A prospective and comparative study between pre and post intra-articular knee injection to evaluate the efficacy of sodium hyaluronate (Hyruan®III) in the treatment of knee osteoarthritis

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Background: *Many reports of sodium hyaluronate intra-articular injections into the knee joint show evidence of improvements of pain and function in osteoarthritis knees. Most of the injection techniques were a single dose once a week for 3 or 5 weeks according to each manufactures' recomendation. Some manufactures prepared this for one single dose, one injection.*

Purpose: *To elucidate a technique of three-in-one single doses of the intra-articular injection of sodium hyaluronate for osteoarthritis of the knee with regards to its safety and clinical outcomes between pre and post injection.*

Methods: *We combined three intra-articular injections of the high molecular weight sodium hyaluronate into a single dose to be administered as one single intra-articular injection to treat 100 osteoarthritis knees who failed the medical conservative treatment and physical therapy. The Visual Analogue Scale (VAS), Western Ontario and McMaster Universities Osteoarthritis (WOMAC) score, Knee Society score, and knee function score were the measurement methods. The mean difference between pre and post intra-articular injections in each efficacy score was compared and the safety of the injection was the main principle of evaluation.*

Results: *Ten knees were excluded due to not fulfilling the criteria. Only 90 knees were included. Using the Ahlback knee grading system, 60 knees were of grade I, 15 knees were of grade II, and 15 knees were of grade III. The average 100 mm VAS scale before injection was 44.26 and was reduced to its lowest point 7.41 at the 8^{th} month follow up($P = 0.008$), and increased to 36.85 at the 8^{th} month after treatment. WOMAC scores were reduced to their lowest point 7.51at 8^{th} month follow up ($P = 0.011$), and increased after 8 months after treatment to 36.75, therefore the VAS scale and WOMAC score decreased significantly. The average Knee Society score was 64.23 before injection and was raised to an average of 78.82 by the first month after injection ($P = 0.002$). At the 8^{th} month after injection, the value was raised up to 90.20 ($P=0.001$). The average knee function score was 60.61 before injection. But after the first month post-injection, the average score was raised to 77.22, ($P = 0.018$). At the 8^{th} month after injection, the value was 86.28($P = 0.001$), therefore the knee score and functional score increased significantly.*

Conclusion: *The combined three to one single dose (high molecular weight) sodium hyaluronate (Hyruan®III) injection yielded high potency of clinical results comparing between pre and post injection in all indicators in this study.*

Keywords: *Sodium hyaluronic acid, knee osteoarthritis, intra-articular single injection.*

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Introduction

The treatment option for knee osteoarthritis (OA) is dependent on age, sex, obesity, joint effusion, joint inflammation, knee deformities, and severity of the joint cartilage involved. The treatment principles follow the American College of Rheumatology (ACR)[1] and the European League Against Rheumatism (EULAR)[2] as standard options in general practice. Surgical treatment is the last option after failure of all conservative treatment regiments. Any surgical intervention for knee osteoarthritis must be based on the knee deformities, pathology, and the proper or corrected indication. In the early stage or gray zone of knee pathology, many conservative treatment regiments should be applied to the patients[1,2]; this depends on each patients' status or condition. Because osteoarthritis of the knee requires a long-term conservative treatment program, selection of the treatment modalities should be appropriate for each patient. Some conservative treatments such as topical gel or spray

treatments (i.e. methylsalicylate, capsaicin etc.), physical therapy, proper exercise, or intra-articular knee injections with steroids[3,4,5] or with high molecular weight sodium hyaluronate[6,7,8,9] may be another choice of treatment. Balazs[10] first proposed the idea of viscosupplementation in 1993. The FDA has approved sodium hyaluronate injections as a viscosupplementation only for knee osteoarthritis. Its clinical outcomes have been reported to be far better than placebos,[6,7,8,9,10,11,12] but when compared to many oral non-steroidal anti-inflammatory drugs, the results were not as effective as steroid injections[13,14,15,16]. Proteoglycans and link proteins facilitate binding of aggrecan to hyaluronic acid[15]. In osteoarthritis of the knee, there is decreased concentration and function[17]. Because the normal substance in healthy knees has been found to have very high viscoelasticity properties, for the treatment of knee osteoarthritis sodium hyaluronate injections will help increase the efficiency of knee lubrication, increase knee viscosity, decrease friction, shock absorption, sharing and reduce articular loading, reduce inflammation, and enhance the cartilage cell nourishment and cartilage cell apoptosis[18,19,20]. There are two methods of sodium hyaluronate preparation, cockscomb extraction (animal source) and synthetic chemical preparation (non-animal source). The non-animal source has minimal risk of contamination with animal allergens or pathogens[21]. Non- or less inflammatory reactions were reported in non-animal sourced sodium hyaluronate injections. But in the animal extracted sodium hyaluronate, painful and severe acute inflammatory reactions have been known to occur[22,23]. The concentrations and molecular weight of sodium hyaluronate preparation were also an issue with much discussion in the previous articles. Key questions included: which concentration provides the highest efficiency to improve knee pain and function? Or which molecular weight gives more effective clinical results? In general practice, a single dose of sodium hyaluronate injection is administered once a week for up to three to five weeks consecutively, depending on each regiment. However, some manufacturers combined all three or five injections into only single injection[24,25]. In this research, the selected sodium hyaluronate was a high molecular weight type, and the technique of injection was also one single injection. Even though the preparation of the sodium hyaluronate was in 3 syringes, which were recommended to be injected once a week for up to 3 weeks, we used three doses of 2 ml each and retained the syringe so it was injected into the knee joint in only one needle injection. The clinical results between pre and post injection were evaluated following the VAS (Visual Analogue Scale)[26], WOMAC score[27,28,29,30,31] (Western Ontario and McMaster Universities Osteoarthritis Index), knee society score,[32] and knee function score[32]. In addition, we verified immediate adverse drug effects on the knee with clinical examination and erythrocyte sedimentation rate at the first week follow up in every case.

Materials and methods

All the patients in this study had to meet definite inclusion and exclusion criteria.

The inclusion criteria

1. OA diagnosis following the American Rheumatism Association diagnostic criteria, 1986
2. Primary treatment following the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR)
3. Every patient is informed of the research project, research program, and accepts our method of study to the end of the program for 1 year.
4. The minimum age of the patients is 45 years old
5. 100 VAS scale and WOMAC scores before the sodium hyaluronate injection start at 30 or more
6. The entire treated knee is x-rayed in antero-posterior, lateral, and sky line view. Ahlback grading[33] is used to evaluate the severity of the knee pathology and must be in between grade 1-3

The exclusion criteria

1. Patients did not agree to the project before or during treatment program.
2. Patients could not follow the project until end of program
3. There were underling diseases such as rheumatoid arthritis, gouty arthritis and septic arthritis.
4. Patients had acute knee arthritis with joint effusion or severe inflammation

The study was conducted at the Faculty of Medicine, King Chulalongkorn University and Memorial Hospital, Bangkok, Thailand from February 2009 to October 2011 under the Chulalongkorn University ethic committee COA. No. 011/2010, IRB No. 419/52. The number of specimens was 100 osteoarthritis knees. During the research data collection, 10 knees were excluded because they did not fulfill our criteria, so there were 90 osteoarthritis knees in this study. All patients received the conservative treatment following the ACR and EULAR. The high molecular weight sodium hyaluronate (Hyruan®III) was injected in cases of conservative treatment failure. The three syringe single dose injection was administered by injecting each 2 ml. syringe of sodium hyaluronate subsequently until 3 syringe were finished. All patients were allowed to

walk normally and also advised to continue normal daily activities. The knee exercise program was advocated to improve the ligaments, muscles, and tendon strengths without giving any medication. The quadricep muscles were the main principle muscles in the strength training. One week after the injection, all patients returned to the clinic for a blood examination for erythrocyte sedimentation rate and knee examination to check knee inflammation and clinical results. Clinical knee pain and its function between pre and post injection were evaluated every month following the 100 mm VAS scale, WOMAC score, Knee society score, and functional score protocol till the 12th month follow up. The general information of the patients is shown in Table 1.

Table 1 Baseline characteristics of all patients

	Female	**Male**
Gender	73	17
average age (yrs)	65.63	64.12
Average weight Kg.	62.16	72.25
Ahlback Grade1	44	16
Ahlback Grade2	15	-
Ahlback Grade3	14	1
Ahlback Grade4	-	-
Average age (yrs)	65.34	
Average weight (kg)	63.19	
Average BMI (kg/m^2)	25.31	

Results

The erythrocyte sedimentation rate was normal in almost all of the patients. Slight ESR elevation was found in a few patients. A high ESR of over 50 was found in only one patient and it remained high along the course of treatment, but the clinical knee inflammation was not significant. This patient had a history of high ESR before the injection and she was aware of her status. For clinical knee inflammation, some patients had knee inflammation higher than the first visit or before the injection.

VAS scale, WOMAC score, knee society score, and function score were indicators to evaluate the clinical outcomes compared between pre and post 6 ml. sodium hyaluronate (Hyruan®III) injections. Statistical analysis was done using the one sample *t-test*, *P-value* and *paired t-test* between pre and post injection.

The 100 mm VAS scale analysis before the injection showed that the VAS score was in between 30-60 and 44.26 in average. After the injections, the average score gradually decreased to the lowest point of 7.41 at the 8th month. After that it increased slightly, but remained less than 10 at the 12th month. These figures are shown in Fig.1 and Table 2.

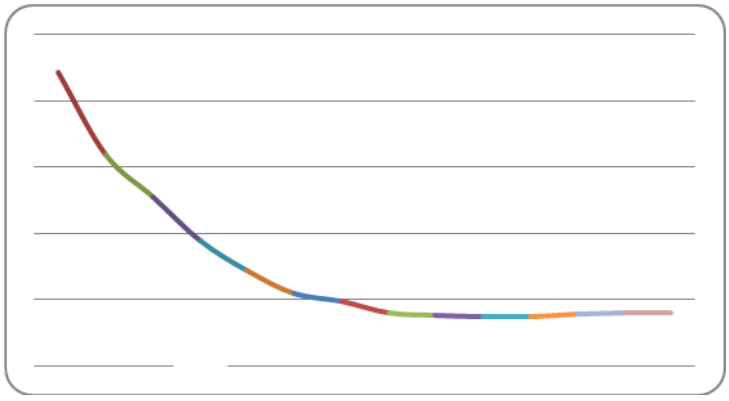

Fig. 1 The trend of Visual Analogue Scale compared between pre and post injection for every month up to 12th month

Table 2 Comparative statistical analyses of 100 mm VAS Scale between pre and post injection

100 mm VAS Scale	**N=90**	***P*-value** [a]
Average scale before injection	44.26	
Average scale after 8th months (Scale < 10, (95% confidence)	7.41	0.008
Improvement of VAS Scale after 8th month	36.85	
Paired *t*-test [b] (pre and post injection)	0.001	

[a] One-Sample t-test
[b] Paired *t*-test

Statistical analysis using the *t-test* at the 8th month of 90 subjects found the *P-value* =0.008, less than the standard value at 0.05, *Paired t-test* (pre and post injection at 8th month) = 0.001.

The WOMAC Scores were analyzed and the results are shown in Fig. 2 and Table 3. The outcome was generally the same as the VAS scale.

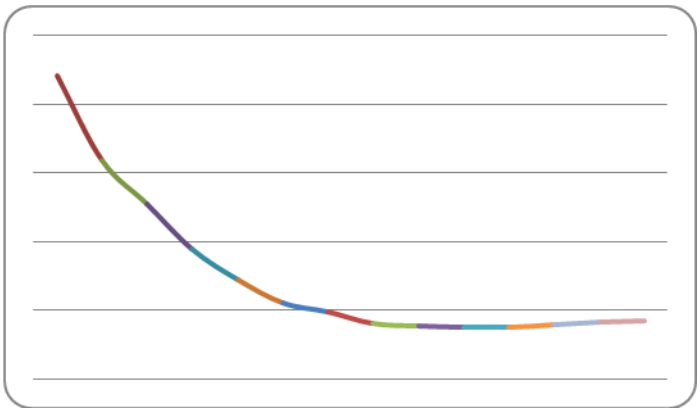

Fig. 2 The trend of WOMAC score compared between pre and post evaluated for every month up to 12th month

The trend of WOMAC scores decreased from the first month and was lowest at the 8th month, similar to the 100 mm VAS Scale.

Table 3 Statistical analysis of WOMAC scores between pre and post injection

WOMAC score	**N=90**	***P*-value**[a]
Pre-injection WOMAC score	44.26	-
Post injection WOMAC score < 10, (95% confidence)	7.51	0.011
WOMAC score improvement	36.75	-
Paired t-test[b] (pre and post injection)	0.001	-

[a] One-Sample *t*-test
[b] Paired *t*-test

Statistical analysis by *t-test* at the 8th month for 90 subjects found the *P-value* =0.011, less than the standard value at 0.05, and found *Paired t-test* (pre and post injection at 8th month) =0.001.

The average Knee Society score before injection was 64.23. The trend for the 12 months after the injections is shown in Fig. 3 and Table 4.

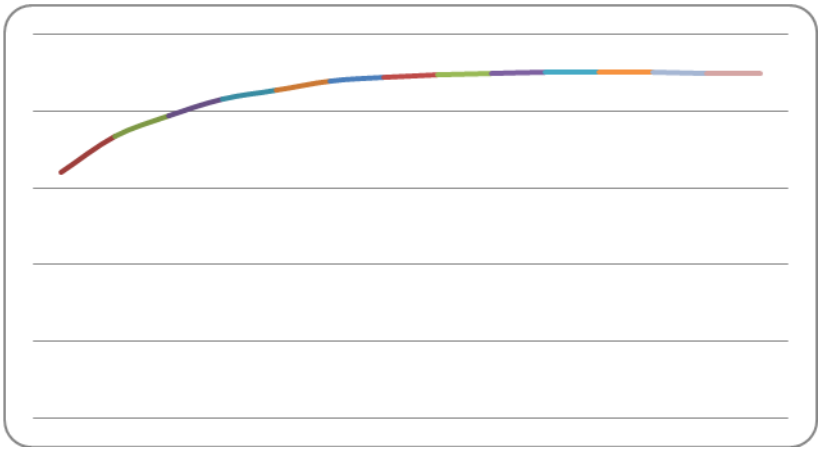

Fig. 3 The trend of Knee Society Scores compared between pre and post evaluated for every month up to 12th month

The average Knee Society score started at > 75, ($P < 0.05$) for the first month and increased to > 90, P= 0.353 at the 8th month.

Table 4 The Knee Society scores before and 12 months after injection

Knee society score value by average	**N=90**	***P*-value**
Before injection	64.23	
1st month after injection (Knee score > 75, (95% confidence)	78.82	0.002
8th month after injection (Knee score > 90, (95% confidence)	90.20	0.353
Knee society score value increase at 8th month	25.97	
Paired *t*-test [b] (pre and post injection at 8th month)	0.001	

[a] One-Sample t-test
[b] Paired t-test

Table 4 reveals that the average Knee Society score before injection was 64.23. After injection at one month it was 78.82, P=0.002 and after 8 months it was 90.20, P=0.353.

The statistical analysis found the average Knee Society score was higher than 75 at the first month and more than 90 at the 8th month. One-Sample t-test at the first month revealed *P*-value = 0.002. The standard analysis found values of knee scores were higher than 90 at the 8th month. One-Sample *t*-test at the 8th month revealed *P*-value = 0.353. Paired *t*-test (pre and post injection at the 8th month) =0.001.

The data of the average functional score before and after injection are shown in Fig. 4 and Table 5.

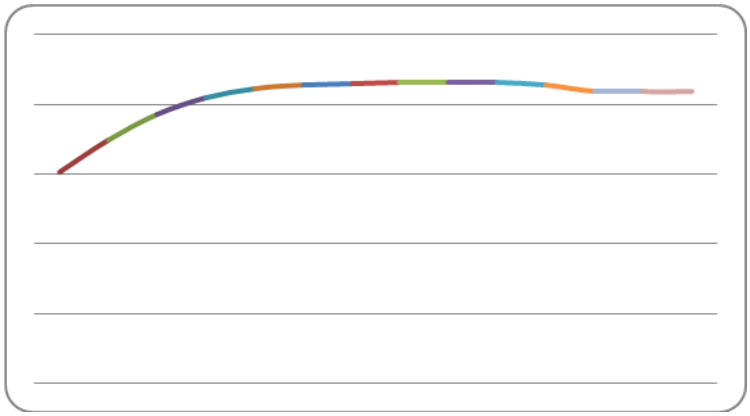

Fig. 4 Trend of the function score before and 12 months after injection

The average functional score increased from the first month and was highest at the 8th month. After that the trend decreased slightly, but was still over 85 on average. All the functional score values are shown in Table 5.

Table 5 The average functional scores before and 12 months after injection

Average Functional score	**N=90**	***P*-value [a]**
Before injection	60.61	
1th month after injection (Functional score > 75, (95% confidence)	77.22	0.018
8th month after injection (Functional score > 85, (95% confidence)	86.28	0.146
Functional score increase at 8th month	25.67	
Paired *t*-test [b] (pre and post injection at 8th month)	0.001	

[a] One-Sample *t*-test
[b] Paired *t*-test

The average functional score before injection was 60.61. At the first and 8th months post-injection, the average functional score increased to 77.22 and 86.28, respectively.

Discussion

In this research study, the researchers (clinician), data collector (research assistant) and statistics analyst individually performed their own work. The clinician treated all of the patients and assisted with progress notes recorded on every follow up visiting date as usual, but not every month. The research assistant collected all the raw data from patients every month and called them if those patients missed a period of follow up time. The data collected were 100 mm VAS scale, WOMAC score, Knee society score, and functional score protocol. The statistic analyst was the only person who analysed the entire raw dataset. To evaluate drug safety after injection, all patients were scheduled to return to the clinic after the first week to look for clinical knee inflammation and ESR. Close observation of patient who had elevated ESR or clinical knee inflammation was followed by repeated ESR tests at every follow up week until rates were considered normal. Even though 10 out of the 90 knees had elevated ESR, no one had a serious untoward reaction in this research. The reason for our very close observation after the injection was because we injected a high volume (6 ml.) at once in to the knee joint. It did not follow the company recomendation (injecting each 2 ml. refilled syringe every week for 3 weeks). We can conclude that this technique was safe and was highly effective. There have been some single injection regiments in the market. But in general practice, the recommened dosage of many sodium hyaluronate intra-articular knee injections is once a week for up to 3 or 5 weeks depending on each manufacturers' recomendation. We thought that the high volume injection concept would gain many more benefits than the standard injection regiments.This concept was, first of all, that the high volume and high concentration of the sodium hyaluronic acid would immediately reduce pain, improve knee function, and increase the viscoelasticity of the joint more than a single dose injection. Moreover, the high volume may yield more lubrication, reduce joint friction, share and reduce load transmission on the articular cartilage, and the last very important issue, it may reduce

load carrying at the pathology site. This action (high/proper volume and high concentration), in our opinion, is a very important point of the success of this paper. It improved knee function and reduced knee pain earlier, a day or a week after the injection in almost all osteoarthritis knees.

Secondly, having only one injection reduced risk of infection, reduced treatment costs and reduced patient anxiety. The aseptic technique of injection was prepared only once. So it also saved the hospital fees, the transportation payment, time to the hospital and so on.

Thirdly, apart from the function mentioned above, it nourished the articular cartilage, enhanced cartilage matrix synthesis, protected cartilage cells from apoptosis, and it was believed to reduce the inflammatory reaction of the joint. Unfortunately for this study, the period of research was quite short being only 12 months. Although there were some clinical results of patients who requested for second and third dose injection without any knee reaction, we did not have the record of such patients. It was quite interesting because some papers report the secondary reaction of knee inflammation and fibrosis[34,35,36,37]. In this paper, we only studied clinical outcomes for 12 months and did not have any information on the long term effects (5 years or more), such as how does the articular cartilage change in the long term, and is the medial joint space narrower or widened by year?

Nevertheless, the 12 months result was satisfactory. This clinical outcome was beyond our expectations and the long-term action of the drug in this regiment was at least the same as the standard injection regiment. However, from our experience from this research point of view, treatment recommendations to use this regiment requires definite knee selection in Ahlback grade I or II. In cases of the knee pain in Ahlback grade I or II with medial collateral ligament tendinitis, this ligament should be treated first. When the tendinitis subsided and patients still had intra-articular knee pain, the regiment of sodium hyaluronate injection was applied. In cases of Ahlback grade IV, in our opinion, it is not a good candidate or should be a contraindication for sodium hualuronate injections. But in some cases or some conditions of the patients, such as heart disease or other operative contraindications, the Ahlback grade III (also grade IV) knee might be suitable for injection to relieve or reduce pain for a short time. The regiments of 3 doses combined into 1 injection need to strictly follow the inclusion and exclusion criteria, a large volume of joint effusion was not suitable for injection, for example. But in cases of dry joint fluid, this regiment worked very well.

This research was intended to compare the outcome or results between pre and post intra articular knee injections of sodium hyaluronate. Most of the reports in the past were a comparative study to placebo or other drugs, such as steroids, NSAIDS, or sodium hyaluronate from other companies. By the comparative technique in this research, we could observe its real clinical results in the same patients and also exactly know the clinical results of the drug's action. This was because we all knew and accepted the efficiency of this drug action far better than placebos and its better long term results than steroids. If we look at the 100mm VAS scale and WOMAC score graph, they significantly declined from the starting point at the first week to the peak period at the 8th month and remained a little high, but still less than 10 points until the 12 month follow up. The Knee Society score and functional score gave the same results. Increases of both scores were seen at the first week after injection and rising up until the 12th month follow up. In this study we wanted to test the effectiveness of high volume (6 ml.) single doses of the high molecular weight sodium hyaluronate (Hyruan®III) in each patient. It reflected the efficiency of the drug to control pain and improve the function of the individual osteoarthritis knee, as we got a very good result from all measurement scales or scores and form statistical analysis. In this project study, we planned for 100 osteoarthritis knees, but 10 of the patients were excluded due to not fullfilling our criteria.

In conclusion, the technique of high volume sodium hyaluronate (Hyruan®III) intra-articular knee injections gave much earlier and long term clinical benefits to the osteoarthritis knees when compared between pre and post injection. The better results after injection could be detected within a week or a few weeks later. All the analysis indicators and the related statistical analysis revealed highly positive results. The single intra-articular knee injection with high volume (6ml.) sodium hyaluronate (Hyruan®III) is recommended in this article, but it must be injected to the osteoarthritis knee under the same criteria.

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การศึกษาเปรียบเทียบประสิทธิภาพของการฉีดสาร Sodium Hyaluronate (Hyruan® III) เข้าข้อในผู้ป่วยโรคข้อเข่าเสื่อมก่อนและหลังการรักษา

นรา จารุวังสันติ, พบ, ประกิต เทียนบุญ, พบ

วัตถุประสงค์ *: เพื่ออธิบายเทคนิคการฉีดสารโซเดียมไฮยารูโลเนต (Hyruan® III) เข้าข้อเข่าครั้งเดียวสามเข็ม ในผู้ป่วยโรคข้อเข่าเสื่อมและศึกษาประสิทธิภาพและความปลอดภัยของยาโดยเปรียบเทียบระหว่างก่อนและหลังการฉีด*

วัสดุและวิธีการ*: ศึกษาข้อมูลแบบไปข้างหน้าจากผลการรักษาผู้ป่วยอาสาสมัครของผู้ป่วยนอก โรงพยาบาลจุฬาลงกรณ์สภากาชาดไทยระหว่างเดือนกุมภาพันธ์ พ.ศ.2552 ถึงเดือนกุมภาพันธ์ พ.ศ.2554 เพื่อเปรียบเทียบผลการรักษาโรคข้อเข่าเสื่อมด้วยการฉีดครั้งเดียว 3 เข็มเข้าข้อเข่า กับงานวิจัยอื่นๆที่เคยฉีดสัปดาห์ละ 1 เข็ม และยังไม่มีงานวิจัยใดที่รักษาด้วยการฉีดครั้งเดียว 3 เข็ม จำนวนผู้รับการรักษา 100 ราย โดยประเมินผลลัพธ์หลัก (Primary efficacy variable): ความรุนแรงของการปวดข้อเข่าโดยใช้ 100 mm Visual Analogue Scale (VAS) , Functional Impairment :ประเมินอาการและผลการรักษาโดยใช้ Western Ontario and McMaster Universities Osteoarthritis (WOMAC) score รวมทั้ง Knee score และ Functional score สำหรับผลลัพธ์รอง (Secondary efficacy variable): ศึกษาการบวม ความตึงเนื่องจากแรงดัน การงอของข้อ (joint flexion) รวมถึงการประเมินความปลอดภัยของการฉีดซึ่งเป็นหลักการสำคัญของการประเมินผลร่วมด้วย

ผลการศึกษา : *จากการศึกษาพบว่ามีผู้ป่วยอาสาสมัคร 10 รายที่ต้องออกจากการศึกษา ดังนั้นงานวิจัยนี้จึงมีผู้ป่วยอาสาสมัครจำนวน 90 รายที่นำมาวิเคราะห์ผล พบว่าค่า VAS ลดลงจาก baseline อย่างมีนัยสำคัญทางสถิติ ระยะเวลา 8 เดือน ค่า WOMAC score ลดลงจาก baseline อย่างมีนัยสำคัญทางสถิติ ระยะเวลา 8 เดือนเช่นกัน สำหรับค่า Knee score หลังการฉีด 1 เดือน (knee score >75) และหลังการฉีด 8 เดือน (knee score >90) มีค่าเพิ่มขึ้นอย่างมีนัยสำคัญทางสถิติตามลำดับ และค่า Functional score หลังการฉีด 1 เดือน (Functional score >75) และหลังการฉีด 8 เดือน (Functional score >85) มีค่าเพิ่มขึ้นอย่างมีนัยสำคัญทางสถิติตามลำดับเช่นกัน*

สรุป : *การฉีดสารโซเดียมไฮยารูโลเนต (Hyruan® III) พร้อมกันครั้งเดียว 3 เข็ม เข้าข้อเข่าให้ผลการรักษาที่ดีเทียบเท่ากับการฉีดสัปดาห์ละ 1 เข็มจำนวน 3 สัปดาห์ หรือ สัปดาห์ละเข็ม จำนวน 5 สัปดาห์ และด้วยเทคนิคพิเศษที่ฉีดนั้นให้ประสิทธิภาพดีเทียบเท่ากับการฉีดแบบสัปดาห์ละเข็ม และให้ประสิทธิภาพในการรักษาถึงร้อยละ 95*