

Comparison of Perioperative Bleeding in Transurethral Resection of Prostate for Benign Prostatic Hyperplasia with and without Preoperative Dutasteride

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ABSTRACT

Introduction: Benign Prostate Hyperplasia (BPH) is characterized by increased proliferation of stromal and acinar cells around the urethra, prolonged by increased gland angiogenesis. The increased vascularity can result in massive bleeding during and after TURP. 5 alpha-reductase inhibitor treatment has been reported to reduce this bleeding. There is conflict regarding use of Dutasteride before surgery to decrease intraoperative blood loss. This study aims to compare the perioperative bleeding in TURP with and without two weeks of preoperative treatment with dutasteride in patients with BPH.

Material and Methods: This is a Single-center, Randomized Controlled Open-label Trial done at Department of Urology and Renal Transplant Unit-II, Mayo Hospital Lahore, Pakistan, from February 17, 2018, to February 17, 2019. Patients fulfilling the inclusion criteria of age over 55, unresponsive to medical therapy, and an enlarged prostate (40-70 grams) with an absolute indication for surgery. Group A received a tablet of dutasteride 0.5 mg once a day. Group B did not receive dutasteride two weeks before transurethral resection of the prostate for BPH. Patients were followed up after 24 hours of surgery in which hematocrit levels were estimated. Blood loss was calculated by recording pre-operative and post-operative (after 24 hours) hematocrit levels.

Results: 64 patients were randomized into two groups, i.e., Group A (TURP with dutasteride) and Group B (TURP without dutasteride). The mean age was 66.4±7.5 years in group A and 66.5±7.2 years in group B. The mean blood loss was 158.3±131.1 ml in group A patients and 311.5±150.7 ml in group B, with a p-value of 0.000054, which is statistically significant.

Conclusions: Patients on dutasteride have less perioperative bleeding during transurethral resection of the prostate for BPH than controls.

Keywords: Transurethral Resection of Prostate, Dutasteride, Benign Prostatic Hyperplasia

Growth of the prostate is dependent upon the androgen hormone dihydrotestosterone, an active metabolite of testosterone formed by the action of two 5-alpha reducing isoenzymes, 5-alpha reductase type I and type II.³ Traditional theory regarding benign prostatic hyperplasia suggests that as the prostate increases in size, the capsule surrounding the gland prevents it from expanding radially, ultimately resulting in bladder outlet obstruction.³

The management modality of BPH depends upon the severity of the symptoms, which comprises self-management, including lifestyle and behavioral modification to decrease urinary symptoms and delay disease progression in mild to moderate symptoms of lower urinary tract symptoms (LUTS).⁴

Lifestyle modification includes decreased body weight, decreased evening fluid intake, change in timing of medications such as diuretics, and avoiding substances like alcohol, nicotine, and caffeine.⁵ Medical treatment is the primary option for the patient with mild to moderate voiding symptoms, which consists of alpha-blockers and 5-alpha reductase inhibitors either as mono-therapy or in combination therapy.⁶

Phosphodiesterase type-5 inhibitors and anticholinergic agents are other alternatives. Type 1 and type 2 isoenzymes of 5 alpha-reductase are present throughout the body, and Dutasteride, a dual 5 alpha-reductase inhibitor, acts competitively and specifically on type 1 and type 2 isoenzymes to inhibit the conversion of testosterone to the more potent dihydrotestosterone.⁷

The American Urology Association recommends surgical options if medical treatment fails or the patient develops BPH-related complications such as hematuria, urinary retention, recurrent urinary tract infection, or bladder calculi.⁸ The different surgical approaches for the BPH comprise open prostatectomy, transurethral resection of the prostate (TURP), transurethral incision of the prostate (TUIP), holmium laser enucleation of the prostate (HoLEP)

INTRODUCTION

Benign prostatic hyperplasia (BPH), sometimes also known as benign prostatic hypertrophy, is an age-dependent disorder characterized by hyperplastic changes in the tissue resulting in enlargement of the prostate that may lead to difficulty in micturition or impairment in the flow of urine from the bladder.¹ The prevalence of BPH is eight percent in the fourth decade of life, whereas 50 % of men had evidence of histological BPH when they were between the ages of 50 and 60 years.²

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and newer robotic techniques.⁹

BPH is characterized by increased proliferation of stromal and acinar cells around the urethra, prolonged by increased gland angiogenesis. The increased vascularity can result in massive bleeding during and after TURP. Finasteride a5-ARI inhibits the conversion of testosterone to DHT and the activation of androgen-controlled growth factor, which stimulates angiogenesis.¹⁰ Preoperative 5 alpha-reductase inhibitor treatment has been reported to reduce this bleeding. It reduced the expression of VEGF and lowered the suburethral microvessel density of the prostate.¹¹ Various studies have been done but show conflicting results. In one study, using 0.5 mg of Dutasteride preoperatively resulted in significantly lower blood loss than the control (p-value <0.0491).¹² While in another study, they found there was no difference in blood loss between the treatment and control group (p-value>0.98).¹³

MATERIAL AND METHODS

This is a Randomized Controlled Trial conducted at the Department of Urology and Renal Transplant Unit-II, Mayo Hospital Lahore from February 17, 2018, to February 17, 2019. A sample size of 64 patients (32 patients in each group) was estimated using a 5% level of significance and 90% power of test with an expected mean value of Dutasteride as 1.29 and control as 1.83.¹² probability sampling technique for patient selection and simple random sampling for group distribution was done. The inclusion and exclusion criteria of the study listed below.

Inclusion Criteria:

- Age over 55 years.
- Unresponsive to medical therapy.
- Enlarged prostate(40-70 grams) with an absolute indication for surgery (any of the following)
 - Vesicle Stone (measuring < 2 cm on ultrasound)
 - Hematuria (RBC > 10/HPF)
 - Recurrent urinary tract infection (presence of > 5 WBC/HPF)
 - Refractory retention (Ultrasound pelvis and PMRV)

Exclusion Criteria:

- Bleeding Disorder (on history)
- Chronic liver disease (on history, ultrasound, and serology)
- Patient with associated co-morbidities as hypertension and diabetes mellitus (on history and random blood sugar)

Operational definitions

Preoperative Bleeding: Blood loss during operation and postoperative bleeding during the first 24 hours.¹¹ This blood loss was measured by hematocrit (calculations details given in Annexure-I). The amount of blood loss was calculated in milliliters in both groups.

Dutasteride Treatment: Dutasteride, a 5 alpha-reductase inhibitor, acts on enzyme 5 alpha-reductase, which helps convert testosterone to dihydrotestosterone, a potent

androgen responsible for the enlargement of the prostate.⁷ A tablet of Dutasteride 0.5 mg once daily for two weeks before transurethral resection of the prostate in benign prostatic hyperplasia in the intervention group helps to minimize blood loss.

Data collection procedure

After approval of the synopsis, sixty-four patients fulfilling inclusion criteria were selected from the outpatient Urology Department, Unit-II, Mayo Hospital, Lahore. Informed consent about the study was taken from the patient. Demographic data/information was recorded. Investigations included a complete blood picture, urine, and ultrasonography of the abdomen and pelvis.

The pre-operative hematocrit of each study patient was recorded. Then, a random number generator on a computer divided the patients into groups, i.e., groups A (intervention) and B (non-intervention).

Two groups (A and B) each contained 32 patients. Group A received Dutasteride 0.5 mg once a day tablet, and group B did not receive Dutasteride two weeks before transurethral resection of the prostate for benign prostatic hyperplasia.

Patients were followed up after 24 hours of surgery in which hematocrit levels were estimated. Blood loss was calculated by recording pre-operative and post-operative (after 24 hours) hematocrit levels. Data were collected by the researcher himself on the approved Performa.

Data analysis procedure

Data were tabulated and analyzed by SPSS v25. The quantitative data like age and duration of operation were presented in the form of mean. Qualitative variables like gender were presented as frequency and percentages. A comparison of two groups, Group A with Dutasteride and Group B without Dutasteride, was done by applying an independent sample t-test. A p-value ≤0.05 was taken as significant.

RESULTS

A total of 64 patients were enrolled in this study. Patients were divided into two groups i.e., Group-A (TURP with Dutasteride) and Group-B (TURP without Dutasteride). The mean age of group-A patients was 66.4±7.5 years and 66.5±7.2 years in group-B. In group A, 9(28.1%) patients were in the 50-60 years age group, while 17(53.1%) and 6(18.8%) were in the 61-70 and >70 years age group, respectively. In group B, 9(28.1%) patients were in the 50-60 years age group, while 16(50.0%) and 7(21.9%) were in the 61-70 and >70 years age group, respectively.

Comparison of IPSS between groups

The mean IPSS of group-A patients was 23.9±2.0 and 21.1±2.3 years in group B with a p-value of 0.000006, which is statistically significant.

Comparison of blood hemoglobin, glucose and hematocrit at baseline between groups

The mean blood hemoglobin of group-A patients was 12.9±1.7 g/dl and 12.9±2.1 g/dl in group-B with a p-value of 0.895, which is statistically insignificant. Mean blood

IPSS	Groups	n	Mean	Standard Deviation	p-value
	TURP with Dutasteride	32	23.94	2.05	0.000006
	TURP without Dutasteride	32	21.19	2.39	

Table-1: Comparison of IPSS between groups

Blood hematocrit after 24 hours (%)	Groups	n	Mean	Standard Deviation	p-value
	TURP with Dutasteride	32	35.43	4.01	0.081
	TURP without Dutasteride	32	32.94	6.86	

Table-2: Comparison of blood hematocrit after 24 hours between groups

Blood loss (ml)	Groups	n	Mean	Standard Deviation	p-value
	TURP with Dutasteride	32	158.35	131.14	0.000054
	TURP without Dutasteride	32	311.50	150.77	

Table-3: Comparison of blood loss between groups

Groups	Blood hematocrit	Mean	n	Standard Deviation	p-value
TURP with Dutasteride	Blood hematocrit at baseline (%)	38.5497	32	4.36048	0.0000001
	Blood hematocrit after 24 hours (%)	35.4347	32	4.00700	
TURP without Dutasteride	Blood hematocrit at baseline (%)	38.9906	32	5.63888	0.000067
	Blood hematocrit after 24 hours (%)	32.9406	32	6.86496	

Table-4: Paired wise analysis at baseline and after 24 hours of blood hematocrit

hematocrit at baseline of group-A patients was 38.5±4.3% and 38.9±5.6% in group-B with a p-value of 0.728, which is statistically insignificant. The mean blood sugar level of group A patients was 112.7±13.1 mg/dl and 111.1±10.9 mg/dl in group B with a p-value of 0.587, which is statistically insignificant.

Comparison of Urine complete examination between groups

The mean urine complete examination of group-A patients was 9.5±5.1 pus cells/HPF and 9.5±6.2 pus cells/HPF in group-B with a p-value of 0.965, which is statistically insignificant.

Comparison of Ultrasound abdomen/Pelvis between groups
The mean ultrasound abdomen/pelvis of group-A patients was 56.1±11.1 gm prostate and 52.8±9.3 gm prostate in group-B with a p-value of 0.203, which is statistically insignificant.

Comparison of blood hematocrit after 24 hours between groups

Mean blood hematocrit after 24 hours of group-A patients was 35.4±4.0% and 32.9±6.8% in group-B with a p-value of 0.081, which is statistically insignificant.

Comparison of blood loss between groups

The mean blood loss of group-A patients was 158.3±131.1 ml and 311.5±150.7 ml in group-B with a p-value of 0.000054, which is statistically significant.

Paired wise analysis at baseline and after 24 hours of blood hematocrit

In group A, mean blood hematocrit at baseline was 38.5±4.3% and 35.4±4.0% after 24 hours with a p-value of 0.0000001, which is statistically significant. In group B, mean blood

hematocrit at baseline was 38.9±5.6% and 32.9±6.8% after 24 hours with a p-value of 0.000067, which is statistically significant.

DISCUSSION

TURP still represents the gold standard in the surgical treatment of symptomatic BPH. One of the most critical complications of TURP is intra- and perioperative bleeding, which sometimes leads to urine retention because of blood clots. BPH is characterized by increased proliferation of stromal and acinar cells around the urethra sustained by increased gland vascularity (neoangiogenesis).

Some studies demonstrated the effect of finasteride in reducing BPH-related hematuria.¹⁴⁻¹⁶ Finasteride, which blocks the conversion of testosterone to dihydrotestosterone, decreases the activity of androgen-controlled growth factors responsible for angiogenesis.

This feature was used to prevent intra-operative bleeding in patients undergoing TURP. Some studies supported the pharmacological use of finasteride to reduce surgical blood loss.^{17,18} Dutasteride is an inhibitor of type 1 and 2 isoenzymes of 5-alpha reductase commonly used, as is finasteride, for treating symptomatic BPH.

Some studies attempted to resolve whether dutasteride could reduce bleeding after TURP in the same way that finasteride is.^{19,20} Hahn et al. used dutasteride for 2-4 weeks before TURP without significantly reducing blood loss compared to the placebo group.²¹

Various studies have been done but show conflicting results. In one study, using 0.5 mg of Dutasteride preoperatively resulted in significantly lower blood loss than the control (p-value <0.0491).¹² While in another study, they found there

was no difference in blood loss between the treatment and control group (p-value>0.98).¹³

Other authors have confirmed these results, concluding that short-term treatment with dutasteride was not superior to the control group in decreasing TURP-related blood loss and suggested that a more prolonged duration treatment will reduce intra-operative and postoperative bleeding.²²

Martov found a significant reduction in blood loss in patients by using dutasteride for at least 1 month before TURP compared to the control group.²³ Kravchick demonstrated that 6 weeks of treatment with dutasteride reduced prostatic vascularity, especially in the peri-urethral area.²⁴

In the study conducted by Kim, lower mean blood loss was observed in the dutasteride group immediately after and 24 hours after surgery peri-operative and post-operative bleeding was significantly reduced in the group taking dutasteride for 2 weeks before TURP.

There were no significant effects on prostate volume or resected prostate volume; statistically meaningful differences were not detected between the 2 groups in PT, aPTT, INR, and BT, and based on these results, dutasteride may only affect vascularity-related bleeding during TURP.¹¹

Based on this evidence, we attempted to evaluate if pretreatment with dutasteride (0.5mg/day) for 6 weeks before TURP could reduce surgical bleeding. None of the previous authors had used dutasteride for 6 weeks before surgery.

The present study showed that treatment with dutasteride for 6 weeks before TURP reduces surgical bleeding. No differences were found concerning prostatic volume, prostate resected weight, and operation time between the Dutasteride and control groups.

CONCLUSION

BPH is a common problem in aging males. Since the beginning of the endoscopic resection of an enlarged prostate, i.e., TURP, surgeons have been very concerned with the bleeding during and after the procedure. Many studies reported that preoperative Dutasteride impacts perioperative hemorrhage during TURP for benign prostatic hyperplasia, but it is still controversial. We conducted a study to observe if two weeks of pretreatment with Dutasteride significantly reduces perioperative bleeding during the procedure. The results were compared with another group of patients undergoing TURP without having preoperative Dutasteride. The result concludes that patients on Dutasteride have less perioperative bleeding during transurethral resection of the prostate for benign prostatic hyperplasia than controls.

Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declaration of competing interest: The authors declare that there is no conflict of Interest.

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