# Cost Analysis of Intra-Articular Treatment of Cross-Linked Sodium Hyaluronate (XLHA-BDDE) for Failure Conservative Treatment Patient with Multiples Stages Knee Osteoarthritis

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***Background:*** *Hyaluronic acid injections are recognized as safe and effective for knee osteoarthritis (OA), with positive clinical evidence demonstrated in clinical trials. The clinical efficacy demonstrated that a single injection cross-linked sodium hyaluronate (XLHA, single injection form, Hyruan One) was non-inferior to three weekly injections of high molecular weight hyarulonic acid (HMWHA), and supports as effective and safe treatment for knee OA. The research is needed to find out more about the aspects of XLHA may influence medical and surgical cost in the clinical practices.*

***Objectives:*** *The primary endpoint is cost analysis about disease-specific costs of medical and surgical treatments for 6 months before and after XLHA injection. The secondary endpoints are proportion of patient who were delayed for surgical interventions.*

*Methods: Cost analysis study was performed by enrolling patient with knee OA that failed conservative treatment, whom were candidate for surgical intervention, including 205 patients (253 knees) 40 males and 165 females during January 2018 till September 2018 and at Orthopedic Clinic, Police General Hospital. Patients were divided into two groups, first group age less than 60 years (48 patients) and second group age more than 60 years (157 patients) due to its different kind of operation. The disease severity was classified according to Kellgren Lawrence classification. Integrated medical and pharmacy claims data were extracted from HIS systems and also financial department of the Police General Hospital.*

***Results:*** *The average age was 63.2 (50-81) years old. Patients were divided into 2 group by age, first under 60 and second above 60 years old, 48 and 157 patients respectively. In first group, there were 7 patient that need arthroscopic surgery, other 41 patients do not required surgery. Therefore, the percentage of patient that were delayed for surgical intervention is 85.42% (41/48) patients and the average cost for arthroscopic surgery were 69,750 baht per knee. In second group, 15 patients (17 knees) from 141 patients need total knee arthroplasty (TKA). We calculate into total proportion of 90.44% (142/157) patients that were delayed for TKA at 6 months and the average cost for TKA were 136,910.71 baht per knee. The cost of injection were 3,588,805 baht. The total medical costs (cox-2& diacerein) were 481,783 baht before 6 months injection and after 6 months injection were 701,714 baht.*

***Conclusion:*** *In our study XLHA may improve outcomes, not only mild to moderate but also severe OA with 6 months follow up. The most common causes of failure under age of 60 years were the complex tear of meniscus and above 60 years were severe cartilage damage. The medical cost of selective cox-2 and diacerein increases but due high amount of patient that were delayed for surgical intervention, the surgical cost decreases significantly.*

***Keywords:*** *Cross linked Sodium Hyaluronate, osteoarthritis of knee, cost analysis, Failure, Conservative treatment, Viscosupplementation, Total knee arthroplasty*

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## Introduction

Viscosupplementation, in which hyaluronic acid (HA) is injected into the knee joint for the symptomatic relief of pain, has been available for treatment of knee OA in the USA since 1997 and in Thailand since 2002. Various mechanisms of action have been suggested to explain the clinical effects of intra-articular injection of hyaluronic acid (IAHA). IAHA provides extra lubrication and cushioning within affected knee joints and has been shown to induce direct anti-inflammatory, chondroprotective, and analgesic effects. HA injections are recognized as safe and effective for the alleviation of joint pain and improvement of joint function in patients with knee

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OA, with positive clinical evidence demonstrated in clinical trials[1].

Intra-articular treatment for knee OA by XLHA has played a role in the treatment of knee OA in Thailand since 2016. The clinical efficacy demonstrated that a single injection of XLHA was non-inferior to three weekly injections of HMWHA, and supports XLHA as an effective and safe treatment for knee OA with mild to moderate knee OA[2].

Regarding molecular weight, one study suggested potential benefit of high molecular weight (HMW) HA through the CD44 receptor binding with greater affinity, but another study suggested better anti-inflammatory effects of HMW HA but better chondroprotective effects of low molecular weight (LMW) HA[3]. By linking the clinical outcome of delay to a major surgery and the cost outcome, There was no any study about the analysis of the prospective cohort database provides real-world evidence that XLHA intra-articular may offer more value in delaying TKA and save the cost outcomes in short to intermediate term[4]. The main purpose not only improve clinical outcomes by also cost analysis study in the clinical practices. The research is needed to find out more about the aspects of XLHA may influence cost outcomes associated in the clinical practice for 6 months follow up.

## Materials and Methods

**Study design**

Cost analysis study was perform by enrolling patient with knee OA that failed conservative treatment, whom were candidate for surgical intervention, including 205 patients (253 knees) 40 males and 165 females during January 2018 till September 2018 and 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 OA all stages according to the American College of Rheumatology criteria, (ii) had prior failure to conservative treatment including anti-inflammatory drugs and others, physical therapy and bracing with unsatisfactory improvement more than 6 months whom were considered as candidates for surgical intervention according to the knee pathology, and (iii) no contraindication for surgery

The exclusion criteria were patients other degenerative arthritis or other diseases unrelated to arthritis, history of knee surgery, allergic to avian protein or of XLHA and using any intra-articular treatment in any form within 6 months before study enrollment. Patients were divided into two groups, first group less than 60 years and second group more than 60 years.

The severity is classified according to Kellgren Lawrence classification, by radiographic evaluation, grade I (no joint spaces loss) and grade II (minimum joint space loss), grade III (osteophyte formation) and grade IV (severe narrowing joint space)[5].

All patients received XLHA together with continuing of home program physical therapy with a fixed arch quadriceps exercise and other pain-killer medications such as selective COX-2 inhibitors for relief their pain as needed. For those who failed, which was classified by lack of improvement in pain and knee functions after the injection, the surgery has been scheduled within 30 days after the most recent Intra-articular Hyaluronic use.

**Data source**

For this study, integrated medical and pharmacy claims data were extracted from HIS systems and also financial department of the Police General Hospital. Data were collected from patient who had been initiated with XLHA injection in outpatient clinics during January 2018 to September 2018. For calculation of disease-specific costs, disease specific claims were denoted by those claims with an OA of the knee diagnosis code while disease-specific drugs included, selective cox-2 inhibitors, and diacerein (due to its high value and leading cost factor).

**Outcome measures**

The primary outcome measurement were disease-specific costs associated with knee OA and time from the index date to surgical intervention. The secondary outcomes were the number of cases that delay surgery within period of study (6 months).

## Result

During January 2018 to September 2018 and at Orthopedic Clinic, Police General Hospital. 240 patients (295 knees) affected by knee OA are enrolled, 35 patients was excluded because steroid injection. All patients were asked to provide informed consent before study enrollment. The average age is 63.2 years. The patients demographic data is according to table 1.

In the first group (less than 60 years) 48 cases the failed conservative treatment need surgical intervention for arthroscopic surgery for 7 cases, no surgical intervention for 41 cases. In the second group (more than 60 years) 157 cases that failed conservative treatment ,15 cases (17 knees) need surgical intervention for TKA, no surgical intervention of 141 cases. 47 cases need repeated dose of XLHA. The detail of medical and surgical intervention is according to table 2.

The expense of XLHA is 3,588,805 baht (253 knees). The cost of Cox2 consumption 6 months before and 6 month after injection were 313,447 baht and 439,256 baht. The cost of Diacerein consumption 6 month before and 6 months after injection were 168,336 baht and 262,458 baht. In the first group (less than 60 years), the total cost of surgical intervention is 488,250 baht, average cost of arthroscopic surgery are 69,750 (47713-103238) baht. The proportion of case that

delayed surgical intervention are 83% (41/49 cases). In the second group (more than 60 years), the total cost for surgical intervention is 2,327,482 baht, average cost of TKA are 136,910 (122338 - 250426) baht. The proportion of cases that delayed TKA are 90.4% (142/183 cases). The total expense for surgical intervention is 2,815,732 baht. The total expense for medical and surgical cost are 7,106,251 baht. The average cost per patients is 34,664.63 baht and the average cost per knee is 28,087.95 baht according to the table 3 and table 4.

**Table 1** Patient Characteristics.

| Characteristic | < 60 yr | > 60 yr | Total |
|---|---|---|---|
| Average age | 52.2 | 66.6 | 63.2 |
| No. of patient female/male | 40/8 | 125/32 | 165/40 |
| Kellegren Lawrence gr 2-3 (knee) | 57 | 173 | 230 |
| Kellegren Lawrence gr 4 (knee) | 3 | 20 | 23 |
| Number (person) | 48 | 157 | 205 |
| Number (knee) (right:left) | 60 (45:15) | 193 (150:43) | 253 |
| Bilateral OA Knee (percentage) | 12 (25.00) | 36 (22.92) | 48 (23.41) |
| repeated dose | 10 | 37 | 47 |
| Number of surgery (person) | 7 | 15 | 22 |
| Number of surgery (knee) | 7 | 17 | 24 |
| Number of non-surgery (person) | 41 | 142 | 183 |
| Number of non-surgery (knee) | 53 | 176 | 229 |

**Table 2** Percentage of medical and surgical intervention.

| | < 60 yr (%) | > 60 yr (%) | Total (%) |
|---|---|---|---|
| repeated dose (person) | 20.83 | 23.57 | 22.93 |
| no. of surgery (person) | 14.58 | 9.55 | 10.73 |
| no. of surgery (knee) | 11.67 | 8.81 | 9.49 |
| no. of non-surgery* (person) | 85.41 | 90.45 | 89.27 |
| no. of non-surgery* (knee) | 88.33 | 91.19 | 90.51 |

**Table 3** Medical Expenses.

| Cost | Baht (6 month before) | Baht (6 month after) |
|---|---|---|
| Hyruan One | - | 3,588,805.00 |
| Selective cox2 | 313,447.00 | 439,256.00 |
| Diacerein | 168,336.00 | 262,458.00 |
| Total Medical Cost | 481,783.00 | 4,290,519.00 |

**Table 4** Total and Medical and Surgical Expenses.

| Cost | Baht |
|---|---|
| Total Medical Cost | 4,290,519.00 |
| Total Surgical Intervention | 2,815,732.00 |
| Total Medical and Surgical Cost | 7,106,251.00 |
| av. cost/person | 34,664.63 |
| av. cost/knee | 28,087.95 |

## Discussion

Evidence from real-life studies of repeat courses of IAHA demonstrates an improvement in pain or function lasting up to 40 months (12 months after the last injection cycle), a reduction in use of concomitant analgesia by up to 50%, and suggests that there may be a delay in the need for TKA of around 2 years[6,7]. The use of IAHA in knee OA patients with mild–moderate disease, and for more severe patients wishing to delay TKA surgery, is recommended by the ESCEO task force[8]. For the comparative effectiveness outcome of TKA delay, all HA cohorts were rather similar in their ability to delay TKA, except the Synvisc cohort which had a statistically significantly greater risk of having a TKA than the other cohorts[9]. XLHA is non inferiority to three doses injection. Many studies revealed improve clinical outcomes. In the real medical practices, the heath economic seems to be the important issues in medical practices. In our study the uses of XLHA surgical intervention significant and but preserve cartilage is still controversy. In our study XLHA may improve outcomes not only mild to moderate but also severe OA with 6 months follow up. This will serve the approaching of aging society. The effect might be from potent anti-inflammation, significant decrease pain and function[10]. The pharmacologic effects by BDDE that increase the resident time for release the medication for 1 months and have sustained effect for minimal 6 months follow up[11,12]. The recent meta-analyses which estimates on a standard mean difference (SMD) scale and compared all treatments against a threshold for clinical importance of 0.5 standard deviation (SD) unit.

Many nonoperative treatments demonstrated significant improvements in pain, data suggested that the greatest effect were from intra-articular injection. Variability among studies suggest that future research into optimal formulation is required. The strongest current evidence supports clinically important and significant treatment effects with IAHA formulations > 6000 kDa[13].

We analyse the most common causes of failure in patient intra-articulary injected with XLHA under age of 60 years are the complex tear of meniscus. If the radiographic degree of damage cartilage is unproportionate to pain and unspecific causes, further investigation is recommended such as MRI.

Other common misdiagnosed pathologies are osteonecrosis of knee, undetected multifocal damage in patient with history of multiple steroid injection.

## Limitation

The limitation are numbers of patients, no quality of life had been assessed for cost utility, short duration for 6 months of follow-up. Further detailed investigation and comparison is recommended.

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***การศึกษาวิเคราะห์ต้นทุนการรักษาด้วยสารโซเดียมไฮยาลูรอเนตชนิดเชื่อมโยงร่างแห (Cross-Linked Sodium Hyaluronate: XLHA-BDDE) ในคนไข้ข้อเข่าเสื่อมที่รักษาด้วยวิธีการรักษาแบบอนุรักษ์ ไม่ได้ผล***

***ธนา ธุระเจน, พบ, ชัยวัฒน์ ศรีรัตนวุฑฒิ, พบ, ปาโมกข์ แสงศิรินาวิน, พบ, วันเพ็ญ ลาภไพวงศ์, จิตตวดี ประสงค์***

**บทนำ:** การฉีดสาร ไฮยาลูรอนิก (hyaluronic acid injections) เป็นการรักษาที่ยอมรับโดยทั่วกันว่าปลอดภัยและมีประสิทธิภาพในผู้ป่วยข้อเข่าเสื่อม (knee osteoarthritis : OA) โดยมีการศึกษาเปรียบเทียบรองรับผลการรักษาจำนวนมาก หนึ่งในการศึกษาดังกล่าวแสดงให้เห็นว่า ผลการรักษาโดยการฉีดเข่า 1 ครั้งด้วยสารโซเดียมไฮยาลูรอเนตชนิดเชื่อมโยงร่างแห (cross-linked sodium hyaluronate : XLHA, single injection form, Hyruan One) ไม่ได้ด้อยกว่าการฉีดสารไฮยาลูรอนิกชนิดโมเลกุลใหญ่ (high molecular weight hyarulonic acid: HMWHA) และแนะนำให้เป็นการรักษาที่ปลอดภัยและให้ผลดีในผู้ป่วยโรคข้อเข่าเสื่อม อย่างไรก็ตามยังต้องมีการศึกษาเรื่องของต้นทุน ค่าใช้จ่ายที่เกี่ยวข้องในด้านการให้ยา และผ่าตัดในการรักษาคนไข้จริง

**วัตถุประสงค์**: วัตถุประสงค์หลักเพื่อศึกษาค่าใช้จ่ายที่เกี่ยวข้องกับโรคข้อเข่าเสื่อม ทางด้านการบริหารยาและการผ่าตัด 6 เดือนก่อนและหลังการฉีด XLHA วัตถุประสงค์รองเพื่อศึกษาสัดส่วนของผู้ป่วยที่ไม่ต้องรับการรักษาโดยการผ่าตัดในระยะเวลา 6 เดือนหลังฉีดยา

**วัสดุและวิธีการ**: การศึกษาวิเคราะห์ต้นทุนนี้เรารวบรวมผู้ป่วยโรคข้อเข่าเสื่อมที่รักษาด้วยวิธีแบบอนุรักษ์ไม่ได้ผลและจำเป็นต้องได้รับการผ่าตัดทั้งหมด 205 ราย (253 ข้อเข่า) เป็นผู้ชาย 40 ราย และ ผู้หญิง 165 ราย ตั้งแต่เดือนมกราคม พ.ศ. 2561 ถึงเดือนกันยายน พ.ศ. 2561 ที่รักษาในคลินิกออร์โธปิดิกส์ โรงพยาบาลตำรวจ โดยแบ่งคนไข้เป็น 2 กลุ่มตามอายุดังนี้ กลุ่มที่ 1 อายุน้อยกว่า 60 ปี จำนวน 48 ราย และกลุ่มที่สอง อายุมากกว่า 60 ปี จำนวน 157 ราย เนื่องจากทั้งสองกลุ่มจะได้รับการผ่าตัดด้วยวิธีการแตกต่างกัน ความรุนแรงของโรคถูกจัดแบ่งตาม Kellgren Lawrence classification โดยค่าใช้จ่ายที่เกี่ยวข้องนำมาจากฐานข้อมูลอิเล็กทรอนิกส์ของโรงพยาบาล (hospital information system: HIS) และหน่วยการเงินโรงพยาบาลตำรวจ

**ผลการศึกษา**: อายุเฉลี่ยของผู้ป่วยคือ 63.2 (50-81) ปี กลุ่มที่ 1 (อายุน้อยกว่า 60 ปี) จำนวน 48 ราย กลุ่มที่ 2 (อายุมากกว่า 60 ปี) จำนวน 157 ราย โดยกลุ่มแรกมีผู้ป่วยจำนวน 7 รายที่ต้องได้รับการผ่าตัดส่องกล้อง (knee arthroscopic surgery) คิดสัดส่วนผู้ป่วยที่ชะลอการรักษาโดยการผ่าตัดคือร้อยละ 85.42 (41 รายจากทั้งสิ้น 48 ราย) โดยค่าใช้จ่ายเฉลี่ยอยู่ที่ 69,750.00 บาทต่อข้อเข่า ส่วนกลุ่มที่สองมีผู้ป่วยจำนวน 15 รายที่ต้องรับการผ่าตัดเปลี่ยนข้อเข่าเทียม (total knee arthroplasty) คิดสัดส่วนผู้ป่วยที่ชะลอการรักษาโดยการผ่าตัดคือร้อยละ 90.45 (142 รายจากทั้งสิ้น 157 ราย) โดยค่าใช้จ่ายเฉลี่ยอยู่ที่ 136,910.71 บาทต่อข้อเข่า ค่าใช้จ่ายต่อการฉีด XLHA คือ 3,588,805.00 บาท โดยค่าใช้จ่ายในการบริหารยา (Selective COX-2 inhibitor NSAIDs และ Diacerein) 6 เดือนก่อนและหลังการฉีด XLHA คือ 481,783.00 บาท และ 701,714.00 บาท ตามลำดับ

**สรุป**: จากการศึกษาพบว่า XLHA ลดอัตราการผ่าตัดในช่วง 6 เดือนในทุกระยะความรุนแรงของโรคข้อเข่าเสื่อม โดยสาเหตุของผู้ป่วยอายุน้อยกว่า 60 ปีที่ต้องได้รับการผ่าตัดคือ การฉีกขาดของหมอนรองกระดูกข้อเข่า ส่วนผู้ป่วยอายุมากกว่า 60 ปี คือการบาดเจ็บอย่างรุนแรงของกระดูกอ่อน ค่าใช้จ่ายทางด้านการบริหารยา (Selective COX-2 inhibitor NSAIDs และ Diacerein) 6 เดือนหลังการฉีด XLHA เพิ่มมากขึ้น อย่างไรก็ตามเนื่องจากมีผู้ป่วยจำนวนมากที่สามารถชะลอการผ่าตัดได้ ค่าใช้จ่ายในการผ่าตัดในผู้ป่วยกลุ่มนี้จึงลดลงอย่างมีนัยสำคัญ