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Role of Dutasteride in Reducing the Complications of Transurethral Resection of Prostate

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Abstract: ***Introduction: The development of prostate is dependent on the dihydrotestosterone. Testosterone conversion into dihydrotestosterone(DHT) is inhibited by the 5alpha reductase inhibitors like Finasteride and Dutasteride. Several studies showed that finasteride prevents recurrent gross hematuria in BPH[(1) (2)]. Aim and Objective: 1. To determine whether preoperative treatment with Dutasteride decreases surgical blood loss in patients who undergo transurethral resection of the prostate for benign prostatic hyperplasia with prostate >30cc volume with acute urinary retention. 2. To assess the postoperative complication like clot retention, blood transfusion, failure to void after the catheter removal and the urinary tract infection in postoperative period. Materials and methods: The study was conducted between January 2016 and December 2016 in Chengalpattu medical college in the department of Urology. We studied 150 patients randomized into three groups of 50 each to undergo TURP. Group 1-receiving placebo for two weeks preoperatively and two weeks postoperatively. Group 2-receiving Tab.Dutasteride 0.5mg BD, for 2weeks preoperatively and two weeks postoperatively. Group 3-receiving Tab. Finasteride 5mg BD,two weeks preoperatively and 2weeks postoperatively. All clinical , blood, urine, imaging work up were done. The total blood loss during transurethral resection of prostate, incidence of clot retention, requirement of blood transfusion, failure to void after the cathter removal and the incidence of urinary tract infection were studied. Results: Micro Vascular Density was significantly reduced in the suburethral prostatic epithelium by preoperative Dutasteride and Finasteride group when compared with the placebo group. Conclusion: The present study shows two weeks preoperative Dutasteride 0.5 mg BD treatment in BPH will reduce the microvessel density in suburethral portion of prostatic urothelium. Dutasteride cause clot retention and blood transfusion in lesser number of post TURP patients. Preoperative Dutastride will reduce the TURP complication in BPH as Finasteride.***

1. Introduction

As the age increases prostate continue to enlarge in size under the influence of dihydrotestosterone and testosterone. Enlargement of the prostate can lead to bladder outlet obstruction and produce lower urinary tract symptoms(LUTS). For BPH managements are, watchful waiting, medical management with alpha blockers or 5 alpha reductase inhibitors[(3)] and various minimally invasive and endoscopic procedures like TURP, Transurethral needle ablation of prostate (TUNA), transurethral ultrasound–guided laser-induced prostatectomy (TULIP), transurethral vaporization of the prostate (TUVP), transurethral incision of prostate (TUIP) and open prostatectomy.

Among the endoscopic procedure TURP is the "gold standard" treatment and most commonly performed surgical procedure for benign prostatic hyperplasia. Bleeding is one of the most important intra operative and post operative complication in TURP. Post TURP bleeding can leads onto clot retention, urinary tract infection and increased the duration of hospital stay.

Hematuria will occur in BPH depends on the microvessel density in the prostatic urothelium. Some research studies suggest that the androgen controlled vascular endothelial growth factor[(4)] is suppressed by finasteride and leads on to decreased angiogenesis. The finasteride inhibits only type2 5alpha reductase and the dutasteride inhibits both type1and type2 isoenzymes.

2. Aim and Objective

1) To determine whether preoperative treatment with Dutasteridedecreases surgical blood loss in patients who undergo TURP.
2) To assess the postoperative complication like clot retention, blood transfusion, failure to void after the catheter removal and the urinary tract infection in postoperative period.

3. Materials and Methods

Period of study:
The study is done between January 2016 and December 2016

Type:
This is a prospective randomised control trail study

Place:
The study is conducted in the Department of Urology, Chengalpattu Medical College, Chengalpattu.

Inclusion criteria
Men with Benign prostate enlargement and prostate volume more than 30cc with acute urinary retention who are undergoing TURP.

Exclusion criteria:
- H/O prostatic surgery in the past.
- Prostatic disease other than BPH
- Who had 5Alpha reductase in the past 12 months
- Requirement of Aspirin,NSAIDS during the restricted periods,
- Bleeding disorder,
- Liver diseases

Method of Study
Patients were randomized into three groups of 50 each to undergo TURP.

Group 1-receiving placebo for two weeks preoperatively and two weeks postoperatively.
Group 2-receiving Tab.Dutasteride 0.5mg BD, for 2weeks preoperatively and two weeks postoperatively
Group 3-receiving Tab.Finasteride 5mg BD,two weeks preoperatively and 2 weeks postoperatively.

Monopolar TURP was done with single stem TUR loop and Glycine as a irrigant. The settings employed was 110W cutting and 80W coagulation for the resection. The setup of instruments for TURP resection, includes 24 – Fr. Karl Storz non-continuous flow sheath with blind and visual obturator, resectoscope, monopolar loop, high frequency cord, 30 degree Karl Storz telescope and unipolar diathermy.

4. Preoperative Workup

Complete clinical history was taken and through clinical examination was done for all the patients. Complete urine analysis, Urine culture and sensitivity were done and patients with positive cultures were treated with appropriate antibiotics. Complete haemogram and renal function tests with electrolytes, coagulation parameters, Blood grouping and typing were done in preoperative period.

X-ray KUBU and Ultra sonogram of KUB region was done for all the patients. The patients were randomly divided into 3groups,which each group consists of 50 patients. Those patients with H/O prostatic surgery in the past &prostatic disease other than BPH(25 in No)**,w**ho had 5Alpha reductase in the past 12 months(29 in No),requirement of Aspirin, NSAIDS during the restricted periods(12 in NO),bleeding disorder(2 in No),liver diseases(7 in No) were excluded(Total 55 in No).

For the Group 1 patients started placebo ,group 2 patients started Tab.Dutasteride 0.5mg BD,group3 patients started Tab.Finasteride 5mg BD two weeks preoperatively and the same treatment was continued postoperatively for 2weeks.The primary efficacy outcome is total blood loss during transurethral resection of prostate which was done under spinal anaesthesia. Secondary efficacy outcomes are the incidence of clot retention, requirement of blood transfusion, failure to void after the catheter removal and the incidence of urinary tract infection. All the patients were monitored for 2weeks in the preoperative period and 4 weeks in the postoperative period.

5. Intraoperative Work Up

Trans Urethral Resection of Prostate was done by the experienced urologists. The resection time of TURP was calculated from the period of initiation of resection to the removal of resectoscope sheath. The 3 way Foley catheter was inserted at the end of the procedure and irrigation was started and continued postoperatively. For all patients, any intraoperative complications and the resected prostatic tissue weight in gm were noted. The resected prostatic chips from the prostatic hyperplasia and the prostatic urethra were send separately for microvessel density(MVD) estimation and the histopathological examination.

6. Postoperative Work Up

Postoperative haemoglobin and packed cell volume(PCV) were done on the first postoperative day after the continuous irrigation was stopped. Preoperative Hb/PCV were compared with the postoperative Hb/PCV for the blood loss in all the three groups. Prostatic chips from the prostatic hyperplasia and the prostatic urothelium were fixed in 10% formalin and stored at 4 degree Celsius and incubated with CD34 monoclonal immunohistochemical antibody before staining with haematoxylin & eosin. The most microvessels within an area of 0.754mm2 was counted by light microscopy with 200 times magnification .

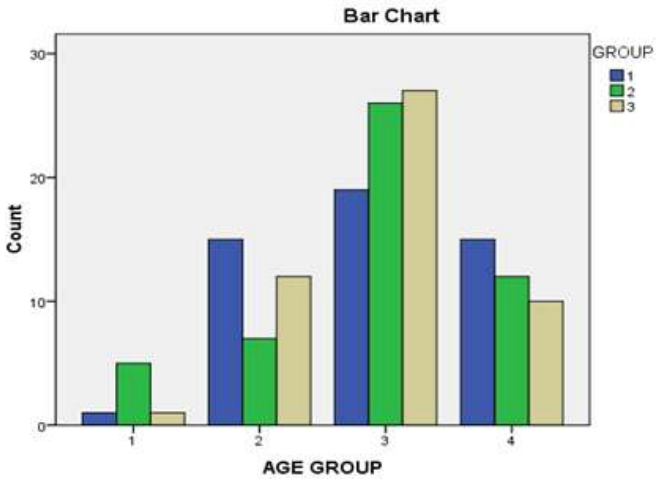
Postoperatively all patients were monitored for hematuria, clot retention, blood transfusion requirement, altered sensorium, urinary tract infection and any change in vital parameters .Bladder Irrigation continued till the next morning as a protocol for all patients and the Foley Catheter was removed on fourth postoperative day and discharged on the same day. They are compared with postoperative complications like clot retention, blood transfusion requirement, failure to void after the catheter removal and the urinary tract infection. Patients were reviewed with biopsy report after a week and all the three group patients were followed up for 4 weeks in postoperative period for the TURP complication and the drug side effects.

STATISTICAL ANALYSIS
Descriptive statistics were used to illustrate the study population. The statistical significance of these correlations was assessed using a two sided p value. A p-value of <0.05 was considered as statistically significant. The Chi Square test and ANOVA test were used to assess the statistical significance. Multiple comparison test and paired T test are also used for the comparison of various descriptive within the groups.

7. Results

Total of 150 patients were completed the study and the 3 randomized groups were compared.
Group 1 received the placebo 2weeks preoperatively and 2 weeks postoperatively,
Group 2 received the Tab.Dutasteride 0.5mg BD 2 weeks preoperatively and 2 weeks postoperatively,
Group 3 received the Tab.Finasteride 5 mg BD 2 weeks preoperatively and 2 weeks postoperatively.

Demographic data of the groups are given in the bar chart.



Group 1: 40-50yrs, Group 2:>50-60 yrs, Group 3:>60-70yrs, Group 4: >70yrs

In digital rectal examination, 61.3% patients had grade 2 and 38.7% had grade1 benign prostate enlargement. All the 3 groups had approximately equal distribution of grade 1&2 benign prostate enlargement without significant p value. Within the groups, smallest prostate volume is 30.09ml and the largest prostate volume is 65.42ml. When the prostate volume is compared in between the 3 groups,the mean difference was not significant.

The mean prostate volume in group1,2 and 3 were 40.14ml,43.41ml,42.66ml respectively. Within the groups, smallest prostate volume is 30.09ml and the largest prostate volume is 65.42ml. When the prostate volume was compared in between the all 3 groups, the mean difference was not significant.

When the multiple comparisions were made in between the 3 groups, there was no significant difference in the mean hemoglobin, PCV, transurethral resection time of prostate.

TURP TISSUE WEIGHT (gm)

(I) GROUP	(J) GROUP	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval Lower Bound	95% Confidence Interval Upper Bound
1 MEAN 24.8	2	-5.800*	1.182	.000	-8.14	-3.46
	3	-5.640*	1.182	.000	-7.98	-3.30
2 MEAN 30.6	1	5.800*	1.182	.000	3.46	8.14
	3	.160	1.182	.893	-2.18	2.50
3 MEAN 30.44	1	5.640*	1.182	.000	3.30	7.98
	2	-.160	1.182	.893	-2.50	2.18

The mean transurethral resected prostatic weight in group 1 is 24.8gm,group 2 is 30.6gm and the group 3 is 30.4 gm. The maximum resected prostatic tissue weight was 42 gm in group 3.In the multiple comparisions, significant mean difference was present when the placebo group is compared with the Dutasteride and the Finasteride group.It indicates that large amount of prostatic tissue can be resected when the 5ARI is started preoperatively.

MVD-SUBURETHRAL PROSTATIC TISSUE

(I) GROUP	(J) GROUP	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval Lower Bound	95% Confidence Interval Upper Bound
1 MEAN 23.315	2	7.7548000*	.4873811	.000	6.791621	8.717979
	3	9.2662000*	.4873811	.000	8.303021	10.229379
2 MEAN 15.561	1	-7.7548000*	.4873811	.000	-8.717979	-6.791621
	3	1.5114000*	.4873811	.002	.548221	2.474579
3 MEAN 14.049	1	-9.2662000*	.4873811	.000	-10.229379	-8.303021
	2	-1.5114000*	.4873811	.002	-2.474579	-.548221

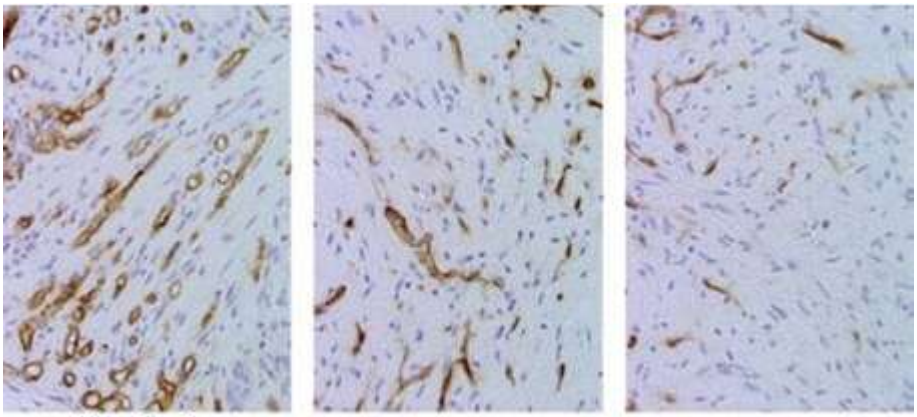
Micro Vessel Density (MVD) –Suburethral Prostatic Tissue

The mean micro vessel density of suburethral prostatic tissue from Group 1, Group 2 and Group 3 were 23.3158,15.561 and 14.0496 respectively. When multiple comparisions were made between the placebo group and 5ARI groups significant mean difference was present. It indicated that MVD was significantly reduced in the suburethral prostatic epithelium by preoperative Dutasteride and Finasteride group when compared with the placebo group.

MVD-HYPERPLASTIC PROSTATICTISSUE

(I) GROUP	(J) GROUP	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
1 MEAN 16.089	2	1.4426000*	.1848879	.000	1.077218	1.807982
	3	3.3606000*	.1848879	.000	2.995218	3.725982
2 MEAN 14.646	1	-1.4426000*	.1848879	.000	-1.807982	-1.077218
	3	1.9180000*	.1848879	.000	1.552618	2.283382
3 MEAN 12.728	1	-3.3606000*	.1848879	.000	-3.725982	-2.995218
	2	-1.9180000*	.1848879	.000	-2.283382	-1.552618

The mean micro vessel density of hyperplastic prostatic tissue from Group 1, Group 2 and Group 3 were 16.089,14.646 and 12.728 respectively. When multiple comparisons were made between the placebo group and Dutasteride, Finasteride groups, significant mean difference was present.



Placebo Group Dutasteride Group Finasteride Group

Micro vessel density CD 34 IHC- TURP PROSTATIC TISSUE

POST OPERATIVE HB - Multiple Comparisons

(I) GROUP	(J) GROUP	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
1 MEAN 9.45	2	-.1660000	.0994814	.097	-.362598	.030598
	3	-.1720000	.0994814	.086	-.368598	.024598
2 MEAN 9.61	1	.1660000	.0994814	.097	-.030598	.362598
	3	-.0060000	.0994814	.952	-.202598	.190598
3 MEAN 9.62	1	.1720000	.0994814	.086	-.024598	.368598
	2	.0060000	.0994814	.952	-.190598	.202598

The mean postoperative haemoglobin from Group 1,Group 2 and Group 3 is 9.452, 9.618 and 9.624 respectively. When multiple comparisions were made between the placebo group and Dutasteride ,Finasteride groups, there was no significant mean difference in the post operative haemoglobin.

CLOT RETENTION- GROUP Crosstab

			GROUP			
			1	2	3	Total
CLOT RET	0	Count	37	43	44	124
		% within GROUP	74.0%	86.0%	88.0%	82.7%
		% of Total	24.7%	28.7%	29.3%	82.7%
	1	Count	13	7	6	26
		% within GROUP	26.0%	14.0%	12.0%	17.3%
		% of Total	8.7%	4.7%	4.0%	17.3%
	Total	Count	50	50	50	150
		% within GROUP	100.0%	100.0%	100.0%	100.0%
		% of Total	33.3%	33.3%	33.3%	100.0%

Postoperative clot retention is occur 26%,14%,12% in Group1,2,3 respectively without significant p value.

TRANSFUSION GROUP CROSS TAB

			GROUP			
			1	2	3	Total
Transfusion	0	Count	42	45	47	134
		% within GROUP	84.0%	90.0%	94.0%	89.3%
		% of Total	28.0%	30.0%	31.3%	89.3%
	1	Count	8	5	3	16
		% within GROUP	16.0%	10.0%	6.0%	10.7%
		% of Total	5.3%	3.3%	2.0%	10.7%
	Total	Count	50	50	50	150
		% within GROUP	100.0%	100.0%	100.0%	100.0%
		% of Total	33.3%	33.3%	33.3%	100.0%

Postoperative blood Transfusion was given 16%,10%,6% in Group 1,2,3 respectively without significant p value.

Failure to Void * Group- Crosstab

			GROUP			
			1	2	3	Total
FAILURE TO VOID	0	Count	45	47	48	140
		% within GROUP	90.0%	94.0%	96.0%	93.3%
		% of Total	30.0%	31.3%	32.0%	93.3%
	1	Count	5	3	2	10
		% within GROUP	10.0%	6.0%	4.0%	6.7%
		% of Total	3.3%	2.0%	1.3%	6.7%
	Total	Count	50	50	50	150
		% within GROUP	100.0%	100.0%	100.0%	100.0%
		% of Total	33.3%	33.3%	33.3%	100.0%

Postoperative failure to void was 10%,6%,4% in Group 1,2,3 respectively without significant p value.

UTI Group Cross Tab

			GROUP			
			1	2	3	Total
UTI	0	Count	42	44	46	132
		% within GROUP	84.0%	88.0%	92.0%	88.0%
		% of Total	28.0%	29.3%	30.7%	88.0%
	1	Count	8	6	4	18
		% within GROUP	16.0%	12.0%	8.0%	12.0%
		% of Total	5.3%	4.0%	2.7%	12.0%
	Total	Count	50	50	50	150
		% within GROUP	100.0%	100.0%	100.0%	100.0%
		% of Total	33.3%	33.3%	33.3%	100.0%

Postoperative Urinary Retention was 16%,12% and 8% in group 1,2 and 3 respectively, without statistically significant difference .

8. Discussion

The primary objective of this randomised controlled study was to assess whether preoperative treatment with Dutasteride reduces the bleeding complication in TURP for BPH.

The mean TURP tissue weight from the placebo, Dutasteride and Finasteride group was 24.8gm,30.6gm,30.4gm respectively. When the placebo group was compared with other groups regarding TURP tissue weight significant mean difference was present. Compared to the Dutasteride, Finasteride group, in placebo group the mean resected prostatic tissue weight was less (30.6gm,30.4gm Vs 24.8 gm). It indicates that by giving preoperative 5alpha reductase inhibitors, the resection of prostatic tissue weight in TURP can be increased.

The microvessel density(MVD) of suburethral portion of prostatic tissue was higher in placebo group(23.31) than in Dutasteride(15.56) and Finasteride group(14.04).David A A Hochberg et al showed MVD in Finasteride and placebo group was 20.2+5.3 Vs14.0+2.8 which was similar to this study.

The microvessel density (MVD) of hyperplastic portion of prostatic tissue in placebo group(16.08) was slightly higher than Dutasteride (14.64) and Finasteride group(12.72) in this study.

Even though significant blood loss was present in all 3 groups due to TURP, when the preoperative and postoperative Hb/PCV were compared in between the groups and there was no statistically significant difference. The most practical way to quantify blood loss during TURP is by measuring the irrigating fluid. Although Hb levels are only 5–10% of that found in whole blood, precision is ensured by using a highly sensitive photometer. In this study blood loss was calculated by comparing the preoperative and postoperative haemoglobin/PCV.

Postoperative clot retention from the group 1,2 and 3 was 26%,14%,12% respectively. Postoperative blood transfusion was required in 16%, 10%, 6% in groups respectively. R.Shanmugasundaram, Nitin S.Kekre et all showed clot retention occurred in 6-11% and 1-3% requirement of blood transfusion which was less than our study.

Failure to void was occurred 10%,6%,4% in group 1,2 and group 3 respectively.Postoperative urinary tract infection was occurred in 16%,12% and 8% in placepo,dutasteride and finasteride group respectively. The above mentioned complications were occurred in higher number in placebo group but there was no statistically significant differences among groups. R.Shanmugasundaram, Nitin S.Kekre et al showed AUR in 11-17% and UTI in 20-30% statistically without significant difference.

5 Alpha reductase inhibitor like Finasteride have been commonly used in the perioperative period to reduce the bleeding complication in TURP. It shrink the prostate size by inhibiting the VEGF and decreasing the microvessel density. Sandfeldt et al showed that Finasteride didn"t produce any difference in blood loss in TURP. Like our study,David A, A Hochberg et al showed that Finasteride decreases suburethral prostatic microvessel density in BPH.

R.Shanmugasundaram, Nitin S.Kekre et al showed that preoperative Dutasteride did not reduce significantly bleeding complication in TURP eventhough it reduced the intraprostatic concentration of DHT[(4)]. Pastore AL,Mariani et al showed six weeks preoperative Dutasteride treatment reduced the surgical bleeding in TURP. J.A.Arratia-Maqueo et al showed that no statistically significant difference were seen in bleeding complication in TURP by preoperative Dutasteride. Je Hyeong Woo et al showed that preoperative 2 weeks short term Dutasteride decreases suburethral prostatic microvessel density in BPH and reduce the bleeding complication in TURP.

This randomised study showed that 2weeks preoperative and 2 weeks postoperative Dutasteride 0.5mg BD significantly reduced the microvessel density in suburethral portion prostatic tissue in BPH patients and reduce the TURP bleeding complications like clot retention, blood transfusion requirement almost similar by the Finasteride.

9. Conclusion

The present study shows two weeks preoperative Dutasteride 0.5 mg BD treatment in BPH will reduce the microvessel density in suburethral portion of prostatic urothelium. Preoperative Dutasteride will be helpful for the larger amount of prostatic tissue resection in lesser time. Even though the preoperative Haemoglobin and PCV were not significantly different from postoperative Hb/PCV, Dutasteride cause clot retention and blood transfusion in lesser number of post TURP patients. When the Dutasteride is compared with Finasteride in reducing the TURP complication, it has efficacy almost similar to the Finasteride. Preoperative Dutasteride will reduce the TURP complication in BPH as Finasteride but needs further large randomized trials to confirm the efficacy with better statistically significant difference.

References

[1] M. T. Sutton, M. Yingling, A. Vyas et al., ―Finasteride targets prostate vascularity by inducing apoptosis and inhibiting cell adhesion of benign and malignant prostate cells,‖ *Prostate*, vol. 66, no. 11, pp. 1194–1202, 2006
[2] Boccon-Gibod L, Valton M, Ibrahim H, Boccon-Gibod L, Comenducci A. [Effect of dutasteride on reduction of intraoperative bleeding related to transurethral resection of the prostate]. *Prog Urol* 2005; 15: 1085–9
[3] J. D. McConnell, J. D. Wilson, F.W. George, J. Geller, F. Pappas, and E. Stoner, ―Finasteride, an inhibitor of 5 -reductase, suppresses prostatic dihydrotestosterone in men with benign prostatic hyperplasia,‖ *Journal of Clinical Endocrinology and Metabolism*, vol. 74, no. 3, pp. 505–508, 1992.
[4] S.H¨aggstr¨om, N. Tørring, K.Møller et al., ―Effects of finasteride on vascular endothelial growth factor—a placebo-controlled randomized study in BPH patients,‖ *Scandinavian Journal of Urology and Nephrology*, vol. 36, no.3, pp. 182–187, 2002
[5] R.Shanmugasundaram,J.Chandra Singh,Nitin S.Kekre et al.Does dutasteride reduce perioperative blood loss after TURP? BJU,2007;99;587