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The effect of viscosupplementation on neuromuscular control of the knee in patients with osteoarthritis

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Abstract. *Objective:* The aim of this study was to investigate the short-term effects of intra-articular injection of hyaluronan (Hylan G-F 20) on proprioception, isokinetic muscle force, self reported pain, and functional condition in patients with knee osteoarthritis (OA).
Methods: 63 patients with stage II-III bilateral knee OA were included in this randomized, placebo controlled, and prospective study. Subjects were randomized with 42 of them into the treatment group and 21 of them into the placebo group. Hyaluronan was intraarticularly injected into both knees of the subjects which were in the treatment group, whereas physiological saline was intraarticularly injected to the subjects which were in the placebo group. Proprioception and the isokinetic muscle force measurement were performed. Visual analogue scale (VAS) and WOMAC scale were used to evaluate pain and physical function.
Results: Statistical analysis was performed on 120 knees of 60 patients completing the trial. The average absolute angular error (AAAE) value showing the proprioceptive error level in the treatment group was detected to be statistically significantly lower compared to placebo at the measurements performed after the 3rd injection ($p = 0.02$) and after one week ($p = 0.01$). While there was no inter-group difference in isokinetic measurements performed at 180 and 240°/sec, a significant difference was detected at the measurement performed at 60°/sec in favor of the treatment group ($p = 0.02$). Activity and resting VAS-pain values, WOMAC parameters (except the WOMAC stiffness) were detected to be significantly lower in the treatment group. Local adverse events were not reported in any patient.
Conclusion: In this study, it was demonstrated that intraarticular injection of hyaluronan in patients with knee OA led to a short-term increase in proprioception and isokinetic muscle force, and also significant improvements in the functional conditions of patients. Long-term studies are needed.

Keywords: Knee osteoarthritis, hyaluronan, proprioception, pain

1. Introduction

Osteoarthritis (OA) is the most common joint disease in the world. It is also the most common cause of disabilities, especially in the elder people [6]. There are various types of treatment used for the knee OA. These include basic analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), glucosamine sulfate, topical capsaicin, intra-articular steroid, physiotherapy methods, ancillary equipment, braces, surgical treatments, exercises, and patient education [8].

Hyaluronan (HA) is a major component of both synovial fluid and articular cartilage, and is responsible for the elastoviscosity of synovial fluid [20]. The quantity of HA in the synovial fluid is reduced in the patients who have osteoarthritis [7]. The purpose of injecting intra-articular HA is to replace HA so that the natural

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viscosity of synovial fluid is maintained.

Proprioception can be defined as the conscious or unconscious perception of extremity position in space and the awareness of movement and position of the joints [16,24]. This sense plays an important role in the organization of periarticular muscle activities, which provide stability of the joints [11–13]. The sense of proprioception is known to decrease with age [21,25]. However, when patients with knee OA are compared to healthy individuals at the same age, there is much more loss of the sense of proprioception [9,18,23]. A correlation has been described between the progression of OA and impairment in proprioception [11,12]. Theoretically, it is not quite known whether osteoarthritis is the cause of loss in proprioception, or the impairment of proprioception results in osteoarthritis.

Various studies have been conducted regarding the effects of intra-articular HA treatment on pain and functional condition in patients with knee OA [4,15], whereas there is only one study investigating the effect of HA injection on proprioception [20]. The purpose of this study is to determine the short-term effects of intra-articular injection of HA on proprioception, isokinetic muscle force, self reported pain and functional condition in patients with knee OA. The hypothesis primarily intended to be tested is as follows: "One of the mode of actions of intra-articular hyaluronan in knee OA is the increase of proprioception."

2. Methods

This is a prospective, randomized, placebo controlled, double-blind (blinded patient/blinded evaluator) study conducted in patients with knee OA. 60 patients were included in the study. Enrolled patients were diagnosed with bilateral knee OA according to the criteria of the American College of Rheumatology, and were at stage II and III according to the Kellgren-Lawrence scale [1,14]. They also had minimum of 50 points from the VAS-pain scale of 100 mm during motion on both knees.

Patients with septic arthritis, Paget's disease, gout and pseudogout, major dysplasia or congenital abnormalities, ochronosis, acromegaly, hemochromatosis, Wilson's disease, primary osteochondromatosis, Ehlers-Danlos syndrome, neuropathic arthropathy (Charcot joints), hyperparathyroidism, hypothyroidism, or active synovitis, patients who have had serious knee trauma or surgical operation, or undergone arthroscopy of the knee joint in the last one year, patients who have received intra-articular steroids or HA injection in the knee joint in the last 6 months, patients with concomitant rheumatoid disease, and pregnant patients were not included in the study.

Subjects were randomized, with 42 of them into the treatment group and 21 of them into the placebo group. Random numbers used in randomization were obtained from the QuickCalcs (©GraphPath Software) program.

Hylan G-F 20 (Synvisc®; Wyeth-Ayerst Pharmaceuticals, Philadelphia, Pennsylvania) was intraarticularly injected into both knees of the subjects which were in the treatment group, whereas sterile physiological saline (0.9% sodium chloride) was intraarticularly injected to the subjects which were in the placebo group. Injections were repeated in both groups three times after every one-week.

The primary endpoint of the trial was proprioceptive level; the secondary endpont was isokinetic muscle force and tertiary endpoint was VAS-pain and WOMAC scores.

Measurement of proprioception was made before and immediately after every injection. It was also repeated one week after the last injection. Measurement of the isokinetic muscle force, 0–100 mm visual analogue scale (VAS), and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC-5-point likert 3.0) were performed before the injection and one week after the last injection [26]. Patients did not use any analgesic medication during the study and were not prescribed any exercise program.

2.1. Measurement of proprioception

There are a variety of tests used for the evaluation of the sense of proprioception. Among these tests are the reproduction tests used to evaluate the sense of position of the joint [24], threshold tests to measure the sense of kinesthesia [22], and the hamstring reflex contraction latency measurement [3].

In this study, the sense of position of the joint was measured using the passive-active reproduction method in the sitting position. Beynnon et al. demonstrated the validity and the repeatability of this method in evaluating proprioception [5]. The Biodex System 3 Pro Multijoint System® (Biodex Medical Inc, Shirley/NY) isokinetic dynamometer was used to take a digital information of the flexion angles of the knee, and also to keep the leg at pre-determined angles. The passively formed knee flexion angles of 20°, 40° and 60° by the isokinetic dynamometer were later on asked to be actively repeated from the subjects. The subjects were

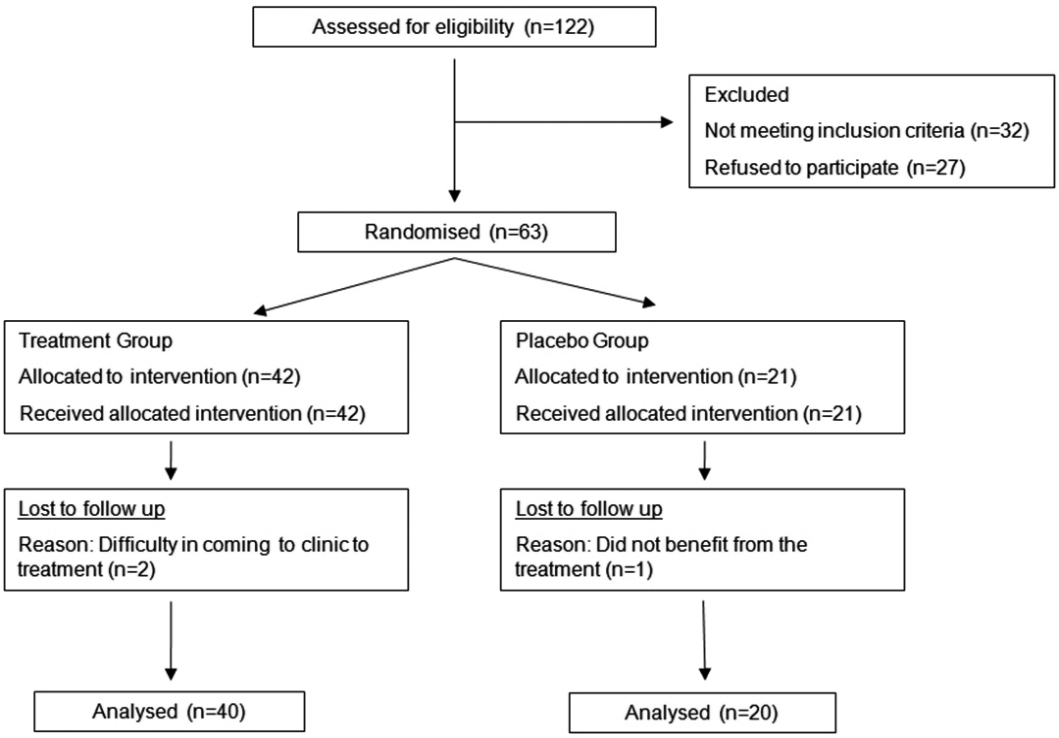

Fig. 1. Consort diagram of the study.

asked to maintain the passively formed knee flexion angles for 5 seconds each. They were later on positioned to 45° knee flexion angle, considered as neutral, and maintained this position for 5 seconds. At the next stage, the subjects were asked to actively re-establish the requested angles. The measurements were repeated on three consecutive days. The test environment was kept quiet and at a fixed temperature. The subjects were asked to wear comfortable clothes and to close their eyes. The average of the three consecutive measurements was used for the evaluation. The angle values of 20°, 40° and 60° obtained from the subjects was subtracted from the real angles and the absolute angles obtained so that the "absolute angular error" (AAE) value for each angle is calculated. The average of the AAE obtained for these three angles was later on calculated and the "average absolute angular error" (AAAE) was obtained.

2.2. Isokinetic measurement

The Biodex System 3 Pro Multijoint System was used for isokinetic measurement. The quadriceps peak torque value, hamstring peak torque value, and the value of the agonist/antagonist ratio were obtained at angular speeds of 60 degree/second (°/sec), 180°/sec and 240°/sec.

Measurements and injections were performed by two different physicians in order to maintain double-blinding. Only the physician who performed injections knew whether the patient was injected HA or physiological saline. Measurement of proprioception, isokinetic parameters, VAS-pain, and WOMAC scale were performed without knowing in which group the patients were enrolled. Before the study, verbal and written informed consent was obtained from the subjects. Approval for the study was obtained from the local ethics committee. The study was a prospective clinical trial carried out in accordance with the principles of the Declaration of Helsinki.

2.3. Statistical analysis

SPSS 11.0 software program was used for statistical analysis. Repeated measures of ANOVA test and Friedman way ANOVA test were used for nonparametric variables (VAS-pain), respectively. By taking baseline measurements as reference, intra-group comparisons were made by using Wilcoxon signed rank test and $p < 0.05$ was accepted as statistically significant.

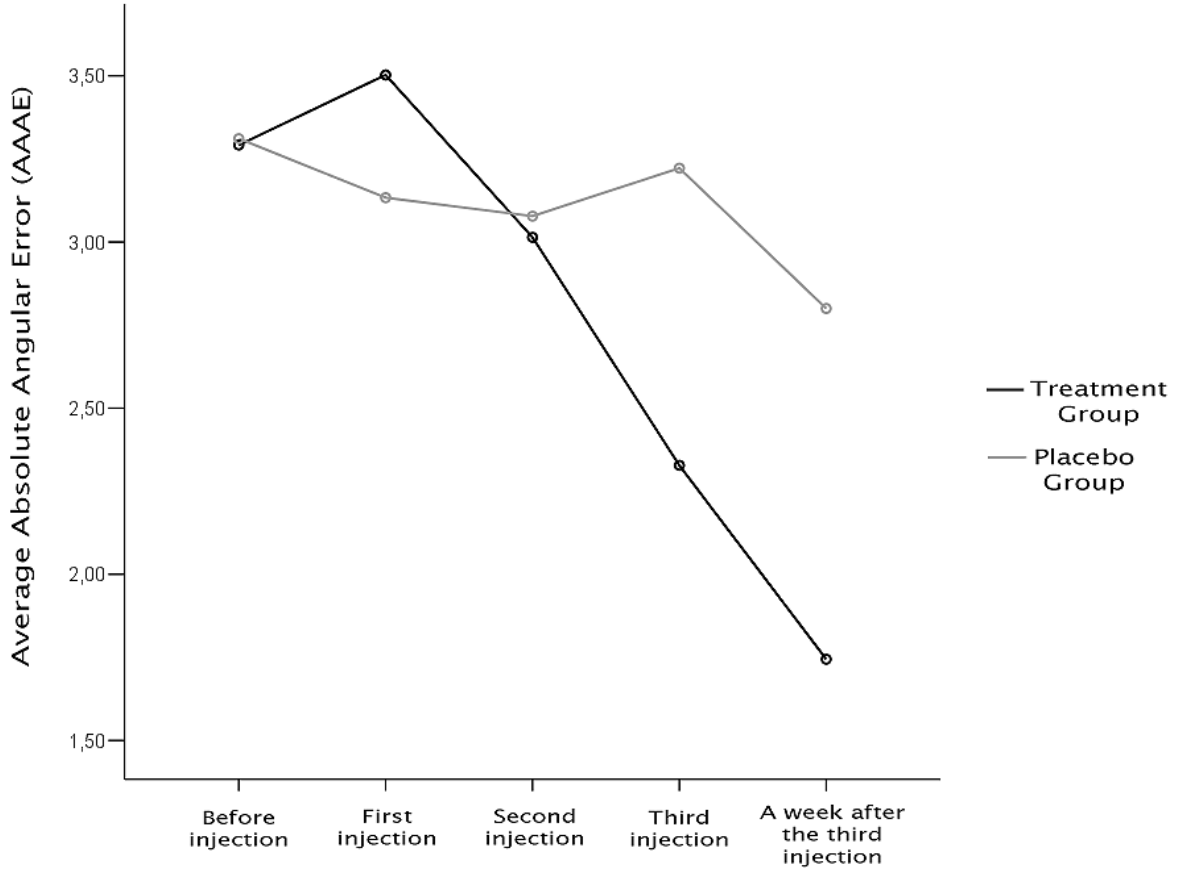

Fig. 2. The proprioceptive error levels following repeated HA injection in the treatment and placebo groups.

3. Results

Two subjects from the treatment group and one subject from the placebo group were expelled from the study because they did not complete their three-week injection protocol (Fig. 1). 60 patients completed the study: 40 from the treatment group and 20 from the placebo group. Effusion in the patello-femoral joint was not observed in any of the patients. No pseudoseptic reaction or adverse event was determined.

The mean age of patients was 59.4 $\pm$ 9.9 and 56.2 $\pm$ 7.2 years in the treatment and placebo groups, respectively. There was no statistically significant difference among the groups with regards to the age ($p >$ 0.05). The treatment group consisted of 36 females and 4 males and the placebo group consisted of 20 females. The mean body mass index of the treatment and placebo groups were 31.1 $\pm$ 5.0 and 31.3 $\pm$ 4.0, respectively, and there was no significant difference between the groups ($p > 0.05$). There was also no significant difference between the groups with regards to the Kellgren-Lawrence scores ($p > 0.05$).

64% of the treatment group were housewives and 23% were retired persons, whereas the placebo group consisted totally of housewives. The majority of the participants in both groups were primary school graduates.

Local adverse events were not reported in any patient.

3.1. Propriception measurement results

120 knees of 60 patients were evaluated at proprioceptive measurements. Before injection, there was no significant difference between the treatment and placebo groups in the AAAE, which demonstrates the level of proprioception ($p > 0.05$). While there were no inter-group differences after the 1st and 2nd injection, the AAAE values of the treatment group were detected to be significantly lower at the measurements performed following the 3rd injection and one week after (Fig. 2 and Table 1).

Table 1
The proprioceptive error levels following repeated injections

Group	AAAE	Mean	Std. Deviation	Difference		
				Median	Mean	Std Deviation
Treatment Group	Before injection	3.25	1.95	–	–	–
($n = 80$)	First injection	3.40	2.28	0.06	−0.15	1.92
	Second injection	2.99	1.39	0.33	0.26	1.69
	Third injection	2.29	1.12	1.22	0.96	1.87
	A week after the third injection	1.72	1.18	1.28	1.53	1.96
Placebo Group	Before injection	3.27	2.21	–	–	–
($n = 40$)	First injection	3.09	2.08	−0.06	0.18	1.38
	Second injection	3.18	2.21	−0.06	0.09	1.79
	Third injection	3.09	2.20	0.11	0.18	1.36
	A week after the third injection	2.71	1.93	0.22	0.57	1.80
Source	Factor	Type III Sum of Squares	df	Mean Square	F	P
AAAE* groups	Level 2 vs. Level 1	2.89	1.00	2.89	0.93	0.34
	Level 3 vs. Level 1	0.77	1.00	0.77	0.26	0.61
	Level 4 vs. Level 1	16.02	1.00	16.02	5.42	0.02*
	Level 5 vs. Level 1	24.92	1.00	24.92	6.81	0.01*

AAAE: Average Absolute Angular Error, Level 1: before injection, Level 2: first injection, Level 3: second injection. Level 4: third injection, Level 5: a week after the third injection.

Table 2
Maximal isokinetic muscle force (peak torque) values obtained prior to injection and 1 week after the third injection

Parameter	Group	Before Injection		After Injection		Difference		P
		Mean	SD	Mean	SD	Mean	SD	
60°/s Ext	Treatment	73.65	26.55	78.35	26.75	−4.70	11.07	–
	Placebo	87.52	25.91	87.54	26.28	−0.02	12.85	0.04*
60°/s Flex	Treatment	34.55	14.54	37.03	14.27	−2.48	6.84	–
	Placebo	36.15	10.24	35.67	10.21	0.49	5.79	0.02*
180°/s Ext	Treatment	54.41	11.51	55.32	13.69	−0.91	7.06	–
	Placebo	55.73	13.47	56.26	12.40	−0.53	7.35	0.79
180°/s Flex	Treatment	42.16	12.76	42.67	14.58	−0.51	7.11	–
	Placebo	34.67	12.14	35.22	11.89	−0.55	4.91	0.98
240°/s Ext	Treatment	53.14	16.53	57.00	17.80	−3.86	11.21	–
	Placebo	55.52	15.93	57.56	15.37	−2.04	6.40	0.34
240°/s Flex	Treatment	34.37	12.73	36.24	12.68	−1.87	7.31	–
	Placebo	33.88	11.78	34.11	10.79	−0.24	6.47	0.24

N: Newton, m: meter, SD:Standard deviation, °: degress, s:second, Ext:Extension, Flex:Flexion. P value indicates the significance between the differences obtained.

3.2. Isokinetic measurement results

120 knees of 60 patients were evaluated at the isokinetic measurements. With respect to 60°/sec angular speed, the post-injection differences were determined to be significantly higher in the treatment group compared to placebo group ($p < 0.05$). However there was no significant difference between the differences obtained in 180 and 240°/sec angular speed ($p > 0.05$) (Table 2).

3.3. Pain and functional status results

Before the injections, there was no significant difference between the treatment and placebo groups regarding the VAS and WOMAC parameters ($p > 0.05$). After the injections, activity and resting VAS-pain values, all WOMAC parameters (except the WOMAC stiffness) were detected to be significantly lower in the treatment group ($p < 0.05$). There was no significant difference between the groups in WOMAC-stiffness values (Figs 3 and 4, Table 3).

4. Discussion

According to the results of our study, following three intra-articular injections of HA into the knee joint, the proprioception was significantly improved. It is not

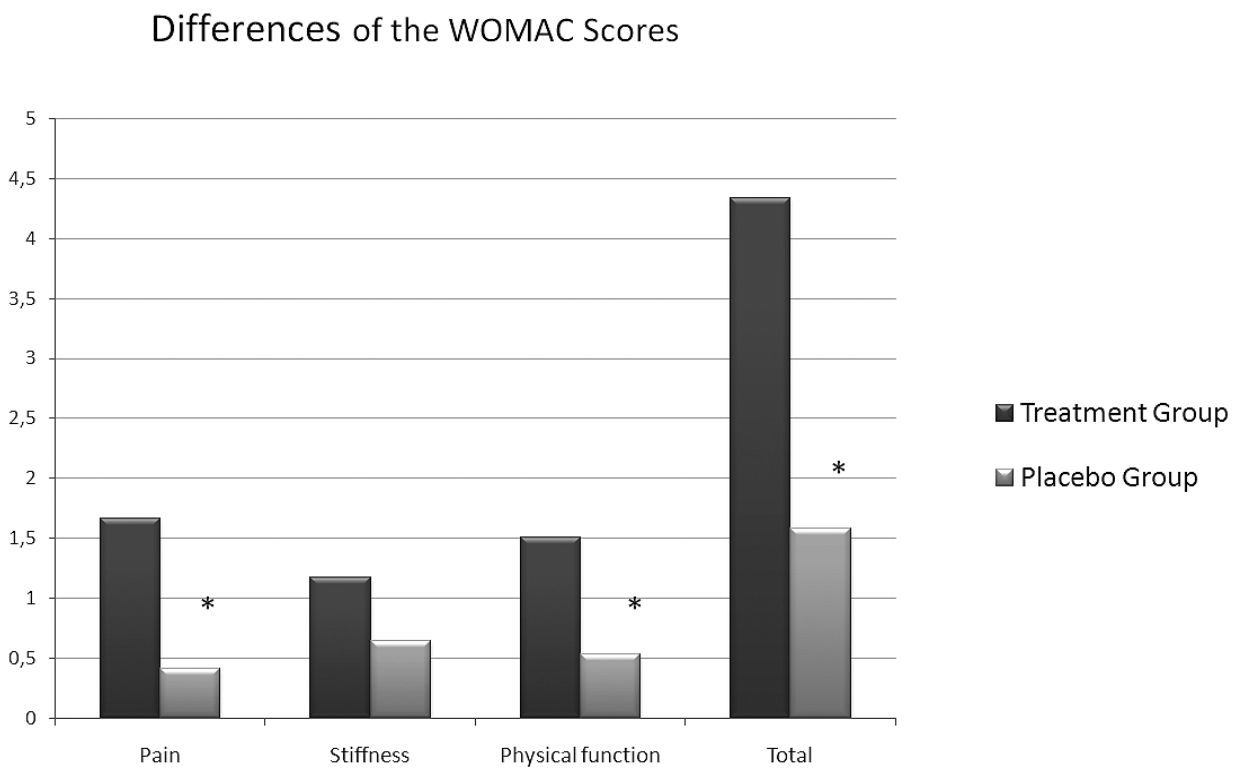

Fig. 3. Differences in VAS pain values occurring following HA injection in the treatment and placebo groups (* : p <0.01).

well known if these effects of injection continue for a long period. In the only study previously conducted by Payne et al. on this subject, measurements of proprioception were made before the HA injection, 3 weeks and 12 weeks after the HA injection, and no difference was found between the HA and the placebo group [20]. However, a significant difference was observed in our study compared to the placebo group. There may be several reasons for the different results obtained from the two studies. In the study of Payne et al., measurements of proprioception were made while the patient was standing; whereas, in our study these measurements were conducted while the patient was sitting. Also, the patients were asked to perform stretching and flexibility exercises and the use of oral analgesics was permitted in the study of Payne et al. As we previously demonstrated in our relevant trials, exercise alone might have assisted in the increase in the proprioception in the placebo group [10]. However, in our study the use of analgesics was not permitted and no exercise program was suggested. In addition, the patients enrolled in the trial by Payne et al. are older than the patients in our study. The proprioceptive receptors may be further degenerated by age and this may decrease the efficacy of treatment. Intra-articular HA injection is not much recommended in highly degenerative joints. All these differences may lead to different results in the two studies [20]. There is a correlation between the increase in proprioception with the improvement in the pain and functional condition of the patients. Improving proprioception can contribute to the functional benefits acquired from the intra-articular injection of HA. On the contrary, pain control obtained through HA injection may have had a positive effect on the proprioception.

Changes in the volume of joint fluids due to intra-articular injection may affect the proprioception by stimulating the receptors in the stretched joint capsule. However, all the proprioceptive changes can not be explained only by this mechanism. If the proprioceptive changes were associated only with capsular tension of the joint, proprioceptive improvement could have also been expected in the group where intra-articular physiological saline was injected. The chemical properties of the substance injected intra-articularly are also important. Moreover, if the changes were only associated with increase in volume, various differences could have been expected to occur in the measurements following every injection. However, proprioceptive differences were established between the measurements performed before the first injection and after the third injection.

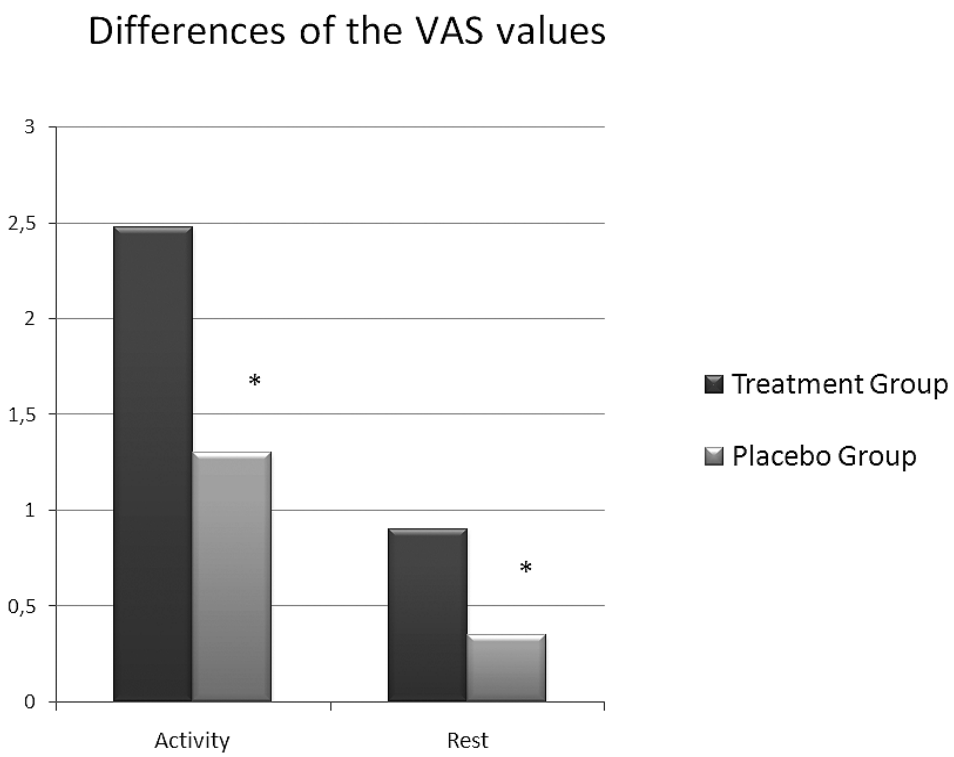

Fig. 4. Differences in WOMAC values occurring following HA injection in the treatment and placebo groups (*: $p < 0.01$).

Table 3
VAS and WOMAC values obtained prior to injection and 1 week after the third injection

		Before Injection				After Injection				Differences	P
		Mean ± SD	Median	Min	Max	Mean ± SD	Median	Min	Max	Mean ± SD	
VAS activity pain	Treatment	6.47 ± 1.56	7.00	2.00	9.00	4.0 ± 1.47	4.00	1.00	7.00	2.47 ± 1.1	–
	Placebo	6.45 ± 1.53	6.00	4.00	9.00	5.55 ± 1.47	5.00	4.00	9.00	0.9 ± 1.3	0.001*
VAS resting pain	Treatment	2.93 ± 1.68	3.00	0.00	7.00	1.63 ± 1.35	2.00	0.00	6.00	1.3 ± 1.3	
	Placebo	3.25 ± 1.29	3.00	2.00	6.00	2.9 ± 1.45	3.00	0.00	5.00	0.35 ± 0.9	0.004*
WOMAC pain	Treatment	5.84 ± 1.32	6.50	2.00	8.00	4.18 ± 1.42	4.00	1.00	7.00	1.66 ± 1.1	
	Placebo	5.6 ± 1.13	5.75	2.50	7.50	5.19 ± 1.15	5.50	2.50	7.00	0.41 ± 0.9	0.001*
WOMAC Stiffness	Treatment	4.47 ± 1.9	3.75	0.00	7.50	3.3 ± 1.62	3.75	0.00	6.25	1.17 ± 1.2	–
	Placebo	4.08 ± 2.12	3.75	0.00	7.50	3.44 ± 1.85	3.75	0.00	6.25	0.64 ± 1.7	0.168
WOMAC Phy.Func.	Treatment	5.87 ± 1.3	6.10	2.35	9.26	4.36 ± 1.16	4.75	1.02	7.05	1.5 ± 1	–
	Placebo	5.7 ± 0.95	6.03	3.38	6.90	5.18 ± 1.04	5.14	3.09	7.05	0.53 ± 1.1	0.001*
WOMAC total	Treatment	16.17 ± 4.14	16.42	5.85	24.26	11.84 ± 3.88	12.12	2.02	19.80	4.33 ± 2.8	
	Placebo	15.38 ± 3.27	15.85	6.88	20.40	13.8 ± 3.49	13.75	6.09	19.80	1.58 ± 3	0.001*

P value indicates the significance between the differences obtained.

The HA, when injected intra-articularly three times, was shown to increase maximal isokinetic muscle force in a short term. However, this increase was significant only at the speed of 60°/sec and 240°/sec in the right extremity. A significant increase in muscle force at an angular speed of 240°/sec in the right extremity was also observed in the placebo group. The reason for this condition may be based on the fact that the right extremity is the dominant extremity in most of the patients, and due to this, right side is more sensitive to the treatment. Besides, the ratio of agonist/antagonist did not change and this demonstrates that injection does not have a negative effect on the flexor-extensor balance. We don't know how intra-articular injection improves isokinetic muscle force. It seems that the injection might have built up the muscle performance because of the diminished friction related to increased viscosity. The increase in muscle force obtained in our

study correlates with that of previous studies. Tang et al. demonstrated that eccentric and concentric muscle force could be increased by five HA injections [27]. Likewise, in a study conducted by Miltner et al., it was established that significant differences existed between the opposite knees where HA injection was applied at an angular speed of 60°/sec and 180°/sec. They also demonstrated that after five injections, significant improvements were observed in the isokinetic muscle force with a decrease in VAS-pain and the Lequesne score [19]. The percentage increases in muscle strength that we observed, appear to be modest compared to the results reported by Miltner et al. and Tang et al.

The recent randomised placebo controlled study by Lundsgaard et al did not find difference in terms of pain level between the HA and placebo groups [17]. However in our study a significant difference in VAS-pain between the groups is observed. The primary endpoint of our study is the proprioception, but it was pain in Lundsgaard et al.'s study. Additionally if the fact that our study was made in a smaller group than this study is considered, the value of the results gained in terms of pain is limited. Although there are many studies about this subject, the efficiency of HA in knee OA is still controversial [2,30]. While there was a significant improvement in all the sub-parameters of WOMAC in the treatment group, no significant difference was established in the placebo group regarding the WOMAC-pain and WOMAC-stiffness sub-parameters. The difference between these two scales can be due to the fact that the WOMAC scale is more specific for OA. Previous studies have demonstrated that there is a decrease in the WOMAC and VAS values with HA injection similarly with our study [28,29].

Limitation of our study is that it shows the short-term effect of the injection on the proprioception. The long-term nature of this effect is not well known. Results from a longer term study would also contribute to previous work examining the causal relationship between proprioception and OA. Due to ethical reasons and the difficulties faced in obtaining appropriate subjects for the study, the placebo group was fewer in number when compared to the treatment group. Besides, there was a difference between the beginning values (though statistically insignificant) of proprioception measurements among the groups. This difference may have an effect on the obtained results.

In this study, it has been demonstrated that intra-articular injection of HA to patients with knee OA can lead to a short-term increase in the proprioception and isokinetic muscle force, and also that significant improvements can be obtained in the self reported pain and functional conditions. The most important effect of the treatment is on proprioception which has an important role in the pathogenesis of OA. The proprioceptive improvement obtained from HA injection may indirectly result in increase in muscle force or reduction in pain, or the proprioceptive progress may have affected the pain and functional condition directly. It should be demonstrated through controlled studies with long-term follow-up if these effects last for a long time.

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