Is Transurethral Resection of Prostate Made Safer by Preoperative Dutasteride Therapy? A Randomized Controlled Trial

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ABSTRACT

Introduction: Bleeding and hyponatremia are important complications of transurethral resection of the prostate (TURP). 5-alpha reductase inhibitors (5-ARI) are reported to reduce angiogenesis and bleeding in benign prostatic hyperplasia (BPH). We therefore performed a double blinded randomized clinical trial to assess the role of preoperative Dutasteride therapy before TURP.

Material and Methods: All patients undergoing TURP in JIPMER Urology Dept. during September 2006 - December 2010 were randomized into two groups – one receiving Dutasteride 0.5mg daily for 2 weeks and the other a placebo. The surgeons and the patients were blinded to the nature of preoperative therapy. Blood hemoglobin, hematocrit and serum sodium levels were estimated a day before and after surgery. The post-operative changes in hemoglobin, hematocrit and sodium concentrations were assessed in both groups. Blood transfusion requirements, ease of surgery and operating times were also assessed.

Results: 104 patients were randomly distributed to receive either Dutasteride (n=52) or placebo (n=52). There was no significant difference between hemoglobin difference (P value- 0.41), hematocrit difference (P value- 0.98), sodium levels (P value- 0.48), amount of resected tissue (P value- 0.67), operating times (P value- 0.24), surgeon's ease score (P value- 0.33) and blood transfusion requirements between the two groups. There were no side-effects attributable to Dutasteride.

Conclusion: There were no significant reductions in blood loss or hyponatremia during TURP with Dutasteride compared with placebo. Though the preoperative use of Dutasteride seems logical and rational, this study shows that there is no real benefit from the use of a short course Dutasteride before performing TURP.

Keywords: Resection of Prostate, Preoperative Dutasteride Therapy

INTRODUCTION

TURP still remains the gold standard for surgical treatment of BPH, despite the development of various minimally invasive therapies. However, TURP is associated with bleeding and hyponatremia during and after surgery, sometimes leading to serious adverse events, particularly in those with larger prostates.[1] Hematuria and clot retention after TURP might increase the need for blood transfusion, prolong the hospital stay and even necessitate re-operation.[2]

Based on the observation that 5-alpha reductase inhibitors(5-ARIs) like Finasteride reduce angiogenesis and bleeding due to BPH,[3–7] pre-operative Finasteride therapy before TURP has been studied and shown to have some benefits in reducing these complications.[1,3,8] The exact mechanism by which blood loss is reduced by 5-ARIs is unknown, but seems to involve a decrease in microvascular density (MVD) within the prostate, leading to decreased prostatic blood flow.[9] 5ARIs such as Finasteride and Dutasteride are known to suppress dihydrotestosterone (DHT) levels and thereby prostate growth, and also suppress the androgen dependent vascular endothelial growth factor (VEGF), leading to decreased angiogenesis.

While Finasteride inhibits only the type II 5AR isoenzyme,[10] the dual 5ARI, Dutasteride, inhibits both type I and type II isoenzymes. Treatment with Dutasteride results in suppression of serum DHT in >85% of men, achieving a 90-95% reduction within 4 weeks, whereas Finasteride suppresses serum DHT by 70%, with only 49% of treated men achieving this reduction.[11,12] Therefore, if Finasteride decreases surgical blood loss, it is logical to expect similar, or even more benefit with Dutasteride. But there are anecdotal reports on the benefits of preoperative use of Dutasteride. We therefore, performed a double blinded randomized clinical trial to assess the role of preoperative Dutasteride therapy on TURP complications.

Objectives of the study were to study the effect of pre-operative Dutasteride therapy on bleeding associated with TURP and to study the effect of pre-operative Dutasteride therapy on electrolyte changes associated with TURP.

MATERIAL AND METHODS

In this double-blind, randomized placebo-controlled study, approved by the institutional review board and ethical committee, we enrolled 104 consenting men, who were scheduled for TURP in a period that allowed 2 weeks of preoperative treatment with study medication in Urology Department, JIPMER during September 2006 to December 2010. Exclusion criteria included a history or evidence of prostatic malignancy, previous prostatic surgery, treatment with any 5ARIs within12 months, presence of medical conditions such as liver disease, bleeding disorders or patients on treatment with aspirin and men with history of allergy to Dutasteride. The sample size was calculated using SPSS software keeping the power at 80%, based on the study by Donohue et al.[24] These men were randomized into two

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groups (Study group, n=52 and control group, n==52) by block randomization– one receiving oral Dutasteride 0.5mg once daily for 2 weeks and the other receiving placebo for same period of time. The surgeons and the patients were blinded to the nature of preoperative therapy. Serum hemoglobin, hematocrit and sodium levels were estimated a day before and after surgery. Surgery was either performed or supervised by experienced surgeons. Spinal anesthesia was used in all the patients. Catheter traction was applied, if clinically imperative. Weight of the resected prostatic tissue was recorded and subjected for histopathological examination. The operating time was recorded. The ease of surgery was assessed by visual analog scale ranging from 1 to 10. Blood transfusion requirements were noted.

STATISTICAL ANALYSIS

Results were analyzed using Student t test, with $P < 0.05$ considered to indicate statistical significance.

RESULTS

All 104 randomized patients underwent TURP. There was no difference between the treatment groups in baseline characteristics, ie age, prostate volume, preoperative- hemoglobin, hematocrit and serum sodium levels.(Table.1) Dutasteride was well tolerated.

After TURP, a mean decrease of 1.46gms in Hb, 2% in hematocrit and 4.92mEq in sodium concentrations were observed in Dutasteride group. A mean decrease of 1.29gms in Hb, 2.01% in hematocrit and 4.36mEq in sodium concentrations were observed in control group. In Dutasteride group, the mean weight of resectate was 28.8gms, mean operating time was 62.3minutes and mean VAS score was 2.65. In control group, the mean weight of resectate was 28.1gms, mean operating time was 64.8minutes and mean VAS score was 2.86. Statistically, there was no significant difference between the groups for these variables.(Table.2)

Clot retention occurred in 1 patient in the study group, in the immediate post op period, which required clot evacuation. Blood transfusion was required for 2 patients in each group. In Dutasteride group, histopathological examination of 2 of the resected specimen was suggestive of acute prostatitis and one was suggestive of chromic prostatitis in addition to benign hyperplasia. In control group, 4 of the specimen were reported to have features of chronic prostatitis in addition to benign hyperplasia. None of the resected specimen was reported to have malignancy.

DISCUSSION

The primary objective of this randomized, double-blind, placebo-controlled study was to assess whether pretreatment with Dutasteride reduces the blood loss during TURP.

The rationale for the view that 5ARIs reduce blood loss during TURP is that these drugs reduce MVD and prostate size by inhibiting conversion of testosterone to dihydrotestosterone, thereby decreasing the activity of androgen dependent growth factors like VEGF, FGF and EGF.[13-16] It is also supported by the studies showing that Finasteride, a 5ARI reduced gross haematuria secondary to prostatic bleeding.[3–7] As a logical extension of this fact, a few studies have been reported on the effect of 5ARIs on blood loss associated with TURP. However, the results of these studies have been less consistent.[17-23]

Pretreatment with Finasteride for duration of 2 weeks[24] and 8 to 10 weeks[18] had been shown to reduce bleeding during TURP for larger glands. However, Sandfeldt et al[20] observed that there was no difference in blood loss intraoperatively and perioperatively even after 3 months of pretreatment with Finasteride on 30 to 90 gm prostates. The majority of the studies showing that 5ARIs are beneficial in reducing blood loss during TURP are single center trials and having less number of patients. The multicentric randomized placebo-controlled trial by Boccon-Gibod et al[22] and a largest double-blind, randomized, placebo-controlled multicentre study by Hahn, R. G et al[23]

have shown no significant difference between the groups treated with Dutasteride 0.5mg and placebo prior to TURP.

In a series of 12 patients, Carlin et al[3] noted that, hematuria associated with BPH, subsided within 2 weeks of treatment with Finasteride. Similarly, Lekas et al[15] reported that prostatic blood flow decreased by upto 60% in rats treated with Finasterid for 7 days. Donohue et al.[25] in a randomized placebo-controlled trial showed that Finasteride reduces prostatic vascularity rapidly within 2 weeks. Based on the positive results of the above studies with a short pretreatment period,

Characteristic	Dutasteride group (n=52)	Placebo group (n=52)	P value
Mean Age-years (Range, SD)	63.8 (53-79, 6.6)	65.5 (50-85, 7.8)	0.22
Mean Prostate volume-cc (Range, SD)	39.8 (20-69, 10.4)	40.4 (26-63, 9.7)	0.76
Mean Pre-operative Hemoglobin-gms/dl (Range, SD)	11.8 (8.5-15, 1.6)	11.6 (9-14.5, 1.3)	0.56
Mean Pre-operative Hematocrit-% (Range, SD)	35.1 (27-41.7, 4.2)	34.1 (26.4-42.9, 3.8)	0.21
Mean Pre-operative Sodium-mEq/L (Range, SD)	137 (126-147, 4.6)	136 (122-147, 5.3)	0.31

Table-1: Baseline characteristics of Patients

Variable	Dutasteride group (n=52)	Placebo group (n=52)	P value
Mean Hemoglobin decrease-gms (Range, SD)	1.46 (-1.3-4.4, 1.22)	1.29 (-1.2-3.4, 0.93)	0.41
Mean Hematocrit decrease-% (Range, SD)	2.0 (-5.0-11.7, 3.39)	2.01 (-5.6-8.9, 2.78)	0.98
Mean Sodium decrease-mEq (Range, SD)	4.92 (-4.0-14.0, 3.65)	4.36 (-7.0-13.0)	0.48
Mean weight of resectate-gms (Range, SD)	28.8 (12.0-52, 8.31)	28.1 (16-50, 7.23)	0.67
Mean operating time-minutes (Range, SD)	62.3 (30-80, 10.4)	64.8 (40-95, 11.3)	0.24
Mean VAS score (Range, SD)	2.65 (1.0-6.0, 0.96)	2.86 (1.0-7.0, 1.25)	0.33

Table-2: Provide heading for the table

we used a treatment arm with 2 weeks preoperative medication with Dutasteride, which is practically a reasonable waiting period before surgery.

The most practical way to quantify blood loss during TURP is by measuring Hb in the irrigating fluid,[8] however, irrigation fluid Hb levels are only 5–10% of that found in whole blood, therefore precision is not ensured in estimating hemoglobin concentration all the time. Moreover, the need for blood transfusion is decided based on the serum hemoglobin concentration. Hence we assessed blood loss by decrease in serum hemoglobin. Hematocrit was also estimated along with hemoglobin to overcome the effect of hydration.

In the present study, no significant difference in blood loss was found between two groups, which is consistent with the findings of previous studies on Dutasteride.[22,23] The overall transfusion rate was 4%, as expected from previous reports.[2,8,23] However, the incidence of clot retention was 1%, which is significantly lower than previously reported.[23] There was no observable effect of preoperative Dutasteride on the serum electrolytes.

The incidentally diagnosed prostatic cancer, following TURP was reported to be 10%.[26] However, in the present study, none of the resected specimen was reported to have malignancy, which might be due to non involvement of peripheral zone in the resection.

CONCLUSION

Preoperative Dutasteride 0.5 mg once daily for 2 weeks is not effective in reducing blood loss during or after TURP and also does not have effect on electrolyte changes associated with TURP. Though the preoperative use of Dutasteride seems logical and rational, this study shows that there is no real benefit from the use of a short course Dutasteride before performing TURP. This study adds to the body of conflicting evidence. Therefore, further trials need to be conducted on the efficacy of preoperative Dutasteride, its dosage and duration of treatment and also to compare the efficacy of preoperative Finasteride versus Dutasteride.

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