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ORIGINAL ARTICLE

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Comparison of the efficacy of lower and higher molecular weight viscosupplementation in the treatment of hip osteoarthritis

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Abstract We aimed to compare the efficacy of intra-articular injections of a lower molecular weight hyaluronan (LMW HA) (Ostenil) with a higher molecular weight viscosupplement (hylan G-F 20, Synvisc) in hip osteoarthritis. For this purpose, 43 patients (56 hips) with hip osteoarthritis with a visual analogue scale (VAS) pain score higher than 50/100, a Lequesne index greater than 6, and persistence of the pain for longer than 3 months despite all conservative methods were enrolled in the study and randomly assigned to two groups: 25 (32 hips) received LMW HA and the remaining 18 patients (24 hips) received hylan G-F 20. Three injections were administered once weekly to each patient under fluoroscopic guidance. During the 6-month follow-up period, the primary outcomes were assessed at the 1st, 3rd, and 6th month by VAS, WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index), and Lequesne index. The intra-articular injections produced a significant reduction in VAS, WOMAC, and Lequesne index scores in both groups. After three injections, improvement was prominent at the 1st month and maintained for 6 months in both groups. The percentage reduction was 38 and 40% ($p < 0.001$) in VAS pain score, 43 and 40% in WOMAC ($p < 0.001$), and 47 and 49% in Lequesne index ($p < 0.001$) in the LMW HA and hylan G-F groups at the 6th month, respectively. However, there were no significant differences in outcomes between any of the measurements at the 1st, 3rd, and 6th month between the two groups ($p > 0.05$). No systemic adverse effect was recorded. Local adverse effects consisting of pain and/or swelling were noted in 3 of 32 hips (9%) injected with LMW HA and in 3 of 24 hips (12.5%) injected with hylan G-F 20. In conclusion, both types of viscosupplementation produced a significant clinical improvement during the 6-month follow-up period. However, no significant difference was found in outcomes between higher and lower molecular weight hyaluronan.

Keywords Efficacy · Hip osteoarthritis · Hylan G-F 20 · Low molecular hyaluronan · Outcomes

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Introduction

Osteoarthritis (OA) is the commonest cause of chronic pain in older people, and the disease of the synovial joints in which cartilage is lost, subchondral bone alters, and new bone is formed around the joint [1]. Although several options are available for the treatment of OA, such as simple analgesics, nonsteroidal anti-inflammatory drugs (NSAID), and glucocorticoids, none of them has been shown to slow or detain disease progression or reverse joint damage in humans [2]. Hyaluronic acid (HA) is an important component of synovial fluid and cartilage. It is thought to have a protective effect in articular cartilage and soft tissue surfaces of joints by acting as a lubricant and imparting viscoelastic properties to the joint because of its high viscosity [3].

In OA, the amount and the molecular weight of HA are reduced and its protective properties are mostly lost [4]. Recent studies showed that injection of viscosupplementation (VS) compounds into osteoarthritic joints could be an alternative and efficient method for alleviating the symptoms and restoring the biological properties of normal HA [5]. Viscosupplementation directly addresses the cause of pain and the decrease in joint mobility by replacing the low elastoviscous osteoarthritic synovial fluid with high elastoviscous solutions of hyaluronan or its derivatives. Initial human studies with

VS therapy were mostly performed with knee OA. In most of them, low molecular weight HA (LMW HA) was used and encouraging results in alleviating the symptoms compared to placebo were reported [6–10]. Lower molecular weight HA preparations generally range from 0.5 to 1.5×10^6 Da in molecular weight. Because of the low elastoviscosity of these hyaluronan solutions compared to native hyaluronan in the synovial fluid, interests were shifted to a VS fluid similar to that of native hyaluronan in the synovial fluids. For this purpose, hylan G-F 20, a higher molecular weight hyaluronan ($6–7\times10^6$ Da) was produced [11]. The elastoviscous property of this newly developed hylan solution is considerably greater than that of hyaluronan solution [12]. Some authors believe that the analgesia produced for painful joints is related to the high concentration, high molecular weight, and high elastoviscosity of the solution [13]. Studies performed with higher molecular hylan G-F 20 solution in patients with hip OA reported a significant decrease in outcome measures and improvement in symptoms [14–17].

However, currently there is no consensus and not enough data are available about the effect of molecular weight and concentration of the hyaluronan on the treatment of OA. To date, the differences between high and LMW HA preparations in terms of their clinical efficacy have been investigated in a few studies in patients with knee OA and contradictory results were published. While Wobig et al. suggested that high molecular type VS injection (hylan G-F 20) is more effective in relieving the pain compared to LMW HA [13], two recent studies were unable to show any significant difference between higher and LMW HA preparations in regard to their clinical efficiency [18, 19].

In an extensive MEDLINE search, there were no data comparing the efficacy of higher and LMW HA injection in patients with hip OA. Thus, the present study was carried out to directly compare the tolerability and clinical efficacy of a high molecular weight viscosupplement hylan G-F 20 (Synvisc) with that of a LMW HA preparation (Ostenil) in patients with OA of the hip.

Material and methods

Patients

Forty-eight patients (ranging between 18 and 75 years old) with primary osteoarthritic hip joint diagnosed according to the American College of Rheumatology (ACR) criteria [20] were enrolled in the study. The radiological classification was performed with anteroposterior pelvic radiography according to the Kellgren score [21]. The inclusion criteria were: Kellgren radiological grade no greater than 3, pain score of least 50 mm on a 100-mm visual analogue scale (VAS), Lequesne index greater than 6, and persistence of the pain for longer than 3 months despite all conservative methods such as analgesics, nonsteroidal anti-inflammatory drugs (NSAID), and/or physical therapy. Patients with erythrocyte sedimentation rate greater than 40 mm/h and ankylosing spondylitis, rheumatoid arthritis, or other inflammatory joint disease as defined by ACR criteria and patients with a recent history of previous intra-articular injections of glucocorticoids or hyaluronan or hip surgery were excluded from the study. Furthermore, patients were not included if they had a known allergy to any substance related to the study, were pregnant, or had active arthritis in the hip joint and any other organ system which could interfere with the assessment of this therapy's efficacy. All subjects gave written informed consent to participate in the study, which was approved by the Ethical Review Committee of the University of Celal Bayar, Faculty of Medicine.

Study design

In this 6-month prospective, randomized, comparative, and single-blinded study, patients were randomly assigned to one of two treatment groups. Patients in the first group received intra-articular injections of LMW HA solution, Ostenil 2.0 ml (molecular weight is $1.2–1.4\times10^6$ Da, and its polysaccharide concentration is %1). Patients in the second group received intra-articular injections of hylan G-F 20, Synvisc 2.0 ml (molecular weight is 7×10^6 Da, and its polysaccharide concentration is %0.8). All injections were performed by the same clinician. A standard technique of fluoroscopically guided hip injection was used in all patients. With the patient lying supine, the femoral artery is palpated in the groin and a marker is placed 2 cm lateral and 2 cm distal to femoral vessels, 20-gauge spinal needles are inserted in a superior direction with fluoroscopic guidance to contact the bone at the junction of the medial aspect of the femoral head and neck using a sterile technique, and local anesthesia was performed using lidocaine 1%. One milliliter of iodinated contrast agent was injected and fluoroscopy was used to check that the position of the needle was in the joint cavity. Three injections were performed in each patient at 1-week intervals.

Assessment

Demographic findings such as age, gender, weight, height, Kellgren radiological grade, and symptom duration were recorded before the first injection. All patients were then reevaluated at the 1st, 3rd, and 6th month after the third injection. All of the assessments were performed by a second clinician who was blinded to the type of preparations injected. The evaluation consisted of the subjective global pain status including resting pain, weight-bearing pain, and walking pain which were assessed by VAS pain score [22]. Pain relief was evaluated using a 100-mm horizontal VAS, on which 0 equaled no pain or normal activity and 100

equaled unbearable pain. The intensity of pain, walking capacity, and activities of daily life were assessed by the Lequesne algofunctional index [23]. Additionally, the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) [24], a self-administered health status instrument for patients with osteoarthritis of the lower extremities, was also used to evaluate clinical status in terms of pain sensation and treatment efficacy during normal daily living activities and patient visits. The original version of this index contains 41 items in 5 domains. The domains are pain, stiffness, physical function, social function, and emotional function. In the present study, we only used pain, stiffness, and physical function because social and emotional domains were shown to have lower validity [24]. The five-point Likert scale was used to assess WOMAC scores. The time periods for walking 30 m, climbing 20 stairs (up and down), and sitting on/standing up from a chair 10 times were also recorded as outcome measurements. The adverse effects due to injections were recorded after each injection during the 1st month. The necessity for NSAID usage was evaluated during each patient visit.

Statistical analysis

Data are expressed as mean ± SD in Tables 1 and 2 and mean ± SEM in Fig. 1. Differences between the pre- and post-treatment values in the same group were analyzed by Friedman's test and their post hoc analyses were performed with Wilcoxon's signed rank test. Differences between the two groups at baseline and at the 1st, 3rd, and 6th month were analyzed with the Mann–Whitney U test; p values < 0.05 were considered to be significant. SPSS version 11.0 was used for all statistical calculations.

Table 1 Demographic findings of the patients included in the study. *BMI* body mass index, *NSAID* nonsteroidal anti-inflammatory drug

	Na-hyaluronan[a] ($n=25$, 32 hips)	Hylan G-F 20 ($n=18$, 24 hips)	p value
Age	58.8 ± 9.8	60.4 ± 9.6	0.4
Gender (%)			
Male	5 (20)	4 (22)	0.9
Female	20 (80)	14 (78)	
BMI (kg/m^2)	28.7 ± 4.3	29.8 ± 3.9	0.45
Symptom duration (months)	62 ± 50	70 ± 62	0.26
NSAID usage			
Yes	15	11	0.6
No	2	1	
Sometimes	8	6	
Radiological grade (%)			
I	2 (6)	1 (4)	0.5
II	10 (32)	7 (29)	
III	20 (62)	16 (67)	

[a]Lower molecular weight hyaluronan

Results

A total of 48 patients were included in the study. During the follow-up period one patient from the LMW HA group and three patients from the hylan G-F 20 group were excluded from the study because they declared they did not want to continue the study after the first injection because of the painful injection procedure. One patient in the hylan G-F 20 group was lost to follow-up in the 3rd month and also excluded from the study. The remaining 43 patients completed the study. Baseline demographics and clinical characteristics of the patients in the LMW HA group ($n=25$) and in the hylan G-F 20 group ($n=18$) are given in Table 1. In the LMW HA group, 18 had unilateral and 7 had bilateral hip OA (total 32 hips). In the hylan G-F 20 group, 12 had unilateral and 6 had bilateral hip OA (total 24 hips). No significant difference was found between age, gender, body mass index, symptom duration, and NSAID usage. Radiological grades assessed by the Kellgren score were also similar in both groups.

Table 2 summarizes the changes in outcomes in both groups. As clearly seen both types of intra-articular injections produced a significant reduction in VAS pain score, WOMAC score, and Lequesne index score at the 1st month, and this effect was maintained for 6 months in both groups. The percentage reduction was 38 and 40% ($p<0.001$) in VAS pain score, 43 and 40% in WOMAC ($p<0.001$), and 47 and 49% in Lequesne index ($p<0.001$) in the LMW HA and hylan G-F groups at the 6th month, respectively (Fig. 1). No significant difference could be demonstrated between the two hyaluronan drugs in terms of the improvements in VAS, Lequesne index, and WOMAC scores at the 1st, 3rd, and 6th month ($p>0.05$)

Three other outcome measurements such as time periods for walking 30 m (s), sitting on and standing up from a chair 10 times (s), and going up and down 20 stairs were also assessed in both groups. A significant reduction was found in both groups during the follow-up period (Table 2). This reduction was prominent at the 1st month and continued throughout the follow-up period as seen in VAS, WOMAC, and Lequesne index. There were also no significant differences in these outcome measurements at the 1st, 3rd, and 6th month among the groups ($p>0.05$). In the LMW HA group, ten patients gave up, five patients reduced, and two patients increased NSAID intake. In the hylan G-F 20 group, three patients gave up and four patients reduced NSAID intake. In statistical analysis NSAID intake was found to be significantly decreased in the low and high MW hyaluronan group at the end of the follow-up period (60 and 56%, respectively, $p<0.0001$). No systemic adverse effect was recorded. Local adverse effects consisted of pain and/or swelling and were noted in 3 of 32 hips (9%) injected with LMW HA and in 3 of 24 hips (12.5%) injected with hylan G-F 20.

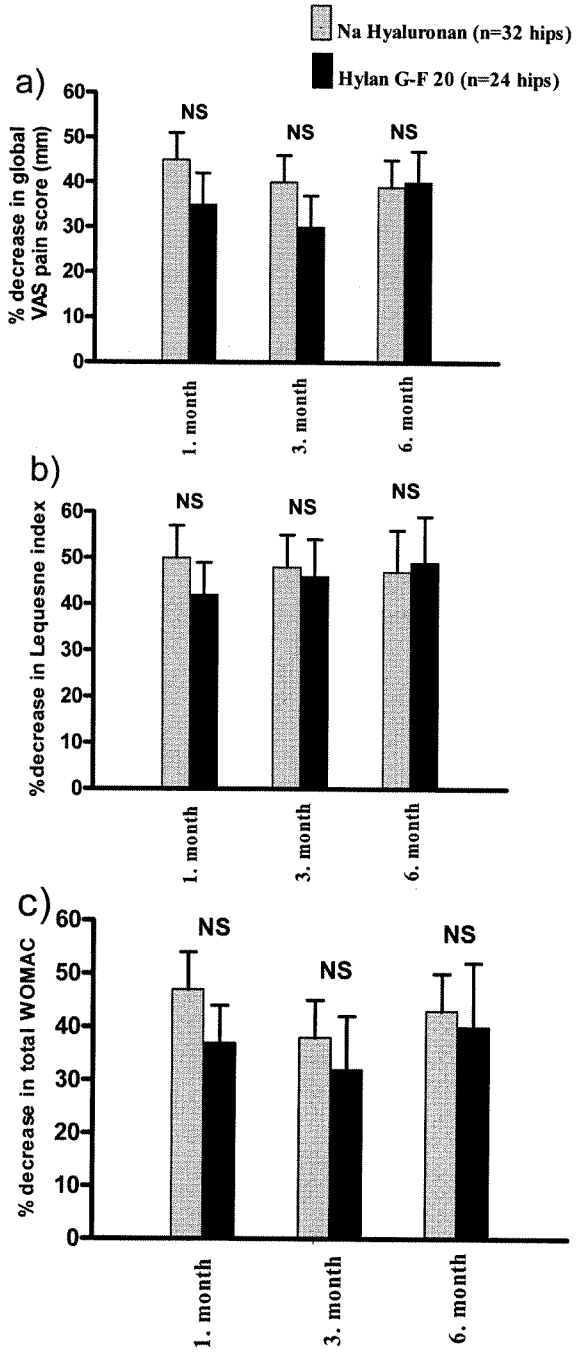

Fig. 1 Percentage decreases **a** in global VAS score, **b** in Lequesne index, and **c** in total WOMAC score are illustrated for both groups of patients at the 1st, 3rd, and 6th month. Both types of viscosupplementation showed similar effects and no significant differences were found in all measurements. Values are given as ±SEM

Discussion

To the best of our knowledge, this is the first study that has compared the effects of different molecular weight HA in the treatment of hip OA. Two main conclusions can be drawn from our study. First, both types of VS solution achieved significant improvements in all outcome measurements in the early period and this benefit was maintained throughout the 6 months. Second, there was no significant difference between their clinical efficacy at the 1st, 3rd, and 6th month of the follow-up period.

Balazs and Denlinger, pioneers of VS treatment with hyaluronan compounds, reported significant reductions in pain and discomfort in osteoarthritic joints [5]. Because the molecular weight and the amount of HA is reduced and eventually its protective effect is mostly lost in OA [4], it seems logical to replace the HA from outside sources to halt or to reverse the pathological process. For this purpose HA has been used therapeutically in humans and animals for nearly 30 years.

Currently in clinical practice, a variety of HA pharmaceutics of different molecular weight (MW) are available for the treatment of OA, but the significance of the MW with respect to their pharmacological activities has not been investigated in detail. Although in vitro studies have generally showed that high MW HA preparations, such as hylan G-F 20, were more biologically active than LMW HA compounds, these findings had not been confirmed in animal studies [25]. This discrepancy between the theoretical and practical findings may be partly explained by the enhanced penetration of the LMW HA preparation through the extracellular matrix of the synovium, thus maximizing its concentration and facilitating its interaction with target synovial cells. Supportive data for this interpretation came from animal models of OA which showed that LMW HA were generally more effective in reducing the synovial inflammation than high MW HA compounds [25]. Moreover, high MW HA had been shown to have some disadvantages such as increased inhibition of migration and chemotaxis of leukocytes, phagocytosis, adherence, and mitogen-induced proliferation [4]. Taking all these findings together, it is not easy to claim that increased concentration, average molecular weight, and elastoviscosity of the solution may achieve better analgesia and improvement in painful joints afflicted with OA.

The safety and efficacy of several types of HA preparations in the treatment of knee OA had been presented in many studies [6–10, 26–28]. Among a few comparative studies performed in patients with knee OA, only Wobig et al. reported that high MW HA (hylan G-F 20) was more effective in relieving the pain compared to LMW HA [13]. In contrast to this finding, two recent studies, which included a placebo or control group, were unable to show any significant difference in terms of efficiency of higher and LMW HA preparations [18, 19]. Although many encouraging results were reported for the use of HA preparations in knee OA, their efficiency in hip OA has been less frequently investigated. Migliore et al. in their preliminary report stated that one to three injections of low MW HA ($0.5–1\times10^6$) caused a significant reduction in VAS pain score and NSAID intake in a short follow-up period [29]. In two studies performed

Table 2 Pretreatment values and the changes in outcomes after injection of both types of viscosupplementation at the 1st, 3rd, and 6th month. Differences between the two groups were not statistically significant. Values are given as ±SD. *VAS* visual analogue scale, *WOMAC* Western Ontario and McMaster Universities Osteoarthritis Index

	Na-hyaluronan ($n=25$, 32 hips)	Hylan G-F 20 ($n=18$, 24 hips)	p value
VAS pain score (mm)			
Pretreatment	7.2 ± 1.5	6.7 ± 1.7	0.15
1 month	4.1 ± 2.6**	4.4 ± 2.3**	0.78
3 months	4.6 ± 2.5**	4.7 ± 2.7**	0.96
6 months	4.6 ± 2.5**	3.4 ± 3.0**	0.18
Lequesne index			
Pretreatment	11.4 ± 4.6	11.8 ± 3.3	0.68
1 month	5.9 ± 4.8**	7.1 ± 4.5*	0.34
3 months	6.2 ± 4.8**	6.3 ± 4.3**	0.84
6 months	6.2 ± 5.8**	5.9 ± 5.4**	0.89
WOMAC (total)			
Pretreatment	63.9 ± 21.3	57.2 ± 16.7	0.36
1 month	37.1 ± 28.4**	35.6 ± 19.5*	0.86
3 months	43.6 ± 31.4**	39.4 ± 27.9*	0.73
6 months	38.7 ± 30.3**	32.5 ± 23.0**	0.38
Walking time for 30 m (s)			
Pretreatment	36.1 ± 9.2	35.4 ± 10.2	0.51
1 month	30.3 ± 7.1*	29.1 ± 6.7*	0.65
3 months	29.6 ± 7.9*	28.4 ± 6.4*	0.74
6 months	28.0 ± 8.2*	27.8 ± 7.3*	0.68
Time to sit on and stand up from a chair 10 times (s)			
Pretreatment	37.4 ± 4.3	36.1 ± 5.2	0.44
1 month	29.9 ± 7.2*	32.6 ± 6.8	0.65
3 months	30.6 ± 8.0*	30.5 ± 7.6*	0.70
6 months	30.0 ± 6.2*	30.4 ± 7.9*	0.90
Time to go up and down 20 stairs (s)			
Pretreatment	46.5 ± 19.0	43.0 ± 18.0	0.34
1 month	36.0 ± 12.1*	35.2 ± 17.1*	0.56
3 months	29.6 ± 13.0**	33.2 ± 10.4**	0.29
6 months	32.1 ± 14.2**	31.8 ± 8.8**	0.85

*Significant decrease compared to basal values in the same group ($p < 0.05$)
**Significant decrease compared to basal values in the same group ($p < 0.001$)

with one to two hip injections of hylan G-F 20, significant improvement in VAS pain score had been reported [15, 17]. However, the difference in the number of hip injections in the two studies makes it difficult to interpret their results. Because VS solutions have a brief reaction time (half-life 1–2 days), their injection needs to be repeated many times [30]. In one study, the three-injection regimen was shown to be superior to the two-injection regimen in knee OA [31]. In contrast, some authors believe that the higher molecular weight product might have a longer duration of action, even if given less frequently. Although there is no consensus on the optimal dose regimen for both low and high molecular weight HA preparations, a three-dose regimen is mostly recommended for most of the hyaluronan preparations and most authors believe that this approach makes it easier to standardize the efficacy of the interventions. In the present study, we preferred a three-dose regimen for both preparations. However, other comparative studies performed with different dose regimens are needed to elucidate the optimal dose for lower and higher molecular weight HA preparations.

In an extensive MEDLINE search, we found only two recent studies performed with three injections once weekly in patients with hip OA as in the present study [14, 16]. Although these were not comparative studies, they were very similar to our study design. In the first of them, Vad et al. [14] investigated the efficacy of hylan G-F 20 in 25 patients with hip OA resistant to conservative treatment methods and reported that at the 1-year follow-up the mean VAS pain decreased from 8.7 mm to 2.3 mm and American Academy of Orthopedic Surgeons (AAOS) Lower Limb Core Scale score improved from a mean of 44.2 to 86.1 ($p < 0.05$). These authors concluded that the use of hylan G-F 20 injection is a viable option for treatment of mild to moderate OA of the hip joint. In the second study, Caglar-Yagci et al. [16] performed three hylan G-F 20 injections in 14 patients with hip OA and evaluated VAS, Lequesne index, and 15-m walking time before injections and 30 and 90 days after injections. They found that all of the measurements were statistically significantly lower than during the pretreatment period and the decrease continued after the 30th day. The results of these two studies are fully in agreement with the results of our hylan group although our evaluation was more detailed compared to theirs. In our study we also observed a 39, 49, and 40% decrease in VAS pain, Lequesne index score, and total WOMAC score at the 6th month in the hylan group, respectively. As in the study of Caglar-Yagci et al. [16], the decrease was prominent at the 1st month and maintained during the follow-up in our study. Moreover, we also documented significant improvement in times for walking 30 m, sitting on and standing up from a chair, and climbing stairs in both groups (Table 2).

Comparing the efficacy of both lower and higher MW HA solutions, we could not demonstrate any significant

difference between the two preparations. We observed that both types of HA preparations achieved similar improvement in very detailed outcome measurements. Our findings on comparison of two different molecular weight hyaluronan preparations support the results of Karlsson et al. [19] and Bayramoglu et al. [18] although they performed the comparisons in knee OA. We also observed a significant reduction in NSAID intake in both groups at the end of the follow-up period compared to the pretreatment values ($p < 0.0001$). This reduction was 60% in the LMW HA group and 56% in the hylan G-F 20 group. This is similar to the study of Migliore at al. who reported a 48% reduction in NSAID intake during the 1st month of the therapy in patients injected with LMW HA [29]. Although their results involved the early period of injection, we also demonstrated that the reduction in NSAID intake was maintained at the 6th month.

In the present study, we performed hip injections under fluoroscopic guidance as did some others [14, 15, 17], and we observed that this method really facilitates the injection procedure and increases the success rate. None of the patients had systemic adverse effects or serious local complications such as hematoma or femoral nerve injury at the injection site. Local adverse effects such as pain and swelling were noted in 3 of 32 hips (9%) injected with LMW HA and in 3 of 24 hips (12.5%) injected with hylan G-F 20. The minor complication rates in the present study were similar to other studies [15, 32].

Study limitations

Our study had some limitations. First, our sample size was relatively small for making a more precise comment on a comparison of treatment efficacy. Thus, future studies with a large number of patients are necessary to confirm our results. Second, we did not have a placebo group. It must be remembered that there is a strong placebo effect from joint injections, which may cause a nearly 30% reduction in pain relief during the first few weeks [4]. Hence, we may be missing the placebo effect and overestimated the real effects of both VS solutions. However, because the placebo effect would have been the same for both groups and mostly seen in the early periods, we believe that the late findings (at 3 and 6 months) of the present study reflect reliable results for the hyaluronan injections. Nevertheless, because most of the previous studies [14–17, 29] including ours did not have a placebo group, newly designed placebo-controlled studies are necessary to confirm the beneficial effects of VS therapy in hip OA.

In conclusion, three intra-articular injections at weekly intervals produced a significant reduction in all outcome measurements for a period of 6 months in patients with OA of the hip. Our results also showed that both lower and higher MW HA solutions resulted in similar levels of pain and disability reduction. We suggest that VS therapy is a safe and effective method in the treatment of OA of the hip which is resistant to conventional treatment modalities. However, our findings do not support the hypothesis that the pain-relieving effect of VS of the osteoarthritic joint is directly related to the molecular weight of the compound used in the treatment.

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