

# The Effect of Finasteride on Vascular Endothelial Growth Factor (VEGF) Expression in the Prostate Tissue and Bleeding Volume during Trans Urethral Resection of the Prostate (TURP)

Kartiko Sumartoyo<sup>1</sup>, Budiono<sup>2</sup>, Ketut Sudiana<sup>3</sup>, Soetojo<sup>1</sup>, Sunaryo Hardjowijoto<sup>1</sup>

<sup>1</sup>Department of Urology, Faculty of Medicine, Airlangga University, Surabaya 60115 Indonesia, <sup>2</sup>Department of Public Health, Faculty of Medicine, Airlangga University, Surabaya 60115 Indonesia, <sup>3</sup>Department of Anatomical Pathology, Faculty of Medicine, Airlangga University, Surabaya 60115 Indonesia

## Abstract

This study was evaluated the efficacy of Finasteride as a neoadjuvant therapy in reducing bleeding volume in patients with Benign Prostatic Hyperplasia (BPH) and urinary retention with prostate volume 30-50 mL who underwent Trans Urethral Resection of the Prostate (TURP). The study respondent consisted 26 patients with BPH and urinary retention who planned to undergo TURP. The study sample was randomly split into 2 treatment groups, 13 patients received Finasteride 5 mg once daily for 2 to 4 weeks before the operation and 13 others defined as control group. The therapy efficacy is evaluated by comparing the Haemoglobin pre-post operation difference, bleeding volume, bleeding volume per gram prostate tissue resected and the Vascular Endothelial Growth Factor (VEGF) expression within the prostate tissue. The treatment group indicated difference Haemoglobin between pre and post operation and average bleeding volume has less significant than the control group. The treatment group showed less amount of bleeding volume per gram of prostate tissue resected compare to control group. The treatment group also found significant lower VEGF expression within prostate tissue than the control group. This study demonstrated Neoadjuvant therapy with finasteride 1 x 5 mg for 2 to 4 weeks can reduce the VEGF expression in prostate tissue and reduce bleeding volume due to TURP.

**Keywords:** Benign Prostatic Hyperplasia (BPH), Bleeding Volume, Finasteride, Urinary Retention, Vascular Endothelial Growth Factor (VEGF)

## Introduction

Benign prostatic hyperplasia (BPH) is a benign tumor that is most commonly suffered by men. The risk of men suffering from symptomatic BPH in the age between 50 - 59 years old is 25% and increases to 43% in men over 60 year old of age<sup>1</sup>.

BPH is one of the causes of the lower urinary tract symptoms (LUTS) in elderly men, whereas in the group of men less than 30 year old benign prostate enlargement has not occurred so that LUTS complaints related to BPH have never been found<sup>2</sup>.

Bleeding is a major complication of TURP. During the 1970 - 1990 periods, TURP-related transfusion rates were reported at 20%<sup>3</sup>. The development of technology in high frequency generators and improvement of techniques in continuous-flow instruments, video-TURP significantly reduced the number of transfusions due to bleeding in TURP where in 2000 and after that the transfusion rate was less than 10%<sup>3</sup>. Heavy bleeding with an open venous sinus is a risk factor for TUR syndrome. Other risk factors related to the incidence of TUR syndrome are length of time of surgery, large prostate volume and a history of smoking. Approximately 2 - 5% of bleeding due to TURP requires transfusion, while the percentage of need for transfusion in open prostatectomy is higher, between 7-14%<sup>3</sup>. S. Madersbacher et al.<sup>4</sup> found an incidence of TURP-related transfusions of 8.6%.

**Corresponding author:**

**Soetojo**

E-mail: soetojo@fk.unair.ac.id

The mechanism of action of Finasteride in reducing or preventing bleeding is estimated through its role in reducing the influence of androgens, which with no DHT formation will result in barriers to various growth factors including Vascular endothelial growth factor (VEGF). VEGF is androgen dependent and has a very important role in the process of angiogenesis and regulation of prostate blood flow<sup>5, 6, 7</sup>. Reduced DHT will reduce VEGF expression so that the process of angiogenesis is inhibited and there is also a decrease in prostate blood flow and eventually the density of blood vessels in the prostate tissue will decrease<sup>8,9</sup>. With this circumstantial a study was conducted on the effect of Finasteride 5 mg once daily for 2-4 weeks before surgery on the amount of bleeding and VEGF expression in prostate tissue in BPH retention patients undergoing TURP compared without Finasteride as a control group.

### Methodology

This study is an experimental study with a post-test only controlled group design with variable measurements such as Hb before TURP, Hb after TURP, Irrigation Hb and weight of VEGF prostate resection. The respondents were the patients who were diagnosed with Benign Prostate Hyperplasia (BPH) with indications that the TUR Prostate was performed at RSUD Dr. Soetomo Surabaya. There were 26 patients involved in this study. The sample study was randomly and equally split into two groups. One group is treated daily with 5 mg of Finasteride. Meanwhile, others group did not treat with Finasteride. The respondents were under observation for 2 to 4 weeks after treatment until the TURP operation.

The study was conducted during April 2014 to September 2014 with 26 patients who met the inclusion criteria. 26 patients were obtained after selected among the 39 BPH patients with urinary retention who undergone TURP surgery at RSUD Dr. Soetomo Surabaya. There were 26 BPH patients with urinary retention who met the inclusion criteria were grouped randomly into two groups. In additions, 13 patients who received 5 mg of finasteride therapy once a day for 2-4 weeks before TURP surgery as a treatment group and another group of 13 patients did not receive therapy as a control group. All patients in the treatment group completed therapy

2-3 weeks. The average duration of taking medication was 15.6 days (14-20 days) before surgery. There are no patients who meet the criteria for drop out. Unpaired t-test is used for parametric data in this study. While, Mann Whitney test is used to test the different from non-parametric data. The data analysis is performed using SPSS V.21 with a significance level of 0.05.

### Result and Discussion

All data were tested for normality by the Shapiro-Wilk test and the result is shown in Table 1. The results of normality test showed that the variables of age, preoperative hemoglobin, initial systolic blood pressure, the amount of bleeding, the weight of the resected prostate tissue and the duration of operation were normally distributed with a significance value of more than 0.05. Thus, the statistical test used is parametric statistics. An independent t test is used to test the differences between finasteride and control groups. There were two types of independent t tests, the pooled or equal variance t tests were assumed and the t separated or equal variance test is not assumed. The selection of the type of independent t test is based on homogeneity between groups. Levene test is used for homogeneity test, if the Levene test significance value is above 0.05. The data of both homogeneous groups and the t test used are pooled or equal variance t test assumed. Whereas if the significance value of the Levene test is below 0.05, the data of the two groups is not homogeneous and the t test used is the t separated or equal variance test not assumed.

Whereas in prostate volume variables, a long history of urinary retention, pre-postoperative hemoglobin difference, Hb irrigation, volume of irrigation, bleeding per gram of resection tissue, mean systolic blood pressure and VEGF expression of prostate tissue were abnormally distributed with a significance value of less than 0.05. Since the data is not normally distributed, the statistical tests used are non-parametric statistics. Different tests for non-parametric data used Mann-Whitney test. For the variable residual history, history of hematuria, urine culture and postoperative hematuria is nominal data so that the Chi square test is used.

**Table 1. Data normality with the Shapiro-Wilk test**

	Kolmogorov-Smirnov			Shapiro-Wilk		
	Statistic	Df	Sig.	Statistic	Df	Sig.
Age	.146	26	.159	.933	26	.093
volume	.220	26	.002	.896	26	.013
Retention	.266	26	.000	.871	26	.004
Hb_pretest	.110	26	.200*	.953	26	.266
HB_posttest	.152	26	.128	.963	26	.458
difference_Hb	.224	26	.002	.873	26	.004
Hb_irrigation	.245	26	.000	.883	26	.007
Vol_irrigation	.251	26	.000	.876	26	.005
bleeding	.141	26	.196	.958	26	.351
Resection	.112	26	.200*	.944	26	.165
bleeding_gram	.234	26	.001	.895	26	.012
initial systole	.176	26	.038	.923	26	.053
final systole	.107	26	.200*	.961	26	.405
flat systole	.130	26	.200*	.920	26	.046
operation duration	.153	26	.122	.959	26	.378
VEGF	.196	26	.011	.898	26	.014

Ten patients in the treatment group and 9 patients in the control group were examined for PSA serum. Patients who were not tested for serum PSA due to age > 70 year old and no suspicion of malignancy on physical examination were found. Table 2 shows the mean serum PSA value in the treatment group was 6.53 ng/mL while the control group was 10.14 ng/mL. Six of the 10 patients

in the treatment group were treated with prostate biopsy with the guide trans rectal ultrasonography (TRUS), in the biopsy control group performed in 6 of 9 patients who were examined for serum PSA. Biopsies in these 12 patients were carried out between 1-2 months before surgery. The results of biopsy pathology examination in both groups did not show any prostate malignancy.

**Table 2. Description of PSA examination, serum PSA values and prostate biopsy in both groups**

Variable	Finasteride, n: 13				Control, n: 13			
	n	Min	Max	Average ± SD	n	Min	Max	Average ± SD
PSA (ng/mL)	10	1.71	11.7	6.53 ± 0.85	9	1.99	23.79	10.14 ± 0.87
Biopsy	6	-	-	-	6	-	-	-

Table 3 showed the information of residual cases, history of hematuria and urine culture for finasteride group and control group. In the finasteride group there were 2 cases of residual BPH while in the control group only 1 case of residual BPH. TURP's operating history in the three residual cases is more than 7 years. There

were 4 treatment group patients who had a history of hematuria before surgery and 3 patients in the control group. All patients were examined for urine culture, there were significant amounts of germs in urine in 6 treatment group patients and 7 in the control group, the rest were patients with sterile urine culture. The most

common type of germs found is Klebsiella pneumonia, in 4 (30.7%) patients. The differences in the three variables in the two study groups were not statistically significant ( $p > 0.05$ ).

**Table 3. Residual cases, history of hematuria and urine culture in both groups**

	Finasteride, n: 13	Control, n: 13	X <sup>2</sup>
Riw. Residual (+/-)	2	1	0.539
Riw. Hematuria (+/-)	4	3	0.658
Urine culture (+) (cfu/mL)	6	7	0.695

### Discussion

Finasteride is a 5 $\alpha$ -reductase type 2 enzyme inhibitor that converted testosterone to 5 $\alpha$ -dihydrotestosterone (DHT). With a single dose of 5 mg Finasteride will rapidly reduce serum DHT levels, consequently blood flow and vascular endothelial growth factor (VEGF) expression will decrease and inhibit the process of angiogenesis, so that the density of the vascular tissue or microvessel density (MVD) will decrease<sup>5,8, 9, 10</sup>. Through this mechanism Finasteride can work to reduce hematuria due to BPH and bleeding in prostate surgery<sup>3</sup>.

The dose of finasteride given was finasteride 5 mg once daily for 14-20 days (2 - 3 weeks) before TURP surgery. One day before surgery the patient will be examined for serum hemoglobin and repeated after surgery while still in the recovery room. Blood mixed with irrigation fluid in containers was taken for inspection of irrigation Hb after the operation was completed. The volume of irrigation, blood pressure during surgery, the incidence of hematuria and postoperative retention clots in the room were recorded. Prostate scraping tissue was sent to the Anatomy Pathology section to find out histopathology and for VEGF expression examination.

Neoadjuvant treatment effect by administering finasteride 5 mg once daily for 14-20 days (2 to 3 weeks) before surgery in this study was found to have significantly lower pre-postoperative Hb (g/dL) than the control group ( $p < 0.001$ ) with a median of 0.7 and 1.3 respectively. Hb irrigation (g/dL) was significantly lower

compared to the control group ( $p < 0.001$ ) with a median of 0.2 and 0.3 respectively. The mean of bleeding (mL) of treatment group was significantly smaller compared to the control group which are  $260.65 \pm 94.86$  and  $523, 39 \pm 156.49$  with  $p = 0.014$ . The amount of bleeding per 1 gram of tissue (mL/g) resected of treatment group was significantly smaller than the control group ( $p < 0.001$ ) with a median of 9.53 and 21.25 respectively. The presence of VEGF expression in prostate tissue (per 15,625  $\mu\text{m}^2$ ) in treatment group was significantly lower compared to the control group ( $p < 0,0 001$ ) with a median of 1.9 and 6.5 respectively.

The amount of bleeding in TURP is estimation because blood coming out of the prostate tissue mixes with irrigation fluid so that the exact amount of bleeding cannot be measured precisely. Estimation of the amount of bleeding in the study was obtained by calculating a formula involving variable Hb irrigation, serum Hb preoperative and the volume of irrigation used during surgery. The formula for estimating the amount of bleeding (mL) equal to the multiplication of volume of irrigation (mL) with the fraction of Hb irrigation (g /dL) and the preoperative blood hemoglobin (g /dL)<sup>11</sup>.

In this study, the range of Hb irrigation was 0.1 - 0.3 gr /dL in the finasteride group and 0.2 - 0.6 gr/dL in the control group with statistically significantly different. Irrigation HBs obtained from blood samples mixed with irrigation in containers, factors for fluid homogenization and sensitivity of examination instruments affect differences in results. Not all other researchers have included the results of irrigation Hb examination. The volume of irrigation fluid used will affect the final result of the amount of bleeding but not all other studies include the amount of irrigation fluid used.

The mean number of hemorrhages of the finasteride group in this study was  $260.65 \pm 94.86$  mL, significantly different compared to controls. Bleeding parameters in Donohue's study differed from this study and other studies, in which Donohue defined bleeding with the loss of gram Hemoglobin in irrigation fluid. However, different tests with the control group had the same results as this study, which was the amount of bleeding was significantly different compared to the control group.

Bleeding per gram of resected prostate tissue is assessed as a more appropriate criterion for assessing and comparing the amount of bleeding that occurs. In this

study, bleeding per gram of resection was significantly different compared to controls, median 9.53 (5.03 - 11.39) vs. 21.25 (9.72 - 28.20), mean  $8.77 \pm 2.17$  vs  $19.67 \pm 5.82$ ;  $p < 0.001$ .

Besides, the study also found the VEGF expression of finasteride group was lower than the control group with median 1.9 (1 - 3.2) vs 6.5 (3.9 - 8.7) mean  $1.81 \pm 0.7$  vs  $6.34 \pm 1.27$  per area of  $15,625\mu\text{m}^2$ , this difference was statistically significant ( $p < 0,0001$ ). VEGF-index is obtained from the number of cytoplasmic cells that react positively multiplied by the intensity score of the positive. This index is measured on the grounds that VEGF staining is difficult to uniform in each cell.

In this study VEGF expression was the mean of the positive number of VEGF expression of cytoplasmic cells of prostate tissue seen with a 100x, 400x magnification microscope and counted in graticule in each area of  $15,625\mu\text{m}^2$  in 10 random locations on each slide. However, the difference in measurements did not influence the results of the study because the same results were obtained where the VEGF expression of the finasteride group was lower than the control group.

The results and several other studies above were in agreement with the theory that VEGF is androgen-dependent, where the administration of finasteride will inhibit the formation of DHT, an androgen that is stronger than testosterone, which will reduce VEGF production. Reduction in VEGF will inhibit the process of angiogenesis so that blood flow and density of blood vessel tissue (microvessel density / MVD) in prostate tissue will be reduced<sup>2, 5, 6, 10</sup>.

### Conclusion

In conclusions, this study indicated a significant decrease in Hb difference before and after TURP, significant decrease in the amount of bleeding, decrease in the amount of bleeding per gram of prostate resection tissue and decrease in VEGF expression in prostate tissue treatment with neoadjuvant therapy with 1 x 5 mg finasteride for 2-3 weeks before surgery in BPH retention patients.

**Ethical Clearance:** Taken from the committee

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**Conflict of Interest:** Nil

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