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Systematic Review

Systematic Review and Meta-Analysis on the Effectiveness of Tranexamic Acid in Controlling Bleeding During Transurethral Benign Prostatic Hyperplasia Surgery

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Abstract: Background: Benign prostatic hyperplasia (BPH) is a frequent condition in ageing men. Surgery is recommended for severe BPH symptoms and BPH-related complications. TURP is the reference standard for BPH surgery, but carries a risk of bleeding, which can lead to significant perioperative morbidity and mortality. To reduce bleeding during TURP, antifibrinolytic agents like tranexamic acid (TXA) have been studied. We aim to review the current evidence regarding TXA use during transurethral BPH surgery. Objective: This review aims to assess the efficacy and safety of tranexamic acid in reducing bleeding during transurethral benign prostatic hyperplasia surgery. Methods: Major clinical research databases such as PubMed, Cochrane Central Register of Controlled Trials, EBSCO, Scopus, Google Scholar, and Web of Science were searched from 2012 to 2022 for randomised controlled trials (RCTs) comparing the use of TXA to placebo in transurethral BPH surgery using the PICOS format. We included RCTs without language restrictions that assessed intraoperative blood loss, transfusion rates, haemoglobin levels, length of hospital stay, postoperative thromboembolic events, and 30-day perioperative mortality as outcomes. The quality assessment of the included studies was performed using the Cochrane risk-of-bias tool, RoB 2, for randomised studies. Results: A total of six RCTs, which included 456 patients, were eventually included in the meta-analysis. The results showed that tranexamic acid is beneficial in reducing blood loss and minimising changes in haemoglobin levels during transurethral resection of the prostate. However, it does not lessen the need for blood transfusions or shorten the hospital stay. Conclusions: Tranexamic acid is useful in decreasing blood loss and reducing changes in haemoglobin in patients undergoing transurethral resection of the prostate. Its utility during BPH surgery in low-resource settings where the latest haemostatic enucleation techniques, such as holmium and GreenLight laser enucleation, may not be readily available needs further evaluation.

Keywords: tranexamic acid; benign prostatic hyperplasia; transurethral benign prostatic hyperplasia surgery; transurethral resection of the prostate

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1. Introduction

Benign prostatic hyperplasia (BPH) is a very common urological condition that affects men as they age. The prevalence increases with age, with nearly 80% of men above 80 years of age having some degree of symptoms [1,2]. Surgery is a recommended standard

treatment for severe BPH symptoms and BPH-related complications [3]. Approximately 25,000 prostatectomies for bladder outlet obstruction due to BPH are carried out annually in the United Kingdom, and over 90% of these are performed transurethrally [4]. Transurethral resection of the prostate (TURP) has long been regarded as the reference standard for surgical treatment of BPH, but concerns about its associated risks, particularly bleeding, have led to the development of other treatment alternatives such as GreenLight laser therapy, holmium laser enucleation of the prostate (HoLEP), UroLift, and others. These procedures have comparable perioperative and functional outcomes [4]. However, as with TURP, most of these procedures may still result in significant bleeding, which can lead to complications such as clot retention, disseminated intravascular coagulation (DIC), prolonged hospital stay, and even death [5–7]. Moreover, these alternatives have a steep learning curve and are not readily available due to cost considerations. Thus, efforts aimed at reducing blood loss during TURP are important in ensuring patient safety and rekindling confidence in the procedure. Several medications have been explored to control bleeding during transurethral BPH surgery, including but not limited to use of intravenous oestrogens, catheter traction, intraprostatic vasopressin injection, phenol solution, and 5-alpha-reductase inhibitor use. However, none of these methods have been adopted into routine clinical practice [8–10]. Another method of bleeding control during TURP that is gaining momentum is the use of tranexamic acid (TXA). Bleeding during TURP is thought to be related to increase in fibrinolytic activity due to the presence of a high percentage of plasminogen activators (urokinase), which stimulate the fibrinolytic system and cause clot dissolution [11].

TXA is an antifibrinolytic agent that inhibits the breakdown of blood clots, thereby reducing bleeding. It has been used in various surgical procedures to reduce bleeding and transfusion requirements. Several systematic reviews and meta-analyses have evaluated the use of TXA in surgical procedures like cardiac surgery, orthopaedic surgery, and liver resection [12–14]. These studies have demonstrated the efficacy of TXA in reducing bleeding and transfusion requirements in these surgical procedures. However, the evidence for the efficacy and safety of the use of TXA in urologic surgery is less clear. Previous systematic reviews included few heterogenous studies and examined prostate surgery in both benign and malignant conditions [15,16]. Similarly, a recent systematic review and meta-analysis that examined the effectiveness of TXA on blood loss during TURP was restricted to articles published in English-language literature [17]. Hence, we proposed to examine the effectiveness and safety of TXA in transurethral BPH surgery (TURP and others) using different primary studies (without language restrictions), and using a robust, more inclusive methodology.

2. Materials and Methods

We conducted a systematic review and meta-analysis of existing literature. Major clinical research databases such as PubMed, Cochrane Central Register of Controlled Trials, EBSCO, Scopus, Google Scholar, and Web of Science were searched for the period from 2012 to 2022 for randomised control trials comparing the use of tranexamic acid to placebo in transurethral benign prostatic hyperplasia surgery using the Population Intervention Comparison and Outcome format (PICO). The study population included adult patients (18 years and above) who underwent transurethral BPH surgery with intervention being tranexamic acid use to control intraoperative bleeding, compared with placebo or no tranexamic acid, and the outcomes studied are intraoperative blood loss, change in haemoglobin, transfusion rates, incidence of thromboembolic events, hospital stay, and 30-day perioperative mortality in randomised control trials.

The search was done in January 2023. Additional entries were added by manual search and cross-references. The benign prostatic hyperplasia surgery was limited to transurethrally performed surgery only (transurethral resection of the prostate, transurethral laser enucleation of the prostate, and other variants of transurethral BPH surgery). The search was conducted independently by PMM and TOM using keywords related to

"Transurethral prostatic enucleation or Transurethral resection of the Prostate" or "TURP*" and Tranexamic Acid". Boolean logic operator "AND" was used to combine the terms, and "OR" was used to search either one of the terms. The same search strategy was used in all the searched databases. The search 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 [18,19]. We included randomised controlled trials (RCTs) without language restriction that compared the use of tranexamic acid in transurethral benign prostatic hyperplasia surgery with a control group and measured intraoperative blood loss, transfusion rates, levels of haemoglobin, length of hospital stay, postoperative thromboembolic events, and 30-day perioperative mortality. Non-English articles were machine-translated to English and read completely to see whether they were comprehensible, and cross-checked with the English abstract to see whether the article translation and abstract correlated. We included the conference abstract with required information. Studies not meeting the above criteria were excluded. The results of the systematic search were imported into Covidence Systematic Review Management software ® (Veritas Health Innovation, Melbourne, Australia), which was used for article screening. Discrepancies were resolved via dialogue and mutual consensus. The protocol for this review was registered and published on the PROSPERO database with registration number CRD42023393519.

Data extraction was done using a specifically designed data extraction sheet in Microsoft Excel® (Microsoft Corporation, Redmond, WA, USA). The data collected included unique study IDs as generated by Covidence, first author name, year of publication, country of publication, title, study population, intervention and control arm, and the various outcome data. Intraoperative blood loss, change in haemoglobin level, and transfusion rates were collected both from the intervention and control arm as continuous variables and expressed in mean and standard deviation. The other outcome measures were collected as categorical variables. Data extractions were done independently by TOM and AS and checked for accuracy by PMM.

Statistical analysis was done using systematic review manager software RevMan version 5.4 (the Cochrane Collaboration, London, UK). The results of the studies which evaluated similar outcomes in similar patients were pooled and displayed using a forest plot. The results for categorical variables were presented as risk ratios (RRs) with their 95% confidence intervals (CIs), while for the continuous variables, the standardised mean difference (SMD) and its 95% CI were calculated, and the overall results and pooled effect size were displayed in a forest plot. In studies that reported continuous outcomes using the median and interquartile range, the corresponding mean and standard deviation were calculated as reported by Wan et al. [20]. The quality assessment of the included studies was performed for haemorrhage and allied indicators of haemorrhage using the Cochrane risk-of-bias tool, RoB 2, for randomised studies [21].

3. Results

The initial search from various databases yielded 3562 articles. After the removal of duplicates, 2320 articles were included for title and abstract screening, while 35 articles were eligible for full-text article screening. Seventeen articles were eventually eligible for inclusion in this systematic review and meta-analysis, as shown in the PRISMA flow chart (Figure 1).

Of the seventeen studies included in the analysis, TURP was performed in sixteen and holmium laser enucleation of the prostate (HoLEP) in one study. All of them were prospective RCTs. The characteristics of all the included trials are as shown in the table (see Supplementary Materials) [22–38]. All the RCTs were conducted in different parts of the world, including Asia and Europe, and the sample size in each group ranged from 50 to 136 participants. The average age of the participants ranged from 57.05 to 71.05 years, and the average prostate size ranged from 38.17 to 69.95 g. The reported dose of tranexamic acid and the routes of administration varied among the studies.

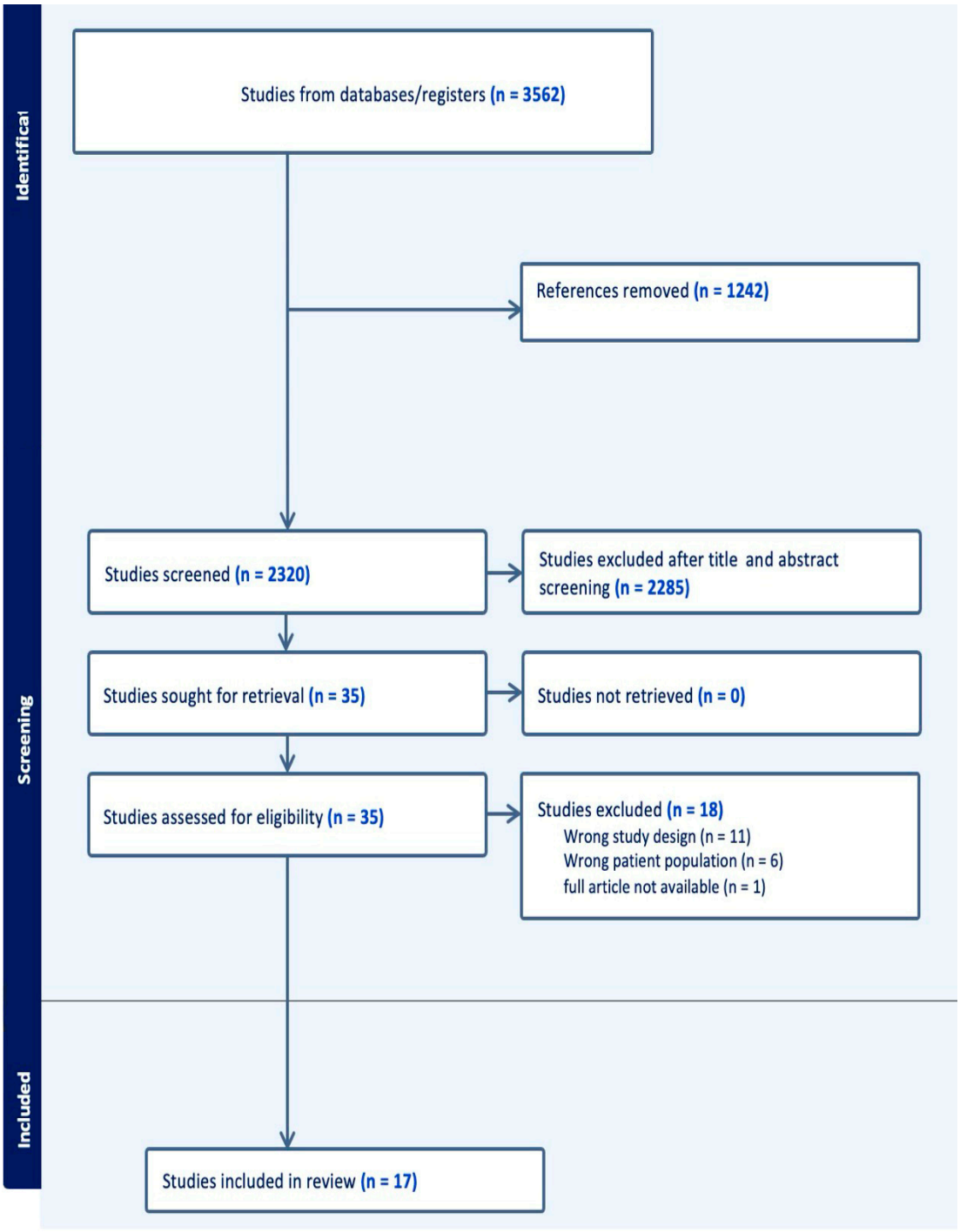


Figure 1. PRISMA flow chart showing steps of study selection. Wrong study design (non-RCT), wrong patient population (patient not having TURPs).

Of these seventeen studies, six had low overall risk of bias, ten had some concerns, and one had a high overall risk of bias. The most common reason for the risk of bias was the randomisation process, followed by deviation from intended interventions and measurement of outcomes. Figure 2 shows the details of quality assessment in the prospective randomised studies.

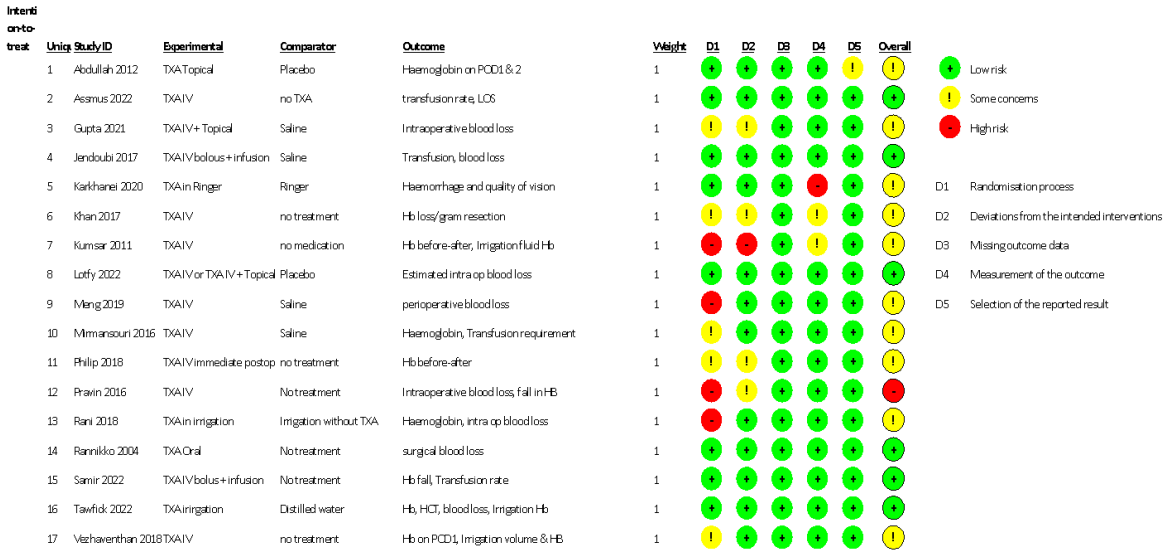
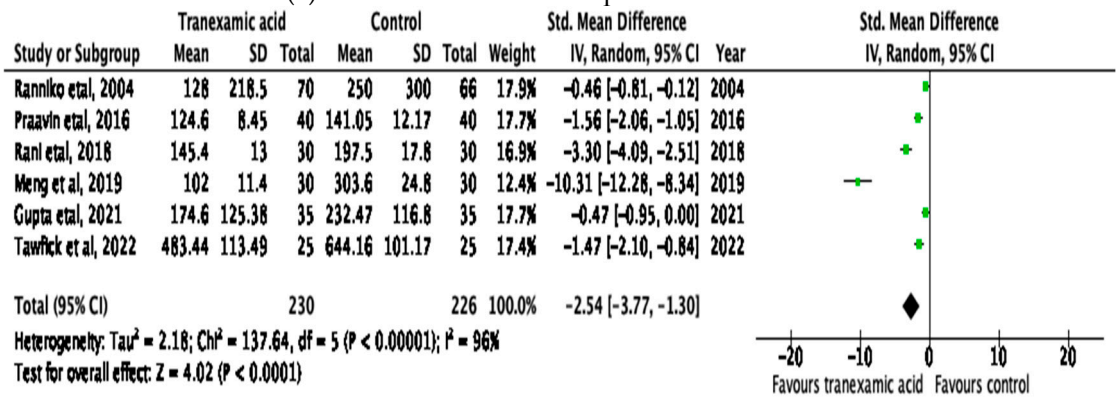


Figure 2. Quality and risk assessment analysis of included studies [22–38].

Heterogeneity between the studies was assessed using the Chi-square test and 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 [39].

Six studies including 456 patients reported on intraoperative blood loss and were included in the meta-analysis [22–27]. The results displayed in Figure 3 showed that TXA is effective in reducing intraoperative blood loss (SMD −2.54, 95% CI (−3.77 to −1.30), $p = 0.00001$).

(**a**). Effect of TXA on intraoperative blood loss.



(**b**). Effect of TXA on changes in haemoglobin.

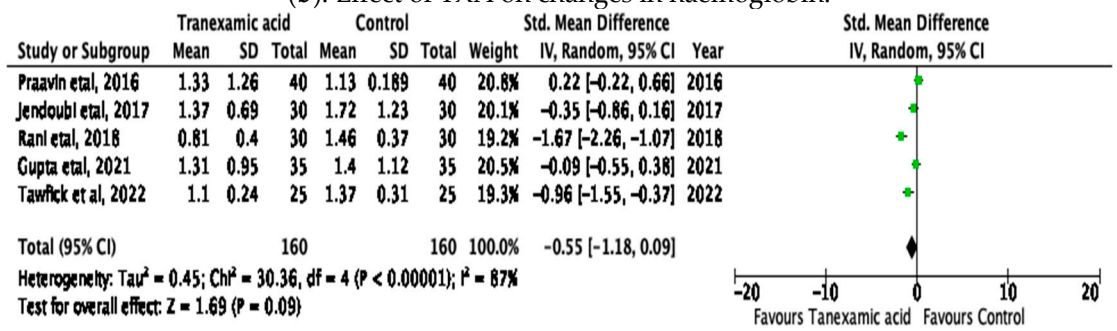
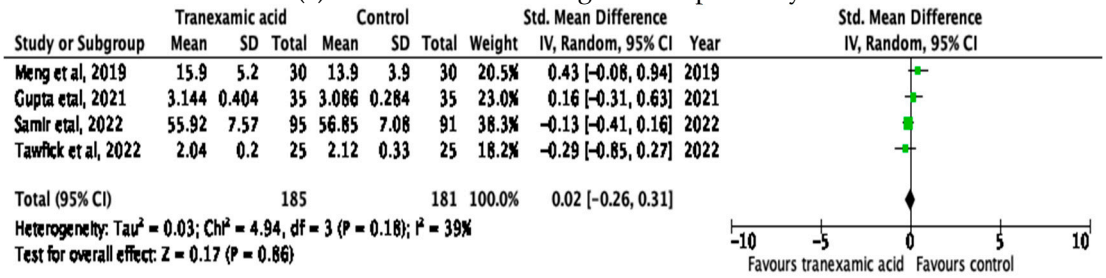


Figure 3. *Cont.*

(**c**). Effect of TXA on length of hospital stay.



(**d**). Effect of TXA on rates of blood transfusion.

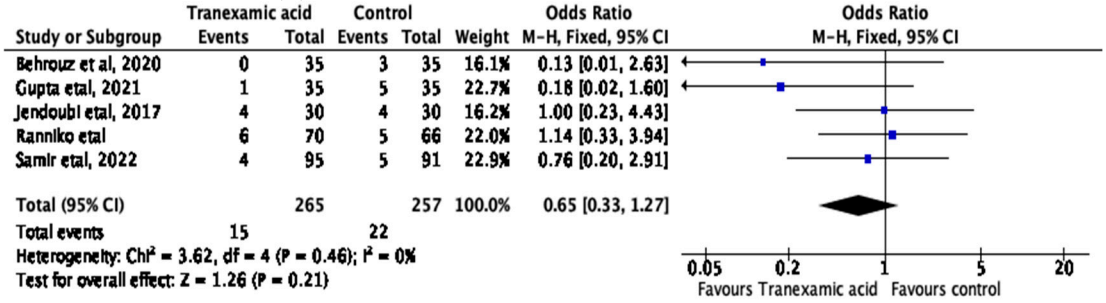


Figure 3. Forest plots of the effect of tranexamic acid during transurethral resection of the prostate on (**a**) intraoperative blood loss, (**b**) change in haemoglobin, (**c**) length of hospital stay, and (**d**) rates of blood transfusion [22–38].

Five studies involving 320 patients reporting the change in haemoglobin were included in the meta-analysis [23,24,26,27,30]. The result of the meta-analysis using the random-effect model showed that tranexamic acid was effective in reducing the change in haemoglobin compared to control during transurethral benign prostatic hyperplasia surgery (Figure 3) SMD −0.55, 95% CI (−1.18 to 0.09), $p = 0.00001$.

Four studies involving 366 patients reported on the effect of TXA on length of hospital stay [25–27,36]. The result of the meta-analysis depicted in Figure 3 showed that tranexamic acid does not lead to a significant change in the length of the hospital stay compared to control (SMD 0.02, 95% CI −0.26 to 0.31, $p = 0.09$).

Five studies involving 522 patients reported the effect of tranexamic acid on the rates of blood transfusion [22,26,29,30,36]. The outcome depicted in Figure 3 showed that tranexamic acid did not reduce the rates of blood transfusion during transurethral benign prostatic hyperplasia surgery (SD 0.65, 95% CI 0.33 to 1.27, $p = 0.21$).

4. Discussion

This review showed that tranexamic acid is effective in reducing intraoperative blood loss during transurethral surgery of the prostate, and this may be related to the fibrinolysis inhibiting effect of tranexamic acid. This is the primary outcome measure in this analysis, and it has significant implications for surgical safety. The reduction of bleeding-related complications post-TURP is a positive development, as these continue to be a major cause of worry after TURP. The finding in this review is largely similar to what has been reported by previous systematic reviews [15,17]. The methods used to estimate blood loss in all six studies included in this analysis were uniform, involving the use of haematocrit and haemoglobin measurements pre- and post-procedure to calculate the estimated blood loss. This method continues to be a valuable indicator of blood loss despite some limitations, as it provides more accurate estimates of blood loss compared to other methods such as weighing blood-soaked materials, such as surgical sponges or dressings, to quantify blood loss. However, the difference in prostate size, the surgeon's dexterity, and the weight of the resected specimen are other variables not assessed that could also have affected the amount of blood loss among the different patients. Moreover, the dose and route of

administration of tranexamic acid varied widely among studies, while Rani et al. [24] and Tawfick et al. [27] administered tranexamic acid in irrigation fluid only, Gupta et al. [26] administered tranexamic acid both as IV and irrigation fluids, and others gave tranexamic acid either by IV or orally [22,32].

Direct measurement of changes in haemoglobin concentration has been suggested as another accurate measure of intraoperative bleeding. The change in the haemoglobin levels is measured solely based on the amount of blood loss, as opposed to estimating blood loss in drain output which may be mixed with irrigation fluid. However, haemoglobin changes may not reflect acute changes in blood loss immediately, and other factors like fluid resuscitation may lead to dilution, thus leading to potential inaccuracies. In this review, TXA use is associated with a smaller decrease in haemoglobin concentration (SMD −0.55, 95% CI −1.18 to 0.09, $p < 0.0001$). This finding is consistent with what was found by Pranata et al. [17], who reported that patients who received tranexamic acid had a significantly smaller change in Hb levels after the TURP compared to the control group, but differs from Longo et al. [15], who reported no change in haemoglobin between patients who received tranexamic acid and those who did not. The latter result may be due to differences in the study population, because more than half of the patients in Longo et al. [15] had open prostatectomy as opposed to TURP. This has implications for patient safety, as Hb changes post-TURP may reflect significant blood loss necessitating blood transfusion. Our review did not find a significant impact of TXA on hospital stay (SMD 0.02, 95% CI −0.26 to 0.31, $p = 0.18$). This finding is consistent with the results reported by Pranata et al. [17] and Kim et al. [40]. Similarly, TXA use did not lead to a reduction in the rates of blood transfusion when compared to control (OR 0.65, 95% CI 0.33 to 1.27, $p = 0.46$). These latest findings appear to contrast with previous ones, as one might have expected the same intervention that led to a decrease in blood loss and a change in haemoglobin to result in a decrease in hospitalization and need for blood transfusion. However, this may be because, beyond blood loss, multiple other factors, such as the level of haemoglobin preoperatively, infections, and associated comorbidity, may influence the need for blood transfusion and the length of hospital stay after surgery.

The incidence of deep-vein thrombosis and 30-day perioperative mortality were not reported by most of the authors whose work was analysed in this review. However, some published studies have found no connection between tranexamic acid use and thrombotic adverse events or increased mortality [41,42].

This review demonstrates that tranexamic acid is beneficial in reducing blood loss and minimizing changes in haemoglobin levels during transurethral resection of the prostate. This finding is of particular importance in BPH surgeries carried out in low-resource settings, where advanced and costlier modalities like holmium and GreenLaser surgery may not be easily available and affordable to the common patient. However, tranexamic acid does not lessen the need for blood transfusions or shorten hospital stays.

This review's strength is found in its extensive approach, robust methodology, and incorporation of non-English-language literature. Nonetheless, there are significant differences in the approaches used by the research to estimate blood loss. This significant heterogeneity among the included studies explains the choice of a random-effect model for the meta-analysis. Consequently, there is a chance that the blood loss calculations used in the trials were inaccurate. Similarly, the ideal dosage and methods of administering tranexamic acid differ greatly and were not examined in this review. Also, some of the studies included in this evaluation were determined to have inadequate methods in the ROB analysis. Furthermore, it is impossible to have a perfect translation of a non-English article to English, and this may affect data extraction and interpretation.

5. Conclusions

Overall, tranexamic acid use may lessen blood loss in patients undergoing transurethral resection of the prostate, but it has no effect on the duration of hospital stay or the need for

transfusion; regardless, before TXA can be recommended for routine use, more studies are required to establish its safety and the optimum dose and route of administration.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/siuj5060060/s1.

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Conflicts of Interest: Author Gyanendra Sharma was employed by Chitale Clinic Pvt Ltd. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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