# Cent European J Urol

**Citation:** Mina SH, Garcia-Perdomo HA. Effectiveness of tranexamic acid for decreasing bleeding in prostate surgery: a systematic review and meta-analysis. **Cent European J Urol**. 2017; doi: 10.5173/ceju.2017.1581 [Epub ahead of print]


## Effectiveness of tranexamic acid for decreasing bleeding in prostate surgery: a systematic review and meta-analysis

[Autor's unedited version]


Sergio Hernando Mina[1,2], Herney Andres Garcia-Perdomo[1,2]

[1]Universidad del Valle, Department of Urology, Santiago de Cali, Colombia
[2]Urology Research Group (UROGIV), Universidad del Valle, Santiago de Cali, Colombia



**Key Words:** prostate surgery, tranexamic acid, blood loss, antifibrinolytic



**Corresponding author**
sergio.mina@correounivalle.edu.co



**Article history**
Submitted: Oct. 17, 2017
Accepted: Dec. 22, 2017
Published online: Jan.1, 2018



**Introduction** Objective. To determine the effectiveness of tranexamic acid in decreasing bleeding inpatients undergoing prostate surgery.

**Materials and methods** All clinical experiments were included without language restrictions.

The inclusion criteria were as follows: men over 18 years of age who underwent prostate surgery (transurethral, prostate adenectomy, and radical prostatectomy) and received tranexamic acid prior to prostate surgery as a preventive measure for perioperative hemorrhage. Prophylactic tranexamic acid vs. no intervention or placebo were compared. The primary outcomes were as follows: 1. intraoperative blood loss and 2. the need for red blood cell transfusion. A systematic search was performed in MEDLINE, EMBASE, CENTRAL and LILACS. Other sources were used to discover published and unpublished literature

sources. The statistical analysis was performed in Review Manager v.5.3.

**Results** Four studies were included with a total of 436 patients. Three of the four studies had small sample sizes. There was a low risk of attrition bias and reporting bias. Unclear risk of selection bias, performance bias, or detection bias was presented. A mean difference (MD) of -174.49 [95% CI (-248.43 to -100.56)] was found for perioperative blood loss (the primary outcome). At the end of the procedure, the hemoglobin concentration had a MD of -1.19 [95% CI (-4.37 to 1.99)].

**Conclusions** Tranexamic acid is effective at preventing perioperative blood loss compared with the placebo in patients undergoing TURP. However, this treatment was not effective neither at preventing the need for transfusions nor to increase hemoglobin values at the end of the procedure.

**Citation:** Mina SH, Garcia-Perdomo HA. Effectiveness of tranexamic acid for decreasing bleeding in prostate surgery: a systematic review and meta-analysis. **Cent European J Urol**. 2017; doi: 10.5173/ceju.2017.1581 [Epub ahead of print]

Benign prostatic hyperplasia (BPH) is a condition related to aging in men regardless of race, ethnicity, or geographic location. Therefore, it is estimated that 50% of men at age 60 and close to 90% of men at age 85 present histopathological changes related to BPH. Lower urinary tract symptoms are the usual presentation, especially those involved with evacuation [1]. Treatment of BPH is conservative in the majority of cases, but under special conditions the management is surgical with open or endoscopic surgery.

Transurethral resection of the prostate (TURP) is the standard for the surgical management of BPH. TURP is an effective procedure that increases the average and maximum urinary flows; however, TURP is associated with a risk of bleeding and requires transfusion in up to 7% of patients [2]. This issue depends on the size of the prostate, the amount of tissue resected, the surgery time, the presence of a presurgical urinary infection, medical treatment with 5-alpha-reductase inhibitors, the use of acetylsalicylic acid, the type of anesthesia, and the arterial pressure, among other factors [3].

Radical surgical procedures are associated with excessive perioperative blood losses in the absence of appropriate strategies to minimize them. Intra- and postoperative bleeding are the most important complications in radical prostatectomy (RP, performed in patients with prostate cancer). Patients undergoing this intervention often require red blood cell transfusions [4]. Blood loss during RP has been documented in the range of 700 to 1500 ml during the perioperative period, and approximately 10% of patients require a blood transfusion [5].

Different interventions attempting to reduce the perioperative blood loss in these procedures have been studied. Tranexamic acid is an antifibrinolytic derivative of the amino acid lysine that acts by binding to plasminogen and blocking the interaction of plasmin with fibrin, thereby preventing the dissolution of the fibrin clot. Therefore, tranexamic acid can be assumed to be a molecule that stabilizes the coagulation process [6].

A systematic review of randomized controlled clinical trials of tranexamic acid in patients undergoing elective surgery (cardiac, hepatic, thoracic, and orthopedic surgery) identified 53 studies involving 3,836 participants. This review demonstrated that tranexamic acid significantly reduced the need for perioperative transfusions [7].

The main complication of prostate surgery is perioperative bleeding. Different strategies have been proposed to reduce operative bleeding in prostatic surgery, such as intravenous administration of estrogen, pulling of catheter, intraprostatic vasopressin, and recently the use ofpresurgical finasteride [8, 9]. Despite seemingly favorable results, nose of these behaviors has been accepted globally for implementation in daily practice [8].

Postoperative bleeding in prostatic surgery is associated with increased urinary fibrinolytic action because urine and urothelium contain high concentrations of plasminogen, which favors the destruction of clots [8]. Therefore, a possible beneficial effect of tranexamic acid in reducing perioperative bleeding has been proposed due to its anti-fibrinolytic action and its renal excretion, which allows it to bind to urokinase and inhibit it as well as plasmin, thereby preventing clot lysis. This effect has been shown to reduce perioperative bleeding in TURP and radical prostatectomy in some studies [9, 10, 11].

Even when there is evidence in other scenarios, no overwhelming evidence has been presented in urological procedures, specifically in prostate surgery. The objective of this study was to determine the effectiveness of tranexamic acid in decreasing bleeding in patients undergoing prostate surgery.

**Citation:** Mina SH, Garcia-Perdomo HA. Effectiveness of tranexamic acid for decreasing bleeding in prostate surgery: a systematic review and meta-analysis. **Cent European J Urol**. 2017; doi: 10.5173/ceju.2017.1581 [Epub ahead of print]

## MATERIAL AND METHODS

This systematic review meets the requirements stipulated by the Cochrane manual and the PRISMA guidelines for reporting systematic reviews and meta-analyses. The registration in PROSPERO is CRD42016041358.

All controlled clinical experiments without language restrictions that met the following criteria were included: men over 18 years of age who underwent prostate surgery (transurethral, prostate adenectomy, and radical prostatectomy) and received tranexamic acid prior to the surgery as a preventive measure for perioperative hemorrhage. Prophylactic tranexamic acid was compared to no intervention or placebo. The primary outcomes were as follows: 1. Intraoperative blood loss and 2. The need for a red blood cell transfusion.

The secondary objectives were as follows: 1. The presence of thromboembolic events (no articles were found that evaluated this outcome) and 2. The hemoglobin values at the end of the procedure.

### Sources of the search

A systematic search was performed in the following databases: MEDLINE via OVID, EMBASE, The Cochrane Central Register of Controlled Trials (CENTRAL), and LILACS from inception to the current date (see the specific search strategies in Appendix 1).

Other electronic sources used to find additional studies were Clinicaltrials.gov, DARE, PROSPERO, gray literature (unpublished), such as conference abstracts and books, and additional studies in the reference lists of the selected articles. Additionally, reviews were performed in Google Scholar and the OpenGrey database. The results of the searches were crosschecked to eliminate duplicates. There were no restrictions on language.

### Extraction and analysis of the data
### Study selection

Two researchers independently and blindly identified and selected the titles, abstracts, and full texts obtained in the electronic searches. Discrepancies were resolved by consensus.

### Information extraction and data management

The researchers extracted the data independently. The following data were extracted: name of the first author, year of publication, country, year of the study, type of study, sample size, outcome, and sociodemographic and clinical variables such as age, prostate size, and presence of comorbidities.

Disagreements between the two authors in evaluating the eligibility, quality, and extracted data were resolved when a consensus was reached.

### Evaluation of the risk of bias in the included studies

The quality of the studies was evaluated based on how the studies were conducted and reported according to the recommendations of the Cochrane Collaboration as follows: 1) generation of the random sequence; 2) concealment of the sequence; 3) masking; 4) loss during follow-up; 5) selective reporting; and 6) other biases.

**Citation:** Mina SH, Garcia-Perdomo HA. Effectiveness of tranexamic acid for decreasing bleeding in prostate surgery: a systematic review and meta-analysis. **Cent European J Urol**. 2017; doi: 10.5173/ceju.2017.1581 [Epub ahead of print]

### Statistical analysis

The statistical analysis was performed in Review Manager v.5.3. The outcome variables are shown in terms of the mean standardized difference, relative risk (RR) or risk difference (RD) according to the type of variable with its corresponding 95% confidence interval (95% CI). We used a fixed or random effects model according to the homogeneity or heterogeneity in the studies.

The results are reported in forest plots of the estimated effect of the included studies. It was not possible to perform subgroup analyses.

### Evaluation of heterogeneity

The heterogeneity between the trials was evaluated by visual inspection of the forest plots. Subsequently, the Chi-squared test of homogeneity was performed with a defined alpha level of 10%. Then, the degree of heterogeneity was quantified using the I2 test.

No sensitivity analysis or analysis of publication bias was performed due to the small number of studies.

## RESULTS

### Study selection

A total of 48 studies were found using the defined search strategies. After exclusions, four articles were included in the quantitative analysis (Crescenti, Rannikko, Kumsar, and Menq) (See Figure 1).

### Characteristics of the included studies

A total of 436 patients were included in the four studies. Three of these studies (Rannikko, Kumsar, and Menq) evaluated the use of tranexamic acid in patients undergoing TURP. The Crescenti study was conducted in patients undergoing radical prostatectomy (RRP). The mean ages of the patients in these studies were 64, 67, 71, and 71.4 years, respectively (see Table 1).

### Characteristics of the excluded studies

The study by L. Anderson was excluded because it did not have information regarding the outcomes of this review.

### Risk of bias of the included studies

The quality of the conduct and reporting of the experiments of the three studies was evaluated according to the Cochrane recommendations.

Three of the four studies had a small sample size. There was a low risk of attrition bias and reporting bias. Additionally, no clear risk of selection bias, performance bias, and detection bias was found (See Figure 2).

The study of Crescenti 2011 presented a low risk of bias in all components, whereas the studies of Rannikko 2004, Kumsar 2011, and Menq 2014 for the most part presented unclear risk in their components (see Figure 3).

**Citation:** Mina SH, Garcia-Perdomo HA. Effectiveness of tranexamic acid for decreasing bleeding in prostate surgery: a systematic review and meta-analysis. **Cent European J Urol**. 2017; doi: 10.5173/ceju.2017.1581 [Epub ahead of print]

### Primary outcomes

Concerning the primary outcome (Intraoperative blood loss), two studies (Rannikko, and Menq) which primary procedure was TURP, showed a mean difference of -174.49 [95% CI (-248.43 to -100.56), I2 = 67%] (See Figure 4). Crescenti 2011, performed RRP and found a MD of -232 95%CI (-398.55 to -65.45).

Concerning the need for transfusion, one study performed TURP (Rannikko 2004), and showed a risk difference of 0.01 95% CI (-0.08 to 0.1). On the other side, Crescenti 2011, performed RRP and had a risk difference of -0.21 95% CI (-0.34 to -0.08).

### Secondary outcome

At the end of the procedure, hemoglobin was taken as a secondary outcome. two studies (Rannikko, and Kumsar) which performed TURP, showed a mean difference of -1.19 [95% CI (-4.37 to 1.99), I2 = 0%] (See Figure 5).

## DISCUSSION

Prostate surgery is one of the most common urological surgical interventions, and perioperative bleeding is the main complication. Multiple preventive strategies have been proposed. However, none of these strategies have been adopted as a preventive management protocol for prostate surgery because the evidence is not sufficiently convincing.

Tranexamic acid has been extensively studied in relation to reducing bleeding and the need for transfusion associated with cardiovascular and orthopedic surgery and severe trauma-related hemorrhages [12, 13].

Similar to other areas, tranexamic acid was shown to be effective at reducing perioperative bleeding in urological surgery, specifically prostate surgery. In our study, a significant reduction in perioperative blood loss was found compared with the placebo or no intervention groups.

Previous studies, such as Miller et al. 1980, demonstrated that the use of antifibrinolytic therapy decreased postoperative bleeding in patients undergoing TURP by 22% compared with the placebo [14].

The secondary objectives evaluated in our study (the need for transfusion and the hemoglobin value after the procedure) showed no differences with respect to the placebo or no intervention group. This finding is consistent with the studies published by Rannikko et al. and even that of Miller in which no significant impact was observed with the use of this therapy on the decrease of the need for transfusion. However, the studies published to date had small sample sizes, which was a great limitation; thus, the possible beneficial effect of the intervention with respect to these two outcomes cannot be ruled out [9, 14].

Different studies have demonstrated that the use of tranexamic acid does not increase the incidence of thromboembolic events [11, 15]. In this study, it was not possible to evaluate this outcome because data on this variable were found in only one publication and there were no significant differences.

Preventive management of perioperative bleeding with tranexamic acid is a very attractive intervention because it is a medicine with a very reasonable cost, wide margin of safety, and demonstrated effectiveness in decreasing perioperative blood loss related to prostate surgery. Controlled clinical trials with greater methodological rigor are needed to allow us to establish

**Citation:** Mina SH, Garcia-Perdomo HA. Effectiveness of tranexamic acid for decreasing bleeding in prostate surgery: a systematic review and meta-analysis. **Cent European J Urol**. 2017; doi: 10.5173/ceju.2017.1581 [Epub ahead of print]

whether there is a truly significant effect on the secondary outcomes raised in our study and to determine the dose-effect relationship.

### Strengths and limitations

Our study is the first systematic review and meta-analysis to investigate the effectiveness of tranexamic acid in the prevention of perioperative bleeding in prostate surgery. The main limitations were the small number of studies found and the resulting low number of patients available for the analysis and we could not summarize the results from Crescenti 2011, since they performed RRP and the rest of the studies performed TURP.

The lack of evaluation of adverse effects associated with the intervention was another limitation.

When performing the quality evaluation of the included studies, a high proportion of studies with an unclear risk of bias was found. Therefore, it is necessary to conduct clinical experiments of higher quality with better reporting.

## CONCLUSIONS

Tranexamic acid is effective at preventing perioperative blood loss compared with the placebo in patients undergoing TURP. However, this treatment was not effective neither at preventing the need for transfusions nor to increase hemoglobin values at the end of the procedure. We recommend to perform high quality clinical trials to support this intervention in patients undergoing different kinds of prostate surgical procedures

### Conflicts of interest

The authors declare no conflicts of interest.

**Citation:** Mina SH, Garcia-Perdomo HA. Effectiveness of tranexamic acid for decreasing bleeding in prostate surgery: a systematic review and meta-analysis. **Cent European J Urol**. 2017; doi: 10.5173/ceju.2017.1581 [Epub ahead of print]

**Table 1.** Characteristics of the included studies

| *Study* | *Country SC/MC* | *Outcome* | *Intervention* | *Mean age* | *Sample size* | *Prostate size (g)* | *Preoperative hb (g/L) mean* | *Hb first postoperative day (mean)* | *Operating time (min)* | *Weight of resected tissue (g)* | *Operative blood loss (mL)* | *Volume of irrigant fluid (L)* | *Type of surgery* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Crescenti 2011** | Italy | Number of patients receiving perioperative blood transfusions | 500 mg of TA iv 20 minutes before surgery and a continuous iv infusion of TA a rate of 250 mg/h from surgical incision until skin closure | 64 | 100 | - | 141 | 112 | 159 | - | 1103 | - | Radical retropubic prostatectomy (RRP) |
| | | | Placebo | 64 | 100 | - | 139 | 108 | 166 | - | 1335 | - | |
| **Kumsar 2011** | Turkey | Decrease blood loss during TURP | 10 mg/kg TXA by IV infusion during the first half hour of the operation | 67 | 20 | 55.2 | - | - | 46.77 | 24.33 | - | 16.34 | TURP |
| | | | no treatment | 65 | 20 | 49.5 | - | - | 63.5 | 16.68 | - | 20.05 | |
| Rannikko 2004 | Finland | Decrease blood loss during TURP | 2 g AT orally three times daily on the operative and postoperative first day | 71 | 70 | 50 | 143 | * | 36 | 16 | 128 | 15 | TURP |
| | | | no treatment | 68 | 66 | 51 | 144 | * | 48 | 16 | 250 | 18 | |
| Menq 2014 | China | Decrease blood loss during TURP | 1 g AT in 200 ml normal saline after induction of anesthesia | 71.4 | 30 | - | 137.9 | 124 | 101 | - | 102 | 27.5 | TURP |
| | | | Placebo | 70.4 | 30 | - | 143.1 | 121.7 | 89 | - | 303 | 25 | |

**Citation:** Mina SH, Garcia-Perdomo HA. Effectiveness of tranexamic acid for decreasing bleeding in prostate surgery: a systematic review and meta-analysis. **Cent European J Urol**. 2017; doi: 10.5173/ceju.2017.1581 [Epub ahead of print]

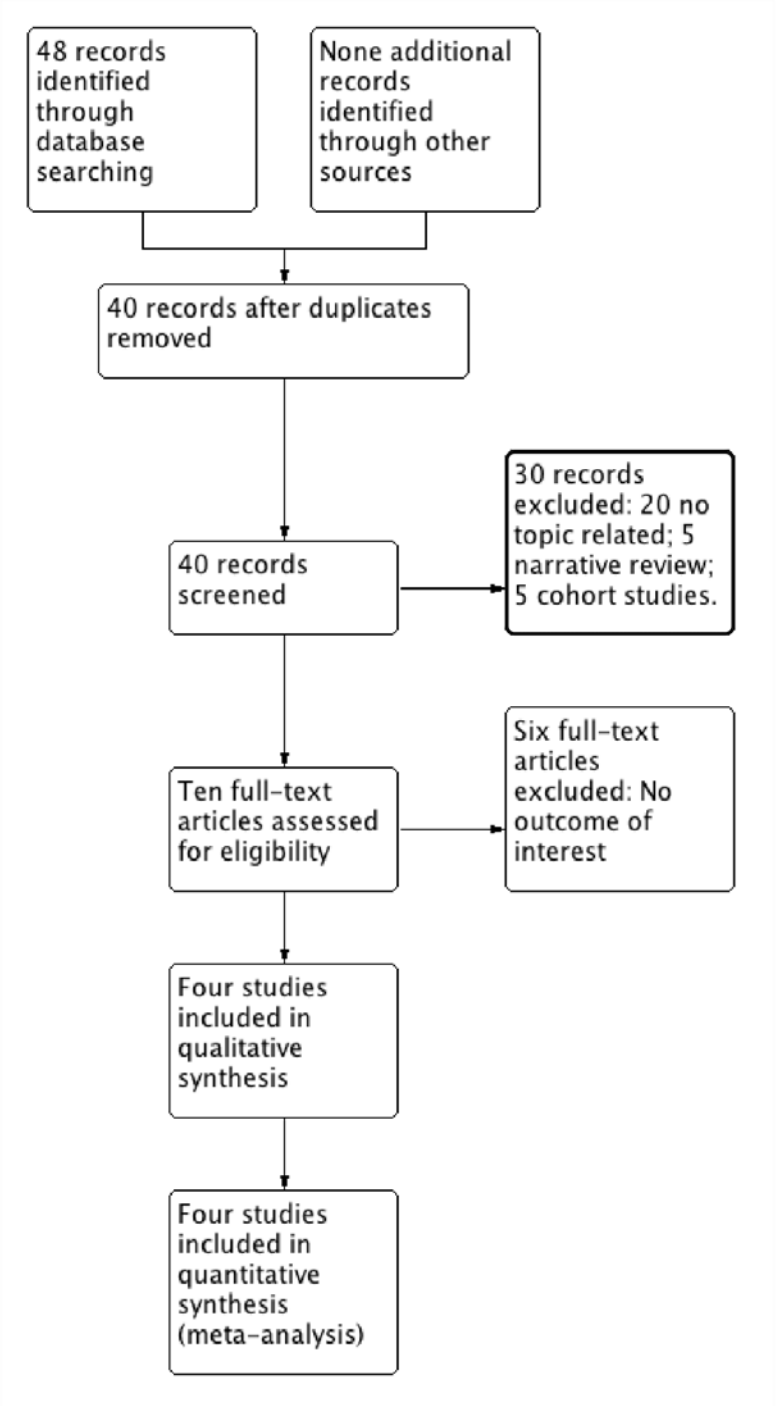


**Figure 1.** Flowchart of study selection.

**Citation:** Mina SH, Garcia-Perdomo HA. Effectiveness of tranexamic acid for decreasing bleeding in prostate surgery: a systematic review and meta-analysis. **Cent European J Urol**. 2017; doi: 10.5173/ceju.2017.1581 [Epub ahead of print]

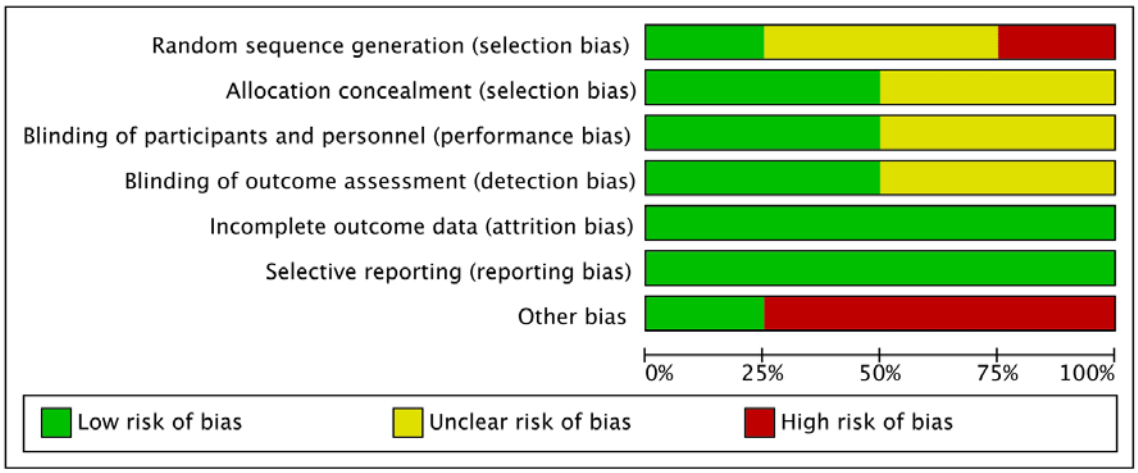


**Figure 2.** Risk of bias among the studies.

**Citation:** Mina SH, Garcia-Perdomo HA. Effectiveness of tranexamic acid for decreasing bleeding in prostate surgery: a systematic review and meta-analysis. **Cent European J Urol**. 2017; doi: 10.5173/ceju.2017.1581 [Epub ahead of print]

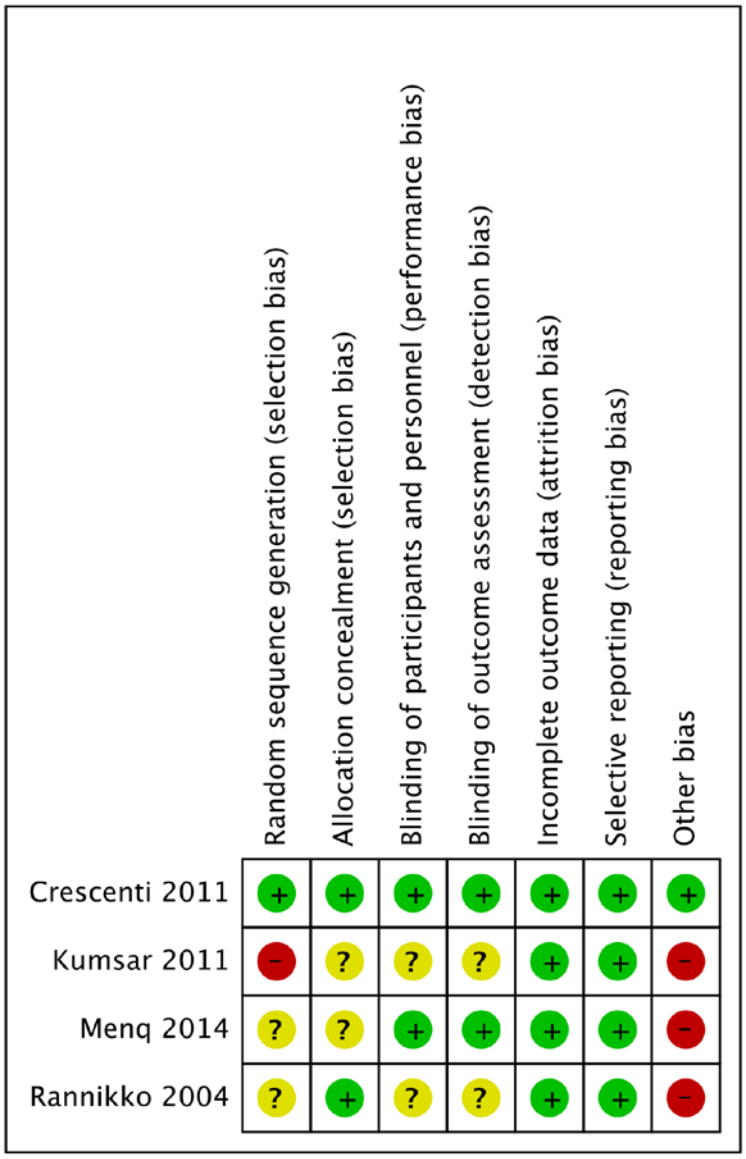


**Figure 3.** Risk of bias within the studies.

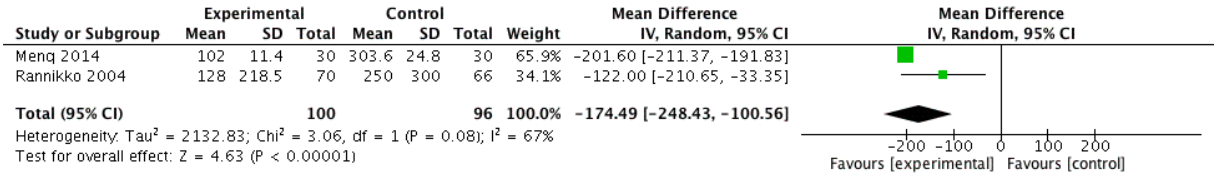


**Figure 4.** Intraoperative blood loss.

**Citation:** Mina SH, Garcia-Perdomo HA. Effectiveness of tranexamic acid for decreasing bleeding in prostate surgery: a systematic review and meta-analysis. **Cent European J Urol**. 2017; doi: 10.5173/ceju.2017.1581 [Epub ahead of print]

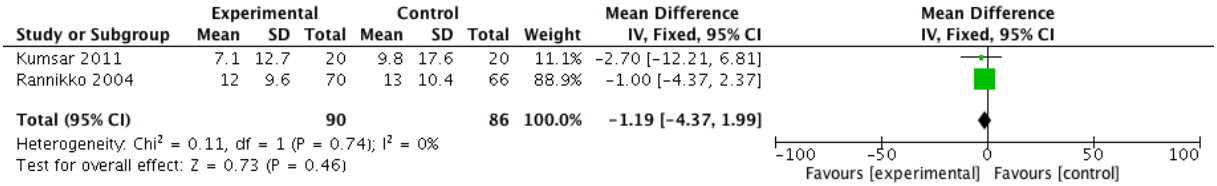


**Figure 5.** Hemoglobin at the end of the procedure.

### References

1. Meigs JB, Mohr B, Barry MJ, Collins MM, McKinlay JB. Risk factors for clinical benign prostatichyperplasia in a community-based population of healthy aging men. J ClinEpidemiol.2001;54(9):935–44.
2. Rassweiler J, Teber D, Kuntz R, Hofmann R. Complications of Transurethral Resection of theProstate (TURP)-Incidence, Management, and Prevention. Eur Urol. 2006;50(5):969–80.
3. Borboroglu PG, Kane CJ, Ward JF, Roberts JL, Sands JP. Immediate and postoperative complicationsof transurethral prostatectomy in the 1990s. J Urol. 1999;162(4):1307–10.
4. Ficarra V, Novara G, Artibani W, Cestari A, Galfano A, Graefen M, et al. Retropubic, Laparoscopic,and Robot-Assisted Radical Prostatectomy: A Systematic Review and Cumulative Analysis ofComparative Studies. Eur Urol. 2009;55(5):1037–63.
5. Djavan B, Agalliu I, Laze J, Sadri H, Kazzazi A, Lepor H. Blood loss during radical prostatectomy:impact on clinical, oncological and functional outcomes and complication rates. BJU Int.2012;110(1):69–75.
6. Dunn CJ. Tranexamic acid a review of its use in surger and other indications. Goa, KL. 1999;57(6):1005–10032.
7. Henry DA, Carless PA, Moxey AJ, O'Connell D, Stokes BJ, McClelland B, et al. Anti-fibrinolytic use forminimising perioperative allogeneic blood transfusion. Cochrane Database Syst Rev. 2007;(4).
8. Fibrinolysis K. J.D Nielsen 1997 BJU.pdf. 1997;105–10.
9. Rannikko A, Pétas A, Taari K. Tranexamic acid in control of primary hemorrhage during transurethral prostatectomy. Urology. 2004;64(5):955–8.
10. Kumsar Ş, Dirim A, Toksöz S, Sa HS, Adsan Ö. Tranexamic acid decreases blood loss duringtransurethral resection of the prostate ( TUR-P ). 2011;2–4.
11. Crescenti A, Borghi G, Bignami E, Bertarelli G, Landoni G, Casiraghi GM, et al. Intraoperative use oftranexamic acid to reduce transfusion rate in patients undergoing radical retropubicprostatectomy: double blind, randomised, placebo controlled trial. Bmj. 2011;343(oct193):d5701–d5701.
12. Williams-Johnson J a., McDonald a. H, Strachan GG, Williams EW. Effects of tranexamic acid ondeath, vascular occlusive events, and blood transfusion in trauma patients with significanthaemorrhage (CRASH-2) a randomised, placebo-controlled trial. West Indian Med J.2010;59(6):612–24.
13. Kagoma YK, Crowther MA, Douketis J, Bhandari M, Eikelboom J, Lim W. Use of antifibrinolytictherapy to reduce transfusion in patients undergoing orthopedic surgery: A systematic review ofrandomized trials. Thromb Res. Elsevier B.V.; 2009;123(5):687–96.
14. Miller R a, May MW, Hendry WF, Whitfield HN, Wickham JE. The prevention of secondaryhaemorrhage after prostatectomy: the value of antifibrinolytic therapy. Br J Urol. 1980;52(1):26–8.
15. Gupta K, Rastogi B, Krishan A, Gupta A, Singh VP, Agarwal S. The prophylactic role of tranexamicacid to reduce blood loss during radical surgery: A prospective study. Anesth Essays Res.2012;6(1):70–3.