EFFECT OF DUTASTERIDE IN DECREASING SURGICAL BLOOD LOSS FOLLOWING UNIPOLAR TRANSURETHRAL RESECTION OF PROSTATE IN PATIENTS WITH BENIGN PROSTATIC HYPERPLASIA: A QUASI EXPERIMENTAL STUDY

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ABSTRACT

Objective: To observe the effect of dutasteride in decreasing surgical blood loss following unipolar transurethral resection of the prostate (TURP) in patients with benign prostatic hyperplasia (BPH).
Study Design: Quasi experimental study.
Place and Duration of Study: Combined Military Hospital, Quetta, Pakistan, from Jul 2017 to Mar 2018.
Methodology: Sixty-six BPH patients were consecutively recruited. Six patients declined participation while 4 were excluded because of chronic kidney disease and/or a bleeding disorder. The included patients underwent an evaluation for hematocrit, serum urea and creatinine, and international normalized ratio. Four patients with impaired renal functions or altered coagulation parameters were also excluded. Patients taking non-steroidal anti-inflammatory drugs and anticoagulant/antiplatelet drugs discontinued these drugs two weeks prior to TURP. After block randomization, the control group was given tablet tamsulosin hydrochloride 0.4 mg once daily while the target group was provided tablet tamsulosin hydrochloride 0.4 mg and dutasteride 0.5 mg orally once daily. All patients started the drugs two weeks before the operation. TURP was carried out under spinal anesthesia. At 48 h after TURP, a blood sample was revaluated for hematocrit. The resected prostatic tissue was also measured.
Results: The mean age of the patients was 68.3 ± 8.4 years. The mean hematocrit before operation was 0.42% ± 0.04% (range: 0.31%-0.53%) while the mean hematocrit after the operation was 0.38% ± 0.04% (range: 0.28%-0.47%). The mean prostatic tissue removed during TURP was 22.3 ± 11.6 g (range: 7-54 g). The mean hematocrit reduction was 0.05% ± 0.02% (range: 0.1%-0.02%) and the mean hematocrit reduction per gram of prostatic tissue removed was 547.2 ± 355.1%/g (range: 1666.7%/g – 100%/g). After statistical analysis, there was no significant difference for the mean reduction in hematocrit (p=0.59).
Conclusion: Dutasteride at a dose of 0.4 mg per day did not produce significant reduction in relative blood loss and relative blood loss per gram of prostatic tissue removed with 2-weeks pretreatment before unipolar TURP in patients with BPH.

Keywords: Prostatic hyperplasia,Dutasteride, Hematocrit, Surgical blood loss, Prostatectomy.

INTRODUCTION

Since 1901 till late 1990s, transurethral resection of the prostate (TURP) remained the principle therapy for benign prostatic hyperplasia (BPH). From the time when 5-alpha reductase Inhibitors (5-ARIs) and alpha-adrenergic blockers were introduced, TURP could be deferred and recommended only for patients with recurrent, acute or chronic urinary retention. The 5-ARIs, such as finasteride and dutasteride might well be used as an adjunct to TURP to control intra-operative as well as postoperative bleeding that remained a common complication of TURP leading to postoperative clot retention and blood transfusion[1]. The standard guidelines though do not exist for the use of 5-ARI's in reduction of bleeding related to TURP. Various studies have shown unequivocal results regarding effects of finasteride and dutasteride on hematuria in TURP, however, there were limited studies in Pakistani population related to the subject. A quasi experimental study was thus aimed to see

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the effects of dutasteride on prostatic bleeding during unipolar TURP in Pakistani population.

METHODOLOGY

It was a single-blind quasi experimental study carried out in the department of Urology, Combined Military Hospital Quetta, from July 2017 to March 2018, after approval from the hospital ethical committee. We consecutively recruited 66 individuals diagnosed with BPH. Six patients declined to participate in the study. Four patients with a history of chronic kidney disease or a bleeding disorder were excluded. Patients taking non-steroidal anti-inflammatory drugs and anticoagulant or anti- platelet drugs discontinued these drugs two weeks prior to unipolar TURP.

After inclusion, all patients underwent an evaluation for hematocrit, serum urea and creatinine, and international normalized ratio. We used hematocrit as it is a measure of relative blood volume[2]. Four more patients found to have impaired renal functions (serum creatinine >145 µmol/L) and altered coagulation parameters (international normalized ratio >1.3) were also excluded. A total of 52 patients were finally selected for the study and randomized into two groups through block randomization. Each group had 26 patients.

The control group was given tablet tamsulosin hydrochloride 0.4 mg (Tamsol, Global Pharmaceuticals, Islamabad, Pakistan) orally once daily while the target group was provided tablet tamsulosin hydrochloride 0.4 mg and dutasteride 0.5 mg (Tamsol-D, Global Pharmaceuticals, Islamabad, Pakistan) orally once daily. The patients were blinded about the drugs.

All patients started the drugs two weeks before the operation. Unipolar TURP was carried out under spinal anesthesia, using a 24-F resectoscope (Karl Storz, Tuttlingen, Germany) at low pressure. At 48 h after unipolar TURP, a blood sample was drawn. The resected prostatic tissue was also measured. Resected prostatic chips were histologically analyzed ensuring separation from those extracted from the urethra. The mean reduction in hematocrit per gram of prostatic tissue removed was also calculated.

The data were analyzed in SPSS version 19.0. Continuous variables were reported as mean and standard deviation with minimum and maximum values. Categorical variables were reported as the number of occurrences and percentages. The normality of the continuous variables was evaluated using Shapiro-Wilk test. The age, pre- and post-operative hematocrit were normally distributed while the amount of removed prostatic tissue, mean reduction in hematocrit, and the mean reduction in hematocrit per gram of the removed prostatic tissue did not follow a normal distribution. Independent samples t-test was used to compare the values between the two groups for normally distributed variables while Mann-Whitney U-test was used for variables that were not normally distributed. The p-value ≤0.05 was considered significant.

RESULTS

Out of a total 52 patients, 26 (50%) were analyzed in the target while 26 (50%) were analyzed in the control group. The mean age of the patients was 68.3 ± 8.4 years (range: 50-90 years). The mean hematocrit before operation was 0.42% ± 0.04% (range: 0.31%-0.53%) while the mean hematocrit after the operation was 0.38% ± 0.04% (range: 0.28%-0.47%). The mean prostatic tissue removed during unipolar TURP was 22.3 ± 11.6 g (range: 7-54 g). The mean reduction in hematocrit was 0.05% ± 0.02% (range: 0.1%-0.02%) and the mean reduction in hematocrit per gram of the prostatic tissue removed was 547.2 ± 355.1%/g (range: 1666.7%/g – 100%/g).

The comparison of values between the two groups is given in the table. After statistical analysis there was no significant difference for the mean reduction in hematocrit (p=0.59) and the mean reduction in hematocrit per gram of prostatic tissue removed between the two groups (p=0.094).

DISCUSSION

BPH is associated with increased vascularity and proliferation of prostatic tissue under effect

of androgens[3]. This augmentation in vascularity is causative of massive hemorrhage during and after TURP. Dutasteride blocks the activity of androgen-controlled growth factors that contribute to angiogenesis and prostatic tissue proliferation[4]. It is a potent antagonizer and theoretically, it is expected to produce effective control of bleeding[5].

Contrary to the theoretical assumption, Zhu and colleagues, in a meta-analysis of randomized controlled trials, found no significant difference regarding estimated blood loss, hemoglobin fall, prostate volume, resection weight, number of required blood transfusions, and operative time[6] for dutasteride when compared with palcebo or the standard treatment. Yang *et al*[7] reported insignificant association between use of 5-ARIs before TURP and the risks of hematuria and need of blood transfusion during and after TURP. Hahn *et al*[8] found inconsequential effect on blood loss in TURP of 2 and 4-week pretreatment with dutasteride. Another meta-analysis of five RCTs and five retrospective cohort studies found no significant difference between dutasteride and the control group in terms of total blood loss during TURP, blood loss per gram of resected prostatic tissue, the weight of resected prostatic tissue, the microvessel density of the prostate, and the transfusion rate[9]. Our study also produced equivocal results and remained inconclusive. There was no significant reduction in relative blood loss following a two-week pretreatment with dutasteride compared to the control group.

The analysis of the available data favoring use of dutasteride revealed results linked to the duration of therapy. A handful of studies have shown benefit with pre-treatment of less than or equal to 2 weeks' duration. Mitterberger *et al*[10] found that after taking dutasteride for only seven days, blood flow to the prostate was reduced when observed by doppler transrectal prostatic ultrasonography, indicating that vascularity of the prostate reduced during the treatment time. In a small RCT conducted by Tuncel *et al*[11], pretreatment with dutasteride decreased blood loss per gram of resected prostate tissue. Kim and colleagues observed that preoperative treatment with dutasteride for two weeks before TURP reduced surgical bleeding and length of hospitalization after TURP[12]. Similarly, Woo *et al*[13] also observed that dutasteride treatment for two weeks before TURP reduced microvessel density in the sub-urethral region.

Increasing treatment duration to 4 or 6 weeks has principally produced favorable results. Koul and colleagues[14] stated significant reduction in peri and post-operative surgical bleeding on pretreatment with 0.5 mg dutasteride for 4 weeks before TURP. Bansal and Arora reported a significant reduction in mean blood loss, blood loss/ time, and total blood loss per gram of resected tissue in the dutasteride group compared with

Table: Comparison of target and control groups based on study parameters.

Variables	Group A (Control group)		Group B (Experimental group)		*p*-value
	No. of patients included (n)	Values (mean ± SD)	No. of patients included (n)	Values (mean ± SD)	
Age (years)	26	68.3 ± 7.8	26	68.3 ± 9	0.974
Pre-op hematocrit (%)	23	0.42 ± 0.04	22	0.43 ± 0.05	0.468
Post-op hematocrit (%)	19	0.37 ± 0.04	18	0.39 ± 0.04	0.198
The mean reduction in hematocrit (%)	19	0.05 ± 0.02	18	0.05 ± 0.02	0.59
The amount of prostate tissue removed (g)	25	20.1 ± 10.8	24	24.7 ± 12.1	0.109
The amount of blood loss per gram of prostate tissue removed (m%/g)	19	463.95 ± 314.4	18	635.08 ± 382.7	0.094

placebo following 4 weeks of preoperative treatment[15]. Martov and Ergakov noted that the treatment group receiving 0.5 mg of dutasteride for 5½ weeks demonstrated shorter operation time (62 vs. 79 min), more amount of the removed tissue (92 vs. 85 g), less volume of the irrigation liquid (16.7 vs. 19.3), shorter duration of urethral catheter tension (10.4 vs. 19.3), and less volume of intraoperative blood loss (93.6 ml vs. 138.6 ml, $p<0.05$) than the other treatment group lacking dutasteride[16]. Pastore *et al*[17] observed a significantly lower mean blood loss in the dutasteride group compared to the control group (Hb= -1.29 ± 0.81 vs. -1.83 ± 1.25, respectively, $p<0.01$; hematocrit =-5.67 ± 2.58 vs. -6.50 ± 2.40, respectively, $p<0.05$) after pretreatment for six weeks. Kravchick and coworkers[18] found that vascularity of the prostate, especially in the periurethral area, was reduced after taking dutasteride for 6 weeks.

Thus, after a review of the studies for and against use of dutasteride, it becomes evident that the unpromising results were generally found in the studies using dutasteride for a duration ≤2 week. Studies with a larger duration (≥4 weeks) had overwhelmingly produced favorable results. Our study also produced equivocal results and remained inconclusive. The short duration of pretreatment might be considered a limitation in this study and further studies with a longer duration of treatment are, therefore, recommended.

CONCLUSION

Dutasteride at a dose of 0.4 mg per day did not produce significant reduction in relative blood loss and relative blood loss per gram of prostatic tissue removed with 2-weeks pretreatment before unipolar TURP in patients with BPH.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

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