A commentary by Benjamin R. Coobs, MD, and Joseph T. Moskal, MD, is linked to the online version of this article at jbjs.org.

Tranexamic Acid Reduces the Rate of Periprosthetic Joint Infection After Aseptic Revision Arthroplasty

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Background: Revision total joint arthroplasty (TJA) has a higher rate of periprosthetic joint infection (PJI) compared with primary TJA, possibly as the result of increased allogeneic blood transfusion. Tranexamic acid (TXA) is gaining popularity in revision TJA to minimize blood loss and the need for transfusion; however, its effect on PJI reduction has yet to be investigated. The hypothesis of this study was that the administration of TXA during revision arthroplasty is protective against subsequent PJI.

Methods: A prospectively maintained institutional database was used to identify patients who underwent revision TJA for aseptic failure from 2009 to 2018 and had a minimum follow-up of 90 days. Patients who developed PJI following revision arthroplasty were identified. All patients with PJI met Musculoskeletal Infection Society (MSIS) criteria. A multivariate analysis was performed to identify variables independently associated with PJI after aseptic revision TJA.

Results: Overall, 1,731 patients who underwent aseptic revision were identified; of these patients, 83 (4.8%) developed PJI. Patients who received TXA had significantly lower rates (p = 0.029) of PJI postoperatively at 3.30% compared with those who did not receive TXA at 5.73%. After controlling for relevant confounding variables, TXA remained a significant independent factor that protected against PJI (odds ratio [OR], 0.47 [95% confidence interval (CI), 0.23 to 0.90]; p = 0.030). Female sex was also identified as a significant independent factor that protected against PJI (OR, 0.52 [95% CI, 0.30 to 0.88]; p = 0.016). However, preoperative anemia was independently associated with an increased risk of subsequent PJI (OR, 2.37 [95% CI, 1.34 to 4.16]; p = 0.003).

Conclusions: Based on this study conducted at a single institution, the use of TXA during aseptic revision arthroplasty was independently associated with a reduced risk of subsequent acute PJI after adjusting for multiple patient characteristics and surgical factors.

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

Revision total joint arthroplasty (TJA) has become an increasingly common procedure in the United States, with the number of revisions performed annually expected to rise substantially over the next decade[1,2]. This, in turn, will result in a substantially larger economic burden on both patients and the health-care infrastructure, with an anticipated cost of $13 billion in 2030[2,3]. Periprosthetic joint infection (PJI), which occurs at a rate of 5% to 15% after aseptic revision TJA, further accentuates the financial impact on the patient and the health-care system[4,5]. Given the additional cost and morbidity associated with PJI and the increasing demand for revision arthroplasty, every attempt should be made to minimize the risk of postoperative PJI prior to and during revision TJA.

Preoperative anemia and blood conservation strategies are areas of focus that have recently gained attention in the endeavor to reduce the rates of PJI. A recent analysis of the National Surgical Quality Improvement Program (NSQIP) database demonstrated that preoperative anemia in patients undergoing revision TJA is the most important modifiable independent predictor of major complications, including PJI[6]. This is substantial, given that as many as 20% of patients who undergo

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TABLE I Characterization of Cohort by Minimum Length of Follow-up

Minimum Follow-up	No. of Patients
90 days	1,731 (100%)
6 months	1,577 (91.1%)
1 year	1,237 (71.5%)
2 years	922 (53.3%)

revision TJA are estimated to present with anemia[6,7]. This relationship between preoperative anemia and an increased risk of infection demonstrates why blood conservation strategies, such as administration of tranexamic acid (TXA), are gaining traction among orthopaedic surgeons. Multiple studies have demonstrated the efficacy of TXA in reducing intraoperative blood loss and the need for postoperative transfusions following revision TJA[8-16]. Similar to preoperative anemia, allogeneic blood transfusions have also been associated with an increased risk of PJI[17-20].

TABLE II Univariate Analyses Comparing Patient Characteristics and Surgical Encounters of Recipients and Nonrecipients of TXA*

Predictor	Total (N = 1,731)	No TXA (N = 1,065)	TXA (N = 666)	P Value
Age† *(yr)*	65.0 (57.0 to 72.0)	66.0 (57.0 to 74.0)	63.0 (56.0 to 70.0)	<0.001†
Male sex§	775 (44.8%)	483 (45.4%)	292 (43.8%)	0.573
White race§	1,424 (82.3%)	890 (83.6%)	534 (80.2%)	0.502
Body mass index† *(kg/m^2)*	29.4 (25.8 to 33.5)	29.5 (25.9 to 34.2)	29.2 (25.8 to 32.9)	0.167
Diabetes§	217 (12.5%)	153 (14.4%)	64 (9.61%)	0.005†
Rheumatologic disease§	95 (5.49%)	64 (6.01%)	31 (4.65%)	0.273
Current smoker§	139 (8.03%)	93 (8.73%)	46 (6.91%)	0.311
Hypothyroidism§	239 (13.8%)	156 (14.6%)	83 (12.5%)	0.226
Coagulopathy§	29 (1.68%)	25 (2.35%)	4 (0.60%)	0.010†
Previous myocardial infarction§	82 (4.74%)	77 (7.23%)	5 (0.75%)	<0.001†
Cardiovascular disease§	20 (1.16%)	17 (1.60%)	3 (0.45%)	0.052
No. of previous revisions†,#	1.00 (1.00 to 1.00)	1.00 (1.00 to 1.00)	1.00 (1.00 to 1.00)	0.029†
Total hip arthroplasty§	1,070 (61.8%)	646 (60.7%)	424 (63.7%)	0.229
Neuraxial anesthesia§	1,289 (74.5%)	783 (73.5%)	506 (76.0%)	0.395
Antibiotics administered§,**	1,541 (89.0%)	976 (91.6%)	565 (84.8%)	<0.001†
Anesthesia time† *(min)*	165 (136 to 202)	168 (139 to 209)	161 (132 to 191)	<0.001†
Surgical time† *(min)*	123 (97.0 to 155)	125 (98.0 to 159)	122 (96.0 to 147)	0.024†
Tourniquet time† *(min)*	97.0 (0.00 to 120)	108 (28.0 to 123)	0.00 (0.00 to 107)	0.002†
Estimated blood loss† *(mL)*	0.00 (0.00 to 0.00)	0.00 (0.00 to 0.00)	0.00 (0.00 to 0.00)	<0.001†
Preoperative hemoglobin† *(g/dL)*	13.2 (12.1 to 14.2)	13.1 (11.9 to 14.1)	13.4 (12.4 to 14.3)	<0.001†
Preoperative anemia§	486 (28.1%)	336 (31.5%)	150 (22.5%)	<0.001†
Intraoperative transfusion§	293 (16.9%)	226 (21.2%)	67 (10.1%)	<0.001†
Postoperative transfusion§	226 (13.1%)	124 (11.6%)	102 (15.3%)	0.033†
Any transfusion§	467 (27.0%)	311 (29.2%)	156 (23.4%)	0.010†
Units of blood received†,††	0.00 (0.00 to 0.00)	0.00 (0.00 to 0.00)	0.00 (0.00 to 0.00)	0.198
Postoperative hemoglobin† *(g/dL)*	9.70 (8.80 to 10.7)	9.60 (8.70 to 10.6)	9.80 (9.00 to 10.8)	0.004†
Length of stay† *(days)*	3.00 (2.00 to 4.00)	3.00 (2.00 to 5.00)	2.00 (2.00 to 3.00)	<0.001†
Any readmission§	90 (5.20%)	66 (6.20%)	24 (3.60%)	0.079
PJI§	83 (4.80%)	61 (5.73%)	22 (3.30%)	0.029†

*Mann-Whitney U tests were used to compare groups on all continuous variables, and chi-square tests were used to compare groups on all categorical variables. All continuous variables required nonparametric analyses; therefore, median values and interquartile ranges were provided as descriptors in place of means and standard deviations. †The values are given as the median, with the interquartile range in parentheses. †Significant. §The values are given as the number of patients, with the percentage in parentheses. #The number of revision procedures on the involved joint prior to the index revision. **Whether antibiotics were given before the incision (a small percentage of patients had antibiotics delayed so that culture specimens could be acquired, but the antibiotics were still administered within 1 hour of incision). ††The number of units of blood received postoperatively.

The purpose of this study was to assess whether the administration of TXA reduces the rate of PJI after revision TJA for aseptic failures. Given that TXA effectively decreases the need for postoperative blood transfusions, which, in turn, have also been shown to confer an increased risk of PJI, it follows logically that the administration of TXA may reduce the occurrence of PJI. To our knowledge, no studies investigating the influence of TXA on postoperative PJI exist in the literature with regard to either primary or revision TJA. We sought to address this gap in medical knowledge and hypothesized that the administration of TXA during revision arthroplasty would be associated with a decreased incidence of subsequent PJI.

Materials and Methods

Following approval from our institutional review board, aseptic total hip arthroplasty and total knee arthroplasty revisions performed from 2009 to 2018 were identified via a query of a prospectively maintained, single-institution, revision joint arthroplasty database. Every revision was performed by a surgeon fellowship-trained in joint arthroplasty. Overall, 1,731 aseptic revisions were included for analysis, with each patient followed either for a minimum of 90 days postoperatively or until demonstrating evidence of infection. Revisions were defined as aseptic if patients did not meet the Musculoskeletal Infection Society (MSIS) criteria for PJI following a review of documented encounters. Patients with a history of joint infection before the index TJA revision (native septic arthritis or previous periprosthetic joint infection after an open reduction and internal fixation) were excluded, as were patients who underwent an index TJA that was a conversion TJA and those with follow-up of <90 days with no evidence of infection. Patient attrition was captured at multiple time points to better describe follow-up, given the minimum of 90 days required for inclusion (Table I). The cohort was then divided into those who received TXA and those who did not receive TXA.

Patient demographic characteristics, comorbidities, operative characteristics, and perioperative data were collected and were compared across the 2 cohorts (Table II). Preoperative anemia was defined according to the World Health Organization (WHO) definition of hemoglobin <13.0 g/dL for men and <12.0 g/dL for women. All patients in the study who received TXA were administered a single 1-g dose intravenously prior to making the incision. All patients were risk-stratified and received chemoprophylaxis for venous thromboembolism as indicated by their risk profile[21]. Low-risk patients received aspirin for venous thromboembolism prophylaxis (81 mg or 325 mg twice a day) for 4 weeks postoperatively. High-risk patients received either enoxaparin or warfarin depending on surgeon preference. All PJIs were confirmed with a manual chart review to ensure that MSIS criteria were met.

Treatment groups (TXA compared with no TXA) were assessed for differences in categorical variables using chi-square tests and continuous variables using Mann-Whitney U tests, as all continuous variables were nonparametric. Preliminary statistical analyses were performed using bivariate logistic regression to determine whether any collected surgical or patient characteristic had an association with the likelihood of postoperative PJI. Any variables that approached a significant relationship with PJI outcomes ($p < 0.25$, as recommended by Hosmer and Lemeshow[22]) were included in the multivariate regression analysis. The multivariate logistic regression analysis was used to assess whether the variables that approached significance in predicting PJI outcomes in the bivariate analyses remained predictive when controlling for confounding variables. Some variables that approached significance on the bivariate regression were removed from the final model for logical reasons, such as whether patients had been readmitted for any reason, as a large majority of readmissions were due to PJI. Therefore, assessing the predictive effect of readmission on PJI would be nonsensical. Some variables were also removed from the final model because of their similarity and collinearity with other variables. For example, anesthesia time was removed from the final model to correct for collinearity with surgical time, which we deemed a more meaningful variable to include in the analysis of risk factors for PJI. The preoperative hemoglobin level was also removed from the multivariate analysis as this metric is incorporated within another variable, preoperative anemia. The same reasoning was used for removal of the receipt of intraoperative blood and postoperative transfusion from the final model, as these variables were incorporated within any transfusion and postoperative transfusion units. A final multivariate logistic regression with the remaining predictors was used to identify variables independently associated with PJI. Variables that had little to no predictive effect on PJI

TABLE III Multivariate Logistic Regression Analysis*

Predictor	OR†	P Value
Female sex	0.52 (0.30 to 0.88)	0.016†
Body mass index	1.03 (0.99 to 1.08)	0.143
Diabetes	0.49 (0.18 to 1.14)	0.127
Coagulopathy	2.51 (0.53 to 8.38)	0.178
Previous myocardial infarction	2.17 (0.67 to 6.51)	0.175
Charlson Comorbidity Index	0.93 (0.67 to 1.24)	0.639
No. of previous revisions	1.28 (0.90 to 1.78)	0.119
Surgical time	1.00 (1.00 to 1.01)	0.156
Preoperative anemia	2.37 (1.34 to 4.16)	0.003†
Any transfusion	0.69 (0.34 to 1.33)	0.279
Units of blood received	1.07 (0.72 to 1.54)	0.724
Antibiotics administered	0.25 (0.07 to 1.02)	0.034†
Length of stay	0.99 (0.91 to 1.07)	0.891
TXA administered	0.47 (0.23 to 0.90)	0.030†

*This analysis demonstrates that administration of TXA independently protects against PJI after revision TJA even when controlling for multiple confounding variables. The analysis also revealed that female sex and perioperative administration of antibiotics are independent factors in protecting against PJI. Preoperative anemia significantly increased the risk of PJI. †The values are given as the OR, with the 95% CI in parentheses. ‡Significant.

outcomes ($p > 0.75$) following initial multivariate regression were removed to better assess the predictive relationship of the remaining variables with PJI (Table III).

Following multivariate analysis, preoperative anemia and receipt of TXA were found to be significant predictors of PJI. We sought to identify any interaction between TXA administration and preoperative anemia using a simple logistic regression, given that the incidence of preoperative anemia was significantly different between treatment groups on univariate analysis. We performed a time-to-event analysis to identify the effect of TXA on infection-free survival. All statistical analyses were performed using R Studio, version 3.5.1 (R Foundation for Statistical Computing).

Results

In the combined cohort, the incidence of PJI after aseptic revision was 4.8%. The prevalence of preoperative anemia was 28.1%, and the rate of blood transfusion was 27.0%. Of the total cohort, 38.5% (666 patients) received TXA. The mean time from revision TJA to PJI was 10.3 months (range, 0.1 to 87.1 months). Included patients had a mean follow-up of 35.3 months (range, 3.0 to 118.6 months).

The univariate analyses revealed significant differences in characteristics between the 2 treatment groups, including age, Charlson Comorbidity Index, surgical duration, preoperative hemoglobin levels, and rates of transfusion (all $p < 0.05$) (Table II). The incidence of PJI in patients who received TXA (3.30%) was significantly lower than in those who did not receive TXA (5.73%) ($p = 0.029$).

After controlling for confounding variables using multivariate regression, TXA remained associated with a decreased risk of PJI (odds ratio [OR], 0.47 [95% confidence interval (CI), 0.23 to 0.90]; $p = 0.030$). Female sex also demonstrated a protective effect against PJI (OR, 0.52 [95% CI, 0.30 to 0.88]; $p = 0.016$). Preoperative anemia was the only factor identified that was associated with an increased risk of PJI after revision TJA (OR, 2.37 [95% CI, 1.34 to 4.16]; $p = 0.003$) (Table III). The relationship between lower preoperative hemoglobin and increased risk of PJI was modified by the receipt of TXA (Fig. 1). The

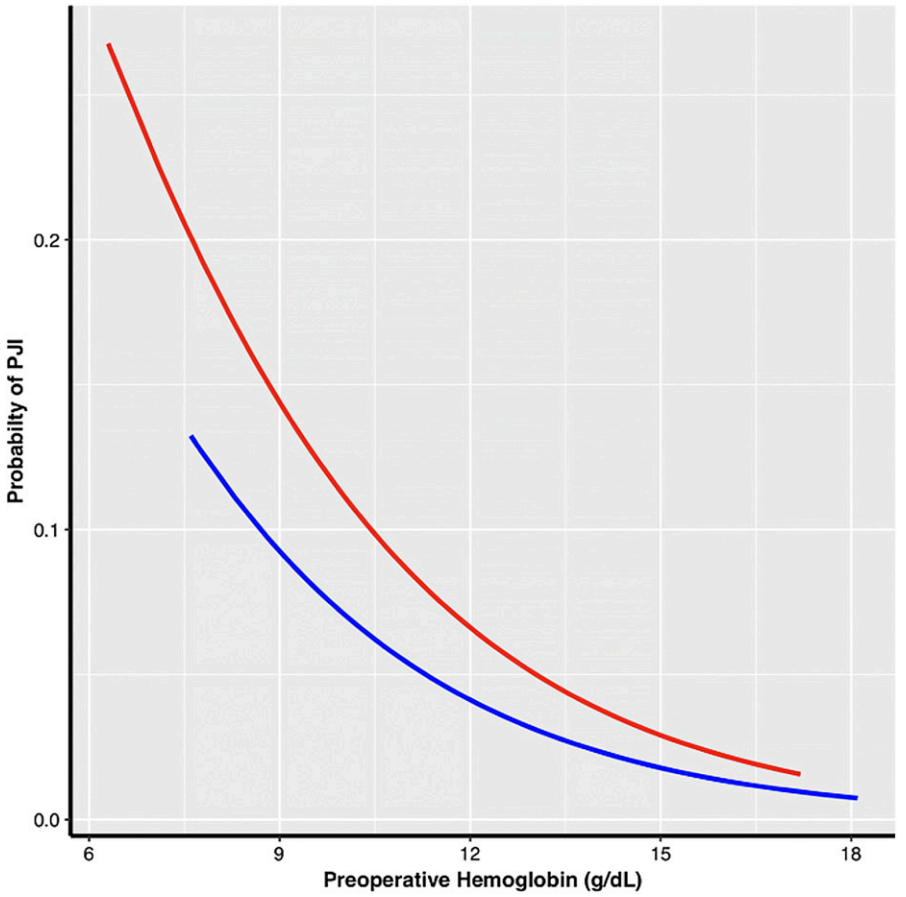

Fig. 1

Graph demonstrating the relationship between preoperative hemoglobin values and the probability of aseptic revision TJA resulting in subsequent PJI when stratified by TXA use (the red line indicates no TXA, and the blue line indicates TXA). The risk of PJI is significantly higher with decreasing hemoglobin levels (OR, 0.75 [95% CI, 0.66 to 0.85]; $p < 0.001$]), but this effect is noticeably reduced via receipt of TXA (OR, 0.61 [95% CI, 0.36 to 1.00]; $p = 0.056$). The figure and statistics were derived from a multivariate logistic regression assessing only the association of preoperative hemoglobin levels and administration of TXA with the development of PJI.

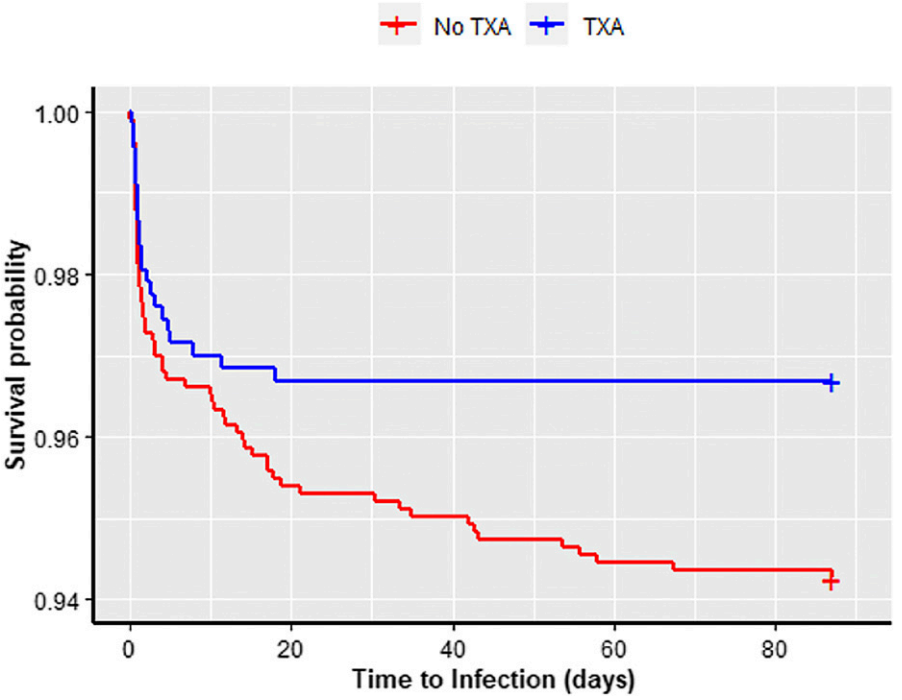

Fig. 2

Time-to-event analysis demonstrating that the likelihood of infection-free survival in the 90-day postoperative period is increased by receipt of TXA.

likelihood of infection-free survival was also increased by the receipt of TXA (Fig. 2).

Discussion

Recent literature has consistently demonstrated a link between preoperative anemia and infection in both primary[23-25] and revision TJA[6,7,25]. The results reported in this institutional study are consistent with national databases demonstrating that preoperative anemia is independently associated with PJI after TJA. The exact reason for the latter association is not clear but is most likely multifactorial. One possible explanation is that preoperative anemia may indicate a more comorbid host and results in reduced oxygen-carrying capacity to the tissues[6,7]. Preoperative anemia is also the strongest predictor for postoperative allogeneic blood transfusion[26-28], and allogeneic blood transfusion itself has also been associated with increased rates of infection[19,20,29]. Transfusion-related immunomodulation is a well-known adverse effect of blood transfusion that could explain the reported increase in infection[30]. Despite the latter hypotheses, data related to this issue have been inconsistent, especially in studies controlling for confounding variables where the association between transfusion and infection was lost[17,18,31]. This was also the case in our study, which demonstrated that, although transfusion had a significant relationship in predicting PJI on preliminary bivariate analysis ($p < 0.05$), the strength of this relationship was weakened when controlling for confounding variables via multivariate regression ($p = 0.279$).

It would stand to reason that, if one could limit blood loss and avoid the need for allogeneic blood transfusion, a reduction in infection may be possible. TXA has consistently demonstrated an ability to limit blood loss and the need for allogeneic blood transfusion[32,33]. In the current study, TXA was indeed associated with a reduced risk of PJI within 90 days after a surgical procedure after controlling for potential confounding variables. To our knowledge, this is the first study to investigate this association in the TJA literature.

This study has several strengths. First, we had the ability to access the patient charts to determine if a patient underwent a revision surgical procedure for aseptic or septic reasons. Although no test or algorithm for the diagnosis of PJI is 100% sensitive, there is likely to be less error arising from a manual review assessing whether patients met diagnostic criteria for PJI than would be found when relying on coding, for example[6,7]. This is coupled with the fact that the revision TJA database is prospectively maintained by research staff to ensure that the information within it is accurate. Second, the ability to query medication administration, such as TXA, allows us to reliably assess its effect on target outcomes over many consecutive cases. Third, many factors that have previously been correlated with infection were recorded and were included in the final multivariate model. Finally, we included a standardized, widely accepted definition for PJI within a defined follow-up period.

Despite its many strengths, this study was not without limitations. First, the retrospective study design with all its inherent biases included potential selection bias with regard to the receipt of TXA and the possibility of distinctly different treatment groups. Although we attempted to minimize this bias

with multivariate analyses, it is possible that some degree of selection bias remained. Second, the data from this study were derived from patients at an urban-based, tertiary care center that consistently accommodates a large number of revision TJAs, so the results may not be generalizable to all practice settings. Third, only a little over one-third of patients undergoing aseptic revision TJA received TXA. This may be explained by the slow implementation of this practice given the relative paucity of empirical literature on TXA in revision surgical procedures compared with primary arthroplasties at present. However, as familiarity with the use of TXA increases and literature emphasizing its safety continues to grow[34-36], our institution has broadened the indications for its use in revision TJA. Fourth, the study included patients who underwent procedures performed by numerous fellowship-trained arthroplasty surgeons with different preferences that may have introduced variability in surgical and postoperative protocols. Finally, although one-half of the cohort had follow-up of >2 years, the minimum follow-up required for inclusion in this study was 90 days. We believe that this was sufficient follow-up for the current study, as we were attempting to isolate the effect that a variable changed during the time of a surgical procedure had on PJI. A specific patient comorbidity, such as diabetes, or other patient factors that were present before, during, and after the procedure may have continued to predispose the patient to an increased risk of PJI and to thereby warrant longer follow-up. However, a 1-time medication given during a surgical procedure was likely to have a brief protective period, and, thus, we believe that 90 days were sufficient to capture this effect. Nonetheless, we sought to address this limitation by characterizing attrition at different time points and performing time-to-event analyses.

In conclusion, the current study is the first, to our knowledge, to demonstrate that the administration of TXA to patients undergoing revision arthroplasty for aseptic failures was associated with a marked reduction in the rate of acute PJI. The relationship between blood management and PJI merits further evaluation and additional studies will be needed to confirm that the administration of TXA reduces PJI in other patient populations undergoing arthroplasty. ■

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