Original Research Article

The role of finasteride on perioperative bleeding in patients undergoing TURP: A randomized controlled study

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Abstract

Background: Benign prostatic hyperplasia (BPH) is the commonest urological condition affecting men over 50 years of age. Medical therapy is usually the first line management of BPH. Finasteride is a 5-alpha reductase inhibitor (5ARI), which blocks the conversion of testosterone into the more potent dihydrotestosterone (DHT).

Materials and methods: We prospectively enrolled 54 BPH patients with prostate size ranging from 30-60 gm based on ultrasound, who were undergoing elective TURP at Gandhi Hospital for a period of 2 years from January 2013 to Jan 2015. BPH patients with hematuria, bothersome symptoms and refractory retention were included in the study.

Results: Totally 54 BPH patients were enrolled in our study, 30 were randomized to finasteride group and 24 to controlled group. There was significantly less (p value <0.01) mean blood loss in irrigation fluid in the finasteride group compared to the control group (54.27 gm in finasteride group Vs 82.45gms in the control group; p value < 0,01) for each transurethral resection of prostate.

Conclusion: Finasteride give daily for 2 weeks before transurethral prostate resection decreased bleeding preoperatively, thereby decreasing the requirement of blood transfusions, post operative episodes of hematuria and clot retention.

Key words

Finasteride, BPH, TURP.

Introduction

Benign prostatic hyperplasia (BPH) is the commonest urological condition affecting men over 50 years of age. Medical therapy is usually the first line management of BPH. Finasteride is a 5-alpha reductase inhibitor (5ARI), which blocks the conversion of testosterone into the more potent dihydrotestosterone (DHT). By the suppression of DHT, finasteride reduces prostatic tissue growth and reduce the overall size of the prostate by 30% within a year [1, 2]. Furthermore, studies have shown that 5ARI also decreases prostatic bleeding by suppressing the androgen controlled vascular endothelial growth factor (VEGF), and decreased angiogenesis [3, 4].

Transurethral resection of the prostate (TURP) is the established surgical modality of treatment for BPH where medical therapy failed. But, significant intra-operative and post-operative bleeding remains a common complication leading to postoperative clot retention and blood transfusion [5, 6]. Several studies have shown that the blood loss can be reduced during TURP in patients taking finasteride preoperatively [7, 8, 9]. However, the American Urological Association's (AUA) guidelines state that there is insufficient evidence to recommend perioperative 5ARI treatment to decrease bleeding [10].

Therefore, we aimed to conduct a study to review of the role of finasteride given 2 weeks prior to TURP in reducing the preoperative bleeding.

Materials and methods

We prospectively enrolled 54 BPH patients with prostate size ranging from 30-60 gm based on ultrasound, who were undergoing elective TURP at Gandhi Hospital for a period of 2 years from January 2013 to Jan 2015. BPH patients with hematuria, bothersome symptoms and refractory retention were included in the study. Patients in who, malignancy was suspected because of abnormal digital rectal examination findings, increased PSA or Biopsy findings were excluded from the study. Patients with vesical calculus, raised renal parameters and patients on anticoagulation or antiplatelet were also excluded from the study. Patients with active infection documented by urine C/S were treated with appropriate antibiotics before patient is taken up for study.

These patients were randomized into two groups; treatment group received finasteride 5mg daily for 2 weeks prior to TURP and the control group received placebo for 2 weeks prior to the surgery. All patients were subjected to Trans rectal random, two core biopsy before starting finasteride or placebo for histopathological examination regarding vascular density. Then patients were kept on finasteride 5mg per day or placebo one tablet per day. Hemoglobin and PCV were measured on the day of surgery preoperatively for all the patients and the day following surgery and compared.

Blood loss during surgery was estimated by obtaining haemoglobin concentration of irrigation fluid during the operation and multiplying by the total volume of irrigation of fluid used i.e., hemoglobin concentration of irrigation fluid X total volume of irrigation fluid used. Hemoglobin concentration or RBC cell count of irrigation fluid was calculated using a cell counter.

Weight of the TURP chips resected was measured in gm and sent for histopathological examination for comparison of vascular density with that of transrectal core biopsy done before starting finasteride or placebo.

By dividing the total haemoglobin lost in the irrigation fluid by the weight of the resected prostate tissue we were able to calculate the amount of hemoglobin lost per each gram of prostate tissue resected. Preoperative episodes of hematuria were recorded. Preoperative or Postoperative requirements of blood transfusion were recorded.

Pre finasteride/ placebo transrectal core biopsies and post finasteride /placebo TURP chips were subjected to histopathological examination and compared regarding vascular density in terms of number of vessels per high power field and vessel characteristics in terms of their tortuosity, sclerosis and width.

Results

Totally 54 BPH patients were enrolled in our study, 30 were randomized to finasteride group and 24 to controlled group. There was significantly less (p value <0.01) mean blood loss in irrigation fluid in the finasteride group compared to the control group (54.27 gm in finasteride group Vs 82.45gms in the control group; p value < 0,01) for each transurethral resection of prostate (**Table - 1**, **Figure - 1**). To correlate accurately we compared haemoglobin lost per gram of tissue resected in both the groups by dividing total hemoglobin lost in irrigation fluid by total weight of the prostate resected in gm. Haemoglobin lost per gm of prostate resected was significantly less in finastride group (3.74 gm) compared to controlled group (6.36 gm), with P value <0.01. (**Table - 2**, **Figure - 2**).

Lower percentage of patients in finasteride (n-9/30, 30%) group had more than 1 gm fall in haemoglobin post operatively compared to control group (n- 18/24, 70%) as depicted in **Figure - 3**. The requirement of blood transfusions were also more in control group 3/24 (12.5%) compared to finasteride group 1/30 (3.3%) finasteride group as shown in **Figure - 4**.

It was also noted that the duration of surgery and requirement of irrigation fluid was also decreased in finasteride group (63.03 minutes and 18.8 litres respectively) compared to control group (74.91 min and 24.08 litres respectively) (P<0.01) shown in **Figure – 5** and **Figure - 6** respectively. Totally 5 patients had post-operative hematuria, 4 (16.66%) in control group and 1 (3.3%) in finasteride group. Two (8.33%) of four patients who had hematuria in control group had clot retention and underwent clot evacuation in operation theatre under anaesthesia. Non from finasteride group had clot retention. TUR syndrome was noted in two patients in the control group and none in finasteride group.

Table - 1: Comparison of mean blood loss in irrigation fluid between finasteride and control group.

	Number (n)	**Mean (gm)**	**SD**	**T & P Value**
Finasteride	30	54.27	20.554	T=5.675
Control	24	82.45ml	14.530	P < 0.01

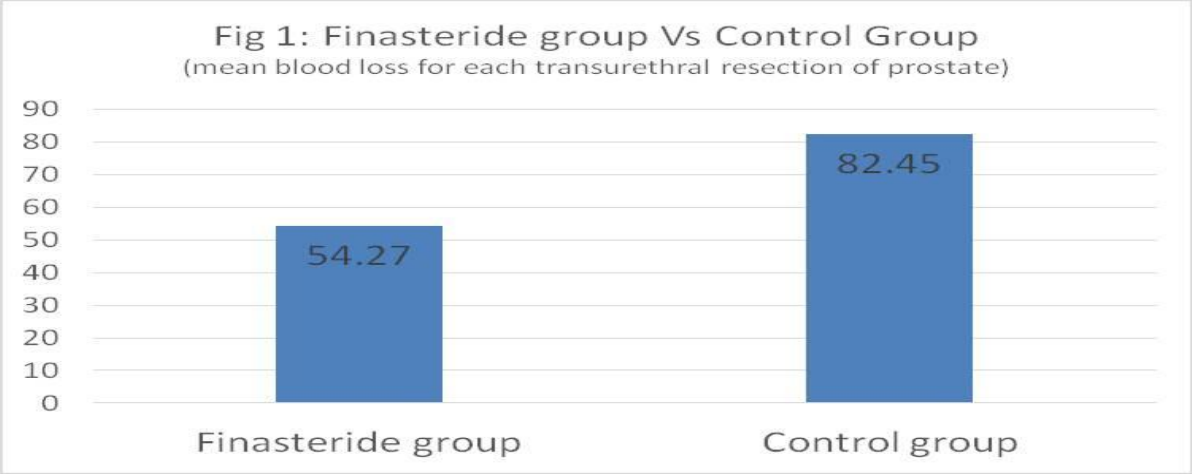
Table - 2: Comparison of hemoglobin lost per gram of prostate tissue resected between finasteride group and control group.

	Number	**Mean (gm)**	**SD**	**T & P value**
Finasteride	30	3.74	1.0551	T=7.534
Control	24	6.36	1.4944	P < 0.01

Histopathological observations

Vascular density was observed as number of micro vessels per High power field (HPF). We compared the prostatic vascularity of transrectal prostatic core biopsies before starting finasteride or placebo with that of post TURP chips in Finasteride and placebo group. We noticed that the micro vessel density had decreased from 1-2 per HPF in transrectal prostatic core biopsies to 1 per 2-3 HPF after finasteride (**Figure - 7**). This was not observed in controlled group.

Other pathological changes observed after finasteride therapy were; focal vascular sclerosis with medical and intimal proliferation occluding the vascular lumen, decreased smooth muscle mass, increased mature fibrous tissue and increased collagen nodule formation (**Figure - 8**).



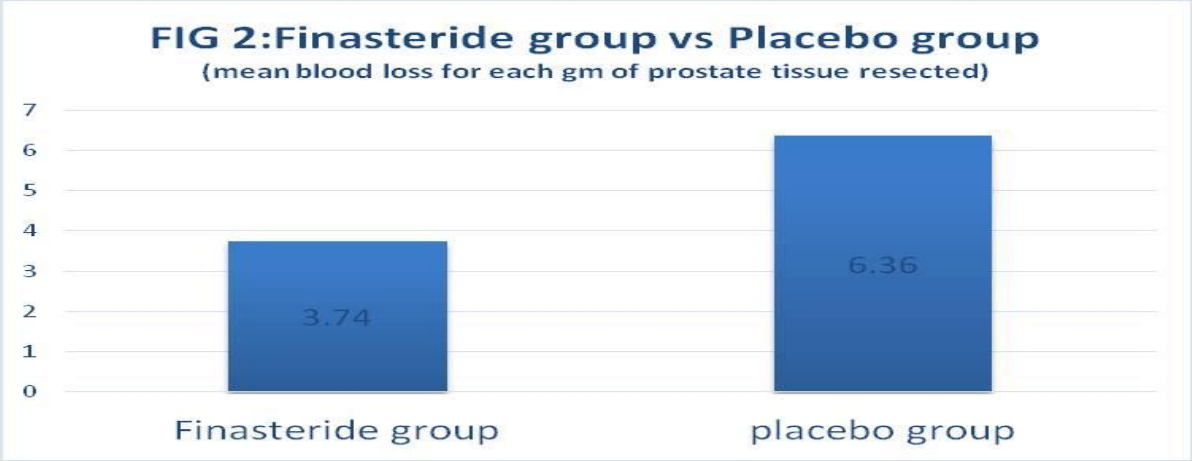


Figure - 3: Percentage of patients with fall in the haemoglobin concentration of more than 1gm% finasteride vs control group.

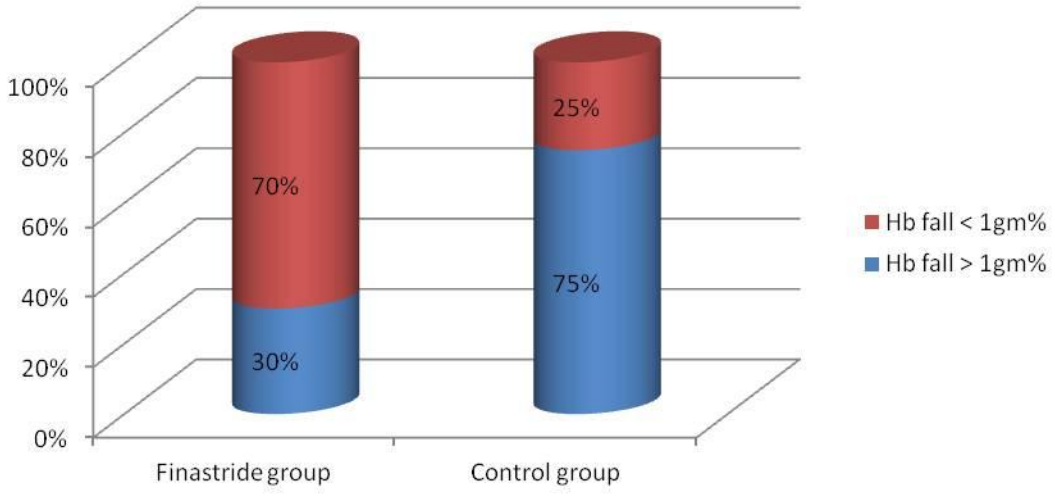


Figure – 4: Requirement of blood transfusion in Finasteride group vs Control group.

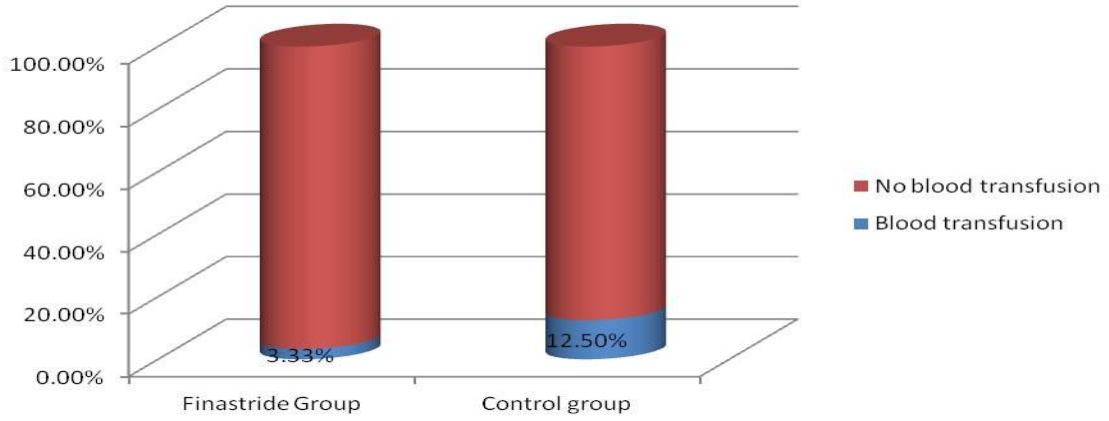


Figure 5 : Comparision of irrigation fluid used for each TURP between finasteride & placebo group

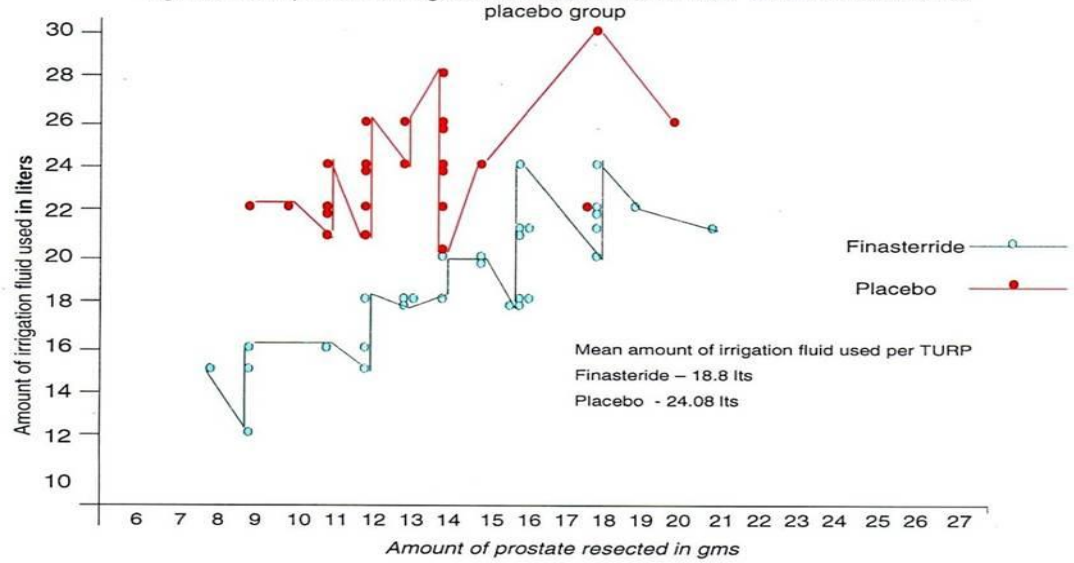


Figure 6 : Comparision of duration of surgery for each TURP between finasteride & placebo group

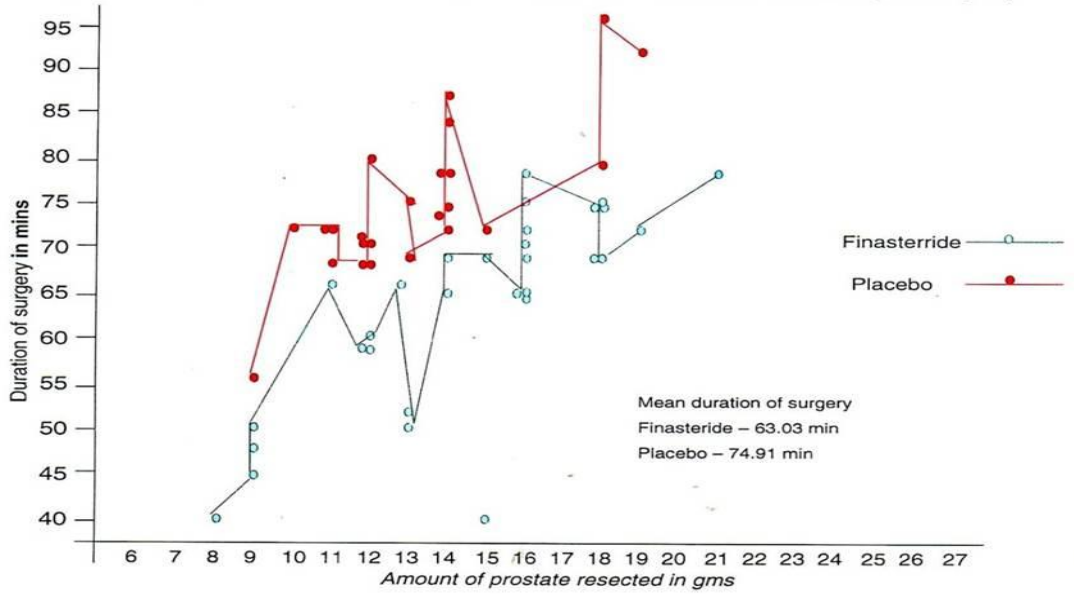
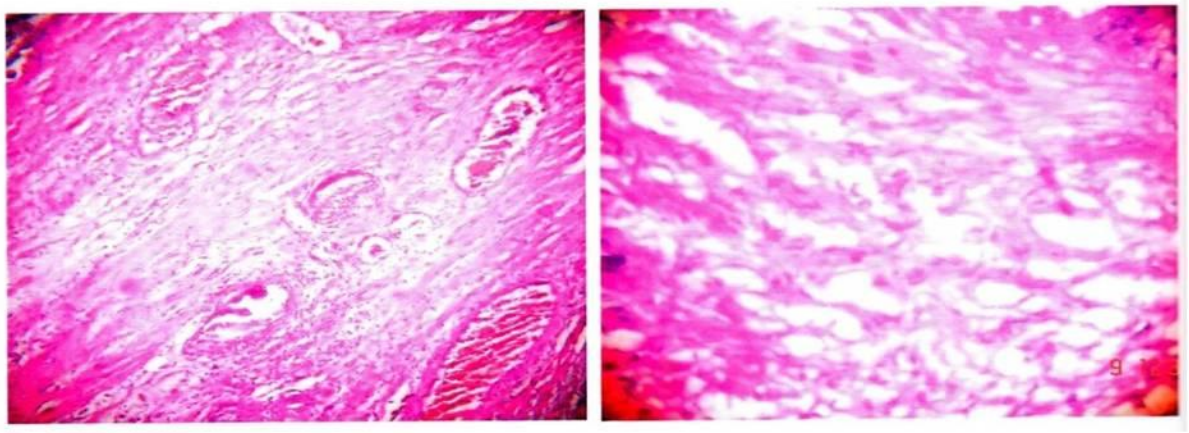


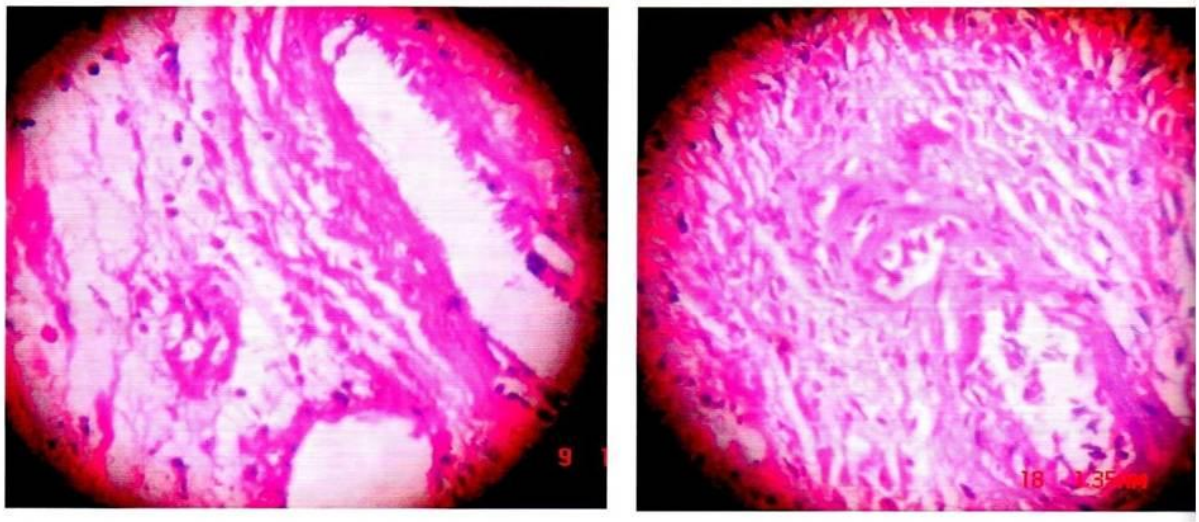
Figure - 7: Histopathological feature of protrate before and after finasteride.



Pre finasteride –showing histopathological features of Benign Prostatic hyperplasia with more number of vessels

Post finasteride –showing histopathological features of BPH with decreased number of vessels

Figure - 8: Other pathological changes of finasteride therapy.



Pre Finasteride – Showing histopathological features of BPH with dilated blood vessels

Post finasteride histopathological features of BPH with sclerosed vessels with intimal and medical hyperplasia occluding the lumen of the vessel

Discussion

The prevalence of intermittent hematuria of prostatic origin is unknown, but it can be devastating and frightening experience for a patient. This can result in repeated medical consultants and emergency treatment and it is an indication for TURP in 12% of cases.

Finasteride results in a decrease in the size of prostate which may require up to 6 months of treatment. There is growing interests in the use of finasteride for treating hematuria of prostate origin. Puncher and Miller [11] proposed that inhibiting the conversion of testosterone to dihydrotestosterone by finasteride leads to decrease in androgen derived growth factor responsible for angiogenesis like VEGF resulting in decreased bleeding. Bailey, et al. [12] noted decreased micro vessel density in prostate tissue

in patients on Finasteride who underwent transurethral prostate resection.

Foley, et al. [13] showed that men treated with finasteride for BPH associated hematuria were less likely to need surgery. In a prospective study of 57 patients with chronic intermittent hematuria randomized to finasteride or placebo over 12 months, bleeding recurred in 17 (63%) in controls with 5 cases (26%) needing surgery, while only four patients (14%) had bleeding in finasteride arm with non-requiring surgery.

Carlin, et al. [14], in a prospective study of 12 men treated with finasteride for gross hematuria secondary to BPH reported that bleeding stopped with in 2weeks.The efficacy of finasteride for treating hematuria is inversely proportional to the size of prostate.

Kearney, et al. [15] in the retrospective case review of patients treated with finasteride for active or recurrent bleeding, the mean time to cessation of bleeding in the actively bleeding group was 12 days ranging from 27 days or longer for prostate weighing < 40 gm to > 45 days for glands of >150gms.

Similar to other studies; Donohue JF, et al. [8], Hagerty, et al. [7] and Sanfedt L Bailey, et al. [6]; our study also showed that pre-treatment with finasteride significantly reduces blood loss in men undergoing TURP, measured as mean blood loss in irrigation fluid (54.27 gm Vs 82.45 gm), haemoglobin lost per gram of tissue resected (3.75gm Vs 6.36 gm) and percentage of patient with fall in haemoglobin level more than 1 gram% (30% Vs 75%).

Donohue JF, et al. [11] showed that there was significantly less mean blood loss in irrigation find in the finasteride group compared to control group (69.3 gm Vs 43.6 gm) (p value <0.01).The mean difference was more significant when blood loss per gram resected prostate was calculated (4.65 gm Vs 2.65 gm) (p value <0.01) per gram of prostate tissue resected.

Vascular density is a histological measurement of angiogenesis and thus a surrogate marker of bleeding, as the prostate of men with BPH and hematuria have a high microvessel desity (MVD) in the suburetheral portion than prostate of men with BPH alone. Finasteride reduces the MVD in the sub urethral portion of prostate but not in nodular portion in men undergoing TURP. This Provides in sighs into the effect and speed of action of finasteride on hematuria.

VEGF is an androgen sensitive growth factor that controls angiogenesis. It was shown VEGF expression is down regulated at 1 week after castration, while testosterone replacement induces VEGF synthesis within a day. Considering the rapidly of action of finasteride on VEGF and micro vessel density we restricted the preoperative duration of finasteride therapy for 2 weeks which would be adequate for decreasing the angiogenesis. Furthermore, 2 weeks is a practical period for patients to be prescribed a drug before elective surgery, improving compliance.

Haggerty, et al. [7] found finasteride to be more useful in larger prostate i.e., 30 gm and above and showed that pre-treatment of patients with BPH for 2-4 months before TURP is more useful in preventing post-operative episodes of hematuria for prostates more than 30 gm. In our study we have seen that Finasteride is effective in decreasing preoperative bleeding and post-operative episodes of hematuria in prostates of size 30 to 60gms when it is given only for two weeks before surgery.

Transurethral prostate resection results in bleeding. Mebust, et al. [5] reported a 3.9 % transfusion rate and 3.3 % clot retention rate. In Our Study we observed the transfusion rate in the placebo group to be 3/24 (12.5%) Vs 1/30 (3.3%) in finasteride group (**Figure - 4**).

The 1994 agency for health care policy and research clinical guidelines for the diagnosis and treatment of BPH estimate that 2.2% of patients require catheterization, evacuation or return to

operating room due to bleeding post operatively. In our study, 4 patients (16.6%) in control group had post operative hematuria out of which 2 cases (8.24%) had clot retention and one patient (4.1%) required clot evacuation in operation theatre under anaesthesia where as only one patient(3.33%) had hematuria in finasteride group and non had clot retention. Haggerty, et al. [7] showed from 36.87% incidence of post-operative hematuria in control group compared to 8.3 % in finasteride group

In addition to benefits of action on angiogenesis shown by decreasing bleeding preoperatively, decreasing requirement of blood transfusions, decreasing postoperative episodes of hematuria and clot retention, it was also observed that duration of surgery and its complications like – fluid absorption and TUR syndrome were also decreased thereby decreasing the morbidity and mortality. In our study the duration of surgery in finastride group was 63.03 min vs 74.91 in control group which was statistically significant.

Similar to previous histological studies; foley S.J., et al. [12], our study have also shown that in patients pre-treated with finasteride for 2 weeks, there was decrease in vascular density. There was also decrease in width and tortuosity of vessels.

Conclusions

Finasteride give daily for 2 weeks before transurethral prostate resection decreased bleeding preoperatively, thereby decreasing the requirement of blood transfusions, post operative episodes of hematuria and clot retention. By decreasing bleeding, it is also observed that duration of surgery is decreased, thereby decreasing the amount of irrigation fluid used, decreasing amount of it being absorbed and its complications. Histologically, present study has shown that there is decreased vascular density in the patients pre-treated with finasteride. However, further studied with greater number of patients are required to confirm the above beneficial effects of finasteride.

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