

Utilization of Hyaluronate and Incidence of Septic Knee Arthritis in Adults: Results from the Korean National Claim Registry

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Background: Septic arthritis of the knee has been reported recently in adult patients who were administered hyaluronate. We evaluated the incidence of septic knees and the utilization of hyaluronate in the Korean adult population using nationwide data from the Health Insurance Review and Assessment Service (HIRA).

Methods: All new admissions to the clinics or hospitals for septic knees were recorded in the HIRA database which was established by the Korean government and covers the Korean population using the International Classification of Diseases-10 revision code. We evaluated the incidence of septic arthritis of the knees in the population above 50 years of age. Hyaluronate prescription data was also collected from the HIRA database.

Results: In 2012, the incidence of septic knees was 2.7 per 100,000 persons in men and 4.2 per 100,000 persons in women, respectively. The age-adjusted incidence of septic knees increased by 6.7% per year (95% confidence interval, 3.3 to 10.1), and the annual number of prescriptions of hyaluronate increased about 1.5-fold during the study period.

Conclusions: Cautious aseptic technique is required when hyaluronate is administered in adult patients with osteoarthritis of the knee due to the concerns of the risk of septic arthritis.

Keywords: *Septic, Arthritis, Hyaluronic acid, Knee*

Septic arthritis is a serious orthopedic disease that is associated with severe adverse effects such as osteomyelitis, joint destruction, ankylosis, sepsis and death.¹⁻³⁾ Septic arthritis can occur in people of any age group, from newborns to the senile population.^{1,2)} In adults, the most commonly affected joint is the knee joint, and osteoarthritis also commonly occurs in the knee joint.⁴⁻⁷⁾ Although some studies reported that the incidence of septic arthritis ranged from 1.6% to 9.2%, using the regional or hospital-based data-

base,⁴⁻⁷⁾ there are few studies on the nationwide incidence of septic arthritis of the knee in adults.⁸⁾

Intra-articular injections are a recommended treatment option for management of osteoarthritis according to several international guidelines.⁹⁻¹¹⁾ The use of intra-articular hyaluronate injections has increased in elderly patients with osteoarthritis.¹²⁾ Physicians commonly use intra-articular injections in symptomatic patients with mild osteoarthritis of the knee because the superficial knee joint can be easily accessed without any assistive device such as ultrasound and fluoroscopy. Although the efficacy of hyaluronate injections has been well-documented, septic arthritis has also been a concern associated with the frequent use of hyaluronate.¹³⁾ Population aging is also prominent in East Asia, reflected by a high prevalence of osteoarthritis.¹⁴⁾ Accordingly, the use of hyaluronate for the

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management of osteoarthritis is increasing in East Asia.^{15,16)} However, an epidemiologic study on the incidence of septic knee and the utilization of hyaluronate in East Asia has not been conducted. Considering the low incidence of septic arthritis of the knees, the nationwide database appears to be useful and provides sufficient statistical power. Our hypothesis was that the trends of incidence of septic knees were similar to that of the utilization of hyaluronate in the elderly Korean population.

The purpose of this study was to evaluate trends in the incidence of septic knees and compare these with the utilization of hyaluronate in the Korean population from 2008 to 2012, using nationwide data from the Health Insurance Review and Assessment Service (HIRA).

METHODS

The data on the utilization of hyaluronate and the incidence of septic arthritis of the knee was retrieved from the HIRA between 2008 and 2012. In Korea, 97.0% of the population is obliged to enroll in the Korean National Health Insurance Program. Patients pay around 30% of the total medical costs to the clinics or hospitals; however, some medical services are not covered by insurance, such as cosmetic surgery and some unproven therapies. The clinics and hospitals then submit the claims for inpatient and outpatient care, including data on diagnoses (as determined by the International Classification of Diseases, 10 revision [ICD-10]), procedures, prescription records, and demographic information to obtain reimbursement for 70% of the total medical costs. The remaining 3% of the population that is uninsured by the Korean National Health Insurance Program, is either covered by another Medical Aid Program or are temporary or illegal residents. These claims are also reviewed by HIRA that was established by the Korean government, and nearly all information about the patients and their medical records can be obtained from the Korean HIRA database, which has been used in several earlier epidemiological studies.¹⁷⁻²⁰⁾

Data regarding hyaluronate prescription and the number of prescriptions was abstracted and collated. The utilization of hyaluronate was determined from the annual number of prescriptions of hyaluronate.

Patients with septic knees essentially require hospitalization for surgical intervention, and these data are recorded prospectively in nationwide cohort using ICD-10 codes, as described above. To identify septic knees in adults, selected ICD-10 codes (ICD-10 M0006 and M0016) and a minimum cut-off value of 50 years were used.²¹⁾ To exclude prevalent patients who visited outpa-

tients clinics, only hospitalizations were included in the study. To determine trends in the incidence of septic knee, the patients were categorized by age (subdivided into 5-year increments) and gender. Age-adjusted and gender-specific incidence rates (per 100,000 persons) were calculated using the respective annual population. The number of men and women above 50 years of age was obtained from the Statistics Korea web site (<http://www.kosis.kr>), the official web site of the Central Government Organization for Statistics.²²⁾ The changes in incidence of septic knee from 2008 to 2012 were calculated using annual percentage change for trends (Joinpoint Regression Program ver. 3.5.2, Statistical Research and Applications Branch, National Cancer Institute, Bethesda, MD, USA). To obtain age-adjusted and gender-specific incidence, the Korean population in 2011 was used as a standard population. Age-adjusted and gender-specific incidences from 2008 to

Table 1. Absolute No. and Age-Adjusted and Gender-Specific Incidences (per 100,000 Persons) of Septic Knees in the Korean Population above 50 Years of Age

Variable	No. of septic knees	Incidence of septic knees	Age-adjusted incidence of septic knees*
Man			
2008	124	2.06	2.07
2009	137	2.17	2.18
2010	167	2.52	2.53
2011	171	2.46	2.46
2012	196	2.69	2.68
Woman			
2008	229	3.24	3.21
2009	252	3.41	3.39
2010	294	3.81	3.81
2011	310	3.86	3.86
2012	350	4.18	4.17
Total			
2008	353	5.30	5.29
2009	389	5.58	5.57
2010	461	6.34	6.33
2011	481	6.32	6.32
2012	546	6.87	6.85

*Age-adjusted to the Korean population in 2011.

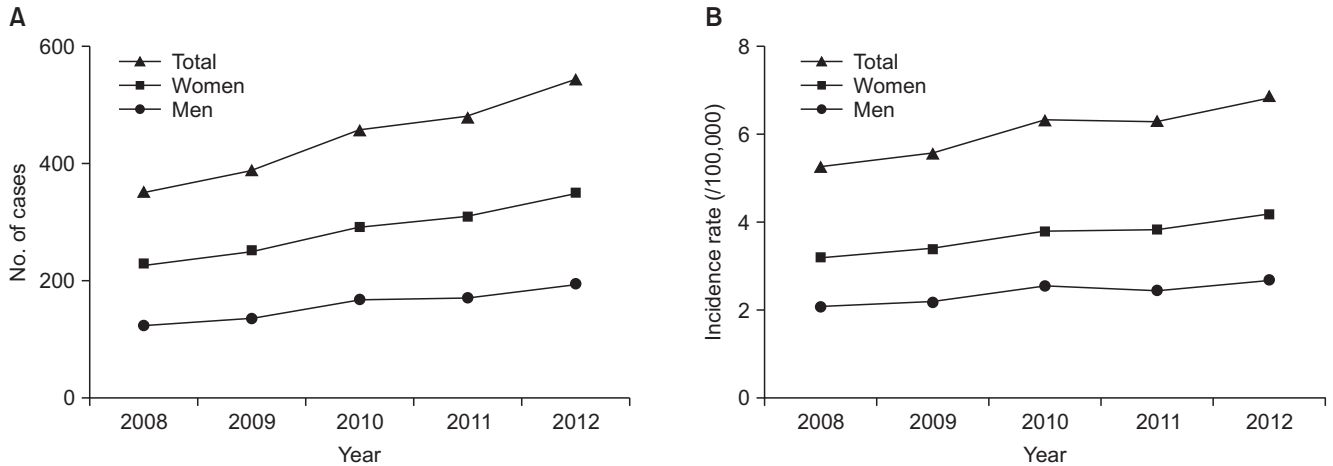


Fig. 1. The number of septic knees (A) and the age-adjusted incidence of septic knees (B) in the population above 50 years of age from 2008 to 2012.

Table 2. Annual Percentage Change (95% Confidence Interval) in Age-Adjusted and Gender-Specific Incidences of Septic Knees from 2008 to 2012

Gender	Annual percentage change (%)*	95% Confidence interval
Man	6.6	2.1–11.2
Woman	6.7	4.2–9.3
Total	6.7	3.3–10.1

* $p < 0.05$.

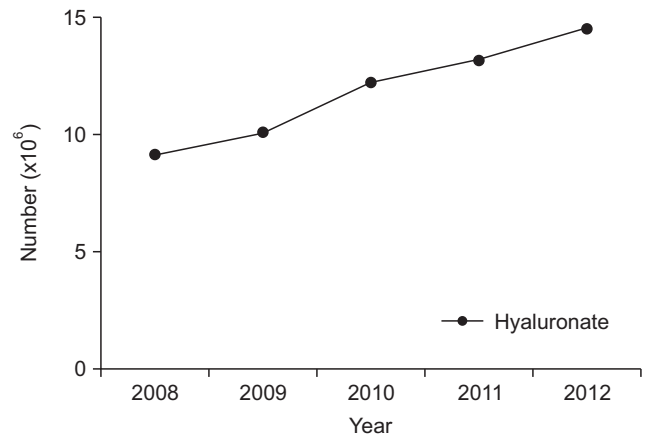


Fig. 2. The number of prescriptions of hyaluronate from 2008 to 2012.

2012 were used in the analysis. Statistical results were presented as 95% confidence interval (CI). Because the data used is available to the public, only the de-identified information was used in the present study. The study protocol was approved by the HIRA Institutional Review Boards.

RESULTS

In 2012, among the population aged 50 years or older, the crude overall incidences of septic knees were 2.7 per 100,000 persons in men and 4.2 per 100,000 persons in women, respectively (Table 1). The absolute number of septic knees increased during the study period (Fig. 1). The age-adjusted incidence of septic knee increased by 6.7% per year (95% CI, 3.3 to 10.1) (Table 2 and Fig. 1). In addition, over the 5-year study period, the annual number of prescriptions of hyaluronate increased about 1.5-fold (Fig. 2).

DISCUSSION

This study showed that the incidence of septic knees signi-

ficantly increased in the Korean population aged 50 years or older, while the annual utilization of hyaluronate increased approximately 1.5-fold from 2008 to 2012.

This finding concurs with the results of an epidemiologic study conducted in Iceland, where the incidence of septic arthritis increased significantly in adults over 12 years.⁸⁾ They reported that interventions such as arthroscopy and joint injections were the main causes of increased incidence of septic arthritis in Iceland.⁸⁾ Although the study included other joints such as the shoulder and hip joint, the knee joint was the most commonly affected joint in that study. The present study was performed over a period of 5 years because the HIRA limited the study period to a maximum of 5 years. However, this is the first epidemiologic study on the incidence of septic arthritis of the knee and the utilization of hyaluronate in East Asia.

We cannot directly compare the incidence of septic arthritis of the knee in Korea with that of other countries because the incidence of septic knee varies according to

Table 3. Comparison of Annual Incidence (per 100,000) of Septic Arthritis among Different Populations

Study	Region	Study period	Age (yr)	Incidence
Morgan et al. ⁶⁾	Australia	1976–1994	All ages	9.2
Kaandorp et al. ⁵⁾	The Netherlands	1990–1993	All ages	5.7
Weston et al. ⁷⁾	The United Kingdom	1982–1991	All ages	2.6
Gupta et al. ⁴⁾	Scotland	1997–1999	> 16	1.6
Geirsson et al. ⁸⁾	Iceland	1990–2002	All ages	7.1
Al Arfaj ²³⁾	Saudi Arabia	2005–2006	All ages	2.1
Present study	Korea	2012	> 50	6.9*

*Only knee joints were included.

the definition of septic arthritis used (Table 3).^{4-8,23)}

A previous community-based survey study in the Netherlands indicated an incidence of 5.7 per 100,000 persons among culture positive cases or cases in which microorganisms in the synovial fluid or tissue were identified.^{5,24)} The entire population was included in that study, but we included only the adult population above 50 years of age. We included the patients who were clinically diagnosed with septic knee by using the ICD-10 code. Generally, the incidence of culture-proven septic arthritis is lower than that of clinically-diagnosed septic arthritis because the yield of culture is below 100%. In addition, we could not exclude the possibility of duplicate case due to recurrence and readmission because we used the de-identified data from the HIRA database. These could be some of the possible reasons for the higher incidence of septic knee arthritis in Korea, as compared to those in other countries (Table 3).

This study has several limitations. First, information regarding the other risk factors for septic knee (e.g., diabetes, malignancy, and immune-compromised) was not available at an individual level because this study was based on the de-identified database. Second, because we used de-identified codes and the number of prescriptions, we could not determine the amount of hyaluronate prescribed on an individual level, although the frequency of hyaluronate administration is likely to be associated with the occurrence of septic knee.^{13,25,26)} Generally, hyaluronate was injected

several times for viscosupplementation. Third, we included hyaluronate, but we did not include other injectates such as local anesthetics and corticosteroid. However, local anesthetics and corticosteroid are indicated in many other conditions. Fourth, we did not include the prescription of hyaluronate for other joints such as the shoulder and hip joints. However, the most commonly affected joint was the knee joint.^{4-8,23)} Finally, we cannot exclude the possibility of duplicate cases because we used de-identified data.

Despite of these limitations, this is the first epidemiologic study to report the nationwide incidence of septic knee and the utilization of hyaluronate in East Asia. Because of the increasing concerns of the risk of septic arthritis, we suggest a cautious aseptic technique and informing patients of the risk of septic arthritis when hyaluronate is administered for viscosupplementation.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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REFERENCES

1. Lee SC, Shim JS, Seo SW, Lee SS. Prognostic factors of septic arthritis of hip in infants and neonates: minimum 5-year follow-up. *Clin Orthop Surg*. 2015;7(1):110-9.
2. Mathews CJ, Weston VC, Jones A, Field M, Coakley G. Bacterial septic arthritis in adults. *Lancet*. 2010;375(9717):846-55.

3. Matthews PC, Dean BJ, Medagoda K, et al. Native hip joint septic arthritis in 20 adults: delayed presentation beyond three weeks predicts need for excision arthroplasty. *J Infect.* 2008;57(3):185-90.
4. Gupta MN, Sturrock RD, Field M. A prospective 2-year study of 75 patients with adult-onset septic arthritis. *Rheumatology (Oxford).* 2001;40(1):24-30.
5. Kaandorp CJ, Dinant HJ, van de Laar MA, Moens HJ, Prins AP, Dijkmans BA. Incidence and sources of native and prosthetic joint infection: a community based prospective survey. *Ann Rheum Dis.* 1997;56(8):470-5.
6. Morgan DS, Fisher D, Merianos A, Currie BJ. An 18 year clinical review of septic arthritis from tropical Australia. *Epidemiol Infect.* 1996;117(3):423-8.
7. Weston VC, Jones AC, Bradbury N, Fawthrop F, Doherty M. Clinical features and outcome of septic arthritis in a single UK Health District 1982-1991. *Ann Rheum Dis.* 1999;58(4):214-9.
8. Geirsson AJ, Statkevicius S, Vikingsson A. Septic arthritis in Iceland 1990-2002: increasing incidence due to iatrogenic infections. *Ann Rheum Dis.* 2008;67(5):638-43.
9. McAlindon TE, Bannuru RR. OARSI recommendations for the management of hip and knee osteoarthritis: the semantics of differences and changes. *Osteoarthritis Cartilage.* 2010;18(4):473-5.
10. Richmond J, Hunter D, Irrgang J, et al. American Academy of Orthopaedic Surgeons clinical practice guideline on the treatment of osteoarthritis (OA) of the knee. *J Bone Joint Surg Am.* 2010;92(4):990-3.
11. Zhang W, Nuki G, Moskowitz RW, et al. OARSI recommendations for the management of hip and knee osteoarthritis: part III: changes in evidence following systematic cumulative update of research published through January 2009. *Osteoarthritis Cartilage.* 2010;18(4):476-99.
12. Evanich JD, Evanich CJ, Wright MB, Rydlewicz JA. Efficacy of intraarticular hyaluronic acid injections in knee osteoarthritis. *Clin Orthop Relat Res.* 2001;(390):173-81.
13. Charalambous CP, Tryfonidis M, Sadiq S, Hirst P, Paul A. Septic arthritis following intra-articular steroid injection of the knee: a survey of current practice regarding antiseptic technique used during intra-articular steroid injection of the knee. *Clin Rheumatol.* 2003;22(6):386-90.
14. Inoue K, Hukuda S, Fardellon P, et al. Prevalence of large-joint osteoarthritis in Asian and Caucasian skeletal populations. *Rheumatology (Oxford).* 2001;40(1):70-3.
15. Huang TL, Chang CC, Lee CH, Chen SC, Lai CH, Tsai CL. Intra-articular injections of sodium hyaluronate (Hyalgan(R)) in osteoarthritis of the knee: a randomized, controlled, double-blind, multicenter trial in the Asian population. *BMC Musculoskelet Disord.* 2011;12:221.
16. Lai HY, Chen YC, Chen TJ, Chou LF, Chen LK, Hwang SJ. Intra-articular hyaluronic acid for treatment of osteoarthritis: a nationwide study among the older population of Taiwan. *BMC Health Serv Res.* 2008;8:24.
17. Kim SH, Ko YB, Lee YK, et al. National utilization of calcium supplements in patients with osteoporotic hip fracture in Korea. *J Bone Metab.* 2013;20(2):99-103.
18. Lee YK, Ha YC, Park C, Yoo JJ, Shin CS, Koo KH. Bisphosphonate use and increased incidence of subtrochanteric fracture in South Korea: results from the National Claim Registry. *Osteoporos Int.* 2013;24(2):707-11.
19. Lee YK, Jang S, Jang S, et al. Mortality after vertebral fracture in Korea: analysis of the National Claim Registry. *Osteoporos Int.* 2012;23(7):1859-65.
20. Park C, Ha YC, Jang S, Jang S, Yoon HK, Lee YK. The incidence and residual lifetime risk of osteoporosis-related fractures in Korea. *J Bone Miner Metab.* 2011;29(6):744-51.
21. Kim I, Kim HA, Seo YI, Song YW, Jeong JY, Kim DH. The prevalence of knee osteoarthritis in elderly community residents in Korea. *J Korean Med Sci.* 2010;25(2):293-8.
22. Korean Statistical Information Service [Internet]. Daejeon: Statistics Korea; c2014 [cited 2015 May 30]. Available from: <http://kosis.kr/>.
23. Al Arfaj AS. A prospective study of the incidence and characteristics of septic arthritis in a teaching hospital in Riyadh, Saudi Arabia. *Clin Rheumatol.* 2008;27(11):1403-10.
24. Newman JH. Review of septic arthritis throughout the antibiotic era. *Ann Rheum Dis.* 1976;35(3):198-205.
25. Morshed S, Huffman GR, Ries MD. Septic arthritis of the hip and intrapelvic abscess following intra-articular injection of hylan G-F 20: a case report. *J Bone Joint Surg Am.* 2004;86(4):823-6.
26. Shemesh S, Heller S, Salai M, Velkes S. Septic arthritis of the knee following intraarticular injections in elderly patients: report of six patients. *Isr Med Assoc J.* 2011;13(12):757-60.