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# Systematic review and meta-analyses of tranexamic acid use for bleeding reduction in prostate surgery

Marcelo A. Longo, MD*, Bárbara T. Cavalheiro, MD, Getúlio R. de Oliveira Filho, MD, PhD

*Department of Surgery, University Hospital, Federal University of Santa Catarina, Florianópolis, Santa Catarina, Brazil*

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ABSTRACT

*Background:* Prostate cancer and benign prostatic hyperplasia have an increased incidence with aging. The most effective treatments are radical prostatectomy and transurethral resection of the prostate. To reduce perioperative bleeding in these surgeries, an approach is the use of tranexamic acid (TXA). Studies show that TXA is effective in reducing the blood loss and the need for transfusion in cardiac, orthopedic, and gynecological surgeries. In prostate surgeries, its efficacy and safety have not been established yet.

*Study objective:* To determine whether there are differences between TXA versus placebo in terms of intraoperative blood loss, transfusion requirements, hemoglobin levels and the incidence of thromboembolic events.

*Design:* Systematic review with meta-analyses.

*Setting:* Anesthesia for prostate surgery.

*Patients:* We searched the Medline, Cochrane, EBSCO, and Web of Science databases up to 2017 for randomized controlled trials that compared TXA administration with a control group in patients who submitted to prostate surgery.

*Measurements:* The primary outcomes were the intraoperative blood loss and transfusion rate. Data on hemoglobin levels and the incidence of deep vein thrombosis (DVT) and pulmonary embolism (PE) were also collected.

*Results:* Nine comparative studies were included in the meta-analyses. The estimated blood loss and transfusion rate were lower in patients receiving TXA, with a standardized mean difference of −1.93 (95% CI = −2.81 to −1.05, $I^2$ = 96%), and a risk ratio of 0.61 (95% CI = 0.47 to 0.80, $I^2$ = 0%), respectively. The hemoglobin levels and the incidence of DVT and PE did not differ between the groups.

*Conclusions:* TXA reduced intraoperative blood loss and the need for transfusion, without increasing the risk of DVT and PE in prostate surgeries. Due to the limited number of studies and the high heterogeneity of the results, more clinical trials with a large number of patients are necessary to confirm these findings.

## 1. Introduction

Prostate cancer and benign prostatic hyperplasia (BPH) have an increased incidence with aging [1,2]. In localized cancer, the most effective surgical treatment is radical prostatectomy (RP), while for BPH it is transurethral resection of the prostate (TURP). These procedures have perioperative bleeding as an important complication [3–5].

The risk of bleeding has been related to the type of anesthesia, the use of acetylsalicylic acid, the size of the prostate and the activation of the fibrinolytic system [6], which is caused by the surgical trauma of the dorsal venous plexus of the prostate. The stimulation of the fibrinolytic system occurs as a result of the high concentrations of tissue plasminogen activator in the prostate gland in combination with the constant urine flow containing high concentrations of urokinase [7,8].

In these surgeries, patients may require blood transfusion. This increases the costs and can cause transfusion reactions, acute lung injury, postoperative infection, coagulopathies, transmission of infections, immunosuppression and increased postoperative mortality [9–11].

To reduce perioperative bleeding and avoid transfusion, many interventions have been tested, including the intravenous administration of estrogens, intraprostatic vasopressin, erythropoietin, finasteride, controlled hypotension, acute normovolemic hemodilution, and the use of antifibrinolytics [4,12,13].

Among the antifibrinolytic drugs, tranexamic acid (TXA) has

* Corresponding author at: Department of Surgery, University Hospital, Federal University of Santa Catarina, Rua Professora Maria Flora Pausewang, s/n, Trindade, 88036-800 Florianópolis, Santa Catarina, Brazil.
*E-mail address:* marceloarent@hotmail.com (M.A. Longo).

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become the most popular, as it has a plasminogen-binding potency 6–10 times greater than others medications of the same class [14]. TXA is a synthetic derivative of the amino acid lysine, which blocks fibrinolysis through the competitive inhibition of plasminogen activation into plasmin. This prevents the dissolution of the clot, leading to the reduction of blood loss in surgeries [15,16]. Its use does not appear to negatively affect morbidity and mortality [17].

Systematic reviews and meta-analyses have shown that TXA is effective in reduction of blood loss and transfusion rates in cardiac, orthopedic, gynecological and transplant surgeries [18–22].

In prostate surgeries, its efficacy and safety have not been established yet. Thus, we performed a systematic review with meta-analyses to determine whether there were differences between TXA and a control group in terms of intraoperative blood loss, transfusion rates, perioperative hemoglobin levels and thromboembolic complications.

## 2. Methods

This systematic review was performed according to the processes described by the PRISMA guidelines [23], including the design, implementation of the steps, analysis and description of the results. The protocol for this study was registered on PROSPERO (registration number: CRD42017071220).

### 2.1. Eligibility criteria

We included randomized controlled trials that compared the use of tranexamic acid for prostate surgeries with a control group and measured intraoperative blood loss, transfusion rates, levels of hemoglobin or postoperative thromboembolic events.

### 2.2. Information sources and search strategy

We searched the MEDLINE, Cochrane Central Register of Controlled Trials, EBSCO, and Web of Science databases, without language restriction, from inception to November 2017. Example keywords and indexing terms included: “tranexamic acid” or “trans-4-(Aminomethyl) cyclohexanecarboxylic Acid” or “t-AMCHA” or “AMCHA” or “AMCA” or “Anvitoff” or “Cyklokapron” or “Ugurol” or “KABI 2161” or “Spotof” or “Transamin” or “Amchafibrin” or “Exacyl” or “tranex” or “TXA” AND “prostate” or “prostatectomy” or “transurethral resection of the prostate” or “TURP”.

### 2.3. Study selection

A systematic search was conducted by the three authors independently. Two authors (MAL and BTC) screened the abstracts of the retrieved articles and excluded reports that did not fulfill the inclusion criteria. Any doubt concerning the inclusion of a trial was resolved by discussion with the third author (GROF).

The reference lists of included articles were screened for further relevant articles. Unpublished reports and studies only published as conference abstracts were not included.

### 2.4. Data extraction process and data items

The primary outcomes were the intraoperative blood loss and blood transfusion rate (expressed as the number of patients requiring transfusion), in both groups. The secondary outcomes were the hemoglobin levels and decline in hemoglobin levels from baseline after 24 h of surgery and the reported incidence of deep vein thrombosis (DVT) and pulmonary embolism (PE) in the perioperative period. The data were extracted by two authors (MAL and BTC) and conferred by the third author (GROF).

### 2.5. Risk of bias in individual studies

The methodological quality of each study was evaluated according to Cochrane Collaboration's tool for assessing the risk of bias [24].

### 2.6. Synthesis of results

The results for the categorical variables are presented as risk ratios (RRs) and their 95% confidence intervals (CIs). For the continuous variables, the standardized mean difference (SMD) and its 95% CI were calculated. Values described only as the median and interquartile range were transformed into the mean and standard deviation [25].

Heterogeneous data (with a Cochrane Q test $p < 0.10$) were assessed by a random-effects model and quantified by the $I^2$ index. If the data were homogenous ($p \geq 0.1$), we applied a fixed-effects model.

Sensitivity analyses were conducted to identify the source of heterogeneity, if present, by removing studies one by one and recalculating the combined estimates. We also planned sensitivity analyses including only trials with a low risk of bias. Studies were considered to have a high risk of bias if one or more of the domains in the Cochrane Collaboration's tool had a high or unclear risk of bias.

Subgroup analyses comparing TURP and prostatectomy, as well as different routes and dosages of TXA were planned.

Statistical analyses were conducted using the software Review Manager 5.3.

### 2.7. Risk of bias across studies

Publication bias would be assessed by the visual inspection of asymmetry in funnel plots and by Egger's test if at least 10 retrieved studies presented data for any of the outcomes [26,27].

### 2.8. Quality of evidence

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) [28] methodology was used to assess the quality of evidence for the outcomes. The quality of evidence for each outcome can be graded as high, moderate, low or very low and it is presented through a summary of findings table.

## 3. Results

### 3.1. Study selection

The systematic search identified 145 potentially relevant citations. Nine trials [29–37] fulfilled all the inclusion criteria and were included in the qualitative review and meta-analyses (Fig. 1). One study [33] included eight cases of bladder tumor resection, which were evenly distributed between TXA and control groups. Another study [31] investigated transurethral resection of the prostate and of the bladder, but we utilized only TURP cases in our analyses.

### 3.2. Study characteristics

In total, 978 patients were included in the meta-analyses, that is, 494 received TXA and 484 were enrolled in control group (Table 1). TXA was administered as a local spray in one study [36], orally in two trials [33,37], and IV in the six remaining studies. The dosage of TXA varied widely in the studies, with no study presenting the same scheme of administration as the others.

### 3.3. Risk of bias within studies

The risk of bias within the studies is summarized in the appendix (see Supplemental digital content [SDC], Figs. 2 and 3). Three studies described an appropriate method of randomization; one trial used an