Review Article

The role of tranexamic acid in reducing bleeding during transurethral resection of the prostate: An updated systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Introduction: Transurethral resection of the prostate (TURP) is regarded as the current gold standard surgical intervention for benign prostatic hyperplasia (BPH). However, this procedure is associated with significant chances of intraoperative and postoperative bleeding. Several studies have reported the role of tranexamic acid in prostatic surgeries, but, its role in TURP is still unclear. This review aims to evaluate the role of tranexamic acid in reducing the blood loss during TURP.

Materials and Methods: A systematic search was performed on Medline, Scopus, Embase, and Cochrane, up to December 2021. Relevant randomized controlled trials (RCTs) evaluating the role of tranexamic acid in TURP were screened using our predefined eligibility criteria. Data were expressed as odds ratio (OR) or mean difference (MD) with 95% confidence intervals (CIs). All analyses were performed using RevMan 5.4 (Cochrane Collaboration, UK).

Results: Six trials were included in this meta-analysis, comprising of 582 patients with BPH who underwent TURP. The meta-analysis revealed an insignificant difference in the rate of blood transfusion (OR 0.68, 95% CI 0.34, 1.34, $P = 0.27$) but, a significantly lower amount of blood loss and a lower reduction in the hemoglobin (Hb) levels in the patients receiving tranexamic acid as compared to the control group (MD – 127.03, 95% CI – 233.11, –20.95, $P = 0.02$; MD – 0.53, 95% CI – 0.84, –0.22, $P < 0.01$; respectively). Also, the operative time ($P = 0.12$) and the length of hospitalization ($P = 0.59$) were similar between the two groups.

Conclusion: The administration of tranexamic acid was not found to be effective in reducing the need for blood transfusion, the operative time, and the length of hospitalization during the TURP. However, it could reduce the amount of blood loss and the fall in the Hb levels.

INTRODUCTION

Benign prostatic hyperplasia (BPH) significantly impacts the quality of life of the ageing men and contributes billions of dollars to the healthcare costs.[1] It currently affects more than 80% of the men around 70 years of age[2] and is associated with many risk factors including degenerative and metabolic comorbidities.[3] Even though the tissue proliferation of the prostate is benign, if left untreated, it can lead to lower urinary tract symptoms and can effect the quality of life of the patients due to symptoms or serious complications such as acute urinary retention.[4] There are multiple treatment options for BPH, including watchful waiting, pharmacotherapy, and surgical management. The

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current gold standard surgical management for BPH is transurethral resection of the prostate (TURP).[5,6] However, this procedure is associated with several complications, including intraoperative and postoperative bleeding, often requiring transfusion.[7] The risk of bleeding is high as the hyperplastic organ is richly vascularised and the chances of significant blood loss requiring transfusion during the TURP is estimated to be 0.4%–7.1%, according to the data from various centers worldwide.[8] Various strategies have been recommended to reduce the blood loss during prostatic surgery, including estrogen administration, intraprostatic vasopressin, and 5 alpha-reductase inhibitors. However, none of these preoperative measures are currently implemented in the daily practice.[8,9] The high urinary fibrinolytic activity, caused by the release of urokinase from the prostatic tissues, is also purported to add to the blood loss.[10] The urine and urothelium contain high concentrations of plasminogen activators, which stimulate the fibrinolytic system.[10] This theory has led the investigators to evaluate the role of various antifibrinolytic agents in reducing the blood loss during the TURP. One of these agents is tranexamic acid, which, is a derivative of lysine and can bind to plasminogen to block the interaction of plasmin with fibrin, thus preventing the dissolution of the fibrin clot. Studies have evaluated the potential role of tranexamic acid in various surgeries.[11-14] Previous reviews and meta-analyses have also attempted to evaluate its role in reducing the blood loss during various prostatic surgeries but included observational studies in their analysis.[8,15] However, a systematic review and meta-analyses, with high level of evidence, focusing on the results of randomized controlled trials (RCTs) to evaluate the role of tranexamic acid during TURP in patients with BPH is still lacking. Therefore, this systematic review and meta-analysis focuses only on the results of the available RCTs to examine the effect of tranexamic acid administration on the bleeding-related outcomes in patients with BPH undergoing TURP.

MATERIALS AND METHODS

This Systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines and the Cochrane Handbook of Systematic Review of Intervention.[16,17] The protocol of this review has been registered and published on the Open Science Framework (OSF) database (DOI 10.17605/OSF. IO/QYS7X)

Literature search and study selection

Seven authors independently performed the literature search for this review through several databases, consisting of Medline, Scopus, Embase, and Cochrane up to December 2021. Keywords related to "Tranexamic Acid" and "TURP" were used to search the relevant articles. Boolean logic of "AND" was used to combine the terms, and "OR" was used to search either one of the terms. We followed the Cochrane Handbook for Systematic Reviews of Interventions for the methodology of the literature search. The full search strategy is provided in the supplementary Table 1. An ethical approval was not required as the analysis included only the already published data.

Eligibility criteria

After duplication exclusion, the studies were independently screened for eligibility by two investigators. Potentially eligible studies were screened by title and abstract in the first stage, and full-text were screened in the second stage. Any disagreements or contradictions were resolved through discussion with the involvement of the supervisor for consultation. Studies were included if they met the following criteria: (1) RCT, (2) enrolled patients with BPH undergoing monopolar or bipolar TURP, (3) received intervention as tranexamic acid compared to a placebo or standard treatment, (4) reported outcomes of blood loss, hemoglobin (Hb) change, blood transfusion, and operative time. Studies for which full texts were not available or those conducted on animals were excluded from this review. The process of article screening and selection was presented as PRISMA 2020 flow diagram.[17]

Data extraction and quality assessment

Data extraction was undertaken by investigators using a prespecified data extraction form. The extracted data was: authors, publication year, sample characteristics (gender, age, and eligibility criteria), intervention information, and the outcomes. The methodological quality of the included studies was independently assessed by the investigators. The risk of bias of the included RCTs was evaluated using the Cochrane Risk of Bias (RoB) Tool 2. Several domains, including the randomization process, deviation from the intended intervention, missing outcomes, methods of outcome measurement, and the selection of the reported results, were evaluated and scored as "low risk," "some concerns," and "high risk" according to the completeness of the description in the methods section of the trials. Any disagreements and discrepancies were resolved through discussion among all the investigators.

Outcomes

The primary outcome of this review was the blood transfusion rate. The secondary outcomes were mean blood loss, Hb change, mean operative time, and the length of stay.

Statistical analysis

The results of the studies which evaluated similar outcomes in similar patients were pooled using a forest plot. Formula developed by Wan *et al*.[18] was used to impute the mean and standard deviation (SD) from studies that reported the outcomes using median and range or the interquartile range. When the SD for change from the baseline was not reported, we used the formula from the Cochrane Handbook of Intervention to calculate the missing SD.[16] For continuous

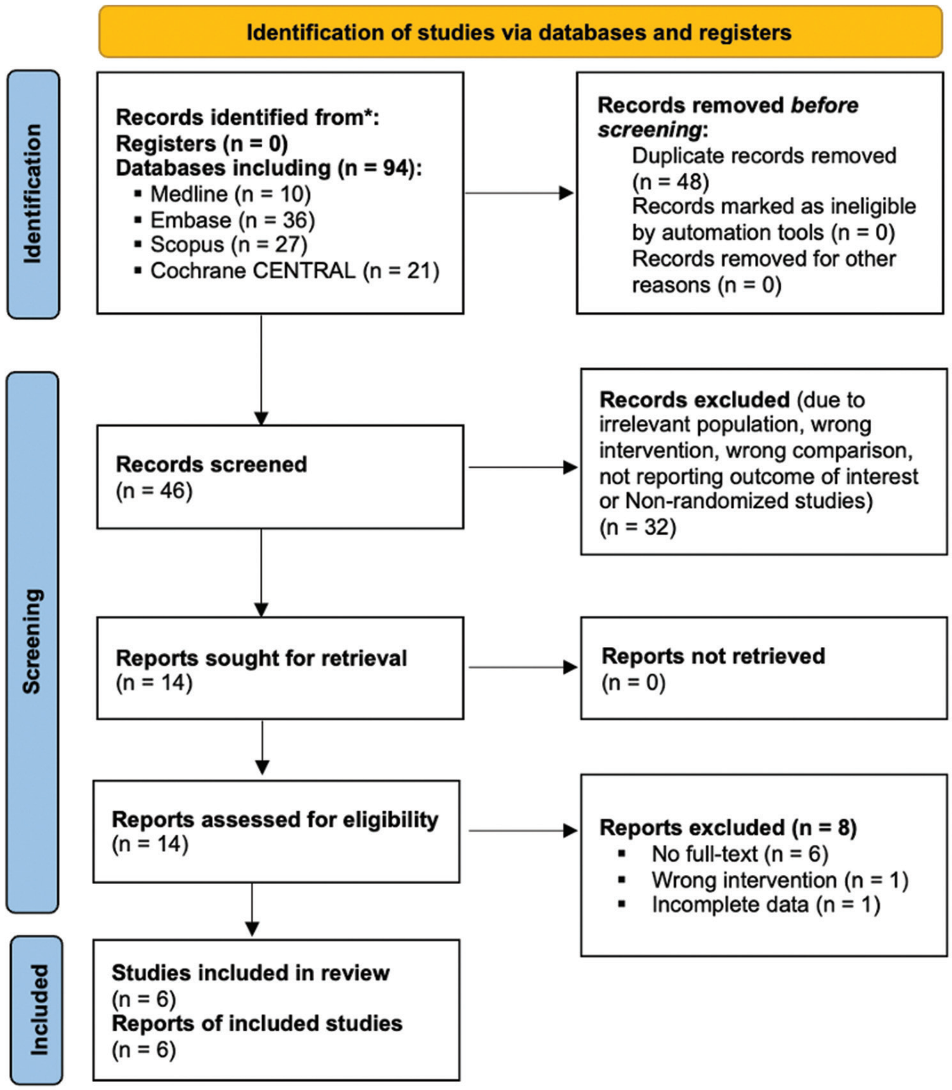


Figure 1: PRISMA flowchart in the systematic search. PRISMA: Preferred reporting items for systematic reviews and meta-analyses

variables, we calculated and pooled the data using mean difference (MD) and 95% Confidence Intervals (CIs). OR and 95% CI were used to assess the categorical outcomes. Heterogeneity between the studies was assessed using the Chi-square test and was quantified with the I^2 test, a value <25% was considered as low risk, 25%–50% was considered as moderate risk, and >50% was considered as high risk for heterogeneity. Fixed effect model was used if the result of test for heterogeneity was <50%, while the random-effects model by DerSimonian and Laird[19] was used if the result was >50%. RevMan 5.4 (Cochrane Collaboration, UK) was used for the data analysis.

RESULTS

Study search and baseline characteristics

PRISMA guidelines were followed while searching the literature evaluating the bleeding-related outcomes in patients with BPH undergoing TURP. The summary of the article screening and selection process is demonstrated in Figure 1. We identified a total of 94 articles from the initial search. After removing the duplicates, 46 records were screened using our predefined eligibility criteria, and the full texts of 14 potentially eligible articles were retrieved for further evaluation. Finally, a total of six RCTs which involved 582 patients were included.[10,20-24] Of these six RCTs, four were randomised double-blind trials. Table 1 presents the characteristics of all the included trials. All the RCTs were conducted in different parts of the world, including Asia and Europe and the sample size in each group ranged from 30 to 95 participants. The average age of the participants ranged from 64.66 to 71.4 years, and the average prostate size ranged from 36.6 g to 108.32 g. None of the trials used other preoperative agents such as dutasteride or finasteride, except the trial by Karkhanei *et al.* which used finasteride before the surgery. The reported dose of tranexamic acid ranged from 10 mg/kg body weight (BW) to 50 mg/kgBW in different trials.

Table 1: Baseline characteristics of the included studies

Authors	Type	Country	Patient	Trial group	Protocol	*n*	Age (years)	Prostate size (g)	Preoperative Hb (g/dL)	Hospital stay (day)	TURP	Administration	Outcome analyzed
Gupta *et al.*, 2021[20]	RCT	India	Patient with prostatic enlargement, LUTS undergoing TURP procedure	Intervention	IV TXA 500 mg	35	68.2	56.87	13.4	3.114	B-TURP	Preoperative adminsstration	Blood loss, ΔHb, operative time, blood Transfusion, length of hospital stay
				Control	No treatment	35	66.5	51.2	13.56	3.08			
Jendoubi *et al.*, 2017[23]	Double-blind RCT	Tunisia	Patients undergoing TURP/TURBT procedure	Intervention	IV TXA 10 mg/kg	30	67.31	47.76	13.68	NR	M-TURP	Preoperative, intraoperative	ΔHb, operative time, blood Transfusion
				Control	Saline	30	71.13	59.08	13.11	NR			
Karkhanei *et al.*, 2020[22]	Double-blind RCT	Iran	BPH patients with prostate weight <100 cc undergoing surgical intervention	Intervention	IV TXA 500 mg	35	66.43	36.62	14.1	NR	M-TURP	Preoperative	ΔHb, operative time, blood transfusion
				Control	Ringer serum	35	69.63	39.14	14.24	NR			
Rannikko *et al.*, 2014[21]	RCT	Finland	BPH patients with obstructive urinary symptoms undergoing TURP	Intervention	Oral TXA 2 g	70	71	50	143	3	NS	Operative and first postoperative day	Blood loss, ΔHb, operative time, blood transfusion, length of hospital stay
				Control	No treatment	66	68	51	144	3			
Meng *et al.*, 2019[24]	Double-blind RCT	China	BPH patients undergoing TURP	Intervention	IV TXA 1 g	30	71.4	73.3	13.7	15.9	NS	Preoperative	Blood loss, ΔHb, operative time, length of hospital stay
				Control	Saline	30	70.7	66.6	14.3	13.9			
Samir *et al.*, 2022[10]	Double-blind RCT	Egypt	Patients with prostate sizes of 80–130 g undergoing B-TURP	Intervention	IV TXA 50 mg/kg	95	64.66	108.32	13.12	2.33	B-TURP	Preoperative	ΔHb, operative time, blood Transfusion, length of hospital stay
				Control	Saline	91	65.75	107.09	12.59	2.37			

Hb=Hemoglobin, TURP=Transurethral resection of the prostate, RCT=Randomized controlled trial, LUTS=Lower urinary tract symptom, IV=Intravenous, TXA=Tranexamic acid, BPH=Benign prostatic hyperplasia, B-TURP=Bipolar TURP, M-TURP=Monopolar-TURP, NS=Not significant, TURBT=Transurethral Resection of the Prostate, TURP: Transurethral Resection of the Prostate

Risk of bias among the study

Figure 2 summarizes the risk of bias among the included trials using the Cochrane RoB 2. Trial by Ranikko *et al.* lacked adequate information on randomization, blinding, and missing outcome data; therefore, this trial was scored as some concerns.[21] However, the methods, as described by the majority of the trials for each of the domain of RoB were adequate, and thus, the overall risk of bias was low.

GRADE quality of evidence

Six randomised controlled trials were included in this meta-analysis, four of them were double-blind RCTs and two were nonblinded studies. The primary outcome, the rate of blood transfusion following the TURP, was reported in five of these six studies (OR = 0.34; 95% CI 0.68–1.34). The role of tranexamic acid in reducing the blood loss in the patients undergoing TURP was analyzed in three studies (MD = –127.03, 95% CI –233.11, –20.95, $P = 0.02$) and all the six studies reported the change in Hb levels following the TURP (MD = –0.53, 95% CI –0.84, –0.22, $P < 0.01$). All the included studies assessed the mean operative time (MD = –11.68; 95% CI –26.31, –2.96) and the length of hospitalization was reported in four of the included studies (MD = 0.05; 95% CI –0.12, 0.21). Several limitations exist among the included studies, notably the non-uniformity in the intervention, in the terms of dose and duration, and the inconsistency in measurement of blood loss-Hb change contributed to the value of inconsistency and indirection. There were no serious imprecisions among the outcomes of the pooled studies. Two studies lacked blinding, and thus had inferior methodological strength as compared to the remaining double-blind RCTs. Two out of six studies are considered high quality, three studies are considered moderate quality, while one study is considered low quality. Overall, the quality of evidence in all included studies is considered adequate [Supplementary Table 2].

Blood transfusion rate

The meta-analysis on the effects of tranexamic acid on the rate of blood transfusion was performed with five trials. Heterogeneity among the included trials was observed to be low ($I^2 = 0\%$, heterogeneity $P = 0.55$), and thus, the analysis was performed using the fixed effects model. The forest plot in Figure 3 demonstrates that the rate of blood transfusion after TURP was similar between the patients who received tranexamic acid and the control group ($P = 0.27$).

Mean blood loss

Three trials evaluated the amount of blood loss during TURP in 266 patients, which were allocated either to the tranexamic group ($n = 135$) or to the control group ($n = 131$). A significant heterogeneity was found on the I^2 index among the included trials ($I^2 = 93\%$); therefore, the random-effects model was used. The pooled analysis, as shown in Figure 4, revealed that the group of patients who received tranexamic acid during the TURP had a significantly lower blood loss as compared to the control group (MD – 127.03, 95% CI –233.11, –20.95, $P = 0.02$).

Hb change

Six studies with 582 participants reported the change in the level of Hb from the baseline. The forest plot on the analysis of change in Hb level after the TURP as presented in Figure 4 revealed a significantly lower change in Hb levels in patients who received tranexamic acid as compared to the control group (MD – 0.53, 95% CI – 0.84, –0.22, $P < 0.01$). The random-effects model was selected as the heterogeneity was observed to be statistically significant ($I^2 = 69\%$).

Mean operative time

Six studies analyzed the mean operative time and included a total of 582 participants who were allocated either into the treatment ($n = 295$) or to the control group ($n = 287$).

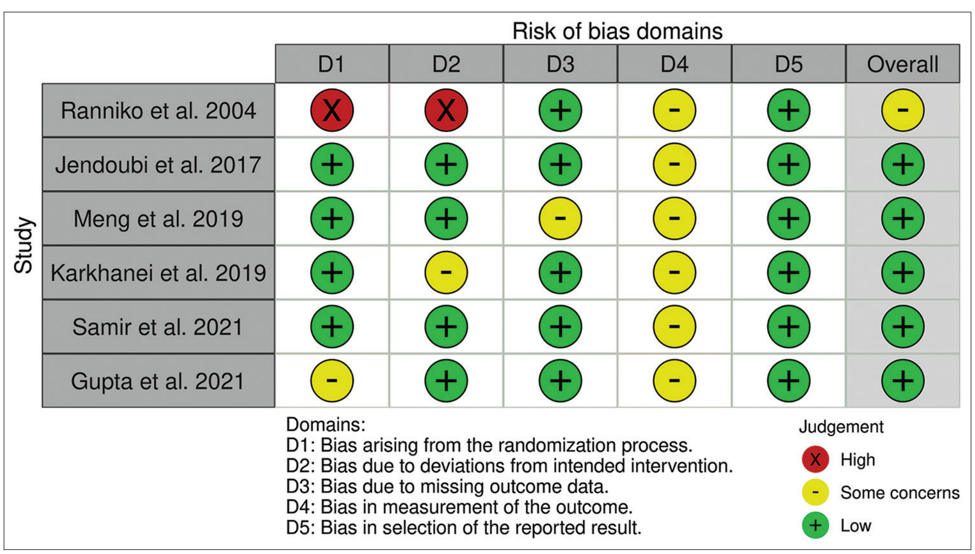
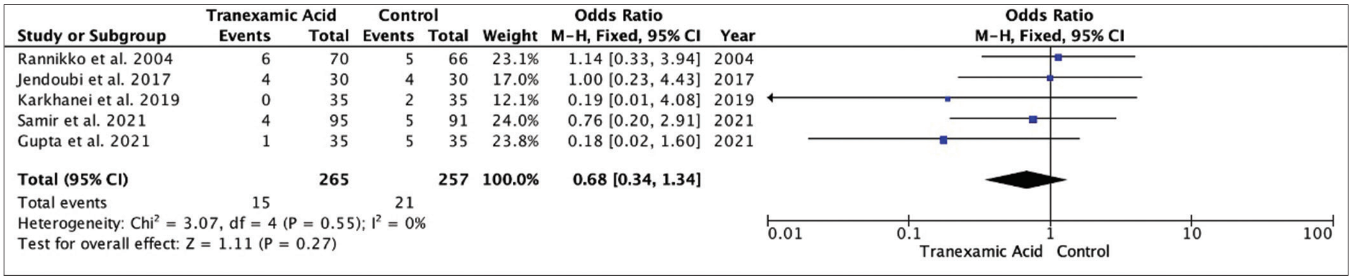


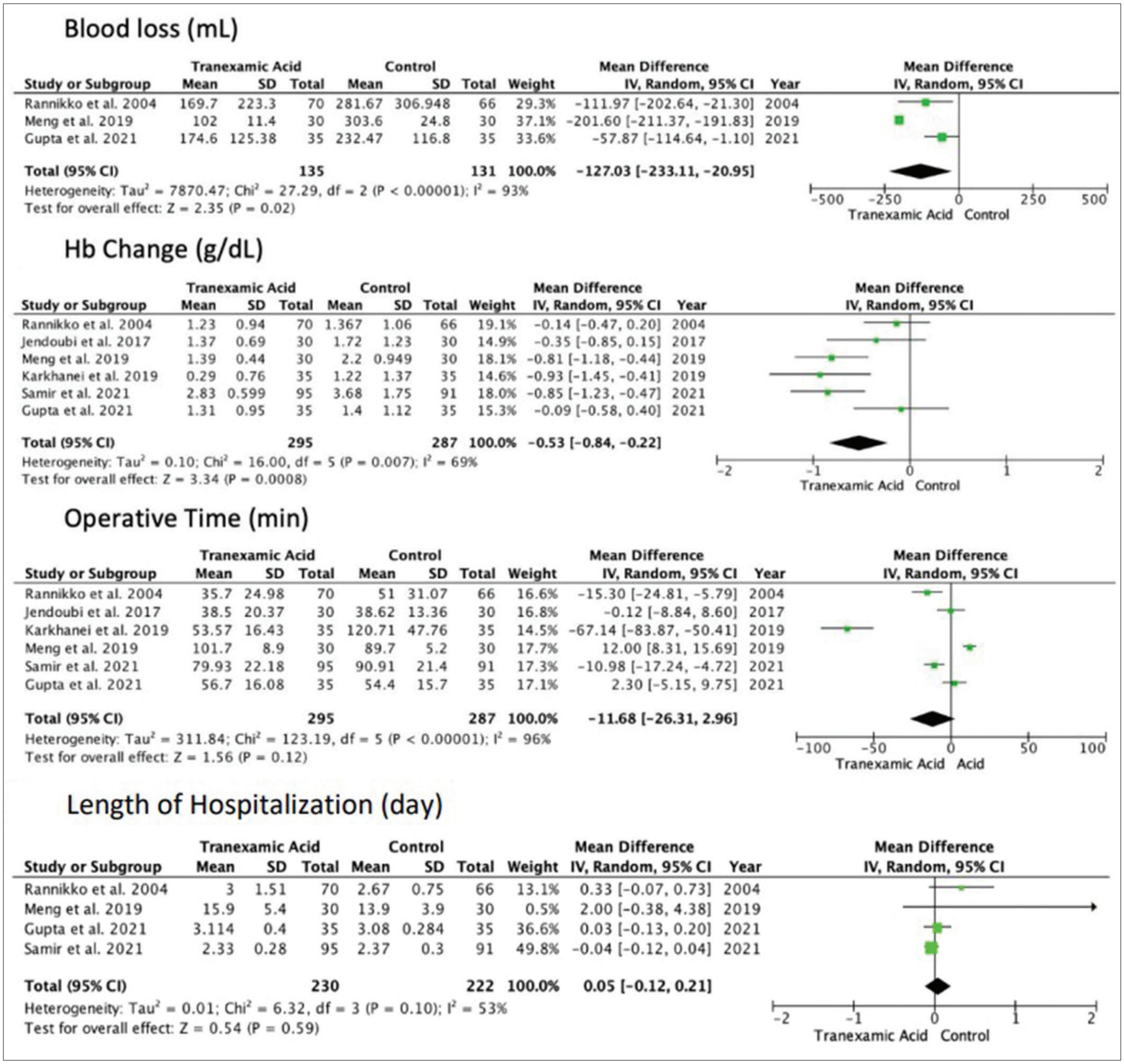
Figure 2: Risk of Bias of included RCT using Cochrane RoB 2. RCT: Randomized controlled trials, RoB: Risk of bias



Study or Subgroup	Tranexamic Acid Events	Tranexamic Acid Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Rannikko et al. 2004	6	70	5	66	23.1%	1.14 [0.33, 3.94]	2004
Jendoubi et al. 2017	4	30	4	30	17.0%	1.00 [0.23, 4.43]	2017
Karkhanei et al. 2019	0	35	2	35	12.1%	0.19 [0.01, 4.08]	2019
Samir et al. 2021	4	95	5	91	24.0%	0.76 [0.20, 2.91]	2021
Gupta et al. 2021	1	35	5	35	23.8%	0.18 [0.02, 1.60]	2021
Total (95% CI)		**265**		**257**	**100.0%**	**0.68 [0.34, 1.34]**	
Total events	15		21				

Heterogeneity: $Chi^2 = 3.07$, df = 4 (P = 0.55); $I^2 = 0\%$
Test for overall effect: Z = 1.11 (P = 0.27)

Figure 3: Forest plot of tranexamic effect on blood transfusion following TURP procedure. TURP: Transurethral resection of the prostate



Blood loss (mL)

Study or Subgroup	Tranexamic Acid Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Rannikko et al. 2004	169.7	223.3	70	281.67	306.948	66	29.3%	-111.97 [-202.64, -21.30]	2004
Meng et al. 2019	102	11.4	30	303.6	24.8	30	37.1%	-201.60 [-211.37, -191.83]	2019
Gupta et al. 2021	174.6	125.38	35	232.47	116.8	35	33.6%	-57.87 [-114.64, -1.10]	2021
Total (95% CI)			**135**			**131**	**100.0%**	**-127.03 [-233.11, -20.95]**	

Heterogeneity: $Tau^2 = 7870.47$; $Chi^2 = 27.29$, df = 2 (P < 0.00001); $I^2 = 93\%$
Test for overall effect: Z = 2.35 (P = 0.02)

Hb Change (g/dL)

Study or Subgroup	Tranexamic Acid Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Rannikko et al. 2004	1.23	0.94	70	1.367	1.06	66	19.1%	-0.14 [-0.47, 0.20]	2004
Jendoubi et al. 2017	1.37	0.69	30	1.72	1.23	30	14.9%	-0.35 [-0.85, 0.15]	2017
Meng et al. 2019	1.39	0.44	30	2.2	0.949	30	18.1%	-0.81 [-1.18, -0.44]	2019
Karkhanei et al. 2019	0.29	0.76	35	1.22	1.37	35	14.6%	-0.93 [-1.45, -0.41]	2019
Samir et al. 2021	2.83	0.599	95	3.68	1.75	91	18.0%	-0.85 [-1.23, -0.47]	2021
Gupta et al. 2021	1.31	0.95	35	1.4	1.12	35	15.3%	-0.09 [-0.58, 0.40]	2021
Total (95% CI)			**295**			**287**	**100.0%**	**-0.53 [-0.84, -0.22]**	

Heterogeneity: $Tau^2 = 0.10$; $Chi^2 = 16.00$, df = 5 (P = 0.007); $I^2 = 69\%$
Test for overall effect: Z = 3.34 (P = 0.0008)

Operative Time (min)

Study or Subgroup	Tranexamic Acid Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Rannikko et al. 2004	35.7	24.98	70	51	31.07	66	16.6%	-15.30 [-24.81, -5.79]	2004
Jendoubi et al. 2017	38.5	20.37	30	38.62	13.36	30	16.8%	-0.12 [-8.84, 8.60]	2017
Karkhanei et al. 2019	53.57	16.43	35	120.71	47.76	35	14.5%	-67.14 [-83.87, -50.41]	2019
Meng et al. 2019	101.7	8.9	30	89.7	5.2	30	17.7%	12.00 [8.31, 15.69]	2019
Samir et al. 2021	79.93	22.18	95	90.91	21.4	91	17.3%	-10.98 [-17.24, -4.72]	2021
Gupta et al. 2021	56.7	16.08	35	54.4	15.7	35	17.1%	2.30 [-5.15, 9.75]	2021
Total (95% CI)			**295**			**287**	**100.0%**	**-11.68 [-26.31, 2.96]**	

Heterogeneity: $Tau^2 = 311.84$; $Chi^2 = 123.19$, df = 5 (P < 0.00001); $I^2 = 96\%$
Test for overall effect: Z = 1.56 (P = 0.12)

Length of Hospitalization (day)

Study or Subgroup	Tranexamic Acid Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Rannikko et al. 2004	3	1.51	70	2.67	0.75	66	13.1%	0.33 [-0.07, 0.73]	2004
Meng et al. 2019	15.9	5.4	30	13.9	3.9	30	0.5%	2.00 [-0.38, 4.38]	2019
Gupta et al. 2021	3.114	0.4	35	3.08	0.284	35	36.6%	0.03 [-0.13, 0.20]	2021
Samir et al. 2021	2.33	0.28	95	2.37	0.3	91	49.8%	-0.04 [-0.12, 0.04]	2021
Total (95% CI)			**230**			**222**	**100.0%**	**0.05 [-0.12, 0.21]**	

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 6.32$, df = 3 (P = 0.10); $I^2 = 53\%$
Test for overall effect: Z = 0.54 (P = 0.59)

Figure 4: Forest plot of tranexamic effect on: (a) blood loss (mL); (b) Hb Change (g/dL); (c) operative time (min); (d) length of hospitalization (day) among patients undergoing TURP procedure. TURP: Transurethral resection of the prostate

The forest plot in Figure 4 reveals that the group of patients treated with tranexamic acid had an insignificant difference in the mean operative time as compared to the control group (MD – 11.68, 95% CI – 26.31, 2.96,

$P = 0.12$). The statistical analysis of I^2 revealed significant heterogeneity among the studies (I2 = 96%) and therefore, the random-effect model was used to conduct the analysis.

Length of stay

Four trials with a total of 452 participants analysed the length of hospitalization. The result from the combined analysis as presented in Figure 4 revealed that the tranexamic acid had no significant effect on the length of hospitalization in patients with BPH undergoing TURP ($P = 0.59$). A random-effects model was used due to the high heterogeneity among the trials ($I^2 = 53\%$).

Complications

No complications of tranexamic acid administration were recorded in the included studies.

DISCUSSION

The role of tranexamic acid in reducing the blood loss during the urological surgeries, including TURP, has been previously investigated.[10,20,23-25] Since its introduction, many improvements and advances have been made to the technique of TURP. Nevertheless, blood loss remains a major problem. Capsular perforation and the opening of the venous sinusoid are the most common causes of venous bleeding. Hence, the trauma to the dorsal venous plexus and the activation of the fibrinolytic system are the main mechanisms of blood loss in TURP.[26] Previous studies have shown that the high concentrations of plasminogen activators in the urothelium and the urokinase released from the prostatic tissues leads to the activation of the fibrinolytic system during the TURP.[26] One of the solutions that has gained attention to tackle this problem is the use of antifibrinolytic agents. Antifibrinolytic agents have been known for their capacity to bind to the plasminogen and inhibit plasmin-fibrin interaction.[27] Based on this mechanism of action, theoretically, the use of antifibrinolytic agents such as tranexamic acid could reduce the amount of bleeding during TURP. In this review, we measured the bleeding-related outcomes during TURP using several parameters such as the blood loss (mL), hemoglobin (Hb) change (g/dL), blood transfusion, and the operative time. According to the results of the meta-analysis, several outcomes were found to be significantly different, while the others were similar between both the groups.

The need for blood transfusion, which is a proxy for major surgical blood loss, was the primary outcome of our study and no significant difference was found.[15] Bleeding and blood transfusions may increase the surgical morbidity and mortality as well as contribute significantly to the financial impact.[28,29] Therefore, reducing the risk of bleeding is is of prime importance during the prostatic surgeries.[30] Various studies have reported the role of tranexamic acid in reducing the blood loss and the transfusion rate during various major surgeries.[31] However, the majority of the trials included in this meta-analysis reported that the tranexamic acid did not alter the transfusion rate after TURP.[10,20-23] After analyzing the results of the eligible trials, we found that the tranexamic acid had no significant effects on the transfusion rates in TURP ($P = 0.27$). However, one should keep in mind that analyzing the amount of blood loss using transfusion rate as the marker might be inaccurate as the rate of transfusion is affected by various factors, such as the different thresholds of blood transfusion at different centers.[32,33]

Perioperative blood loss is a crucial parameter for research related to the techniques and strategies to reduce surgical bleeding.[34] Therefore, we included intraoperative blood loss as one of the primary outcomes in this meta-analysis. An earlier trial by Rannikko *et al.*[21] demonstrated that tranexamic could significantly reduce the blood loss during TURP ($P = 0.018$). Similar findings were also reported by Meng *et al.*[24] and Gupta *et al.*,[20] in which there was a significant reduction in the intraoperative blood loss in the tranexamic group compared to the control group. After pooling the result of all the included trials, we found that the patients who received tranexamic acid during the TURP had a significantly lower blood loss compared to the control group (MD –127.03 ml, 95% CI –233.11, –20.95, $P = 0.02$). This finding is in accordance with the previous meta-analyses, which also demonstrated that tranexamic acid could reduce the bleeding in other prostatic surgeries.[8,15] However, determining the volume of blood loss is an inaccurate method to measure the bleeding as the volume contained in the drain may not accurately reflect the actual amount of blood lost because of the differing amount and duration of postoperative irrigation utilized among the various trials. The difference in the prostate size and the resection weight might also have affected the amount of blood loss among the different patients. Volume estimation is often unreliable and inaccurate but it still remains one of the commonly reported outcomes for perioperative blood loss.[15]

The assessment of change in the hemoglobin might be a more accurate method of evaluating the perioperative blood loss. This is because the change in the hemoglobin levels are measured solely based on the amount of blood lost, which could reduce the potential inaccuracies that occur when the blood loss is measured in drain output which is usually diluted with irrgation fluid.[28] Evaluating the combined analysis from the included trials, we found that the patients who receive tranexamic acid had a significantly smaller change in the Hb levels after the TURP compared to the control group (MD –0.53, 95% CI –0.84, –0.22, $P < 0.01$). These findings were in accordance with the trials by Karkhanei *et al.*[22] and Kumsar *et al.*(38) who reported a smaller change in the Hb levels in the group of patients who received tranexamic acid as compared to the controls. Even though the results from this meta-analysis showed that the tranexamic acid had a significant effect on the amount of blood loss, previous trials had failed to demonstrate a significant effect of tranexamic acid on the change in the Hb levels after TURP.[20,21]

The importance of short surgical time was explained by Lowe *et al*.[35] who stated that a longer surgical time is associated with a higher risk of perioperative thrombosis. By keeping the surgical time of TURP short, complications can be prevented. Our findings suggest that there was no significant difference in the operative time between the two groups (MD –11.68, 95% CI –26.31, 2.96, $P = 0.12$). This is in accordance with the study by Meng *et al*.[24] who reported an insignificant difference in the operative time between those who received tranexamic acid and those who did not. Kumsar *et al*.[26] in their study also reported an insignificant difference in the operative time between the tranexamic acid and the control group with 56.71 min versus 54.5 min, respectively. However, Karkhanei *et al*. reported a significantly shorter operative time in the tranexamic acid group compared to the control group with 53 min versus 120 min, respectively.[22] Another study also reported a significantly shorter operating time in the tranexamic acid group as compared to the control group, with 36 min versus 48 min. Several other studies have also reported a shorter operative time in patients receiving tranexamic acid.[26,36,37] A possible explanation is that the tranexamic acid leads to a reduction in the bleeding and as a consequence a reduction in the operative time. This theory was supported by the previous studies which stated that the absorption of the irrigation fluid was associated with an increase in the operative time.[38,39] In this review, we could not prove a significant association between tranexamic acid and a shorter operative time. However, a difference in the prostate size and the skill of the surgeon in the included trials might have also affected the operative time.

Finally, a reduction in the blood loss was expected to result in a shorter hospitalization time. However, our findings suggest that there are no significant differences between in the hospitalisation times between the tranexamic acid and the control group (OR: 0.55; 95% CI – 0.12, 0.21 $P = 0.59$). Despite reducing the operative blood loss, tranexamic acid did not result in a shorter hospitalization time. Our results were also in line with another study[26] which did not report a significant difference in the length of stay between both the groups. Ranniko *et al*. also reported that the hospitalization time did not differ between the two groups. These findings were similar to that observed with finasteride.[21] The study by Meng *et al*. also reported that the length of stay was same in both the groups.[24] Our results were also in accordance with Gupta *et al*. who did not find a significant difference in the length of stay between the tranexamic acid group and the control group.[20]

A subset analysis evaluating the effects of various routes of administration of tranexamic acid on the outcomes could not be performed. However, the route of administration of tranexamic was similar in all the studies included this meta-analysis. Several studies administered tranexamic acid before the procedure, just before the induction of anesthesia.[10,20,22-24] In most of the studies included, the tranexamic acid was administered via the intravenous route. However, it was given orally, three times a day, in one of the studies.[21] The same administration was continued in the intraoperative period.[10,22,23] Some studies continued tranexamic acid in the post-operative period also, ranging from 5 h to 24 h, after the procedure.[21,23] Tranexamic acid was mostly used in the patients with an increased risk of bleeding such as those with large prostates. However, it was contraindicated in patients with conditions such as deep vein thrombosis, renal failure, and subarachnoid hemorrhage.[21] The most commonly prescribed dose of tranexamic acid prior to the TURP was 10–20 mg/kg/h.[10,22,23] However, other studies have reported the dose to be 500 mg, 1 g, or 2 g.[20,21,24] Furthermore, no serious adverse events such as myocardial infarction or thromboembolic complication were reported in the group receiving tranexamic acid in the included studies.[10,20-24]

There are several limitations of this review. First, we could not analyze the optimal dose of tranexamic acid. The included RCTs were heterogeneous and prescribed several different doses of tranexamic acid, such as 500 mg, 2 g, and 1 g, with different routes of administration. Therefore, we could not conclude the optimum dosage and route which would result in the best outcomes. Also, we could not prove a significant association between the tranexamic acid administration and shorter operative time. The blood loss calculations might also be inaccurate, due to the limited or incomplete data provided in the studies. The dosing and route of administration analysis could not be performed, and warrants further studies. Second, several outcomes had high heterogeneity and thus the measurement might not be precise. Therefore, sensitivity or subgroup analyses should be performed in the future studies. The technique of TURP also varied and so did the energy source. Furthermore, the trial by Karkhanei *et al*. included finasteride in their intervention protocol, which may have affected the results. Finally, despite selecting only randomized studies for this meta-analysis, two of the included studies were nonblinded. The sample size of this study is considered small and mostly represents the data from centers in Asia, Africa, and Europe, and thus may limit widespread application. The size of the prostate and the time of administration of tranexamic acid also varied between the studies. Also, on ROB analysis, some studies included in this analysis were found to be poorly conducted. Therefore, thorough research, preferably with homogenous data, is required to better understand the effects of tranexamic acid on bleeding related outcomes during TURP.

CONCLUSION

This review provides evidence on the use of tranexamic acid in patients with BPH undergoing TURP. Tranexamic acid was found to have beneficial effects in term of reducing the blood loss and the fall in the hemoglobin levels. However, the findings pertaining to the measurement of the volume loss and the optimal dose of tranexamic acid warrants further research. Tranexamic acid was not found to reduce the need for blood transfusion, operative time, and the length of hospitalization.

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Supplementary Table 1: Keywords used in Search Strategy		
Database	**Keywords**	**Articles (*n*)**
Medline	("tranexamic acid"[MeSH Terms] OR ("tranexamic"[All Fields] AND "acid"[All Fields]) OR "tranexamic acid"[All Fields]) AND ("transurethral resection of prostate"[MeSH Terms] OR ("transurethral"[All Fields] AND "resection"[All Fields] AND "prostate"[All Fields]) OR "transurethral resection of prostate"[All Fields] OR ("transurethral"[All Fields] AND "resection"[All Fields] AND "prostate"[All Fields]) OR "transurethral resection of the prostate"[All Fields]) AND ("bleedings"[All Fields] OR "hemorrhage"[MeSH Terms] OR "hemorrhage"[All Fields] OR "bleed"[All Fields] OR "bleeding"[All Fields] OR "bleeds"[All Fields])	10
Embase	TITLE-ABS-KEY (tranexamic acid) AND TITLE-ABS-KEY (transurethral resection of the prostate) AND TITLE-ABS-KEY (bleeding)	36
Scopus	(TITLE-ABS-KEY (*tranexamic* AND *acid*) AND TITLE-ABS-KEY (*transurethral* AND *resection* AND *of* AND *the* AND *prostate*) AND TITLE-ABS-KEY (*bleeding*)	27
Cochrane CENTRAL	TITLE-ABS-KEY (tranexamic acid) AND TITLE-ABS-KEY (transurethral resection of the prostate) AND TITLE-ABS-KEY (bleeding)	21

Supplementary Table 2: GRADE quality of evidence						
Number of studies (design)	**Limitation**	**Inconsistency**	**Indirection**	**Imprecision**	**Outcome (95% CI)**	**Quality**
Blood transfusion following TURP procedure (5 RCTs)	No serious limitation	No serious inconsistency	No serious indirectness	No serious imprecision	OR: 0.68 (0.34–1.34)	⊕⊕⊕⊕ High
Blood loss during TURP procedure (3 RCTs)	Includes two non-blinded studies, high heterogeneity	Serious inconsistency	Serious indirectness	No serious imprecision	Mean difference: −127.03 (−233.11–−20.95)	⊕⊕ Low
Hb change following TURP procedure (6 RCTs)	No serious limitation	No serious inconsistency	Serious indirectness	Serious imprecision	Mean difference: −0.53 (−0.84–−0.22)	⊕⊕⊕ Moderate
Operative time during TURP procedure (6 RCTs)	High heterogeneity	Serious inconsistency	No serious indirectness	No serious imprecision	Mean difference: −11.68 (−26.31–−2.96)	⊕⊕⊕ Moderate
Length of hospitalization (4 RCTs)	No serious limitation	No serious inconsistency	No serious indirectness	No serious imprecision	Mean difference: 0.05 (−0.12–0.21)	⊕⊕⊕⊕ High

OR=Odds ratio, CI=Confidence interval, TURP=Transurethral resection of the prostate, RCTs=Randomized controlled trials, Hb=Hemoglobin