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Systematic Review and Meta-Analysis

Association Between Tranexamic Acid and Decreased Periprosthetic Joint Infection Risk in Patients Undergoing Total Hip and Knee Arthroplasty: A Systematic Review and Meta-Analysis of Over 2 Million Patients

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ABSTRACT

Background: The purpose of this study was to perform a systematic review and meta-analysis to evaluate the association between tranexamic acid (TXA) use during primary total hip arthroplasty (THA) and primary total knee arthroplasty (TKA), and the risk of developing periprosthetic joint infection (PJI) after these procedures.

Methods: A systematic review was carried out from inception to October 17, 2022. There were 6 studies that were ultimately included in the meta-analysis. The association between the development of PJI and TXA was analyzed using odds ratios (ORs) with 95% confidence intervals (CIs) and estimates of risk difference (RD). Subgroup analysis was performed to evaluate only studies reporting out to 90 days of follow-up versus more than 90 days of follow-up.

Results: Among 2,098,469 arthroplasties, TXA utilization was associated with an overall lower risk of PJI (OR = 0.63 [95% CI 0.42 to 0.96], $P < .001$) and a 0.4% lower incidence of PJI (RD = −0.0038, 95% CI [-0.005 to −0.002], $P < .001$). When subgrouping the studies according to length of follow-up, TXA was associated with a lower risk of PJI (OR = 0.43 [95% CI 0.35 to 0.53], $P < .001$) and a 1% lower incidence of PJI (RD = −0.0095 [95% CI −0.013 to −0.005], $P < .001$) in patients followed for more than 90 days.

Conclusions: This meta-analysis demonstrates that TXA use is associated with a reduced risk of PJI, with our RD analysis identifying an approximately 0.4% reduction in PJI rates with TXA use. These findings provide even more data to support the routine use of TXA during primary THA and primary TKA.

Tranexamic acid (TXA) inhibits plasmin from binding to fibrin and thus helps maintain hemostasis [1]. It is a safe and effective drug regardless of the route of administration [2], that is widely used to reduce perioperative bleeding in cardiac, obstetric, trauma, and orthopaedic surgery [1,3,4]. The use of TXA in orthopaedic surgery has increased dramatically in the last decade. A recent study estimates that TXA usage in total joint arthroplasty (TJA) has increased from 0.1% of cases in 2008 to 89.2% of cases in 2020 [5]. The use of TXA in total knee arthroplasty (TKA) and total hip arthroplasty (THA) has led to reductions in blood loss and the need for blood transfusions following these procedures [6–9].

In addition to decreasing blood loss and rates of transfusion after TJA, recent data have suggested that TXA may also be associated with decreased rates of periprosthetic joint infection (PJI) [10–12]. Hong et al. found that TXA administration in primary THA and TKA was associated with reductions in PJI in the 90 days

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following surgery (odds ratio [OR] = 0.69, 95% confidence interval [CI] 0.55 to 0.75) [11]. A PJI is a devastating complication following surgery and is associated with substantial patient morbidity, mortality, and increased hospital costs [13,14]. However, the link between TXA and PJI risk is still under investigation, and it is not clear whether TXA is truly associated with decreased PJI risk. A systematic review and meta-analysis of the available literature would help to better understand the link between TXA and PJI risk. Therefore, the purpose of this study was to perform a systematic review and meta-analysis to evaluate the association between TXA use and PJI risk following primary TKA and primary THA. To the best of our knowledge, this meta-analysis is the first to examine the link between TXA administration and PJI in primary total hip and knee arthroplasty in such a large population.

Materials and Methods

The systematic review search strategy was designed and conducted by a health sciences librarian, with expertise in literature searches for systematic reviews. The search strategy was developed by the librarian who had input from 2 authors. The comprehensive search was performed on several databases from each database's inception to October 17, 2022. The databases included Ovid MEDLINE and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, and Daily, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, Scopus, and Web of Science. A controlled vocabulary supplemented with keywords was used to search for studies evaluating TXA and reporting PJI rates after primary THA and primary TKA. The formal strategy listing all search terms used and how they were combined is available in Appendix A. This study was registered in Prospective Register of Systematic Reviews Reporting under the registration number CRD42022369350, and followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines [15]. Our inclusion criteria were studies that were peer-reviewed and reported the numbers of PJI with and without the use of TXA following primary THA and primary TKA. We excluded animal studies, studies that have no definition for PJI diagnosis, revision THA, revision TKA, and studies that are not peer-reviewed. We applied these criteria in screening the retrieved articles from the database search. The numbers of articles and details of screening are shown in the Preferred Reporting Items for

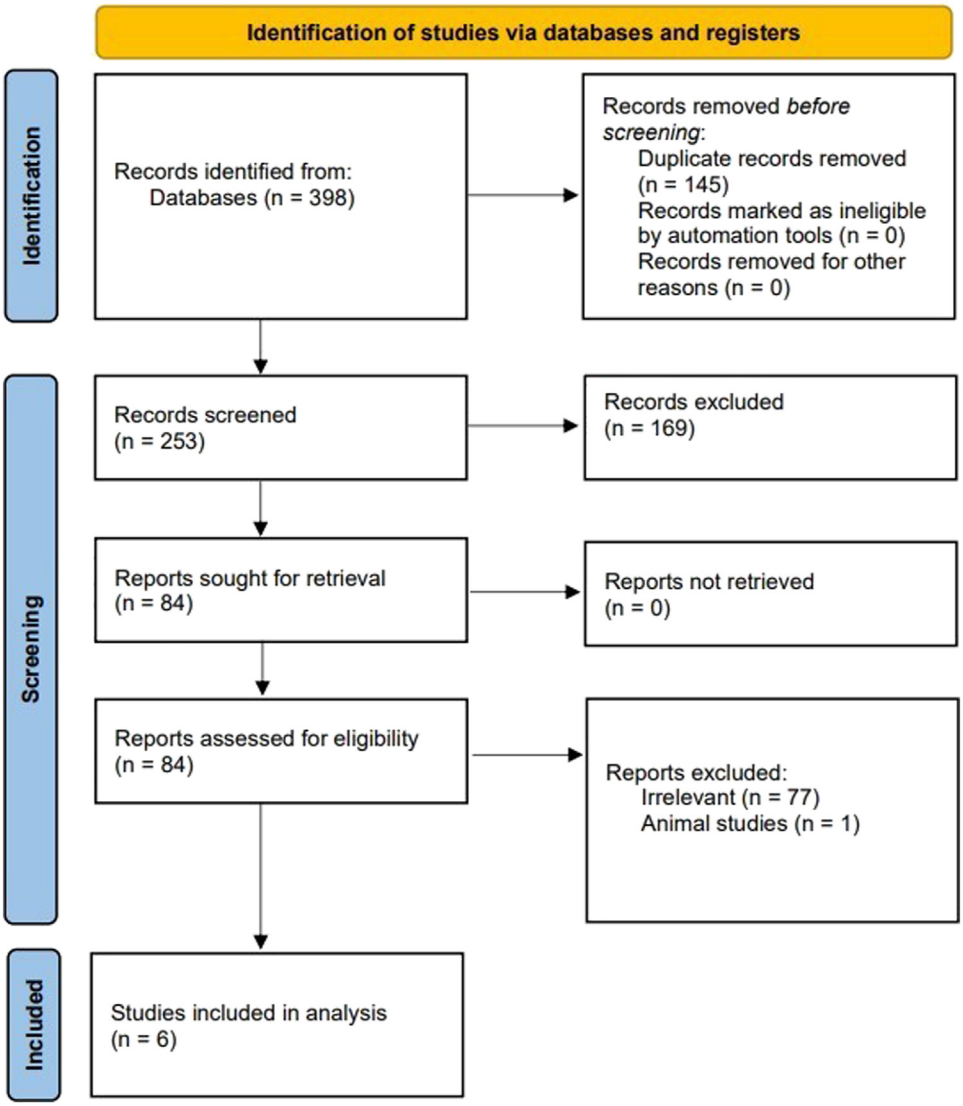

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow chart.

Table 1
Summary of Included Studies.

Study	Year	Country	Arthroplasty Type	Number of Patients			TXA Route of Admin	TXA Dose	Follow-Up Period	Criteria for PJI Diagnosis
				With TXA	Without TXA	Total				
Heckmann et al. [5]	2023	USA	Primary THA and TKA	87,4627	24,6231	1,120,858	NR	NR	90 d	ICD-10 diagnosis code (specific codes NR)
Shohat et al. [16]	2022	USA	Primary THA and TKA	14,883	16,448	31,331	NR	NR	Minimum 1 y	2018 ICM criteria [17]
Hong et al. [11]	2021	USA	Primary THA and TKA	421,029	493,961	914,990	NR	<1,000 mg in 92% of patients	90 d	ICD-9 diagnosis code 996.66
Drain et al. [12]	2020	USA	Primary TKA	4,423	18,998	23,421	61% IV, 23% oral, 16% topical	NR	2 y	ICD-9 diagnosis code 996.66
Lacko et al. [18]	2020	Slovakia	Primary TKA	787	742	1,529	NR	10 mg/kg	Minimum 2 y	MSIS criteria [19]
Yazdi et al. [20]	2020	USA	Primary THA and TKA	3,683	2,657	6,340	NR	15 mg/kg	Mean duration of 26.3 mo (range, 12 to 67.3)	2018 ICM criteria [17]

USA, United States of America; THA, total hip arthroplasty; TKA, total knee arthroplasty; TXA, tranexamic acid; PJI, periprosthetic joint infection; ICM, international consensus meeting; MSIS, musculoskeletal infection society; NR, not reported.

Systematic Reviews and Meta-analyses diagram (Figure 1). In total, 398 studies were retrieved from searching databases and registers. After removing the duplicates, we screened the titles and abstracts of the remaining articles (n = 253) for inclusion. We identified 84 studies relevant to our research topic and retrieved the full text of each article for screening. Only 6 studies met our inclusion criteria and were included in the analysis (Table 1). In total, our analysis included 2,098,469 TJA procedures. Of these procedures, 760,358 (36%) were primary THA and 1,338,111 (64%) were primary TKA. TXA was given at the time of surgery for 1,319,432 (63%) of the surgical cases in the analyses, and the remaining 779,037 cases (37%) did not receive any TXA. Due to the differing lengths of follow-up reported among the included studies, subgroup analyses were also performed on 2 groups: (1) studies reporting PJI outcomes only out to 90 days after the index TJA procedure [5,11] and (2) studies reporting PJI outcomes past 90 days of follow-up following the index TJA procedure [12,16,19,21].

Data Extraction

There were 2 authors who independently extracted the data from the included articles. The data extracted from each study, when reported, included the following: number of patients, number of PJI events, route of TXA administration, dose of TXA, criteria for PJI diagnosis, type of TJA, study design, country, and year of publication. The decision to administer TXA or not was unable to be determined from the included studies, but was likely based upon multiple factors, including patient overall health and comorbidities. Studies are summarized in Table 1.

Quality Assessment

There were 2 authors who independently assessed the quality of the included studies. A consensus was reached by the authors on both quality assessment and extracted data. The Newcastle-Ottawa Scale (NOS) was used to assess the quality of the included studies [21]. A score of 7 to 9 was considered good quality, a score of 5 or 6 was considered moderate quality, and a score of 0 to 4 was considered poor quality. The following references scored an 8 on the NOS [5,11,12,20] and 2 references [16,18] scored 7 on the NOS. Details of the quality assessment are available in Appendix B.

Data Analyses

This meta-analysis was performed using Review Manager (version 5.4.1, The Cochrane Collaboration, Copenhagen) [22]. The analysis was conducted by analyzing the reported number of patients and events to estimate the OR and risk difference (RD). Calculating the RD provides an estimate of the actual change in the risk of PJI with and without TXA. We conducted the analysis using the random-effect model of DerSimonian-Laird [23]. The heterogeneity of the analysis was measured using the *P* value, I^2, and *Chi*-square tests. Heterogeneity of more than 50% in the I^2 test was considered high. A *P* value less than .05 was considered significant for the measured effect, and a *P* value of less than .1 was considered significant for the heterogeneity. Due to the relatively small number of included studies, publication bias and meta-regression are not applicable. Sensitivity analyses were performed by removing the following references [5,11], and observing changes in the overall effect.

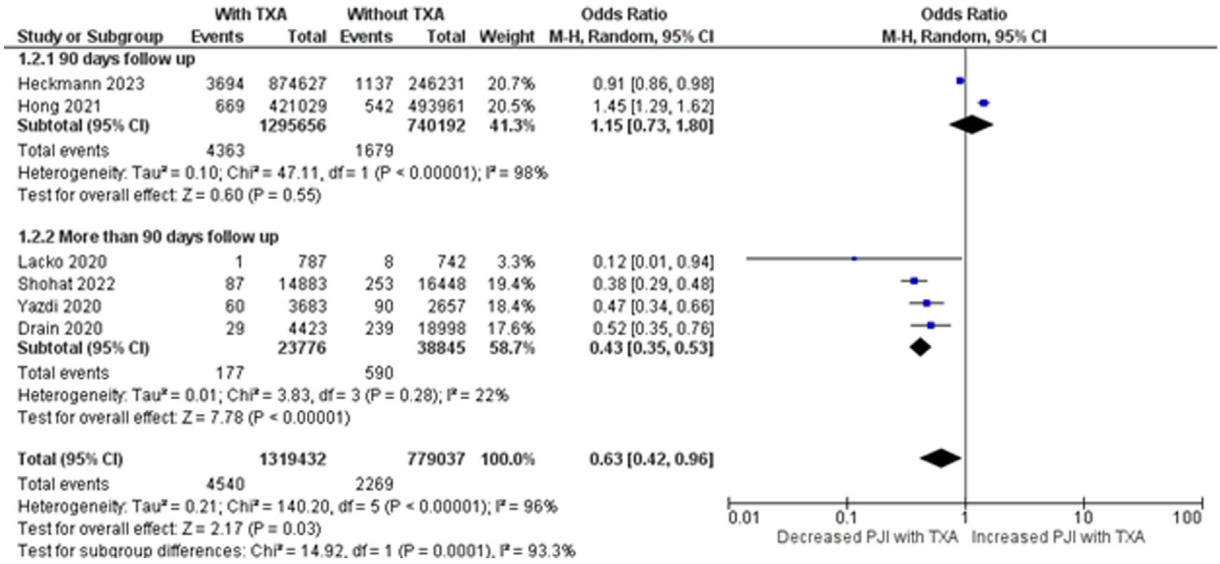

Fig. 2. Forest plot of the odds ratio of periprosthetic joint infection (PJI) with and without tranexamic acid (TXA).

Results

Risk of PJI With and Without TXA

When evaluating the 2 studies reporting PJI outcomes within 90 days of surgery, there was an insignificant association between TXA use and PJI (1.15 [0.73, 1.80], $P = .55$) with significant heterogeneity present ($P < .001$, $I^2 = 98\%$). In contrast, when analyzing the 4 studies that reported PJI outcomes past 90 days of follow-up, TXA utilization was associated with a reduction in PJI (OR = 0.43, 95% CI 0.35 to 0.53, $P < .001$). Heterogeneity for this subgroup was insignificant ($P = .28$, $I^2 = 22\%$). When all studies were included in the analysis, we found significantly lower odds of PJI with the use of TXA (OR = 0.63, 95% CI 0.42 to 0.96, $P < .001$). The overall heterogeneity for this analysis was significant ($P < .001$, $I^2 = 96\%$). Results are shown in Figure 2. When 2 studies (Heckman et al. and Hong et al.) were removed for sensitivity analysis, TXA still had statistically significant lower odds of PJI (OR = 0.43, $P < .001$).

Risk Difference Between PJI With and Without the Use of TXA

When evaluating the 2 studies reporting outcomes within 90 days of surgery, there was an insignificant RD ($P = .92$) with TXA use and significant heterogeneity ($P < .001$, $I^2 = 97\%$). Patients who had more than 90 days of follow-up had a significant reduction in PJI when they received TXA (RD = −0.0095, 95% CI −0.013 to −0.005, $P < .001$), with high heterogeneity present in this subgroup ($P = .02$, $I^2 = 69\%$). The overall RD for all 6 studies included in the analysis was significant (RD = −0.0038, 95% CI −0.005 to −0.002, $P < .001$), with high heterogeneity ($P < .001$, $I^2 = 97\%$) as shown in Figure 3. A RD of −0.0095

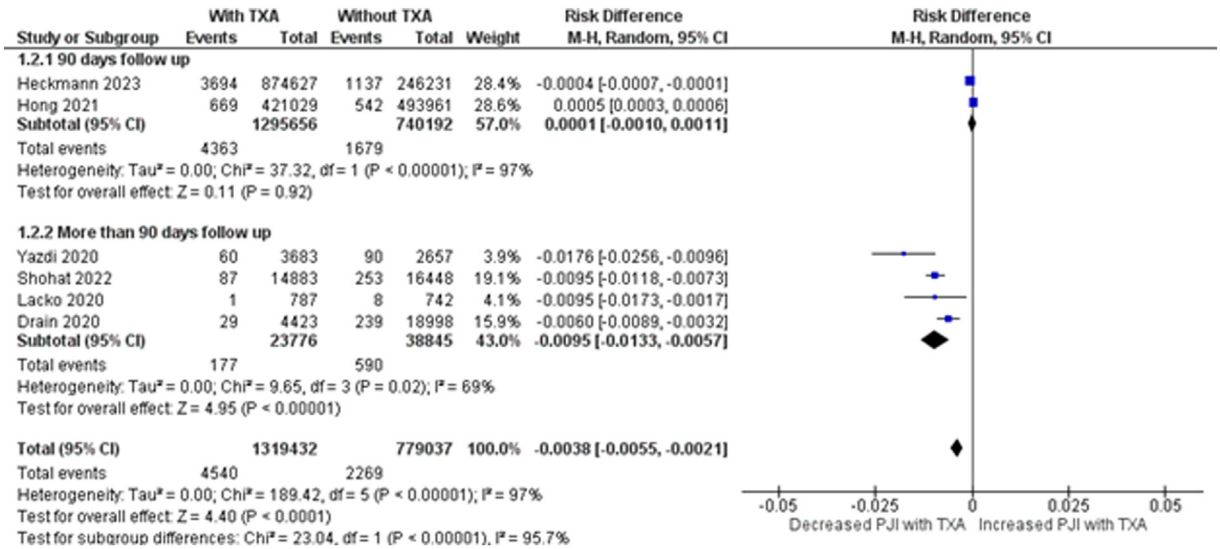

Fig. 3. Risk difference of periprosthetic joint infection (PJI) with and without tranexamic acid (TXA).

(0.95%) means that those who received TXA had an almost 1% lower incidence of PJI than those who did not receive TXA. When removing Heckmann et al. and Hong et al. for sensitivity analysis, a lower incidence of PJI remained associated with TXA use (RD = −0.01, $P < .001$).

Discussion

TXA administered during THA and TKA has been shown to substantially reduce blood loss and the risk of needing a blood transfusion following surgery [6–9]. To our knowledge, this is the first meta-analysis to directly evaluate the association between TXA and PJI in patients undergoing primary TKA and primary THA over such a large cohort of patients. Our systematic review identified 6 studies [5,11,12,16,18,20] for inclusion in our meta-analysis, which amounted to more than 2 million cases of TJA. This study demonstrated that TXA administration was associated with a lower risk of PJI (OR = 0.63, $P < .001$), and this finding remained when we analyzed only studies that evaluated patients who had outcomes longer than 90 days (OR = 0.43, $P < .001$). Use of TXA was also associated with an approximately 1% lower rate of PJI (RD = −0.0095, $P < .001$) when analyzing outcomes over the past 90 days. When all studies were included, our risk reduction analysis revealed TXA use to be associated with an approximately 0.4% lower rate of PJI (RD = −0.0038, $P < .001$). Due to having 2 studies with statistically insignificant RD [5,11], the overall RD for both groups was lower (0.4%) than the subgroup with more than 90 days of follow-up (1%). Given the relatively rare incidence of PJI, a 0.4% reduction in PJI rates with TXA use is likely a clinically relevant finding. In a subgroup analysis of the 2 studies that only reported outcomes for 90 days [5,11], we did not identify a statistically significant association between TXA and early PJI rates. The shorter follow-up duration and how data are recorded and captured in the 2 database studies could explain the different findings relative to institutional studies with a longer follow-up. However, both studies reported a statistically significant lower risk of PJI with the use of TXA after adjusting for covariates within their respective studies [5,11]. The findings for these individual studies support the results of our overall analysis and our subgroup analysis for only studies with more than 90 days of follow-up.

The association between TXA use and decreased PJI risk identified in this meta-analysis could be explained by the ability of TXA to reduce the need for allogenic transfusions, postoperative wound drainage, or hematoma formation, all of which have been associated with the development of PJI [24–28]. However, it is also possible that TXA itself may have a direct antimicrobial effect, as a recent *in vitro* study demonstrated a potential antimicrobial effect of TXA [29]. Benjumea et al. reported a synergistic antimicrobial effect against *Staphylococcus aureus* isolated from patients who had a PJI when combining TXA with both vancomycin and gentamycin [29].

In addition to being effective at reducing the rates of blood transfusion and being associated with reduced PJI risk, a recent study found that TXA is a highly cost-effective intervention [14]. Premkumar et al. [14] used a break-even model to see if routine administration of TXA lowered the economic costs by preventing PJI. They found that TXA as a preventive measure is cost-effective even when adjusting for different costs of TXA, different PJI rates, and different treatment costs of PJI [14]. According to Premkumar et al. [14], the average cost of 1 THA PJI was $32,100 in 2017. Therefore, preventing even 1 PJI could have major cost reductions. These results, paired with our meta-analysis and the well-documented reduction in blood loss from TXA administration, provide even more data to support the broad use of this medication during primary THA and primary TKA.

Potential Limitations

The main limitation of our study is the relatively small number of studies included in the analysis. However, a detailed systematic review was performed to identify all studies reporting TXA use and rates of PJI after primary THA and primary TKA. Another limitation is the significant heterogeneity found in the studies. The overall heterogeneity in our analysis was statistically significant, but only 2 studies accounted for the heterogeneity [5,11]. These studies differed from the other studies in having a shorter follow-up period. Additionally, Hong et al. and Heckmann et al. are large database studies that could have duplicate cases with other studies in the analysis. However, our sensitivity analysis found no significant change in the overall effect when Hong et al. and Heckmann et al. were removed. During the subgroup analysis of only studies with more than 90 days of follow-up, the heterogeneity was no longer significant. Also, the diagnostic criteria for PJI differed across some studies, which could be a confounding factor in our findings.

Conclusions

We believe that this present study represents the most comprehensive evaluation of the association between TXA use during primary THA and primary TKA and the risk of subsequent PJI. Our results demonstrate that TXA use is associated with a significant reduction in a patient's risk of PJI, with our risk reduction analysis identifying a 0.4% ($P < .001$) reduction in PJI rates with TXA use. These findings provide additional data to support the routine use of TXA during primary THA and primary TKA.

CRediT authorship contribution statement

Khaled A. Elmenawi: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Farah A.E. Mohamed:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation. **Hervé Poilvache:** Writing – review & editing, Visualization, Validation, Methodology. **Larry J. Prokop:** Methodology, Investigation, Data curation. **Matthew P. Abdel:** Writing – review & editing, Visualization, Validation, Supervision. **Nicholas A. Bedard:** Writing – review & editing, Visualization, Validation, Supervision.

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Appendix A. Search Strategies

Ovid

Database(s): EBM Reviews - Cochrane Central Register of Controlled Trials September 2022, EBM Reviews - Cochrane Database of Systematic Reviews 2005 to October 12, 2022, Embase 1974 to 2022 October 14, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions 1946 to October 14, 2022.

Search Strategy:

#	Searches	Results
1	arthroplasty, replacement/or exp arthroplasty, replacement, hip/or exp arthroplasty, replacement, knee/	102,837
2	1 and total.ti,ab,kf.	77,493
3	((THA and hip*) or (TKA and knee*) or "hip joint replacement arthroplast*" or "hip replacement arthroplast*" or "knee joint replacement arthroplast*" or "knee replacement arthroplast*" or "total hip arthroplast*" or "total hip joint arthroplast*" or "total hip joint prosthes*" or "total hip joint replacement*" or "total hip prosthes*" or "total hip replacement*" or "total joint arthroplast*" or "total joint prosthes*" or "total joint replacement*" or "total knee arthroplast*" or "total knee joint arthroplast*" or "total knee joint prosthes*" or "total knee joint replacement*" or "total knee prosthes*" or "total knee replacement*").ti,ab,kf.	159,489
4	2 or 3	167,013
5	exp Prosthesis-Related Infections/	26,302
6	infect*.ti,ab,kf.	4,774,045
7	5 or 6	4,778,774
8	4 and 7	25,398
9	exp Tranexamic Acid/	23,101
10	"Tranexamic Acid".ti,ab,kf.	18,679
11	9 or 10	28,002
12	8 and 11	394
13	limit 12 to (conference abstract or erratum or note or addresses or autobiography or bibliography or biography or blogs or dictionary or directory or interactive tutorial or interview or lectures or legal cases or legislation or news or newspaper article or overall or patient education handout or periodical index or portraits or published erratum or webcasts) [Limit not valid in CCTR, CDSR, Embase, Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update, Ovid MEDLINE(R) PubMed not MEDLINE, Ovid MEDLINE(R) In-Process, Ovid MEDLINE(R) Publisher; records were retained]	24
14	12 not 13	370
15	remove duplicates from 14	244

Scopus

(1) TITLE-ABS-KEY((THA and hip*) OR (TKA and knee*) OR "hip joint replacement arthroplast*" OR "hip replacement arthroplast*" OR "knee joint replacement arthroplast*" OR "knee replacement arthroplast*" OR "total hip arthroplast*" OR "total hip joint arthroplast*" OR "total hip joint prosthes*" OR "total hip joint replacement*" OR "total hip prosthes*" OR "total hip replacement*" OR "total joint arthroplast*" OR "total joint prosthes*" OR "total joint replacement*" OR "total knee arthroplast*" OR "total knee joint arthroplast*" OR "total knee joint prosthes*" OR "total knee joint replacement*" OR "total knee prosthes*" OR "total knee replacement*")
(2) TITLE-ABS-KEY (infect*)
(3) TITLE-ABS-KEY ("Tranexamic Acid")
(4) 1 and 2 and 3
(5) DOCTYPE(ab) OR DOCTYPE(bk) OR DOCTYPE(er) OR DOCTYPE(no) OR DOCTYPE(sh)
(6) 4 and not 5
(7) INDEX (embase) OR INDEX (medline) OR PMID (0* OR 1* OR 2* OR 3* OR 4* OR 5* OR 6* OR 7* OR 8* OR 9*)
(8) 6 and not 7

Web of Science

(1) ((THA and hip*) OR (TKA and knee*) OR "hip joint replacement arthroplast*" OR "hip replacement arthroplast*" OR "knee joint replacement arthroplast*" OR "knee replacement arthroplast*" OR "total hip arthroplast*" OR "total hip joint arthroplast*" OR "total hip joint prosthes*" OR "total hip joint replacement*" OR "total hip prosthes*" OR "total hip replacement*" OR "total joint arthroplast*" OR "total joint prosthes*" OR "total joint replacement*" OR "total knee arthroplast*" OR "total knee joint arthroplast*" OR "total knee joint prosthes*" OR "total knee joint replacement*" OR "total knee prosthes*" OR "total knee replacement*") (Topic) and infect* (All Fields) and ("Tranexamic Acid") (All Fields) and Abstract of Published Item OR Article OR Editorial Material OR Letter OR Proceedings Paper OR Review (Document Type)
(2) PMID=(0* or 1* or 2* or 3* or 4* or 5* or 6* or 7* or 8* or 9*)
(3) 1 not 2

Appendix B

Table Shows the Quality Assessment Scores for the Included Studies Using the Newcastle-Ottawa Scale.

Study	Cohort Representation (0 or 1)	Non Exposed Group Selection (0 or 1)	Reliability of Exposure (0 or 1)	Measured Outcome was Absent at the Beginning of the Study (0 or 1)	Comparable Design or Analysis for Both Groups (0 - 2)	Outcome was Properly Assessed (0 or 1)	Sufficient Follow-Up Period (0 or 1)	Adequate Follow-Up (0 or 1)	Final Score out of 9
Heckmann et al. 2023 [5]	1	1	1	1	2	1	0	1	8
Shohat et el. 2022 [16]	1	1	1	1	0	1	1	1	7
Drain et al. 2020 [12]	1	1	1	1	1	1	1	1	8
Lacko et al. 2020 [18]	1	1	1	1	1	0	1	1	7
Hong et al. 2020 [11]	1	1	1	1	2	1	0	1	8
Yazdi et al. 2020 [20]	1	1	1	1	1	1	1	1	8