


Is Intra-Articular Injection of Synvisc Associated with a Delay to Knee Arthroplasty in Patients with Knee Osteoarthritis?

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Abstract

Objective. There is debate about the effectiveness of intra-articular (IA) hyaluronic acid (HA) injections. We asked the following questions: (1) What is the epidemiology of IA HA use in knee arthroplasty (KA) patients? (2) Is Synvisc associated with a delay to KA? (3) Is there a difference in the delay to KA with the number of HA courses? **Design.** The Optum Clinformatics data set (2006–June 2016) was used to identify patients with knee osteoarthritis (OA). Patients who did not receive IA HA were identified, along with those who received Synvisc or non-Synvisc HA. The median duration from knee OA to KA was compared using quantile regression modeling with propensity score weighting. The trend in time to KA with each HA course was evaluated. **Results.** Of 4,027,848 knee OA patients, 141,305 patients underwent KA. Overall median time from knee OA diagnosis to KA was 1.2 years (average: 1.9 ± 1.9 years; interquartile range of 0.4–2.8 years). HA patients had significantly longer adjusted median time to KA by at least 7 months ($P < 0.001$). After adjusting for the time to HA and number of injections, Synvisc patients had 1.7 months longer time to KA than non-Synvisc HA patients ($P < 0.001$). There was a trend toward longer time to KA with more HA courses. **Conclusions.** Most KA patients did not use HA (73.7%) and when received, it was associated with a longer median time to KA by at least 7 months, though the cause and effect could not be examined. The delay to KA increased with more HA courses.

Keywords

hyaluronic acid, knee osteoarthritis, knee arthroplasty, intra-articular

Introduction

Knee osteoarthritis (OA) affects a large number of the population, contributing significantly to healthcare costs and leading to the rise of costlier surgical interventions, such as knee arthroplasty (KA). Today more than 50 million Americans have arthritis and about 43% of them have arthritis-attributable activity limitations.¹ By 2040, these numbers are projected to increase 49% to 78.4 million patients with arthritis (25% of all adults) and 52% to 34.6 million with arthritis-related limitations (11% of all adults). As of 2015, the prevalence of OA was estimated in 30.8 million adults. Knee OA is one of the leading causes of disability among noninstitutionalized elderly adults,² affecting an estimated 14 million individuals in the United States.¹ Knee OA contributes more than \$27 billion in health care expenditures annually.¹ Patients suffering from knee OA can show signs of severe pain with impaired activity, loss of work productivity, and quality of life.^{3–5} Annually, around 658,000 Americans undergo surgery for end-stage OA.¹ The rate of total knee replacements in many industrialized countries around the world has grown rapidly, with a 6.8%

historical compound annual growth rate in the United States.⁶ It has been estimated that the annual number of primary total knee replacement in the United States will exceed 1.3 million in 2020.⁷

Knee OA patients have the option to undergo intra-articular (IA) hyaluronic acid (HA) injection treatment; however, there is ongoing debate about its effectiveness.^{8–19} IA HA administration is intended to restore the decrease in HA concentration and average molecular weight distribution in the knee joint from OA progression.²⁰ It is believed that there are several mechanisms in which IA HA act on the structure and function of the knee. Chondroprotection is most frequently cited, whereby chondrocyte apoptosis is reduced, while chondrocyte proliferation is elevated.²⁰

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Enhanced proteoglycan and glycosaminoglycan synthesis and anti-inflammatory effects from suppression of interleukin-1 β expression are also commonly described mechanisms of action for HA treatment.

With questions being raised about the effectiveness of IA HA, we asked the following research questions: (1) What is the epidemiology of IA HA use in KA patients? (2) Is the use of IA Synvisc associated with a delay to KA? (3) Is there a difference in the delay to KA with the number of HA courses?

Methods

Study Design

This study used a retrospective, observational study design based on the Optum Clinformatics data from 2006 until the end of the second quarter of 2016. Patients with knee OA were identified based on whether they were coded with principal/secondary diagnosis code of knee OA (**Table A1** in the appendix). If patients were coded with nonspecific OA and knee pain, they were also included in the study.²¹ The first knee OA diagnosis was verified with a look-back period of 6 months with no prior knee OA diagnosis.

Study Cohort

The study cohort was limited to those aged at least 18 years. Patients were further limited to those who (1) had undergone KA (total knee arthroplasty [TKA] or unicompartmental knee arthroplasty [UKA]) and had at least 6 months of follow-up after knee OA diagnosis. Patients that had IA HA treatment prior to the knee OA diagnosis were excluded. Patients were then divided in 3 different cohorts: (1) no HA cohort who did not receive any IA HA following knee OA diagnosis; (2) non-Synvisc cohort who received either multiple types of HAs during the study period or who used only one type of non-Synvisc HA during the study period; and (3) Synvisc cohort who received only Synvisc HA (Sanofi US, Inc.).

After their diagnosis of knee OA, patients were identified for having used IA HA treatment based on the presence of Healthcare Common Procedure Coding System (HCPCS) Q and J codes for HA (**Table A1** in the appendix). Patients who subsequently received a KA were further identified based on the Current Procedure Terminology codes for KA (**Table A1** in the appendix). The KA patients were then stratified into those who received at least one IA HA (HA group) and those who did not (no HA group) before the KA.

Statistical Analysis

To evaluate the effect of the covariates on the median duration from knee OA to KA, a quantile regression model was

used, adjusting for the different clinical confounding factors. The use of median time rather than average time was due to the non-normal distribution of times to KA. Confounding factors, such as Charlson score, age, race, region (state), gender, treatment group, and year of knee OA diagnosis were evaluated. The time to HA and the number of HA injections were also included as covariates for the HA patients. The use of IA corticosteroid injection, prescription of nonsteroidal anti-inflammatory drug and opioid use (from pharmacy claims), knee arthroscopy, ultrasound/fluoroscopy use, or physical therapy (PT) use between the knee OA diagnosis and KA were also considered as confounding factors. These were identified using either HCPCS codes or brand names (**Table A2** in the appendix).

Since the baseline characteristics of treated subjects may differ systematically from those of untreated subjects, propensity score weighting was used to account for such differences, to minimize the confounding effects when using observational data, and to account for misspecification of the relationship between the risk factors and outcome.²² The propensity scores were estimate from the probability of receiving IA HA, conditional on covariates of the patient group mentioned above. The propensity scores were used to weight responses for each subject as an inverse measure to their probability of receiving treatment that the subject actually received. SAS, version 9.4 (SAS Institute Inc., Cary, NC), was used for all statistical analyses. The trend in time to KA for the HA cohort with each additional course of HA was also evaluated. Each course of injection was evaluated based on an interval of 3+ months between each IA HA use.

Results

Epidemiology of KA Cohort

From the initial cohort of 4,027,848 knee OA patients, 141,305 KA patients who met the inclusion/exclusion criteria were identified (**Fig. 1**). The distribution by the different treatments received are as follow: 104,145 patients (73.7%) without any HA injection; 22,523 patients (15.9%) who received at least 1 non-Synvisc HA injection; and 14,637 patients (10.4%) who received Synvisc HA injections. There was clear disparity between states of the distribution of KA patients who used HA (see **Fig. A1** in the appendix). The 3 states with the lowest percent of KA patients who used HA were Hawaii (14.5%), Indiana (16.3%), and Arkansas (16.7%), while the 3 states with the highest percent of KA patients who used HA were New Jersey (39.1%), Louisiana (33.9%), and Mississippi (31.8%). The total number of HA injections in the KA cohort ($n = 125,445$) during the time period considered in this study showed an increasing trend of annual utilization from 10,178 in the first full year of the study period (2007) to a peak in 2012 (n

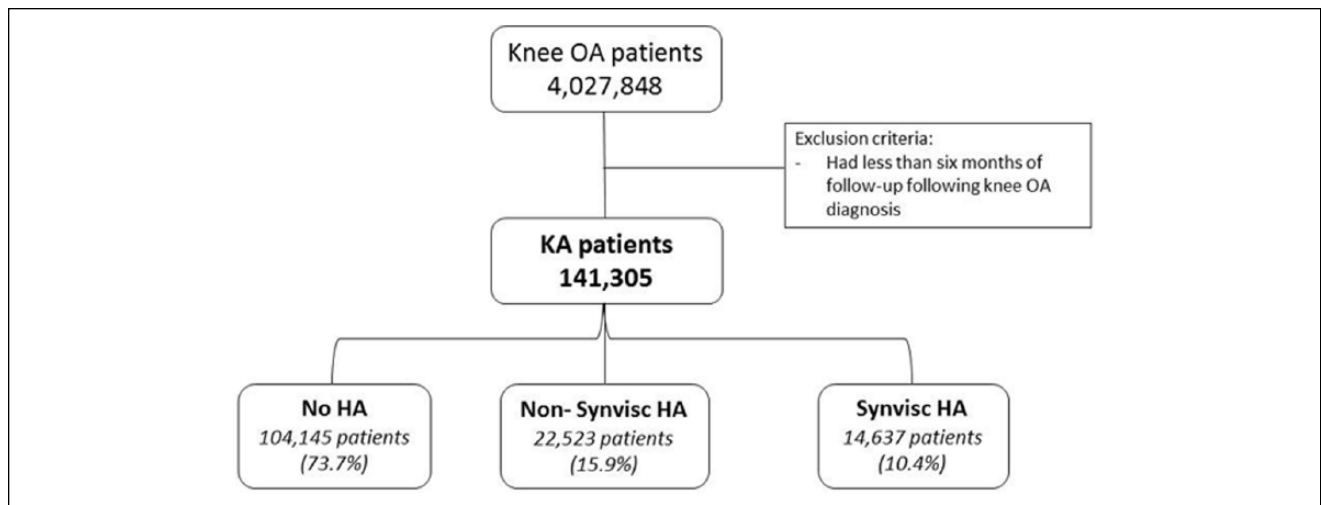


Figure 1. Study design. HA = hyaluronic acid; OA = osteoarthritis; KA = knee arthroplasty.

= 16,741), followed by decline in utilization to 9,223 in 2015. The prevalence of HA injections was higher in the 55- to 69-year age groups compared to the other age groups and slightly higher in the female population (**Fig. 2**). There was a large distribution of HA injections among white patients when compared with other races. In terms of comorbidity history, our results suggested that most patients presented none (0) or low (1-2) scores for their comorbid conditions before their knee OA diagnosis.

Delay to KA

The overall median time from the first knee OA diagnosis to KA was 1.2 years (average: 1.9 ± 1.9 years) with a corresponding interquartile (25th and 75th percentile) range of 0.4 to 2.8 years. The median times to KA were also longer for the HA cohort. The unadjusted median time to KA for the no HA, non-Synvisc, and Synvisc cohorts were 0.9 years (interquartile range [IQR] 25th to 75th percentile): 0.3-2.3 years), 2.1 years (IQR: 1.1-3.8 years), and 2.0 years (IQR: 1.0-3.7 years), respectively (**Fig. 3**). After propensity score adjustment, the quantile regression showed that HA patients had significantly longer median time to KA by at least 7 months ($P < 0.001$; Table 1). When the HA cohort was compared after adjusting for the time to HA and number of injections, a longer time was observed for Synvisc patients than non-Synvisc HA patients by close to 2 months ($P < 0.001$).

Number of HA courses

The majority of the KA patients received at least 1 course of HA injection (**Table 2**). There were still a large percentage of patients who underwent multiple courses of HA injections (25.6% of non-Synvisc HA patients, 19.7% of Synvisc

patients). There was a trend toward longer time to KA the more HA treatment courses the patient underwent (**Fig. 4**). For example, in the non-Synvisc HA group, the unadjusted median time to KA increase from 20 months (1.7 years) for those who had 1 treatment course to 61 months (5.1 years) for those who had five or more treatment courses. Similarly, the unadjusted median time to KA increased from 21 months (1.8 years) to 59 months (4.9 years) as patients in the Synvisc group increased their treatment courses from 1 to 5 or more.

Discussion

This study evaluated the delay to KA following IA HA injections using a large data set of patients of both young and elderly groups from Optum Clinformatics. Our analysis indicated that most of KA patients did not use HA injection (73.7%) and the ones that did receive it were associated with a longer median time to KA by at least 7 months. Such trend of longer time to KA was shown to increase with more HA courses.

Our data revealed that the majority of KA patients did not use HA, along with substantial regional variation in utilization in our KA cohort. There was a 2.7-fold difference between the state with the highest (New Jersey; 39.1%) and the state with the lowest (Hawaii; 14.5%) percent of KA patients who used HA. Yet, the regional disparity and relatively small proportion of KA patients who had not used HA provide an opportunity for more patients to potentially benefit from the promising results of an extended time to KA when receiving HA. The delay to KA suggests a possible benefit of using this kind of therapy, although causation cannot be proven with observational data. When compared to non-HA patients, the HA patients in this study exhibited an additional delay to KA of at least 7 months (median). In

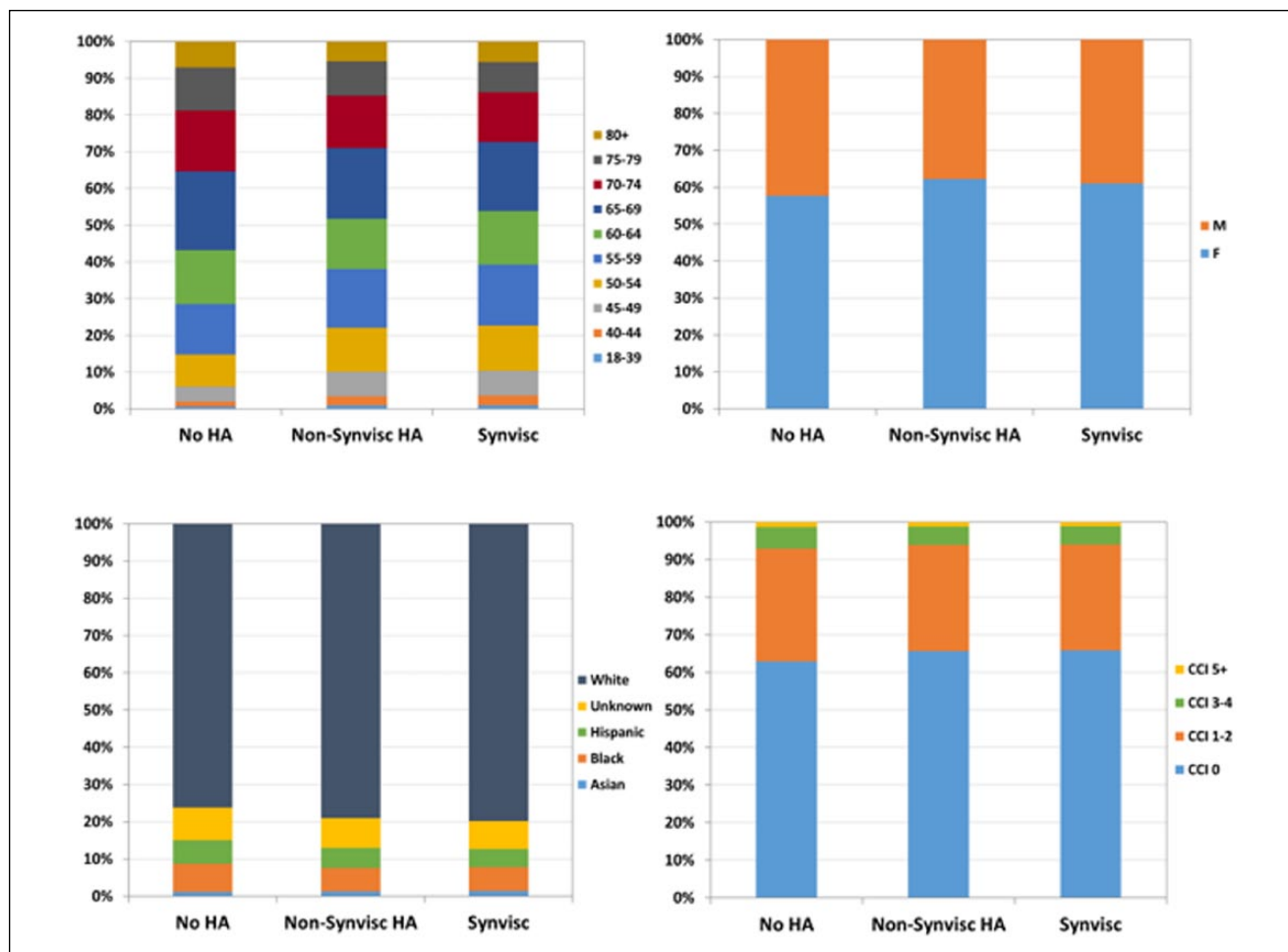


Figure 2. Distribution of age (top left), gender (top right), race (bottom left), and Charlson comorbidity index (bottom right) for each cohort. HA = hyaluronic acid; CCI = Charlson comorbidity index.

terms of actual time between knee OA and KA, our cohort of HA patients had median time to KA of about 2 years, while the non-HA patients had a time to KA of 0.9 years. This was consistent with the reported delay to KA of about 1.8 years for 225 KA patients treated with Synvisc.²³ Ong *et al.*²⁴ also found a delay to KA of 1.3 to 1.9 years in the elderly Medicare population, but only when IA-HA was used with corticosteroid therapy. Otherwise, the time to KA was 0.6 to 1.2 years for those elderly patients. Since the non-Synvisc HA cohort included a variety of HA products with different molecular weights and formulations, it is possible that the time to KA may be affected by these factors as shown in several studies. Berenbaum *et al.*²⁵ found that intermediate molecular weight HA might be superior to low molecular weight HA on knee OA symptoms over 6 months, with similar safety profiles. Similarly, Maheu *et al.*²⁶ described a slightly lower efficacy for low molecular weight preparations versus intermediate and high molecular weight HA, although they suggested further investigations were

needed. A recent meta-analysis by Altman *et al.*²⁷ also identified HA products with molecular weight of 3,000 kDa or more having superior efficacy. Despite the fact that preparations with high molecular weight have regularly shown a superior effect on relieving pain, according to the European League Against Rheumatism (EULAR) Recommendations²⁸ the management plan for knee OA patients has to be individualized and adjusted to the patient's response. Moreover, these studies have not compared the association between molecular weight and the delay to KA.

In our data set, a large percentage of the patients who underwent multiple courses of HA injection presented considerably longer times to KA. The beneficial effects of extended use of HA have also been reported in several studies, which corroborates with our results. In a systematic review on repeated treatment courses of SUPARTZ injections, it was shown that multiple courses were safer than the first course with lower adverse effect rates.²⁹ In a multicenter and randomized study on the efficacy and safety of

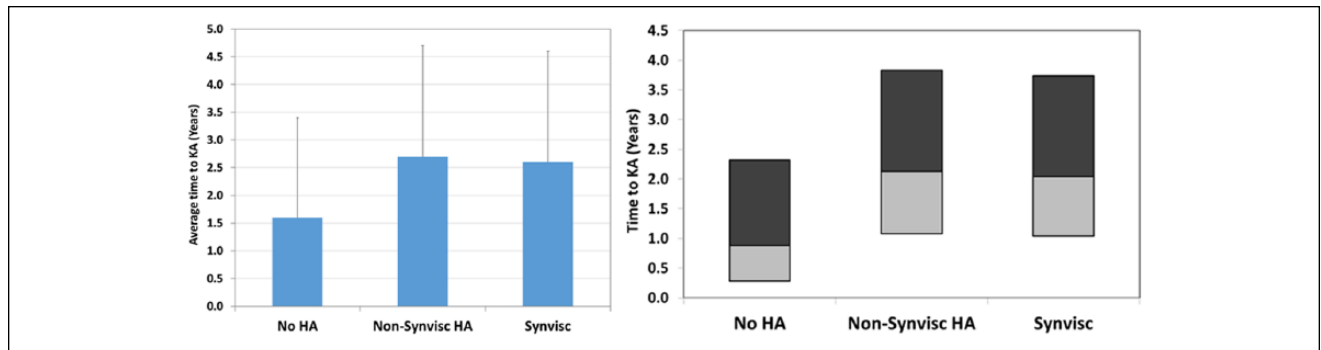


Figure 3. Average (left) and median (right; top and bottom of each bar corresponds to the 75th percentile and 25th percentile, respectively) time to knee arthroplasty (KA) for each cohort. HA = hyaluronic acid.

Table 1. Differences in Median Time to Knee Arthroplasty (KA).

Reference Group	Treatment Type	Quantile (Median; in Months)	
		Without Propensity Score	With Propensity Score
No HA	Non-Synvisc HA	7.60 (7.28 to 7.92), <0.001	7.77 (7.36 to 8.17), <0.001
	Synvisc HA	7.55 (7.14 to 7.95), <0.001	7.31 (6.90 to 7.71), <0.001
Non-Synvisc HA	Synvisc HA	0.05 (−0.37 to 0.46), 0.825	−0.29 (−0.83 to 0.26), 0.300
		1.95 ^a (1.72 to 2.17), <0.001	1.68 ^a (1.43 to 1.93), <0.001

HA = hyaluronic acid.

^aAdjusting for time to HA and number of injections.

Table 2. Distribution of Hyaluronic Acid (HA) Patients by the Number of HA Courses.

Patient Group	No. of HA Courses, n (%)				
	1	2	3	4	5+
Non-Synvisc HA	16,762 (74.4)	3,737 (16.6)	1,114 (4.9)	461 (2.0)	449 (2.0)
Synvisc	11,757 (80.3)	1,997 (13.6)	547 (3.7)	185 (1.3)	151 (1.0)

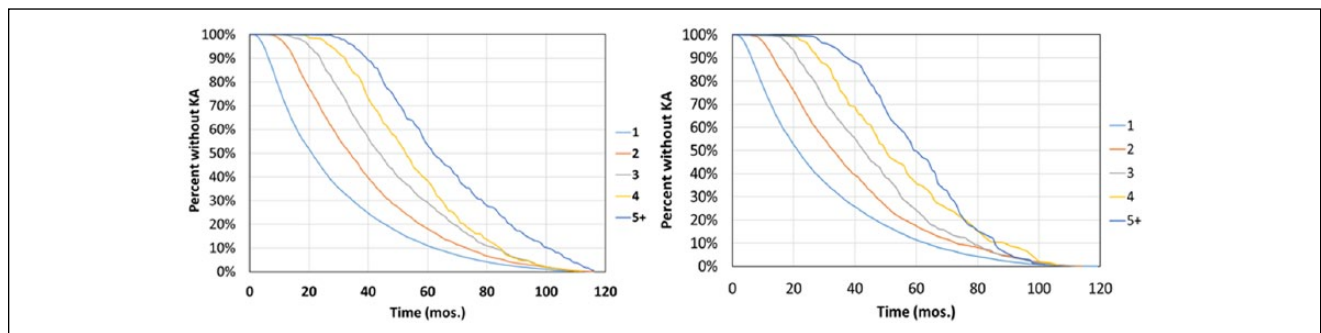


Figure 4. Kaplan-Meier curves with knee arthroplasty (KA) as the endpoint by the number of hyaluronic acid (HA) courses for the non-Synvisc HA cohort (left) and Synvisc cohort (right).

multiple injections of HA, it was shown that repeated cycles of IA HA injections improved the knee OA symptoms during the in-between cycle period for at least 1 year.³⁰

However, they could not demonstrate if such changes translated into true OA remission or a modification of the disease. A prospective cohort study evaluated the effectiveness

of repeated cycles of IA HA injections during a 54-month follow-up period, demonstrating the benefit in the function of delaying time to total knee replacement (TKR) and even reducing the number of these procedures in elderly population.³¹ The dose response was also observed by Altman *et al.*,³² who found that the median time to KA was 1.4 years following 1 course of HA, compared to 3.6 years following 5 or more HA courses.

Our study presents some limitations. The severity of OA was unknown in these patients due to the use of claims data. It is unclear to what extent the non-HA group might have more rapid evolution or more advanced disease compared with the HA groups. Our study focused on those who had KA to attempt to control for differences in baseline conditions and other potential confounding factors, including patient demographics, propensity score, and other clinical factors such as surgeon's decision, surgeon's availability, and patient access to care, and so on. The reasons to delay surgery are unknown for both the HA and non-HA groups due to the use of claims data. The cause-and-effect of HA use with the delay to KA cannot be examined due to the use of observational data, but this study, along with others, provides compelling data that HA use, especially with more courses of HA, may have beneficial effect in terms of delaying KA. Moreover, it is unclear if the increased delay to KA for the Synvisc HA group with more HA courses may be due to the therapy being used in patients with slower evolution of the disease. It is uncertain if the use of HA treatment slows down

the evolution of OA or if the slow evolution of the disease may allow repeated cycles of HA use. We also found that the Synvisc group had 1.7 months longer delay to KA compared to the non-Synvisc group after accounting for propensity score, time to HA and number of injections, but it is unclear if further stratification of the non-Synvisc group by molecular weight would continue to demonstrate similar differences. Additionally, the further delay of 1.7 months was statistically significant, its clinical significance is unclear. Because the research questions of our study centered around KA patients, we did not evaluate whether HA-treated patients were able to avoid KA. Despite such limitations, our data has the advantage of being from a real-world large sample size, which includes both young and elderly knee OA patients.

Conclusions

The association of HA injections, including those specific to Synvisc, with the delay to KA was evaluated in this study. We concluded that a substantial percentage of patients use other therapies prior to KA and it varied by state. We also found that the time to KA was longer for patients who used HA prior to surgery when compared with the ones who did not receive any injection. The time to KA was also longer for Synvisc than non-Synvisc patients, after adjusting for the time to HA and number of injections. The clinical significance of the delay to KA should continue to be investigated.

Appendix

Table A1. Procedure and Diagnosis Codes for Knee Osteoarthritis (OA), Hyaluronic Acid (HA), and Knee Arthroplasty (KA).

Primary/secondary knee OA diagnosis	ICD-9 code: 715.x6 ICD-10 code: M17.x
Primary/secondary nonspecific OA diagnosis	ICD-9 codes: 715.x8, 715.x9, 715.x0
Primary/secondary knee pain diagnosis	ICD-9 code: 719.46
Hyaluronic acid (HA)	Q3030, Q4083-Q4086, J7315-J7317, J7319-J7327, C9471, J7328 and Q9980. This also required the concurrent diagnosis codes of 711.x6 (ICD10: M00.06, M00.16, M00.26, M00.86, M02.36, M02.16, M02.06, M02.26, M02.86, M01.x6), 712.x6 (M11.86, M11.26, M11.16, M11.06), 716.x6 (M12.06, M12.16, M12.26, M12.36, M12.46, M12.56, M13.86, M12.86, M13.16), 717.x (M23), 718.x6 (M24.36, M24.46, M24.56, M24.66), 719.x6 (M25.26, M25.36, M25.46, M25.06, M25.76, M25.56, M25.66, M25.16, M25.86), 836.x (S83.0, S83.1, S83.2), 844.x (S83.4, S83.5, S83.6, S83.8, S83.9) to limit the injections to the knee joint.
Knee arthroplasty (KA)	27446, 27447

Table A2. HCPCS Codes or Brand Name for the Clinical Factors Considered.

Clinical Factor		CPT Code	
Physical therapy (PT) service	Range of motion/strength training	97110	
	Gait training	97116	
	Mechanical traction	97012, 97140, 97150	
	Electrical stimulation	97014, 97032	
	Hydrotherapy including aquatic therapy	97022, 97034, 97036, 97113	
	Vasopneumatic device use	97016	
	Ultrasound	97035	
	Neuromuscular re-education of movement and balance	97112	
	Therapeutic activities, use of dynamic activities	97530	
	PT services in home health setting	G0151	
Corticosteroids (CS)	J0702, J0704 (expired after Dec 31, 2010), J1020, J1030, J1040, J1094, J1100, J1700, J1710, J1720, J2650, J2920, J2930, J3300, J3301, J3302, and J3303 (only effective from Jan 1, 2009)		
Knee arthroscopy	29866 to 29868, 29870 to 29871, 29873 to 29877, 29879 to 29887, 29999, G0289		
Ultrasound/fluoroscopy	20611 (effective 2015 onward), 76942 or 77002 (have to be coded at same time/on same claim as HA injection)		
Clinical Factor		Brand Name	
Nonsteroidal anti-inflammatory drug (NSAID)	Celecoxib		
	Diclofenac		
	Etodolac		
	Fenoprofen		
	Flurbiprofen		
	Ibuprofen		
	Indomethacin		
	Ketoprofen		
	Ketorolac		
	Lecoprofen		
	Nabumetone		
Naproxen			
Oxaprozin			
Clinical Factor	Drug Name	Trade Name	
Opioid	Alfentanil hydrochloride or alfentanyl or alfentanil		
	Anileridine		
	Alphaprodine		
	Bromadol		
	Buprenorphine	Butrans, Belbuca, Buprenex	
	Butorphanol		
	Codeine		
	Dextropropoxyphene		
	Dihydroetorphine		
	Dihydrocodeine	Synalgos	
	Diamorphine		
	Etorphine		
	Fentanyl	Fentora, Lazanda, Subsys, Abstral, Actiq	
	Fentanyl citrate		
	Fentanyl patch (fentanyl transdermal system)	Duragesic	
	Heroin		
	Hydrocodone	Zohydro, Hysingla Vicoprofen	
	Hydrocodone bitartrate		
	Hydromorphone	Exalgo, Dilaudid	

(continued)

- and medical costs among working patients with knee osteoarthritis. *Arthritis Care Res (Hoboken)*. 2012;64(6):853-61.
4. Leardini G, Salaffi F, Caporali R, Canesi B, Rovati L, Montanelli R, *et al*. Direct and indirect costs of osteoarthritis of the knee. *Clin Exp Rheumatol*. 2004;22(6):699-706.
 5. Dibonaventura MD, Gupta S, McDonald M, Sadosky A. Evaluating the health and economic impact of osteoarthritis pain in the workforce: results from the National Health and Wellness Survey. *BMC Musculoskelet Disord*. 2011;12:83.
 6. Kurtz SM, Ong KL, Lau E, Widmer M, Maravic M, Gómez-Barrena E, *et al*. International survey of primary and revision total knee replacement. *Int Orthop*. 2011;35(12):1783-9.
 7. Kurtz SM, Ong KL, Lau E, Bozic KJ. Impact of the economic downturn on total joint replacement demand in the United States: updated projections to 2021. *J Bone Joint Surg Am*. 2014;96(8):624-30.
 8. Agency for Healthcare Research and Quality. Systematic review for effectiveness of hyaluronic acid in the treatment of severe degenerative joint disease (DJD) of the knee. 2015. Available from: https://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0084719/pdf/PubMedHealth_PMH0084719.pdf.
 9. Altman RD, Schemitsch E, Bedi A. Assessment of clinical practice guideline methodology for the treatment of knee osteoarthritis with intra-articular hyaluronic acid. *Semin Arthritis Rheum*. 2015;45(2):132-9.
 10. American Academy of Orthopaedic Surgeons. Treatment of osteoarthritis of the knee: evidence-based guideline, 2nd edition. 2013. Available from: <https://www.aaos.org/research/guidelines/TreatmentofOsteoarthritisoftheKneeGuideline.pdf>.
 11. Bannuru RR, Schmid CH, Kent DM, Vaysbrot EE, Wong JB, McAlindon TE. Comparative effectiveness of pharmacologic interventions for knee osteoarthritis: a systematic review and network meta-analysis. *Ann Intern Med*. 2015;162(1):46-54.
 12. Cheng OT, Souzdałnitski D, Vrooman B, Cheng J. Evidence-based knee injections for the management of arthritis. *Pain Med*. 2012;13(6):740-53.
 13. Colen S, van den Bekerom MP, Mulier M, Haverkamp D. Hyaluronic acid in the treatment of knee osteoarthritis: a systematic review and meta-analysis with emphasis on the efficacy of different products. *BioDrugs*. 2012;26(4):257-68.
 14. Evaniew N, Simunovic N, Karlsson J. Cochrane in CORR®: viscosupplementation for the treatment of osteoarthritis of the knee. *Clin Orthop Relat Res*. 2014;472(7):2028-34.
 15. Hochberg MC, Altman RD, April KT, Benkhalti M, Guyatt G, McGowan J, *et al*. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. *Arthritis Care Res (Hoboken)*. 2012;64(4):465-74.
 16. Ishijima M, Nakamura T, Shimizu K, Hayashi K, Kikuchi H, Soen S, *et al*. Intra-articular hyaluronic acid injection versus oral non-steroidal anti-inflammatory drug for the treatment of knee osteoarthritis: a multi-center, randomized, open-label, non-inferiority trial. *Arthritis Res Ther*. 2014;16(1):R18.
 17. McAlindon TE, Bannuru RR, Sullivan MC, Arden NK, Berenbaum F, Bierma-Zeinstra SM, *et al*. OARSI guidelines for the non-surgical management of knee osteoarthritis. *Osteoarthritis Cartilage*. 2014;22(3):363-88.
 18. Rodriguez-Merchan EC. Intra-articular injections of hyaluronic acid (viscosupplementation) in the haemophilic knee. *Blood Coagul Fibrinolysis*. 2012;23(7):580-3.
 19. Trigkilidas D, Anand A. The effectiveness of hyaluronic acid intra-articular injections in managing osteoarthritic knee pain. *Ann R Coll Surg Engl*. 2013;95(8):545-51.
 20. Altman RD, Manjoo A, Fierlinger A, Niazi F, Nicholls M. The mechanism of action for hyaluronic acid treatment in the osteoarthritic knee: a systematic review. *BMC Musculoskelet Disord*. 2015;16:321.
 21. Wright EA, Katz JN, Cisternas MG, Kessler CL, Wagenseller A, Losina E. Impact of knee osteoarthritis on health care resource utilization in a US population-based national sample. *Med Care*. 2010;48(9):785-91.
 22. Inacio MC, Chen Y, Paxton EW, Namba RS, Kurtz SM, Cafri G. Statistics in brief: an introduction to the use of propensity scores. *Clin Orthop Relat Res*. 2015;473(8):2722-6.
 23. Waddell DD, Bricker DC. Total knee replacement delayed with Hylan G-F 20 use in patients with grade IV osteoarthritis. *J Manag Care Pharm*. 2007;13(2):113-21.
 24. Ong KL, Anderson AF, Niazi F, Fierlinger AL, Kurtz SM, Altman RD. Hyaluronic acid injections in Medicare knee osteoarthritis patients are associated with longer time to knee arthroplasty. *J Arthroplasty*. 2016;31(8):1667-73.
 25. Berenbaum F, Grifka J, Cazzaniga S, D'Amato M, Giacobelli G, Chevalier X, *et al*. A randomised, double-blind, controlled trial comparing two intra-articular hyaluronic acid preparations differing by their molecular weight in symptomatic knee osteoarthritis. *Ann Rheum Dis*. 2012;71(9):1454-60.
 26. Maheu E, Rannou F, Reginster JY. Efficacy and safety of hyaluronic acid in the management of osteoarthritis: Evidence from real-life setting trials and surveys. *Semin Arthritis Rheum*. 2016;45(4 Suppl):S28-33.
 27. Altman RD, Bedi A, Karlsson J, Sancheti P, Schemitsch E. Product differences in intra-articular hyaluronic acids for osteoarthritis of the knee. *Am J Sports Med*. 2016;44(8):2158-65.
 28. Jordan KM, Arden NK, Doherty M, Bannwarth B, Bijlsma JW, Dieppe P, *et al*. EULAR recommendations 2003: an evidence based approach to the management of knee osteoarthritis: Report of a Task Force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT). *Ann Rheum Dis*. 2003;62(12):1145-55.
 29. Bannuru RR, Brodie CR, Sullivan MC, McAlindon TE. Safety of repeated injections of sodium hyaluronate (SUPARTZ) for knee osteoarthritis: a systematic review and meta-analysis. *Cartilage*. 2016;7(4):322-32.
 30. Navarro-Sarabia F, Coronel P, Collantes E, Navarro FJ, de la Serna AR, Naranjo A, *et al*. A 40-month multicentre, randomised placebo-controlled study to assess the efficacy and carry-over effect of repeated intra-articular injections of hyaluronic acid in knee osteoarthritis: the AMELIA project. *Ann Rheum Dis*. 2011;70(11):1957-62.
 31. Turajane T, Amphansap T, Labpiboonpong V, Maungsiri S. 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. *J Med Assoc Thai*. 2009;92(Suppl 6):S63-8.
 32. Altman R, Lim S, Steen RG, Dasa V. Hyaluronic acid injections are associated with delay of total knee replacement surgery in patients with knee osteoarthritis: evidence from a large US Health Claims Database. *PLoS One*. 2015;10(12):e0145776.