

Efficacy of a Single Intra-Articular Injection of 2% Sodium Hyaluronate Plus 0.5% Mannitol in Patients with Symptomatic Osteoarthritis of the Knee: A Preliminary Report

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Background: Intra-articular injection of hyaluronic acid is widely used as a treatment for osteoarthritis of the knee. The recommended dosing regimens have generally ranged from 3 to 5 injections.

Objective: To assess efficacy and safety of a single intra-articular injection of 2% sodium hyaluronate plus 0.5% mannitol in patients with symptomatic osteoarthritis of the knee.

Material and Method: Twenty patients between 40-70 years of age with osteoarthritis of the knee (Kellgren-Lawrence grade II or III) were included in the study. After a 2-week NSAIDs washout period, ten patients in the intervention group received a single intra-articular 2 ml dose of the combination of 2% sodium hyaluronate and 0.5% mannitol and ten patients in the control group received no injection. No other pain-killer medication was allowed during the study except diclofenac as rescue pain medication in both groups. The efficacy parameters were the WOMAC Index and diclofenac consumption. All adverse events were recorded.

Results: Patients who received a single intra-articular injection of 2% sodium hyaluronate plus 0.5% mannitol had a significant improvement from baseline in all WOMAC subscales over 24 weeks ($p < 0.001$). Pain, stiffness, and physical function subscales were significantly lower in the intervention group than in the control group until Week 20, 12, and 16, respectively ($p < 0.05$). Patients who received sodium hyaluronate also required significantly lower amounts of diclofenac ($p < 0.05$). No serious adverse event related to the intervention was reported.

Conclusion: Symptomatic OA knee patients who received a single intra-articular injection of 2% sodium hyaluronate plus 0.5% mannitol had better outcomes over the 24-week follow-up period than control group patients who received no injection intervention.

Keywords: Osteoarthritis, Hyaluronic acid, Viscosupplement, Intra-articular injection

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Osteoarthritis (OA) is the most common arthritis of the knee. OA results in pain, stiffness, and reduced physical function^(1,2). Various pharmacological and non-pharmacological modalities are used to treat this condition⁽³⁻⁶⁾. Hyaluronic acid (HA) is a major component of the extracellular matrix of articular cartilage, and is present in high concentration in the synovial fluid. This substance acts as a lubricant and a shock absorber. In patients with OA, there is a decrease in the concentration and molecular weight of synovial

HA. As a result, intra-articular injection of HA or viscosupplementation is widely used as a treatment for OA due to its essential role in normal knee function^(7,8).

Different viscosupplement formulations have been developed that contain HA of different molecular weights and origins (e.g., rooster combs or fermentation) or cross-linked HA. Positive clinical results of HA viscosupplementation were demonstrated in recent systematic reviews, including pain reduction and improved physical function⁽⁹⁻¹¹⁾. Several reviews, however, have reported discordant conclusions⁽¹²⁻¹⁵⁾. The recommended dosing regimens of intra-articular injection have generally ranged from 3 to 5 injections, with injections given at weekly intervals. A new viscosupplement (Ostenil®Plus) contains 2%

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sodium hyaluronate and 0.5% mannitol. Mannitol functions as an antioxidant and protects HA from depolymerization⁽¹⁶⁾, resulting in a prolonged intra-articular HA residence time. If the efficacy of this treatment can be established, it may be possible that the number of injections can be reduced from multiple injections to a single intra-articular injection, which may improve patient compliance and decrease the risk of local complications.

The primary objective of this preliminary study was to assess the efficacy of a single intra-articular injection of 2% sodium hyaluronate plus 0.5% mannitol in patients with OA of the knee. The secondary objective was to evaluate the safety of this intervention. It was hypothesized that a single injection of 2% sodium hyaluronate plus 0.5% mannitol would result in reduction of knee pain, improve physical function, and decrease in NSAIDs consumption with no serious adverse events.

Material and Method

This open-label, randomized, controlled, add-on clinical trial was conducted at the Faculty of Medicine Siriraj Hospital, Mahidol University. The study protocol and patient informed consent form were approved by the Siriraj Institutional Review Board (SIRB). This study was registered with the US National Institutes of Health ClinicalTrials.gov registry (NCT01288001).

Patient selection

Patients meeting the following inclusion criteria were eligible for enrollment: male or female gender; 40 to 70 years of age; diagnosis of primary tibiofemoral OA of the knee according to American College of Rheumatology (ACR) criteria⁽¹⁷⁾; knee pain of at least 4 (10-point scale) for at least 2 of 5 subscales of the WOMAC (Thai version) pain subscore at baseline; Kellgren-Lawrence grade II or III⁽¹⁸⁾ diagnosed by an anteroposterior standing radiograph of the knee taken within 3 months prior to enrollment; and giving written informed consent. In cases of bilateral OA in patients in the intervention group, the most painful knee would be treated and assessed.

Patients were excluded for any one or more of the following reasons: secondary OA; clinical signs of acute flare; painful knee condition other than OA; concomitant rheumatic disease; varus or valgus malalignment more than 15 degrees on a standing radiograph; clinically significant instability of the knee; significant injury to the target knee within 6 months

prior to screening; skin disease in the area to be injected; disease of the spine or other lower extremity joints of sufficient degree to affect assessment of the target knee; concomitant condition requiring regular use of analgesic medications; any surgery of the target knee; intra-articular corticosteroid injection into the target knee within the last 3 months; and/or, intra-articular HA injection into the target knee within 6 months prior to screening.

Patients were assessed for eligibility at the screening visit. After providing written informed consent to participate in the study, medical examination was performed and demographic characteristics and medical history were recorded. The use of oral and topical NSAIDs and other analgesics was discontinued for 14 days prior to the baseline visit in order to obtain more reliable unmodified baseline values. During this washout period, paracetamol was available as rescue pain medication. Patients were instructed not to take any paracetamol within 12 hours prior to the baseline visit.

Intervention

At the baseline visit (week 0), patients were randomized into one of two study groups. Ten patients were assigned to the intervention (injection) group and 10 patients were assigned to the control (no injection) group. Computerized randomization software was used to randomly allocate patients. Patients in the intervention group received a single intra-articular injection of 2 ml Ostenil®Plus (TRB Chemedica AG, Munich, Germany), without an injection of local anesthetic. If present, joint effusion was aspirated before the administration of treatment. After injection, the knee was moved passively. Patients were advised to rest the knee by avoiding strenuous activity for 48 hours. Patients in the control group received no injection. Both groups were provided with a sufficient supply of diclofenac 25 mg (maximum daily dose 150 mg) as rescue pain medication. Omeprazole was also supplied to control gastric side effects, as needed. Patients were instructed to record the number of diclofenac tablets taken per day in their medication intake diary. Patients were also instructed not to take any diclofenac within 12 hours before the next scheduled follow-up visit.

Evaluation of efficacy

The study protocol included 6 follow-up visits, which were scheduled at weeks 4, 8, 12, 16, 20, and 24 after the baseline visit. At each visit, patients

were evaluated using a modified Thai version of the Western Ontario McMaster (WOMAC) Osteoarthritis Index. The WOMAC Thai version consists of 3 subscores-one for pain, another for stiffness, and a third for physical function⁽¹⁹⁾. Diclofenac consumption was also recorded at each visit.

Evaluation of safety

All adverse events were recorded, including those observed by the investigator and those reported by the patient. Adverse event entries included a description of the event, date of onset, duration, intensity, treatment, outcome, and relationship to the study intervention. Concomitant treatments were also recorded, given their potential participatory role in being indicators of adverse events or disease progression.

Statistical analysis

Patient characteristics and safety variables in both groups were evaluated using descriptive statistics. Inter-group comparison of WOMAC OA index and diclofenac consumption at each visit was performed using independent t-test. Values obtained for these two parameters at each follow-up visit were compared to baseline values using repeated measures ANOVA. Statistical analysis was performed using SPSS Statistics version 18.0 (SPSS, Inc., Chicago, IL, USA). A *p*-value less than 0.05 was regarded as being statistically significant.

Results

A total of 25 patients were assessed for eligibility. Five patients were excluded, as follows: 4 patients had radiographic OA grading lower than the level stipulated in the study protocol (Kellgren

Lawrence grade I), and one patient refused to participate in the study. Twenty patients were randomized 1:1 into the intervention group (10 patients) and the control group (10 patients). All patients completed the 24-week follow-up period (Fig. 1). Given that no major protocol deviations were reported, all randomized patients (*n* = 20) were included in both the intent to treat and per protocol populations for this analysis. There were no statistically significant differences between groups for any demographic or disease characteristics (Table 1). Both groups were also homogeneous at baseline for total WOMAC Index (Thai version) score, as well as for each of the pain, stiffness, and physical function subscores (Table 2).

Results of WOMAC Index scoring are shown in Table 2. Patients in the intervention group who received a single intra-articular injection of 2% sodium hyaluronate plus 0.5% mannitol (Ostenil®Plus), and oral

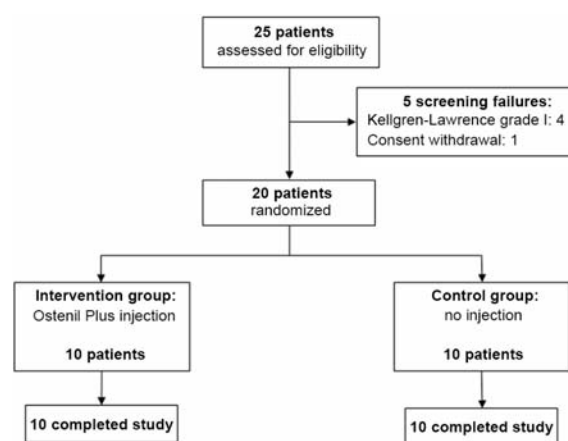


Fig. 1 Flow chart of the study protocol.

Table 1. Baseline characteristics of study groups

	Intervention (n = 10)	Control (n = 10)	<i>p</i> -value
Mean age, years (SD)	58.0 (7.7)	56.6 (3.0)	0.600
Female, n (%)	9 (90)	9 (90)	1.000
Mean height, cm (SD)	154.3 (5.7)	154.7 (3.8)	0.873
Mean weight, kg (SD)	65.0 (8.0)	68.1 (6.2)	0.375
Mean BMI, kg/m ² (SD)	27.5 (4.5)	28.5 (3.2)	0.578
Patients with bilateral osteoarthritis of the knee, n (%)	5 (50)	7 (70)	0.650
Right knee as the index knee, n (%)	6 (60)	6 (60)	1.000
Kellgren-Lawrence grade, n (%)			1.000
Grade II	9 (90)	8 (80)	
Grade III	1 (10)	2 (20)	

Table 2. Efficacy outcomes

WOMAC index	Intervention group (n = 10)			Control group (n = 10)			p-value ^a
	Mean (SD)	Difference from baseline	95% CI of difference	Mean (SD)	Difference from baseline	95% CI of difference	
Pain subscore (0-50)							
Week 0	25.5 (6.6)	-	-	28.9 (6.2)	-	-	0.248
Week 4	12.4 (3.6)	-13.1	-5.2 to -21.0	27.0 (7.6)	-1.9	9.7 to -13.5	<0.001*
Week 8	10.2 (4.4)	-15.3	-7.6 to -23.0	24.3 (7.6)	-4.6	4.3 to -13.5	<0.001*
Week 12	12.0 (6.1)	-13.5	-3.2 to -23.8	22.3 (7.6)	-6.6	7.8 to -21.0	0.004*
Week 16	12.8 (7.2)	-12.7	-1.5 to -23.9	20.8 (6.4)	-8.1	1.3 to -17.5	0.018*
Week 20	10.7 (6.7)	-14.8	-3.1 to -26.5	19.1 (6.9)	-9.8	1.2 to -20.8	0.013*
Week 24	12.7 (8.3)	-12.8	-0.6 to -26.2	16.7 (8.1)	-12.2	-0.6 to -24.3	0.287
p-value ^b		<0.001*			<0.001*		
Stiffness subscore (0-20)							
Week 0	11.7 (3.1)	-	-	10.0 (4.3)	-	-	0.329
Week 4	4.6 (3.1)	-7.1	-4.8 to -9.5	10.1 (5.8)	0.1	5.6 to -5.4	0.016*
Week 8	5.2 (2.3)	-6.5	-4.0 to -9.0	8.1 (3.4)	-1.9	1.8 to -5.6	0.038*
Week 12	5.2 (1.9)	-6.5	-4.6 to -8.4	8.5 (3.7)	-1.5	3.0 to -6.0	0.023*
Week 16	5.0 (2.9)	-6.7	-4.5 to -8.9	7.6 (3.4)	-2.4	1.4 to -6.2	0.080
Week 20	5.7 (4.4)	-6.0	-2.6 to -9.4	6.9 (2.9)	-3.1	-0.4 to -6.6	0.483
Week 24	4.7 (2.8)	-7.0	-4.6 to -9.4	6.4 (3.8)	-3.6	-0.1 to -7.3	0.272
p-value ^b		<0.001*			0.091		
Physical function subscore (0-150)							
Week 0	79.0 (16.5)	-	-	88.3 (18.7)	-	-	0.254
Week 4	37.8 (13.2)	-41.2	-16.9 to -65.5	76.3 (25.3)	-12.0	25.1 to -49.1	<0.001*
Week 8	33.8 (15.4)	-45.2	-22.1 to -68.3	71.9 (23.6)	-16.4	12.0 to -44.8	0.001*
Week 12	40.9 (18.9)	-38.1	-7.6 to -68.6	67.7 (24.4)	-20.6	15.8 to -57.0	0.013*
Week 16	38.0 (19.7)	-41.0	-10.7 to -71.3	67.0 (22.9)	-21.3	5.3 to -47.9	0.007*
Week 20	41.3 (22.4)	-37.7	-0.7 to -74.7	56.6 (24.0)	-31.7	6.9 to -70.3	0.158
Week 24	38.1 (21.9)	-40.9	-9.0 to -73.8	56.4 (22.8)	-31.9	5.1 to -68.9	0.084
p-value ^b		<0.001*			0.002*		
Total score (0-220)							
Week 0	116.0 (24.6)	-	-	127.2 (24.8)	-	-	0.333
Week 4	54.8 (17.1)	-61.2	-27.5 to -95.3	113.4 (35.8)	-13.8	38.2 to -65.8	<0.001*
Week 8	49.2 (20.9)	-66.8	-35.2 to -98.8	104.3 (35.9)	-22.9	11.9 to -57.7	<0.001*
Week 12	58.1 (26.4)	-57.9	-16.3 to -99.9	98.5 (34.9)	-28.7	26.9 to -84.3	0.009*
Week 16	55.8 (29.1)	-60.2	-16.7 to -104.1	95.4 (31.9)	-31.8	5.8 to -69.4	0.009*
Week 20	57.7 (32.7)	-58.3	-4.9 to -112.1	82.6 (33.4)	-44.6	8.2 to -97.4	0.110
Week 24	55.5 (32.7)	-60.5	-11.6 to -109.8	79.5 (33.8)	-47.7	4.2 to -99.6	0.124
p-value ^b		<0.001*			<0.001*		

^aIndependent t-test, ^b Repeated measures ANOVA

NSAIDs experienced significant improvement in each of the WOMAC subscores over the 24-week follow-up period, as compared to baseline values ($p < 0.001$). In the control group, patients who received oral NSAIDs alone showed a statistically significant improvement in the total WOMAC Index score compared to baseline

($p < 0.001$), as well as in the pain ($p < 0.001$) and physical function subscores ($p = 0.002$). No significant improvement was observed for the stiffness subscore ($p = 0.091$).

In comparison between groups at each visit (Table 2), the intervention group had a significantly

lower WOMAC pain subscore than the control group up to week 20 ($p<0.05$), a significantly lower WOMAC stiffness subscore up to week 12 ($p<0.05$), and a significantly better WOMAC physical function subscore up to week 16 ($p<0.05$). Overall, the total WOMAC Index score was significantly lower in the intervention group than in the control group up to week 16 ($p<0.01$).

Patients in both groups used diclofenac as rescue pain medication. Daily consumption of diclofenac was significantly lower over the 24-week follow-up period in the group of patients that received a single intra-articular injection of Ostenil®Plus ($p<0.05$) (Table 3).

No serious adverse events were reported in the intervention group; however, one patient in the control group developed enterocolitis. In the control group, 6 adverse events occurred in 5 patients, as follows: 1 nasopharyngitis, 1 herpes zoster, 1 skin papilloma, 1 diarrhea, and 2 falls. In the intervention group, 9 adverse events occurred in 6 patients, as follows: 2 nasopharyngitis, 1 somnolence, 1 nausea, 1 vomiting, 1 toothache, 1 chloasma, 1 soft tissue injury, and 1 tooth extraction. None of the adverse events in either group were found to be related to the study treatments.

Discussion

This study demonstrated that patients with knee OA who received a single intra-articular injection of Ostenil®Plus experienced significant improvement in total WOMAC Index score, as well as improvement

in the 3 WOMAC subscores up to different time points over the 24-week follow-up period. Compared with the control group, the intervention group showed significantly better outcomes at 20 weeks post-injection for the WOMAC pain subscore, at 12 weeks for the WOMAC stiffness subscore, at 16 weeks for the WOMAC physical function subscore, and at 16 weeks for the total WOMAC score. Patients who received a single intra-articular injection of 2% sodium hyaluronate plus 0.5% mannitol also required a lower amount of oral NSAIDs than the control group at every 4-week time point from baseline to the 24-week follow-up. No serious adverse event or local adverse event affecting the index knee was found to be related to intra-articular HA injection in this study.

Exogenous HA produces positive mechanical and biological effects that relieve knee OA symptoms⁽²⁰⁾. A meta-analysis of placebo-controlled trials conducted by Bannuru et al⁽²¹⁾ that evaluated intra-articular HA in knee OA showed efficacy in pain reduction at 4 weeks, reaching a peak at 8 weeks, and with residual detectable effect at 24 weeks. In the present study, peak effect of HA for pain reduction was demonstrated at 8 weeks after injection and therapeutic effect was maintained for at least 24 weeks.

A recent non-comparative study that evaluated single intra-articular injection of Ostenil®Plus in 79 symptomatic OA knee patients reported improvement in joint pain, stiffness, and physical function on the WOMAC Index over a 6-month period⁽²²⁾. Joint pain evaluated using a 100-mm visual analogue scale significantly decreased at the first follow-up visit at 15 days post-injection, and this observed reduction in pain was maintained up until the end of the 6-month study period. No severe adverse events were reported; however, four patients (5%) had mild local adverse events, such as pain and swelling at the injection site. The authors reported that all mild local adverse events had resolved by the subsequent follow-up visit.

Single-dose regimens of other HA products have also been reported. Hylan G F 20 is a very high molecular-weight (6 million Da) hylan polymer that is derived from HA (chemically cross-linked avian origin HA) whose standard posology is a 2 ml intra-articular injection every week for 3 consecutive weeks^(23,24). Chevalier et al⁽²³⁾ conducted a randomized, multi-center, double-blind, controlled trial that evaluated the effect of a single injection of a 6 ml hylan preparation in comparison with an intra-articular placebo injection of buffered saline solution in 253 patients with Kellgren-

Table 3. Secondary efficacy outcomes: daily diclofenac consumption

Follow-up visits	Daily amount of diclofenac in mg, mean (SD)		<i>p</i> -value ^a
	Intervention group (n = 10)	Control group (n = 10)	
Week 4	27.7 (21.6)	70.7 (44.0)	0.011*
Week 8	25.5 (16.5)	67.2 (45.3)	0.011*
Week 12	34.0 (24.3)	76.3 (40.6)	0.007*
Week 16	32.1 (19.3)	56.2 (31.3)	0.035*
Week 20	26.8 (14.3)	57.5 (33.6)	0.007*
Week 24	27.2 (10.4)	64.5 (48.7)	0.021*
<i>p</i> -value ^b	0.289	0.004*	

^a Independent t-test, ^b Repeated measures ANOVA

Lawrence grade II or III knee OA. The patients that received hylan GF 20 showed a significant improvement in WOMAC pain subscore compared to placebo over a 26-week period. However, no significant difference in paracetamol consumption between groups was observed throughout the course of that study. Pain in the target knee, joint stiffness, and joint effusion were the most commonly reported adverse events. Incidence of treatment- or procedure-related adverse events was slightly higher in the hylan GF 20 group (6%) than in the placebo group (3%), but the difference was not statistically significant.

From a clinical study by Leighton et al⁽²⁵⁾, a single intra-articular injection of non animal stabilized hyaluronic acid (NASHA, another cross-linked HA product) was shown to be well-tolerated and non-inferior to methylprednisolone at 12 weeks. Moreover, the effect size for WOMAC pain, stiffness, and physical function subscores favored the NASHA preparation over methylprednisolone from 12 to 26 weeks, post-injection. Arthralgia was the most commonly reported treatment-related adverse event, with a significantly higher occurrence in the NASHA group (17%) than in the methylprednisolone group (3%).

A single intra-articular injection of Gel-200 (another cross-linked HA product) was evaluated for treatment of knee OA in a clinical study by Stand et al⁽²⁶⁾. This randomized controlled trial compared a single intra-articular injection of Gel-200 with intra-articular injection of phosphate-buffered saline in 379 patients. Mean improvement in WOMAC pain subscore favored Gel 200 at each follow-up visit from week 3 to week 13. Adverse events were not significantly different between groups. Common treatment-related adverse events after injection of Gel 200 were joint swelling (14%), joint effusion (11%), and arthralgia (8%).

The main limitations of this preliminary clinical trial are its open design and the add-on HA injection intervention without placebo injection in the control group.

Conclusion

Symptomatic OA knee patients who received a single intra-articular injection of 2% sodium hyaluronate plus 0.5% mannitol had better outcomes over the 24-week, follow-up period than control group patients who received no injection intervention.

What is already known on this topic?

Viscosupplementation has been and

continues to be used for treating symptomatic OA knee. Recommended dosing regimens of intra-articular injection generally range from 3 to 5 injections at an interval of 1 injection per week.

What this study adds?

A single intra-articular injection of 2% sodium hyaluronate plus 0.5% mannitol provides good outcomes in treatment of symptomatic OA knee.

Potential conflicts of interest

The authors received a research grant from TRB Chemedica (Thailand).

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ประสิทธิภาพของการฉีดยา sodium hyaluronate 2% ร่วมกับ mannitol 0.5% เข็มข้อเข่าครั้งเดียวเพื่อรักษาผู้ป่วยข้อเข่าเสื่อมที่มีอาการ: การรายงานเบื้องต้น

พิสิฏฐ์ เลิศวานิช, ชนินทร์ ลำคำ

ภูมิหลัง: การฉีดยา hyaluronic acid เข็มข้อ เป็นการรักษาโรคข้อเข่าเสื่อมวิธีหนึ่ง ซึ่งโดยทั่วไปแนะนำให้ฉีดยาเข็มข้อ 3 ถึง 5 ครั้ง

วัตถุประสงค์: ประเมินประสิทธิภาพและความปลอดภัยในการฉีดยา sodium hyaluronate 2% ร่วมกับ mannitol 0.5% เข็มข้อเข่าครั้งเดียวเพื่อรักษาผู้ป่วยข้อเข่าเสื่อมที่มีอาการ

วัสดุและวิธีการ: ผู้ป่วยข้อเข่าเสื่อม Kellgren-Lawrence ระดับ 2 หรือ 3 ซึ่งมีอายุระหว่าง 40-70 ปี จำนวน 20 ราย ผู้ป่วยกลุ่มทดลองจำนวน 10 ราย จะได้รับการฉีดยาเข็มข้อเข่าเพียงครั้งเดียวโดยใช้ sodium hyaluronate 2% ร่วมกับ mannitol 0.5% ปริมาณ 2 มิลลิลิตร ส่วนผู้ป่วยกลุ่มควบคุมจำนวน 10 รายไม่ได้รับการฉีดยาใดๆ เข็มข้อ ผู้ป่วยทั้งสองกลุ่มสามารถรับประทานยา diclofenac เพื่อบรรเทาอาการปวดได้เพียงอย่างเดียวโดยทำการเก็บข้อมูลค่าคะแนน WOMAC ปริมาณยา diclofenac ที่รับประทานและเหตุการณ์ไม่พึงประสงค์ทั้งหมด

ผลการศึกษา: ผู้ป่วยที่ได้รับการฉีดยา sodium hyaluronate 2% ร่วมกับ mannitol 0.5% เข็มข้อเข่าครั้งเดียวมีคะแนน WOMAC ที่ดีขึ้นจากเดิมตลอดช่วงเวลาของการศึกษา 24 สัปดาห์ ($p < 0.001$) โดยกลุ่มทดลองมีคะแนนความปวด ข้อฝืดและระดับความสามารถการใช้งานข้อต่ำกว่ากลุ่มควบคุมอย่างมีนัยสำคัญทางสถิติ ตั้งแต่ได้รับการฉีดยาจนถึงสัปดาห์ที่ 20, 12, และ 16 ตามลำดับ ($p < 0.05$) นอกจากนี้ผู้ป่วยในกลุ่ม ทดลองมีการใช้ยา diclofenac ในปริมาณที่ต่ำกว่าอย่างมีนัยสำคัญทางสถิติ ($p < 0.05$) โดยไม่พบเหตุการณ์ไม่พึงประสงค์ที่รุนแรงในผู้ป่วยทั้งสองกลุ่ม

สรุป: ผู้ป่วยข้อเข่าเสื่อมที่มีอาการซึ่งได้รับการฉีดยา sodium hyaluronate 2% ร่วมกับ mannitol 0.5% เข็มข้อเข่าครั้งเดียวมีผลการรักษาที่ดีกว่ากลุ่มควบคุมในช่วงเวลา 24 สัปดาห์
