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Original Article

Multicenter experience with photoselective vaporization of the prostate on men taking novel oral anticoagulants

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Abstract *Objective:* Photoselective vaporization of the prostate (PVP) is a widely performed surgical procedure for benign prostatic obstruction. This approach has become particular favoured for men on anti-platelet and anticoagulation agents such as clopidogrel and warfarin but there is minimal published experience in the setting of novel oral anticoagulants (NOACs). This study was to examine the perioperative outcomes in men on NOACs undergoing PVP, with particular reference to perioperative morbidity.
Methods: A retrospective analysis of PVP datasets was undertaken from three centres in Sydney (Australia), Toulouse (France) and Boston (USA). Subjects who had been treated whilst on NOACs without discontinuation or bridging were identified. Perioperative outcomes and treatment parameters were examined and morbidity recorded according to Clavien-Dindo (CD) classification.
Results: There were a total of 20 subjects who had undergone PVP whilst NOACs had been continued during the perioperative period. The mean age was 77±6.5 years. The mean prostate volume, energy utilization and vaporisation time was 94±56 mL, 301±211 kJ, and 35±21 min respectively. The mean postoperative duration of catheterization and duration of hospitalization was 2.2±2.4 days and 2.4±2.4 days respectively. There was a single episode of urinary tract infection and four subjects required re-catheterisation for non-hematuric retentions.
Conclusions: This study supports the safety of men on NOACs undergoing PVP. Whilst this study represents the largest experience of PVP in these men, larger studies are necessary to confirm the safety of PVP in this group of men undergoing BPH-related surgery.

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1. Introduction

Benign prostatic hyperplasia (BPH) is a disease primarily confined to older males with 50%—75% of men over 50 years of age experiencing symptoms [1]. While initial treatment is conservative, some patients' symptoms progress to a point no longer controlled by oral medication [2]. New evidence suggests that BPH, cardiovascular risk factors and metabolic disease are all influenced by chronic inflammation [3] and thus these men are at increased risk of co-morbid cardiovascular conditions requiring anticoagulation.

Recent pharmacological developments have led to widespread use of direct, or novel, anticoagulants, also known as non-Vitamin K anticoagulants (NOACs) [4]. Due to the continual cardiovascular requirement for anticoagulation, high-risk patients may require ongoing therapy whilst low-risk patients are able to cease their anticoagulation [5,6]. Surgeons may also be hesitant to operate on patients concurrently taking NOACs given the perceived risks of perioperative bleeding.

Transurethral resection of the prostate (TURP) is the surgical gold-standard for men with BPH [1,2], however it requires prior cessation of anticoagulant therapy. Several alternative procedures are available including holmium laser enucleation of the prostate, prostatic artery embolization and photoselective vaporisation of the prostate (PVP, also known as Greenlight™ laser prostatectomy) [2,7,8]. Previous studies into PVP have assessed its efficacy and safety with concurrent administration of warfarin and/or antiplatelet medications with reassuring results [5,9—18]. There have not been, however, to our knowledge any previous reports of efficacy and safety of performing PVP when NOAC therapy was continued.

The objective of this study was to analyse morbidity and early functional outcomes following PVP where NOAC therapy was continued throughout the perioperative period.

2. Methods

A retrospective, multicentre cohort study was used to assess the incidence of morbidity in patients undergoing PVP while on NOAC therapy, with particular reference to bleeding complications. Three centers with extensive local experience in performing PVP participated in this study.

Existing databases at participating institutions were analysed for patients who had undergone PVP whilst NOACs were continued perioperatively. We defined NOACs as apixaban, rivaroxaban and dabigatran. Twenty patients were identified and assessed in this study. Patients concurrently on anti-platelets and NOACs were included. Medications unrelated to bleeding risk were not assessed in this paper, and other medications were continued as per the anaesthetic assessment preoperatively. The indications for surgery were at the discretion of surgeons at each participating center and were consistent with indications as defined in current practise guidelines. Each patient was consented appropriately prior to surgery by the operating team.

Perioperative factors considered in this analysis include co-morbid cardiovascular conditions, types of anti-coagulation and anti-platelet agents, International Prostate Symptom Score (IPSS), prostate volume and American Society of Anesthesiologists (ASA) score.

Each center received local institutional review board approval (Sydney Adventist Hospital: HREC 2012-025; Massachusetts General Hospital: IRB 2015P000919; Clinique Pasteur local governance: No specific number applies).

Data analysis was performed using Microsoft Excel for Mac 2016. For descriptive statistics, the mean was expressed with standard deviations.

3. Results

Twenty patients met the requirements for this retrospective assessment. The choice of NOAC was varied with six patients on apixaban (30%), ten on dabigatran (50%) and four on rivaroxaban (20%). Almost half of the patients were on other NOACs or anti-platelets in addition to the NOACs. Four patients were on aspirin (20%), three on clopidogrel (17%) including one on dual anti-platelet drugs (5%) and two patients were concurrently on warfarin (10%) (Table 1). Almost all patients were on anticoagulation for atrial fibrillation (n=18; 90%), with one patient being on treatment for pulmonary embolism and one for ischaemic heart disease.

Our patient cohort had a mean age of 77±6.5 years and mean body mass index (BMI) of 27±4.4 kg/m^2. The ASA score for all patients was 2 (37%) or 3 (58%), with one score unavailable. Total IPSS score preoperatively had a mean of 17.4±6.1, noting that six patients (30%) were unable to be assessed preoperatively due to indwelling catheters (one patient was not listed as IDC, however IPSS is unavailable). Prostate volume was available for 16 of our patients, with a

Table 1 Anticoagulant and anti-platelet use.

Agent	Patients, n (%)
Aspirin	4 (20%)
Clopidogrel	3 (17%)
Warfarin	2 (10%)
Apixaban	6 (30%)
Dabigatran	10 (50%)
Rivaroxaban	4 (20%)

mean of 94±56 mL and the smallest volume being 34 mL and the largest 245 mL (Table 2).

Surgical parameters varied considerably given the wide range of prostate size, where the mean energy utilisation was 301±211 kJ, mean laser vaporisation time was 35±21 min and mean intervention/operative time was 55±44 min. Mean kilojoules per gram were 3.54±0.96, which is in line with practise suggesting a minimum energy use of 3 kJ/g [19].

Despite the age and comorbidities of our cohort, there were few adverse postoperative outcomes reported. Four patients (20%) required re-catheterisation for urinary retention. One (5%) patient had a urinary tract infection. Notably, not a single patient had a complication from bleeding including clots, significant haematuria or requirement for re-catheterisation secondary to clot retention. Two patients (10%) had a Clavien-Dindo score of II (Table 3). All complications were thus minor.

The majority of patients were discharged Day 1 post-operatively ($n=11$; 55%) with a mean length of stay 2.4±2.4 days. The longest patient stay was 11 days in an 84-year old patient with retention as a complication. Two other extended lengths of stay were noted, one for urinary retention requiring re-catheterisation and the other for primarily social reasons and associated medical surveillance. Note two patients developed postoperative urinary retention but did not have a prolonged length of stay. Catheterisation time after surgery had a mean length of 2.2±2.4 days. This does not include the time after re-catheterisation resulting from urinary retention.

4. Discussion

This analysis was performed due to the increasing volume of BPH patients with concurrent requirement for anti-coagulation presenting to the urologists involved in this study. There is, to our knowledge, no similar available study or data on this subject matter. An important finding in this study is the absence of complications related to bleeding or clot retention. Four patients (20%) experienced urinary retention in the postoperative period but none of these were related to bleeding and this is a well-documented adverse event for patients undergoing any BPH surgical intervention [20]. All complications were less than III on the Clavien-Dindo score. These results are in keeping with other similar studies on patients taking warfarin [12,21].

NOACs came to market in the late 2000s and early 2010s as an alternative anticoagulant to the traditional, but somewhat inconvenient, warfarin. These drugs were useful in that they did not require, nor had available, laboratory tests for serum level titration [22]. The international normalised ratio, the measure used to assess adequacy of warfarin's effect on coagulation, is well-known to be affected by diet, drug-drug interactions and other health factors. NOACs offered an appealing alternative to prescribers and patients due to the ease of use and administration [23]. The increasingly well-known issues with NOACs are their inability for and/or expense of reversal. Dabigatran, used by 10 (50%) of our cohort, has a reversal agent called idarucizumab (praxbind) with an approximate cost of $3000 [24]. Multiple vials are often required for complete reversal. Rivaroxaban, used by four (20%) of our cohort, and apixaban, used by the remaining six (30%) of our cohort, have no currently widely available reversal agent [23]. The risks and expense of anticoagulation reversal are of concern to surgeons given the associated morbidity and mortality with bleeding. Due to the increasing number of patients presenting with a requirement for surgery for the symptomatic BPH while also requiring anticoagulation, steps towards surgical innovation are required for best quality of life outcomes.

A strength of this study is that all participating surgeons have had extensive experience in operating on patients with continued anticoagulant therapy. This approach is supported by significant data regarding the safety of PVP in patients on warfarin, aspirin and clopidogrel [5,10,11,15–17]. Our collective experience has been of safety of NOACs and anti-platelet agents in PVP with acceptable levels of morbidity in these cohorts.

This study has a number of limitations. It was relatively small retrospective with no comparison group. However, it would be almost impossible to perform a randomised control trial to assess the effects of NOACs on morbidity in PVP. It would be possible to perform a comparative prospective cohort study in institutions, though this sort of study would potentially involve bridging patients to agents such as enoxaparin or heparin, which come with their own risk of perioperative bleeding as well as a potential risk of cardiovascular or thrombotic complications resulting from the period of time, whilst of short duration, when there was no anticoagulation coverage. At the time of publishing, the Stop or Ongoing Oral Anticoagulation in Patients Undergoing PVP (SOAP; Clinical Trials: NCT03297281) trial is recruiting patients to a multi-center randomized trial to further assess the risks of NOAC use in PVP patients.

This study involved multiple centers with variations in standard practise. It is not possible to ascertain from the data available whether all patients had standard Foley or three-way catheters postoperatively which may affect interpretation of postoperative clot retention results.

Table 2 Patient factor.

Patient factor	Value
Age, year	77±6.5
BMI, kg/m^2	27±4.4
ASA	2.6
IPSS	17.4±6.1
Prostate volume, mL	94±56 (range: 34–245)

BMI, body mass index; ASA, American Society of Anesthesiologists; IPSS, International Prostate Symptom Score.

Table 3 Complications.

Complication	Patients affected, *n* (%)
Urinary tract infection	1 (5%)
Re-catheterisation for urinary retention	4 (20%)
Clot retention	0 (0%)
Haematuria requiring transfusion	0 (0%)

This study benefited from all surgeries being performed by one of three very experienced BPH-focused urologists, all of whom already had significant experience in PVP. As such, they are likely to have lower complication rates. Their experience may not translate to other institutions with general urologists or general surgeons performing urological procedures.

Additionally, we do not have long-term data sets assessing possible complications related to continuing NOAC therapy perioperatively.

Further research in this area needs to focus on several areas: Larger scale experience, surgical outcomes in less specialised settings, cost related to surgery and the costs of avoiding operations in patients with symptomatic BPH. Additionally, it is important to consider the relative risks of bleeding with usage of the different NOAC agents. Increasing evidence is pointing to higher risk of bleeding with use of rivaroxaban and dabigatran, and in the latter particular risk for gastrointestinal haemorrhage [25]. The results of the currently recruiting randomised control trial for patients treated with PVP while on oral anticoagulation (Clinical Trials: NCT03297281) are eagerly awaited.

5. Conclusion

As our population ages and the presence of an increasing number of co-morbid conditions become the norm, BPH patients are frequently using NOAC therapy. Our multicenter experience has failed to identify any significant bleeding-related outcomes. Larger scale, prospective trials will be required to further confirm these findings and to demonstrate cost-benefit to the community.

Author contributions

Study concept and design: Henry H. Woo.
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Conflicts of interest

The authors declare no conflict of interest.

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