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Research Article

Risk of Infection After Total Knee or Hip Arthroplasty After Receipt of Multiple Corticosteroid or Hyaluronic Acid Injections

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ABSTRACT

Background: Few studies have assessed the relationship between the quantity of preoperative corticosteroid injections (CSIs) or hyaluronic acid injections (HAIs) and postoperative infection risk after total knee or hip arthroplasty (TKA, THA). We aimed to (1) determine whether the number of injections administered before TKA/THA procedures is associated with postoperative infections and (2) establish whether infection risk varies by injection type.

Methods: This retrospective cohort study included 230,487 THAs and 371,511 TKAs from the 2017 to 2018 Medicare Limited Data Set. The quantity of CSI or HAI, defined as receiving either CSI or HAI ≤2 years before TKA/THA, was identified and categorized as 0, 1, 2, or >2. The primary outcome was 90-day postoperative infection. Multivariable regression models measured the association between the number of injections and 90-day postoperative infection. Odds ratios and 95% confidence intervals were reported.

Results: The percentage of THA patients receiving 1, 2, and >2 preoperative CSIs was 6.1%, 1.6%, and 0.8%, respectively. Receiving >2 CSIs within 2 years before THA was associated with higher odds of 90-day postoperative infection (odds ratios = 1.74, 95% CI = 1.11 to 2.74, $P = 0.02$). The percentage of TKA patients receiving 1, 2, and >2 CSIs was 3.0%, 1.2%, and 1.1%, respectively. For HAIs in TKA patients, percentage receiving injections was 98.3%, 0.6%, 0.2%, and 0.9%, respectively. Quantity of CSIs or HAIs administered was not associated with postoperative infection among TKA patients.

Conclusion: Patients receiving >2 injections before THA had higher odds of 90-day postoperative infection. This finding was not observed in TKA patients. These results suggest that the use of >2 injections within 2 years of THA should be avoided.

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Both intra-articular corticosteroid injections (CSIs) and hyaluronic acid injections (HAIs) are treatment modalities frequently used by orthopaedic surgeons.[1] However, their utility for the management of osteoarthritis has come into question. The American Academy of Orthopaedic Surgeons treatment recommendations vary for injection type (HAI versus CSI) and the involved joint.[2-8] There is strong evidence recommending CSI in the management of both hip and knee osteoarthritis; however, there is moderate-to-strong evidence against the use of HAI in hips and knees. In addition, HAI is only Food and Drug Administration–approved for use in knees. Recently, the safety of administering injections before total knee and hip arthroplasty (TKA, THA) procedures has been subject to increasing scrutiny. While various studies have failed to show an association between injections and postoperative infection risk, recent data demonstrate an association that is time-dependent.[9-11] The number of preoperative injections administered has also been suggested to be associated with increased infection risk after THA, but not TKA.[12-18] However, these studies are limited by small sample sizes or the confounding variable of time from injection to surgery. Furthermore, there is limited literature evaluating the infection risk associated with CSI versus HAI.[15,19]

Using a large, nationally representative sample, we aimed to (1) determine whether the number of CSIs administered before TKA and THA procedures is associated with increased risk of postoperative infection and (2) establish whether infection risk varies by injection type (CSI versus HAI) in TKA patients. In addition, we probed the types of providers administering these injections and to what extent timing of injections plays a role in the association between quantity of injections and postoperative infection. We hypothesized a dose-dependent risk of postoperative infection and that CSIs will confer a higher infection risk compared with HAIs.

Methods

Study Design and Sample

Institutional review board approval was not needed for this retrospective cohort study. All TKA or THA procedures recorded in the Medicare Limited Data Set, from January 2017 to June 2019 defined through International Classification of Diseases, Ninth Revision (ICD-9) and 10th Revision (ICD-10) procedural codes (Appendix A, http://links.lww.com/JAAOS/A939), were included in this study. Cases were excluded if they were not in Medicare for ≥2 years before their THA or TKA procedure and 6 months after the procedure. In addition, cases with nonosteoarthritis diagnoses and nonelective procedures were excluded. Finally, patients were excluded if they had >1 procedure during the study period to correctly attribute the timing of injections and infections to index procedures.

Administration of preoperative CSI and HAI was identified by Current Procedural Terminology (CPT) codes (Appendix A, http://links.lww.com/JAAOS/A939) reported at an outpatient visit and associated with ICD diagnosis codes for hip or knee osteoarthritis. Injections were included when they met three criteria: (1) defined by one of the aforementioned Current Procedural Terminology codes, (2) have an associated code specific to CSI or HAI, and (3) have an indication for injection as hip or knee pain, joint effusion, or osteoarthritis.[20] The number of CSIs administered within 2 years of THA or TKA was categorized as 0, 1, 2, or >2. The quantity of HAIs administered before TKA was similarly categorized. HAI was not analyzed in THA because of minimal sample size.

Study Variables

The primary outcome was 90-day postoperative infection, defined by ICD-9 and 10 codes (Appendix A, http://links.lww.com/JAAOS/A939). Secondary outcomes were 30 and 90-day readmission rates. Demographic data included race (White, Black, other), age, sex, obesity, and Deyo Comorbidity Index (DCI). Hospital data, including hospital region, safety net status rating (1-5), teaching status (nonteaching, minor teaching, major teaching), bed size (small <100 beds, medium 100-499 beds, large >=500 beds), hospital type (government, private, nonprofit, other), were also recorded. In addition, hospital-specific annual volume of TKA or THA was noted.

Statistical Analysis

Analyses for THA and TKA were conducted separately. Descriptive analyses assessed differences between groups categorized by the number of preoperative injections received (0, 1, 2, >2). Unadjusted group differences were assessed by standardized mean differences (SMDs); a SMD of >0.10 was considered to represent a meaningful difference between groups.[21] Multilevel, multivariable regression models assessed the association between number of CSIs and HAIs administered within 2 years before surgery and 90-day postoperative infection. Multilevel models account for the correlation between patients treated at the same hospital because

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they will receive similar treatment and care.[22] All aforementioned study variables were included in the multivariable models. Odds ratios (ORs) and 95% confidence intervals were reported. *P*-values <0.05 were considered significant. All analyses were conducted using SAS, version 9.4 (SAS Institute).

Sensitivity and Post Hoc Analyses

A sensitivity analysis probed whether the timing of injections for patients with >2 injections affected our results. We modeled the association between injections and postoperative infection risk among those receiving >2 injections, specifically separating cases with >2 injections within 1 year and cases with >2 injections within 2 years. In post hoc analyses conducted to address issues raised during the peer-review process, we additionally described the specialty of the provider listed as the attending for the administered injections. This analysis was restricted to patients who had the same attending provider listed for each injection claim. Type of provider (orthopaedic, nonorthopaedic, or missing) was determined using publicly available healthcare provider taxonomy information available from the Washington Publishing Company (www.wpc-edi.com) and maintained by the National Uniform Claim Committee (www.nucc.org); crosswalks between Medicare Specialty Code and Provider Taxonomy are publicly available.

Post hoc analyses also addressed timing of CSIs or HAIs and its relation to postoperative infection risk. For each cohort and injection type, median time from injection to operation was calculated. The relationship between timing of the last injection and 90-day infection rate was plotted.

Results

Among 973,509 included cases, 230,487 were THAs and 743,022 were TKAs. Among TKA patients, 3.0%, 1.2%, and 1.1% received 1, two, and >2 CSIs, respectively (Table 1). This was 0.6%, 0.2%, and 0.9%, respectively, for HAIs. Among THA patients, 6.1%, 1.6%, and 0.8% received 1, two and >2 CSIs, respectively. Age, race, and sex did not meaningfully differ between injection groups (all SMD<0.10; Tables 1 and 2). However, patients with >2 injections were more likely to have a higher DCI (SMD>0.10; Tables 1 and 2). Meaningful differences were observed in demographics between patients who did and did not develop infections (SMD>0.10; Appendix Table B, http://links.lww.com/JAAOS/A939).

Among TKA patients who received 0, 1, 2, or >2 CSIs, 30-day postoperative infection rates were 0.5%, 0.6%, 0.6%, and 0.9%, respectively (SMD = 0.02), and 90-day postoperative infection rates were 0.7%, 0.7%, 0.8%, and 1.0%, respectively (SMD = 0.02; Table 1). Among TKA patients who received 0, 1, 2, or >2 HAIs, 30-day postoperative infection rates were 0.5%, 0.8%, 0.4%, and 0.5%, respectively (SMD = 0.03), and 90-day postoperative infection rates were 0.7%, 1.0%, 0.4%, and 0.7%, respectively (SMD = 0.03; Table 1). Among THA patients who received 0, 1, 2, or >2 CSIs, 0.3%, 0.4%, 0.4%, and 0.9% had infections within 30 days postoperatively, respectively (SMD = 0.04), and 0.4%, 0.6%, 0.6%, and 1.1% had an infection within 90 days postoperatively, respectively (SMD = 0.05; Table 2).

In the adjusted models (adjusted for all available covariates), receiving >2 CSIs within 2 years before THA was associated with higher odds of 90-day postoperative infection (OR = 1.74, 95% confidence interval = 1.11 to 2.74, *P* = 0.02; Table 3). There was no increased risk of 90-day postoperative infection in TKA patients who received >2 CSIs nor >2 HAIs (all *P* > 0.05; Tables 3 and 4). Analysis of specialty of providers listed as attendings for injections demonstrated that 33.6% of knee CSIs, 32.9% of knee HAIs, and 56.0% of hip CSIs were administered by nonorthopaedic providers.

Regarding timing of injections before TKA, the highest infection rates in the CSI cohort were identified when the final injection was administered 8 months before surgery (1.4%; Figure 1). The highest infection rate in the HAI cohort was identified when the final injection was administered 1 month before TKA (2.9%). For THA, the highest infection rate was identified when the final CSI was administered 8 months before surgery (0.9%). Median time from last injection to operation varied by injection type and injection number. Notably, in patients receiving three CSIs before THA, the median time from the final injection to operation was 4.4 months (Table 5). This was shorter than the median times between final injection and surgery in patients receiving three CSIs or HAIs before TKA (4.9 and 7.2 months, respectively; Table 5).

Discussion

This study, using national claims data, demonstrated that administration of more than two intra-articular CSIs within 2 years before THA is associated with increased risk of 90-day postoperative infection. However, the

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Table 1. Characteristics of Total Knee Arthroplasty Patients Identified

	Corticosteroid Injection					Hyaluronic Acid Injection				
	0	1	2	>2	SMD	0	1	2	>2	SMD
No. (%)	351,722 (94.7%)	11,021 (3.0%)	4,546 (1.2%)	4,222 (1.1%)	—	365,126 (98.3%)	2,141 (0.6%)	835 (0.2%)	3,409 (0.9%)	—
Median age [yr (IQR)]	73 (69–78)	73 (69–78)	74 (70–78)	73 (70–78)	0.05	73 (69–78)	74 (70–78)	74 (70–78)	73 (69–78)	0.07
Race [no. (%)]	—	—	—	—	0.08	—	—	—	—	0.09
White	317,424 (90.2%)	10,061 (91.3%)	4,153 (91.4%)	3,906 (92.5%)	—	329,641 (90.3%)	1,955 (91.3%)	769 (92.1%)	3,179 (93.3%)	—
Black	16,949 (4.8%)	488 (4.4%)	190 (4.2%)	190 (4.5%)	—	17,571 (4.8%)	94 (4.4%)	33 (4.0%)	119 (3.5%)	—
Other	17,349 (4.9%)	472 (4.3%)	203 (4.5%)	126 (3.0%)	—	17,914 (4.9%)	92 (4.3%)	33 (4.0%)	111 (3.3%)	—
Female (no. [%])	223,705 (63.6%)	7,123 (64.6%)	3,040 (66.9%)	3,004 (71.1%)	0.08	232,693 (63.7%)	1,378 (64.4%)	556 (66.6%)	2,245 (65.9%)	0.03
DCI (no. [%])	—	—	—	—	0.35	—	—	—	—	0.35
0	230,343 (65.5%)	4,613 (41.9%)	1,848 (40.7%)	1,650 (39.1%)	—	235,775 (64.6%)	888 (41.5%)	341 (40.8%)	1,450 (42.5%)	—
1	53,913 (15.3%)	2,561 (23.2%)	1,071 (23.6%)	1,005 (23.8%)	—	57,079 (15.6%)	474 (22.1%)	205 (24.6%)	792 (23.2%)	—
2	31,216 (8.9%)	1,569 (14.2%)	669 (14.7%)	649 (15.4%)	—	33,180 (9.1%)	318 (14.9%)	115 (13.8%)	490 (14.4%)	—
3	36,250 (10.3%)	2,278 (20.7%)	958 (21.1%)	918 (21.7%)	—	39,092 (10.7%)	461 (21.5%)	174 (20.8%)	677 (19.9%)	—
30-day readmission (no. [%])	20,613 (5.9%)	787 (7.1%)	314 (6.9%)	357 (8.5%)	0.06	21,571 (5.9%)	162 (7.6%)	67 (8.0%)	271 (7.9%)	0.05
90-day readmission (no. [%])	27,245 (7.7%)	1,066 (9.7%)	448 (9.9%)	466 (11.0%)	0.07	28,561 (7.8%)	220 (10.3%)	84 (10.1%)	360 (10.6%)	0.06
30-day infection (no. [%])	1,764 (0.5%)	64 (0.6%)	28 (0.6%)	36 (0.9%)	0.02	1,853 (0.5%)	18 (0.8%)	3 (0.4%)	18 (0.5%)	0.03
90-day infection (no. [%])	2,332 (0.7%)	80 (0.7%)	36 (0.8%)	41 (1.0%)	0.02	2,441 (0.7%)	22 (1.0%)	3 (0.4%)	23 (0.7%)	0.03

DCI = Deyo Comorbidity Index; IQR = interquartile range; SMD = standardized mean difference

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Table 2. Characteristics of Total Hip Arthroplasty Patients Identified

	Corticosteroid Injection				
	0	1	2	>2	SMD
No. (%)	210,960 (91.5%)	14,113 (6.1%)	3,563 (1.6%)	1,851 (0.8%)	—
Median age (yr [IQR])	73 (69–78)	74 (70–79)	74 (69–79)	74 (70–80)	0.08
Race (no. [%])	—	—	—	—	0.08
White	194,864 (92.4%)	13,203 (93.6%)	3,314 (93.0%)	1,739 (93.9%)	—
Black	8,505 (4.0%)	487 (3.5%)	156 (4.4%)	66 (3.6%)	—
Other	7,591 (3.6%)	423 (3.0%)	93 (2.6%)	46 (2.5%)	—
Female [no. (%)]	129,018 (61.2%)	8,908 (63.1%)	2,257 (63.3%)	1,260 (68.1%)	0.08
DCI [no. (%)]	—	—	—	—	0.36
0	145,078 (68.8%)	6,779 (48.0%)	1,607 (45.1%)	775 (41.9%)	—
1	28,131 (13.3%)	2,937 (20.8%)	770 (21.6%)	405 (21.9%)	—
2	17,379 (8.2%)	1,941 (13.8%)	490 (13.8%)	277 (15.0%)	—
3	20,372 (9.7%)	2,456 (17.4%)	696 (19.5%)	394 (21.3%)	—
30-day readmission (no. [%])	12,977 (6.2%)	1,315 (9.3%)	294 (8.3%)	190 (10.3%)	0.10
90-day readmission (no. [%])	17,014 (8.1%)	1,721 (12.2%)	414 (11.6%)	251 (13.6%)	0.11
30-day infection (no. [%])	535 (0.3%)	50 (0.4%)	16 (0.4%)	16 (0.9%)	0.04
90-day infection (no. [%])	835 (0.4%)	83 (0.6%)	21 (0.6%)	21 (1.1%)	0.05

DCI = Deyo Comorbidity Index; IQR = interquartile range; SMD = standardized mean difference

number of CSIs or HAIs administered before TKA was not associated with increased infection risk.

Total Hip Arthroplasty Risk

A few previous studies have evaluated the relationship between preoperative injections and postoperative THA infection risk. Kaspar et al and Chambers et al both evaluated this risk with matched cohort studies.[16,17] Kaspar et al[16] showed no association between number of preoperative CSIs and postoperative THA infection; however, their study was underpowered with 40 patients in the injection and no injection cohorts. Chambers et al, on the other hand, did show increased postoperative infection risk between patients who received two or more CSIs versus those who received a single CSI.[17] In their database study, Forlenza et al[18] also analyzed this relationship and demonstrated increasing postoperative THA infection risk with the administration of one, two, or three or more CSIs within 3 months of THA.

These studies are limited by either small sample sizes or the inability to isolate risk associated with number of injections from the confounding variable of timing of injection. We demonstrated similar results to Forlenza et al and Chambers et al, further supporting the association between the number of preoperative CSIs administered and postoperative THA infection risk.[17,18]

Table 3. Risk of 90-D Postoperative Infection for Patients Receiving Corticosteroid Injection Before Total Knee or Hip Arthroplasty

	TKA		THA	
Number of Injections	OR (95% CI)	*P*	OR (95% CI)	*P*
0	Ref.	—	Ref.	—
1	0.93 (0.74–1.18)	0.54	1.08 (0.86–1.36)	0.52
2	1.02 (0.72–1.44)	0.92	1.03 (0.66–1.60)	0.90
>2	1.25 (0.90–1.76)	0.19	1.74 (1.11–2.74)	0.02

CI = confidence interval; OR = odds ratio; TKA = total knee arthroplasty; THA = total hip arthroplasty

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Table 4. **Risk of 90-D Postoperative Infection for Patients Receiving Hyaluronic Acid Injection Before Total Knee Arthroplasty**

	TKA	
Number of Injections	OR (95% CI)	*P*
0	Ref.	—
1	1.23 (0.79–1.91)	0.36
2	0.48 (0.16–1.42)	0.18
>2	0.87 (0.56–1.34)	0.53

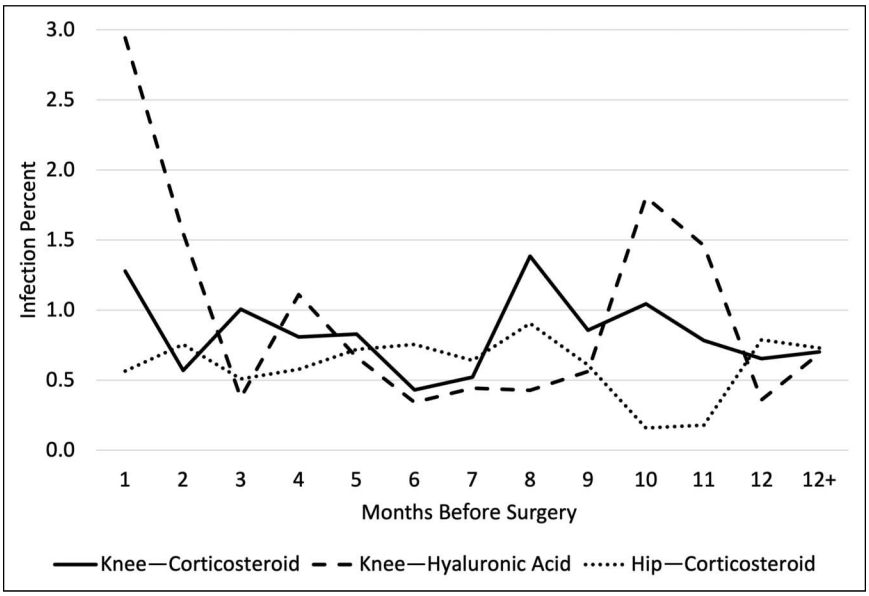
CI = confidence interval; OR = odds ratio; TKA = total knee arthroplasty

Total Knee Arthroplasty Risk

A number of studies have assessed the risk of infection after TKA associated with preoperative number of injections.[12-15] Two matched cohort studies by Horne et al and Papavasiliou et al along with a retrospective cohort study by Kokubun et al all showed evidence that the number of preoperative CSIs administered is not associated with postoperative TKA infection.[12-14] In a large observational study, Richardson et al[15] also showed no increased risk of infection associated with receiving multiple compared with a single CSI or HAI within 3 months before TKA. Similar to the THA literature, these TKA studies are limited in their analyses by either a small and select sample or the confounding variable of injection timing. Nonetheless, our results are consistent with these studies because we did not find the number of preoperative CSIs or HAIs to be associated with infection risk after TKA.

The reason for the observed differences in infection risks after TKA versus THA is unknown. Patients requiring a hip injection are commonly referred to an outside provider (ie, musculoskeletal radiologist or pain management),[16,17] introducing variability in injection techniques used. It may be that alternate providers are not as strictly adherent to sterile injection techniques, which results in the observed discrepancy between TKA and THA infection risks. In fact, our analysis did demonstrate that hip compared with knee injections were more commonly administered by non-orthopedic providers. Most of these providers had a listed specialty of diagnostic radiology, physical medicine and rehabilitation, and pain medicine/anesthesiology. In addition, Kurtz et al[23] demonstrated that the risk of postoperative infection after TKA was diminished if the preoperative injection was administered by a surgeon with a higher annual volume of CSI or HAI administration compared with one with a lower volume. This could be another potential explanation because knee injections are more commonly administered than hip. Another proposed explanation for this discrepancy is there may be a higher relative concentration of CSI or HAI when administered in hips compared with knees because the hip has a lower intracapsular volume than the knee. Consequently, this higher relative concentration may result in a more immunocompromised environment in hips compared with knees.

Figure 1



Graph showing timing of last corticosteroid or hyaluronic injection before total knee or hip arthroplasty and 90-day infection rates after surgery.

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Table 5. Median Timing of Corticosteroid or Hyaluronic Acid Injections Before Total Knee or Hip Arthroplasty

	Median Time Before Surgery [months (IQR)]		
	Knee—CSI	Knee—HAI	Hip—CSI
Patients receiving 1 injection	—	—	—
1	7.6 (4.1–13.6)	8.0 (4.4–14.1)	5.1 (3.2–9.6)
Patients receiving 2 injections	—	—	—
1	12.5 (8.5–17.9)	13.2 (7.8–18.2)	10.4 (7.0–15.4)
2	5.6 (3.5–9.5)	7.3 (4.4–12.6)	4.6 (3.0–7.5)
Patients receiving 3 injections	—	—	—
1	16.5 (12.3–20.5)	8.4 (5.1–14.5)	14.7 (11.0–19.5)
2	10.3 (7.2–14.0)	8.1 (4.8–13.2)	9.3 (6.5–13.4)
3	4.9 (3.2–7.9)	7.2 (4.3–12.2)	4.4 (2.9–7.0)

CSI = corticosteroid injection; HAI = hyaluronic acid injection; IQR = interquartile range

Corticosteroid Versus Hyaluronic Acid Injections

The etiology behind the causal relationship of injections and increased risk of postoperative total joint arthroplasty (TJA) infection is unclear. There are two major mechanisms theorized: (1) the introduction of a contaminant at the time of injection or (2) the injected agent creates an immunocompromised environment more susceptible to infection. Regarding the first theory, a contaminant can be introduced by breech of the sterile technique, the invasiveness of the needle, or contamination of the injectable itself.[16,24] With this theory, we would expect there to be equal infection risk associated with CSI versus HAI. Regarding the latter theory, steroids interfere with the native inflammatory and healing processes that typically occur after a surgery and aid in the prevention of infection.[25-27] Consequently, we would expect to see higher postoperative infection rates with CSI compared with HAI. However, there is also some evidence suggesting that HAI interferes with local immunomodulating factors.[28-31]

Richardson et al[15] found no difference in postoperative TKA infection risk between CSI and HAI. The current study supports the findings that both CSI and HAI have similar infection risks because the postoperative infection risks after TKA were similar in both the CSI cohort and the HAI cohort.

Frequency and Timing of Injections

Previous studies have identified a time-dependent association between injections and infection after TKA.[11,20] However, we failed to identify an absolute increase in infection risk after TKA when any number of CSI or HAI are administered within the 2 years before TKA, irrespective of frequency or timing of injection. In addition, prior studies have identified an increased infection risk after THA that is dependent on the timing of preoperative injection. Werner et al and Schairer et al identified an increased risk when the final injection was administered within 3 months before THA, but not when administered three to six or six to 12 months before surgery.[9,10] We were unable to elucidate a clear pattern regarding the best timing to receive a CSI before THA because the highest infection rates were observed at an injection time eight or 12 months before surgery. Other studies have suggested that when >2 injections are administered, the final injection should not be given in the 90 days before surgery.[9,10] Therefore, it is reassuring that when >2 CSIs are administered before THA, we found a median time of 4.4 months between the last injection and the index surgery.

Limitations

As an observational, retrospective study, this work can only demonstrate associations, not causations. In addition, the quality of the data is dependent on the accuracy and completeness of the coding as in any database study. Our data were extracted from the Medicare Claims Limited Data Set. Future studies may look at whether the identified differences are present in commercially insured patients. Our study was also limited by the fact that it is difficult to isolate differences between CSI and HAI, specifically the number of HAIs administered is very low. Furthermore, this study does not have available other types of injections such as platelet-rich plasma, bone marrow, or amniotic derivatives. Future studies may include additional exploration into the mechanisms behind infection risks of THA versus TKA and among injection types.

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Conclusion

Patients who received >2 CSIs before THA had higher odds of 90-day postoperative infection. No association was observed between number of injections and 90-day postoperative infection in TKA patients. These results suggest that timing as opposed to quantity of preoperative injections may be responsible for the observed increased postoperative infection risk. Additional research is needed to elucidate the etiology of the observed variations in infection risk between THA and TKA patients and to better evaluate how risk differs between CSI and HAI.

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