Research Article

Impact of Preoperative Intra-articular Injection on Infection Rates Following Total Knee Arthroplasty: An Analysis of Over 19,000 Patients

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Abstract

Background: Studies examining the relationship between timing of intra-articular injections and risk for periprosthetic joint infection (PJI) after total knee arthroplasty (TKA) are conflicting.

Methods: The TriNetX Research database was retrospectively queried to evaluate all patients with a diagnosis of osteoarthritis undergoing primary TKA between January 1, 2010 and September 30, 2018. Patients were then grouped based on whether they had a preoperative intra-articular injection of hyaluronic acid or corticosteroid within the three months prior to surgery. Analysis was performed using unmatched and propensity score matched cohorts. The primary endpoint was periprosthetic joint infection within 12 months of surgery.

Results: After propensity score matching for age and comorbidities, no difference in one-year PJI rates was observed between groups (No Injection: 20 PJI (2.21%) vs. Injection: 28 PJI (3.10%), No Injection OR=0.708, p=.244).

Conclusion: After propensity score matching for age and comorbidities, no increased risk in periprosthetic infection rate at one year following TKA was observed between for patients receiving hyaluronic acid, corticosteroid or triamcinolone injection within three months of surgery, compared to those receiving no injections in the three-month preoperative period. A large, multicenter, retrospective review of outcomes is warranted if consensus regarding appropriate preoperative timing of injections is to be reached. We continue to recommend caution in administering injections in the three months prior to surgery until a consensus can be reached.

Keywords: Total knee arthroplasty; Injection; Infection

1. Background

Total knee arthroplasty (TKA) is a mainstay treatment option for patients suffering from degenerative osteoarthritis (OA) of the knee, and is expected to grow to a total of 3.48 million annual procedures by 2030 [1]. Prior to surgical intervention, intra-articular injection of corticosteroids or hyaluronic acid (HA) into the knee to improve pain and function is commonly performed in up to 30% of patients undergoing TKA [2]. Despite the expanded use of intra-articular injections, debate regarding their efficacy and durability of effect in the treatment of OA remains [3-6]. This ambiguity is reflected by the American Academy of Orthopedic Surgeons (AAOS) 2013 treatment guidelines, which 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 knee OA [7]. Further, there is controversy surrounding whether the timing of preoperative intra-articular injections increases the risk of periprosthetic joint infection (PJI) following both total hip arthroplasty (THA) [8-10] and TKA [11-17]. Proposed reasons for this increased risk include the immunosuppressive effects of corticosteroids and the direct infiltration of the joint from the injection itself [13].

The concepts of real world data and real world evidence refer to the use of health information from multiple sources outside of typical clinical research settings, such as electronic health records, claims data, registries and personal devices [18-20]. Evidence from these non-traditional sources can be complimentary to clinical trials and may efficiently allow for the investigation of broad populations, although limitations of data quality and the potential for confounding and bias must be considered when evaluating these studies [20]. To investigate the relationship between preoperative injection timing and risk of postoperative PJI, we analyzed a large, multicenter longitudinal database.

2. Methods

After receiving institutional review board exemption, the TriNetX Research database was retrospectively queried as of October 1, 2019 to evaluate all patients with a diagnosis of osteoarthritis undergoing primary TKA between January 1, 2010 and September 30, 2018. Patients were then classified based on whether they received a preoperative intra-articular injection of hyaluronic acid or corticosteroid within the three months prior to surgery. Analysis was performed using unmatched and propensity score matched cohorts. The primary endpoint was periprosthetic joint infection within 12 months of surgery, identified by relevant diagnosis or procedure codes. Statistical analysis was performed within the TriNetX Analytics platform and Microsoft Excel, with odds ratios calculated as described by Altman [21].

2.1 Cohort definitions

Surgery was defined by the presence of the primary total knee arthroplasty current procedural terminology (CPT) code along with the appropriate international classification of disease 10th edition (ICD-10) diagnosis code for unilateral post-traumatic or primary osteoarthritis of the left or right knee, respectively, between January 1, 2010 and September 30, 2018. Injection within 3 months of surgery was defined as any instance of the CPT code for arthrocentesis, aspiration and/or injection of a major joint or bursa (with or without ultrasound guidance), along with the matching ICD-10 laterality code, and a healthcare common procedure coding system (HCPCS) code for one of the included injection types. All patients with a concurrent ICD-10 code of post-traumatic or primary OA of the contralateral knee at the time of injection were excluded to control for laterality. Patients not receiving injections were defined by the presence of a surgery with a laterality code, excluding patients with any instance of injection on the ipsilateral knee within 3 months of the surgery date. The 3 month preoperative period was selected to allow for comparison with previous studies, and because our institutional protocol is to not perform TKA within 3 months of intra-articular injection on the operative knee.

2.2 Risk adjustment

Propensity scores were developed based on age and the presence or absence of the following comorbidities, as defined by ICD-10 codes, within one-year prior to surgery: essential (primary) hypertension, overweight and obesity, diabetes mellitus, personal history of nicotine dependence, other cardiac arrhythmias, chronic ischemic heart disease, nicotine dependence, and atrial fibrillation and flutter.

2.3 Endpoint

In alignment with prior studies, PJI was identified by the ICD-10 code for infection due to internal knee prosthesis or the CPT codes for treatment of infection. Surgical treatments of infection that were included were incision and drainage, deep incision with opening of bone cortex, arthrotomy with exploration and drainage or removal of foreign body, or removal of prosthesis with or without insertion of a spacer within one year of primary surgery. A full list of codes used to define the treatments, comorbidities, and endpoint is included as Appendix A.

2.4 About TriNetX

TriNetX is a "global health research network that optimizes clinical research and enables discoveries through the generation of real-world evidence" [22]. The research platform includes a federated health research network providing access to statistics on electronic medical records (diagnoses, procedures, medications, laboratory values, genomic information) including longitudinal data from 26 health care organizations and includes over 37 million patients. TriNetX received a waiver from Western IRB, as no protected health information is included in the database. On average, participants submit data retrospectively for seven years, with some providing historical data 13 years or older [23]. Diagnoses and procedures coded using ICD-9 (prior to October 1, 2015) are converted to ICD-10 using General Equivalence Mapping (GEMS) [24]. Using this methodology, all ICD-9 OA codes lacking laterality are mapped to non-laterality specific ICD-10 codes and are therefore excluded from this analysis. Statistical analysis is performed within the analytics platform [23].

3. Results

A total of 19,510 patients undergoing primary unilateral TKA between January 1, 2010 and September 30, 2018 were retrospectively reviewed. Of the 903 patients receiving injections within 3 months of surgery, 125 (14%) received hyaluronic acid only, 715 (79%) received corticosteroid only, and the remaining 63 (7%) received a combination of hyaluronic acid and corticosteroid. In unmatched analysis of the total sample of 19,510 subjects, no significant difference in one-year PJI rate was observed (No injection: 416 PJI (2.24%) vs. Injection: 28 PJI (3.10%), No Injection OR=0.715, 95% CI: 0.485-1.054, p=.090) (Table 1). Patients were then propensity score matched to control for potentially confounding comorbidities. No significant differences in age or comorbidities remained after propensity score matching and controlling for laterality (Table 2). After propensity score matching, no significant difference in infection rate between groups at one year was observed (No injection: 20 PJI (2.21%) vs. Injection: 28 PJI (3.10%), No Injection OR=0.708, 95% CI: 0.396-1.266, p=.244) (Table 1).

	No Injection < 3 Months N=18,607		Injection < 3 Months N=903				
	PJI (N)	PJI (%)	PJI (N)	PJI (%)	No Injection Odds Ratio	OR 95% CI	P Value
Unmatched	416	2.24%	28	3.10%	0.715	0.485-1.054	0.090
Propensity Score Matched*	20	2.21%	28	3.10%	0.708	0.396-1.266	0.244

*Number of subjects in each propensity score matched cohort = 903.

Table 1: One year PJI rates after TKA: unmatched and propensity score matched analysis.

	Left TKA									
	Unmatched Cohorts					**Propensity Score Matched Cohorts**				
	No Injection < 3 Mos. N=6,324		Injection < 3 Mos. N=442			No Injection < 3 Mos. N=442		Injection < 3 Mos. N=442		
Comorbidity/Demographics	N	%	N	%	P Value	N	%	N	%	P Value
Essential (primary) hypertension	4125	65.23%	304	68.78%	0.129	304	68.78%	304	68.78%	1.000
Overweight and obesity	2488	39.34%	132	29.86%	**<.001**	130	29.41%	132	29.86%	0.883
Diabetes mellitus	1477	23.36%	94	21.27%	0.315	92	20.81%	94	21.27%	0.869
Personal history of nicotine dependence	1363	21.55%	82	18.55%	0.137	82	18.55%	82	18.55%	1.000
Other cardiac arrhythmias	775	12.26%	61	13.80%	0.340	63	14.25%	61	13.80%	0.846
Chronic ischemic heart disease	453	7.16%	40	9.05%	0.140	37	8.37%	40	9.05%	0.720
Nicotine dependence	519	8.21%	39	8.82%	0.649	36	8.15%	39	8.82%	0.717
Atrial fibrillation and flutter	481	7.61%	34	7.69%	0.947	35	7.92%	34	7.69%	0.900
Age at Index (Avg. SD)	65.4	10.0	66.4	10.2	**0.040**	66.5	10.4	66.4	10.2	0.958
At least 75 years	1167	18.45%	106	23.98%	**0.004**	107	24.21%	106	23.98%	0.937
65-75 years	2320	36.69%	157	35.52%	0.623	154	34.84%	157	35.52%	0.833
55-65 years	1984	31.37%	124	28.05%	0.145	127	28.73%	124	28.05%	0.823
At most 55 years	853	13.49%	55	12.44%	0.533	54	12.22%	55	12.44%	0.919
	Right TKA									
	Unmatched Cohorts					**Propensity Score Matched Cohorts**				
	No Injection < 3 Mos. N= 12,283		Injection < 3 Mos. N=461			No Injection < 3 Mos. N=461			Injection < 3 Mos. N=461	
Comorbidity/Demographics	N	%	N	%	P Value	N	%	N	%	P Value
Essential (primary) hypertension	8263	67.27%	328	71.15%	0.081	328	71.15%	328	71.15%	1.000
Overweight and obesity	4676	38.07%	175	37.96%	0.963	176	38.18%	175	37.96%	0.946
Diabetes mellitus	2811	22.89%	115	24.95%	0.302	115	24.95%	115	24.95%	1.000
Personal history of nicotine dependence	2504	20.39%	102	22.13%	0.363	102	22.13%	102	22.13%	1.000
Other cardiac arrhythmias	1573	12.81%	74	16.05%	**0.041**	75	16.27%	74	16.05%	0.929
Chronic ischemic heart disease	925	7.53%	46	9.98%	0.052	45	9.76%	46	9.98%	0.912
Nicotine dependence	929	7.56%	36	7.81%	0.845	35	7.59%	36	7.81%	0.902
Atrial fibrillation and flutter	925	7.53%	31	6.73%	0.519	30	6.51%	31	6.73%	0.895
Age at Index (Avg. SD)	65.7	9.7	66.6	10.0	0.051	66.7	9.3	66.6	10.0	0.965
At least 75 years	2267	18.46%	96	20.82%	0.199	95	20.61%	96	20.82%	0.935
65-75 years	4675	38.06%	188	40.78%	0.238	189	41.00%	188	40.78%	0.947
55-65 years	3832	31.20%	128	27.77%	0.118	128	27.77%	128	27.77%	1.000
At most 55 years	1509	12.29%	49	10.63%	0.287	49	10.63%	49	10.63%	1.000

Table 2: TKA propensity score matching, controlling for laterality.

4. Discussion

The rates of infection following TKA observed in our study are similar to those previously reported [13, 16, 17]. Our findings suggest that even after controlling for age and comorbidities, patients undergoing ipsilateral intra-articular injections within three months of TKA may not be at significantly increased risk for PJI.

Our findings align with those of Amin et al, whose 2016 retrospective review of 1,628 TKA patients is the largest study concluding that there does not appear to be a correlation between timing of injection before surgery and increased risk of infection [25]. The authors found a deep postoperative infection rate of 0.77% in patients receiving preoperative injections within 12 months prior to surgery and 1.18% in the control group of those who did not. No differences in infection rate between the no injection group (1.18%), patients receiving steroid injections (1.11%) or patients receiving viscosupplementation (0.47%) were observed. No difference in infection rate was found regardless of the timing of the preoperative injection, with patients undergoing injections within 3 months of surgery demonstrating a PJI rate of 1.4%. Average time to deep infection was 5 months in the control group and 8.67 months in the injection group. While our study and Amin's reached similar conclusions, at 2.24% for no injection and 3.10% for injections, the rates of PJI observed in our study are higher than those reported by Amin. A strength of our study is that it further supports these previous conclusions, while incorporating risk adjustment through propensity score matching to control for the impact of age and comorbidities on risk for PJI.

Other smaller studies have also reached the conclusion that preoperative injections do not increase the risk of PJI after TKA. In a review of 442 patients undergoing primary TKA, Kokubun et al found that after controlling for confounding variables, intra-articular corticosteroid, viscosupplementation, and any injection within 90 days were not associated with an increase in complications, infection, or poor functional outcomes after TKA (all p> .05). On multivariate logistic regression analysis, injection within 90 days resulted in no significant increase in risk for infection (OR=0.534, 95% CI 0.116-2.446, p= .419) [16]. Desai et al examined the risk of superficial and deep infections in patients receiving intra-articular steroid injections within 12 months of TKA. They found a superficial infection rate of 4.4% in the injection group (n=45) and 2.8% in the control group (n=180)—a difference that was not statistically significant—and no deep infections in either group [17]. In addition to these primary evaluations, two systematic reviews [2, 26] concluded that preoperative intra-articular injection does not increase the risk of PJI following TKA, but also highlighted that current studies are often underpowered and may suffer from selection bias.

In contrast to our findings, a retrospective review of 144 patients by Papavasiliou et al raised concern that intra-articular steroid injections may increase risk for postoperative deep infection following TKA, as evidenced by a 22.2% rate of wound complications in the 54 patients who underwent injection prior to surgery compared to a rate of 11.1% in 90 controls. Three of 54 (5.6%) patients undergoing preoperative injections within 12 months of TKA had deep infections, compared to zero in the control group [14]. Due to the small sample size [27], ambiguous definition of infection [28], and lack of correlation between injection timing and infection rate, the validity of the study has been debated [17].

The strongest evidence supporting an increased risk of postoperative PJI for patients undergoing viscosupplementation or steroid injections prior to TKA is presented by Richardson et al's 2019 review of 58,337 patients from a national database [13]. The overall 6-month postoperative infection rate, including the control group of patients not receiving injections within 12 months of TKA, was 2.83% (No injection PJI rate=2.74%, HA within 3 months of TKA PJI rate=4.18% and corticosteroid within 3 months of TKA PJI rate=3.25%). These results closely align with our finding of a 2.24% PJI rate in the unmatched and 2.21% in the propensity score matched no-injection cohorts, compared to a PJI rate of 3.10% in patients receiving an injection within 3 months of TKA. [13]. Despite demonstrating similar trends in infection rates, our studies reached opposing conclusions based on the statistical significance of the differences observed. Both studies are comparable in their use of large, administrative databases to assess risk of PJI, and utilization of statistical controls for potentially confounding factors. Significant differences in approach include Richardson's exclusion of patients receiving both corticosteroids and hyaluronic acid injection, which were included in our analysis, Richardson's use of a 6-month postoperative infection rate in comparison to our evaluation of infections up to 12 months postoperatively, and Richardson's stratification of PJI rate and risk by injection type, whether multiple injections were received, and comparison of risk between multiple preoperative injection time points.

Based on the conflicting conclusions reached by the studies presented, we suggest the current state of the literature is not sufficient to reach a consensus regarding the risk of PJI following TKA after injections within three months of surgery. Until consensus is reached, our institution will continue to utilize a conservative approach and not perform TKA within three months of intra-articular injection. Given the inherent limitations of administrative datasets relying on coded data—which has been demonstrated to have inaccuracies, [29] we suggest a large-scale, multisite retrospective review of outcomes using clinician validated measures is needed if a consensus treatment guideline is to be reached.

5. Limitations

The primary limitation of our study is its reliance on coded data submitted to an administrative database in a blinded fashion. This data structure inherently limits our granularity of analysis, and limits the ability to evaluate potentially clinically significant factors such as whether dosing vials were single or multi-use, exact number of doses received, and methods of controlling for sterility at the time of injection. Despite these potential limitations, which are inherently present in aggregated databases, we suggest the use of large-scale real world data is a valuable supplement to smaller, but potentially more robust data sets from institutional reviews. Finally, our study was limited by the relatively small number of patients receiving injections within the three-month preoperative period (903). This left the study underpowered to assess differences in PJI rate by injection type, as sample sizes of 2,000 patients per group are recommended to rule out a 50% increase in infection rate across cohorts [17].

6. Conclusion

Based on analysis of 19,510 patients undergoing TKA from a longitudinal multicenter database, after controlling for age and comorbidities, preoperative injection within three months of surgery was not associated with increased risk for postoperative periprosthetic joint infection. A large, multicenter, retrospective review of outcomes is warranted to establish a true consensus regarding appropriate preoperative timing of injections. We continue to recommend caution in administering injections in the three months preceding surgery until a consensus can be reached.

Conflict of Interest

None of the authors have any relevant conflict of interest to disclose.

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Institutional Review Board

Study was deemed exempt by the institutional Clinical Research Committee.

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