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Review Article

Evaluating the Role of 5α-Reductase Inhibitor in Transurethral Prostatectomy Related Hematuria in Anticoagulated Patients

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Abstract

Transurethral Resection of the Prostate (TURP) is associated with significant morbidity related to post-operative haematuria. Over the last decade, various direct oral anticoagulants (DOAC) have become the predominant therapy, and their use have become prevalent. It is known that 5α-reductase inhibitor (5-ARI) decreases bleeding in patients undergoing TURP. However, there is paucity of evidence to evaluate impact of 5-ARI in TURP patients receiving DOAC. Our objective is to evaluate post-operative bleeding risk in this group of patients. This is a single-centre retrospective analysis of 629 patients who underwent TURP from April 2019 to December 2023. Twenty-three variables including patient clinical, operative, and pathological details were included. Perioperative management of anticoagulant and antiplatelet therapy were recorded. Bleeding related morbidities were captured within 3-months postoperatively. Weight-adjusted treatment effect analysis was performed to evaluate the impact of 5-ARI on postoperative bleeding. The cohort was divided into the anticoagulant group (n=113) and no-anticoagulant group (n=516). In the anticoagulant group, 62% of patients received 5-ARI preoperatively and they were at 0.61-time risk of developing clinically significant haematuria. In the no-anticoaglant group, 52% of patients received 5-ARI preoperatively and they were at 0.57-time risk of developing clinically significant haematuria. It appears that 5-ARI has similar impact in reducing development clinically significant haematuria between anticoagulated and non-anticoagulated patients. Given anticoagulated patients are intrinsically at higher risk of developing bleeding complications, we recommend all anticoagulated patients undergoing TURP should be commenced with 5-ARI preoperatively.

Abbreviations: 5-ARI: 5α-Reductase inhibitor; AC: Anticoagulant; DOAC: Direct Oral Anticoagulant; BPH: Benign Prostate Hyperplasia; TURP: Transurethral Resection of Prostate

Keywords: 5α-Reductase inhibitor; Anticoagulant; Bleeding; DOAC; Dutasteride; Finasteride; Haematuria; Transurethral prostatectomy; TURP

Introduction

Bothersome Lower Urinary Tract Symptoms (LUTS) is a common clinical manifestation of Benign Prostatic Hyperplasia (BPH) for men above 50-years of age [1]. Medical therapy with 5-alpha reductase inhibitor (5-ARI), including finasteride and dutasteride, is commonly recommended as part of conservative management to improved symptoms [2]. Surgical management options are considered when patient failed to achieve adequate symptomatic relief with medical therapy [3]. Despite availability of various urological procedures developed over the last two decades, TURP remains the most prevalent surgical option [4]. Despite its effectiveness, TURP entails significant bleeding-risk in the immediate 2-3 weeks post-operative period in which patient frequently represent acutely with haematuria and/or clot retention

requiring further intervention [5].

5-ARI had been established to reduce the risk of BPH-related haematuria [6]. Its mechanism is thought to be secondary to 5-ARI blockade, thereby preventing conversion of testosterone to dihydrotestosterone, thereby reducing prostatic angiogenesis with decreasing Micro-Vessel Density (MVD) in the hyperplastic prostatic tissue [7]. Several studies had demonstrated its use in reducing peri-operative blood loss in patients undergoing TURP. Pre-operative treatment with finasteride for as short as two weeks had been demonstrated to reduce prostate MVD and reduced operative estimate blood loss [8,9]. The effectiveness of pre-treatment with dutasteride to reduce operative bleeding remains inconclusive within current literature [9]. These studies were mostly conducted on non-anticoagulated patients, and there remain a paucity of evidence on effect of 5-ARI in the anticoagulated group.

Patient receiving Anticoagulant (AC) undergoing TURP is known to have increased morbidity related to clinically significant haematuria even with appropriate peri-operative management of the AC [10]. With the aging population, the prevalence of men requiring management of symptomatic BPH is expected to increase [11]. In addition, prevalence of patient with co-morbidities requiring anticoagulation is expected to rise. For instance, it is estimated that patients with atrial fibrillation is projected to triple in the coming decades, and at present, approximately 65% of 46.3 million patient with AF globally receive anticoagulation therapy [12,13]. This epidemiological trajectory highlights the importance of minimizing post-operative haematuria risk in patients undergoing TURP, particularly for the anticoagulated patients.

Previous studies on 5-ARI and TURP that demonstrated reduced peri-operative haematuria had been conducted on non-anticoagulated patients. At present, there is a paucity of evidence in current literature to guide clinician in minimizing haematuria risk for TURP patients, except for withholding anticoagulant in the peri-operative period [10,14]. Our objective is to evaluate the effectiveness of 5-ARI in anticoagulated patients in reducing development of clinically significant haematuria and compare the risk to a non-anticoagulated cohort.

Methods

Study Population

A single centre retrospective cohort analysis was conducted at a high-volume referral centre at Gold Coast University Hospital, Australia. A cohort of patients that underwent elective TURP for symptomatic BPH were collated from 2019 to December 2023. All patients were reviewed in a multidisciplinary fashion pre-operatively. Decision to proceed to TURP would be made with a urologist, and patient would subsequently review by an anaesthetist, and relevant specialist if patient was deemed high surgical risk. A clinical pharmacist would review and document a patient's up-to-date medication lists. Patient's use for 5-ARI and/or anticoagulant will be documented at this encounter. For patients receiving anticoagulation, perioperative management of their AC would be decided via a multidisciplinary approach after assessment of their thromboembolic risk. Routine blood test including patient's full blood count, renal function, liver function, and coagulation profile would be conducted for baseline assessment. Clinical data were retrieved from an integrated electronic medical record system utilized by the state-wide health care system. Over 23 relevant data variables including peri-operative, and operative details were collected. Patient demographics such as age, body mass index, and ethnic origin were recorded. Pre-operative parameter including indication for TURP, urinary catheter dependence, treatment with 5-ARI, pre-operative Prostate Specific Antigen (PSA) level, prostate size, and prostate cancer history were recorded. Anticoagulant details were collected for patients receiving AC therapy. These included indication for AC, pre-operative and post-operative withholding duration, and use of bridging therapy. Several well-established scoring systems were utilized as surrogate measure for patient's baseline parameters. Patients' co-morbidities were recorded with American Society of Anaesthesiologist (ASA) physical status classification [15]. Baseline bleeding risk was recorded with HAS-BLED score [16] as a surrogate measure. CHA_2DS_2-VASc score was used to stratified a patient's thromboembolic risk [17].

Bleeding complications were defined as acute hospital representation with clinically significant haematuria, requiring further investigation and review by urology service, insertion of indwelling catheter for bladder irrigation, clot retention requiring manual washout, or haematuria requiring cytotropic intervention under general anaesthetics. Blood transfusion requirement was also recorded as a surrogate measure for severity of haematuria. All representations would be captured through the state-wide integrated electronic medical record. All patients had routine outpatient follow-up 3 months after TURP.

Statistical Analysis

Statistical analyses were performed using STATA 18 software (Stata Corp., College Station, Texas, USA). The cohort were separated into two groups, the Anticoagulated (AC) group, and the non-anticoagulated (No-AC) group. Comparison was made between patient treated with 5-ARI preoperatively versus patient without 5-ARI pre-treatment amongst the two groups. Two-sided t-test were performed to compare the continuous variable, and Chi-square test was performed to compare categorical variables between the groups. Complex probably-weight adjusted regression analysis was performed as a form of treatment-effect analysis to

compared risk of clinically significant haematuria between patients receiving 5-ARI versus no 5-ARI in both anticoagulated, and non-anticoagulated cohort. The variables in the weight-adjustment analysis were identified using univariate logistic regression to look for co-variables, which might have influenced on outcome measured. A cut off threshold of p-value = 0.10 for co-variables to be included in the treatment-effect was used.

Results

Cohort Summary

There are 629 patients in the retrospective cohort, 113 (17.9%) received anticoagulation and 516 (82%) were not anticoagulated (Table 1a). In the overall cohort, the number of patients receiving preoperative 5-ARI, and no 5-ARI were almost even, 325 (51.7%) and 304 (48.3%) patients, respectively (Table 1b). Of all the patients receiving 5-ARI, majority of patients were treated with dutasteride, and only 28 (4.5%) received finasteride. This pattern remained similar in both the anticoagulated and the non-anticoagulated cohort, with patients 5.9% and 4.3% of patients receiving finasteride, respectively. Almost even number of patients received 5-ARI (50.9%) in the non-anticoagulated cohort (Figure 1a). An increased proportion of patients received pre-operative 5-ARI in the anticoagulated cohort, 60.8% (Figure 1b) and this finding was statistically significant (P = 0.02).

	Cohort Breakdown n = 629 (%)
Non-anticoagulated	516 (82)
Anticoagulated (AC)	113 (17.9)
Apixaban	44 (7.0)
Rivaroxaban	50 (7.9)
Dabigatran	8 (1.3)
Warfarin	11 (1.7)

Table 1a: Overview of anticoagulation status in 629 patients and management in the perioperative period.

	Cohort Breakdown n = 629 (%)
No 5-ARI Received 5-ARI	304 (48.3)
Finasteride	28 (4.5)
Dutasteride	297 (47.2)

Table 1b: Overview of 629 patients receiving 5-ARI.

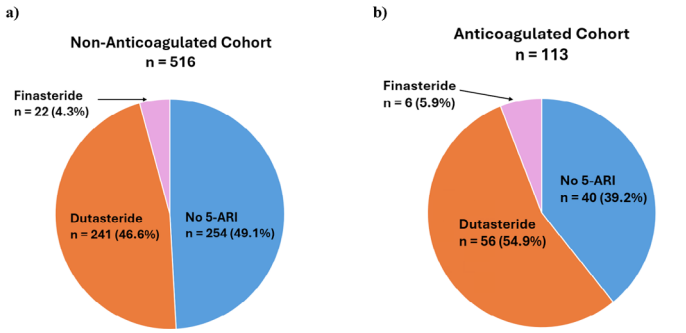

Figure 1: a) 5-ARI treatment breakdown of the non-anticoagulated cohort and **b)** 5-ARI treatment breakdown for the anticoagulated cohort.

Overall Cohort Outcome

Cohort characteristics were compared between the AC vs. no-AC cohort, and 5-ARI vs. No 5-ARI cohorts (Table 2). The independent variables and outcomes between the AC versus no-AC cohorts were important. Any statistically significant differences between the two cohorts will need to be accounted for final adjusted analysis. It was noted that patients in the anticoagulated cohort were significantly older, higher in BMI, higher incidence of pre-operative urinary tract infection, and more likely to received 5-ARI. It was also important to note that patients in the anticoagulated had higher baseline bleeding risk, as this is reflected in higher portions of patient categorized to have high to very-high risk HAS-BLED score. It was also worth noting that anticoagulated patients had significantly higher co-morbidities reflected in higher proportion of higher ASA score. The anticoagulated cohort patient had significantly higher risk of developing clinically significant haematuria post TURP (Table 2). AC patients were more likely to represent with haematuria requiring further assessments and interventions compare to the no-AC group, 27% vs. 9.9% (P < 0.01). AC patients were more likely to developed transfusion requirement (AC: 4.4% vs. No-AC: 1%, P <0.01). reflecting more severe bleeding. We have observed that more patients from the AC group require bladder catheterization for manual and continuous irrigation for haematuria management. However, this finding was not statistically significant. We observed that there were more patients in the no-AC cohort requiring cystoscopy washout under general anaesthesia. This finding was statistically insignificant and given this was a rare event (less than 1% of cases), it would require a much larger study cohort to be able to observe demonstrable

statistical difference if existent. It was worth noting that more patient in the AC cohort was more likely to report prolonged haematuria of greater than 14 days (AC: 19% vs. No-AC 1.6%, P < 0.01) with a longer mean duration of haematuria of 42 days. There were differences in mortality rate between the two groups.

Cohort characteristics were compared between the 5-ARI and no 5-ARI group. This comparison was important in the subsequent adjustment for the treatment-effect analysis as statistically significant covariables between the two cohort would need to be accounted for. We have observed that patients who received 5-ARI were statistically significant older in age, had higher pre-operative PSA, and had higher prostate volume. On our unadjusted analysis, patients receiving 5-ARI were more likely to developed clinically significant haematuria prompting acute representations (5-ARI: 16.3% vs. No 5-ARI: 9.4%, P = 0.01). Other than this, there were no significant differences in complications between the two groups.

5-ARI Treatment-Effect Analysis (Non-Anticoagulated Vs. Anticoagulated)

Weight-adjusted analysis was performed from the above results to further assess the treatment effect of pre-operative 5-ARI on reducing clinically significant haematuria. Covariable with statistically significant difference in the above analyses (Table 2) between the AC vs. no-AC group, and 5-ARI vs. no 5-ARI group were carried forward for adjusting final analysis. Separate univariate linear regression analyses were performed on remainder covariables to potential variables that may impact outcome for adjustment. The weight-adjusted result from our treatment-effect model were demonstrated in Table 3. In the overall cohort, patients who received pre-operative 5-ARI were at 0.56 times reduced risk of developing clinically significant haematuria compared to the no 5-ARI group (5-ARI: 5.8%, P = 0004; No 5-ARI: 10.2%, P < 0.001). Similar risk reduction ratio was observed in the anticoagulated patients as well. In the AC group, patients who received pre-operative 5-ARI were at 0.61 times reduced risk of developing clinically significant haematuria compared to the no 5-ARI group (5-ARI: 11.6%, P = 0.012; No 5-ARI: 18.9%, P = 0.032). It was also worth noting that patients in the anticoagulated group had overall higher risk of developing haematuria related complications regardless of whether pre-operative 5-ARI was administered. However, it is worth noting that the risk of clinically significant haematuria in anticoagulated with 5-ARI treatment was similar to patients without receiving 5-ARI in the non-anticoagulated group.

Total Cohort n = 629	Total	No AC (n = 513)	AC (n = 113)	P	No 5-ARI (n = 294)	5-ARI (n = 325)	P
Peri-operative parameter							
Mean age	72.9	72.2	76.2	<0.01	72.2	73.5	0.02
Mean Body Mass Index	28	27.8	29.2	0.03	27.7	28.4	0.06
Mean PSA (ng/ml)	5.2	9	5.64	0.07	9.42	5.73	<0.01
Mean Prostate Volume (ml)	67.8	67.8	67.8	0.99	64.5	70.6	0.01
Mean Haemoglobin (g/L)	137.8	138	136	0.45	137	138	0.27
Bladder Catheter Dependent	308 (49.2%)	250 (49%)	58 (51%)	0.62	154 (52%)	154 (47%)	0.18
Urinary Tract Infection (treated)	306 (49%)	240 (46%)	66 (58 %)	0.02	142 (48%)	164 (50%)	0.64
Treatment with 5-ARI + α-Blocker	324 (51%)	255 (49%)	69 (61 %)	0.02	NA	NA	-
Receiving antiplatelet	166 (26%)	160 (31 %)	6 (5%)	<0.01	73 (25%)	93 (28%)	0.32
HAS-BLED Score							
0 - 2 (Low to moderate risk)	382 (61%)	331 (64%)	51 (45%)	<0.01	181 (61%)	201 (61%)	0.96
3 - 8 (High to very high risk)	248 (39%)	186 (36%)	62 (55%)	<0.01	117(39%)	131 (39%)	0.96
Complications							

Clinically significant Haematuria	**82 (13%)**	**51 (9.9%)**	**31 (27%)**	**<0.01**	**28 (9.4%)**	**54 (16.3%)**	**0.01**
Conservative	33 (5.2%)	21 (4.1%)	12 (11%)	0.83	8 (2.7%)	25 (7.7%)	0.12
Re-catheterize for irrigation	42 (6.7%)	24 (4.7%)	18 (16%)	0.33	16 (5.4%)	26 (8%)	0.44
Cystoscopy washout	7 (1.1%)	6 (1.2%)	1 (0.9%)	0.18	4 (1.3%)	3 (0.9%)	0.18
Blood transfusion requirement	10 (1.6%)	5 (1%)	5 (4.4%)	<0.01	4 (1.3%)	6 (1.8%)	0.21
Prolonged Haematuria	29 (4.6%)	8 (1.6%)	21 (19%)	<0.01	9 (3%)	20 (6.1%)	0.08
Mean Days of Prolonged Haematuria	36.1	22	42	<0.01	40.7	34.3	0.21
All-Cause Mortality	3 (0.5%)	2 (0.4%)	1 (0.9%)	0.49	2 (0.7%)	1 (0.3%)	0.5
TURP Related Death	1 (0.15%)	0	1 (0.9%)				

Table 2: Cohort comparison of patient characteristics and outcome - with or without oral anticoagulation, and with or without 5-ARI treatment.

	Clinically Significant Bleeding		
	Risk of Bleeding %	95% C. I	P
Total Cohort (n = 517)			
No 5-ARI	10.20%	7.4 - 12.4%	<0.001
Receiving 5-ARI	5.80%	2.3 - 8.1%	0.004
Risk Ratio	**0.56**		
Anticoagulated Cohort (n = 112)			
No 5-ARI	18.90%	4.1 - 33.6%	0.032
Receiving 5-ARI	11.60%	0.9 - 22.3%	0.012
Risk Ratio	**0.61**		

Table 3: Treatment effect analysis of 5-ARI effect on clinically significant bleeding for the total cohort and the anticoagulated cohort**.**

Discussion

To our knowledge, this is the first study to evaluate the treatment effect of pre-operative 5-ARI for anticoagulated patients undergoing TURP for BPH. In this study cohort, it appeared that pre-operative treatment with 5-ARI were more prevalent in the anticoagulated patient group (AC-group: 61% vs. No AC-group: 49%; P = 0.02). This observation could likely be explained by other significant covariable observations. It was noted that anticoagulated patients were significantly older in age and has higher BMI. In addition, they have higher HAS-BLED score reflecting increased baseline risk, and higher ASA scores reflecting more co-comorbidities. We postulate that clinicians were more likely to commenced 5-ARI for anticoagulated patients in hope to achieve significant improvement in LUTS and ultimately avoid surgical intervention with TURP considering their elevated operative risks.

Similarly, we observed patients who received 5-ARI pre-operatively were significantly older in age, has higher PSA, and larger prostate volume. We postulate that clinicians were more likely to trial older patients on medical therapy to improve LUTS prior to preceding to TURP, given older patients generally had more significant medical co-morbidities. 5-ARI therapies were more likely to be prescribed to patients with larger prostate as it is believed that the therapy is more effective for larger BPH. In our initial unadjusted univariable analysis, it demonstrated that patients receiving 5-ARI were more likely to have acute representation with clinically significant haematuria (5-ARI: 16.3% vs. No 5-ARI: 9.4%; P = 0.01). This finding was unexpected as its mechanism of 5-ARI decreased vascular endothelial growth factor thereby reducing microvascular density of prostate. Prior studies have demonstrated that 5-ARI should improved patient's bleeding risk. However, it was important to note that patients receiving 5-ARI were significantly older in age, had large prostate, and more significant medical co-morbidities. After adjusting for these significant covariables, our treatment-effect analysis demonstrated that 5-ARI demonstrated risk reduction of clinically significant haematuria. In anticoagulated patients, the bleeding risk was reduced by 0.61 times. In non-anticoagulated patients, the bleeding risk was reduced by 0.56 times.

The present study two significant limitations. Firstly, we evaluated the treatment effects of 5-ARI as if it was a single agent. However, both finasteride and dutasteride were included in our study into the treatment group. We have combined patients receiving finasteride to dutasteride group given only a small percentage (4.5%) of patients received finasteride. This low number would not have statistical power to demonstrate the treatment effect of finasteride. It is worth noting that despite finasteride and dutasteride are similar class of therapy, there are some inherent differences. Finasteride is a Type II 5-ARI receptor [18], whereas dutasteride is a dual Type I and II 5-ARI receptor [19], and in theory should have better haemostatic effect. However, consensus from current literature suggests that finasteride has more observable effect in reducing perioperative blood loss in TURP patients, and the effect for dutasteride remains equivocal [9]. Secondly, it is difficult to compare the outcomes of present study to other studies evaluating the role of 5-ARI in TURP patients. In our study, we have used representation with clinically significant haematuria as outcome measure for 5-ARI treatment effect. In a well-summarised metanalysis, more direct outcome measures have been utilized by existing studies [9]. For instance, the commonly measured outcomes are estimated blood loss, interval haemoglobin drop, blood transfusion requirement or even post treatment histological changes. However, these outcome measures may not necessarily equate to a measure to assess patient's clinical outcomes. For example, a reduction in intraoperative blood loss at time of TURP from finasteride treatment may not necessarily equate to reduced risk of developing haematuria in the 2-3 weeks post operative period.

Conclusion

5-ARI appeared to have significant effect in reducing the risk of developing clinically significant haematuria for TURP patients who received long term anticoagulation. We have demonstrated the effect of bleeding risk reduction in anticoagulated patients (Risk Ratio 0.61 times) is similar to the reduction in non-anticoagulated patients (Risk Ratio 0.51 times). In an era where increasing numbers of anticoagulated patients requiring surgical intervention for BPH, pre-operative 5-ARI treatment should be considered to minimize patient's risk in developing clinically significant haematuria.

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