart yöntemlerle artroskopik debridman sonrası HA enjeksiyonu (n=33) ve sadece takip (kontrol, n=34) gruplarına rastgele ayrıldı. Artroskopik girişimden üç hafta sonra başlanan sodyum hiyalüronat (Orthovisc) enjeksiyonu birer hafta arayla üç kez tekrarlandı. İki grup, artroskopi öncesi ve artroskopi sonrası 6, 12 ve 24. haftalarda WOMAC osteoartrit indeksinin ağrı ve fiziksel fonksiyon altskalalarıyla değerlendirildi.

Sonuçlar: Altıncı haftada ağrı skorundaki düzelme iki grup arasında anlamlı farklılık göstermezken (HA %21, kontrol %16; p=0.478), fonksiyon skorundaki düzelme enjeksiyon grubunda anlamlı derecede fazla idi (HA %23, kontrol %9.2; p=0.018). Sonraki değerlendirmelerde, her iki grupta ağrı ve fonksiyon parametrelerinde süren belirgin düzelme gruplar arasında anlamlı farklılık göstermedi. Fonksiyon skorunda başlangıca göre en az %30 ve %40 düzelme gösteren hastaların oranı, sadece altıncı haftada enjeksiyon grubunda anlamlı derecede yüksek bulundu (sırasıyla p=0.025 ve p=0.038).

Çıkarımlar: Artroskopik debridman sonrası eklemiçi HA tedavisinin erken dönemde ek yararı olsa da, bu tedavi kombinasyonunun önerilebilmesi için daha uzun takip süresi olan daha geniş kontrollü çalışmalara ihtiyaç vardır.

Anahtar sözcükler: Artroskopi; kıkırdak, eklem/cerrahi; debridman; hiyalüronik asit/terapötik kullanım; enjeksiyon, eklemiçi; osteoartrit, diz/tedavi.

Objectives: The purpose of this study was to evaluate the effect of intra-articular hyaluronic acid (HA) injections after arthroscopic debridement on pain and functional parameters in patients with mild-to-moderate knee osteoarthritis.

Methods: Sixty-seven patients (21 men, 46 women; mean age 56 years; range 40 to 65 years) who underwent standard arthroscopic debridement for primary knee osteoarthritis of Kellgren-Lawrence grade II-III were randomly assigned to HA injections (n=33) or to only follow-up as controls (n=34). Intra-articular sodium hyaluronate injections (Orthovisc) were started three weeks after arthroscopic debridement, totaling three injections interspersed with a week. The two groups were evaluated with the pain and physical function subscales of the WOMAC osteoarthritis index before and after 6, 12, and 24 weeks of arthroscopic debridement.

Results: Improvement in pain scores at 6 weeks did not differ between the two groups (HA 21%, control 16%; p=0.478), whereas improvement in function scores was significantly higher in the HA group (23% vs 9.2%; p=0.018). The rates of improvement in pain and function scores increased in subsequent evaluations, but these did not differ significantly between the two groups. The percentages of patients who exhibited at least 30% and 40% improvement from baseline function scores were significantly greater in the HA group only at six weeks (p=0.025 and p=0.038, respectively).

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

Key words: Arthroscopy; cartilage, articular/surgery; debridement; hyaluronic acid/therapeutic use; injections, intra-articular; osteoarthritis, knee/therapy.

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Osteoarthritis (OA) is a chronic disorder and when symptomatic, is the most common cause of musculoskeletal disability as well as the most common type of arthritis.^[1] The treatment of the disease is a challenge among researchers with a rising prevalence parallel with the increasing age of the population.^[2] Patients with symptomatic OA of the knee who have pain that has failed to respond to medical therapy and lifestyle alterations, have progressive limitations in activities of daily living, should be referred for further consideration. While surgical treatments include osteotomies and arthroplasty, there are minimal invasive treatment options including arthroscopic débridement (AD) and intra-articular steroid or hyaluronic acid (HA) injections.^[3] One of the characteristic features of OA is loss of articular cartilage and decrease in rheological properties of synovial fluid. This is supposed to be the result of reduction in molecular size and concentration of hyaluronan.^[4] Therefore; HA injections, i.e. supplementing the viscous environment, appear as a viable solution definitely, with supporting clinical evidence.^[5] During degenerative process of the cartilage and menisci, wear and tear results in loose body formations. Also, some biochemical markers of inflammation increase. Therefore, a wash-out or a minimal invasive AD seems also another feasible option. Arthroscopic débridement involves lavage, partial meniscectomy, limited synovectomy, loose body removal, cartilage shaving or chondroplasty and excision of osteophytes if needed. There appears to be a select group of patients who would benefit from AD with regard to pain relief and functional improvement and, therefore, may be able to postpone or even avoid more complex and morbid procedures.^[6, 7] Both AD and/or HA injections are commonly performed modalities in the treatment of OA. Despite several experimental^[8] and clinical^[9, 10] studies favoring injections in OA, meta-analyses stress the need for prospective, randomized, controlled studies to elucidate the place of HA after AD. In this study, we tried to find out if there is a positive effect of AD in patients with OA of the knee and to assess the further potential benefits of using HA as an adjunctive therapy with AD.

Patients and methods

Selection criteria included: symptomatic primary knee OA according to American College of Rheumatology criteria^[11] with a Kellgren-Lawrence (K-L) severity grade^[12] of level II or III as deter-

mined radiographically at screening. There were 67 patients (21 male, 46 female with a mean age of 56, range: 40-65 years). Patients meeting the inclusion and exclusion criteria, who provided informed consent, were randomized into one of the two study groups. These groups were defined as only AD treatment group (control group, n: 34) or intra-articular HA injection following AD treatment group (injection group, n: 33). Patients' age, gender and body mass index variables were used by computer software specially produced for randomization to ensure a homogeneous distribution among the groups. The following criteria excluded patients from the study: Patients who refused to provide the written informed consent and agreed to follow study procedures; patients who have any form of contraindication for an arthroscopy procedure; patients with previously known bleeding diathesis or coagulation disorder; patients with known allergies against chicken or chicken products for intra-articular sodium hyaluronate injection; patients with secondary arthritis, like rheumatoid arthritis or suspected to have any other form of an inflammatory arthritis; patients in whom "microfracture" technique was used during AD; patients with major frontal plane deformities (varus or valgus more than 15 degrees); patients with patellar disorder necessitating interventions like lateral release or quadriceps mechanism disorders.

Local ethics committee approved the study and registration was completed as a prospective, randomized, controlled study to ANZCTR database (www.anzctr.org.au) with a registration number of ACTRN12608000195358. The surgical procedure (AD) was performed under spinal or general anesthesia. The standard performed in these patients included lavage of the joint with varying amounts of serum saline solution. If needed, limited synovectomy was performed. Partial meniscectomies were carried out removing only loose unstable fragments. Care was taken to preserve as much meniscal tissue as possible. Patients were discharged on the first day after surgery. The patients were encouraged to bear as much weight as tolerated. They began range of motion and isometric exercises as soon as possible and only parasetamol was prescribed for pain medication. The HA used in this study was Orthovisc®, (30 mg sodium hyaluronate dissolved in 2 ml physiological saline; Anika Therapeutics Inc., Woburn, MA, USA).

The treatment course for patients randomized to the AHA group continued with a series of three intra-articular injections of 2 ml HA administered during 3 consecutive weeks starting 3-weeks postoperatively. Patients returned for visits at 6, 12 and 24 weeks after AD. All individual Western Ontario and McMaster Universities (WOMAC) OA Index pain and function responses (a valid, reliable, and responsive disease-specific instrument) were graded using a 5-point scale (0: none, 1: mild, 2: moderate, 3: severe, 4: extreme).^[13] Five questions on pain (scored 0-20), and 17 questions on physical functions (scored 0-68) were asked, where higher scores indicate worse symptoms. Patients completed the WOMAC pain and function questionnaires before treatment (baseline) and at each visit after treatment.

SPSS statistical package was used. Mean, median, standard deviations, and frequencies were calculated. Independent t-test, and chi-square tests were used where applicable. P<0.05 was regarded as statistically significant.

Results

The distribution and demographics of patients completing the study with respect to groups were presented in Table 1. There were no statistically significant differences for age and gender between the groups.

WOMAC pain and function scores at baseline (week 0) and at weeks 6, 12 and 24 were presented in Table 2. Percent change values from baseline were used to compare the differences in pain and function. In injection group, there was more reduction in pain

Table 1. Age and gender distribution according to groups

	Arthroscopy and injection	Only arthroscopy	p
Number of patients	33	34	NS
Male	12	9	NS
Female	21	25	NS
Mean age	56.7	54.4	NS

NS: Non significant.

for all follow ups, however, these differences were not statistically significant (p:0.478, p:0.934, p:0.482, respectively.) There was a 22.4% improvement in injection group for WOMAC function scores at week 6 compared to baseline (week 0), while this improvement was 9% for controls, which was statistically significant (p:0.018). Improvement in function scores were found for both groups, however there was not any statistically significant decrease between groups.

Another way to analyze the data for similar studies in literature is to examine the proportion of “treatment successes” in each group.^[14] For example, treatment success can be defined as at least of 30% and 40% improvement (thresholds) from baseline in pain or function score. Table 3 presents the WOMAC function scores as a proportion of patients achieving “treatment success” in each group with success defined first as at least a 30% improvement from baseline in function score and second, as a 40% improvement. With respect to proportion of subjects with percent improvement from baseline, the two groups are significantly different at week 6 for both 30% and 40% (p: 0.025, p:0.038, respectively) and increase of success rate over time was observed for both groups.

Table 2. WOMAC pain and function scores for both groups

Weeks	Injection group (n=33)				Control group (n=34)				p	
	Mean±SD	Median	Distribution	%change	Mean±SD	Median	Distribution	%change		
Pain										
0	8.5±3.1	8.0	3-14	-	7.9±2.8	8.0	3-12	-	0.406	
6	6.7±3.5	6.0	1-15	21.0±28.0	6.5±3.1	5.5	2-13	16.0±30.0	0.478	
12	6.1±2.9	6.0	1-11	24.0±40.0	6.0±2.8	5.5	1-11	21.0±32.0	0.934	
24	5.0±2.2	5.0	1-11	35.0±33.0	5.45±2.3	5.5	1-10	27.0±33.0	0.482	
Function										
0	28.6±9.2	27.0	7-42	-	26.7±10.9	23.0	4-54	-	0.443	
6	22.2±11.9	19.0	7-45	23.0±26.0	24.3±11.3	21.5	3-52	9.2±22.3	0.018	
12	21.2±9.0	20.0	5-40	24.0±26.0	22.0±9.5	21.0	3-43	16.0±27.0	0.289	
24	16.5±7.2	16.0	4-41	39.0±23.0	18.6±7.5	18.5	3-41	27.0±21.0	0.059	

Table 3. The percentages of minimum 30% and 40% improvement in WOMAC function scores for both groups.

	Weeks	Injection group (n=33)		Control group (n=34)		<i>p</i>
		Number	Percentage	Number	Percentage	
Treatment success %30	6	14	42.4	5	14.7	0.025
	12	14	42.4	9	26.5	0.264
	24	22	66.7	18	52.9	0.370
Treatment success %40	6	12	36.4	4	11.8	0.038
	12	8	24.2	5	14.7	0.498
	24	14	42.4	9	26.5	0.264

Discussion

In this study, favorable results were obtained with AD in patients with mild and moderate OA with better pain and function scores. At the last follow up at week 24, half of the patients obtained “at least 30% improvement” with AD alone, and this rate was even higher (two thirds) in patients whom injection was performed. The only statistically significant difference between groups was found at the first follow up at week 6, for function parameters in favor of injection group.

Arthroscopic débridement is frequently advocated as a treatment option to relieve the symptoms of a painful degenerative knee. The rationale for offering AD in the selected patients is that it may improve symptom and functions, has minimal morbidity, provides a therapeutic procedure, and documents the stage of the disease process. The duration of effect however is variable. Adjunctive therapies such as nonsteroidal anti-inflammatory drugs and other medications, physiotherapy and intra-articular steroid injections may be incorporated.^[15, 16]

Intra-articular injections of HA have been shown to provide relief of pain and improved function in patients with OA of the knee. HA is found in the cartilage matrix and synovial fluid. The properties of the HA molecule are altered in knee OA. The elasticity and viscosity of synovial fluid is less than that of a normal joint. There is a decrease in molecular weight and concentration of HA in OA. Therefore, to restore the protective effect of healthy synovial fluid, it has been advised that the deficient HA should be replaced. There are supportive studies in the literature.^[17, 18]

Both AD and intra-articular HA injections are treatment modalities that have been carried out for knee

OA treatment, usually separately.^[19] Its effects has not been determined yet when applied in combination. Muckley and Hempfling^[20] in a comparative study between “only lavage” with “lavage and débridement” found that débridement group had a favorable course persisting over 2-years. Hempfling, in his “overall assessment”; found out that best results were obtained in HA débridement group, when HA washout, only washout and only débridement groups were considered. The author concluded that the “additional benefit of the HA treatment becomes very evident”.^[21] Vad et al.^[22] in a prospective study of 81 patients with OA of the knee, compared the efficacy between joint lavage using the closed method by a needle one week before the HA injection (n: 44), with HA alone (n: 37). Three injections at weekly intervals were given and 1.1 years after the treatment, success rate for combined treatment was 79.5% whereas 54% for HA alone. Quite similar results were obtained in our study, in favor of combined treatment. When “minimum 30% improvement from baseline” was searched 66.7% vs. 52.9% success rates were found at week 24 in favor of combined.

Some reasons may be suggested for this effect. For instance, during the AD procedure, irrigation removes the synovial fluid and the HA layer over the cartilage. In experimental studies, the negative effects of the irrigation fluids used in arthroscopic procedures have been shown on the metabolism and structure of the joint cartilage.^[23] In order to prevent this, combination of some pharmacological agents with the washout fluid has been experimented and positive results were obtained.^[24] Loss of proteoglycans during AD and washout is well known and there are supporting electron microscopic studies.^[25] Jansen et al.^[26] on a very recent study, concluded that hyaluronan has a potential role in preventing cell death following ar-

ticular cartilage injury in an experimental study on rabbit knees where with even single one injection of hyaluronan improved cartilage metabolism in knees with 6-month-old cartilage defects.

Systematic reviews are widely used as an evidence-based decision making instrument in routine clinical care. Campbell et al.^[27] reviewed six systematic reviews that have been published within the last years to answer the question of “Should HA be used for the treatment of knee OA?”. The authors found differences in trial selection, inclusion, data extraction and statistical methods for data synthesis. Therefore, it was not surprising to find out that, different results and a variety of conclusions were reached by the reviewers. Wang et al.^[28] confirmed the therapeutic efficacy and safety of intra-articular injection of HA for the treatment of OA of the knee; while Modawal et al.^[29] mentioned a “moderate effect”; Lo et al.^[30] “small effect when compared with placebo”, Medina et al.^[31] “short term relief of pain and improved functionality. Bellamy^[32] concluded as follows: “analyses support the use of the HA class of products, despite there is a considerable between-product, between-variable and time-dependent variability in the clinical response”. The only unenthusiastic comment was by Arrich et al.^[33] stating that “HA has not been proven clinically effective”. Some side effects of HA treatment should also be noted, like effusions or pseudosepsis which can mimic septic arthritis.^[32]

The same debate continues for AD of the OA of the knee.^[34] In search of the literature there are not many level I studies. Within the scarce literature the most argued one is by Moseley et al.^[35] who concluded that AD is no better than placebo. However, this study has been criticized as having too many drawbacks like, ill defined inclusion and exclusion criteria and inadequate data collection.^[7] For the AD treatment of knee OA, the consensus seems to be as; “Of good value in selected patient groups, like low grade OA with mechanical symptoms”^[34].

Some weaknesses of our study have to be noted, for instance, our relatively short follow-up period for a chronic musculoskeletal disorder. Another is lack of evaluation of the psychological status of the patients. Rosemann et al.^[36] emphasized that psychological factors as well as physical; need to be addressed similarly to improve functional ability of patients suffering from OA.

The psychological factor which may be associated with injection was not equalized with a placebo injection to the controls because of ethical conditions. Another issue was comparing homogenous group of patients because the knee having more than one compartment. In our study, we tried to homogenize the groups by using K-L scale, and tibiofemoral problems. Patients with patellofemoral problems, microfractured patients, were excluded for homogeneity. Future studies should be planned not only by radiological classifications but assessing the patients according to subgroups which necessitate multi center studies. Finally, obesity and its relation should be investigated with not only body mass index –as in our study- to organize even groups, but also the relationship between scores and obesity should better be taken into concern.

As a result; addition of HA injections after AD in knee mild and moderate OA showed statistically significant improved function scores at week 6 only. At follow up, the injection group showed better function and pain scores however the differences were not statistically significant. Therefore, although HA injections after AD resulted in certain benefits in short term, further investigations with longer follow up and larger groups are needed to justify its use as a cost-effective intervention. In addition, it is advisable to find out patient groups who are more likely to benefit from HA injections by forming more homogenous groups of patients. We believe that it is important to work on mentioned aims to improve quality of life and to prevent disability, loss of work and further interventions.

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