

Effect of preoperative finasteride on perioperative blood loss during transurethral resection of the prostate and on microvessel density in patients with benign prostatic hyperplasia: An open label randomized controlled trial

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Abstract

Objective: Transurethral resection of the prostate (TURP) is a common procedure for the treatment of benign prostatic hyperplasia (BPH). Previous studies on the effect of 5-alpha reductase inhibitors on perioperative blood loss in TURP and microvessel density (MVD) in the prostate are equivocal. We evaluated whether pretreatment with finasteride for 2 weeks before surgery can reduce perioperative blood loss in TURP and MVD in the prostate.

Materials and Methods: Sixty-eight patients of BPH planned for TURP were randomized into two groups. The study group comprising 34 patients was treated with finasteride (5 mg/day) for 2 weeks and the placebo group comprising 34 patients received placebo for 2 weeks, before TURP. Blood loss was measured in terms of a reduction in the blood hemoglobin (Hb) and hematocrit (HCT) levels between preoperative values and 24 h after surgery. MVD was measured in the resected prostate tissue stained with anti-CD31 monoclonal antibody.

Results: The reduction of Hb and HCT in the finasteride group was significantly lower than the reduction in the placebo group ($P < 0.05$). The artery ($P = 0.005$), vein ($P = 0.05$), and gland ($P = 0.008$) densities were significantly less in the finasteride group than in the placebo group. There was no significant correlation between blood loss and MVD.

Conclusions: Our study suggests a clear advantage of the preoperative use of finasteride for 2 weeks by reducing the perioperative blood loss in TURP in patients with BPH. While there is a significant reduction in MVD in the prostate on treatment with finasteride, it is not clear that this is the mechanism of reduction in blood loss in TURP.

Keywords: Benign enlargement of the prostate, blood loss, five alpha reductase inhibitor, microvascular density, transurethral resection of prostate

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INTRODUCTION

Benign prostatic hyperplasia (BPH) is a histological diagnosis that is defined as the proliferation of muscle and epithelial cells within the transition zone of the prostate. Dihydrotestosterone (DHT) is the principal androgen responsible for transition zone expansion and BPH in elderly men.^[1] The prevalence of BPH is increasing in men, which significantly affects their daily life.^[2] BPH is associated with aging and nearly all men would show BPH by the time they reach average life expectancy. It is not a life-threatening disease, but some men have progressive lower urinary tract symptoms (LUTS). They suffer from deterioration of urinary symptoms and quality of life and sometimes unfavorable outcomes, such as acute retention of urine and chronic urinary retention with renal failure.^[3] A weak relationship has been found between the size of the prostate and the presence of LUTS, retention, and its complications.^[4] Pharmacotherapy with α_1 -adrenergic blockers, 5 α -reductase inhibitors (5ARIs), antimuscarinic agents, or a combination of these drugs is the first line of treatment in symptomatic BPH.^[5] The most common surgical treatment option for patients with BPH not responding to medical therapy is transurethral resection of the prostate (TURP). TURP is more effective than medical management of BPH but is associated with complications.^[6] Perioperative blood loss is the main complication of TURP, which can lead to urinary clot retention and the need for blood transfusions.

The mechanisms of BPH are multifactorial and not yet fully established. However, BPH is known to depend on androgens particularly DHT, that is important for the normal growth and development of the prostate. DHT is produced from testosterone in the prostate by the action of the enzyme 5-alpha reductase. 5ARIs such as finasteride and dutasteride block the conversion of testosterone to DHT and thereby, cause a reduction in the size of the prostate. They are, therefore, used for the treatment of BPH.^[7,8] The exact pharmacodynamic action of finasteride is speculative. One study showed that it decreases the microvessel density (MVD) of suburethral prostatic glands, which is a vascularity indicator.^[9] A study by Aminsharifi *et al.* have assessed the perioperative effects of dutasteride on blood loss associated with TURP and the prostatic MVD using CD31 or CD34 monoclonal antibody which stains endothelium of vessels, with equivocal results.^[10] A study by Hahn *et al.* comparing preoperative dutasteride with placebo on the blood loss following TURP and MVD did not show any benefit of dutasteride.^[11] Similarly, Tuncel *et al.* studied the effect of preoperatively administered dutasteride and *Serenoa repens* and concluded that these

therapies were not superior as compared to controls in reducing perioperative blood loss.^[12] They also did not notice any significant difference between the treatment and the control groups in relation to MVD. The present literature thus shows conflicting reports on the effect of preoperative 5ARI on the prostatic MVD and perioperative blood loss associated with TURP.^[13]

In view of the above, our study aimed to find out the effect of finasteride on perioperative blood loss, the effect on MVD in resected prostatic tissue in BPH patients and to see if any correlation exists between the two. As fluid absorption would likely depend on the vascularity of prostate gland, this study, as a secondary objective, also tried to find out if there was any effect of pretreatment with finasteride on postoperative serum sodium level.

MATERIALS AND METHODS

This study was an open-label randomized controlled trial conducted in the Department of Urology, of our institution from November 2015 to December 2016. The study was approved by the Institute Ethics Committee and registered with the Clinical Trial Registry of India (No.REF/2016/02/010758). All patients of BPH recommended to undergo TURP, with prostate size >30 g as measured by transabdominal ultrasonography using the ellipsoid formula, were screened for eligibility and consenting participants were included in this study. Those with a history of surgery on the prostate, prostate cancer, previous use of 5ARIs, radiation therapy to the pelvis, and allergy to finasteride were excluded.

The patients were randomized into the two study groups by simple randomization using computer-generated random numbers. Allocation concealment was done by sealed envelope technique. One group of patients (finasteride group) was given 5 mg of finasteride daily for 2 weeks, preoperatively and the second group (placebo group) was given 2 weeks of inert placebo. The patients were then admitted to the hospital and standard (monopolar) resection was performed. Postoperatively, the catheter was removed once the patient's hematuria had settled and he was afebrile. Thereafter, the patient was discharged. The resected prostatic chips were processed for histopathologic and morphometric studies as described below.

The patients' baseline variables recorded prior to the administration of finasteride or placebo included age, co-morbidities, prostate volume, serum prostate-specific antigen (PSA), and preoperative hemoglobin (Hb), and hematocrit (HCT). After TURP, operation time, resected

prostate volume, postoperative sodium within 1 h of surgery, postoperative Hb and HCT obtained after 24 h, the number of perioperative blood transfusions given, complications till discharge, and duration of catheterization were recorded. On histopathology of the resected prostate chips, artery density, vein density, and gland density were measured.

Technique of morphometric studies

The resected prostatic tissue was stained with hematoxylin and eosin stain and examined to rule out prostate cancer. Thereafter, sections were stained using immunohistochemical methods with the anti-CD31 monoclonal antibody. A section of one chip at the center of the slide and an additional four sections of chips surrounding this first section was scanned with a microscope [Figure 1a and b]. Among five chips in each high-power field, the chip with the highest and the one with least CD31 positivity were used for assessment, thereby giving a near accurate average density. The average artery density/mm², average vein density/mm², and average gland density/mm² were calculated.

Statistical analysis

The sample size was estimated using the formula for comparing two independent means with equal variance with 5% level of significance and 80% power, the minimum expected differences in the MVD as 0.17 counts/mm² with standard deviation of 0.25 counts/mm².^[1] The sample size was also estimated using the effect size of others study parameters also. Since the sample size for the effect size of MVD yielded the largest sample size of 34 in each group, the same was taken for the study.

Comparison of categorical variables between the groups was carried out using Chi-square test or Fisher's exact test as appropriate. Continuous variables, such as MVD and perioperative blood loss, were compared between the study groups by independent student *t*-test or Mann-Whitney U test based on the distribution of data. All statistical analyses were carried out using the software IBM SPSS Statistics for Windows, version 19 (IBM Corp., Armonk, N.Y., USA) and a $P \leq 0.05$ was considered as statistically significant.

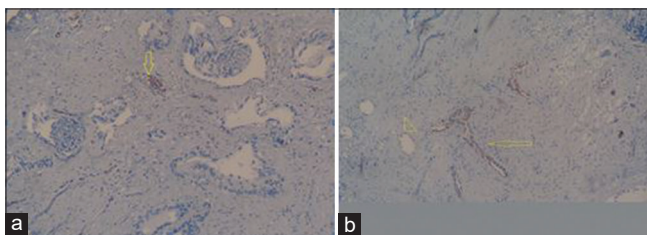


Figure 1: High power view of a section of the prostate showing vein/venule (arrow head) and arteries/arterioles (arrow) (immunohistochemistry CD31, $\times 400$), (a) Pre finasteride, (b) Post finasteride

RESULTS

A total of 73 patients were screened for eligibility to participate in the study from December 2015 to January 2016. Five were excluded due to declining consent (two cases) or falling under the exclusion criteria (three cases). Thus, a total of 68 consenting patients, fulfilling the inclusion and exclusion criteria, were recruited for study. The patients were randomized to the two study groups, i.e., the finasteride group and the placebo group and the data analyzed [Figure 2]. The mean and range of age, body mass index, prostate volume, PSA, preoperative Hb and HCT, and preoperative serum sodium level were similar in the two study groups [Table 1]. The average reduction of Hb and HCT at 24 h following surgery, the average change of serum Na, and the average microvessel, arterial, venular, and glandular density are shown in [Table 1]. The average reduction of Hb at 24 h after surgery was 0.52 g/dl lower in the finasteride group as compared to the placebo group ($P < 0.03$, 95% confidence interval [CI] [0.07, 0.96]). The average reduction in HCT at 24 h was 1.43% ($P < 0.03$, 95% CI [0.11, 2.75]) less in the finasteride group as compared to the placebo group [Table 1]. The difference in average change of serum (Na) between the two groups was not significant.

The average resection time was significantly more in finasteride group ($P < 0.013$) by 6 min as compared to

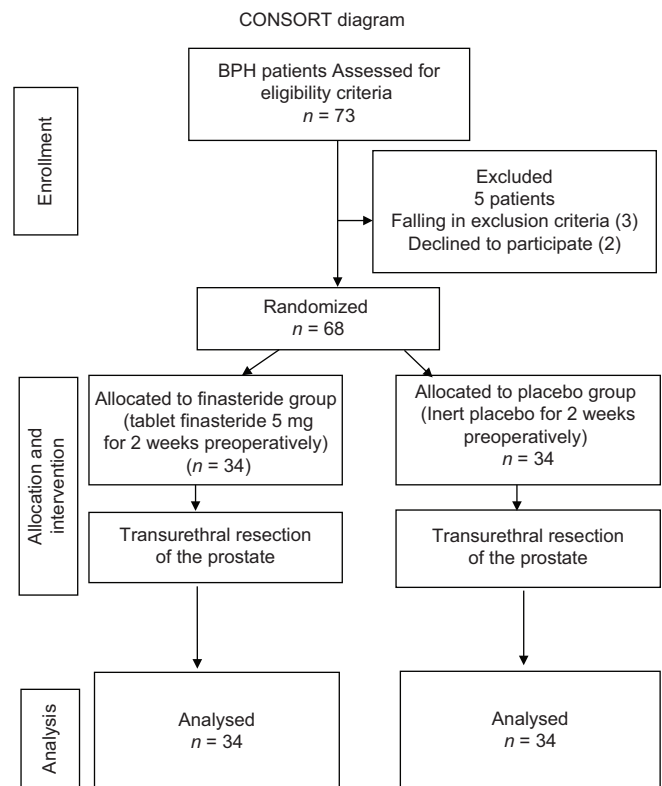


Figure 2: Consort flow chart for data analyses

Table 1: Comparison of preoperative and outcome variables in the two study groups

Variables	Finasteride group (n=34)	Placebo group (n=34)	Statistics (P)
Preoperative variables			
Age (years)	67.21±6.9	67.26±9.10	0.97
BMI (kg/m ²)	22.39±1.60	22.07±1.06	0.35
Prostate volume (ml)	46.08±10.18	42.41±11.18	0.16
Serum PSA (ng/ml)	2.92±1.87	3.65±3.52	0.96
Preoperative Hb (g/dl)	13.00±1.56	12.39±1.62	0.12
Preoperative HCT (%)	39.75±4.3	38.95±4.28	0.44
Preoperative Na (nmol/L)	137.35±4.07	137.29±2.393	0.94
Postoperative outcome variables			
ΔHb (g/day)	0.87±0.89	1.39±0.94	0.022
ΔHCT (%)	2.76±2.69	4.19±2.76	0.025
Serum Na (mEq/L)	2.38±2.66	1.94±3.45	0.95
Resection time (min)	57.08±11.14	51.02±11.53	0.013
Resected weight of gland (g)	18.17±3.81	15.19±4.63	0.005
MVDa (counts/mm ²)	1.26±0.87	2.00±1.19	0.005
MVDv (counts/mm ²)	1.77±1.19	2.32±1.12	0.05
Gland density (counts/mm ²)	1.98±1.11	2.94±1.71	0.008

ΔHb: Difference between preoperative and 24 h postoperative blood hemoglobin, ΔHCT: Difference between preoperative and 24 h postoperative hematocrit, ΔSerum Na: Difference between preoperative and 24 h postoperative serum sodium. MVDa: Mean vascular density of artery, MVDv: Mean vascular density of vein, BMI: Body mass index, PSA: Prostate-specific antigen, Hb: Hemoglobin, HCT: Hematocrit, Na: Sodium

the placebo group which may be attributable due to larger gland size in finasteride group. The average weight of resected prostatic tissue in the finasteride group was more by 3 g than in the placebo group. The average artery density in the finasteride group was 1.26 ± 0.87 as compared to 2.00 ± 1.19 in the placebo group and the difference was highly significant ($P < 0.01$). The average vein density was significantly less ($P < 0.05$) in the finasteride group ($1.77 \pm 1.19/\text{mm}^2$) as compared to $2.32 \pm 1.12/\text{mm}^2$ in the placebo group. The average gland density was $1.98 \pm 1.11/\text{mm}^2$ in the finasteride group as compared to $2.94 \pm 1.7/\text{mm}^2$ in the placebo and the difference was highly significant ($P < 0.01$). No significant correlation was found between change in Hb or HCT and MVD. The high power view of a section of prostate showing increased number of blood vessels with endothelial cells showing positivity to CD31 [prefinasteride, Figure 1a] and decreased number of blood vessels (after finasteride) in immunohistochemistry, $\times 10$ [Figure 1b].

DISCUSSION

Our study aimed to find the effect of a 2-week course of finasteride on perioperative blood loss in TURP and on the MVD of resected prostatic tissue in patients with BPH, and to see if any correlation exists between the two. Our study showed that the reduction of Hb and HCT in the finasteride group was significantly lower than the reduction in the placebo group, indicating that 5 mg of finasteride administered daily for 2 weeks prior to TURP decreases perioperative blood loss. We also found that the average artery density, vein density as well as the gland density was significantly less in the finasteride group as compared to the placebo group. The shrinkage of the glandular portion

of the prostate upon administration of finasteride is well known and explains the lower gland density seen in the finasteride group in our study. The finasteride group also demonstrated a lower MVD and we feel this is also due to the action of finasteride on the prostate. We, therefore, feel that reduction in MVD may have contributed to the reduction in the perioperative blood loss.

Our results confirm the observations of Zaitso *et al.* and Donohue *et al.* Zaitso *et al.* compared a group of patients who were administered 0.5 mg of dutasteride daily with an average duration of 16.3 weeks to an untreated group. They found that the MVD was lower in the dutasteride-treated group as compared to the untreated group and concluded that dutasteride causes a reduction in the MVD in the prostatic tissue.^[1] Donohue *et al.* compared administration of 5 mg of finasteride daily for 2 weeks with placebo, to patients undergoing TURP for BPH and found that MVD and vascular endothelial growth factor (VEGF) expression is decreased in patients treated with finasteride.^[8] Pastore *et al.* randomized 142 patients with BPH into two groups (the dutasteride group and the control group) and performed TURP after 6 weeks of dutasteride administration. They concluded that when dutasteride is used for 6 weeks preoperatively, it significantly reduced surgical bleeding risk.^[14]

However, not all studies have yielded uniform results. Busetto *et al.* recently did a study on the short-term effect of dutasteride for 8 weeks on intraoperative bleeding while doing bipolar TURP and concluded that dutasteride was able to reduce operative and perioperative bleeding only in with large prostates (≥ 50 mL) that underwent bipolar TURP. Their study showed a reduction in Hb and HCT

values as well as levels of VEGF and CD34 in patients treated with dutasteride.^[6] Although we did note a greater reduction in the postoperative change in Hb in patients the gland size >50 ml treated with finasteride, the difference was not statistically significant, perhaps due to the small proportion of study subjects with gland size more than 50 ml.

Our observations are different from those of Lund *et al.* who carried out a randomized study to find out the effect of finasteride on perioperative blood loss before TURP and found that finasteride did not decrease perioperative blood loss, as compared to the placebo group.^[15] The study, however, randomized only 35 patient and the authors themselves concluded that a larger sample size is required to validate their results. Hahn *et al.* did a multicentric randomized controlled trail comparing administration of dutasteride 0.5 mg/daily for 2–4 weeks prior to TURP followed by continuation of therapy for two more weeks after TURP with placebo, to find out the blood loss and postoperative complications in BPH patients who were planned for surgery in a double-blinded, randomized, placebo-controlled manner. They measured blood loss, complications, and MVD and found that treatment with dutasteride did not reduce blood loss or complications as compared to placebo and concluded that dutasteride did not decrease MVD.^[11] One reason could be that the study by Hahn *et al.* measured only intraoperative blood loss while the present study measured a change in blood Hb estimates between the preoperative value and the 24 h postoperative value that would reflect the sum of intraoperative and postoperative blood loss.

Even though, we found a significant reduction in blood loss as well as a reduction in MVD we could not find a correlation between blood loss and MVD either across groups or within a group. It is possible that finasteride may reduce blood loss through multiple mechanisms one of which may be a decrease in MVD. This may explain the lack of correlation between MVD and perioperative blood loss. A study on the pathogenesis of BPH that explored the role of angiogenesis has shown that MVD usually increases in BPH.^[16] However, the factors underlying changes in MVD are not fully known and may also be different for BPH and for other prostatic diseases. Wong *et al.* have shown that there is a decrease in proangiogenic factor mRNA expression associated with endothelial proliferation and increased MVD during inflammation and hence increase in MVD may have different mechanisms in inflammation and in normal development.^[17] A study done by Stefanou and colleagues showed that VEGF was expressed in 81.25%

of BPH patients sample.^[18] We, therefore, feel there may be multiple mechanisms that affect MVD in the prostate.

To summarize, our study clearly shows that a short period of treatment with finasteride before planned TURP could reduce perioperative blood loss. The reduction in perioperative blood loss was likely due to multiple effects of finasteride on the prostate, one of which could be the reduction in MVD of the prostate gland.

CONCLUSIONS

Although the present study was a randomized controlled trial that was adequately powered, it had the limitation of not being blinded. Nevertheless, the findings suggest a clear advantage of the preoperative use of finasteride for 2 weeks for reducing the perioperative blood loss in patients. It also provides evidence in support of a potential mechanism, i.e., reduction in microvascular density by finasteride. Nevertheless, more studies are needed to elucidate the precise mechanism by which finasteride reduces perioperative blood loss as there was an insignificant correlation between microvascular density and perioperative bleeding. The present study, however, does make out a strong case for routine use of 2 weeks of finasteride prior to TURP in patients with BPH of size 30 ml or above.

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Conflicts of interest

There are no conflicts of interest.

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