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The Role of Dutasteride in Acute Prostatic Haematuria

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Abstract

Background: Dutasteride has been found to reduce chronic prostatic bleeding and when taken 2 - 6 weeks preoperatively reduces bleeding during transurethral prostate resection. The aim of this study is to determine if the drug will be effective in the control of acute gross prostatic haematuria. **Patients and Method:** 87 Consecutive patients with gross haematuria were enrolled. Clotting Profile, Cystoscopy and Intravenous Urography were done to exclude haematuria from medical, renal and bladder causes. Patients suspected to have prostatic haematuria were further evaluated using serum Prostate specific antigen (PSA) and Prostate scan. Those with elevated PSA ≥ 10 ng/ml and abnormal digital rectal examination (DRE) finding had prostate biopsy. The patients were randomly divided into 2 treatment groups. The control group had Normal saline irrigation and broad spectrum antibiotics while the second group received 0.5 mg oral dutasteride in addition. The time taken and volume of irrigation fluid used before haematuria stopped were noted. Statistical analysis was done using SPSS version 20.0. **Result:** 75 patients had haematuria of prostatic origin. 49 (65.3%) of these had benign prostatic hyperplasia (BPH) and 26 (34.7%) had cancer of prostate. 25(51%) of the 49 patients with BPH had Normal saline irrigation and antibiotics while 24 (49%) had oral dutasteride in addition. 14 (53.8%) of the prostate cancer patients had Normal saline irrigation and antibiotics while 12 (46.2%) had dutasteride in addition. Haematuria resolved in significantly shorter length of time using lesser volume of irrigation fluid in those treated with dutasteride than in those on control arm. **Conclusion:** Addition of 0.5 mg oral dutasteride daily leads to early resolution of acute prostatic haematuria.

Keywords

Dutasteride, Acute, Prostatic Haematuria

1. Introduction

Haematuria caused by benign prostatic hyperplasia or adenocarcinoma of the prostate is a common clinical condition and may account for up to 27% and 8% of cases of gross haematuria respectively [1]. The treatment is non-specific and could require emergency prostatectomy [2] [3] with its attendant morbidities [2]. An effective oral drug would be of immense benefit. Dutasteride belongs to a class of drugs known as 17β substituted 4-aza-steroids with the chemical name (5α, 17β)-N {2,5 bis (trifluoromethyl) phenyl}-3-oxo-4-azaandrost-1-ene-17-carboxamide [4]. It is a competitive inhibitor of type 1 and type 2, 5α reductase isoenzymes [5]. The drug binds to 5α reductase enzymes forming a stable complex with a slow rate of dissociation, thereby preventing the enzymes from binding to testosterone [6]. In the absence of dutasteride, successful binding of 5α reductase enzyme to testosterone usually results to formation of dihydrotestosterone, DHT the active form of androgen. Dutasteride therefore prevents the formation of DHT.

Hence intervention with a 5 alpha reductase inhibitor such as dutasteride is a method that safely deprives the prostate of DHT, the primary growth stimulus. This causes prostate gland shrinkage, relieves lower urinary tract symptoms, and lowers the risk of disease progression and complications [7] [8]. Apart from these, DHT is known to stimulate angiogenesis [9] in the prostate.

Removal of DHT through the activity of dutasteride or other 5α reductase inhibitors therefore prevents angiogenesis and reduces prostatic blood flow and vascular density [10].

These various mechanisms are thought to be the reasons why dutasteride and finasteride have been used successfully to reduce chronic or long standing prostatic bleeding and also for reduction of prostate size. In this regard the drugs have been given pre-operatively for 2 - 6 weeks to reduce bleeding during transurethral resection of prostate [11]. When used for 6 months or more they improve lower urinary tract symptoms significantly [7].

Although dutasteride has been so used to reduce long standing prostate bleeding, we are not aware of any documentation on its use in acute prostatic bleeding. The successful use of oral dutasteride for the control of acute prostatic bleeding will certainly reduce the morbidities associated with use of emergency prostatectomy as the last option for management of recalcitrant prostatic haematuria.

The aim of this study therefore is to evaluate the effectiveness of dutasteride in the treatment of acute gross prostatic haematuria caused by benign prostatic hyperplasia or cancer of the prostate.

2. Patients and Method

87 consecutive male patients with gross haematuria who presented to the University of Port Harcourt Teaching Hospital between January 2011 and June 2014 were prospectively evaluated for causes of haematuria and enrolled for the study.

Ethical approval was obtained from the ethical committee of University of Port Harcourt Teaching Hospital. Informed consent was obtained from all the participants after explaining the benefits of the treatment and possible adverse outcomes. All adult male patients with prostatic haematuria were included in the study. Upon enrolment, a comprehensive medical examination which included full history, clinical examination and relevant investigations were carried out. Those found to have deranged clotting profile, or abnormal liver and kidney function tests were excluded. Patients who had undergone orchidectomy and those on androgen blockade were also excluded. Cystoscopy and Intravenous urography as indicated were done to rule out haematuria from renal and bladder malignancies. Patients suspected to have prostatic haematuria were further evaluated using Prostate Scan and Serum PSA. Those with elevated PSA ≥ 10 ng/ml and or abnormal DRE finding had prostate biopsy. The patients were then stratified into two diagnostic groups-BPH and CaP, based on histopathology report.

Each patient upon admission, and while undergoing evaluation for cause of haematuria, had 3-way size 22 or 24 G Foley urethral catheter passed. The urinary bladder was then vigorously flushed with normal saline using a catheter tip bladder syringe, to evacuate all blood clots. Continuous bladder irrigation with normal saline was then instituted with rate dependent on the severity of haematuria. Broad spectrum antibiotics were added based on sensitivity or on anticipation of infection.

Patients were than randomized into two treatment groups, irrespective of the diagnostic type. One treatment group received only bladder irrigation and broad spectrum antibiotics as outlined above while the second group received 0.5mg oral dutasteride in addition to bladder irrigation and antibiotics. The time taken before haematuria resolved and the volume of irrigation fluid required were noted for each treatment group for both diagnoses. Statistical analysis was done using SPSS version 20.0.

Two Sample Student t-test was used to compare the mean volume of irrigation fluid used for the two treatment types. Kaplan Meier Survival Analysis was used to examine if there were differences in time before resolution of haematuria between the two different types of treatment. To determine whether the observed differences were due to chance, the means, medians and percentiles for the time to resolution of haematuria were compared for the two arms. Log Rank, Breslow, and Tarone-Ware tests for significance were also compared for the two treatment arms. Statistical significance was determined at P value less than 0.05 ($p < 0.05$).

3. Result

75 patients had haematuria of prostatic origin. 49 (65.3%) of them had BPH while 26 (34.7%) had prostate cancer. The mean age of the entire distribution was 68.8 ± 9.5 years. The mean age of patients with BPH was 67.0 ± 9.6 years while the mean age of patients with prostate cancer was 71.4 ± 9.0 years. The mean serum PSA was 14.8 ± 9.1 ng/ml for patients with BPH while the mean serum PSA of patients

with prostate cancer was 47.9 ± 42.1 ng/ml.

Of the 49 patients with BPH 25 (51%) received normal saline irrigation and antibiotics while 24 (49%) received 0.5mg oral dutasteride in addition. Also, 14 (53.8%) of the 26 patients with prostate cancer received saline irrigation while 12 (46.2%) received 0.5mg oral dutasteride in addition.

Haematuria stopped in all 24 (100%) patients with BPH who were treated with 0.5 mg dutasteride and in 24 (96%) of the 25 patients that were on the control arm. The remaining 1 (4%) had open prostatectomy before haematuria stopped.

Similarly, haematuria stopped in all of the 12 (100%) prostate cancer patients on the dutasteride arm but on 12 (85.7%) of the 14 patients on the control arm. The 2 (14.3%) prostate cancer patients whose haematuria did not resolve had bilateral subcapsular orchidectomy before haematuria resolved. In all, haematuria resolved in all 36 patients on the dutasteride arm but in 36 (92.3%) of 39 patients on control. 3 (7.7%) patients on the control arm needed surgery before haematuria resolved.

BPH patients on the normal saline control arm required between 6 litres and 55 litres of irrigation fluid with a mean volume of 21.0 ± 11.9 litres to stop haematuria while those that had dutasteride in addition required between 4 litres and 20 litres with a mean volume of 10.4 ± 5.2 litres before haematuria stopped (Table 1). Two sample student *t*-test showed statistically significant difference in the amount of irrigation fluid used in favour of those treated with dutasteride (t = −2.885, $p = 0.008$) (Table 2). Similarly, the CaP patients on the control arm

Table 1. The minimum, maximum and mean duration of haematuria (in days) and minimum, maximum and mean volume of irrigation fluid (in litres) used for each diagnosis and for each treatment type.

Diagnosis	TT	N	Min DUR	Max DUR	MD + SD	Min Vol	Max Vol	MV + SD
BPH	N/S + DUT	24	2	15	4.9 ± 2.9	4	20	10.4 ± 5.2
	N/S only	25	3	38	8.0 ± 6.8	6	55	2.0 ± 11.9
CaP	N/S + DUT	12	1	8	4.7 ± 1.9	3	20	8.3 ± 4.6
	N/S only	14	3	10	6.9 ± 2.3	4	48	17.4 ± 9.7

BPH = Benign prostatic hyperplasia, CaP = Prostate cancer, TT = Treatment type, N/S = Normal saline, DUT = Dutasteride, N = No of patients, Min = Minimum, Max = Maximum, DUR = Duration, MD = Mean Duration, MV = Mean Volume, SD = Standard deviation.

Table 2. Cross tabulation of diagnosis and treatment showing mean volume of irrigation fluid used before haematuria resolved, and two sample student t-test and *p* value.

Diagnosis	N/S and DUT	N/S only	t-test	t-test
	Mean ± SD	Mean ± SD		
BPH	10.3 ± 5.2	21. 0 ± 11.9	−2.885	0.008
CaP	8.3 ± 4.6	17.4 ± 9.7	−4.155	0.000

N/S = Normal saline, DUT = Dutasteride, BPH = Benign prostatic hyperplasia, CaP = Prostate cancer.

required between 4 litres and 48 litres of irrigation fluid with a mean volume of 17.4 ± 9.7 litres before haematuria stopped while those on the dutasteride arm required between 3 litres and 20 litres with a mean volume of 8.3 ± 4.6 litres (Table 1). Student t-test showed statistically significant difference in the amount of irrigation fluid used in favour of the dutasteride group (t = −4.115, $p = 0.000$) (Table 2).

In patients with BPH on the control arm, haematuria lasted between 3 days and 38 days with a mean duration of 8.0 ± 6.8 days and between 2 days and 15days with a mean duration of 4.9 ± 2.9 days for those on dutasteride arm. Similarly, haematuria in prostate cancer patients on the control arm lasted between 3 days and 10 days with a mean duration of 6.9 ± 2.3 days whereas it lasted between 1day and 8 days with a mean duration of 4.7 ± 1.9 days in those treated with dutasteride (Table 1).

Kaplan Meier Survival Analysis showed that there was a statistically significant difference in time before haematuria resolved between the two treatment arms (Figure 1). The plot for the dutasteride group was below that of the Normal Saline only group throughout most of the trial which suggests that addition of dutasteride may give a faster relief than normal saline irrigation only. Also, means and median for the time to resolution of haematuria showed significant difference in the average time in favour of the dutasteride group ($p = 0.009$) (Table 3), signifying that the observed difference in the survival curve was not due to chance. The percentile table for the survival curve for the two arms of treatment also showed significant difference in favour of the group treated with dutasteride (Table 4). Test of equality of the survival curve using Log Rank, Breslow and Tarone Wares were all less than 0.05 showing significant difference between the treatment types (Table 5).

Table 3. Mean and median for survival time (time to resolution of haematuria).

Treatment	Mean				Median			
	Estimate	Std Error	95% Confidence Interval		Estimate	Std Error	95% Confidence Interval	
			Lower Bound	Upper Bound			Lower Bound	Upper Bound
N/S and DUT	6.492	0.819	4.885	8.098	5.000	0.458	4.102	5.898
N/S only	11.039	2.512	6.116	15.962	8.000	0.596	6.832	9.168
Overall	8.779	1.390	6.005	11.503	7.000	0.628	5.770	8.230

N/S = Normal saline, DUT = Dutasteride, Std = standard.

Table 4. Percentiles table for the survival curve (probability of resolution of haematuria).

Treatment	25.0%		50%		75%	
	Estimate	Std Error	Estimate	Std Error	Estimate	Std Error
N/S and DUT	9.000	2.043	5.000	0.458	4.000	0.313
N/S Irrigation Only	11.000	2.521	8.000	0.598	6.000	0.770
Overall	11.000	1.044	7.000	0.628	4.000	0.398

N/S = Normal saline, DUT = Dutasteride, Std = Standard.

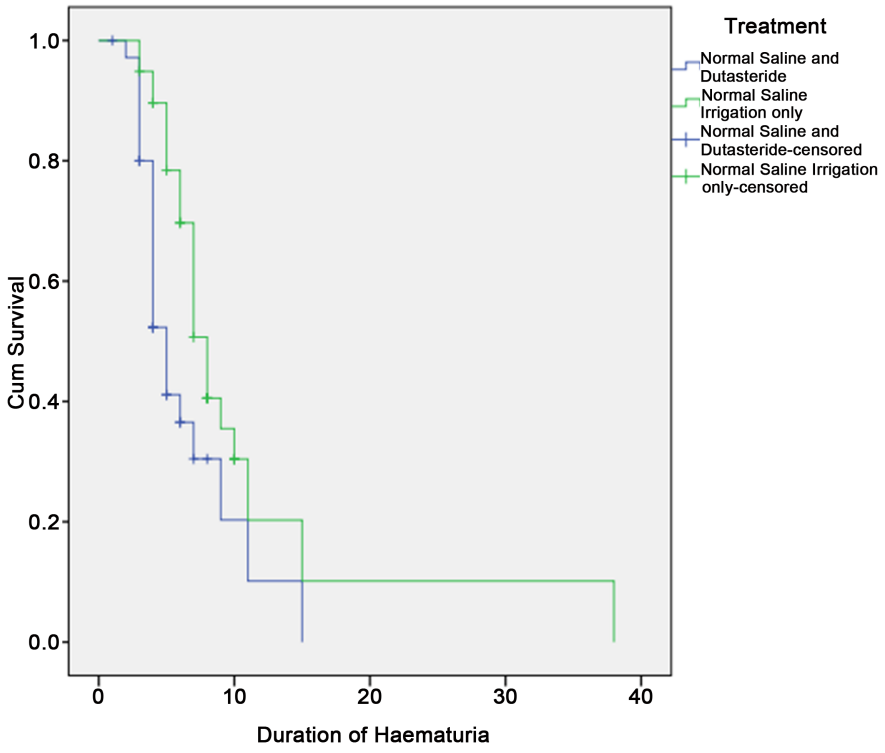

Figure 1. Kaplan Meier analysis of the duration of haematuria for the two treatment types.

Table 5. Overall comparisons using Log Rank, Wilcoxon, and Tarone Wares tests in relation to time to resolution of haematuria.

	X2	df	*p*-value
Log Rank	6.779	1	0.009*
Breslow (Generalized Wilcoxon)	10.207	1	0.001*
Tarone-Ware	8.944	1	0.003*

*$p \leq 0.05$.

4. Discussion

The treatment of gross prostatic haematuria is nonspecific. The initial approach which depends on the severity of bleeding may include observation, irrigation, use of antibiotics and emergency prostatectomy. Bladder irrigation is used as a supportive form of treatment, not as a form of treatment itself since its role is mainly prevention of clot retention. Some scholars have argued that bladder irrigation may decrease the duration of haematuria since it washes off urokinase, a serine protease that prevents clot formation in the bladder [12]. Clot formation on the other hand will cause retention and infection which may paradoxically increase bleeding [13] [14]. Because bladder irrigation was done in both arms of treatment in this study, whatever influence it had would have been neutralized. Accordingly, the observed difference in volume of irrigation fluid and time is supposedly a measure of the influence of dutasteride.

Haematuria resolved in median time of less than 5 days in patients treated

with dutasteride in this study whereas it resolved in median time of 7 and 8 days for prostate cancer and BPH patients treated without dutasteride respectively. The Kaplan Meier survival curve (**Figure 1**) demonstrates shorter duration of haematuria in those treated with dutasteride. Any point on the survival curve shows the probability that a patient on a given treatment will have experienced relief at that time. The curve for patients who had dutasteride lies below that for those who had saline irrigation alone and this signifies earlier relief. The percentile table defines the percentage of patients yet to be relieved of haematuria at the particular time. For instance, the 75th percentile was the time at which 75% of the patients were yet to have their haematuria resolved. This means that 25% were already free of haematuria. This corresponds to 4 days for those treated with dutasteride and 6 days for those who had irrigation only.

The fact that haematuria resolved in less than 5 days when dutasteride was used does not agree with the mechanisms of apoptosis and prostate shrinkage which were earlier considered as the main mechanisms of action of 5-*α* reductase inhibitors (5ARIs) [15]. Prostate shrinkage occurs only after about 6 months of treatment with 5ARIs [5] [16]. Furthermore, inhibition of angiogenesis, thought to be another mechanism of action of 5ARIs [17] may not explain this quick resolution of haematuria as angiogenesis is thought to occur between 5 - 7 days. The rapidity with which haematuria resolved when dutasteride was used suggests that it may influence an associated pathological condition that resolves in a short time. This pathological condition has been identified as inflammation [17]. Vascular endothelial growth factor, vegf causes neovascularization, increased vascular permeability, oedema, increased fragility and bleeding. Dutasteride reverses these effects by preventing the formation of vegf. This leads to reduction in extra vascular oedema. Reduction of extravascular oedema reduces intravascular pressure and prevents the destruction of the fragile new vessels, thereby reducing haematuria [17].

In this study, dutasteride was also effective in the control of gross prostatic haematuria in patients with prostate cancer who had not had androgen deprivation therapy before they developed haematuria. The influence of 5ARIs on prostatic haematuria has been mainly demonstrated on patients with BPH before now. In fact, Dahala *et al.* [18] suggested that finasteride a type 1 5α reductase inhibitor should not be used for treatment of prostatic haematuria caused by prostate cancer. The finding of this study however suggests that dutasteride can reduce prostatic haematuria of prostate cancer origin if androgen ablation has not taken place and can be used for such haematuria while awaiting androgen ablation.

It is noteworthy that mean duration of haematuria of 4.7 ± 1.9 for CaP patients treated with dutasteride is similar to the mean duration of 4.9 ± 2.9 days for BPH patients with haematuria treated with dutasteride but the difference was not statistically significant. However one expects that the mean duration of haematuria should have been significantly higher in BPH since the microvascular densities and neovascularization are located in the suburothelium in BPH [9] [19]. The difference in the sample sizes (12 for CaP and 24 for BPH) may account for this.

Another notable finding in this study was the rapidity of resolution of haematuria following bilateral orchidectomy. Two CaP patients on the control arm continued to bleed for more than 30 days of irrigation. These patients had bilateral total orchidectomy and haematuria stopped within 24 hours of orchidectomy in both patients. This supports the fact that androgens play key roles in the pathogenesis of prostatic bleeding [2] [17] [20]. Serum levels of testosterone and DHT drop by greater than 90% after orchidectomy [21]. So, orchidectomy removed the influence of DHT and its associated inflammatory effects mediated through vegf.

5. Conclusion

Oral 5ARIs can reduce bleeding in acute prostatic haematuria from both benign prostatic hyperplasia and pre castration prostate cancer patients and so should be used in such cases while awaiting definitive treatment. This is to be confirmed in a study with larger sample size.

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