Total Knee Replacement Following Repeated Cycles of Intra-articular Sodium Hyaluronate (500-730 Kda) in Failed Conservative Treatment of Knee Osteoarthritis: A 54-Month Follow-up

Thana Turajane MD*, Tanawat Amphansap MD*,
Viroj Labpiboonpong MD*, Samart Maungsiri MD*

** Department of Orthopedic Surgery, Police General Hospital, Bangkok, Thailand*

Background: *Treatment with repeated cycles of Intra-Articular Sodium Hyaluronate (IA-HA), from previous study, can improve symptoms and delay surgical interventions in knee osteoarthritis patients who failed conservative treatment within minimum 2-years follow-up. This is a continued study to follow-up responded patients in the mentioned study whether continuing treatment with IA-HA could prolong time to surgery until the end of follow-up.*

Objective: *To evaluate the incidence of total knee replacement (TKR) in patients receiving repeated cycles of IA-HA during a 54-month follow-up period.*

Material and Method: *This was a prospective cohort study with 54-month follow-up period. All patients received at least a single course of 3-weekly injections of IA-HA (500-730 Kilodalton, Hyalgan®). Patients who well responded to the treatment were recommended to repeat the administration of a 3-weekly injections every 6-12 months based on their symptoms. The incidence of TKR and time was recorded. Time to event analysis using Kaplan-Meier survival analysis was performed.*

Results: *183 patients were recruited during March 2001 and March 2004 and followed-up until October 2008. Patients were classified into three groups according to Ahlback radiological grading system. 46 patients were in group 1 (Ahlback grade I-II), 70 patients were in group 2 (Ahlback grade III-IV) and 67 patients were in group 3 (Ahlback grade V). The incidence of TKR was 28.4% with a mean time to TKR of 15.4 months (0.7-51.7 months). For the rest of patients who had no TKR during study period (80.4%, 64.3% and 73.1% for group 1, 2, and 3 respectively), their mean follow-up time was 45.6 months (19.0-53.1 months). Mean survival time was 42.1 months (95% CI = 39.4-44.9 months).*

Conclusion: *The repeated cycles of intra-articular sodium hyaluronate treatment in delay time to TKR in patients with knee osteoarthritis which failed conservative treatment was found efficacious during a 54-month follow-up period.*

Keywords: *Sodium hyaluronate, Conservative treatment, Failure, Repeated doses, Total knee replacement*

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Intra-articular sodium hyaluronate (IA-HA; 500-730 Kda, Hyalgan®) has played a role in the treatment of knee osteoarthritis in Thailand since 2001. The published paper showed its effectiveness in knee OA patients who failed conservative treatments by delaying surgical interventions in 79.8% of patients over a 24-months follow-up period[1]. Even though the surgical interventions seem to be a successful treatment with 75-95% success rate and long term survival ratio of Total Knee Arthroplasty (TKA) is 92-95% in 10 years, the anterior knee pain after TKA was also found in 8-12%[2]. Moreover, there is 5-10% of complications risk and early arthroplasty may need revision. Decision making for surgical treatment should

Correspondence to: Turajane T, Department of Orthopaedics, Police General Hospital, 492/1 Rama I Rd, Pathumwan, Bangkok 10400, Thailand. Phone: 0-2253-5836, Fax: 0-2253-5836, E-mail: thanaturajane@yahoo.com

depend on the severity of disease evaluated by clinical and radiographic parameters. Most common indication for surgery is severe pain with poor quality of life which cannot be treated with conservative treatments even it is not an appropriate time to surgery. However, because of some drawback of surgical intervention as mentioned above, IA-HA treatment seems to be a good choice for OA patients who failed conservative treatment in order to improve their symptoms and delay surgery until appropriate time. Even though IA-HA has been used for the treatment of osteoarthritis more than 10 years, there are still no clear evidence in certain issues *i.e.* repeated use, appropriate time to repeat treatment, whether or not the repeated use could delay time to surgery. The purpose of this study was to determine the effectiveness of repeated cycle of 3-weekly injections of IA-HA treatment every 6-12 months by evaluating the incidence of TKR in knee osteoarthritis patients over a 54-month follow-up period.

Material and Method

This was a prospective cohort study which has been approved by the hospital ethical committee. One hundred and eighty-three patients with knee osteoarthritis were recruited during March 2001 and March 2004 and consequently followed-up until October 2008 with a 54-month period at Orthopedic Clinic, Police General Hospital. All patients were asked to provide informed consent before study enrollment. The inclusion criteria were (i) patients with primary knee osteoarthritis according to the American College of Rheumatology criteria[3], (ii) had prior failure to conservative treatment including anti-inflammatory drugs and others, physical therapy and bracing with unsatisfactory improvement more than 6 months which were considered as candidates for TKR, and (iii) no contraindication for surgery. The exclusion criteria were patients with other degenerative arthritis or other diseases unrelated to arthritis, history of knee surgery, allergic to avian protein or sodium hyaluronate, and using any intra-articular treatment in any form within 6 months before study enrollment. Patients were divided into three groups according to radiographic evaluation, group1- Ahlback grade I (joint spaces lost less than 5 mm) and grade II (joint space lost more than 5 mm), group 2- Ahlback grade III (minor bone attrition) and grade IV (major bone attrition), group 3- Ahlback grade V (lateral subluxation)[4]. All patients received at least a single course of 3-weekly IA-HA injections (500-730 Kda; Hyalgan®) together with a continuing home program physical therapy with a fixed arch quadriceps exercise and other pain-killer medications such as NSAIDs, selective COX-2 inhibitors for relief their pain as needed. Patients who well responded to IA-HA treatment were recommended to repeat administered 3-weekly injections of IA-HA every 6-12 months according to their symptoms. For those who failed, which was classified by lack of improvement in pain and knee functions after completion of the first course of three injections (< 20% reduction in average WOMAC score from baseline), the surgery has been scheduled within 3-4 weeks after the most recent IA-HA use. The efficacy parameters were incidence of TKR, time to TKR and follow-up time in patients who had not required surgery throughout the follow-up period. Number of repeated cycle of 3-weekly IA-HA injections in each group was also reported.

Statistical analysis

The incidence of TKR was recorded. For patients undergoing a TKR during the follow-up period, the mean time to TKR was considered which defined since patients received the first IA-HA injection until the time that TKR was performed was included in the time to event analysis. For response patients who had not required surgery or lost to follow-up patients, the mean follow-up time which was a period of first recruitment until end of follow-up period even by lost to follow-up or finished the study was recorded. Kaplan-Meier survival analysis was reported for these two analyses by STATA version 10.0. The survival differences among groups were expressed by hazard ratios with 95 percent confidence intervals. A p-value of less than 0.05 was considered statistically significant. Number of repeated cycle of 3-weekly IA-HA injection was calculated.

Results

The incidence of total knee replacement (TKR) and time to TKR

Baseline characteristic data of included patients were shown in Table 1. The overall incidence of TKR over a 54-month follow-up period was 28.4% with the mean time to TKR of 15.4 months. Number of patients who underwent TKR in group 1, 2 and 3 were 9 (19.6%), 25 (35.7%) and 18 (26.9%) respectively. The incidence of TKR in group 2 of patients (Ahlback grade III and IV) was highest and the mean time to TKR for this group was 8.0 months (Table 2).

There were 131 patients (71.6%) who well responded to IA-HA treatment and had not required

Table 1. Baseline characteristics of patients

Characteristic	Group 1	Group 2	Group 3	Total
Ahlback Classification	grade I-II	grade III-IV	grade V	
Number of patients (Male:Female)	46 (18:28)	70 (20:50)	67 (8:59)	183 (46:137)
Mean (range) age (years)	64.85 (50-82)	68.57 (50-83)	71.6 (62-84)	68.74 (50-84)
Mean (range) bodyweight(kg)	67.24 (58-85)	67.4 (58-106)	64.5 (58-80)	67.0 (58-106)
Mean height(cm)	162.8	163	164.2	163
Mean body mass index (kg/m^2)	25.36	25.36	23.92	25.21
Number of knees (Right:Left)	49 (32:17)	78 (35:43)	81 (38:43)	208 (105:103)
Bilateral Knee(s)	3	8	14	25
Mean (range) TF angle* (degree)	6.9 (2-10)	10.7(6-15)	10.5 (2-18)	9.87 (2-18)
Household ambulation (patients)	6	29	41	76
Independent ambulation without walking aid gait (patients)	36	28	18	82
Independent ambulation with walking aid gait (patients)	4	13	8	25

* TF angle: Tibiofemoral angle

Table 2. Number of patients with/without TKR with mean time to TKR or mean follow-up time and number of repeated cycle of IA-HA

Group	Patients who underwent TKR			Patients without TKR		
	No. of patients (%)	Mean time to TKR, month (range)	No. of repeated cycles	No. of patients (%)	Mean follow-up time month (range)	No. of repeated cycles
Group 1, n = 46 Ahlback I-II	9 (19.6)	27.6 (1.0-51.7)	1.44	37 (80.4)	44.6 (19.0-53.1)	5.46
Group 2, n = 70 Ahlback III-V	25 (35.7)	8.0 (0.7-45.5)	1.20	45 (64.3)	46.6 (25.7-52.1)	6.11
Group 3, n = 67 Ahlback V	18 (26.9)	19.5 (0.8-44.4)	2.50	49 (73.1)	45.5 (23.5-52.9)	6.08
Overall, n = 183	52 (28.4)	15.4 (0.7-51.7)	1.69	131 (71.6)	45.6 (19.0-53.1)	5.92

TKR until the end of study with the mean follow-up time of 45.6 months. Of 131 patients, 121 patients were available until the study end, 7 patients were lost to follow-up and 3 patients were death. Eighty percent of patients in group 1 (Ahlback grade I and II) had not yet undergone TKR. Even though the largest number of patients who well responded to treatment was in group 1, the mean follow-up time was shorter than of the other two groups (Table 2).

Number of repeated cycle of IA-HA injection

Number of repeated cycle of 3-weekly IA-HA injections of patients in group 1, 2 and 3 were 1.44, 1.20, and 2.50 cycles respectively for patients who underwent TKR and were 5.46, 6.11 and 6.08 cycles respectively for patients who had not yet undergone TKR (Table 2). An average time in delayed surgery in patients who had not had TKR was 7.7 months per one cycle.

Survival analysis of patients who had not yet undergone TKR was shown in Fig. 1. There were 75% of patients could delay surgical interventions for about 38.7 months. The mean survival time of all patients from Kaplan-Meier curve was 42.1 months (95% CI = 39.4-44.9 months). Survival analysis of each group is also shown in Fig. 2. The mean survival time of group 1, 2 and 3 were 47.6, 36.3, and 43.8 months respectively.

Comparing with group 1, there was a significant higher risk of TKR in group 2 (hazard ratio 2.2; 95% CI = 1.0 to 4.7; p = 0.045) and higher risk but not significant in group 3 (hazard ratio 1.4; 95% CI = 0.6 to 3.2; p = 0.381).

Discussion

The benefits of intra-articular sodium hyaluronate in knee osteoarthritis patients who failed from conservative treatment use have been

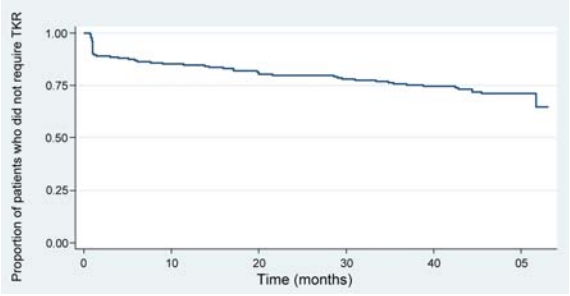

Fig. 1 Survival analysis of patients who had no TKR

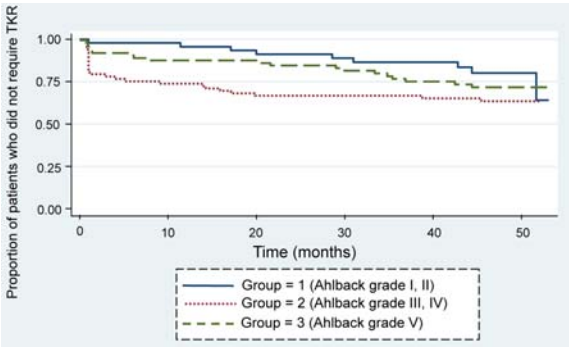

Fig. 2 Survival analysis of patients who had no TKR categorized by Ahlback grade

established in many literatures[5,6]. As a result of the efficacy in symptom improvement, IA-HA use can decrease the consumption of traditional NSIADs and selective COX-2 inhibitors. This leads to the reduced risks of gastrointestinal and cardiovascular side effects. Moreover, its benefit to delay time to surgery in Thai population was demonstrated from previous study[7], however, this effect was found depending on the disease severity classified by radiographic assessment, age, ambulatory status and patient's expectation.

In this study, the number of repeated cycle of 3-weekly IA-HA injections used in the patient groups with longer follow-up period at 54 months was considered to be a factor affecting the delay of TKR. We found that patients who received more repeated doses had extended time to TKR. These results supported the continued use of repeated doses of IA-HA especially in responsive patient groups with an aim to be able to delay time to surgery. In addition, IA-HA treatment reduced the number of TKR in elderly population who has normally suffered from the undesirable complications.

The peri-operative mortality rates for TKR have been reported 0.17%- 0.46% for primary total knee arthroplasty within 90 days and 0.33%-0.78% for bilateral knee replacements within 30 days[8-10]. Using the IA-HA injection treatment was reported having no major side effects or no association with mortality and morbidity[11]. It then could provide noticeably clinical advantage in terms of delay time to surgery.

Nowadays, whether or not the repeated cycle regarding the clinically proper number of injections is efficacious, and with a certain time interval of IA-HA use is still debated. Some recommendations for repeated interval are every 4 months, 6 months, or one year. For the number of injection, the maximum benefit of IA-HA treatment was observed from a 5-weekly injections over a 6-months period[12-14]. In this study, it was demonstrated that only 3-weekly injections every 6-12 months still provided benefit in the function of delaying time to TKR which is the desired long-term treatment outcomes. However, it is known that not all of IA-HA uses provide the long term benefit, as reported in the Cochrane systematic review[15]. Long-term benefit of IA-HA might relate to its molecular weight. There are some studies shown that sodium hyaluronate at specific range of molecular weight such as 500-730 Kda can well penetrate and attach to receptors resulting in effective pharmacological and chodroprotective effects[16-20]. However, in order to receive better results with IA-HA treatment in long-term, patients selection criteria, assisted home program for quadriceps exercise, designed lifestyle modifications, specialized injection techniques and repeated used of IA-HA must be taken into account. As shown in this study results, group 2 patients who were in less severity than group 3 patients had a higher incidence of TKR. This result supported our previous study that the disease severity itself is not the only affecting factor to successful treatment. We should also consider patients' expectation and ambulatory status as well.

Given that this study was a prospective cohort study, so the outcomes may be influenced to some extent by the natural history of OA knee. However, we aimed to present the benefit of repeated cycles of IA-HA in real-world situation, so this finding, which might be confounded by uncontrollable factors, can still serve as valuable information for clinical practice.

Conclusion

Repeated use of Intra-articular sodium hyaluronate injection in knee osteoarthritis patients

who failed conservative treatment is important to maintain long term benefits. From this study, it showed that the treatment with repeated cycles of 3-weekly IA-HA every 6-12 months was found efficacious in delaying time to TKR during a 54-month follow-up period.

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การผ่าตัดข้อเข่าเทียมในผู้ป่วยที่ได้รับการรักษาด้วยยา โซเดียม ไฮยาลูโรเนต (500-730 กิโลดาลตัน) โดยการฉีดเข้าข้อซ้ำติดต่อกัน ในผู้ป่วยข้อเข่าเสื่อมที่รักษาด้วยวิธีการรักษาแบบดั้งเดิมไม่ได้ผล: การศึกษาแบบไปข้างหน้าในระยะเวลา 54 เดือน

ธนา ธุระเจน, ธนวัฒน์ อำพันทรัพย์, วิโรจน์ ลาภไพบูลย์พงศ์, สามารถ ม่วงศิริ

ภูมิหลัง: *การฉีดยาโซเดียม ไฮยาลูโรเนต เข้าข้อเป็นระยะติดต่อกันในผู้ป่วยข้อเข่าเสื่อม ที่รักษาด้วยวิธีการรักษาแบบดั้งเดิมไม่ได้ผลสามารถบรรเทาอาการของโรค และลดอุบัติการณ์การทำผ่าตัดข้อเข่าเทียม ได้อย่างมีประสิทธิภาพจากการติดตามผลอย่างน้อย 2 ปี ซึ่งการศึกษานี้เป็นการศึกษาต่อเนื่องเพื่อติดตามผลระยะยาวในผู้ป่วยกลุ่มเดิม*

วัตถุประสงค์: *เพื่อประเมินอุบัติการณ์ของการผ่าตัดข้อเข่าเทียมในผู้ป่วยที่ได้รับการฉีดยาโซเดียม ไฮยาลูโรเนต เข้าข้อซ้ำเป็นระยะ ๆ โดยติดตามผลเป็นระยะเวลา 54 เดือน*

วัสดุและวิธีการ: *การศึกษานี้เป็นการติดตามผลการรักษาในระยะยาว โดยผู้ป่วยทุกรายจะได้รับการฉีดยาโซเดียม ไฮยาลูโรเนต (500-730 กิโลดาลตัน, ชื่อการค้า: ยัลแกน) เข้าข้อเข่าสัปดาห์ละ 1 เข็ม ติดต่อกัน 3 สัปดาห์ อย่างน้อย 1 ครั้ง โดยผู้ป่วยที่มีการตอบสนองต่อการรักษาจะได้รับการพิจารณาให้ได้รับการฉีดยาเข้าข้อซ้ำทุก ๆ 6-12 เดือน ขึ้นอยู่กับอาการของผู้ป่วย ผลลัพธ์การใช้ยาคือการวัดอุบัติการณ์ของการผ่าตัดข้อเข่าเทียม และระยะเวลาในการได้รับการผ่าตัดข้อเข่าเทียมหลังจากได้รับการฉีดยาเข้าข้อ ซึ่งวิเคราะห์โดย time to event analysis จาก Kaplan-Meier survival analysis*

ผลการศึกษา: *มีผู้ป่วยข้อเข่าเสื่อมที่รักษาด้วยวิธีการรักษาแบบดั้งเดิมไม่ได้ผลเข้าร่วมโครงการทั้งสิ้น จำนวน 183 ราย (ระหว่างปี พ.ศ. 2547-2551) โดยแบ่งผู้ป่วยเป็น 3 กลุ่มตามความรุนแรงของภาวะข้อเข่าเสื่อม โดยพิจารณาจากภาพถ่ายทางรังสี โดย 46 ราย จัดอยู่ในกลุ่มที่ 1 (Ahlback grade 1-2; ภาพรังสี มีการแคบของช่องข้อเข่า), 70 ราย ในกลุ่มที่ 2 (Ahlback grade 3-4; ภาพรังสีมีกระดูกติดกันของข้อเข่า) และ 67 รายในกลุ่มที่ 3 (Ahlback grade 5; ภาพรังสีมีการเคลื่อนของกระดูกทางด้านนอกของข้อเข่า) โดยอุบัติการณ์โดยรวมของการผ่าตัดข้อเทียมคิดเป็นร้อยละ 28.4 ของผู้ป่วยที่เข้าร่วมโครงการทั้งหมด โดยมีค่าเฉลี่ยของระยะเวลาตั้งแต่ได้รับยาฉีดเข้าข้อจนถึงเวลาที่เข้ารับการผ่าตัดเท่ากับ 15.4 เดือน (0.7-51.7 เดือน) ส่วนในกลุ่มผู้ป่วยที่สามารถชะลอหรือยกเลิกการผ่าตัดข้อเข่าเทียมได้ตลอดระยะเวลาของการติดตามผลนั้น (ร้อยละ 80.4, 64.3 และ 73.1 สำหรับผู้ป่วยกลุ่ม 1, 2 และ 3 ตามลำดับ) มีค่าเฉลี่ยของระยะเวลาติดตามผลการรักษาเท่ากับ 45.6 เดือน (19.0-53.1 เดือน) และจากการวิเคราะห์โดย Kaplan-Meier survival analysis ของผู้ป่วยทั้งหมด พบมีค่าเฉลี่ยของระยะเวลารอดชีพเท่ากับ 42.1 เดือน (ช่วงความเชื่อมั่นร้อยละ 95 เท่ากับ 39.4-44.9 เดือน)*

สรุป: *การใช้ยาโซเดียม ไฮยาลูโรเนต ฉีดเข้าข้อต่อเนื่องเป็นระยะ ในผู้ป่วยข้อเข่าเสื่อม ที่รักษาด้วยวิธีการรักษาแบบดั้งเดิมไม่ได้ผลนั้น มีประสิทธิภาพดีในการชะลอการผ่าตัดข้อเข่าเทียมในช่วงระยะเวลา 54 เดือนของการติดตามผล*