

Systemic vs. in-irrigation tranexamic acid in percutaneous nephrolithotomy: A systematic review, Bayesian network meta-analysis, and meta-regression

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ABSTRACT

Introduction: Percutaneous nephrolithotomy (PCNL) is the gold-standard treatment for large renal stones. One potentially significant complication of PCNL is blood loss, which can result in transfusion requirement and poorer stone-free outcomes. Tranexamic acid (TXA) has emerged as a promising intervention, administered systemically (TXA-S) or as part of irrigation fluid (TXA-I) in endourology. This study aimed to comprehensively analyze existing evidence regarding the applications of TXA in PCNL through a Bayesian network meta-analysis, offering insights into its efficacy and comparative effectiveness.

KEY MESSAGES

- PCNL for large renal stones poses bleeding risks, prompting exploration of tranexamic acid (TXA) intervention to mitigate complications.
- TXA in irrigation fluid (TXA-I) outperforms systemic administration (TXA-S), showing superior results in decreasing complications, transfusions, bleeding, and postoperative hemoglobin decrease.
- TXA, especially TXA-I, enhances operative efficiency, shortens operative times, and increases stone-free rates during PCNL.
- The study recommends urologists consider TXA, particularly TXA-I, to reduce bleeding in select PCNL patients, emphasizing the need for future trials comparing administration routes.

Methods: In February 2022, a PRISMA-compliant systematic review (PROSPERO registration number CRD42021270593) was performed to identify randomized controlled clinical trials (RCT) on TXA as either systemic therapy or in irrigation fluid. Studies in other languages other than English and Spanish were not considered. A Bayesian network was built using results from identified studies to create models that were later run through Markov Chain Monte Carlo sampling through 200000 iterations.

Results: Eight RCTs compared TXA-S vs. placebo, one TXA-I vs. placebo, and one TXA-I vs. TXA-S. TXA-I had lower risk of transfusion (relative risk [RR], 0.63 [0.47,0.84], SUCRA 0.950) than TXA-S (RR 0.79 [0.65,0.95], SUCRA 0.545). TXA-I had a lower risk of complications (RR 0.38 [0.21,0.67], SUCRA=0.957) compared to TXA-S (RR 0.55 [0.39, 0.78], SUCRA 0.539). TXA-I had a lower postoperative decrease in hemoglobin (MD -1.2 [1.3, 1.0], SUCRA 0.849) compared to TXA-S (MD-0.97 [-1.0, -0.93], SUCRA 0.646).

Conclusions: TXA, regardless of the route of administration, is an effective intervention in decreasing bleeding, postoperative complications, and risk of transfusion when compared with placebo. Further studies directly comparing TXA-S to TXA-I would be useful to determine the optimal route of delivery.

INTRODUCTION

Percutaneous nephrolithotomy (PCNL) is the standard of care for renal stones over 2cm (1) PCNL is more effective, achieving higher stone-free rates than other interventions, such as ureteroscopy and shockwave lithotripsy for larger stones. However, PCNL is also associated with a higher risk of complications, estimated at up to 20% (2). Specifically, bleeding-related complications are a major concern, with post-PCNL transfusion rates ranging from 0-24% (2).

Tranexamic acid (TXA) is a synthetic lysine derivative with a high affinity for binding sites in plasminogen. Its mechanism of action inhibits fibrinolysis by blocking the conversion of plasminogen to plasmin (3). Due to its antifibrinolytic properties, TXA has been widely utilized in various medical procedures as systemic therapy and diluted in irrigation fluid. TXA has been employed in cardiac, spine, orthopedic, and gynecologic procedures, consistently demonstrating its efficacy in reducing operative bleeding and minimizing the need for transfusion (4–7).

Recently, there has been a growing focus on utilizing TXA during PCNL to decrease bleeding and potentially improve visibility. This heightened attention is due to the compelling evidence emerging from multiple RCTs and their subsequent meta-analyses, which consistently demonstrate the efficacy of systemic TXA in reducing bleeding and associated complications and the favorable side-effect profile of this medication (8–10).

This review aims to analyze the existing evidence on the applications of TXA in PCNL using a Bayesian network meta-analysis. While prior meta-analyses have demonstrated the utility of TXA in PCNL, traditional meta-analysis methods do not facilitate direct comparisons between

different TXA-related interventions within the network (traditional meta-analysis do not allow for direct comparisons between different interventions within a network). In contrast, a Bayesian network meta-analysis allows for such comparisons, even when direct comparisons are lacking within the network (11).

METHODS

In February 2022, we conducted a systematic search using online databases MEDLINE, Scopus, Web of Science, and Google Scholar. The search terms were Humans; Kidney Calculi; Nephrolithotomy, Percutaneous; Nephrostomy, Percutaneous; and Tranexamic Acid. we employed a snowball approach by screening similar articles, related articles, and references cited in identified reviews. We completed The PROSPERO registration before searching (Registration number CRD42021270593). Google Scholar was incorporated after creating the PROSPERO registry, thereby broadening its scope to encompass non-indexed literature.

Study inclusion criteria

Eligible articles were RCTs comparing the use of tranexamic acid as either systemic therapy through intravenous or intramuscular routes to placebo or vs each other in patients undergoing PCNL. Only studies in English and Spanish were considered for review. Primary outcomes were transfusion rates and drop in hemoglobin (Hb). Secondary outcomes were complication rates, stone-free rates, and operative time. The shortlist of screened studies underwent assessment for eligibility and data extraction, carried out independently by two authors. Additionally, both authors independently extracted the data. To evaluate bias, we employed Cochrane's Risk of Bias assessment tool.

The PRISMA flowchart of systematized search with included studies is shown in Figure 1.

Statistical analysis

Extracted means, standard deviations, group size, events, and totals were inputted into Review Manager 5.3 for pairwise meta-analysis reporting mean difference and 95% confidence intervals or risk ratio with 95% confidence interval. Higgins; I^2 % was used to assess heterogeneity, with values over 50% considered heterogeneous (12). Reported confidence intervals were used to estimate standard error using the formula $(\text{Upper Limit} - \text{Lower Limit})/3.92$ (13). Placebo was the reference group for all studies' treatment effects and standard errors except for one study, which compared TXA-I vs TXA-S. (See Network Diagram in Figure 2).

Trial data were analyzed using a Bayesian network meta-analysis framework using the *gemtc* package in R. A model was created from the analyzed network, which was used to run Markov chain Monte-Carlo simulations with 5,000 burn-ins, 100,000 inference iterations and a thinning factor of 10. Model fits were assessed by analyzing trace and density. Random and fixed effects models were compared using the Bayesian deviance information criterion (DIC), with differences of 2–5 considered significant, favoring the lowest-scoring model.

Additionally, Gelman-Rubin plots were analyzed for the Potential Scale Reduction Factor (PSRF) with values of 1.05 at the last iteration or less considered adequate. Network model consistency was analyzed using the node split method. For treatment ranking, both P-rank and surface under the cumulative ranking (SUCRA) curve were considered as both are non-different. SUCRA was chosen due to package familiarity, using dmetar's package SUCRA function. Due to non-standard reporting in criteria and verification of stone-free rates and transfusion thresholds and criteria, a meta-regression for these variables was performed to determine if this lack of homogeneity introduced bias with a significant impact on our results. All studies that met the inclusion criteria were considered for the statistical analysis.

RESULTS

A total of 10 RCTs were included. Of these, eight compared TXA-S vs placebo, 1 TXA-I vs placebo and 1 TXA-S vs TXA-I. A total of 1,761 patients were included, of which 678 patients received TXA-S, 280 received TXA-I and 803 received placebo. Table 1 summarizes included studies, while Table 2 displays overall SUCRA rankings for analyzed variables.

Drop in Hb

Analysis of reported changes in Hb revealed TXA-I to have the greatest effect size of mean difference (MD) vs placebo -1.2 (-1.3,-1.0) SUCRA = 0.849. TXA-S also had a significant MD vs placebo of -0.97(-1.0, -0.93) SUCRA = 0.646. This suggests that TXA-I is more effective at decreasing operative blood loss. These findings are summarized in Figure 3.

Operative time

Operative time analysis demonstrated TXA-I to have the largest effect size (MD vs Placebo -19 [-21, -16] SUCRA = 0.999) followed by TXA-S at MD vs Placebo -12(-14,-11) SUCRA = 0.500. This suggests that TXA-I is more effective at decreasing operative time. These findings are summarized in Figure 4.

Transfusion rates

Of the included studies for analysis, total unweighted transfusion rates were as follows - 28 out of 598(4.6%) for TXA-S, 15 out of 280(5.3%) for TXA-I 87, and out of 743(11.7%) for placebo. Both TXA-I and TXA-S had a lower risk of transfusion (RR 0.63[0.47,0.84], SUCRA 0.950) and (RR 0.79[0.65,0.95] SUCRA=0.545), respectively. These findings are summarized in **Figure 5**. Meta-regression adjusting for studies' description of transfusion criteria revealed a non-significant β of 0.15(-0.70,0.36).

Stone-free rates

Analysis of SFR revealed both TXA-I (RR vs Placebo 5.0[1.8,14.0], SUCRA = 0.962) and TXA-S (RR vs Placebo 2.8[1.6,5.4], SUCRA = 0.536) had significantly increased SFR. Meta-regression adjusting for the study description of SFR criteria revealed a non-significant β of 0.016(-1.02,1.09). These findings are summarized in Figure 6.

Postoperative complications

Overall complications

Network analysis of overall complications described by included studies revealed significant reductions in complication rates by both TXA-I (RR vs Placebo 0.38[0.21,0.67] SUCRA = 0.957) and TXA-S (RR vs Placebo 0.55[0.39,0.78] SUCRA = 0.539). TXA-I had the highest probability of being the best treatment. These findings are summarized in Figure 7.

Minor complications

TXA-I had a RR vs Placebo of 0.37(0.17,0.73) SUCRA=0.929 and TXA-S an RR vs Placebo of 0.51(0.33,0.81) SUCRA = 0.564. TXA-I had the highest probability of being the best treatment. These findings are summarized in Figure 8.

Major complications

Major complication analysis revealed a significantly reduced risk of major complications for both TXA-I (RR vs Placebo 0.50[0.37,0.68] SUCRA=0.992) and TXA-S (RR vs Placebo 0.75[0.60,0.92]SUCRA =0.507). These findings are summarized in Figure 9.

Length of stay

Analysis of reported length of stays showed both interventions significantly reduced stay, with a MD vs Placebo of -1.1 days, SUCRA = 1 for TXA-I and -0.79 days for TXA-S SUCRA = 0.50. These findings are summarized in Figure 10.

DISCUSSION

This is the first comparative analysis through Bayesian networks of tranexamic acid applications for PCNL. Prior to starting the study, deliberations were made regarding both the frequentist and Bayesian approaches. While both methodologies have yield comparable outcomes, the Bayesian approach was selected due to its enhanced capability for meta-regression. (14). The kidney receives around 20% of the cardiac output and has a complex vascular network within its parenchyma(15). It is susceptible to clinically significant bleeding from trauma during percutaneous access tract creation (16,17). While several historical studies have focused on reduction in tract size to decrease bleeding risk (18) more recent studies have evaluated pharmacologic treatment with tranexamic acid to reduce bleeding risk (19). Recent meta-analyses and review articles assessing the use of systemic TXA have demonstrated significant decreases in post-PCNL bleeding and transfusion rates with the use of this medication (20,21)and a recent RCT published looking at the use of TXA for complex PCNL demonstrated decreased transfusion and improved stone clearance (19). In the current study, we sought to add to the literature by utilizing a novel statistical method to evaluate the effects of TXA during PCNL (Bayesian network meta-analysis and meta-regression) as well as included TXA irrigation (TXA-I) in addition to systemic TXA (TXA-S) in the analysis. See the Network Diagram in Figure 1.

When specifically considering PCNL, our analysis reveals three significant findings. First, compared to a placebo, TXA significantly reduces the length of hospital stay. Second, we found a noteworthy reduction in operating times associated with the intervention. These outcomes support the procedure's safety, demonstrating no increased risk of major complications while highlighting the potential for improved efficiency. Third, the findings of this study suggest that irrigation TXA is more effective at reducing bleeding and transfusion rates, resulting in higher stone-free rates.

It is noteworthy that in other disciplines, the effectiveness of TXA has been observed through its versatile applications via oral, intravenous, or topical administration in different surgical procedures, which is congruent with our study findings. For instance, Wang et al. conducted a retrospective analysis of 18,380 cardiac surgery patients, with 10,969 individuals receiving TXA. Their findings revealed reduced blood loss at various time intervals and lower transfusion rates, all without an increased risk of thromboembolic events (22). Additionally, in a recent network meta-analysis investigating different dosage regimens of TXA in spinal surgery, TXA consistently demonstrated effectiveness in reducing intraoperative blood loss, regardless of the specific dosing regimen employed (23)

While TXA has demonstrated its cost-effectiveness and gained recognition for effectively reducing operative blood loss and managing bleeding-related complications in various medical disciplines (24), some authors have expressed concerns about potential thrombotic complications associated with its use (25). Nevertheless, literature reviews have failed to identify any substantial increase in thrombotic events (26). None of the studies included in a systematic review by Chornenki et al., which included 22 studies representing 49,538 patients, reported elevated rates of thrombotic complications among the groups receiving TXA. Furthermore, the only study we found that reported such complications concluded that the two documented cases were attributable to undisclosed preexisting conditions (27). The findings from these studies align closely with the results obtained from our meta-regression analysis, reinforcing the absence of any significant increase in major complications. Based on the effectiveness of TXA-I reported in this study, we would also suggest that for those urologic surgeons who have concerns about the potential pro-thrombotic effects of TXA-S but who are still interested in the benefits of TXA use during PCNL, that TXA-I may be an appropriate alternative, especially given the favorable results for TXA-I reported in this study.

Regarding topical TXA administration, which in the context of PCNL would be analogous to TXA-I, a Cochrane Review by Ker et al., which analyzed 29 trials, found a significantly reduced risk of transfusion and blood loss reduction without an increased risk of thrombotic-related complications (28). Farzanegan et al. also tested topical TXA during posterior laminectomy and found decreased bleeding without increased complications (29). Similar findings on topical applications of TXA have been reported by various authors in other fields, such as orthopedic, cardiac, and plastic surgery (30–32). The findings of the studies mentioned above are also congruent with our results, showing a decrease in operative blood loss without an

overall increase in complication rates, demonstrating a significant reduction in both major and minor complications.

This study faces various limitations, mainly stemming from the disproportionate amount of evidence for systemic TXA, which has been analyzed by 8 RCTs, compared to TXA-I, which has only been examined by one. In addition, only one trial has directly compared both and thus could bias our network. Other factors, such as undisclosed criteria for transfusion and stone-free rates, have been adjusted for through a meta-regression.

CONCLUSIONS

TXA-I and TXA-S improve stone-free rates while reducing complication rates, transfusion rates, and operative bleeding. TXA-I is less well-studied, but the limited number of studies included in this paper suggest that it may be more effective than TXA-S in PCNL. However, future trials directly comparing TXA-I and TXA-S are needed to clarify these findings. Urologists should consider using TXA for PCNL to reduce bleeding in select patients.

DRAFT

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FIGURES AND TABLES

Figure 1. PRISMA flowchart of systematized search.

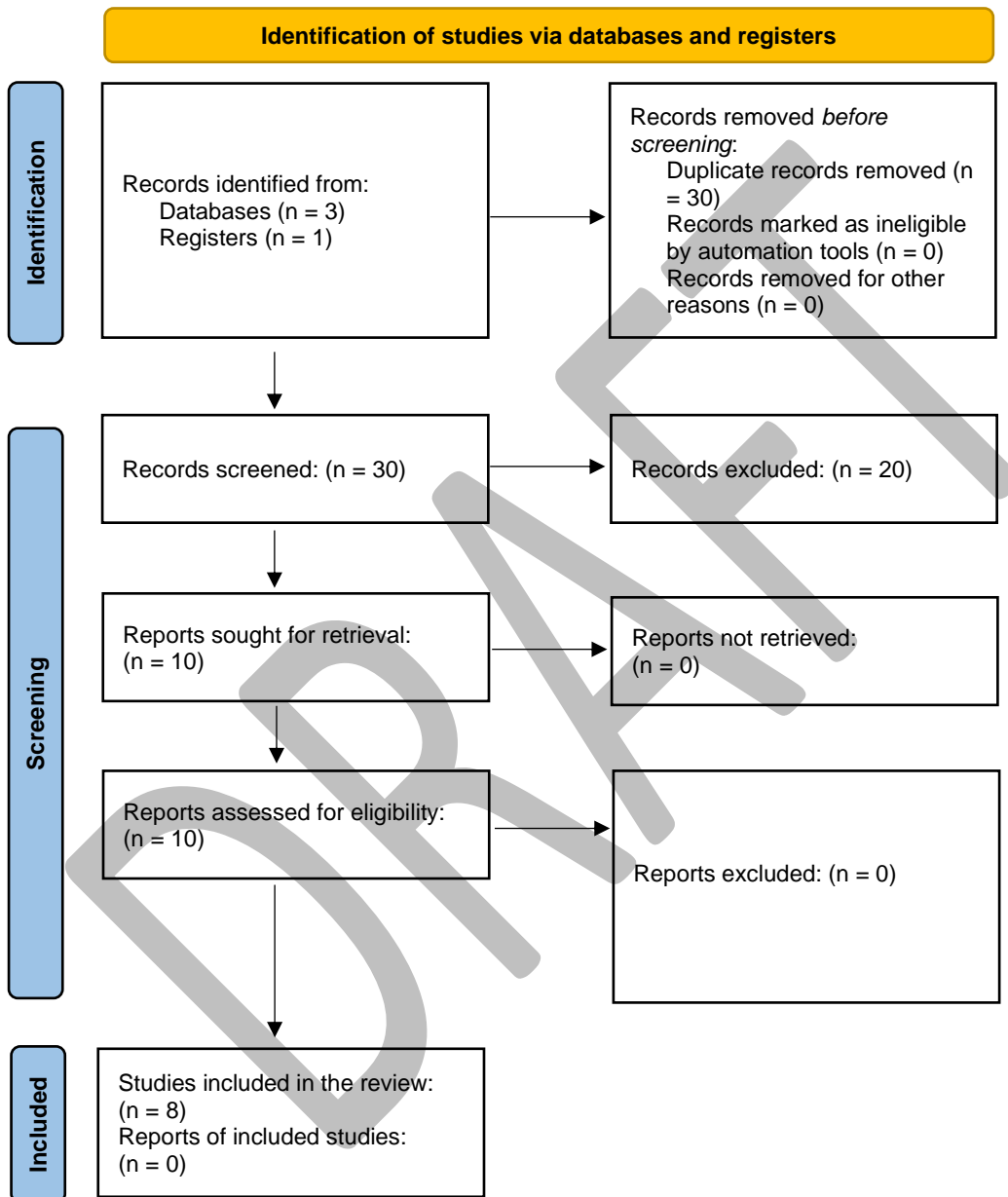


Figure 2: Network Diagram

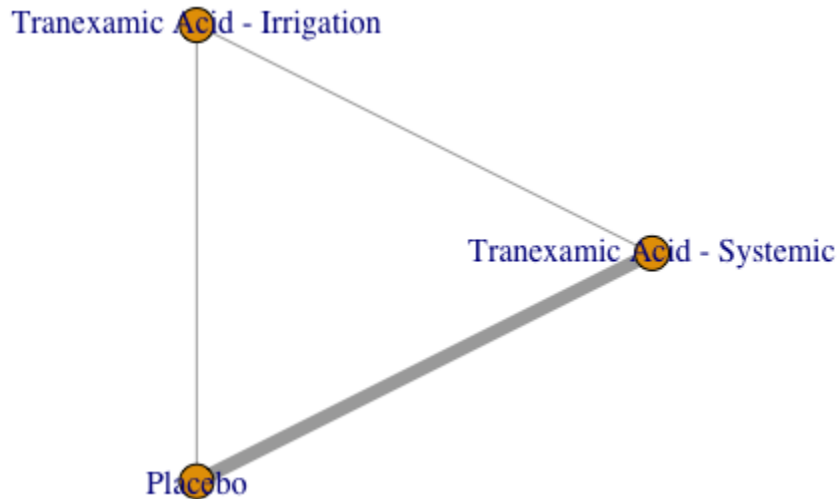


Figure 3. Comparative effectiveness of TXA-I in decreasing operative blood loss: Changes in hemoglobin levels.

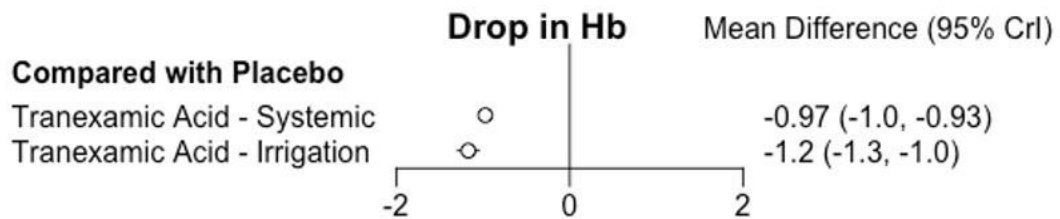


Figure 4. Comparative effectiveness of TXA-I in decreasing operative time.

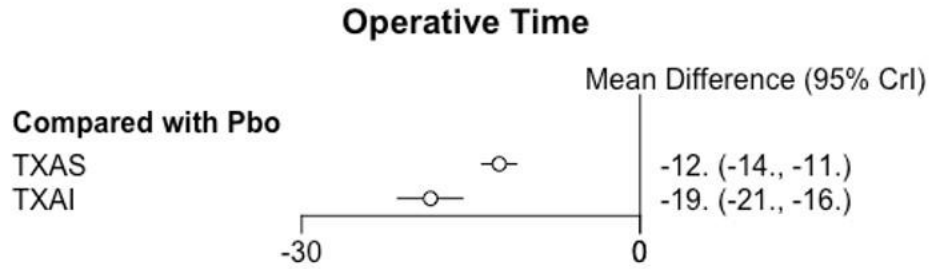


Figure 5. Comparative transfusion rates of TXA-I in included studies.

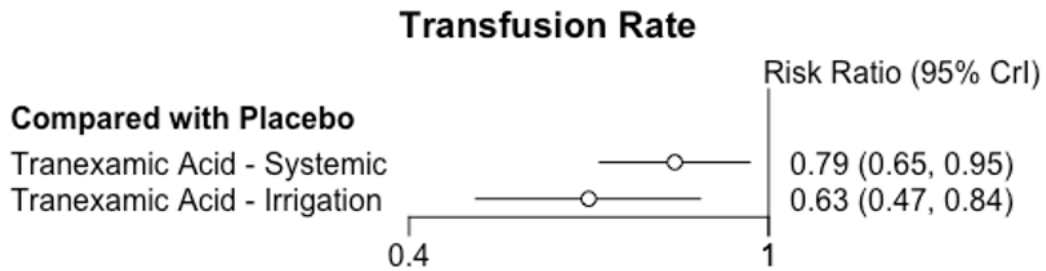


Figure 6. Effect of TXA-I on stone-free rate analysis.

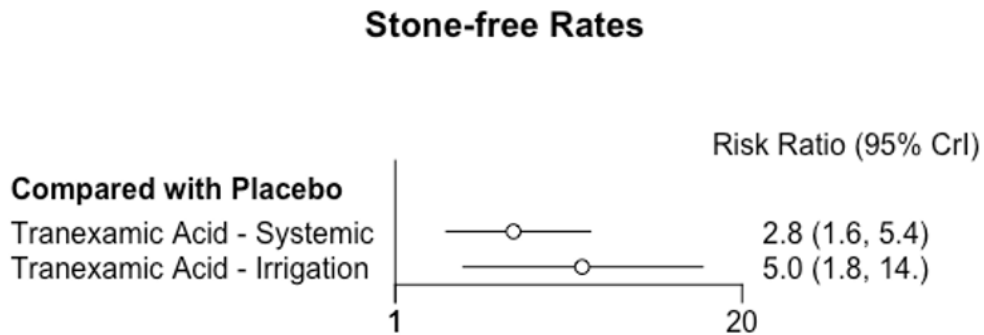


Figure 7. TXA-I effect on overall complication rates.

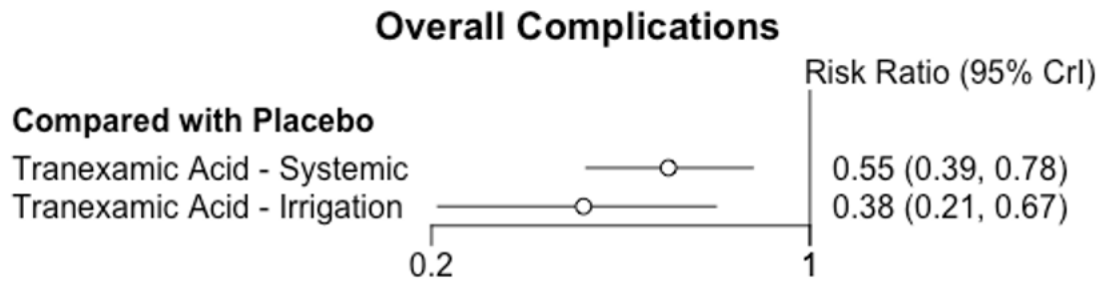


Figure 8. TXA-I effect on minor complication rates.

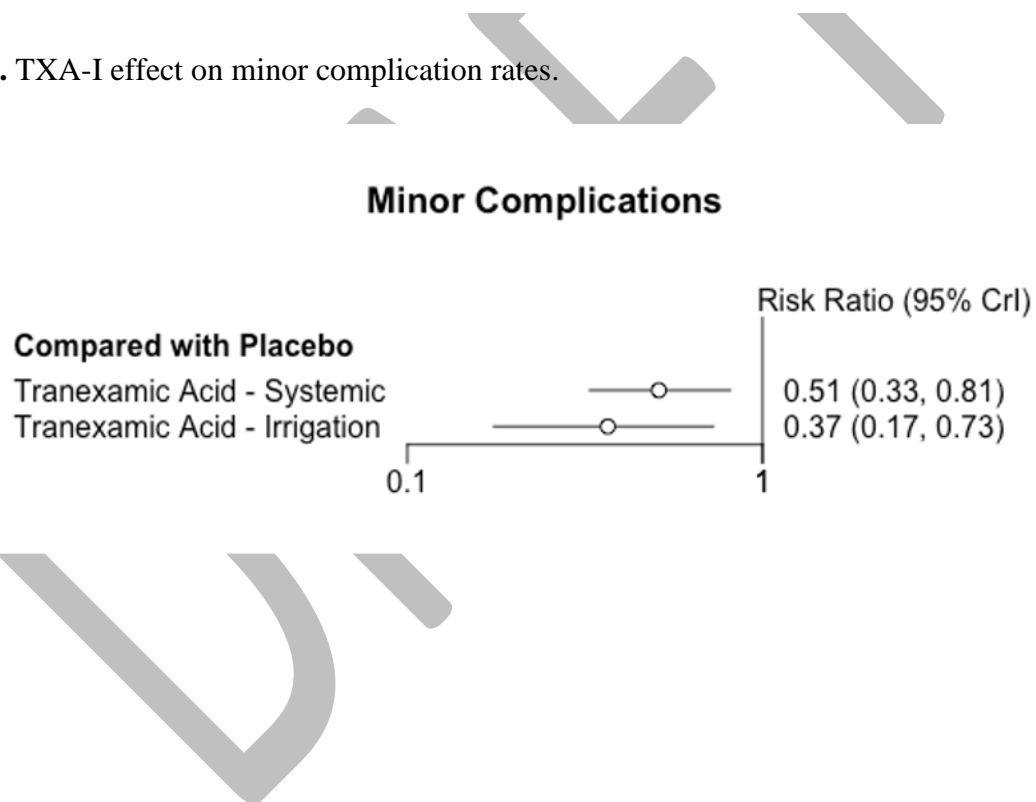


Figure 9. TXA-I effect on major complication rates.

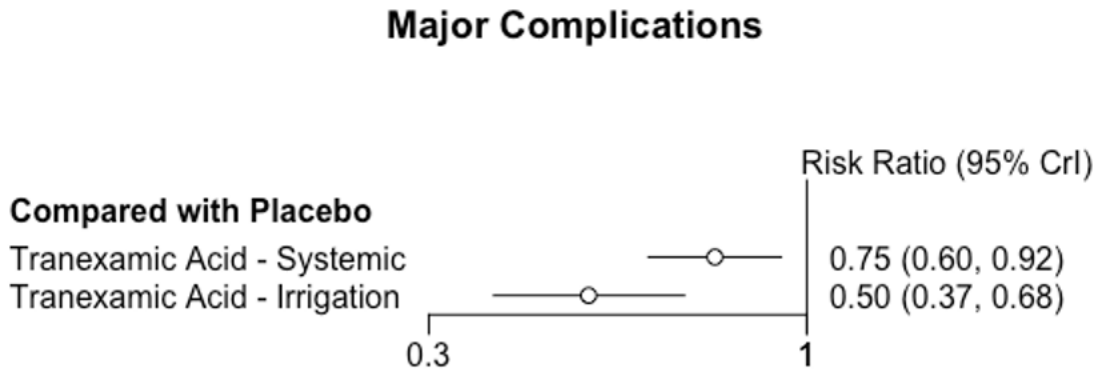


Figure 10. Effect of TXA-I on length of hospital stay.

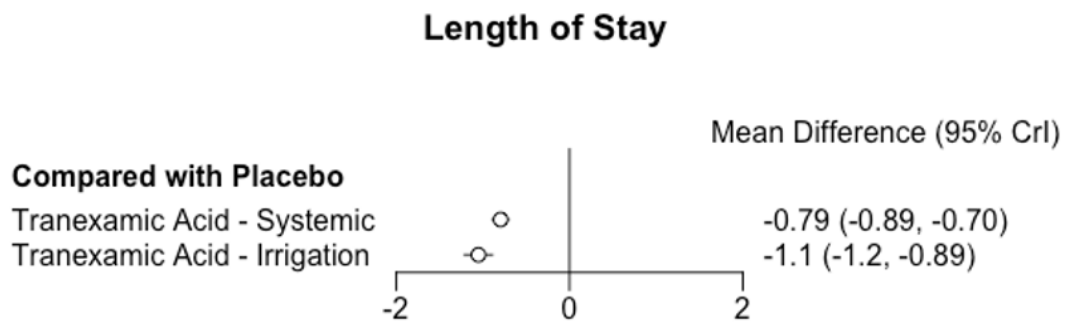


Table 1. Summary of included studies								
Author, Year	Comparison	TXA dosification	Inclusion criteria	Exclusion criteria	Change in Hb determination	Procedure description	Transfusion indication	SFR description
Kumar 2013	TXA vs. placebo	1gm at the start of the procedures followed by 3x500 mg at 8-hour intervals	Patients with stone disease undergoing PCNL	Creatinine + 1.5 Known TXA allergy active intravascular clotting acquired defective colour vision subarachnoid hemorrhage	Preoperative Hb and 24-postoperative Hb	Prone, FQ guided puncture with 30 Fr dilation	ND	Complete stone clearance or residual fragments smaller than 4 mm
Bansal 2017	TXA irrigation vs. placebo	Group 1 received 0.1% tranexamic acid solution [1000 mg (10 mL) in 1 L of irrigant solution (normal saline)]	The patients of renal calculi who were planned to undergo PCNL were included in this study.	Patients having hypersensitivity to tranexamic acid, defective color vision, anticoagulant usage, subarachnoid hemorrhage, abnormal liver function test, unstable cardiovascular disease, acute or chronic renal	Serum Hb and hematocrit level were measured 1 h prior to surgery and on the second postoperative day	Prone, FQ guided puncture with 28fr dilation.	The indication of blood transfusion at our institution during this study was hematocrit of less than 30%.	Success was defined as either complete stone clearance or the presence of residual fragments less than 4 mm.

				failure or any hematological disease were excluded from the study				
Isakov 2017	TXA vs. placebo	Infusion of TXA in 10–100 ml	Patients with stone disease undergoing PCNL	Not described	Preoperative HB and 24 postoperative Hb	Prone, FQ guided puncture with 30fr dilation	ND	ND
Siddiq 2017	TXA vs. placebo	1g intramuscular injection prior to transportation to OR	Patients 18–75 undergoing PCNL for Renal stone >2cm on US	Hb <12 known bleeding disorder creatinine + 1.5 use of antiplatelets or anticoagulants	Preoperative HB and 24 Postoperative Hb	Prone FQ guided puncture dilated to 30 Fr.	Not described	Intraoperative visualization with FQ + postoperative KUB
Rashid 2018	TXA vs. placebo	1g intramuscular 20 prior to the procedure		Patients with creatinin >1.5 bleeding disorder on anticoagulation congenital renal anomalies	Preoperative HB and 24 Postoperative Hb	ND	ND	ND

Mohamadi 2019	TXA vs. placebo	1g IV at initiation plus continuous IV infusion of 1g in 8-hour intervals for 48 hours.	Patients >18 undergoing PCNL.	Creatinine + 1.5 Known TXA allergy Active Intravascular Clotting Acquired defective colour Vision Subarachnoid hemorrhage OCPs, antiplatelets, anticoagulants	Preoperative Hb, 48-hour postoperative Hb	Prone FQ guided puncture dilated to 30F	HB <8 symptoms of inadequate oxygenation	ND
Mohamadi 2019	TXA vs. placebo	1g 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 disorder skeletal disorders subarachnoid hemorrhage aspirin, warfarin or vitamin e	ND	ND	ND	ND

<p>Bagatello 2021</p>	<p>TXA Vs Placebo</p>	<p>1g of TXA in 250 ml infused during induction</p>	<p>Patients >18 with complex kidney stones (Guy’s III, IV)</p>	<p>Known allergy to TXA Anticoagulation or antiplatelets History of thrombosis Coronary artery disease treated with drug eluting stents HB <11 Estimated GFR <30</p>	<p>Preoperative Hb and 24-Postoperative Hb</p>	<p>Prone/supine, FQ guided puncture to 30 Fr dilation</p>	<p>Hb <7 Hb <10 with fluid unresponsive hypotension</p>	<p>Non-Contrast CT performed 24 hours postoperatively with no residual fragments >4 mm.</p>
<p>Mokhtari 2021</p>	<p>TXA vs Placebo</p>	<p>1 gr IV at the beginning and 5 mg orally every 8hr for 3 days</p>	<p>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</p>	<p>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 transpalantation.</p>	<p>Hb and Hct were measured 24hrs before and 48hrs after the operation</p>	<p>Prone, single-surgeon</p>	<p>ND</p>	<p>ND</p>

Chouhurry 2022	TXA I vs. TXA S	Group 1 receives 0.1% tranexamic acid solution (1000mg in 1L of irrigation solution (normal saline)	Open fixation of pelvic and acetabular fractures	Patients having hypersensitivity to tranexamic acid, defective color vision, anticoagulant usage, subarachnoid hemorrhage, abnormal liver function test, unstable cardiovascular disease, uncontrolled hypertension, acute or chronic renal failure or any hematological disease were excluded from the study.	Hemoglobin and hematocrit estimated 24 hours before and 48hours	ND	Varies among amalized studies	Success was defined as complete stone clearance or presence of residual fragments <4 mm in size.
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*ND: not described.

	TXA-S	TXA-I	Placebo
Change in Hb	0.647	0.849	0.004
Operative time	0.5	0.999	0
Transfusion rates	0.545	0.951	0.004
Stone-free rates	0.536	0.962	0.002
Complication rates			
Overall	0.539	0.957	0.003
Minor	0.564	0.929	0.006
Major	0.507	0.992	0.001
Length of stay	0.5	1	0

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