**ORIGINAL ARTICLES**

# Cost – effectiveness analysis of hyaluronic acid injection relative to oral medication for knee osteoarthritis treatment at Nguyen Trai hospital in the period of 2022 – 2023

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## ABSTRACT

**Objective:** Pharmacological treatments, primarily oral NSAIDs, constituted 73.9% usage for knee osteoarthritis. Despite the known adverse effects of NSAIDs, they are recommended for KOA management. Hyaluronic acid injections, an emerging alternative, lack consensus and evidence of cost-effectiveness in Vietnam. This study aimed to analyze the cost-effectiveness of hyaluronic acid injections relative to oral medication treatment in patients with KOA from health insurance payer's perspective.

**Methods:** A retrospective study was conducted using electronic medical records of KOA patients from March 1, 2022, to May 31, 2023, at Nguyen Trai Hospital to analyze costs. A cross-sectional descriptive study of two groups receiving hyaluronic acid injections (HA) or oral medication treatment (PO) was conducted using the WOMAC scale converted to EQ-5D-5L to measure treatment effectiveness in QALYs. Seemingly unrelated regression equation was utilized to estimate the Incremental Cost-effectiveness Ratio (ICER) of HA relative to PO while simutaneously adjusting for other confounding factors.

**Results:** The PO group exhibited a higher total WOMAC score than the HA group (PO group: 45.12; HA group: 44.29), indicating greater severity in the WOMAC Pain, Function, and Stiffness categories. The QALYs of HA group was higher than those of the PO group, with QALYs values of 0,719 and 0,661, respectively. The total medical direct costs increased by 6.232.445 VND, and QALYs increased by 0,041 when using HA compared to PO. The ICER reached a 151.184.110 VND/QALY gained. With WTP of 1GDP and 3GDP, the probability of achieving cost-effectiveness of HA compared to using PO was respectively 20.06% and 100%.

**Conclusions:** The study demonstrated that ICER based on QALYs of hyaluronic acid injections is cost-effective compared to the standard oral medication approach.

***Keywords:*** *Cost analysis; WOMAC; Cost-effectiveness analysis; Hyaluronic acid injections; Knee osteoarthritis.*

## INTRODUCTION

Osteoarthritis (OA) is a prevalent bone and joint disease worldwide, causing significant disability among elderly patients and resulting in painful muscles, loss of walking function, and diminished quality of life. Knee osteoarthritis (KOA) is one of the most common form of OA. A systematic review conducted in 2020 on the global prevalence of KOA revealed that there were approximately 654.1 million patients aged 40 years and older afflicted with KOA (1). In the United States, knee osteoarthritis accounted for 80%

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of the arthritis burden, affecting at least 19% of the population over 45 years old (2). In Vietnam, the prevalence of X-ray-diagnosed knee osteoarthritis was 34.2%, with a higher incidence in women compared to men (35.3% vs. 31.2%). Incidence escalated with age, reaching 8% in the 40-49 age group, 30% in the 50-59 age group, and 61.1% in those aged 60 and above (3). KOA imposes a substantial morbidity and economic burden. Disability and changes in quality of life linked to KOA increased risk of all-cause mortality rate (4). The rise in knee osteoarthritis incidence aligned with the upward trajectory of healthcare costs, estimated to range from 0.25% to 0.5% of a country's GDP (5).

There are no mandatory indications for individualized knee osteoarthritis treatment, as treatment options hinge on the extent of joint degeneration and the economic conditions of each patient (6). Available treatment modalities encompass pharmacological and surgery, with pharmacological being the predominant choice (73.9%) (7). Among the pharmacological treatments for knee osteoarthritis (OA), oral non-steroidal anti-inflammatory drugs (NSAIDs) act quickly and are recommended for OA management, despite the well-acknowledged frequent and serious adverse effects associated with NSAIDs (8). In recent years, intra-articular therapy, particularly hyaluronic acid injections, has gained popularity, especially among high-risk patients seeking an alternative to oral medications and postponed surgery (9,10). However, consensus on the practical use of Hyaluronic acid injection in treatment in Vietnam and evidence regarding the cost-effectiveness of this approach were limited. This study aimed to analyze the cost-effectiveness of hyaluronic acid injections relative to oral medication treatment in patients with KOA at Nguyen Trai Hospital from health insurance payer's perspective.

## METHODS

**Study design:** A retrospective and cross-sectional study was conducted on two cohorts of KOA patients receiving treatment with hyaluronic acid injection (HA group) and oral medication (PO group) at Nguyen Trai Hospital during the period 2022 - 2023. Specifically, the retrospective study focused on gathering data on direct medical costs for both patient groups, with a perspective from the paying agency (Health Insurance), spanning from March 2022 to March 2023. Simultaneously, the cross-sectional descriptive study aimed to assess the effectiveness of the two treatment groups using the WOMAC questionnaires from February 2023 to May 2023.

By analyzing both cost and effectiveness data, the study aimed to evaluate the Incremental Cost-Effectiveness Ratio (ICER) index to assess the cost-effectiveness of hyaluronic acid injections treatment in comparison to the utilization of oral medication.

**Research subjects:** The study included inpatients in the HA group and outpatients in the PO group undergoing treatment for KOA at Nguyen Trai Hospital in 2022-2023. The WOMAC survey was conducted for patients in 2023, simultaneously conducting a retrospective review of the patients' electronic medical record data in 2022 – 2023 with the following selection criteria:

***Inclusion Criteria:***

- Patients were diagnosed with primary knee osteoarthritis (ICD: M17.0).

- Patients were categorized as stage 2 and 3 according to Kellenge Lawrance criteria.

- Patients who have completed the hyaluronic acid injection or used oral medication KOA treatment medication for a period of 1 year.

***Exclusion Criteria:***

- Patients were diagnosed with traumatic, secondary, non-specific knee diseases (ICD: M17.1, M17.2, M17.3, M17.4, M17.5, M17.9).

- Patients have consciousness and mental problems.

- Patients had undergone surgical intervention.

**Study site and time:** The study was conducted at Nguyen Trai Hospital, located at 314 Nguyen Trai Street, Ward 8, District 5, Ho Chi Minh City. The study extended over a period of 13 months, from July 2022 to August 2023.

**Sample size and sampling method:** The sample size for the study was estimated with the hypothesis of comparing the mean WOMAC scores between two patient groups, using a research selection of $\alpha = 0.05$. Due to objective limitations (difficulties in selecting patients for HA joint injection) and subjective reasons from previous studies (significant fluctuations in recording WOMAC scale components (11–13) and incomplete recording of input data in Vietnam), these factors might have influenced the evaluation of WOMAC scores for both groups. This could have resulted in the inability to detect differences between the groups (increasing the likelihood of Type II error). Given that this was a pilot study, a power factor of 0.7 (corresponding to a 70% chance of avoiding false-negative conclusions) was applied (14). Using G*Power software, the study estimated the minimum sample size of the HA group and PO group to be 41 patients (15). In fact, the study collected data from 42 individuals in the HA group and 94 individuals in the PO group.

**Research variables and indicators:**
Detailed information onf variables analyzed is presented in Table 1.

**Table 1. Description of variables**

| Variable | Description | Variable classification |
|---|---|---|
| ***Patient characteristics*** | | |
| Gender | Based on medical records, including: Male and Female | Binary variables |
| Age | Based on medical records: Year of birth | Continuous variables |
| Body Max Index | Patient's weight divided by the square of height | Continuous variables |
| Stage of KOA | Following Kellen- Lawrance System with five grades: grade 0 (none); grade 1 (doubtful); grade 2 (minimal); grade 3 (moderate); grade 4 (severe) | Categorical variables |
| Comorbilities | The 5 most prevalent comorbilities | Binary variables |
| ***Cost Assessment*** | | |
| Hospital bed / Medical examination cost | Cost of hospital bed cost (HA group) and medical examination (PO group) for the patient | Continuous variables |

| Variable | Description | Variable classification |
|---|---|---|
| Medication cost | Cost of the medicaions based on the list of medications for treating KOA from the "Guidelines for Diagnosis and Treatment of Musculoskeletal Diseases 2014" by the Ministry of Health, specified at Nguyen Trai Hospital, Circular 40/2014/BYT on the list of medications covered by health insurance (16). | Continuous variables |
| Hyaluronic acid injection cost | Cost of intra-articular hyaluronic acid injection, intra-articular corticosteroid injection | Continuous variables |
| Service cost | Cost of services (diagnostic imaging, tests, surgical procedures) | Continuous variables |
| Total cost | Total direct medical treatment cost of the patient | Continuous variables |
| ***Effectiveness Assessment*** | | |
| WOMAC Total | Total score WOMAC | Continuous variables |
| WOMAC Pain | WOMAC pain score estimated based on the intensity and frequency of pain experienced during various activities such as walking, climbing stairs, and resting. | Continuous variables |
| WOMAC Function | WOMAC function score estimated based on an individual's ability to perform daily activities and tasks. | Continuous variables |
| WOMAC Stiffness | WOMAC stiffness score estimated based on the duration and severity of joint stiffness, especially in the morning and after periods of inactivity. | Continuous variables |
| Utility (EQ-5D-5L) | Converted based on the scores of components of the WOMAC scale using the Ordinary Least Squares regression method (17). | Continuous variables |
| ***Cost-effectiveness analysis*** | | |
| Incremental Cost-Effectiveness Ratio (ICER) | Defined by the difference in cost between two interventions, divided by the difference in their effect (18). | Continuous variables |

**Data collection:** The study retrieved data from patients' electronic medical records and stored it in *.csv* file format. For research purposes, the data was segmented into two files: (1) Information of patients and treatment cost data, and (2) Hospital drug list during the period 2022 - 2023. Subsequently, the data was collected, cleansed, processed, and analyzed.

**Data analysis**

***Cost Assessment:***

The study evaluated direct medical costs from the health insurance perspective, utilizing Bottom-up costing method. Direct medical costs were converted to 2023 annual values based on the consumer price index (CPI).

***Effectiveness Assessment:***

The study evaluated the treatment effectiveness in knee osteoarthritis (KOA) patients through the WOMAC scale. Employing Feng Xie's 2010 OLS method, it converted WOMAC questionnaire results to EQ-5D-5L for sample

sizes of 50 and 100 (17). Subsequently, the study quantified the Quality-Adjusted Life Years (QALY) index based on the utilities.

***Cost-effectiveness analysis:***

The research utilized the Systemfit package in the R programming language for estimating Ordinary Least Squares (OLS) models related to cost, efficiency, and Incremental Cost-Effectiveness Ratio (ICER) using the seemingly unrelated regression (SUR) method(19). Independent variables incorporated into the model encompass treatment method (HA/PO), age, gender, BMI, stage of KOA and occupation (manual labor: yes/no). Subsequently, the study aimed to evaluate Incremental Cost-Effectiveness Ratios (ICER) and compared them with the willingness-to-pay threshold (WTP).

- If ICER ≤ WTP: HA demonstrates a cost-effective advantage over PO.

- If ICER > WTP: HA lacks a cost-effectiveness advantage compared to PO.

According to WHO recommendations, the WTP is assessed at 1-3 times GDP per capita. Based on World Bank data from 2022, Vietnam's WTP is estimated to be in the range of 98,721,382 VND to 296,164,146 VND.

**Ethics approval:** This research had received approval from the Board of Directors and the Scientific Research Outline Approval Council of Nguyen Trai Hospital according to decision No. 691/QD-BVNT.

## RESULTS

### Patient characteristics

Table 2 presents the patient characteristics of the HA and PO groups. The gender rate showed no statistically significant difference (p-value = 0.813). Notably, the HA group had exhibited a higher median age of 71 compared to 66 in the PO group, with a statistically significant age difference (p-value = 0.009). Both groups had over 50% of patients with a BMI of ≥ 25, and this disparity was not statistically significant (p-value = 0.780). Additionally, the incidence of stage 3 knee osteoarthritis had been notably higher in the HA group (71.43%) than in the PO group (15.96%). Common comorbidities observed in both groups included I10 and I83.

**Table 2. Patient characteristics**

| Characteristics | HA Group (n = 42) | PO Group (n = 94) |
|---|---|---|
| **Female** | 33 (78.57%) | 74 (78.72%) |
| **Age (Median - IQR)** | 71 (68 – 74) | 66 (60 – 71) |
| **BMI (Body Max Index)** | | |
| < 18 | 4 (9.52%) | - |
| 18 – 25 | 16 (38.09%) | 39 (41.49%) |
| 25 | 22 (52.39%) | 55 (58.51%) |
| **Stage of KOA** *(follow Kellen- Lawrance System)* | | |
| Stage 2 | 12 (28.57%) | 79 (84.04%) |
| Stage 3 | 30 ( 71.43%) | 15 (15.96%) |
| **Comorbilities** | | |
| 1 | I10 (12.01%) | I83 (11.02%) |

| Characteristics | HA Group (n = 42) | PO Group (n = 94) |
|---|---|---|
| 2 | M47 (7.69%) | I10 (9.52%) |
| 3 | I83 ( 6.01%) | E78 (6.81%) |
| 4 | I25 (5.06%) | M13 (4.13%) |
| 5 | K21 (4.53%) | M47 (4.00%) |

**Cost Assessment**

Direct medical costs of two groups are presented in Table 3, revealing a statistically significant difference in the average total treatment costs. Specifically, the average total cost in the HA group (7,792,020 VND) exceeded that of the PO group (1,219,801 VND). In terms of cost composition, the hospital bed charge in the HA group was significantly higher than the medical examination cost in the PO group, attributed to the HA group being comprised of inpatients while the PO group consisted of outpatients. Additionally, both the cost of Hyaluronic acid injection and service costs in the HA group were higher than those in the PO group. Conversely, drug costs for the PO group surpassed those for the HA group, amounting to 63,373,094 VND and 6,811,612 VND, respectively.

**Effectiveness Assessment**

The total WOMAC score across three subscales reflects the severity of knee osteoarthritis. A higher WOMAC score suggests more pronounced issues related to joint degeneration and pain. The PO group exhibited a higher total WOMAC score than the HA group, indicating greater severity in the WOMAC Pain, Function, and Stiffness categories (see Table 4).

The EQ-5D score assesses quality of life, with higher scores indicating better overall well-being. The HA group demonstrated a significantly higher EQ-5D score (0.719) compared to the PO group (0.661). Based on the WOMAC and EQ-5D score, the study indicates that patients in the HA group experienced a superior quality of life compared to those in the PO group.

**Table 3. Direct medical costs for knee osteoarthritis treatment**

| Cost (VND) | HA Group (n = 42) | PO Group (n = 94) | p-value |
|---|---|---|---|
| **Hospital bed/Medical examination cost** | | | |
| Mean (95% CI) | 3,954,930 (3,757,183 – 4,152,676) | 441,996 (419,896 – 464,095) | <0.001 |
| **Medication cost** | | | |
| Mean (95% CI) | 162,181 (154,071 – 170,290) | 674,181 (640,471 – 707,890) | <0.001 |
| **Hyaluronic acid injection cost** | | | |
| Mean (95% CI) | 2,962,142 (2,814,034 – 3,110,249) | - | |
| **Service cost** | | | |

| **Cost** (VND) | **HA Group (n = 42)** | **PO Group (n = 94)** | **p-value** |
|---|---|---|---|
| Mean (95% CI) | 712,766 (677,127 – 748,404) | 103,623 (98,441 – 108,804) | < 0.001 |
| **Total cost** | | | |
| Mean (95% CI) | 7,792,020 (7,402,419 – 8,181,621) | 1,219,801 (1,158,810 – 1,280,791) | < 0.001 |

** Kruskal – Wallis test*

**Table 4. WOMAC and EQ5D scores of HA group and PO group**

| **Characteristic** | **HA Group n = 42** | **PO Group n = 94** | **p-value*** |
|---|---|---|---|
| **WOMAC Total** | | | |
| Mean | 44.29 | 45.12 | 0.012 |
| 95% CI | (41.57 – 47.00) | (40.45 - 49.79) | |
| **WOMAC Pain** | | | |
| Mean | 9.43 | 10.80 | 0.023 |
| 95% CI | (8.62 – 10.23) | (9.79 - 11.81) | |
| **WOMAC Function** | | | |
| Mean | 29.62 | 31.56 | 0.045 |
| 95% CI | (27.51 – 31.72) | (27.85 – 35.28) | |
| **WOMAC Stiffness** | | | |
| Mean | 3.83 | 3.95 | 0.042 |
| 95% CI | (3.44 – 4.47) | (3.20 - 4.46) | |
| **EQ – 5D** | | | |
| Mean | 0.719 | 0.661 | <0.001 |
| 95% CI | (0.711 - 0.726) | (0.647 – 0.675) | |

** Kruskal – Wallis test*

**Cost – effectiveness analysis**

The study presented the cost-effectiveness outcomes, seen in Table 5. Model SUR results indicated an incremental cost of 6,232,445 VND, incremental QALYs of 0.041, and an ICER index result of 151,184,110 VND. In comparison to Vietnam's payment threshold, set at 3 times GDP (296,164,146 VND), the ICER based on QALYs affirmed the cost-effectiveness of the intra-articular hyaluronic acid injection over the oral medication. The results of the sensitivity analysis are presented in Figures 1 and 2. With WTP of 1GDP and 3GDP, the probability of achieving cost-effectiveness of Hyaluronic acid injection compared to using oral drugs was respectively 20.06% and 100%.

**Table 5. Cost-effectiveness analysis of hyaluronic acid injection vs oral medication**

| | Value Added Estimation Coefficient |
|---|---|
| Total cost (VND) | 6,232,445 |
| Quality-adjusted life years (QALYs) | 0.041 |
| ICER/QALY (VND/QALY) | 151,184,110 |

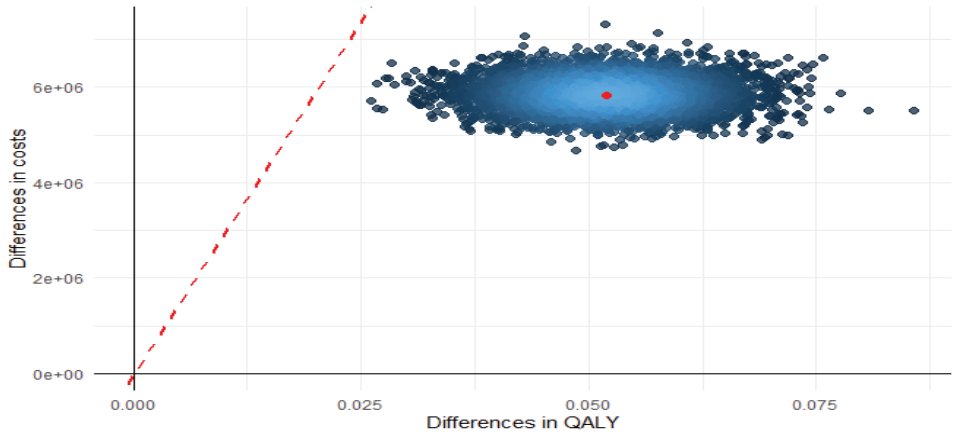


**Figure 1. Cost-effectiveness plane for hyaluronic acid injection vs oral medication**

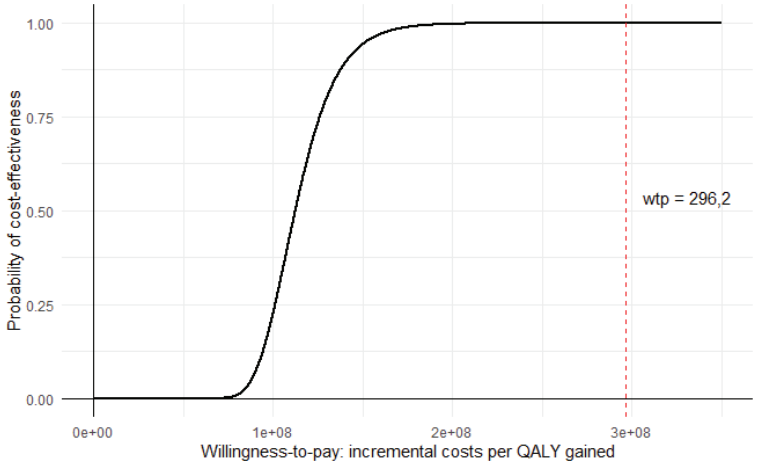


**Figure 2. Cost-effectiveness acceptability curve**

## DISCUSSION

The study conducted a cost assesment, effectiveness assesment, and cost-effectiveness analysis of hyaluronic acid injection versus oral medication for the HA group (42 patients) and the PO group (94 patients). The results indicated that the total cost of the HA group was significantly higher than that of the PO group. This difference was mainly attributed to the fact that the HA group included inpatients who had to cover the majority of hospital bed costs (3,954,930 VND/patient) and Hyaluronic acid injection

costs (2,962,142 VND/patient). In contrast, the costs of the PO group were primarily medical examination costs (441,996 VND/patient) and medication costs (674,181 VND/patient). This analysis result aligned with the treatment characteristics of the two methods.

The study utilized the WOMAC questionnaire to assess treatment effectiveness. For the four aspects of the WOMAC questionnaire, the HA group had lower scores than the PO group, with a statistically significant difference. This indicated that the severity of knee osteoarthritis in the HA group was milder than in the PO group. The results were consistent with the research of Larry E. Miller (2014) (20) and the conclusion of the systematic review on the effectiveness of hyaluronic acid injection versus oral medication (2020) (21). After converting from WOMAC score to EQ-5D score scale, the study recorded that the EQ-5D score of the HA group was 0.661, and the EQ-5D score of the PO group was 0.719. The difference between the two groups was statistically significant and consistent with the results of Thierry Thomas and colleagues (2017) on a cost-effectiveness analysis study between Hyaluronic acid injection and NSAIDs (22). Until now, in Vietnam, there has been no research conducted to evaluate the effectieness treatment of KOA patients using the WOMAC scale. Therefore, the study demonstrated a new approach to measuring treatment effectiveness for KOA patients in Vietnam and was consistent with previous studies involving this patient population (23,24).

The research utilized seemingly unrelated regression equation to estimate the ICER index to evaluate the cost-effectiveness of hyaluronic acid injection versus oral medication. This was an approach for prognostic factor adjustment and subgroup analysis in cost-effectiveness studies with censored data developed by Andrew R. Willan in 2005 (25). This method has been applied in many cost-effectiveness analysis studies with censored data, evaluating the cost-effectiveness of interventions as a secondary outcome in clinical trials or using real-world data among patient groups (26). The results indicated that the Hyaluronic acid injection method incurred more costs than patients using the PO drug, amounting to 6,232,445 VND for an additional 0.041 QALYs points. Therefore, the Hyaluronic acid injection method was be cost-effective compared to oral medication. This result aligned with the findings of the study by Thierry Thomas (2017) (22). The limitation of the study is the lack of similarities between the groups in background characteristics such as disease duration and age. Additionally, the number of research samples in the Hyaluronic intra-articular injection group was relatively small. However, it's crucial to note that this study was a pilot study with a relatively limited sample size. The research served as a preliminary exploration of the effectiveness of Hyaluronic acid injection at Nguyen Trai Hospital, illustrating the considerations of Hyaluronic acid injection in treatment. To bolster evidence for choosing appropriate treatment methods for patients with KOA, larger-scale studies are necessary, requiring collaboration between managers, clinical practitioners, and pharmacy departments to include comprehensive patient treatment processes in the research sample.

## CONCLUSION

The study revealed an increased treatment effectiveness of hyaluronic acid injection compared to oral medication among KOA patients, as assessed using the WOMAC questionnaire. Simultaneously, the SUR results demonstrated that hyaluronic acid injection was cost-effective in comparison to

oral medication at an ICER of 151,184,110 VND/QALY. This formed the foundation for conducting more extensive studies to assess the cost-effectiveness of these two methods on a larger sample size of patients, thereby establishing a solid basis for selecting treatment modalities for KOA patients.

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