Effectiveness of short Pre-operative treatment with Dutasteride on per-operative blood loss in TURP: A Randomized Controlled Trial

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ABSTRACT

Objective: To evaluate the effectiveness of Dutasteride in patient of Benign Prostatic Hyperplasia (BPH), who are undergoing Transurethral Resection of Prostate in term of mean blood loss.
Study Design: Randomized Control Trial (RCT)
Place and Duration: Department of Urology, Pakistan Institute of Medical Sciences, Islamabad from 5th Feb, 2016 to 5th Aug, 2016
Methodology: Patients age between 50 to 85 years with prostate size more than 40 grams and International prostate symptoms score (IPSS) more than 19 were included and randomly divided into two groups, ie Treatment (Group-I) and Control groups (Group-II). The Treatment group received a 0.5 mg tablet dutasteride daily for two weeks prior to transurethral resection of prostate (TURP) as compared to control group. Post- Transurethral resection of prostate blood loss accessed by measuring hemoglobin level one day preoperatively and on 1st post transurethral resection of prostate.
Results: Among 130 patients studied, the mean age was 60.22+4.04 year and having mean IPSS score of 23.20+4.00. In study, mean change of blood loss in both the groups was 1.85+2.75 and 1.56+1.79 which was statistically significant (p-value 0.468).
Conclusion: The use of Dutasteride preoperatively for two weeks has a significant effect in reducing blood loss during Transurethral Resection of the Prostate (TURP).
Keywords: Benign prostatic Hyperplasia (BPH), International prostate symptoms score (IPSS), Transurethral Resection of the Prostate (TURP), Blood loss, Dutasteride, Per-operative

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INTRODUCTION

Trans-urethral resection of Prostate (TURP) is considered as a gold standard in Benign Prostatic Hyperplasia (BPH) treatment in patients who are not responding to medical treatment[1]. The efficacy and safety of TURP has been validated, and the mortality of procedure has reduced to less tha 0.25 % in the past three decades due to better expertise. However, it can results in significant perioperative hemorrhage and clot retention[2] These complications undoubtedly add into the postoperative morbidity ,results in prolong hospital admission, need for blood transfusion and even may require re-operation , particularly in patient with large (>30 mL) prostates[3,4].

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The BPH is a normal part of the aging process which is dependent on testosterone and dihydro-testosterone (DHT) production in body. Almost 50% of male has histologically demonstrate benign prostatic hyperplasia at the age of 60 years which reaches up 90% by the age of 85 years[5].

Among the medical treatment options, patients and treating physicians can choose from a wide variety of phytotherapy or herbal products or combination pharmacotherapy including the use of anticholinergic in case of a predominant storage symptoms suggestive of overactive bladder[6,7]. Evidence have shown that patients who are presenting with baseline symptoms, a suitable dose of α-adrenergic receptor blocker can results in improvement in the IPSS by 3 to 6 points or by as much as 50%[8]. Therefore, medical management of BPH has been found to be very effective in the treatment of patients with LUTS and BPH resulting in greater reduction of symptoms and thereby improves quality of life[9]. Advancements in medical therapy for the management of BPH were seen in 2003 which included more then 3000 patients of LUTS and BPH who were managed for approximately 4 to 5 years with either doxazosin, finasteride, placebo or by combination of doxazosin and finasteride. It was observed that the progression of BPH in patients enrolled in the trial was 22% with doxazosin, 26% with placebo, 18% with finasteride and 12% in combination regimes respectively[10].

Histologically the diagnosis of BPH is made on the finding proliferation of epithelial cell and smooth muscle in transition zone of prostate. The Dihydrotestosterone (DHT) is primarily and mainly the cause of this proliferation in elderly male. The DHT is synthesized from testosterone by the isoenzyme found in prostate called type 1 and 2 5-α-reductase (5-AR). Dutasteride inhibits both type I and type II isoenzymes, while Finasteride inhibits only the type II 5AR isoenzyme at therapeutic dose. Dutasteride treatment results in more consistent suppression of serum DHT as compared to the Finasteride, with more than 85% of male achieving almost more than ninety percent reduction in Dihydro-testosterone levels within 4 weeks, whereas the Finasteride reduces the serum DHT around 70%[6,7]. The Dutasteride also inhibits the 5-AR which reduces the prostate size after six months leading to reduction in BPH complications such as acute urinary retention, improvement in quality of life (QoL) and need for surgery. The 5-ARI also inhibit vascular endothelial growth factor (VEGF), causing reduced angiogenesis and reducing the risk of bleeding during surgery. This effect is also supported by different studies published in past[1,4,6,7] . The Kim et[1] al has reported that mean Hb dropped in dutasteride group is less as compared with control group[1]. Similarly, Zaitsu et al[11] observed that the vessels density and area were reduced in their patients leading to less blood loss during surgery after two weeks Dutasteride treatment.

In year 2002, the FDA has approved Dutasteride as a treatment option for BPH because it improves the urinary flow rate and reduces the need of surgery by reducing the Prostate size[10]. Furthermore, different studies in literature have reported an improved Dutasteride (0.5 mg/day) efficacy as compared to Finasteride (5 mg/day) in improving urinary flow, symptom score and life quality[2,3,9]. The Dutasteride efficacy in gross hematuria management due to BPH is also well reported in literature. The rationale of this belief is considered as that 5-ARI reduces loss of blood during or post-TURP by causing prostate to shrink, due to reduction in the angiogenesis. But the evidence suggesting the efficacy of preoperative Dutasteride on blood loss during TURP is scarce in literature. So, there is a need to assess the effect of pre-operative Dutasteride on blood loss during TURP because in this way this critical group of patients can be prevented from the loss of blood and thus, reduce the subsequent consequences in terms of per-operative blood loss and postoperative anemia. So, we have conducted this study with an objective to evaluate the effectiveness of Dutasteride in patient of Benign Prostatic Hyperplasia (BPH), who are undergoing Transurethral Resection of Prostate in term of mean blood loss.

METHODOLOGY

This Randomized Control Trial (RCT) that was conducted at Department of Urology, Pakistan Institute of Medical Sciences, Islamabad from 5th Feb, 2016 to 5th Aug, 2016. Non probability consecutive sampling technique was used for the purpose of data collection. All patient undergoing TRUP for BPH, prostate size of more than 40 grams, between 50 to 85 years of age and having International Prostate Symptoms Score (IPSS) above 19 were included in the study. The Patients with previous prostate surgery, history of any prostate pathology other than BPH, having any of 5-ARI in last 12-Months, on anticoagulants or aspirin and having severe medical disease like renal failure, liver Disease, unstable cardiovascular disease, bleeding disorders were excluded from study.

Patients were evaluated for the severity of their symptoms by the IPSS score, all relevant baseline investigations, trans-abdominal ultrasonography for the prostate volume, post void residual urine, back pressure changes in the bladder and upper renal tract. Informed consent was taken and patients were randomized into two equal groups i.e. the treatment group or the control group by a lottery method. The patients in Group-I (Treatment group received dutasteride 0.5 mg daily for two weeks prior to surgery and patients in Group 2 (Control group) were not given dutasteride before TURPs.

Enlargement of prostate gland causes problems with urinating which is significant when IPSS is above 19 was considered as Benign Prostatic Hyperplasia (BPH) whereas IPSS is a screening tool comprises of seven questions which is used to diagnose and plan the management of the symptoms of BPH.

All TURPs were done under spinal anesthesia. During the postoperative period, it was mandatory to hour monitor the vitals of the patient, measuring the urine output, and watching the effluence for clarity. When the returning irrigation fluid is clear, irrigation was suspended and the patient effluent was observed for one hour. If the effluent remains clear, the irrigation was stopped, and urethral catheter removed. The study outcome was noted in terms of blood loss measured as fall in hemoglobin one day after surgery (1st post- operative day) as compared to preoperative hemoglobin level which was measured one day before surgery between the two study groups i.e. dutasteride group and control group. The demographic characteristics of patients and international prostate symptoms score (IPSS) was noted on the specifically designed study proforma.

Data Analysis: The collected data was entered and analyzed using SPSS software version 17.0. The categorical continuous variables like age, IPSS score and Hb (at baseline, 1 hour and change) were measured as mean and standard deviation. As per study objective the mean change in Hb level was compared between intervention and control groups using student's t-test. P-value of ≤ 0.05 was considered statistically significant.

RESULTS

A total of 130 patients were included in the study and randomized (65 in each group) into two groups. Mean age (years) in the study was 60.22 ± 4.04 with ranges from 51 to 72 years whereas descriptive statistics of International Prostate Symptoms Score (IPSS) was calculated in terms of mean and standard deviation was 23.20 ± 4.00. Mean duration Hb at 1 day before and after surgery was 15.20 ± 9.58 and 13.23 ± 4.00 respectively as shown in Table-I.

Table-I: Descriptive statistics of variables (N=130)

Parameters		Mean±SD
Age (years)		60.22±4.04
IPSS score		23.20±4.00
Hb (at 1 day)	before surgery	15.20+9.58
	after surgery	13.23±2.12

Mean blood loss was compared among dutasteride with control in patients of Benign Prostatic Hyperplasia (BPH) who were undergoing Trans-urethral resection of Prostate (TURP). Mean change of blood loss among both the groups was 1.85±2.75 and 1.56±1.79 respectively which was statistically significant (p-value 0.468), as shown in Table-II

Table-II: Comparison of Mean Blood loss among both groups (N=130)

		Mean±SD	p-value
Mean Hb loss	Group-I (=65)	1.85±2.75	0.468
	Group-II (n=65)	1.56±1.79	

DISCUSSION

The TURP has been considered as a gold standard for surgical treatment of patients with symptomatic BPH. Major complication like occurrence of bleeding was observed mostly intraoperatively and during the postoperative period[1,7]. In our study, mean age was 60.22±4.04 with ranges from 51 to 72 years. Whereas, Kim et al.[1] in their study found that mean age ion years was 71.98±6.40 with an International Prostate Symptoms Score (IPSS) of 21.04±7.69. In our study, mean duration of IPSS score was 23.20±4.00 which is inconsistent with the studies due to more severe prostate disease as compared to western society as reported in literature review[3,4,7].

The Peri-operative blood loss is among the commonest complications of TURP[1,3] may require blood transfusion and can cause clot retention in immediate post-operative period. Dihydrotestosterone (DHT) blocker or 5-ARI is a widely used medication for treatment of BPH and is usually prescribed as combination therapy with alpha-1 adrenergic receptor blocker. Early experimental and animal studies with finasteride showed a decrease in prostatic blood supply and mean vascular density. This results in considerable interests in the use of 5-ARI for preoperative treatment for patients undergoing TURP to reduce perioperative blood loss[2,11]. This was reported by Kravchick et al[2] and that prostate vascularity decreased after 6 weeks of Dutasteride treatment. The efficacy of dutasteride in the management of gross haematuria associated with BPH is well documented[11,,13,14]. Our study was conducted to assess the effectiveness of pre-operative Dutasteride treatment on blood loss during TURP.

In our patients, the mean blood loss in both the groups (dutasteride group vs control group) was 1.85±2.75 and 1.56±1.79 respectively. However, Kim et al[1] reported that mean Hb dropped in dutasteride group compared with control group was 1.30±1.00 g/dL vs. 1.86±1.05 g/dL respectively. In our patients, the difference between the levels of pre-operative hemoglobin and hematocrit among both groups were not significant statistically. But post-operatively, a significant difference was found in the levels of both hemoglobin and hematocrit between two groups. Martov et al[4] has reported a substantial blood loss reduction among patients who were given dutasteride for at least one month prior to TURP as compared to the control group. Whereas the Kravchick et al[2] has observed that after six weeks of treatment, the Dutasteride has reduced the prostatic vascularity, especially in transitional zone area. Hahn et al[5] reported no statistically significant reduction in blood loss after using dutasteride for 2 - 4 weeks before TURP as compared to placebo group. However, the Boccon-Gibod et al[6], Shanmugasundaram and colleagues[8] and Pastore et al[7] has observed that a longer duration treatment will reduce intra-operative and post-operative bleeding as compared to short pre-operative course with dutasteride in reducing TURP related blood loss. In our study, the difference between pre-operative hemoglobin between the two groups were not statistically significant. However, there were significant differences in postoperative hemoglobin levels between the two groups. Kim et al[1] and Pastore et al[1,7] has demonstrated almost same conclusion. In our study, a statistically significant difference was observed in term of pre-postoperative hemoglobin levels among Dutasteride group compared to the control group. Moreover, a significant lower mean blood loss has been observed in the Dutasteride group as compared to control group. These results seem to be sufficient to demonstrate decrease prostatic vascularity and resultant reduce blood loss in patients using dutasteride prior to TURP.

Several studies showed a significant reduction in blood loss among patients who have used Dutasteride for at least few weeks prior to TURP as compared to control group[12,13,15-18]. In our study, the pre-operative Dutasteride use has reduced the blood loss in terms of pre-postoperative hemoglobin change among dutasteride group as compared to control group. It is suggested that a longer period of dutasteride intake before TURP should be compared with short-term use in terms of blood loss. A large multi-centre comparative study is required in this regard for further evaluation.

CONCLUSION

The study concludes that preoperative use of dutasteride results in decreased bleeding after Transurethral Resection of the Prostate (TURP).Therefore, pretreatment with dutasteride for two weeks before surgery reduce the subsequent consequences in terms of postoperative anemia.

Limitation: This was a single center study with relatively a small sample size and moreover, all complications of TURP reported in literature were not included in this study. In addition, the operating surgeon's heterogeneity was another mentionable aspect in the limitation of this study.

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