The Efficacy of Different Derivatives of Viscosupple-mentation use in Patients with Knee Osteoarthritis

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Abstract
Objective: The aim of this study is to examine the effects of vis-co-supplementation with two different agents on pain and functionality in patients with knee osteoarthritis with surgical indication at stage 4 according to Kellgren-Lawrence radiological staging and who do not accept surgery.
Design: Within the scope of the study, 68 patients were studied. According to Kellgren-Lawrence radiological staging criteria, patients were selected from among patients who had surgery at stage 4 but were not accepted for surgery.
Setting: The patients were divided into 2 groups with similar gender and age characteristics. For 34 patients in the first group, 16 mg/2 ml Hylan-GF 20 was applied 3 times to both knees with a one-week inter-val, while the same application was applied with 15 mg/2 ml sodium hy-aluronate to 34 patients in the second group. Case assessments of patients before and 24 weeks after treatment were made in the context of the Lysholm knee scale.
Result: The use of hyaluronic acid and its derivatives for viscosupplementation is preferred for symptomatic treatment in the 2nd and 3rd stages of knee osteoarthritis.
Conclusion: It has been shown that more than 5 injections do not affect the results, and 3-5 injections will be sufficient for the intended therapeutic effect
Keywords: Knee osteoarthritis, viscosupplementation, hyaluronic acid, lysholm knee scale, exercise
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1. INTRODUCTION

In the treatment of knee osteoarthritis, which is a progressive, degenerative joint disease, hya-luronic acid (HA) is generally preferred in the early stages of the disease for viscosupplemen-tation. The aim here is to provide symptomatic treatment, especially pain, to increase the ef-fectiveness of other conservative treatment methods and to delay the transition to the surgical treatment phase. HA derivatives used for vis-cosupplementation have general effects such as tissue hydration, proteoglycan organization, embryonic development, forming the main com-ponent of the extracellular matrix, cell differentiation, cell motility, as well as providing an increase in viscosity by supporting the lubrication feature of the synovial fluid, stimulating endogenous HA synthesis, cartilage It has functions such as being a matrix structural element and reducing the levels of synovial fluid PGE-2 and cAMP [1].

While hyaluronic acid stabilizes the macromolecular structures in the cartilage tissue, it also increases the elasticity and load-bearing ability of the cartilage by increasing its hydration abil-ity. In the pathogenesis of osteoarthritis, there are effects related to its macromolecular struc-ture, such as a decrease in mechanical strength as a result of the depo-limerization of HA molecule, a decrease in HA molecular weight and concentration, and loss of viscoelastic char-acter. In addition, an increase in cartilage destruction is observed as a result of changes in metabolic pathways related to the synthesis of substances such as IL-1α, PG E2 and TIMP-1 (Tissue Inhibitor of Metalloprotease-1) as a result of impaired effects on cellular functions [2].

The aim of this study was to determine the effect of viscosupplementation with two different agents on pain and functionality in patients with knee osteoarthritis with surgical indication in stage 4 according to Kellgren-Lawrence radiological staging and who did not accept surgery. was to examine.

2. MATERIALS AND METHODS

2.1 Research Materials and Methods

Ministry of Health Ankara Training and Research Hospital 1st Orthopedics and Traumatology Polyclinic with knee pain complaint between November 2011-November 2012 Knee radio-graphs of the patients who were diagnosed with clinical osteoarthritis according to the criteria of the American College of Rheumatology (ACR) were taken, and 68 patients who were stage 4 according to the Kellgren-Lawrence radiological staging criteria [3] were entitled to study. After being informed in detail, their consent was obtained and they were included in the study. Complete blood count, routine biochemistry, CRP and rheumatoid factor values were checked at the first application of these patients. Patients with severe systemic disease, drug allergy or history of hypersensitivity, signs of infection, or those who received intra-knee injection therapy within the last 3 months were not included in the study. Analgesic and NSAID drugs were discontinued one week before the knee injection of the patients. During the 6-month period after the injection, they were asked to use only an-algesics (paracetamol) when they needed it. The physical examination and Lysholm knee scoring of all patients included in the study were performed by the same specialist. The age range of the patients was 42-73, and 58 (91%) were female and 6 (9%) were male.

The patient group constituting the study population was divided into 2 groups by simple ran-domization according to similar age and gender distributions. The patients in the first group; While Hylan-GF 20 (16 mg/2 ml) was administered 3 times with an interval of 1 week, the patients in the second group; 15 mg/2 ml sodium hyaluronate preparation was applied at simi-lar intervals and frequency. Intra-knee injections were made by the same doctor from the an-tero-lateral knee region. Quadriceps muscle strengthening and joint range of motion exercises were started in all patients with the first examination, and no movement restriction was ap-plied before and after the injection. The clinical evaluations of the patients were made ac-cording to the Lysholm knee scale (Table 1) [4] at the 24th week of treatment, at the time of admission to the first outpatient clinic [5].

This scale is an evaluation of the patients' pain, knee joint disruption, locking, instability, swelling, squatting when climbing stairs and the supports they use. The results of the treat-ment method and the comparison of the efficacy differences of the two different agents were evaluated on the baseline and 24th week scores. If Lysholm knee score values are between 0-64, the clinical result is poor, 65-83 moderate, 84-90 good, and 91-100 excellent.

2.3. Analysis

Analyzes were made with the SPSS 11.0 program. The distribution within the group (one sample Kolmogorov Smirnov test) was observed as normal. Mann-Whitney U test was used for the comparison of test parameters between groups, and Wilcoxon test was used for the initial and final comparisons within the group.

3. RESULTS

When the demographic data of the participants were examined, a statistically significant dif-ference was found between the mean ages ($p < 0.05$).

All but 2 patients showed improvement in Lysholm knee scores with intra-knee injection. The highest score as a result of the treatment was found to be 91. While the mean initial score in-creased from 55.60±4.72 to 79.93±4.85 at the 24th week of treatment in patients in group 1 who received Hylan-GF 20 (16 mg/2 ml) injection, It was found that the mean increase from 56.21±4.49 to 80.12±4.59 in patients in group 2 who were administered 15 mg/2 ml sodium hyaluronate (Table 2). While no statistically significant difference was observed between the groups' values at baseline and after 24 weeks (Mann-Whitney U test, $p>0.05$), in-group base-line and final scores were compared. A difference was observed in both groups (Wilcoxon test, $p<0.001$). When Lysholm knee score values were evaluated according to clinical results, it was seen that 97% of the cases went from bad to moderate. No local or systemic side effects were detected in any of the patients during the treatment.

4. DISCUSSION

The concept of viscosupplementation is an attempt to recover the viscoelasticity insuf-ficiency caused by the decrease in intra-articular hyaluronic acid concentration and molecular weight, which is involved in the pathogenesis of osteoarthritis, with hyalu-ronic acid or its derivatives given externally. It should be done [6]. Viscosupplementation therapy was first introduced by Endre A. Balazs [7] in the early 1970s. The use of hyaluronic acid and its derivatives for viscosupplementation is preferred for symptomatic treatment in the 2nd and 3rd stages of knee osteoarthritis. Studies on viscosupplementation therapy in patients with stage 4 knee osteoarthritis are limited. In a 6-year retrospective study by Waddell and Bricker, hylan GF 20 was applied to the knees of 863 patients who needed total knee replacement in stage 4, and 3 of 1187 knees (75%) were treated with hylan GF 20. After 8 years, they saw that they still continued their functions without the need for surgery, and they reported that total knee replacement surgery could be delayed with viscosupplementation [8]. Ulucay et al. [9] on the other hand, they obtained positive results from the viscosupplementation treatment they applied after arthroscopic deb-ridement in 77 female patients ranging from stage 1 to 4. In this study, we performed this application with two drugs with different pharmacological properties in our pa-tients with stage 4 knee osteoarthritis who had surgery indications but did not accept surgery, and they improved their pain and function in both groups. we found signifi-cant improvement at the same level.

Long-term improvement is seen in patients treated with hyaluronic acid or its deriva-tives. However, the residence time of the injected substance in the synovial fluid is ex-pressed in hours, and the residence time in the tissue is expressed in days. This shows that the applied material is not just a temporary liquid prosthesis. In order for the fre-quently occurring clinical benefit to be permanent and long-lasting, there must be mechanisms other than temporary replacement of the viscoelastic property. Hyaluronic acid injection reduces inflammation, stimulates endogenous hyaluronic acid synthesis, and prolongs the therapeutic effect beyond the time the drug stays in the joint [10].

The clinical efficacy of hyaluronic acid treatment in osteoarthritis cases has been demonstrated in many studies [11, 12]. Decrease in movement or spontaneous pain, increase in joint range of motion and improvement in functional scoring are seen as general clinical response. Aydeniz et al. simultaneous treatment of their joints in patients who were diagnosed with hip and knee osteoarthri-tis together in their study; reported that it was more effective than traditional applica-tions [13]. Only 6 of 25 patients with knee osteoarthritis included in the study are stage 3-4. They reported that these patients benefited from the treatment.

There are different opinions about the time of onset of efficacy and the time of de-crease in pain complaints. It has also been shown in the literature that the efficacy of the treatment starts between 21-28 days and continues until the 6th month [14]. Also, Stitik et al. [15] emphasized the necessity of combining home exercise program with hyaluronate injection for the treatment of 60 patients who were in the 2nd and 3rd stages. In our study, the final evaluation of the patients was made at the sixth month. During this period, home exercises were also recom-mended to the patients and it was observed that the clinical results of the patients went from bad to moderate.

Regarding the number of hyaluronic acid applications, it has been shown that more than 5 injections do not affect the results, and 3-5 injections will be sufficient for the intended therapeutic effect. In our study, the results of the application 3 times with a 1-week interval and the evaluation of the results of the 6th month follow-up gave results consistent with the literature.

The limitations of this study are the inability to evaluate how much home exercises recommended together with viscosupplementation are applied by the patients, that is, patient compliance, and after the evaluations in the 6th month, the patients' cannot be followed. As a result, we think that patients with knee osteoarthritis in stage 4 can ben-efit from viscosupplementation with hyaluronic acid and its derivatives, and surgery may be delayed.

Declarations

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Conflict of Interest: The author certifies that he has affiliations with or involvement in any organization or entity with any financial interest

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Tables

Table 1: Lysholm Knee Scale

Fındıgs	Poınts
Hitch	
No	5
Mild or intermittent	3
Severe or persistent	0
Support	
No 5	5
Walking stick or crutch	2

Unable to weight	0
Locking	
No	15
No feeling of entanglement/locking	10
Rare crash	6
Frequent crashing	2
Deadlock on exam	0
İnstability	
None	25
Rare (with strain)	20
Frequently (with strain)	15
Rare (daily activity)	10
Frequent (daily activity)	5
at every step	0
Pain	
None	25
Light with compulsion	20
Prominent	10
Continuous	0
Engagement	
No	10
with coercion	6
with daily activity	3
Continuous	0
Step Up	
no problem	10
Slightly problematic	6
one by one	3
Cannot exit	0
Squatting	

no problem	5
Slightly problematic	4
Can't bend index	2
Not possible	0

Table 2: Means of Lysholm score before and 24 weeks before starting Group I and II viscosupplementation therapy

		Grup I Hyalan-GF 20		Grup II Sodyum Hyaluronat		
		Age 42-73				
		n= 34 (K/E, 31/3)		n= 34 (K/E, 31/3)		
Lysholm II Score	Clinical Results	Start	24.week	Start	24.week	
0 - 64	Bad	55.6 ± 4.72	56.21 ± 4.49	-	-	p>0.05
65 - 83	Medium	79.93 ± 4.85	80.12 ± 4.59	-	-	p>0.05
84 - 90	Good	-	-	-	-	-
90 - 100	Excellent	-	-	-	-	-