

EFFECTIVENESS OF TRANEXAMIC ACID IN TRANSURETHRAL RESECTION OF THE PROSTATE (TURP) PROCEDURE ON BENIGN PROSTATE HYPERPLASIA (BPH): A SYSTEMATIC REVIEW AND META-ANALYSIS

¹Yustika Veronica, ²Syah Mirsyah Warli, ²Dhirajaya Dharma Kadar, ³Sri Amelia.

¹ Faculty of Medicine, University of Sumatera Utara, Medan.

² Department of Urology, Faculty of Medicine/University of Sumatera Utara, University of Sumatera Utara Hospital, Medan.

³ Department Microbiology, Faculty of Medicine/University of Sumatera Utara, Medan.

ABSTRACT

Objective: This study aims to determine the effectiveness of tranexamic acid in the TURP procedure in BPH patients. **Material & Methods:** This meta-analysis research was performed online literature from Pubmed, Google Scholar, Cochrane, and Science Direct with a data collection period from July 2020 to October 2020. The journals used are journals regarding all studies on the effectiveness of tranexamic acid in the TURP procedure on BPH with criteria inclusion were BPH patients receiving TURP-invasive therapy and receiving tranexamic acid before or after surgery vs. no intervention or placebo. The results assessed were in terms of the amount of bleeding, volume of irrigation fluid, duration of operation, and weight of the resected prostate tissue. The statistical analysis was performed in Review Manager v.5.4. **Results:** We found 6 studies that fitted into our criteria with 436 patients were identified. We found a significant difference of decreasing blood loss between tranexamic acid and control that tranexamic acid was more effective than control (MD -125.39, 95% CI: -247.21 - 3.36, $P = 0.04$). There was no significant difference of the amount of Hb (MD 0.06, 95%, CI: -0.17 - 0.28, $P = 0.63$). There was also no significant differences of volume irrigation fluid (MD 0.79, 95%, CI: -1.18 - 2.76, $P = 0.43$), duration of operation (MD 14.55, 95%, CI: -32.56 - 3.47, $P = 0.11$) and weight of resected prostate tissue (MD 0.77, 95% CI: -1.06 - 2.6, $P = 0.77$). **Conclusion:** Tranexamic acid is effective in decreasing blood loss in the TURP procedure.

Key words: Tranexamic acid, TURP, BPH.

ABSTRAK

Tujuan: Penelitian ini bertujuan untuk mengetahui efektivitas asam traneksamat pada prosedur TURP pada pasien BPH. **Bahan & Cara:** Penelitian meta analisis ini menggunakan literatur online yang berasal dari Pubmed, Google Scholar, Cochrane dan Science Direct dengan rentang waktu pengumpulan data dari bulan Juli 2020 sampai Oktober 2020. Jurnal yang digunakan adalah jurnal mengenai seluruh penelitian efektivitas asam traneksamat pada prosedur TURP pada BPH dengan kriteria inklusi adalah pasien BPH yang mendapatkan terapi invasif TURP dan menerima pemberian asam traneksamat sebelum atau sesudah operasi vs. tanpa intervensi atau placebo. Hasil yang dinilai ialah dalam hal banyaknya perdarahan, volume cairan irigasi, durasi operasi dan berat jaringan prostat yang direseksi. Analisis statistik menggunakan Review Manager v.5.4. **Hasil:** Enam studi yang membandingkan asam traneksamat dengan dan tanpa pemberian placebo diikuti sertakan dalam penelitian ini dengan total 436 pasien. Berdasarkan hasil analisis, terdapat perbedaan yang signifikan dalam hal mengurangi perdarahan dimana asam traneksamat lebih efektif dalam mengurangi kehilangan darah dibandingkan kontrol (MD -125.39, 95% CI: -247.21 - 3.36, $P = 0.04$). Dalam hal jumlah Hb tidak ditemukan perbedaan yang signifikan (MD 0.06, 95%, CI: -0.17 - 0.28, $P = 0.63$). Dalam hal penurunan jumlah cairan irigasi tidak ditemukan perbedaan yang signifikan antara asam traneksamat dan kontrol (MD 0.79, 95%, CI: -1.18 - 2.76, $P = 0.43$). Dalam hal durasi operasi (MD 14.55, 95%, CI: -32.56 - 3.47, $P = 0.11$) dan berat prostat yang direseksi (MD 0.77, 95% CI: -1.06 - 2.6, $P = 0.77$). **Simpulan:** Penelitian metaanalisis ini mengindikasikan bahwa asam traneksamat efektif dalam mengurangi perdarahan pada prosedur TURP.

Kata kunci: Asam traneksamat, TURP, BPH.

Correspondence: Yustika Veronica; c/o: Faculty of Medicine, University of Sumatera Utara. Jl. Dr. Mansyur No. 5, Padang Bulan, Medan Baru, Medan, Sumatera Utara, Indonesia. Mobile Phone: 081224464566. Email: yustikaveronica93@gmail.com.

INTRODUCTION

Benign Prostate Hyperplasia (BPH) is a histopathological term, which is an enlargement of the prostate size due to hyperplasia of the stromal cells and epithelial cells of the prostate gland. BPH is a condition that is common in older men.¹ It is estimated that 50% of men by the age of 60 and nearly 90% of men by the age of 85 have histopathological changes related to BPH.² According to Clinical Pathway 10 Most Common Urological Diseases, BPH is the second most common disease in prostate gland disease in the Indonesian Urology Clinic.¹

Although rarely life-threatening, BPH is a disease that can increase morbidity and interfere with the patient's quality of life. In Pietryzk's study, 22.4% of BPH patients had a fourfold risk of experiencing depression.³ Patient with BPH will experience symptoms commonly called low urinary tract symptoms (LUTS) such as hesitancy, poor and/or intermittent stream, straining, prolonged micturition, feeling of incomplete bladder emptying, frequency, urgency, urge incontinence, and nocturia.⁴

Transurethral Resection of the Prostate (TURP) is the gold standard and most commonly performed surgical procedure in BPH patients with a prostate volume of 30-80 ml.¹ Although TURP is the main choice in BPH therapy, the possibility of complications cannot be avoided intraoperatively, perioperatively and in advance.⁵ Because prostate hyperplasia is rich in blood vessels, bleeding is a

frequent complication during and after the TURP procedure. This can result in the surgeon's visual impairment, increased operation duration, and decreased quality of surgery.⁶ Type the first sentence of the third paragraph of the introduction of your research. Many interventions have been done to decrease bleeding during TURP, one of which is the administration of tranexamic acid.⁶

Tranexamic acid is an antifibrinolytic agent that can prevent fibrin breakdown and can stabilize blood clotting and can reduce bleeding during fibrinolysis.⁷ Tranexamic acid works by inhibiting the conversion of plasminogen to plasmin by preventing plasminogen from binding to fibrin molecules. By inhibiting tranexamic acid fibrin cleavage can reduce the risk of bleeding as well as inhibiting binding α 2-antiplasmin so that the inflammatory reaction can also be inhibited.⁸ Several recent studies have proven that the role of intravenous tranexamic acid can reduce blood loss after orthopedic, urological, and dental surgery.⁹

OBJECTIVE

This study aims to determine the effectiveness of tranexamic acid in the TURP procedure in BPH patients.

MATERIAL & METHODS

This type of research is a systematic review and meta-analysis using the method Preferred Reporting Items for Systematic Reviews a Meta-

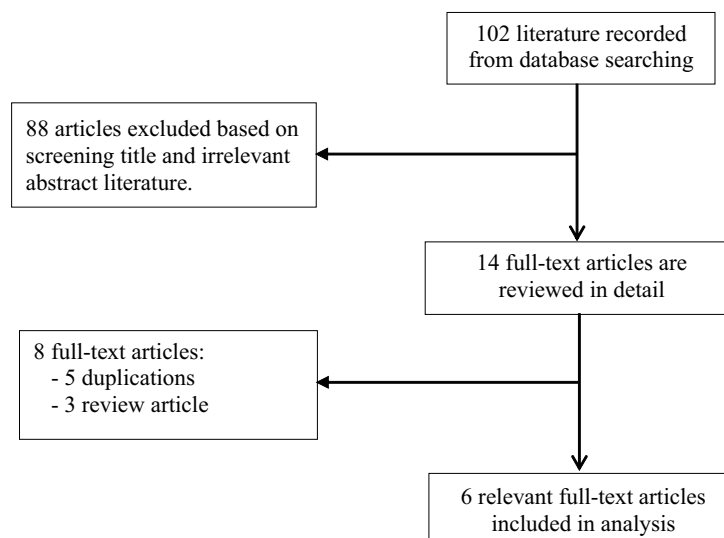


Figure 1. Flowchart of the study design process.

analyzes (PRISMA). The Literature search was online sourced from Pubmed, Google Scholar, Science Direct, and Cochrane with a data collection period starting from July 2020 to October 2020. The keywords used were "tranexamic acid" AND "TURP" AND "BPH".

Some of the exclusion criteria in this study were irrelevant literature abstracts, literature review articles, and duplicate literature. The study of the quality of the journals used in this study is the Jadad criteria with the interpretation of the Jadad scores ranging from 0 to 5. The criteria contained in the Jadad scores are whether or not there is randomization, double-blinding, and information on withdrawals and dropouts of journal. Each journal will be assessed based on those criteria and will be given an overall score and that value is used to group the journals.

In this study, 6 studies were relevant to be analyzed regarding the intervention, characteristics, and outcomes of patients who were collected using the data collection standards set by four reviewers. There are 4 outcomes to be analyzed. The first outcome in this study was blood loss. The second outcome was the amount of irrigation fluid. The third outcome was the duration of operation required and the last outcome was the weight of the resected prostate.

The statistical analysis was performed in Review Manager Software v.5.4. (The Cochrane

Collaboration, Oxford, UK). Weighted mean difference (WMD) and odds ratio (OR) was used to analyze each variable in this study. Confidence Interval (CI) is set at 95%. P-value < 0.05 indicates statistically significant data. Cochran Q test was used to see the heterogeneity of these statistical data. The heterogeneity of the statistical data is marked with I², if I² is less than 50%, it means that this meta-analysis study uses a fixed effect model, and if I² is more than 50%, then the randomized effect model is used.

RESULTS

A total of 102 studies were found using the defined search strategies. Six relevant studies were qualified the inclusions criteria of the study with a total of 436 patients were included. This meta-analysis study to determine the effectiveness of tranexamic acid in TURP procedure in patients with BPH is based on the outcome of blood loss, the amount of irrigation fluid, the duration of surgery, and weight of resected prostate. All of these studies used a method randomized controlled trial (RCT) which is described in Table 1.

The first outcome in this study was blood loss during surgery. Analysis of blood loss during surgery using 3 journals (Rannikko, Meng, and Rani) which have been reviewed and can be analyzed by meta-analysis. The total mean

Table 1. Characteristic of RCT included in the meta-analysis study.

Study	Year	Method	Jadad Score	Number of patients	Mean age (years)	Interventions
Rannikko et al Tranexamic acid Control	2004	RCT	5	70 66	71 68	2 g TXA x 3 (oral) n.r
Kumsar et al Tranexamic acid Control	2011	RCT	4	20 20	67 65	10 mg/Kg TXA (IV) no medication
Meng et al Tranexamic acid Control	2014	RCT	4	30 30	71.4 70.7	1 g TXA in 200ml NaCl Placebo
Khan N et al Tranexamic acid Control	2017	RCT	4	35 35	65 62	1 g TXA no medication
Rani et al Tranexamic acid Control	2018	RCT	4	30 30	66.7 64.3	1 g TXA in 5L glycine Glycine
Karkhanei et al Tranexamic acid Control	2019	RCT	5	35 35	66.43 69.63	500 mg TXA in 500cc ringer serum Ringer serum

difference in blood loss during surgery was -125.39 (95% CI: -247.21-3.36) $I^2 = 100\%$. This means that the administration of tranexamic acid can decrease blood loss by as much as 125 mL than the control. The Diamond (Total Mean Difference) which touched the vertical line, and the p-value = 0.04 proved that giving tranexamic acid was significant in decreasing blood loss in the TURP procedure.

Postoperative hemoglobin value after surgery was the second outcome to determine the effectiveness of tranexamic acid in decreasing bleeding in the TURP procedure. There are 4 journals (Rannikko, Kumsar, Meng, and Karkhanei) that can be analyzed. The total mean difference was obtained 0.06 (95%, CI: -0.17- 0.28) $I^2 = 13\%$ in which the administration of tranexamic acid in postoperative Hb was not much different from the control. The Diamond (Total Mean Difference) which touched the vertical line, and the p-value = 0.63 proved that the difference in postoperative Hb of tranexamic acid and control was not significant.

The third outcome from this study using 2 journals (Meng and Rani) which have been systematically reviewed and can be analyzed by meta-analysis. The total mean difference was obtained 0.79 (95%, CI: -1.18-2.76) $I^2 = 93\%$ Where the ability of tranexamic acid in reducing the volume of irrigation fluid did not differ significantly from the control. This can be seen from the diamond (total mean difference) reaching the vertical line, and the p-value = 0.43 proves that the difference in the mean decrease in the volume of irrigation fluid on the administration of tranexamic acid and control was not significant. Duration of operation was the fourth outcome analyzed in this study. There are 3 journals (Meng, Rani, Karkhanei) that have been reviewed and analyzed using a review manager. Total the mean difference of the duration of operation required was shorter by 14.55 (95%, CI: -32.56-3.47) $I^2 = 98\%$. The administration of tranexamic acid in the TURP procedure showed that the mean duration of operation was shorter than the control, although the p-value was 0.11.

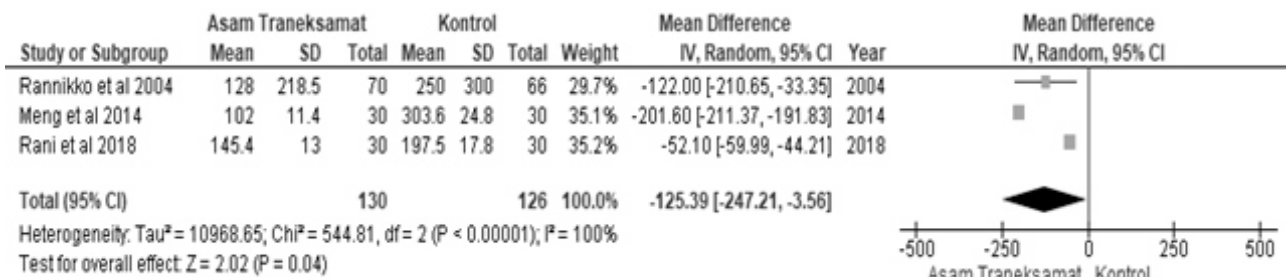


Figure 2. Blood loss.

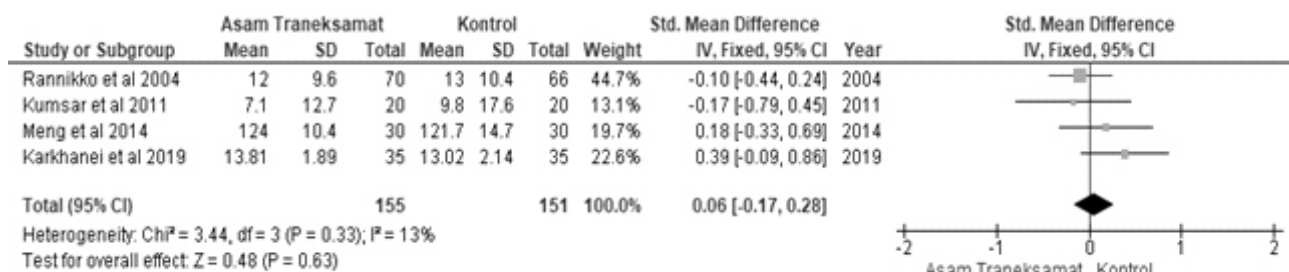


Figure 3. Postoperative Hb.

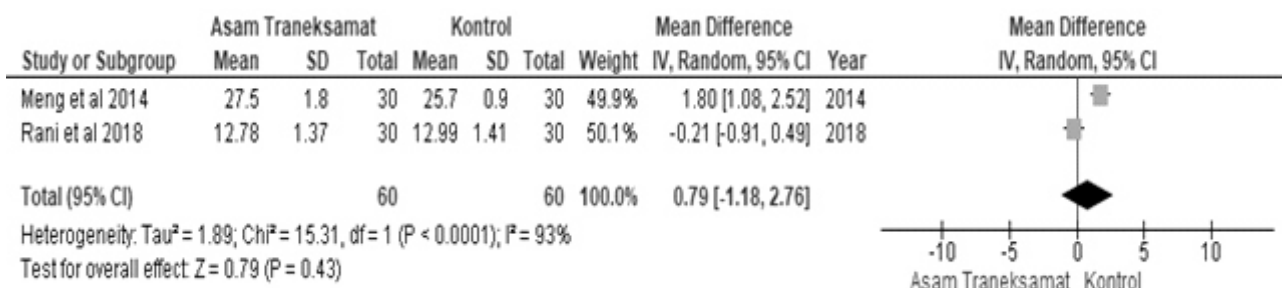


Figure 4. Volume of irrigation fluid.

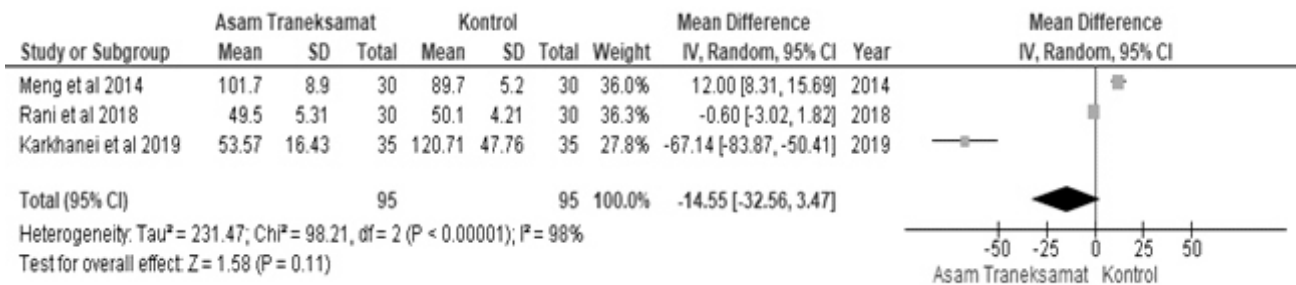


Figure 5. Duration of operation.

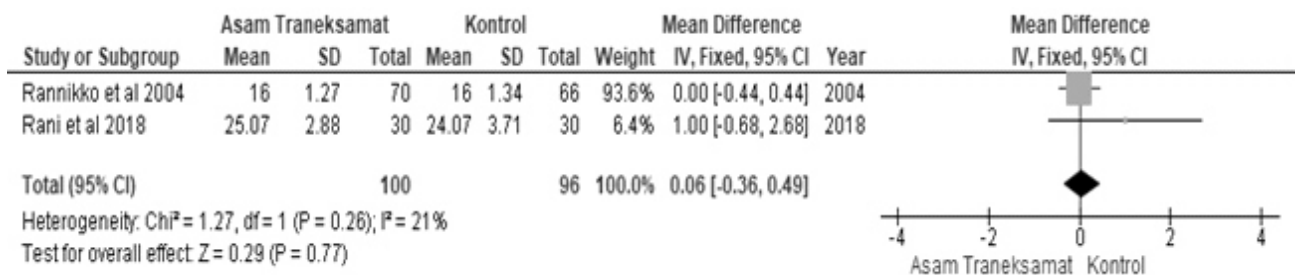


Figure 6. Weight of resected prostate.

The last outcome was the weight of resected prostate using 2 journals (Rannikko and Rani). It was found that the weight of the prostate tissue resected in the administration of tranexamic acid and control showed no significant difference obtained from the total mean difference 0.06 (95% CI: -0.36-0.49) $I^2 = 21\%$. Diamond (Total Mean Difference) which reached the vertical line and the value of $P = 0.77$ proved that the difference in the mean weight of the prostate tissue resected with the administration of tranexamic acid and the control was not significant.

DISCUSSION

TURP is the gold standard surgical procedure in BPH patients until now.¹⁰ Bleeding is a complication that can occur during the operation or after surgery in the TURP procedure. Tranexamic acid is an antifibrinolytic agent that is known to decrease bleeding. The results of this meta-analysis showed that tranexamic acid was effective in decreasing bleeding compared with controls ($p = 0.04$) during the TURP procedure in BPH patients. Previous studies, such as Mina and Sergio 2018 demonstrated that tranexamic acid was effective in preventing perioperative blood loss compared with the placebo in patients undergoing TURP, where the mean difference from her study was -174.49 (95% CI: -248.43-100.56 $I^2 = 67\%$)(2). The result of this study also parallels with Pabinger et al. 2017 theory

which stated that tranexamic acid can be indicated as a therapy in decreasing bleeding in patients undergoing prostate surgery.⁸

The results of postoperative Hb analysis on tranexamic acid administration showed no significant difference with control ($p = 0.63$). Mina and Sergio 2018 study demonstrated that tranexamic acid was not very effective in preventing blood transfusions and increasing Hb at the end of the TURP procedure with a mean difference of -1.19 (95% CI: -4.37 - 1.99, $I^2 = 67\%$). Different from Karkhanei 2019 study where the amount of Hb reduction in the control group was 1.22, which was 0.93 more than the tranexamic acid group ($p < 0.05$).⁶

Decreasing blood loss during TURP with the administration of tranexamic acid can fix up other surgical problems such as a reduced amount of irrigation fluid required and shorten the duration of surgery. This is related with another TURP problems, namely TURP syndrome which is the absorption of irrigation fluids causing relative hyponatremia which is associated with increased duration of surgery.¹¹ However, this meta-analysis results were different from the theory described, there was no difference in the amount of irrigation fluid ($p = 0.43$) and duration of operation ($p = 0.11$) on tranexamic acid administration. Syndrome. The result of this meta-analysis is parallel with Rani 2018 study, there was no difference in operating time recorded in the

two groups and the amount of irrigation fluid used was almost with difference of about 1 liter that was not statistically significant.⁹

Similar to the amount of irrigation fluid and duration of operation, the weight of the resected prostate tissue was also not a significant difference in the weight of the prostate tissue between patients receiving tranexamic acid and control patients. This is because the research published to date has a small sample size which was a limitation. So that the possibility of a beneficial effect from the intervention of these three outcomes cannot be ruled out. In addition, tranexamic acid is a drug with a very reasonable cost and a wide margin of safety that makes this drug very effective for use.²

Tranexamic acid is recommended as a therapeutic preference to decrease bleeding in the TURP procedure. However, controlled clinical trials are needed to enable us to determine whether there is a truly significant effect on the outcome in our study and to determine a dose-effect relationship so that tranexamic acid can be more relevant for clinicians to provide perioperative hemorrhage prevention management of undergoing the TURP procedure in BPH patients

CONCLUSION

The result of this meta-analysis indicate that tranexamic acid is effective in decreasing blood loss during TURP procedure in BHP patients. However, this treatment for increasing hemoglobin values at the end of the procedure, reducing the amount of irrigation fluid, shorten the duration of operation, and the weight of the prostate that was resected with tranexamic acid were not quite effective.

REFERENCES

1. Tjahjodjati, Soebadi DM, Umbas R, Poernomo BB, Wijanarko S, Mochtar CA, et al. Panduan Penatalaksanaan Klinis Pembesaran Prostat Jinak (Benign Prostatic Hyperplasia / BPH). Ikatan Ahli Urologi Indonesia. 2017.
2. Mina SH, Garcia-Perdomo HA. Effectiveness of tranexamic acid for decreasing bleeding in prostate surgery: A systematic review and meta-analysis. *Cent Eur J Urol*. 2018; 71(1): 72-7.
3. Pietrzyk B, Olszanecka-Glinianowicz M, Owczarek A, Gabryelewicz T, Almgren-Rachtan A, Prajsner A, et al. Depressive symptoms in patients diagnosed with benign prostatic hyperplasia. *Int Urol Nephrol*. 2015; 47(3): 431-40.
4. Kapoor A. Management in the Primary Care Setting. 2012; 19(October): 10-7.
5. Djavan B, Teimoori M. Surgical Management of LUTS/BPH: TURP vs. Open Prostatectomy. *Lower Urinary Tract Symptoms and Benign Prostatic Hyperplasia*. Elsevier Inc.; 2018. 241-255.
6. Karkhanei B, Musavi-Bahar SH, Bayat M, Kaseb K, Rezaee H, Moradi A, et al. Safety and efficacy of intraoperative administration of intravenous tranexamic acid in transurethral resection of prostate: A double-blind, randomised, placebo-controlled trial. *J Clin Urol*. 2019; 13(2): 125-31.
7. Lier H, Maeglele M, Shander A. Tranexamic Acid for Acute Hemorrhage: A Narrative Review of Landmark Studies and a Critical Reappraisal of Its Use Over the Last Decade. *Anesth Analg*. 2019; 129(6): 1574-84.
8. Pabinger I, Fries D, Schöchl H, Streif W, Toller W. Tranexamic acid for treatment and prophylaxis of bleeding and hyperfibrinolysis. *Wien Klin Wochenschr*. 2017; 129(9-10): 303-16.
9. Rani dr R, Mittal dr S, Choubey dr SK, Pipara dr G. International Journal Of Scientific Research Use Of Tranexemic Acid As A Topical Agent To Reduce Bleeding During Turp?: A Novel Technique?! *Anesthesiology Dr Surya Kant Choubey Dr Rashmi Rani Dr Gotam Pipara*. 2018; (1): 66-8.
10. Woodard TJ, Manigault KR, McBurrows NN, Wray TL, Woodard LM. Management of benign prostatic hyperplasia in older adults. *Consult Pharm*. 2016; 31(8): 412-24.
11. Hahn RG, Ekengren JC. Patterns of irrigating fluid absorption during transurethral resection of the prostate as indicated by ethanol. *J Urol*. 1993.