

# Tranexamic acid vs placebo and its impact on bleeding, transfusions and stone-free rates in percutaneous nephrolithotomy: a systematic review and meta-analysis

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**Introduction** Percutaneous nephrolithotomy (PCNL) is the standard of care for the treatment of large renal stones. Bleeding-related complications remain a major concern when performing this procedure. Tranexamic acid (TXA) has recently been studied in both urologic and non-urologic procedures to reduce bleeding, transfusions and complications.

**Material and methods** In June 2021 a systematic review was conducted following PRISMA guidelines on randomized prospective studies comparing the effects of TXA on bleeding complications during PCNL. Data was analyzed using Review Manager 5.3.

**Results** Eight studies were included with a total 1,201 patients, of which 598 received TXA and 603 received placebo. TXA was associated with less bleeding (decreased change in hemoglobin)-0.79 Hb g/dl [-1.09,-0.65]  $p < 0.00001$  and decreased transfusion rates (OR 0.31 [0.18, 0.52]  $p < 0.00001$ ). This was also associated with lower complication rates, both minor, major and overall, OR 0.59[0.41, .85]  $p = 0.005$ , OR 0.31 [0.17, 0.56]  $p = 0.0001$  and OR 0.40 [0.29, 0.56]  $p < 0.00001$  respectively. TXA was also associated with improved stone-free rates as compared with placebo (OR 1.79 [1.23, 2.62]  $p = 0.003$ ). TXA resulted in shorter operative times (11.51 minutes [-16.25,-6.77]  $p = .001$ ) and length of stay (-0.74 days [-1.13-0.34]  $p = 0.0006$ ). Two pulmonary embolisms were registered in a single study in the TXA group.

**Conclusions** In this meta-analysis, the use of TXA during PCNL was associated with a statistically significant reduction in the following parameters when compared with placebo: change in hemoglobin, transfusion rates, complication rates, operative time, and length of stay. It was also associated with improvement in stone-free rates. These data should be considered by surgeons performing PCNL.

**Key Words:** tranexamic acid ↔ percutaneous nephrolithotomy ↔ urolithiasis

## INTRODUCTION

Percutaneous nephrolithotomy (PCNL) is the gold standard for treatment of large renal stones [1, 2]. While modernization of technique has decreased complication rates for PCNL, bleeding complications remain a concern. Significant bleeding/hemorrhage during PCNL may lead to various unwanted outcomes and/or complications including inability to safely remove stones, hemodynamic instability,

need for transfusion, need for angiography/embolization, prolonged hospital or intensive care unit stays and rarely death. Studies have reported that PCNL accounts for 4–7% of all stone procedures performed in Canada and the United States [3, 4]. A recent study using claims data representing United States Hospitals and trends in PCNL from 1999–2009 noted transfusion rates of 4% after PCNL as well as increasing rates of vascular complications [5].

Tranexamic (TXA) acid is a low cost synthetic lysine analog that prevents fibrin degradation by binding plasminogen. Its use in operative and postoperative bleeding reductions has been widely studied in other fields with favorable results [6, 7, 8]. Recently, a small number of prospective randomized controlled trials have been published comparing the results of PCNL in patients who received intra-operative TXA versus placebo. The current study aims to analyze current available high-quality literature and determine tranexamic acid's impact on complications and outcomes during PCNL.

## MATERIAL AND METHODS

Following the Preferred Instrument for Systematic Reviews and Meta-Analysis (PRISMA), with prior PROSPERO registration CRD42021270593, a systematic database search was performed in August 2021 with no limit on date search (Figure 1) [11]. Search engines/databases PubMed, Web of Science,

Scopus and Google Scholar employing search terms 'Tranexamic Acid', 'Placebo', 'Percutaneous Nephrolithotomy' 'PCNL', 'Urolithiasis' 'Nephrolithiasis' in title or abstract were used to identify prospective studies featuring randomization comparing tranexamic acid to placebo for PCNL. Publication date was not taken into consideration as a possible restriction, linguistic inclusion was limited to english or spanish. Only prospective studies with randomization were considered. Two separate, independent reviewers (DEHG, EFV) further screened for possible inclusion, stratified Risk of Bias (RoB), while a third reviewer (DOP) performed data conciliation. Additional articles identified through related articles were also screened.

## Study inclusion

Included prospective randomized controlled clinical trials statistically compared transfusion rates, operative bleeding or changes in hemoglobin after surgery as primary outcomes. Studies were also screened for non-different baseline characteristics of studied cohorts in both preoperative comorbidities and urologic specific characteristics including location, size, burden and complexity.

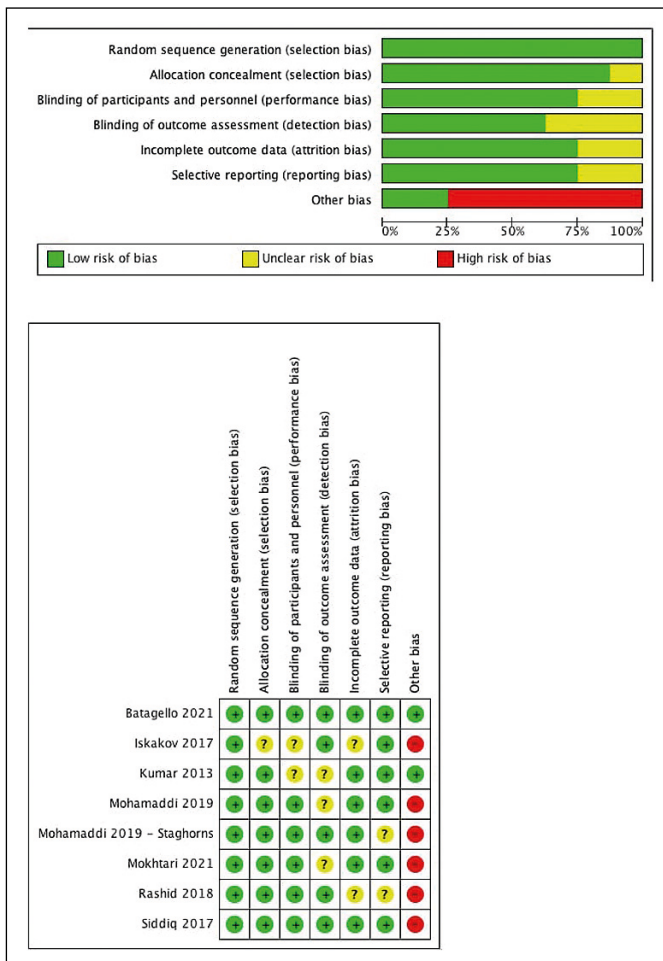


Figure 1. Displays Risk of Bias assessment graph (A) and summary (B).

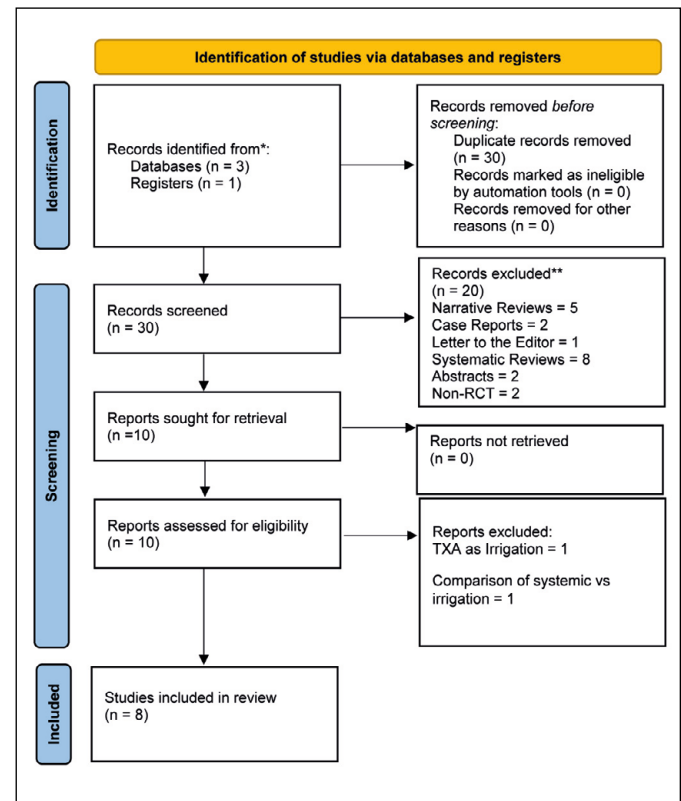


Figure 2. PRISMA flowchart of systematized search with included studies.

**Table 1.** Summarizes included studies' dosification, inclusion and exclusion, procedures, indications for transfusion and stone-free rate definitions

Author	TXA dosification	Inclusion criteria	Exclusion criteria	Change in Hb determination	Procedure description	Transfusion indication	SFR description
Kumar 2013	1 g at the start of the procedures followed by 3x500 mg at 8 hour intervals	Patients with stone disease undergoing PCNL	Creatinine +1.5 Known TXA allergy Active intravascular clotting Acquired defective color vision Subarachnoid hemorrhage	Preoperative Hb and 24 hrs postoperative Hb	Prone, FQ guided puncture with 30 Fr dilation	ND	Complete stone clearance or residual fragments smaller than 4 mm
Iskakov 2017	Infusion of TXA in 10–100 ml	Patients with stone disease undergoing PCNL	ND	Preoperative Hb and 24 hrs postoperative Hb	Prone, FQ guided puncture with 30 Fr dilation	ND	ND
Siddiq 2017	1 g intramuscular injection prior to transportation to OR	Patients 18–75 undergoing PCNL for Renal stone >2 cm on US	Hb <12 Known bleeding disorder Creatinine +1.5 Use of antiplatelets or anticoagulants	Preoperative Hb and 24 hrs postoperative Hb	Prone, FQ guided puncture with 30 Fr dilation	ND	Intraoperative visualization with FQ + postoperative KUB
Rashid 2018	1 g intramuscular 20 prior to the procedure	Patients >18 undergoing PCNL	Patients with creatinine >1.5 Bleeding disorders On anticoagulation Congenital Renal Anomalies	Preoperative Hb and 24 hrs postoperative Hb	ND	ND	ND
Mohamadi 2019	1 g IV at initiation plus continuous IV infusion of 1 g in 8 hour intervals for 48 hours	Patients >18 undergoing PCNL	Creatinine +1.5 Known allergy to TXA Ongoing thrombosis Acquired defective color vision Subarachnoid Hemorrhage OCPs, antiplatelets, anticoagulants	Preoperative Hb, 48 hrs postoperative Hb	Prone FQ guided puncture dilated to 30 F	Hb <8 Symptoms of inadequate oxygenation	ND
Mohamadi 2019	1 g of TXA IV 12 hours until discharge and then orally for 1 week after discharge	Patients >18 with staghorn calculi and Cr <1.5	Intravascular coagulation Color vision disorders Skeletal disorders Subarachnoid hemorrhage Aspirin, warfarin or vitamin E	ND	ND	ND	ND

Table 1. Continued

Author	TXA dosification	Inclusion criteria	Exclusion criteria	Change in Hb determination	Procedure description	Transfusion indication	SFR description
Batagello 2021	1 g of TXA in 250 ml infused during induction	Patients >18 with complex kidney stones (Guy's III, IV)	Known allergy to TXA Anticoagulation or antiplatelet therapy History of thrombosis Coronary artery disease treated with drug eluting stents Hb<11 Estimated GFR <30	Preoperative Hb, 24 Hour postoperative Hb	Prone/supine, FQ guided puncture to 30 Fr dilation	Hb <7 Hb <10 with fluid-unresponsive hypotension	Non-Contrast CT performed 24 hrs postoperatively with no residual fragments >4 mm
Mokhtari 2021	1 g intravenously at the beginning and 5 mg orally every 8 hrs for 3 days)	Kidney or upper ureteral stone 4 (stones bigger than 2 cm at pelvic or upper calices and bigger than 1.5 cm of lower calices) – failed SWL, and candidate of PCNL	DVT, PTE, and Cr >1.5, drug allergy, cerebral arteries damage or SAH, color blindness, using OCP pills, using coagulation factors, surgery and heart valve transplantation	Hb and Hct were measured 24 hrs before and 48 hrs after the operation	Prone, single-surgeon	ND	ND

TXA – tranexamic acid; PCNL – percutaneous nephrolithotomy; Hb – hemoglobin; Fr – French; FQ – fluoroscopy; Cr – creatinine; SAH – subarachnoid hemorrhage; OCP – oral contraceptive pills; SWL – shockwave lithotripsy; DVT – deep vein thrombosis; PE – pulmonary embolism; KUB – kidney, ureter, bladder; ND – not described

## Data extraction

Data was extracted independently by two reviewers. Data relevant to this meta-analysis besides authorship and year of publication were as follows: risk of bias assessment, cohort size, dosing and timing of TA, operative blood loss, transfusion rates, minor complications as defined as Clavien Dindo I–II, major complications as defined as Clavien Dindo III–IV, thrombotic complications, and stone-free rates. Studies providing data in median and ranges were used to estimate mean and standard deviation using Wan's method [9]. Bias was assessed using Cochrane's Risk of Bias tool and is displayed in supplemental Figure 2.

## Statistical analysis

Data analysis was performed in Review Manager V5.3 (Cochrane). Higgins' I<sup>2</sup> test was employed to test heterogeneity, using 50% as a cutoff value. Random-effects models were used in place of fixed-effects for heterogeneous variables. Continuous data is reported in mean difference with 95% confidence intervals (CI). Dichotomous data such as complications were reported using Odds Ratios (OR) with 95% CI. The resulting values with associated p-values <0.05 were considered significant.

## RESULTS

Eight randomized studies met inclusion criteria and were analyzed [10–17]. A total of 1,201 patients, of which 598 received TXA and 603 received placebo. Overall characteristics of included studies are displayed in Table 1.

### Operative time

Operative time was described in 6 studies, totaling 418 patients in the TXA group and 423 in the placebo group. Analysis revealed a statistically significant mean difference between groups of -11.51 minutes [-16.26, -6.77]  $p = .00001$ , suggesting significantly decreased operative times in the TXA group. This finding is displayed in Figure 3A.

### Change in hemoglobin

Change in preoperative and 24–48-hour postoperative hemoglobin was described in 8 studies. This analysis was composed of 598 patients in TXA and 603 in placebo. Analysis revealed a significant mean difference in favor of patients receiving TXA of -0.87 Hb g/dl [-1.09, -0.65]  $p < .00001$ . This finding is displayed in Figure 3B.

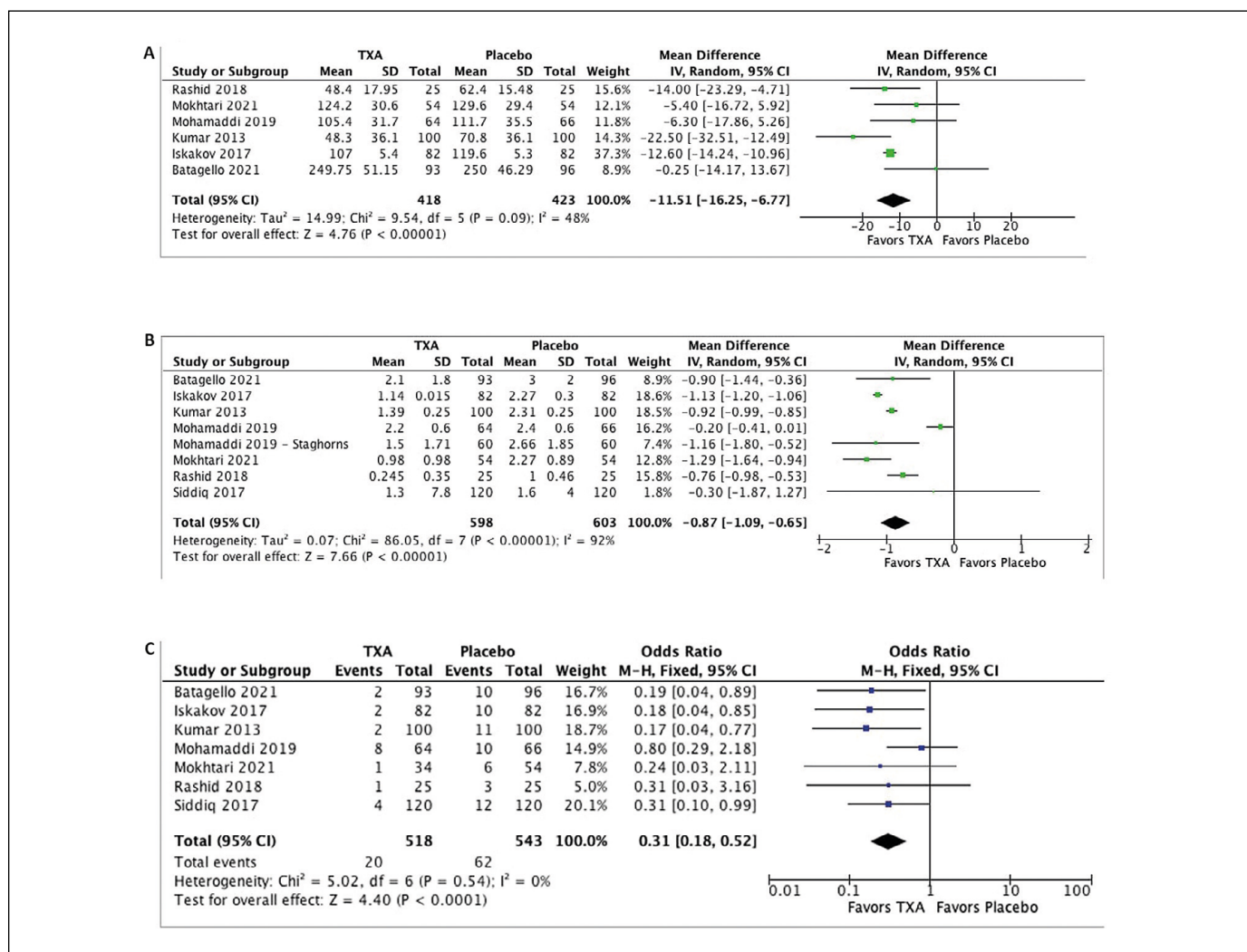


Figure 3. Forest plots for mean difference of operative time (A), change in hemoglobin (B) and odds ratio of transfusion (C).

## Transfusion rates

Transfusion rates were described in 7 studies, these were made up by 518 patients receiving TXA and 543 placebo for a total of 1,061. Transfusion rate for patients receiving TXA as 3.8% compared with 11.4% for placebo. The associated odds ratio for transfusion was 0.31[0.18, 0.52] p <0.0001. This finding is displayed in Figure 3C.

## Complication rates

Complication rates were described in 4–5 studies, totaling 364 patients in the TXA group and 367 in the placebo group. Complication rates were as follows: TXA minor complications = 31% versus placebo minor complications = 41%; TXA major complications = 4.5% versus placebo major complications = 13%. Odds of minor complications were statistically

significant between groups OR 0.59 [0.41, .85] p = 0.005 as were the odds of major complications OR 0.31 [0.17, 0.56] p = 0.0001. Overall odds of complication rates were significantly significant OR 0.45 [0.36, 0.56] p <0.00001. This finding is displayed in Figure 3A.

## Embolizations

Only 4 embolization procedures were reported across 3 studies, all of which occurred in the placebo group, however analysis revealed non-statistically significant odds between TXA and placebo OR 0.20 [0.02, 1.69] p = 0.14. This finding is displayed in Figure 4B.

## Urinary blood clot obstruction

Three studies described blood clot obstruction occurring after PCNL. These recorded 3 events, all



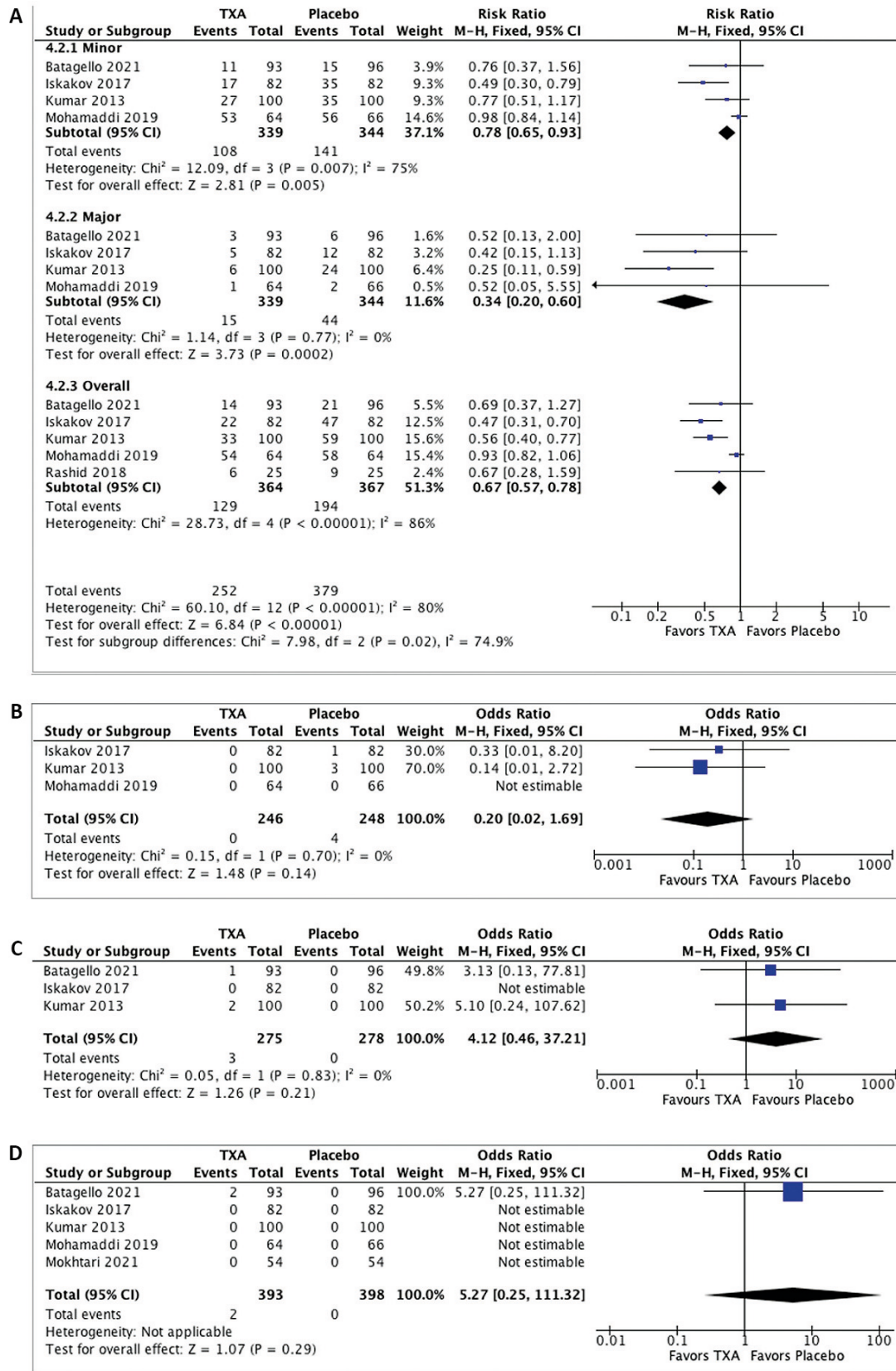


Figure 4. Forest plots for odds ratio of complications (A), embolizations (B), urinary blood clot obstruction (C) and thrombotic complications (D).

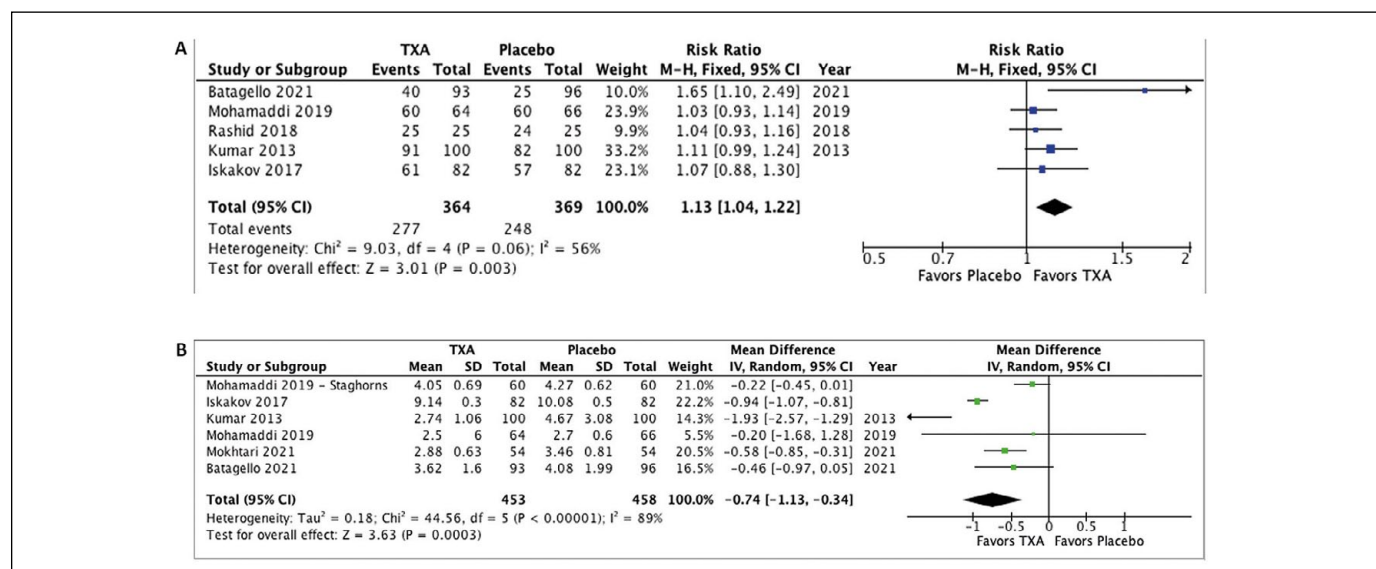


Figure 5. Forest plots for odds ratio of stone-free rates (A) and mean difference of length of stay (B).

in the TXA group, however odds were not-significantly different. OR 4.12 [0.46, 37.21]  $p = .21$ . This finding is displayed in Figure 4C.

### Thrombotic complications

Thrombotic complications, which included deep vein thrombosis and pulmonary embolism, were reported only in 2 cases from a single study in the TXA group. This results in a local 2% and global pooled 0.5% incidence of thrombotic complications. This finding is displayed in Figure 4D.

### Stone-free rates

Stone-free rates were described in 4 studies, totalling 339 patients in the TXA group and 344 in the placebo group. Of these, TXA reported 252 (78%) SFR and Placebo 224 (73%) SFR. This difference was statistically significant OR 1.78 [1.21, 2.61]  $p = 0.003$ . This finding is displayed in Figure 4A. As displayed in Table 1, only 2 studies determined SFR through postoperative computed tomography (CT) showing no residual fragments or fragments  $<4$  mm and 1 relied on operative verification with postoperative kidney, ureter, bladder X-ray (KUB). This finding is displayed in Figure 5A.

### Length of stay

Length of stay (LoS) was described in 6 studies. Analysis of reported LoS demonstrated a significantly decreased mean difference of -0.74 days [-1.13, -0.34]  $p = 0.0001$ , favoring shorter stays in the TXA group. This finding is displayed in Figure 4B.

### Sensitivity analysis

Of the analyzed variables, only change in Hb had significant levels of heterogeneity. Progressive stepwise addition of studies identified Kumar et al., Mohamaddi et al., and Rashid et al., randomized controlled trials (RCTs) as the significant sources of heterogeneity. Exclusion of these studies resulted in 0% heterogeneity and a OR of -1.13 [-1.19, -1.07] [12, 14, 17].

### DISCUSSION

PCNL is the standard of care for large and/or complex stones. Significant bleeding during this can lead to morbidity and mortality – control of bleeding during PCNL remains a concern of urologists who perform this procedure. Minor bleeding may decrease visibility and result in longer operative times as well as lower stone free rates due to impairment of the nephroscope's visual field. Major bleeding, while infrequent may result in unwanted complications, need for transfusion, angiography, increased hospital stay and increased costs to the patient and the system. Historically, efforts to decrease bleeding complications during PCNL have focused on improvements in surgical technique and devices including efforts for greater precision of percutaneous puncture and miniaturization of percutaneous renal sheath size [18, 19]. TXA is a low cost synthetic lysine analog that prevents fibrin degradation by binding plasminogen. The drug was invented in 1962 and initial use was for bleeding after major trauma. It is not novel insofar as it has been used in various medical indications for over 50 years. However, only recently has the use

of TXA been studied to prevent bleeding complications after PCNL. Our current study evaluates the global experience of the use of TXA during PCNL. Our meta-analysis has demonstrated that the use of TXA during PCNL is associated with a statistically significant improvement in outcomes (including stone free rate and operative time) as well as a statistically significant decrease in minor and major operative complications.

TXA has been studied in other fields as well as in other areas of urology. Other meta-analysis in orthopedics, cardiothoracic, vascular and neurosurgery as well as obstetrics have all consistently concluded benefits in bleeding and transfusion reduction without increased thrombosis risk [6, 7, 8, 20, 21]. Gong et al analyzed 529 patients undergoing lumbar interbody fusion from 7 studies. They found significantly reduced operative and postoperative blood loss without increased risk of thrombotic events [19]. Similarly, Zhao et al analyzed 1,168 patients undergoing cardiac surgery of which 619 received TXA finding significant reductions in blood-loss and transfusions [21]. Its use in other urologic procedures such as TURP and open prostatectomy has been studied, with relatively similar results to those of the studies included in this analysis and our results [22]. These benefits come at a low-dose cost, making this tool accessible to wide cohorts of both patients and physicians in various settings. Additionally, its low-cost implementation could lead to increased savings and optimization as transfusion and embolizations pose a much more expensive alternative [23].

Concerns over increased risk of thrombotic complications have also been studied previously, with both dedicated trials and meta-analysis finding no significant increased risk [24, 25]. Taeuber et al., robust meta-analysis of 216 studies with over 125,000 patients is the largest and most current study to date. This found a non-significant .001 risk difference  $p = .49$ , for venous thrombosis, pulmonary embolism or infarction [26]. However, conflicting evidence remains [27]. In our analysis, we noted for only 2 (2% of study cohort, .5% of the overall cohort) thrombotic complications in the TXA group, both from Batagello's study, with other studies reporting no thrombotic complications. Batagello et al. reviewed this in their manuscript and hypothesized that in those 2 patients, that the thrombotic complication was more likely due to significant patient co-morbid risk factors for thrombotic com-

plication than from the administration of TXA itself [10]. Other concerns include possible risk of convulsive seizures possibly related with dosing [28].

Batagello et al. also hypothesized decreased operative bleeding allowed surgeons better visualization and this could possibly impact stone free-rates. Our results showing improved stone free-rates in patients treated with TXA supports this hypothesis. Better visualization might also at least partially explain the significant differences in operative time, which were -10.41 minutes in the TXA group. This notion has also been explored in TURP, in which researchers compared the infusion volumes between TXA and placebo. In this study, both decreased operative time and infusion volumes were seen, supporting this hypothesis [10]. Additionally, Bensal et al. studied TXA as an irrigation solution, in this application, benefits in reductions in bleeding, operative and transfusions were also seen [29].

While current evidence for the adoption of TXA for PCNL is promising, more studies are needed to better define its role in patient care and consideration of incorporation into guidelines. This must aim to determine the appropriate patient for this additional intervention and further define its possible interactions with other medications and adjustments in patients with comorbidities. While this study aimed to analyze high-quality studies, possible limitations may stem from varying dosing and timing of administration, as well as varying inclusion and exclusion criteria. In regards to stone-free rates, varying definitions make for heterogeneous grouping that could benefit from further dedicated studies as well as homogeneous criteria for transfusion. These variables however, had low heterogeneity, suggesting similar outcomes between studies.

## CONCLUSIONS

Current evidence suggests preoperative administration of tranexamic acid provides a safe and economic decrease in operative bleeding, need for transfusion, and postoperative complications. Decreased bleeding may allow for better procedural visualization, achieving higher stone free-rates. Its role and implementation into guidelines and clinical practice must be further determined.

## CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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