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# Comparison of Infection Risk with Corticosteroid or Hyaluronic Acid Injection Prior to Total Knee Arthroplasty

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**Background:** Recent studies have shown that intra-articular injections  $\leq 3$  months before total knee arthroplasty increase the risk of periprosthetic joint infection. We are aware of no previous study that has differentiated the risk of periprosthetic joint infection on the basis of the type of medication injected. In addition, we are aware of no prior study that has evaluated whether hyaluronic acid injections increase the risk of infection after total knee arthroplasty. In this study, we utilized pharmaceutical data to compare patients who received preoperative corticosteroid or hyaluronic acid injections and to determine whether a specific injection type increased the risk of periprosthetic joint infection.

**Methods:** Patients undergoing unilateral primary total knee arthroplasty were selected from a nationwide private insurer database. Ipsilateral preoperative injections were identified and were grouped by medication codes for corticosteroid or hyaluronic acid. Patients who had received both types of injections  $\leq 1$  year before total knee arthroplasty were excluded. The outcome of interest was periprosthetic joint infection that occurred  $\leq 6$  months following the total knee arthroplasty. The risk of periprosthetic joint infection was compared between groups (no injection, corticosteroid, hyaluronic acid) and between patients who received single or multiple injections. Statistical comparisons were performed using logistic regression controlling for age, sex, and comorbidities.

**Results:** A total of 58,337 patients underwent total knee arthroplasty during the study period; 3,249 patients (5.6%) received hyaluronic acid and 16,656 patients (28.6%) received corticosteroid  $\leq 1$  year before total knee arthroplasty. The overall infection rate was 2.74% in the no-injection group. Multivariable logistic regression showed independent periprosthetic joint infection risk for both corticosteroid (odds ratio [OR], 1.21;  $p = 0.014$ ) and hyaluronic acid (OR, 1.55;  $p = 0.029$ ) given  $\leq 3$  months before total knee arthroplasty. There was no increased risk with injections  $> 3$  months prior to total knee arthroplasty. Direct comparison of corticosteroid and hyaluronic acid showed no significant difference ( $p > 0.05$ ) between medications or between single and multiple injections.

**Conclusions:** Preoperative corticosteroid or hyaluronic acid injection  $\leq 3$  months before total knee arthroplasty increased the risk of periprosthetic joint infection. There was no difference in infection risk between medications or between multiple and single injections. On the basis of these data, we recommend avoiding both injection types in the 3 months prior to total knee arthroplasty.

**Level of Evidence:** Therapeutic Level III. See Instructions for Authors for a complete description of levels of evidence.

**N**onoperative management of knee osteoarthritis often includes therapeutic injections. Many different types of injections exist, including corticosteroid, hyalur-

onic acid, platelet-rich plasma, and others. The goal of these injections is to control patient symptoms and, in cases of more advanced osteoarthritis, to delay the need for a surgical

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procedure<sup>1,2</sup>. A large body of evidence exists with regard to the efficacy of many types of injections, often with contradictory conclusions as to whether the injections provide any meaningful clinical benefit to patients<sup>3-11</sup>.

In addition to the lack of clear evidence with regard to the efficacy of these injections, conflicting evidence exists with regard to their safety in the preoperative period<sup>3,12-16</sup>. Multiple large retrospective cohort studies have attempted to determine whether intra-articular injections prior to total knee arthroplasty increase the risk of periprosthetic joint infection postoperatively; some have discovered an increase in infection rate if injections were given in proximity to the surgical procedure<sup>3,13,16</sup>, and others showed no difference<sup>12,14,15</sup>. A similar controversy exists with respect to injections and periprosthetic joint infection risk prior to total hip arthroplasty<sup>17-21</sup>. For both hip and knee corticosteroid injections, it has been postulated that any increase in periprosthetic joint infection risk is due to the immunosuppressive effect of corticosteroids and/or from direct inoculation of the joint from the injection procedure.

Prior large-scale studies have relied on a generic Current Procedural Terminology (CPT) injection code that does not identify the medication given in the injection. This is a major flaw, especially given that immunosuppression from corticosteroids is one of the leading explanations for increased periprosthetic joint infection risk. Furthermore, this code may represent a joint aspiration rather than injection, potentially indicating physician concern for infection. In these cases, it would be unlikely for a physician to give corticosteroid or hyaluronic acid at the time of aspiration, but the CPT coding remains identical. The medication administered must be examined to accurately determine the impact of specific injections on postoperative infection risk. We are aware of no prior study that has evaluated whether hyaluronic acid injections increase the risk of infection after total knee arthroplasty. In this study, pharmaceutical data were utilized to determine whether a specific injection type (corticosteroid or hyaluronic acid) given in the

preoperative period prior to total knee arthroplasty increased the risk of periprosthetic joint infection postoperatively.

## Materials and Methods

### Patient Selection

Subjects were identified in the PearlDiver Patient Records Database ([www.pearldiverinc.com](http://www.pearldiverinc.com)), a nationwide health insurance-derived database. The Humana full claims database was queried, representing over 20.9 million patients. All patients who underwent unilateral primary total knee arthroplasty between 2007 and 2016 and were active in the insurance plan for the year prior to and 6 months after the total knee arthroplasty were included on the basis of the appropriate CPT procedure code (27447). CPT codes were preferred over International Classification of Diseases (ICD) codes, as CPT codes contain laterality information.

### Injections

Ipsilateral preoperative injections  $\leq 1$  year prior to total knee arthroplasty were identified by the appropriate CPT code (20610) associated with a knee-related ICD-9 or ICD-10 diagnosis code. The medication utilized in the injection (corticosteroid or hyaluronic acid) was determined using a number of Healthcare Common Procedure Coding System (HCPCS) J or Q codes (see Appendix). The laterality of injections and of the subsequent total knee arthroplasty were confirmed using CPT laterality modifiers. To simplify the comparison, patients who had received both types of injections  $\leq 1$  year before total knee arthroplasty were excluded. The cohort whose most recent injection was  $\leq 3$  months prior to the total knee arthroplasty was further subdivided on the basis of the number of injections (single compared with multiple) received  $\leq 3$  months prior to the surgical procedure.

### Outcomes

Age and demographic information were recorded for all patients (Table I). Comorbidities were identified using ICD-9 and ICD-10

TABLE I Demographic Characteristics \*

	No Injection (N = 38,432)	Hyaluronic Acid $\leq 3$ Months (N = 646)	P Value	Corticosteroid $\leq 3$ Months (N = 6,653)	P Value
Age			0.255		<0.001†
<50 years	1.31%	<1.7%		1.28%	
50 to 59 years	8.28%	8.20%		7.86%	
60 to 69 years	31.21%	26.93%		29.61%	
70 to 79 years	46.21%	48.92%		46.08%	
80 to 89 years	11.63%	12.54%		13.51%	
$\geq 90$ years	1.37%	1.86%		1.65%	
Sex			0.663		<0.001†
Female	61.68%	60.84%		65.97%	
Male	38.32%	39.16%		34.03%	

\*A comparison of the age and sex for patients who received no injection and those who received corticosteroid or hyaluronic acid  $\leq 3$  months before total knee arthroplasty. A comparison of comorbidities between these groups can be found in the Appendix. †Significant.

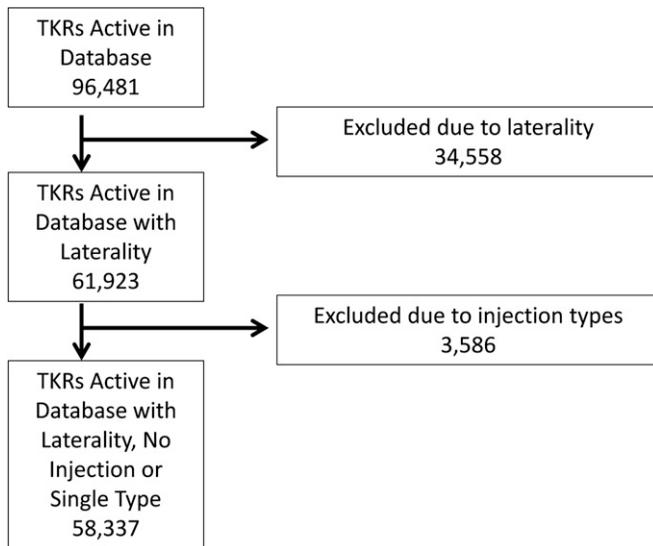


Fig. 1

Flowchart showing patient inclusion and exclusion. The initial cohort included all patients in the database undergoing total knee replacement (TKR) who were active in the database 1 year prior to and 6 months after TKR. Patients were subsequently excluded if no laterality was coded. Patients were then excluded if they received both corticosteroid and hyaluronic acid injections within the preoperative period or if the injections that they received did not include either medication type.

codes<sup>22</sup> as previously described by Elixhauser et al.<sup>23</sup>. Periprosthetic joint infection was defined via appropriate ICD-9, ICD-10, and CPT diagnosis and procedure codes within the first 6 months following the total knee arthroplasty (see Appendix). Patients were tracked longitudinally for 6 months after the total knee arthroplasty to determine whether they were diagnosed with or underwent a procedure related to periprosthetic joint infection.

### Statistical Analysis

Patients included in the study were subdivided on the basis of the timing of their most recent corticosteroid or hyaluronic acid injection or into a control group that had received no injection  $\leq 1$  year before the total knee arthroplasty. The rate of periprosthetic joint infection was compared between patients in each injection group and patients who had received no injection. Using chi-square tests, demographic and comorbidity data were compared between the group receiving no injection, the group receiving hyaluronic acid  $\leq 3$  months preoperatively, and the group receiving corticosteroid  $\leq 3$  months preoperatively. Multivariate logistic regression was then performed to determine the odds of infection based on the type and timing of the most recent injection. A separate multivariate logistic regression including only patients who had received an injection  $\leq 3$  months before the total knee arthroplasty was performed comparing corticosteroid and hyaluronic acid directly. Furthermore, for each injection subtype, a multivariate logistic regression was performed comparing patients who had undergone single or multiple injections in the 3-month preoperative period. All multivariate logistic regressions controlled for patient age,

sex, and comorbidities. The baseline for comparison was female patients with no injection, age of  $< 50$  years, and no known comorbidities. Analyses were performed using the PearlDiver software or Stata version 14.2 (StataCorp). All p values were 2-sided; significance was set at  $p < 0.05$ . Odds ratios (ORs) with 95% confidence intervals (CIs) for each variable were calculated.

## Results

### Demographic Characteristics

A total of 58,337 patients were included; a flow diagram depicting patient inclusion and exclusion may be found in Figure 1. In the study, 3,249 patients (5.6%) received hyaluronic acid and 16,656 patients (28.6%) received corticosteroid  $\leq 1$  year before the total knee arthroplasty. Among those who received hyaluronic acid, 646 patients (19.9%) received their most recent injection  $\leq 3$  months before the total knee arthroplasty, 1,113 patients (34.3%) received their most recent injection  $> 3$  to 6 months before the total knee arthroplasty, and 1,490 patients (45.9%) received their most recent injection  $> 6$  to 12 months before the total knee arthroplasty. Within the corticosteroid cohort, 6,653 patients (39.9%) received their most recent injection  $\leq 3$  months before the total knee arthroplasty, 5,569 patients (33.4%) received their most recent injection  $> 3$  to 6 months before the total knee arthroplasty, and 4,434 patients (26.6%) received their most recent injection  $> 6$  to 12 months before the total knee

TABLE II Modeling of Periprosthetic Joint Infection Risk by Injection Type and Timing\*

	OR†	P Value
Hyaluronic acid injection		
$\leq 3$ months	1.55 (1.02 to 2.25)	0.029‡
$> 3$ to 6 months	0.84 (0.55 to 1.23)	0.397
$> 6$ to 12 months	0.83 (0.57 to 1.16)	0.289
Corticosteroid injection		
$\leq 3$ months	1.21 (1.04 to 1.40)	0.014‡
$> 3$ to 6 months	1.07 (0.90 to 1.27)	0.414
$> 6$ to 12 months	1.17 (0.98 to 1.40)	0.081
Age		
50 to 59 years	0.67 (0.48 to 0.97)	0.027‡
60 to 69 years	0.51 (0.37 to 0.72)	$< 0.001$ ‡
70 to 79 years	0.44 (0.32 to 0.62)	$< 0.001$ ‡
80 to 89 years	0.46 (0.33 to 0.67)	$< 0.001$ ‡
$\geq 90$ years	0.51 (0.30 to 0.84)	0.009‡
Male sex	1.29 (1.16 to 1.43)	$< 0.001$ ‡

\*The results of a multivariate logistic regression comparing periprosthetic joint infection risk for patients stratified by the timing and medication used in their most recent injection. The no-injection cohort with female sex, age of  $< 50$  years, and no comorbidities was used as the baseline. The effect of individual comorbidities may be found in the Appendix. †The values are given as the OR, with the 95% CI in parentheses. ‡Significant.

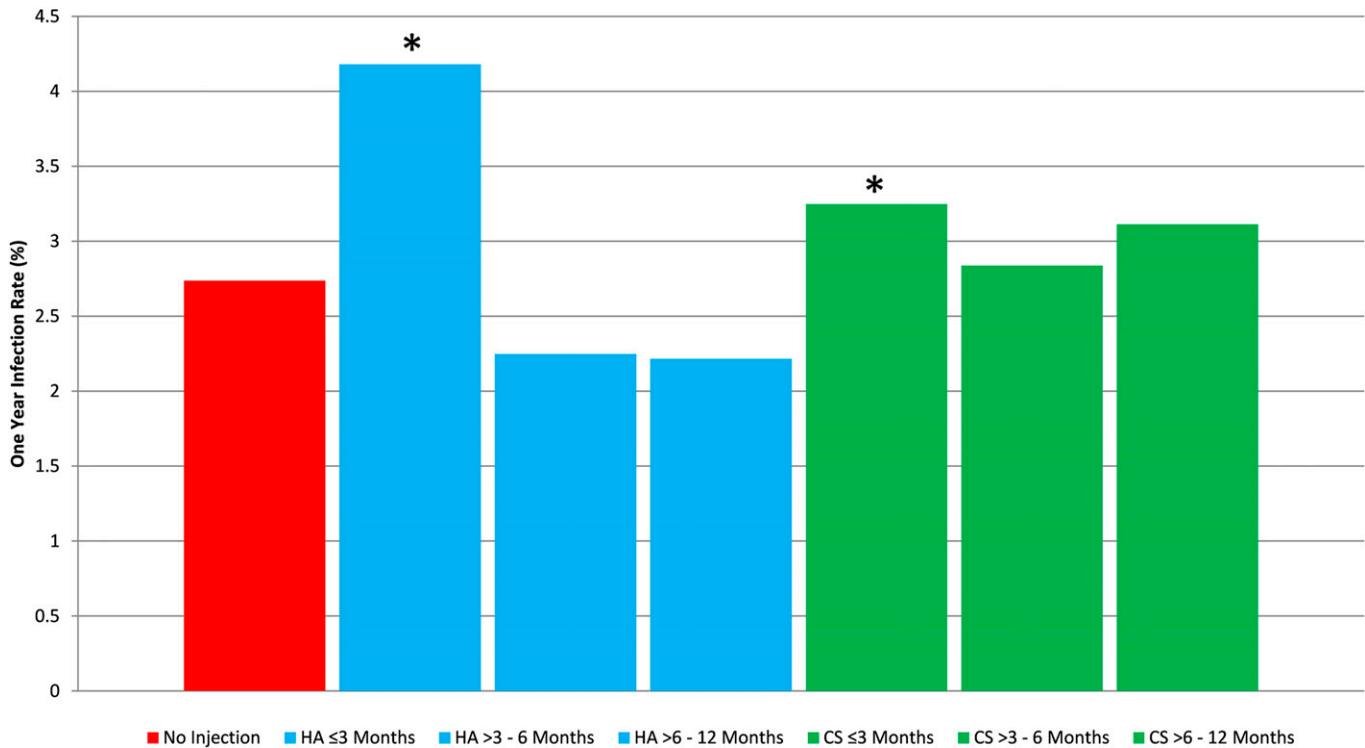


Fig. 2

Bar graph showing the rate of periprosthetic joint infection 6 months after total knee arthroplasty stratified by the type and timing of the most recent injection prior to total knee arthroplasty. The no-injection cohort was used as the baseline. The asterisk indicates significant differences in the multivariate logistic regression. HA = hyaluronic acid and CS = corticosteroid.

arthroplasty. Sixty-three percent of patients were female. The majority of patients were 60 to 79 years of age. The distribution of age and sex in the no-injection group and cohorts of patients who received hyaluronic acid or corticosteroid ≤3 months before the total knee arthroplasty is displayed in Table I, and comorbidity data are found in the Appendix. Although there were few significant differences ( $p < 0.05$ ) in the rates of comorbidities between groups, patients receiving injections ≤3 months before the total knee arthroplasty tended to have a lower prevalence of obesity, diabetes, and renal failure (see Appendix).

### Injection Type and Timing

There were a total of 1,649 infections (2.83%), 1,052 of which occurred in the no-injection group (rate, 2.74%). The infection rate for patients who received an injection ≤3 months before the total knee arthroplasty was 53% higher for hyaluronic acid (4.18% compared with 2.74%) and 19% higher for corticosteroid (3.25% compared with 2.74%) than for patients with no injection. Controlling for age, sex, and comorbidities, the odds of periprosthetic joint infection were significantly higher in patients who received either type of injection ≤3 months before the total knee arthroplasty; the OR was 1.55 ( $p = 0.029$ ) for the hyaluronic acid group and 1.21 ( $p = 0.014$ ) for the corticosteroid group (Table II). There was no significant increase ( $p > 0.05$ ) in infection rate if the injection had occurred >3 months prior to the total knee arthroplasty (Fig. 2).

Among patients who had received an injection ≤3 months before the total knee arthroplasty, there was no significant difference ( $p > 0.05$ ) in the odds of infection based on medication type (Table III).

**TABLE III Modeling of Periprosthetic Joint Infection Risk for Hyaluronic Acid Relative to Corticosteroid\***

	OR†	P Value
Hyaluronic acid injection ≤3 months	1.24 (0.80 to 1.85)	0.305
Age		
50 to 59 years	1.11 (0.42 to 3.87)	0.845
60 to 69 years	0.67 (0.26 to 2.25)	0.447
70 to 79 years	0.73 (0.29 to 2.46)	0.554
80 to 89 years	0.75 (0.28 to 2.61)	0.603
≥90 years	0.77 (0.19 to 3.28)	0.705
Male sex	2.04 (1.55 to 2.68)	<0.001‡

\*The results of a multivariate logistic regression comparing periprosthetic joint infection risk for patients who received injections ≤3 months before the total knee arthroplasty. The corticosteroid cohort with female sex, age of <50 years, and no comorbidities was used as the baseline. The effect of individual comorbidities may be found in the Appendix. †The values are given as the OR, with the 95% CI in parentheses. ‡Significant.

### Comorbidities

Patients who were  $\geq 50$  years of age had a decreased likelihood of periprosthetic joint infection compared with patients who were  $< 50$  years of age. Male patients had a higher likelihood of infection compared with female patients (OR, 1.29;  $p < 0.001$ ). Numerous comorbidities were also found to increase a patient's infection risk, including congestive heart failure, cardiac arrhythmias, peripheral vascular disorders, hypertension, neurologic disorders, chronic pulmonary disease, human immunodeficiency virus (HIV), lymphoma, obesity, electrolyte disorders, anemia, psychoses, depression, and smoking, and renal failure was associated with a decreased risk of infection (see Appendix).

### Multiple Injections

Within the subgroup of patients who received injections  $\leq 3$  months before the total knee arthroplasty, 60% of patients receiving hyaluronic acid (390 of 646) and 23% of patients receiving corticosteroid (1,501 of 6,653) had undergone multiple injections within that period. There was no difference in the odds of periprosthetic joint infection for the multiple injection cohort for the hyaluronic acid group (OR, 0.98;  $p = 0.967$ ) or the corticosteroid group (OR, 0.83;  $p = 0.291$ ) compared with the cohort that received a single injection.

### Discussion

Our data show that intra-articular injection of corticosteroid or hyaluronic acid  $\leq 3$  months before a total knee arthroplasty increases the odds of periprosthetic joint infection within the first 6 months postoperatively, independent of age, sex, or comorbidities. This increased risk is mitigated as the interval between injection and total knee arthroplasty increases; injections  $> 3$  months prior to a total knee arthroplasty did not lead to a significant increase in the odds of periprosthetic joint infection. This result is similar to many other large retrospective database studies examining injections prior to total knee arthroplasty<sup>3,13</sup> and total hip arthroplasty<sup>20,21</sup>. Furthermore, a direct comparison of hyaluronic acid and corticosteroid showed that the odds of infection were not significantly different. Patients who received multiple injections of either medication  $\leq 3$  months before the total knee arthroplasty had no further increase in risk of periprosthetic joint infection compared with those who received a single injection.

Decreasing age and male sex were found to be associated with increased odds of periprosthetic joint infection, as were many comorbidities. It is possible that the effect of demographic characteristics, such as age and sex, may result from differences in the underlying etiology leading to total knee replacement. These patients may have higher rates of post-traumatic arthritis, inflammatory arthritis, or other conditions that increase the risk of infection independently. Unfortunately, these data are not available in the utilized database. Many of the comorbidities found to increase a patient's infection risk, such as peripheral vascular disorders, HIV, obesity, and smoking, may also have independent effects on the patient's immune system. However, further research would be necessary to demonstrate causation.

Despite seemingly clear evidence from high-volume database studies, some conflicting evidence exists in the literature with regard to infection risk secondary to preoperative injections. The studies showing no increase in periprosthetic joint infection risk are typically smaller cohorts<sup>15,16,19,24</sup>, calling into question whether they were underpowered to detect a difference in a rare outcome. Amin et al. published the largest cohort study claiming no relationship between injection and periprosthetic joint infection for patients undergoing total knee arthroplasty (1,628 patients), but their study did not control for confounding variables, such as comorbidities<sup>12</sup>.

The exact mechanism by which these medications increase infection risk remains unknown. Potential etiologies include direct inoculation of the joint or immunosuppression caused by the medications themselves. Despite sterile technique, it is possible that injections introduce small amounts of bacteria into the otherwise sterile joint space. If these bacteria remain present, they could later colonize the arthroplasty implant, leading to periprosthetic joint infection. Corticosteroids are well-known immunosuppressants used to treat a wide array of autoimmune diseases, and thus local or systemic effects of corticosteroid injections might lead to decreased immune response following total knee arthroplasty and increased infection rate. However, in this study, hyaluronic acid was found to have equivalent risk to corticosteroid. Experiments examining the mechanism of action of intra-articular hyaluronic acid have shown that hyaluronic acid may reduce immunity via changes in production of immunomodulating factors in the synovium<sup>25,26</sup>, cartilage<sup>27</sup>, and subchondral bone<sup>28</sup>. It is possible that a combination of direct inoculation and local immune suppression could result in the increased odds of periprosthetic joint infection associated with both injection types. However, we are aware of no study demonstrating a direct mechanistic link between intra-articular injections and periprosthetic joint infection.

Interestingly, our study found no increase in infection risk with multiple injections  $\leq 3$  months before a total knee replacement compared with a single injection. The reason for this remains unclear. It is possible that a single injection provides enough of an inoculation of the joint and/or enough immunosuppression to increase the risk, and additional injections do not cause any further changes to the knee environment. Future studies may examine this further.

The evidence for efficacy of corticosteroid or hyaluronic acid injections is also mixed. A recent randomized trial comparing a 2-year treatment course of injections (triamcinolone) with placebo for patients with symptomatic knee osteoarthritis showed a small amount of increased cartilage volume loss in the triamcinolone cohort, with no difference in knee pain<sup>29</sup>. However, a systematic review of trials comparing corticosteroid injections with placebo found that corticosteroid injections provided clinically important reduction in pain 1 week after injection<sup>7</sup>. The most updated Cochrane systematic review on the efficacy of intra-articular corticosteroid injections showed that most trials in the literature are of low methodological quality and concluded that it remains unclear whether these

injections have any clinically important benefits after 1 to 6 weeks<sup>9</sup>. One systematic review evaluating the efficacy of hyaluronic acid similarly concluded that it has no benefit<sup>8</sup>, and other systematic reviews concluded that these injections provide modest short-term improvement in symptoms<sup>5,6,10,11</sup>.

This study has several strengths. This is the first study, to our knowledge, that included medication type when analyzing the relationship between preoperative injection and infection. As the CPT code used to identify knee injections may also denote knee joint aspirations, it is conceivable that prior studies included patients who underwent an arthrocentesis to rule out infection in their injection cohort, potentially capturing patients with culture-negative infections and increasing the periprosthetic joint infection rate. Controlling for medication minimizes this error, as surgeons concerned for infection would be unlikely to administer corticosteroid or hyaluronic acid at the time of aspiration. Furthermore, this study includes a large number of patients, maximizing the power to detect a relationship between injection and periprosthetic joint infection should one exist. The laterality of injections was matched to the subsequent total knee arthroplasty, an advantage of this database over others that include ICD codes only. Patients were only included if they were active in the database for the year prior to and 6 months after the total knee arthroplasty, and thus no patients were lost to follow-up. Controlling for age, sex, and comorbidities decreases the chance of confounding or other potential sources of bias. Additionally, utilizing a health insurance-based database maximizes the ability to track patients across geographic and health-care settings, a limitation of state or individual hospital databases.

This study did have limitations common with large database studies. The quality of data relies on accurate and complete biller coding, and any coding errors could introduce study error. CPT and ICD codes are also not entirely specific; the injection code used in this study could denote joint aspiration rather than injection. However, by requiring medication administration at the time of injection, we minimized this error. Our study population was also limited to patients enrolled in Humana's health insurance plan, including only privately insured patients, and thus may not be reflective of the general population.

Ultimately, the decision to provide intra-articular injections in patients with osteoarthritis should be based on a balance of expected benefits of treatment and associated risk of complications. As mentioned previously, evidence for the efficacy of various injection types is limited. Some may even argue that these medications are not efficacious or are potentially harmful. For this reason, the American Academy of Orthopaedic Surgeons (AAOS) Clinical Practice Guidelines are

unable to recommend for or against the use of intra-articular corticosteroids and recommend against the use of hyaluronic acid for patients with symptomatic osteoarthritis of the knee<sup>2</sup>. This recommendation has led to small decreases in the utilization of both corticosteroid and hyaluronic acid, but, despite this, continued use remains widespread<sup>30</sup>. Our data demonstrate that receiving an injection of corticosteroid or hyaluronic acid  $\leq 3$  months before a total knee replacement increased infection risk to a magnitude similar to that with certain comorbidities, including peripheral vascular disease and obesity. Given the available data with regard to the safety of injections, both in our study and many others in the literature, injections in the immediate preoperative period may put patients at substantial risk of devastating complications and may increase cost of care with a low likelihood of a clinically important benefit.

In conclusion, in this nationwide health insurance-based database study, patients who underwent preoperative corticosteroid or hyaluronic acid injection  $\leq 3$  months before total knee arthroplasty had an increased risk of periprosthetic joint infection postoperatively. There was no significant difference in periprosthetic joint infection risk between medication types or between patients receiving multiple injections compared with a single injection. The increased infection risk with preoperative injection overall is consistent with past studies. On the basis of these data, we recommend avoiding both injection types in the 3 months prior to total knee arthroplasty.

## Appendix

**eA** Tables showing the codes used in the study, comorbidities, effect of comorbidities in modeling of periprosthetic infection risk by injection timing, and effect of comorbidities in modeling of periprosthetic joint infection risk for hyaluronic acid relative to corticosteroid are available with the online version of this article as a data supplement at <http://links.lww.com/JBJS/F72>. ■

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