



Original Research

Intra-Articular Corticosteroid Injections Into a Preexisting Total Knee Arthroplasty are Associated With Increased Risk of Periprosthetic Joint Infection and Revision

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ABSTRACT

Background: This study aims to determine the risks of periprosthetic joint infection (PJI) and revision associated with injecting a preexisting total knee arthroplasty (TKA) with intra-articular corticosteroids (IACSs).

Methods: The PearlDiver database was used to identify patients who underwent elective, primary TKA between 2015 and 2019. Patients who received IACS injections into the ipsilateral knee within 1 year after their primary TKA were matched 2:1 on age, gender, and Charlson comorbidity index and compared to a no-injection control group. The incidence of PJI at 1 year postoperatively and revision at 2 years postoperatively were compared between groups.

Results: A total of 27,059 patients were in the injection cohort and 54,116 patients in the control cohort. The overall PJI rate was 1.3% in the injection cohort and 0.8% in the control cohort ($P < .001$). The rate of PJI increased with the number of post-TKA IACS injections received: 1 injection (1.3%), 2 injections (1.4%), and >3 injections (1.8%) ($P < .001$ for all, compared to controls). The revision rate was 3.1% in the injection cohort and 1.3% in the control cohort ($P < .001$). Revision rates increased with the number of post-TKA IACS injections received: 1 injection (2.5%), 2 injections (4.2%), and >3 injections (7.3%) ($P < .001$ for all, compared to controls).

Conclusions: IACS injections into a preexisting TKA are associated with an incremental increased risk of prosthetic joint infection and revision. Considering the potential deleterious impact of PJI and complexity of revision procedures, IACS injections into a preexisting TKA should be strongly discouraged.

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Introduction

Osteoarthritis (OA) of the knee is a debilitating disease that affects an estimated 20% of the US population over the age of 60 years [1]. Total knee arthroplasty (TKA) is widely recognized as the standard of care for patients suffering from moderate to severe OA who have failed nonsurgical management; however, despite advancements in surgical technique and implant design, an estimated 15%–20% of patients remain unsatisfied following surgery [2–4].

Unremitting pain, stiffness, and instability are among the most frequently cited reasons for dissatisfaction and treatment options for these patients are limited [5,6]. Together with periprosthetic joint infection (PJI), which occurs in 0.5%–2.3% of TKAs, patient dissatisfaction may lead to revision surgery [7].

The practice of injecting a pre-existing TKA with corticosteroids occurs, albeit infrequently, in patients with unremitting postoperative pain. The majority of studies analyzing the safety of intra-articular corticosteroid (IACS) injections have focused upon injections administered prior to TKA; however, in recent years, further attention has focused on evaluating the risks associated with these injections when given postoperatively [8–17]. In 2018, Mills et al [18] published the finding that, of the 625 patients who received postoperative IACS injections, each injection increased the risk of PJI by 0.16%. In contrast, none of the 129 patients included in

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the single-institution review conducted by Klement et al [19] in 2019, developed PJI within 1 year of injection. Both single-institution studies were likely underpowered which may explain their contradictory findings. More recently in 2020, Roecker et. al, published the results of a large, national database study which found a statistically significant increase in the incidence of PJI following IACS injection into a pre-existing total knee at 6 months and 1 year following injection [20].

To date no study has used a similar national database to investigate the association between PJI within 1 year or revisions within 2 years following IACS injection into a preexisting TKA or whether multiple injections increase the likelihood risks of these complications. Furthermore, to our understanding, no study has excluded patients with records of intra-articular injections within 3 months of TKA which, based on the findings of Richardson et al [8], may confound the current data on the subject. The aim of our study is to address these gaps in the existing literature by utilizing a nationwide database to analyze the association between corticosteroids injected into a pre-existing TKA and postoperative complications. Moreover, we aimed to determine whether the likelihood of PJI or revision increased after subsequent injections. Our hypothesis is that patients receiving IACS into a preexisting TKA will have a higher likelihood of PJI and revision compared to a control group and that risks will increase with each additional injection administered.

Material and methods

Database and study design

The PearlDiver database (PearlDiver Patient Records Database, www.pearldiverinc.com, Fort Wayne, IN) is a national health insurance claims database that includes approximately 151 million

Table 1
Patient characteristics after matching.

Characteristic	Injection (n = 27,059)	Control (n = 54,116)	P-value
No. Female	18,805 (69.5%)	37,608 (69.5%)	1.000
Medicare/Medicaid	9389 (34.7%)	18,120 (33.9%)	<.001
Mean age (y)	66 ± 8.9	66 ± 8.9	1.000
<50	893 (3.3%)	1785 (3.3%)	
50–59	5286 (19.5%)	10,572 (19.5%)	
60–69	9982 (36.9%)	19,964 (36.9%)	
70–79	9044 (33.4%)	18,088 (33.4%)	
≥80	1854 (6.9%)	3707 (6.9%)	
Mean CCI	2.0 ± 2.1	2.0 ± 2.1	.950
0	6701 (24.8)	13,402 (24.8)	
1	6648 (24.6)	13,296 (24.6)	
2	5103 (18.9)	10,206 (18.9)	
≥3	8607 (31.7)	17,212 (31.7)	
Comorbidities:			
Hypertension (%)	22,175 (82.0)	43,857 (81.0)	.001
Coronary artery disease (%)	6820 (25.2)	13,094 (24.2)	.001
Congestive heart failure (%)	2778 (10.3)	5487 (10.1)	.579
Arrhythmia (%)	2375 (8.8)	4207 (7.8)	<.001
Chronic kidney disease (%)	5103 (18.9)	10,895 (20.1)	<.001
COPD (%)	4954 (18.3)	9416 (17.4)	.001
Ischemic heart disease (%)	811 (3.0)	1543 (2.9)	.245
Diabetes mellitus (%)	9509 (35.1)	19,780 (36.6)	<.001
Valvular disease (%)	356 (1.3)	733 (1.4)	.685
Peripheral vascular disease (%)	2962 (10.9)	5434 (10.0)	<.001
Liver disease (%)	1230 (4.5)	2381 (4.4)	.341
History of organ transplant (%)	6 (0.0)	14 (0)	.752

CCI, Charlson comorbidity index; COPD, chronic obstructive pulmonary disease.

Table 2
Mean time between episodes of care for control and injection cohorts.

Time Interval (mo)	Injection (n = 27059)	Control (n = 54116)
TKA to injection	11.7 ± 11.6	-
TKA to PJI	17.5 ± 11.6	3.7 ± 3.5
Injection to PJI	4.9 ± 3.6	-
TKA to revision	19.2 ± 11.7	8.6 ± 7.1
Injection to revision	8.8 ± 7.7	-

privately insured and Medicare patients. The database includes deidentified claims data from between 2010 to 2021 and is updated on a quarterly basis. Patients, injectables, and outcomes of interest were identified within PearlDiver using International Classification of Diseases (ICD), Healthcare Common Procedure Coding System J codes, and Current Procedural Terminology (CPT) codes. PearlDiver does not include laterality specific CPT code modifiers. As such, we required a laterality specific ICD 10th Revision (ICD-10) diagnostic code to have been entered on the same day of the CPT code of interest in order to control for laterality throughout our analysis. Approval from our institutional review board was not required for this study. Reporting for this study adhered to the modified Standards for Presenting Orthopedic Database Information checklist described by Ng et. al [21].

Patient selection

Patients who underwent primary TKA between 2015 and 2019 for unilateral, primary knee OA were identified within PearlDiver. Those who received any ipsilateral knee injection within 3 months prior to or a hyaluronic acid injection within 5 years following TKA were excluded in an effort to minimize confounding factors which may have contributed to PJI rates. Patients who received ipsilateral IACS injections following TKA were included in the injection cohort. The injection group was matched 2:1 on age range (5-year intervals), gender, and Charlson comorbidity index (CCI) to a control group that did not receive postoperative injections. After matching, there were no significant differences in age, CCI, and gender between groups though hypertension ($P = .001$), coronary artery disease ($P = .001$), arrhythmia ($P < .001$), chronic obstructive pulmonary disease ($P < .001$), and peripheral vascular disease were more prevalent in the injection group, while chronic kidney disease ($P < .001$) and diabetes mellitus ($P < .001$) were more prevalent in the control group (Table 1). Additionally, the injection cohort

Table 3
Distribution of corticosteroids used in first postoperative intra-articular injection.

Injectable	J code	Frequency (%)
Triamcinolone acetonide	J3301	41.8
Methylprednisolone acetate	J1030	25.1
Methylprednisolone acetate	J1040	14.1
Betamethasone acetate and betamethasone sodium phosphate	J0702	12.0
Dexamethasone sodium phosphate	J1100	5.9
Methylprednisolone acetate	J1020	0.8
Triamcinolone preservative-free extended release	J3304	0.2
Triamcinolone acetonide preservative-free	J3300	0.1
Methylprednisolone sodium succinate	J2930	0.1
Dexamethasone acetate	J1094	0.04
Hydrocortisone sodium succinate	J1720	0.04
Methylprednisolone sodium succinate	J2920	0.04
Triamcinolone diacetate	J3302	0.04

Table 4

Comparison of periprosthetic joint infection (PJI) and all-cause revision rates between injection and control groups.

Complication	Injection (n = 27059)	Control (n = 54116)	P-value
PJI (%)	362 (1.3)	406 (0.8)	<.001
Revision (%)	847 (3.1)	711 (1.3)	<.001

included a higher percentage of Medicare/Medicaid patients ($P < .001$) (Table 1).

Within the injection cohort, patients were subdivided according to whether they received 1, 2, or ≥ 3 injections.

Outcomes

One-year PJI and 2-year all-cause revision rates were compared between injection and control groups. For the purposes of this article, PJI was defined as patients who underwent a reoperation procedure for PJI. CPT codes 27,486 and 27,487 were used to identify 1-component and/or multicomponent revision procedures. Indications for revision procedures were identified using ICD-10 diagnostic codes and included pain, stiffness, PJI, loosening, and instability.

Statistical analysis

Statistical analysis was performed using R statistical software, version 4.2.1 (R Core Team, Vienna, Austria). Independent-samples t-test was used to compare continuous variables. Chi-squared test was used to compare categorical outcomes between groups. All odds ratios are reported relative to the control group. A P -value of .05 was used as the threshold of statistical significance.

Results

A total of 81,175 patients were included in this study; 27,059 (33.3%) were in the injection group and 54,116 (66.7%) were in the control group. The timing of each treatment intervention was recorded for both cohorts (Table 2) along with the identity of the corticosteroids utilized in the injection cohort (Table 3).

The 1-year PJI rate was 1.3% in the injection cohort and 0.8% in the control cohort ($P < .001$). (Table 4) (Fig. 1) The rate of PJI

increased with the number of post-TKA IACS injections received: 1 IACS (1.3%), 2 IACS (1.4%), and ≥ 3 IACS (1.8%) ($P < .001$ for all, compared to controls) (Table 5) (Fig. 2). The odds ratio of PJI in the injection cohort relative to the control cohort was 1.8 (95% confidence interval [CI]: 1.7, 1.9). The odds of infection increased with each subsequent IACS injection relative to controls: 1 injection 1.7 (95% CI: 1.6, 1.9), 2 injections 1.9 (95% CI: 1.6, 2.1), and ≥ 3 injections 2.4 (95% CI: 2.0, 2.9) ($P < .001$ for all, compared to controls). There were significant differences in patient characteristics between injection patients who later developed PJI and those who did not. (Table 6) Within the injection cohort, mean CCI score (<0.001) and the prevalence of congestive heart failure ($P < .001$), cardiac arrhythmia ($P = .001$), chronic kidney disease ($P = .002$), chronic obstructive pulmonary disease ($P = .031$), ischemic heart disease ($P = .005$), and diabetes mellitus ($P = .012$) were all significantly higher among patients who later developed PJI compared to injection patients who did not. Additionally, these patients were younger ($P < .001$) with a higher percentage of being males ($P < .001$).

The overall 2-year all cause revision rate was 3.1% in the injection cohort and 1.3% in the control cohort ($P < .001$) (Table 4) (Fig. 1). The rate of revision increased with the number of post-TKA IACS injections: 1 injection (2.5%), 2 injections (4.2%), and ≥ 3 injections (7.3%) ($P < .001$ for all, compared to controls) (Table 5) (Fig. 2). The odds ratio of revision in the injection cohort relative to the control group was 2.4 (95% CI: 2.3, 2.6). The odds of revision relative to controls increased with each subsequent IACS injection: 1 injection 2.0 (95% CI: 1.8, 2.1), 2 injections 3.3 (95% CI: 3.0, 3.6), and 3 injections 5.9 (95% CI: 5.4, 6.5) ($P < .001$ for all, compared to controls). On average, injection patients who later required revision TKA were younger ($P < .001$) with higher CCI scores ($P = .036$) compared to injection patients who did not require revision. Additionally, there was higher prevalence of male patients ($P = .001$), hypertension ($P = .031$), and chronic obstructive pulmonary disease ($P = .011$) amongst injection patients who underwent revision TKA.

Discussion

This study found a significantly increased risk of PJI at 1 year postoperatively and revision at 2 years postoperatively following injection of IACS into a preexisting TKA. The risk of both PJI and revision increased in accordance with the number of IACS injections that the patient received. Patients with more than 3

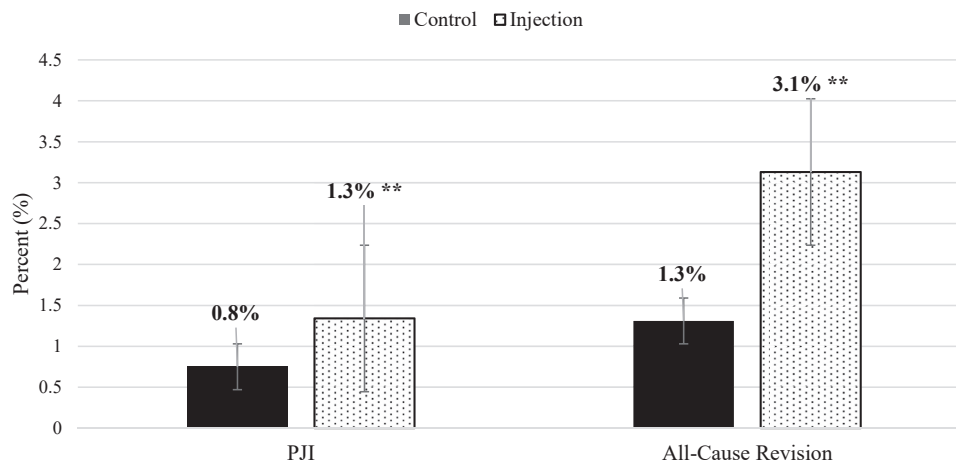


Figure 1. Bar graph comparing rates of periprosthetic joint infection (PJI) and all-cause revision rates between control and injection groups. Both PJI and all-cause revision rates were significantly higher in the injection group relative to the control.

Table 5
Incidence of periprosthetic joint infection (PJI) and all-cause revision by number of postoperative intra-articular corticosteroid injections received.

Complication	1 injection (n = 20751)	2 injections (n = 4471)	≥ 3 injections (n = 1837)
PJI (%)	267 (1.3)	62 (1.4)	33 (1.8)
Revision (%)	525 (2.5)	188 (4.2)	134 (7.3)

injections had a statistically increased PJI and revision risk compared to patients with only 1 or 2 injections, and patients with 2 injections had statistically increased PJI and revision risk compared to patients with only 1 injection. Within the injection cohort, the risk of either of PJI or revision was highest amongst younger, male, patients with a higher comorbidity burden.

Two theories have emerged to explain the increased risk of periprosthetic joint infection associated with intra-articular joint injections. First, the injection may inoculate the joint with contaminated skin and flora contained on that skin which may establish residence within the joint leading to infection [22]. Second, Eliasberg et al. [23] proposed that the biologic activity of the steroid may cause an immunomodulation of the intra-articular environment and/or alter the cell-based host defenses. The presence of the avascular arthroplasty implants creates an environment conducive to infection. The surfaces allow glyocalyx and biofilm formation which effectively shield bacteria from host defenses and even antibiotics.

It is possible that the TKAs which were persistently painful despite medications and physical therapy and injected with IACS had an indolent infection at the time of injection or had a failed reconstruction which would have required revision even without the injection. Since IACS injection is not frequently utilized after TKA, the injections may have been administered as a last attempt to avoid further surgery and may not have been the proximate cause of the infection or the revision.

This study had several limitations. First, PearlDiver is an insurance claims database, and it is possible that complications that occurred in patients who changed insurance plans during the 2-year study period were not captured. However, the large sample size of our study likely minimized the effect of patients who changed plans. Second, while PearlDiver does not report coding error rates, studies evaluating the accuracy of similar insurance claims databases have reported up to a 1.1% coding error rate [24].

In addition to applying strict exclusion criteria throughout our query in order to mitigate these confounding factors, we conducted a sub-analysis assuming a 1.1% type I error rate in the injection group and a 1.1% type II error rate in the control group for both PJI and all-cause revision. Under these conditions, differences in PJI (injection: 1.3% vs control: 0.8%; $P < .001$) and all-cause revision (injection: 3.1% vs control: 1.3%; $P < .001$) rates remained statistically significant. Finally, as mentioned previously, this study is limited as we are unable to establish causality between the IACS injection and ultimate infection or revision. Nevertheless, the significantly increased risk of both PJI and revision in those TKAs injected with IACS should call into question the utility and safety of this intervention.

Conclusions

In our query of a national insurance database, we found an increased incidence of both PJI at 1 year postoperatively, and revision surgery at 2 years postoperatively in patients who had an IACS injection into a preexisting TKA. This incidence further increased with each subsequent injection. We believe that patients with a painful total knee which is resistant to noninjection, nonsurgical management, are unlikely to benefit from injections. Furthermore, based on our data, any injection, and especially repeated injections subject the patient to a potentially unacceptably incrementally increased risk of infection and revision. Even amongst patients with an undiagnosed periprosthetic joint infection or who are destined for a revision anyway, IACS injections, if anything, are associated with an increased risk, rather than any substantial therapeutic benefit. Therefore, it is our opinion, based on our data, that IACS injections into a preexisting TKA should be strongly discouraged, especially amongst patients at high risk for infection or revision as detailed previously.

Conflicts of interest

Sean S. Rajaei reports being an educational consultant in DePuy and Biomet Zimmer and received research support from Biomet Zimmer. Andrew I. Spitzer is a part of speakers bureau of, a paid consultant for, and received research support from Depuy Pacira. All other authors declare no potential conflicts of interest.

For full disclosure statements refer to <https://doi.org/10.1016/j.artd.2023.101237>.

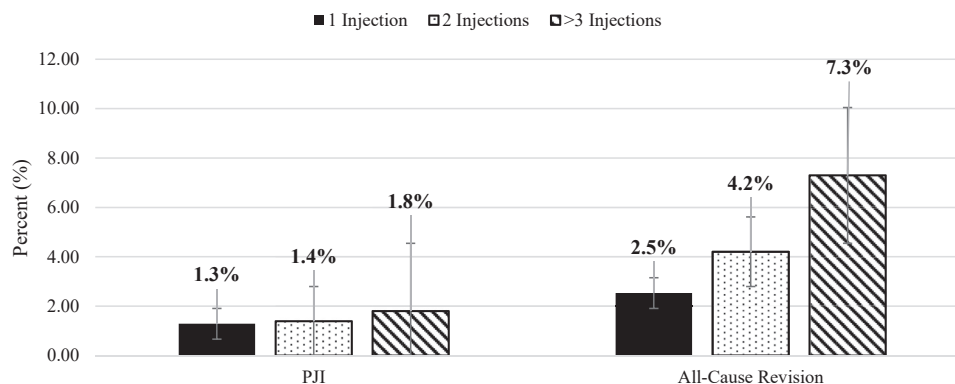


Figure 2. Bar graph comparing periprosthetic joint infection (PJI) and all-cause revision rates according to the number of postoperative injections received. Both PJI and all-cause revision rates increased with each subsequent injection.

Table 6
Subanalysis of patient characteristics in the injection cohort.

Characteristic	PJI (n = 362)	No PJI (n = 26,697)	P-value	Revision (n = 847)	No revision (n = 26,212)	P-value
Mean age (y)	64.1 + 9.2	66.8 + 8.9	<.001	63.7 + 8.8	66.9 + 8.9	<.001
No. of female (%)	222 (61.3)	18,583 (69.6)	<.001	546 (64.5)	18,259 (69.7)	.001
Mean CCI	2.5 + 2.1	2.0 ± 2.1	<.001	2.2 + 2.0	2.0 + 2.1	.036
Comorbidities:						
Hypertension (%)	308 (85.1)	21,867 (81.9)	.136	717 (84.7)	21,458 (81.9)	.031
Coronary artery disease (%)	91 (25.1)	6729 (25.2)	1.000	197 (23.3)	6623 (25.3)	.172
Congestive heart failure (%)	58 (16.0)	2720 (10.2)	<.001	89 (10.5)	2689 (10.3)	.805
Cardiac arrhythmia (%)	49 (13.5)	2326 (8.7)	.001	82 (9.7)	2293 (8.7)	.358
Chronic kidney disease (%)	91 (25.1)	5012 (18.8)	.002	169 (20.0)	4934 (18.8)	.435
COPD (%)	82 (22.7)	4872 (18.2)	.031	183 (21.6)	4771 (18.2)	.011
Ischemic heart disease (%)	20 (5.5)	791 (3.0)	.005	20 (2.4)	791 (3.0)	.351
Diabetes mellitus (%)	150 (41.4)	9359 (35.1)	.012	316 (37.3)	9193 (35.1)	.179
Valvular disease (%)	5 (1.4)	351 (1.3)	1.000	7 (0.8)	349 (1.3)	.305
Peripheral vascular disease (%)	46 (12.7)	2916 (10.9)	.273	91 (10.7)	2871 (11.0)	.918
Liver disease (%)	17 (4.7)	1213 (4.5)	.900	41 (4.8)	1189 (4.5)	.724
History of organ transplant (%)	0 (0)	6 (0)	1.000	0 (0)	6 (0)	1.000

CCI, Charlson comorbidity index; COPD, chronic obstructive pulmonary disease.

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