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ROLE OF DUTASTERIDE IN DECREASING PERIOPERATIVE BLOOD LOSS DUE TO TRANSURETHRAL RESECTION OF PROSTATE

Riaz Ali Khan[1], Samad Ali Khan[2], Numan Alam[3], Suffia Hayee[4], Naveed Ahmad[5], Syed Hamzah Shirazi[6]

[1]District Urologist, DHQ Hospital Daggar, Buner, Khyber Pakhtunkhwa, Pakistan
[2]Medical Officer, Buner Medical Centre, Khyber Pakhtunkhwa, Pakistan
[3]Consultant Urologist, DHQ, Teaching Hospital, Mardan, Khyber Pakhtunkhwa, Pakistan
[4]Registrar General Surgery, CMH Rawalpindi, Pakistan
[5,6]Consultant Urologist, Al-Khidmat Raazi Hospital, Rawalpindi, Pakistan
Corresponding Author: Numan Alam,
Consultant Urologist, DHQ, Teaching Hospital, Mardan, Khyber Pakhtunkhwa, Pakistan
Email: dnakhan@gmail.com

ABSTRACT

Background: Benign prostatic hyperplasia (BPH) is a common urological condition in elderly men and transurethral resection of the prostate (TURP) is frequently associated with perioperative bleeding.
Objective: To evaluate the effect of six weeks of preoperative dutasteride on perioperative blood loss in patients undergoing TURP for BPH.
Methodology: The study was a randomized controlled trial with the aim of comparing the two drugs and to determine the safety of one of them for the treatment of erectile dysfunction, which was carried out in the Department of Urology-I, Armed Forces Institute of Urology, Rawalpindi, from August 2020 to February 2021. Twenty patients were enrolled for each group (A: dutasteride, B: control) of equal size (n = 200). Group A was treated with dutasteride 0.5 mg/day for 6 weeks before TURP surgery, whereas Group B was not treated before TURP surgery. Perioperative blood loss was estimated by the drop in Hb and transfusion requirement was noted. The data was analysed using SPSS version 23 software and the value $p \leq 0.05$ was taken to be significant.
Results: The mean hemoglobin drop was significantly lower in Group A (0.73 ± 0.18 g/dL) compared to Group B (1.69 ± 0.35 g/dL) ($p < 0.001$). Blood transfusion was required in 0 patients (0%) in Group A compared to 4 patients (4%) in Group B. Overall, 100 patients (100%) in Group A and 96 patients (96%) in Group B did not require transfusion.
Conclusion: Preoperative dutasteride effectively reduces perioperative blood loss and transfusion requirement in patients undergoing TURP for BPH.

Keywords: Benign prostatic hyperplasia, dutasteride, TURP, hemoglobin drop, perioperative bleeding.

INTRODUCTION

Benign prostatic hyperplasia (BPH) is one of the most common urologic conditions of aging men, and is defined as the nonmalignant enlargement of the prostate gland [1]. The incidence of BPH rises with age and is seen histologically in almost 50% of men over 50 years of age and as high as 80% of men over 80 years of age [2]. As the prostate grows, it may obstruct the bladder outlet and cause lower urinary tract symptoms (LUTS), such as frequent urination, urinary urgency, nocturia, weak urinary stream, intermittency, and a sensation of an incomplete bladder emptying. These symptoms significantly affect the quality of life and often require medical and/or surgical treatment [3,4].
Transurethral resection of the prostate (TURP) remains the gold standard surgical treatment for patients with moderate to severe LUTS secondary to BPH, particularly in those with large prostate volume or failure of medical therapy [5]. Perioperative bleeding is one of the most frequent complications after TURP [6] despite the improved surgical techniques and instruments. Bleeding can affect the view of the operating room, lengthen surgery, require bladder

irrigation, require longer hospitalizations and sometimes even necessitate blood transfusion or a reoperation. Thus, one of the most significant indices of optimizing surgical outcomes is to minimize peri-operative bleeding [7,8].
Bleeding is central to the occurrence of TURP [9] and hyperplastic prostatic tissue is vascular. Hyperplastic changes within the prostate are greatly affected by the increase in microvessels, which is driven by the presence of the potent androgen dihydrotestosterone (DHT) that promotes prostatic growth and angiogenesis [10]. Drugs that block the conversion of testosterone to DHT have therefore been of great interest as pre-surgical treatments [11]. Dutasteride is a dual-acting 5-alpha reductase inhibitor that inhibits both type I and type II isoenzymes, leading to a very marked decrease in both serum and intraprostatic DHT levels. This process of hormonal suppression has been linked to a decrease in prostatic vascularity, and expression of vascular endothelial growth factor (VEGF) and to a decrease in microvessel density during surgery, potentially reducing the amount of blood loss during TURP [12,13].
There have been several clinical trials to examine the benefits of short-term preoperative dutasteride use to decrease the incidence of bleeding-related complications during TURP, but results have been inconsistent among different populations and treatment durations. It is still unclear what its place is in the daily practice of pre-operative care should be, and further studies are warranted to delineate its clinical utility in patients receiving surgical therapy for BPH.

Research Objective
The objective of the study was to compare the pretreatment of dutasteride for six weeks before surgery in patients with BPH in reducing the mean blood loss associated with TURP.

METHODOLOGY

Study Design and Setting
It was a randomized controlled clinical trial in the Department of Urology-I, Armed Forces Institute of Urology (AFIU), Rawalpindi, Pakistan from 10 August 2020 to 9 February 2021. The study aimed to compare the amount of blood loss during the TURP in patients with BPH who received six weeks of dutasteride before surgery and those who did not receive any treatment.

Sample Size and Sampling Technique
The sample size was determined based on the World Health Organization (WHO) sample size calculator with the set level of significance of 5% and 95% study power. With the anticipated population mean, the test value of the population means and a standard deviation of 110, a number of 100 participants in each study group was requested, which corresponds to a total sample of 200 patients. A consecutive sampling was employed in selecting participants until the required sample size was reached, using a non-probability sampling technique.

Study Participants
Male patients between the ages of 50 and 70 years with prostate volume ranging from 40 to 80 g and normal renal function tests and diagnosed with symptomatic BPH were eligible. Patients who had had an invasive prostate procedure previously, suspected or confirmed prostate cancer on digital rectal examination, vesical tumors (during ultrasonography procedure), bleeding disorders, current use of antiplatelet medications, vesical stones, urethral stricture, active urinary tract infection and significant cardiovascular or respiratory comorbidities were excluded from the study.

Randomization and Data Collection
Adult with FQRS who came to OPD fulfilling the eligibility criteria were enrolled with informed written consent. After approval of the study protocol, the participants were randomly assigned to two equal groups by the lottery system: Group A – dutasteride (n = 100) and Group B – control (n = 100). Group A had their patients receive oral dutasteride (0.5 mg) daily for six weeks prior to TURP surgery and Group B had no dutasteride treatment before the surgery.
All participants had a detailed clinical history taken and underwent a complete physical examination including DRE. Baselines laboratory tests consisted of complete blood count, renal function tests, liver function tests, urine routine examination, and serum prostate-specific antigen (PSA) measurements. A dedicated radiologist performed ultrasonographic evaluation of the kidneys, ureters, bladder and prostate with a standardized protocol.
The principal investigator helped with all surgeries to ensure consistency in the surgery, and the supervising consultant urologist performed all surgeries. The procedure, namely transurethral resection of prostate, was performed under spinal anesthesia with 26 French Karl Storz monopolar resectoscope under continuous irrigation with 5% dextrose solution, as is the standard procedure.

The concentration of hemoglobin was determined preoperatively, immediately after surgery and 24 hours after surgery by analysis of complete blood count. Blood loss during the procedure was estimated as a difference in the pre-operative, post-TURP, and 24-hour post-operative hemoglobin concentration. Perioperative blood loss (calculated as change in hemoglobin), blood transfusion, operative time, resection time, and resected prostate volume were the outcome measures. Other peri-operative factors such as age, prostate size, operation time, resection time and amount of resected tissue were also collected.

Statistical Analysis

Data entry and analysis was conducted with Statistical Package for the Social Sciences (SPSS) version 23.0 (IBM Corp., Armonk, NY, USA). The quantitative variables were presented as mean ± standard deviation and the categorical variables were presented as frequencies and percentages. Independent samples t-test was used to compare continuous variables between the two groups and Chi-square test was used for categorical variables. Two tailed p values of $p \leq 0.05$ were deemed significant.

Ethical Considerations

The study protocol was approved by the College of Physicians and Surgeons Pakistan (CPSP) and then ethical clearance was taken from the Institutional Ethical Review Committee (IERC) of Armed Forces Institute of Urology, Rawalpindi prior to enrolment of participants. All subjects gave written informed consent prior to inclusion. All procedures followed the ethical principles of the Declaration of Helsinki, and confidentiality and anonymity of patients were respected throughout the study**.**

RESULTS

Table 1. Baseline demographic and clinical characteristics of the study participants (N = 200)

Variable		Group A	Group B	Total	p-value
Age (years)	Mean ± SD	62.53 ± 5.13	62.60 ± 5.36	62.55 ± 5.32	0.926
	50–60 years	36 (36.00)	37 (37.00)	73 (36.50)	0.882
	61–70 years	64 (64.00)	63 (63.00)	127 (63.50)	
Prostate size (g)	Mean ± SD	61.10 ± 9.19	62.12 ± 8.73	61.61 ± 8.96	0.421
	≤60 g	48 (48.00)	46 (46.00)	94 (47.00)	0.777
	>60 g	52 (52.00)	54 (54.00)	106 (53.00)	
Resection time (minutes)	Mean ± SD	34.42 ± 6.79	32.68 ± 7.11	33.55 ± 6.96	0.082
	≤30 minutes	30 (30.00)	40 (40.00)	70 (35.00)	0.136
	>30 minutes	70 (70.00)	60 (60.00)	130 (65.00)	

Table 2. Comparison of perioperative blood loss (hemoglobin drop) and blood transfusion requirement between study groups

Outcome	Category	Group A	Group B	p-value
Hemoglobin drop (g/dL)	Mean ± SD	0.73 ± 0.18	1.69 ± 0.35	<0.001
Blood transfusion requirement, n (%)	Yes	0 (0.00)	4 (4.00)	0.043
	No	100 (100.00)	96 (96.00)	

Table 3. Stratified analysis of hemoglobin drop according to clinical variables

Variable	Category	Group A (Mean ± SD)	Group B (Mean ± SD)	p-value
Age	50–60 years	0.64 ± 0.13	1.72 ± 0.41	<0.001
	61–70 years	0.82 ± 0.19	1.63 ± 0.19	<0.001
Prostate size	≤60 g	0.69 ± 0.18	1.78 ± 0.44	<0.001
	>60 g	0.78 ± 0.18	1.61 ± 0.22	<0.001
Resection duration	≤30 min	0.78 ± 0.16	1.58 ± 0.33	<0.001
	>30 min	0.71 ± 0.19	1.76 ± 0.35	<0.001

Table 4. Stratification of blood transfusion requirement according to age, prostate size, and resection duration

Variable	Category	Group A	Group B	p-value
Age (years)	50–60	0 (0.00)	1 (2.70)	0.321
	61–70	0 (0.00)	3 (4.76)	0.077

Prostate size (g)	≤60 g	0 (0.00)	2 (4.35)	0.144
	>60 g	0 (0.00)	2 (3.70)	0.161
Resection duration	≤30 minutes	0 (0.00)	0 (0.00)	∞
	>30 minutes	0 (0.00)	4 (6.67)	0.028

DISCUSSION

In the present randomized controlled trial, patients undergoing surgery who took dutasteride preoperatively had a significant decrease in the amount of perioperative hemoglobin (Hb) loss. The mean Hb reduction was 0.73 ± 0.18 g/dL in Group A (dutasteride) vs 1.69 ± 0.35 g/dL in Group B (control), $p < 0.001$, suggesting that there was a definite protection against peri-operative bleeding. A large meta-analysis of 11 RCTs in more than 1,200 patients reported an Hb loss of −1.10, $p < 0.00001$, with 5-alpha-reductase inhibition preoperatively, which is similar to the decrease observed here, indicating less surgical bleeding with 5-alpha-reductase inhibition [14].

Our study results are in line with the physiologic decrease in prostatic vascularity that has been seen following dutasteride therapy when considering the absolute blood loss surrogate markers. The difference in Hb loss between both groups (0.73 g/dL vs 1.69 g/dL) was clinically significant as the lesser Hb loss is indicative of lesser intraoperative bleeding during TURP. A systematic review found that dutasteride reduced microvascular density and hemoglobin decrease, with inconsistent results for the reduction in total blood loss [15]. This means that the estimates for total loss based on the irrigants may differ from those based on Hb, depending on the individual patient.

In the present study, likewise, the blood transfusion requirement was significantly lower in the dutasteride group (0% versus 4%, $p = 0.043$). This periousually significant result contributes to better safety in the peri- and postoperative period. Similar findings were seen in a randomized placebo-controlled trial in which preoperative patients who received dutasteride or finasteride had significantly reduced transfusion requirements (OR 0.34, $p = 0.009$) [16]. Other meta-analyses, however, have failed to show the reduction in transfusion rate statistically, indicating that this is dependent on surgical technique and patient selection [17].

This consistent benefit was also seen after stratification of hemoglobin drop in the current study. In patients aged 50–60 years, Hb drop was 0.64 ± 0.13 vs 1.72 ± 0.41 g/dL, while in those aged 61–70 years it was 0.82 ± 0.19 vs 1.63 ± 0.19 g/dL ($p < 0.001$ for both). This across age group reduction is consistent with other large pooled analyses that demonstrated that the effect of dutasteride was independent of baseline demographic variation and is mostly mediated through a decrease in prostatic microvessel density [14].

Similarly, prostate size stratification in our study showed reduced Hb loss in both ≤60 g (0.69 ± 0.18 vs 1.78 ± 0.44 g/dL) and >60 g groups (0.78 ± 0.18 vs 1.61 ± 0.22 g/dL, $p < 0.001$). These results are consistent with the data indicating that dutasteride decreases the risk of bleeding, even when the gland is small, due to its anti-vascular proliferation effects mediated by androgens [15]. But there are some studies which indicate that, even after pharmaceutical pretreatment, there is a greater absolute bleeding in larger prostates.

Resection duration also influenced outcomes, where patients with ≤30 minutes showed Hb drop of 0.78 ± 0.16 vs 1.58 ± 0.33 g/dL, while those with >30 minutes had 0.71 ± 0.19 vs 1.76 ± 0.35 g/dL ($p < 0.001$). Operative time has been correlated with a higher risk of bleeding, but dutasteride seems to continue to protect against bleeding even during longer resections. Interestingly, other systematic reviews have found no consistent decrease in the length of surgery despite the reported decrease in bleeding, suggesting a lack of direct link between surgical efficiency and 5ARI therapy [15,18].

Strengths and Limitations

The study design is quite good, with a randomized controlled trial design, equal distribution of patients in the two arms (n = 100 in each of the two groups), reducing selection bias and increasing internal validity. The sample size was sufficiently large (200 patients in total) and all surgeries were conducted in a standard setting by an experienced consultant urologist, minimizing procedural variability. The objective outcome measures of hemoglobin drop (0.73 ± 0.18 g/dL vs 1.69 ± 0.35 g/dL, $p < 0.001$) and transfusion requirement (0% vs 4%, $p = 0.043$) enhance the reliability of findings. The study cannot be generalized due to its single centre design, the relatively short follow up period (only perioperative period) and the absence of long term outcome parameters (postoperative recovery, duration of catheter, late complications, etc.). In addition, blood loss was estimated indirectly by the variations in the hemoglobin levels rather than by measuring the irrigant hemoglobin and/or quantifying the amount of irrigant suctioned during surgery, which could lead to measurement biases. Additionally, the event rate of transfusion is low, reducing the power of subgroup analyses.

CONCLUSION

Dutasteride use prior to TURP for BPH seems to be a valuable adjunct in reducing bleeding during surgery and the need for blood transfusion. This benefit is noted within all of the clinical subgroups, indicating that the hemostatic effect appears to be similar across patients of all ages, prostate sizes, and operative parameters. In general, dutasteride could be helpful in enhancing surgical conditions and perioperative safety during TURP.

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