The Effectiveness and Safety of Intra-Articular Injection of Sodium Hyaluronate (500-730 kDa) in the Treatment of Patients with Painful Knee Osteoarthritis

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Background: *Sodium Hyaluronate (500-730 kilodalton (kDa); Hyalgan®) is recommended to administer intra-articularly once a week for 3-5 weeks in patients with osteoarthritis of the knee which its efficacy has been shown, from many clinical studies, to persist for at least 6 months. However, only a few studies were done in Thai patients.*

Objective: *To assess the efficacy and safety of intra-articular Sodium Hyaluronate, administered once a week for four weeks (four injections) in Thai patients with painful Tibio-Femoral osteoarthritis of the knee over a six-month period.*

Material and Method: *Thirty-one patients with painful knee osteoarthritis in grade I (32.3%) and grade II (67.7%) severity on Ahlback radiological criteria from Orthopedic Clinic in Bhumibol Adulyadej Hospital were included in this study. All patients were administered with 4-weekly injections of intra-articular Sodium Hyaluronate (500-730 kDa; Hyalgan®; 20mg/2ml). Only paracetamol was permitted for escape analgesia. The efficacy parameters were the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) for pain, stiffness and physical function, intake of paracetamol, and overall efficacy judgment by investigators and patients. The occurrence of adverse event was recorded at each visit.*

Results: *After the second injection of Sodium Hyaluronate, all WOMAC index revealed the significant improvement from baseline ($p < 0.05$). The WOMAC-VAS for pain at baseline, Day 14, 28, 84, and 168 were 50.3, 33.3, 29.1, 23.1, and 21.4 mm respectively. At the end of study, most patients and investigators evaluated treatment efficacy as moderate to very effective. There was a decrease in paracetamol consumption from baseline until the last follow-up. Nine adverse events were recorded, which were transient events; most of them consisted of pain at injection site. No systemic or serious adverse event was reported.*

Conclusion: *The results of this study showed the efficacy and safety of 4-weekly injections of Sodium Hyaluronate in the treatment of knee osteoarthritis in Thai patients over a six-month period.*

Keyword: *Sodium hyaluronate, Hyaluronic acid, Knee osteoarthritis, Pain*

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Disability from primary osteoarthritis (OA) of the knee is common in the old aged patient especially in the people who require more of the deep knee flexion activity. The United States Centers for Disease Control and Prevention (CDC) reports the prevalence per 100 of OA knee in term of radiographic (moderate to severe) as 0.9 and symptomatic OA as 12.1 of 4.3 million adults aged over 60 years[1]. Physical disability arising from pain and loss of functional capacity reduces quality of life and increases the risk of further morbidity. Current treatments aim at alleviating these symptoms of OA knee depend mostly on both the clinical and radiographic stages of the patients. Mild to moderate OA cases can be treated by several different methods, non-pharmacological treatment (education, exercise,

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and lifestyle changes) or pharmacological treatments (such as paracetamol, NSAIDs, and viscosupplement therapy). The substance used most often in visco-supplement therapy is hyaluronic acid (HA).

HA forms the backbone of the proteoglycan aggregates necessary for the functional integrity of articular cartilage and other extra-cellular matrices. It is simultaneously a solid phase matrix element, in association with aggrecans and link proteins forming the compressible structure of cartilage, while a liquid phase matrix element circulates in plasma and flows in synovial space under normal and abnormal conditions. In its unaggregated form, HA is secreted continuously into the joint space by synovium where it comprises the major macro-molecular components of synovial fluid. It is responsible for the unique viscoelastic properties of synovial fluid, which is otherwise a simple plasma dialysate. HA is highly concentrated at the surface coating the articular cartilage *in vivo*, as well as the superficial layers of the synovial membranes. In the synovial fluid, HA acts as a lubricant, a shock absorber, an energy storing agent between opposing cartilages, a semi-permeable barrier regulating metabolic exchanges between the cartilage and the synovial fluid, a cell traffic controlling agent, and a viscoelastic shield around synoviocytes and adjacent nerve endings[2].

In an osteoarthritic knee joint, synovial hyaluronic acid is fragmented and depolymerised, with a corresponding reduction in synovial fluid viscosity and increase in dialysable hyaluronic acid fragments and saccharide monomers. As synovial fluid contains no hyaluronidase activity, it was demonstrated that reactive oxygen derived metabolites are involved in hyaluronic acid depolymerisation[3]. This depolymerisation reduces the viscosity of the synovial fluid, its lubricating and anti-oxidant capacities, which result in cartilage breakdown. *In vitro* response of synovial fibroblast to exogenous HA, this osteoarthritic joint derived cell shows a stimulation of HA synthesis with preparations of weight-average molecular weight > 500 kDa in a concentration dependent manner[4]. Intra-articular Sodium Hyaluronate (500-730 kDa, Hyalgan®; Fidia S.p.A., Italy) is a viscous solution of highly purified avian HA (10mg/ml), buffer (pH 6.8-7.5) in physiologic saline. It is recommended to administer intra-articularly once a week for 3-5 weeks. This has been shown by many studies to have the therapeutic effects persist for at least six months after the end of treatment. However, most of the studies were conducted in Europe[5-7]. This study was carried out to validate the efficacy of 4-week injection of Sodium Hyaluronate in Thai population.

Material and Method

This was a prospective, open-labeled, one group pretest-posttest study which has been approved by Ethical Committee of Bhumibol Adulyadej Hospital.

Thirty-one knee osteoarthritis patients were enrolled and followed-up at Orthopedic Clinic in Bhumibol Adulyadej Hospital during August 2004 and April 2006. All patients were asked to provide informed consent before enrollment. The inclusion criteria were male or female aged between 50 and 75 years with primary knee OA of Tibio-Femoral joint, pain $\geq$ 40 mm on $\geq$ 2 items of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) subscale for pain using 100 mm visual analogue scale (VAS), pain presented for at least 15 days in the month prior to the start, radiological staging ascertained grade I or II severity knee OA on Ahlback criteria. The exclusion criteria were secondary OA, accompanying osteo-arthritis of the hip, intra-articular treatment with any product within two months prior to the starting of this study, history of joint lavage and arthroscopic procedure within six months, using oral SYSADOA treatment within four months before recruitment to the study, allergic to avian protein, Sodium Hyaluronate or paracetamol.

All patients received 4-weekly injections of intra-articular Sodium Hyaluronate (500-730 kDa; Hyalgan®; 20mg/2ml) to a more painful side of patient's knee. The sites of injection were antero-medial area in flexed position or supero-lateral area in extended position. Painkillers or other osteoarthritis medications were not allowed throughout the study except paracetamol (with maximal dose of 4 gm/day) when pain was unbearable and the number of tablets used per day was recorded. Any painkillers such as NSAIDs and COX-II inhibitors had been stopped for at least seven days before the study started. The efficacy parameters were WOMAC index for pain, stiffness, and physical function, while number of paracetamol intake, global efficacy, and tolerability assessment by investigators and patients were recorded as well. These parameters were assessed at baseline (Day 0), Day 7, 14, 21, 28, 56, 84, 112, 140, and 168. Sodium Hyaluronate was administered on visit 2 (baseline, Day 0), Visit 3 (Day7), Visit 4 (Day 14), and Visit 5 (Day 21). All efficacy parameters were assessed before patients received an injection. The occurrence of adverse event was recorded at every visit.

Statistical analysis

Characteristics of the patients such as age, gender, weight, height, body mass index (BMI), and previous medication in a treatment group were analyzed by using descriptive statistics.

WOMAC index efficacy variables assessed at Visit 2 were considered as the baseline values and would be compared with other values from Visit 3 to Visit 11 using parametric statistics, Repeated Measure ANOVA. Bonferroni was used for post hoc comparisons.

Patient and Investigator Global Efficacy and Tolerability Assessments were assessed at Visit 3 and would be compared with values from Visit 4 to Visit 11 by nonparametric statistics for repeat measure of ordinal scale, using Friedman test. A p-value of less than 0.05 was considered statistical significance different.

Results

Patient characteristics

Baseline characteristic of patients are summarized in Table 1.Thirty-one patients participated in this study, 90.3% were female. A mean duration of knee osteoarthritis was 3.87 years. There were 32.3% patients classified as Ahlback grade I and 67.7% as grade II. WOMAC index at baseline were 50.3, 57.2, and 55.2 for pain, stiffness, and function respectively.

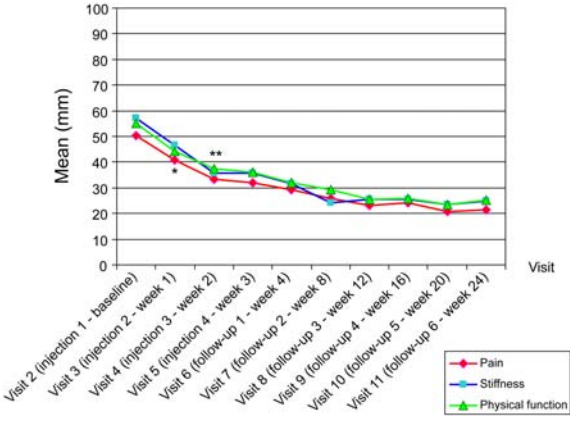
WOMAC index for pain, stiffness, and physical function

WOMAC index were used as the efficacy parameters, these parameter were repeatedly measured 10 times along six months from the baseline visit (week 0) to visit 11 (week 24). During the first and second treatment visit, between baseline visit or the first treatment with 20 mg/2 ml of Sodium Hyaluronate and the second treatment visit, there was no significant difference of pain scores (50.3 and 40.9 mm respectively, p = 0.108) and stiffness scores (57.2 and 46.8 mm respectively, p = 0.548). However, for patients' physical function, there was significant difference between the baseline visit and the second injection (55.2 and 44.1 mm respectively, p = 0.002). Mean score of three parameters of visit 1 to visit 11 are shown in Table 2.

After the second injection of 20 mg/2 ml of Sodium Hyaluronate, all three efficacy parameters were significantly better than at the baseline ($p < 0.05$) (Fig. 1). The improvement of these three efficacy parameters had obviously increased from the second injection or week 1 of the treatment until the week 3 of treatments. However, even when the injection of Sodium Hyaluronate was discontinued in week 4, there were continuous improvements of the efficacy parameters until week 8 or during the early follow-up period. After week 8, there were minimal changes of the efficacy parameters but those were still significantly better than the baseline visit (Fig. 1, Table 3).

Table 1. Demographic and baseline clinical characteristics of the sample (n = 31)

Baseline characteristics of paitents	% or mean ± SD
Percentage of female	90.3%
Age (year)	61.81 ± 6.20
Duration of OA (year)	3.87 ± 1.69
Height (meter)	1.56 ± 0.60
Weight (kg)	66.76 ± 12.20
Body mass index, BMI (kg/m2)	27.37 ± 4.28
Percentage of previous NSAIDs or Analgesic consumption	71.0%
Percentage of patient with knee effusion	9.7%
Percentage of right index knee	54.8%
Ahlback criteria - Grade 1	32.3%
Ahlback criteria - Grade 2	67.7%
WOMAC scale for pain (mm)	50.30 ± 21.20
WOMAC scale for stiffness (mm)	57.20 ± 27.70
WOMAC scale for function (mm)	55.20 ± 21.90



* Significant improvement of physical function between visit 2 (baseline, injection 1) and visit 3 (injection 2)
** Significant improvement of pain and stiffness between visit 2 (baseline, injection 1) and visit 4 (injection 3)

Fig. 1 Efficacy parameters (WOMAC Index) at each of assessment visits

Table 2. Efficacy parameters of knee (WOMAC Index; rated on a 100-mm VAS scale) over visit 1 and visit 11; mean ± SD (mm) for ITT population

Visit	WOMAC Index (mean ± SD)		
	Pain	Stiffness	Function
Visit 1 (screening) - week 1	53.9 ± 19.8	62.5 ± 22.1	60.1 ± 19.6
Visit 2 (1st injection) - baseline	50.3 ± 21.2	57.2 ± 27.7	55.2 ± 21.9
Visit 3 (2nd injection) - week 1	40.9 ± 23.4	46.8 ± 24.3	44.1 ± 22.5
Visit 4 (3rd injection) - week 2	33.3 ± 23.4	35.6 ± 26.3	37.3 ± 26.1
Visit 5 (4th injection) - week 3	31.8 ± 24.9	35.8 ± 29.1	36.0 ± 27.1
Visit 6 (1st follow-up) - week 4	29.1 ± 22.4	31.6 ± 26.8	31.8 ± 25.3
Visit 7 (2nd follow-up) - week 8	26.0 ± 22.1	24.1 ± 24.7	29.1 ± 24.5
Visit 8 (3rd follow-up) - week 12	23.1 ± 19.2	25.4 ± 20.7	25.5 ± 20.5
Visit 9 (4th follow-up) - week 16	24.0 ± 22.3	25.4 ± 24.6	25.9 ± 24.2
Visit 10 (5th follow-up) - week 20	20.7 ± 20.5	23.6 ± 23.3	23.4 ± 22.5
Visit 11 (6th follow-up) - week 24	21.4 ± 22.1	24.7 ± 27.3	25.3 ± 25.7
p-value*	<0.001	<0.001	<0.001

* Test with repeated measure ANOVA

Table 3. Change in mean WOMAC Index (rated on a 100-mm VAS scale) at baseline versus follow-up visits; mean difference (mm) for ITT population

Visit	Improvement from baseline in WOMAC Index by visit (mean difference**)		
	Pain	Stiffness	Function
Visit 1 (screening) - week 1	-	-	-
Visit 2 (1st injection) - baseline	-	-	-
Visit 3 (2nd injection) - week 1	9.4 p = 0.108	10.5 p = 0.548	11.1 p = 0.002*
Visit 4 (3rd injection) - week 2	17.0 p = 0.007*	21.6 p = 0.015*	17.9 p = 0.002
Visit 5 (4th injection) - week 3	18.5 p = 0.001	21.5 p = 0.008	19.3 p = 0.001
Visit 6 (1st follow-up) - week 4	21.2 p < 0.001	25.6 p = 0.002	23.4 p < 0.001
Visit 7 (2nd follow-up) - week 8	24.3 p < 0.001	33.2 p < 0.001	26.1 p < 0.001
Visit 8 (3rd follow-up) - week 12	27.2 p < 0.001	31.8 p < 0.001	29.7 p < 0.001
Visit 9 (4th follow-up) - week 16	26.3 p < 0.001	31.8 p < 0.001	29.3 p < 0.001
Visit 10 (5th follow-up) - week 20	29.6 p < 0.001	33.6 p < 0.001	31.8 p < 0.001
Visit 11 (6th follow-up) - week 24	28.9 p < 0.001	32.6 p < 0.001	29.9 p < 0.001

* The mean difference is significant at the .05 level
** Adjustment for multiple comparisons: Bonferroni

Global assessment of efficacy and tolerability

There were significant differences of global evaluation of treatment efficacy by patients and investigators (p = 0.001 and 0.002 respectively), and the increasing of effectiveness of the treatment from the Visit 3 to Visit 11 (Fig. 2).

In terms of global evaluation of treatment tolerability by patient and investigator, patients and investigators were asked whether how well the patient tolerate the treatment. They identified in the same order of scale with the gradual increasing of ranking from poor (1) to very good (4). These results are shown in Fig. 2.

Paracetamol consumption

Even if there was no significant reduction of paracetamol consumption between before and after the injection of Sodium Hyaluronate, but there was decreasing trend of an average number of paracetamol tablet consumption per day from baseline (2.9 tablets per day) to the first follow-up (1 tablet per day) until the last follow-up (0.66 tablet per day).

Safety

Nine local adverse events were recorded, all were transient events, and most of them consisted of pain at injection site. None of systemic or serious adverse event was reported. The adverse events occurred only in Visit 2 (first injection, 7 events) and Visit 3 (second injection, 2 events), there was no adverse event reported in other visit. The overview of adverse events is shown in Table 4.

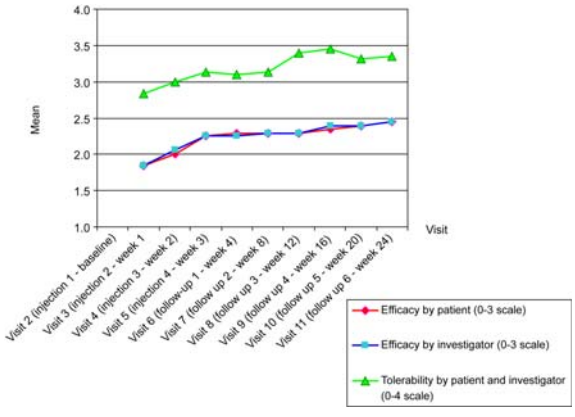


Fig. 2 Mean global evaluation of treatment efficacy and tolerability by patient and investigator at each of assessment visit

Table 4. Overview of adverse events reported in the study patients

Adverse event	Frequency (n = 31)
No. of serious adverse events	-
No. of adverse events	9
Mild	7
Moderate	2
Total number of adverse events reported primarily as probably or possibly related to the drug	9
Pain during/after injection	8
Stiffness	1

Discussion

This study was a study of weekly injection of Sodium Hyaluronate for totally of four injections into the study knees in Thai population. The study showed baseline characteristics of 31 patients who were above middle age range. Most of them (90.3%) were women with mild overweight. The average duration of symptoms was 3.87 years with Ahlback criteria determined grade I or II. As the study of Dougados et al[8] and Bunyaratavej et al[9] revealed the result of treatment of Tibio-femoral primary OA knees which was treated with 4-weekly injection of Sodium Hyaluronate, there were significant improvement of pain and function. Compare to this study, there were marked improvement of physical function after the first injection. This immediate response may be due to the mechanical properties of Sodium Hyaluronate as viscoelastic solution in joint, which is effective as lubricants under slow movement and as shock absorbers under rapid movement[10,11]. After the second injection, there were also significant improvement of pain and stiffness and continuously improvement of all of three important parameters, pain, stiffness, and physical function, until the last follow-up at 6-month. This last-long treatment effect does not come from only mechanical properties of Sodium Hyaluronate as it was eliminated from the joint within a week, but also from pharmacological properties of this agent. The potential pharmacological properties are inhibition of inflammatory mediators, enhancing neosynthesis of endogenous hyaluronic acid, stimulation of matrix synthesis, and decreasing degradation of cartilage matrix[4,12-19]. The duration of symptom relief in this study is consistent with the results of previous studies that have shown the efficacy and safety of

Sodium Hyaluroate in improving osteoarthritis symptoms for at least six months[7-9,20-22].

For the global assessment of efficacy and tolerability of this study, there were similarity of the efficacy of treatment determined by ranking, both the patients and investigators. Ranking showed continuous increasing of the efficacy and level of tolerability along the 6-month period of follow-up, which were statistical different compare to the baseline.

The only pain relief medication is paracetamol, which showed no significant reduction of the consumption rate. However, decreasing trends were observed as seen in the decreasing daily dose of consumption compare to the baseline data of previous NSAIDs or analgesic consumption before the study, which showed 71.0%. This may be due to the effectiveness of the injection. However, all of the patient had been advised for common self-rehabilitation program such as quadriceps exercise and appropriate activities for OA knee patients. The benefit of home exercise program combined with Sodium Hyaluronate injection was shown in the Stitik study[21]. In that study, patients who received Sodium Hyaluronate injection and participated in home exercise program had a significantly faster onset and longer duration of pain relief compared with patients who received Sodium Hyaluronate injection alone.

Concerning the safety of this treatment, there was no serious adverse events, most were pain at injection site. In the nine adverse events, seven were mild and two were moderate, but all were transient, which showed the safety of this treatment.

Conclusion

This prospective study of the osteoarthritis knee patient treated with a single course of four weekly injections of Sodium Hyaluronate has shown the effectiveness of intra-articular hyaluronic acid in term of improvement of three WOMAC indexes (pain, stiffness, and physical difficulty), significantly differences of global evaluation of treatment efficacy by patients and investigators. The WOMAC index efficacy parameters revealed significantly better scores after the second injection and the significant sustain of improvements compared to the baseline parameters still be observed in all patients after the end of 6-month period. The adverse effects were local and transient. They were pain at the injection site. Therefore, 4 weekly-injection-course of Sodium Hyaluronate (500-730 kDa; Hyalgan®) was safe and effective in improving the six efficacy parameters in patients with mild to moderate degree (Ahlback grade I or II) of knee osteoarthritis for a 6-month period.

Disclosure

The authors have no financial or other interests related to this study.

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ประสิทธิภาพและความปลอดภัยของ โซเดียม ไฮยาลูโรเนต ฉีดเข้าข้อ ในผู้ป่วยข้อเข่าเสื่อม

วัชระ พิภพมงคล, ม.ล.วุฒิพงศ์ สุทัศนีย์

ภูมิหลัง: *การใช้ยา โซเดียม ไฮยาลูโรเนต (500-730 กิโลดาลตัน; ยัลแกน) ฉีดเข้าข้อสัปดาห์ละ 1 เข็ม ติดต่อกัน 3-5 สัปดาห์ในผู้ป่วยโรคข้อเข่าเสื่อมจากหลายๆการศึกษาพบมีประสิทธิภาพในการรักษาเป็นระยะเวลาอย่างน้อย 6 เดือน อย่างไรก็ตามการศึกษาในผู้ป่วยชาวไทยนั้นมีเพียงไม่กี่การศึกษา การศึกษานี้จึงเป็นการศึกษาเพื่อยืนยันถึงประสิทธิภาพและความปลอดภัยของยาโดยฉีดเข้าข้อ สัปดาห์ละ 1 เข็ม ติดต่อกัน 4 สัปดาห์ในผู้ป่วยข้อเข่าเสื่อมชาวไทย*

วัตถุประสงค์: *เพื่อศึกษาถึงประสิทธิภาพและความปลอดภัยของการฉีดยา โซเดียม ไฮยาลูโรเนต เข้าข้อ สัปดาห์ละ 1 เข็ม ติดต่อกัน 4 สัปดาห์ ในผู้ป่วยข้อเข่าเสื่อมชาวไทยที่มีอาการปวด โดยติดตามผลเป็นระยะเวลานาน 6 เดือน*

วัสดุและวิธีการ: *ผู้ป่วยข้อเข่าเสื่อมที่มาเข้ารับการรักษาที่ ออร์โธปิดิกส์คลินิก โรงพยาบาลภูมิพลอดุลยเดช ถูกคัดเลือกเข้ามาทำการศึกษาทั้งหมด 31 ราย โดยร้อยละ 32.3 มีความรุนแรงของโรคตามเกณฑ์ประเมินออบัค (Ahlback criteria) ในระดับเริ่มต้น (เกรด 1) และ ร้อยละ 67.7 อยู่ในระดับปานกลาง (เกรด 2) ผู้ป่วยทุกรายจะได้รับการฉีดยาโซเดียม ไฮยาลูโรเนต (500-730 กิโลดาลตัน; ยัลแกน; 20 มก./2 มล.) เข้าข้อ สัปดาห์ละ 1 เข็มติดต่อกัน 4 สัปดาห์ โดยในระหว่างการศึกษาอนุญาตให้ใช้ยาพาราเซตามอลเพื่อบรรเทาอาการปวดในกรณีที่จำเป็นเท่านั้น ประสิทธิภาพในการรักษาประเมินโดยโวแมคสกอร์ (the Western Ontario and McMaster Universities Osteoarthritis Index; WOMAC score) สำหรับอาการปวด การฝืดขัดข้อ และการทำงานของข้อ รวมทั้งพิจารณาจากปริมาณพาราเซตามอลที่ใช้ และจากแบบประเมินประสิทธิภาพโดยรวมจากความเห็นของแพทย์และผู้ป่วย และในแต่ละครั้งที่ผู้ป่วยมาพบแพทย์จะได้รับการสอบถามถึงอาการไม่พึงประสงค์ที่เกิดขึ้น*

ผลการศึกษา: *ค่าการประเมินโวแมคสกอร์หลังจากการฉีดยาเข็มที่ 2 ของทั้ง 3 หัวข้อแสดงให้เห็นอาการที่ดีขึ้นอย่างมีนัยสำคัญ ($p < 0.05$) โดยค่าโวแมคสำหรับอาการปวด ณ วันแรกที่เข้าโครงการ, วันที่ 14, 28, 84 และ 168 เท่ากับ 50.3, 33.3, 29.1, 23.1 และ 21.4 มม. ตามลำดับ รวมทั้งผลการประเมินโดยผู้ป่วยและแพทย์ ณ วันสิ้นสุดการศึกษา โดยส่วนมากประเมินว่า ยาโซเดียม ไฮยาลูโรเนตมีประสิทธิภาพปานกลางถึงมาก และการใช้ยาพาราเซตามอลบรรเทาปวดมีปริมาณลดลง พบรายงานการเกิดอาการไม่พึงประสงค์ 9 รายงาน โดยเป็นอาการเพียงชั่วขณะ และส่วนมากเป็นเพียงอาการปวด ณ บริเวณตำแหน่งที่ฉีดยา ไม่พบเหตุการณ์ ไม่พึงประสงค์ที่ร้ายแรง*

สรุป: *การศึกษานี้แสดงถึงประสิทธิภาพและความปลอดภัยของการใช้ยา โซเดียม ไฮยาลูโรเนต ฉีดเข้าข้อสัปดาห์ละ 1 เข็ม ติดต่อกัน 4 สัปดาห์ ในผู้ป่วยข้อเข่าเสื่อมชาวไทย โดยมีประสิทธิภาพในการรักษายาวนาน 6 เดือน*