Best practice in the management of benign prostatic hyperplasia in the patients requiring anticoagulation

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Abstract: In today’s aging population, urologists are often treating older patients with multiple comorbidities. Lower urinary tract symptoms from benign prostate hyperplasia (LUTS/BPH) is a common condition that affects men, with increasing prevalence as men age. In a subset of patients, the symptoms are too severe or refractory to medical therapy and, therefore, surgical therapy is required to improve their LUTS. The use of medical therapy often delays the need to intervene surgically in men with LUTS/BPH and with advances in the management of cardiovascular disease, urologists are increasingly encountering more men requiring BPH surgery on chronic anticoagulation therapy. The decision of when to offer surgical intervention and how to manage anticoagulation medication in the perioperative setting is a dilemma with which surgeons are dealing with increasing frequency. The purpose of this review is to clarify the optimal approach to the surgical patient with LUTS/ BPH requiring anticoagulation therapy.

Keywords: lower urinary tract symptoms (LUTS), benign prostate hyperplasia (BPH), anticoagulation therapy, anthiplatelet thrapy, surgical interventions

Introduction

In populations where life expectancy is increasing, the prevalence of lower urinary tract symptoms (LUTS) secondary to benign prostatic hyperplasia (BPH) is on the rise. Additionally, although medical therapy is effective at mitigating immediate LUTS, it often does not cure the underlying condition and delays intervention. As a result, urologists are faced with treating older patients with multiple comorbidities refractory or intolerant of BPH medications in need of surgical intervention for LUTS/BPH. This aging population of men suffering from LUTS/BPH often has concurrent cardiovascular diseases requiring anticoagulation (AC) or antiplatelet (AP) therapy.

The challenge of when to offer surgical intervention, which BPH surgery to perform, and how to manage blood thinners in the perioperative period is common among practicing urologists. In fact, in 2017, a survey completed by members of the Endourological Society found that the majority of BPH surgeons prefer to continue some form of anticoagulant therapy, in most cases, low-dose aspirin, during BPH procedures. In this review, we aim to clarify the approach to surgical management of BPH in the anticoagulated patient.

Current anticoagulants/antiplatelets

Prior to the advent of direct oral anticoagulants (DOACs) in 2010, there were limited therapeutic options for patients requiring AC therapy. Vitamin K antagonists such as warfarin were the mainstay of therapy in secondary stroke prevention for atrial fibrillation and venous thrombosis prevention. The use of warfarin posed a challenge for clinicians due to its multiple interactions with food and medications. DOACs, also referred to as novel anticoagulants, reduced the involvement of clinicians and patients in the treatment and monitoring of AC therapy by decreasing the need for routine lab monitoring and reducing the number of drug–drug and diet interactions with therapy. Additional benefits of DOACs included shorter therapeutic half-life, and fewer major bleeding complications compared with warfarin.
Examples of DOACs include direct factor Xa inhibitors such as: rivaroxaban (Xeralto®, Janssen Ortho LLC Gurabo, Puerto Rico or Bayer AG Leverkusen, Germany), apixaban (Eliquis®, Bristol-Myers Squibb Company, Princeton, NJ), Enoxaparin (Lovenox®): sanofi-aventis U.S. LLC, Bridgewater, NJ, Enoxaparin (Lovenox, sanofi-aventis U.S. LLC, Bridgewater, NJ) and direct thrombin inhibitors like dabigatran (Pradaxa®, Boehringer Ingelheim Pharmaceuticals, Inc. Ridgefield, CT) (Table 1). Though DOACs provide much benefit, they do have disadvantages, such as a lack of reversal agents for factor Xa inhibitors, and only recently was idarucizumab approved by the US Food and Drug Administration for reversal of dabigatran.5 Like warfarin, the current indications for DOAC treatment are venous thromboembolism (VTE) prevention, embolic stroke prevention in nonvalvular atrial fibrillation, and prevention of VTE after orthopedic surgery.6

As opposed to anticoagulants, AP therapy continues to be the principal treatment to reduce risk of thrombosis of coronary stents or coronary artery bypass grafts (CABGs). Primary and secondary prevention treatment of ischemic heart disease postcoronary stenting or CABG includes dual AP therapy of aspirin with a P2Y12 inhibitor, most commonly, clopidogrel. According to the updated 2016 American College of Cardiology guidelines, dual AP therapy should be given for at least 12 months in patients with recent acute coronary syndrome treated with either CABG or percutaneous coronary stenting.7

Current guidelines/recommendations
In 2014, the American Urological Association (AUA) published a review paper on AC and AP therapy in urological practice. The review suggests that a multidisciplinary approach to the management of antithrombotic medications in patients with recent thromboembolic events, mechanical valves, atrial fibrillation and cardiac stents reduces high morbidity and mortality when managing medications.8 According to the review paper, no elective procedure should be performed in patients within 1 year after placement of bare metal or drug-eluting stent. In the setting of BPH surgery, low-dose aspirin should be continued perioperatively in patients with cardiac risk factors because the data suggest no increased risk of major bleeding. Most relevant, the bleeding risk for patients who require continuation of aspirin for laser prostate outlet procedures is significantly low.8 The AUA best practice review states that there is not enough evidence to determine the best time to resume anticoagulant therapy postoperatively except that therapy be resumed once the bleeding risk has decreased.8 The 2018 AUA surgical management of LUTS attributed to BPH guidelines recommend that holmium or thulium laser enucleation (HoLEP/ThuLEP) or GreenLight photovaporization (PVP) be considered in patients who are at higher risk of bleeding, specifically those on AC drugs.9

According to the 2018 European Association of Urology (EAU) guidelines for treatment of non-neurogenic male LUTS, all types of laser prostatectomy seem to be safe in chronically anticoagulated patients. The guidelines concluded that PVP (532 laser) is safe and effective, HoLEP has been performed safely, diode laser is an alternative and thulium laser is safe as well.10

Procedures
Transurethral resection of the prostate
Transurethral resection of the prostate (TURP) is still the most common surgical intervention offered for LUTS/BPH.3 The most common practice, before TURP, is to discontinue all oral AC or AP therapy for a few days prior to surgery and to preoperatively bridge with heparin or low-molecular-weight heparin (LMWH) therapy.11 Descazeaud and colleagues studied the impact of oral AC on the morbidity of patients undergoing TURP and found that chronic oral AC has a significant impact on bleeding complications, duration of hospitalization and thromboembolic events. Duration of hospitalization was 6.4 days in the anticoagulated group versus 4.7 days in the control group, while bladder clots occurred in 13% of anticoagulated groups versus 4.7% in nonanticoagulated group.2 Ong and colleagues reported that chronic anticoagulated patients who underwent enoxaparin bridging had higher risk of bleeding complications (44%) when compared with no oral AC (8%). Additionally, patients continuing perioperative AP therapy had a higher complication rate (17%) versus patients who stopped (4%) therapy. These complications included requiring continuous bladder irrigation (CBI) greater than 2 days and clot retention necessitating catheter reinsertion. Patients on oral AC also had significantly higher thromboembolic
complications and prolonged hospital stay when compared to non-anticoagulated patients. A retrospective study by Taylor and colleagues found higher bleeding complication rates in patients continuing AP therapy or in chronically anticoagulated patients undergoing TURP (26.3% versus 9.8%). Most importantly, the study found that patients who withheld their oral AC preoperatively had significantly higher rates of cardio and cerebrovascular complications. The AUA best practice review paper suggests that due to the high rate of bleeding complications in oral AC patients undergoing TURP that alternative bladder outlet procedures, such as laser therapy, be offered.

**Laser ablation**

Overall, laser ablative procedures of the prostate have been found to be safe and effective in the anticoagulated patient. Chung et al. analyzed 162 men undergoing 532 nm PVP while on chronic AC. Of the patients 19% were on warfarin, 62% on asa, 12% were on clopidogrel and 7% were on 2 or more anticoagulants. All anticoagulants were continued at time of surgery except warfarin which was stopped 1–3 days preoperatively. Average age was 72 years with a mean transrectal ultrasound volume measurement of 91 g. There were no significant differences in length of stay between the control and anticoagulated groups (1.1 days versus 1.2 days). Delayed bleeding requiring CBI occurred in six (3.7%) patients and three of these required a blood transfusion. Reoperation for clot evacuation and fulguration of bleeding was required in one (0.6%) patient. The study concluded that PVP in patients with systemic AC is safe and effective.

**Laser enucleation**

HoLEP has been proven safe and effective in anticoagulated patients. In 2006, Elzayat and colleagues published one of the first studies assessing the safety of HoLEP in patients on antithrombotic therapy. A total of 81 patients were on AC; 14 underwent HoLEP without withdrawal of oral anticoagulants, 34 were with LMWH bridging, and 33 stopped 5 days prior surgery without bridging. Mucosal bladder injury and capsular perforation occurred in two and one patients, respectively. One patient who did not stop clopidogrel required intraoperative platelet transfusion due to bleeding, and morcellation was postponed because of decreased vision. Blood transfusion was required postoperatively in seven patients (8.4%). Three patients (3.6%) had clot retention and required rehospitalization for CBI within 2 weeks of surgery. The study compared these complication rates with TURP and determined that complication rates with HoLEP in the anticoagulated patient were considerably lower. The authors concluded that the hemostatic
properties of the holmium laser allow HoLEP to be safer and effective when compared with other BPH treatment options on anticoagulated patients. Specifically, the low depth of penetration of the holmium laser limits eschar formation which can contribute to delayed bleeding seen with other BPH procedures.20

El Tayeb and colleagues compared 116 patients taking AC therapy with 1558 nonanticoagulated patients who underwent HoLEP at their institution. There was no difference in specimen weight between groups (69.8 g in the AC group versus 68 g in the control). There was no significant difference in both enucleation (51 min versus

Table 1. Common anticoagulant/antiplatelet medications encountered by urologists.24

| Warfarin (Pradaxa®) | Dabigatran (Pradaxa®) | Rivaroxaban (Xarelto®) | Apixaban (Eliquis®) | Enoxaparin (Lovenox®) | Clopidogrel (Plavix®) |
|---------------------|-----------------------|------------------------|---------------------|-----------------------|-----------------------|
| Target | Vitamin K epoxide reductase | Thrombin | Factor Xa | Factor Xa | Antithrombin III | ADP [P2Y12] |
| Half-life (h) | 20–60 | 12–17 | 5–9 | 9–14 | 4.5 | N/A |
| Onset of peak effect (h) | 72–96 | 2 | 2–3 | 3 | 3–5 | 2–8 |
| Duration of action | 2–5 days | 24–36 h | 24 h | 24 h | 24 h | 7–10 days |
| Metabolism | Via cytochrome P450 | Via P-glucoprotein transporter | Via cytochrome P450 (30%) and via P-glucoprotein transporter | Via cytochrome P450 (15%) and via P-glucoprotein transporter | metabolized in the liver by desulfation and depolymerization | Via cytochrome P450 (15%) 85% inactive |

ADP, adenosine diphosphate.

Table 2. Bleeding complication and transfusion rates in comparative studies on patients requiring anticoagulation.

| Study | Year | Procedure | n | Bleeding complication rate (%) | Transfusion rate (%) | Level of evidence |
|-------|------|-----------|---|-------------------------------|----------------------|------------------|
| Descazeaud et al. | 2011 | TURP | 206 | 15 | 1.9 | II |
| Ong et al. | 2015 | TURP | 126 | 12.6 | 2.4 | II |
| Taylor et al. | 2011 | TURP | 72 | 2.6 | 5.5 | II |
| Ruszat et al. | 2008 | PVP | 222 | 9.8 | 0 | II |
| Chung et al. | 2011 | PVP | 162 | 4 | 2 | II |
| Woo et al. | 2011 | PVP | 43 | 4.7 | 0 | II |
| Knapp et al. | 2017 | PVP | 59 | 1.7 | 0 | II |
| El Tayeb et al. | 2016 | HoLEP | 116 | 0 | 3.5 | II |
| Bishop et al. | 2013 | HoLEP | 52 | 0 | 7.7 | II |
| Elzayat et al. | 2006 | HoLEP | 83 | 3.6 | 8.4 | II |

HoLEP, holmium laser enucleation; PVP, GreenLight photovaporization; TURP, transurethral resection of the prostate.
65 min, AC versus control, respectively) and morcellation (5 g/min versus 4.5 g/min AC versus control, respectively) times between cohorts. There was no difference in postoperative outcomes except for longer length of stay (27.8 h versus 24 h) and duration of CBI (15 h versus 13.5 h) in the anticoagulated group, which was of low clinical significance. The transfusion rate was not significantly different (3.5% anticoagulated versus 1.6% control) and only two patients (1.9%) in the anticoagulated HoLEP group required clot evacuation versus 10 (0.7%) in the control group.

Bishop and colleagues compared the immediate postoperative outcomes in patients with and without AC therapy undergoing HoLEP. The authors compared 52 patients on antithrombotic therapy at the time of HoLEP with 73 patients not on anticoagulant therapy at time of HoLEP. The median length of hospital stay was longer in the antithrombic group (2 days versus 1 day). Blood transfusion was required in four (7.7%) patients versus none in the nonanticoagulated group. Studies such as the ones highlighted from Bishop and colleagues and El Tayeb and colleagues confirm that HoLEP is a safe and feasible treatment option for patients with large-gland BPH on anticoagulant or AP therapy requiring surgical intervention.

Thulium laser vapoenucleation (ThuVEP) and thulium laser enucleation (ThuLEP) utilize a similar technique as HoLEP, and the AUA guidelines recommend them as alternative to HoLEP in medically complex patients, specifically those requiring AC.

**Open simple prostatectomy and robotic simple prostatectomy**

There are no studies or case reports within the literature evaluating the safety of open prostatectomy or robotic simple prostatectomy (RASP) in patients on AP/AC. In 2008, Krane and colleagues compared outcomes of patients undergoing robotic radical prostatectomy (RALP) who required AC therapy versus standard nonanticoagulated patients. Though the surgical technique of RALP compared to RASP is significantly different, the risk of bleeding and bleeding sequelae can be considered equivalent and thus RALP in patients on AC can be considered a surrogate for potential outcomes of RASP on AC. Patients on AC in this study either discontinued AC 7 days prior or were bridged with LMWH for 3 days before surgery. The authors found 6.7% transfusion rate compared with 1.7% in standard patients. Readmission rates (5% versus 0.6%) were higher after RALP in the anticoagulated population compared with standard patients. More data are needed prior to advocating AC bridging and RASP for men with LUTS due to large-gland BPH.

**Novel/emerging therapies**

New minimally invasive novel therapies for BPH lack evidence for specific recommendation on the management of antithrombotic therapy. To our knowledge, there are no published studies or data specifically focusing on the safety of Urolift™, Rezum™, Aquablation™ and prostate artery embolization in patients requiring AC. The use of these modalities to surgically treat LUTS/BPH in anticoagulated patients was not commented on in the 2018 AUA guidelines on BPH.

**Conclusion**

As longevity improves and prevalence of cardiovascular disease increases, urologists should anticipate a rise in surgical consultations for LUTS/BPH in patients on antithrombotic therapy. According to the AUA best practice statement and published data, laser enucleation and ablation procedures such as HoLEP and PVP provide clinicians with the safest surgical management options for BPH in patients requiring chronic antithrombic medication (Table 2). The decision on how to manage these patients should utilize a multidisciplinary approach involving the urologist, cardiologist, primary care and anesthesiologist to develop a patient-specific management plan.

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**References**

1. Vela-Navarrete R, Gonzalez-Enguita C, Garcia-Cardoso JV, et al. The impact of medical therapy on surgery for benign prostatic hyperplasia: a study comparing changes in a decade (1992-2002). *BJU Int* 2005; 96: 1045–1048.

2. Descarzeaud A, Robert G, Lebdai S, et al. Impact of oral anticoagulation on morbidity of
transurethral resection of the prostate. World J Urol 2011; 29: 211–216.
3. Becker B, Knipper S, Gross AJ, et al. Current management in transurethral therapy of benign prostatic obstruction in patients on oral anticoagulation: a worldwide questionnaire. J Endourol 2017; 31: 163–168.
4. Chai-Adisaksopha C, Crowther M, Isayama T, et al. The impact of bleeding complications in patients receiving target-specific oral anticoagulants: a systematic review and meta-analysis. Blood 2014; 124: 2450–2458.
5. Almegren M. Reversal of direct oral anticoagulants. Vasc Health Risk Manag 2017; 13: 287–292.
6. Milling TJ Jr and Frontera J. Exploring indications for the use of direct oral anticoagulants and the associated risks of major bleeding. Am J Manag Care 2017; 23(Suppl. 4): S67–S80.
7. Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Thorac Cardiovasc Surg 2016; 152: 1243–1275.
8. Culkin DJ, Exaire EJ, Green D, et al. Anticoagulation and antiplatelet therapy in urological practice: ICUD/AUA review paper. J Urol 2014; 192: 1026–1034.
9. Foster HE, Barry MJ, Dahm P, et al. Surgical management of lower urinary tract symptoms attributed to benign prostatic hyperplasia: AUA guideline. J Urol 2018; 11: 43201–43206.
10. Gravas S, Cornu JN, Drake MJ, et al. Tikkinen treatment of non-neurogenic male LUTS. EAU guidelines. Copenhagen: EAU Annual Congress, 2018.
11. Berger J, Robert G and Descaczeaud A. Laser treatment of benign prostatic hyperplasia in patients on oral anticoagulant therapy. Curr Urol Rep 2010; 11: 236–241.
12. Ong WL, Koh TL, Fletcher J, et al. Perioperative management of antiplatelets and anticoagulants among patients undergoing elective transurethral resection of the prostate—a single institution experience. J Endourol 2015; 29: 1321–1327.
13. Taylor K, Filgate R, Guo DY, et al. A retrospective study to assess the morbidity associated with transurethral prostatectomy in patients on antiplatelet or anticoagulant drugs. BJU Int 2011; 108 (Suppl. 2): 45–50.
14. Marien T and Shah O. Bladder outlet procedures in the setting of anticoagulation therapy. Curr Opin Urol 2013; 23: 30–37.
15. Chung DE, Wysock JS, Lee RK, et al. Outcomes and complications after 532 nm laser prostatectomy in anticoagulated patients with benign prostatic hyperplasia. J Urol 2011; 186: 977–981.
16. Woo HH and Hossack TA. Photosensitive vaporization of the prostate with the 120-W lithium triborate laser in men taking coumadin. Urology 2011; 78: 142–145.
17. Ruszat R, Seitz M, Wyler SF, et al. GreenLight laser vaporization of the prostate: single-center experience and long-term results after 500 procedures. Eur Urol 2008; 54: 893–901.
18. Knapp GL, Chalasani V and Woo HH. Perioperative adverse events in patients on continued anticoagulation undergoing photosensitive vapourisation of the prostate with the 180-W Greenlight lithium triborate laser. BJU Int 2017; 5(Suppl. 119): 33–38.
19. Michalak J, Tzou D and Funk J. HoLEP: the gold standard for the surgical management of BPH in the 21st century. Am J Clin Exp Urol 2015; 3: 36–42.
20. Elzayat E, Habib E and Elhilali M. Holmium laser enucleation of the prostate in patients on anticoagulant therapy or with bleeding disorders. J Urol 2006; 175: 1428–1432.
21. El Tayeb MM, Jacob JM, Bhojani N, et al. Holmium laser enucleation of the prostate in patients requiring anticoagulation. J Endourol 2016; 30: 805–809.
22. Bishop CV, Liddell H, Ischia J, et al. Holmium laser enucleation of the prostate: comparison of immediate postoperative outcomes in patients with and without antithrombotic therapy. Curr Urol 2013; 7: 28–33.
23. Krane LS, Laungani R, Satyanarayana R, et al. Robotic-assisted radical prostatectomy in patients receiving chronic anticoagulation therapy: role of perioperative bridging. Urology 2008; 72: 1351–1355.
24. Rivera M, Krambeck A and Lingeman J. Holmium laser enucleation of the prostate in patients requiring anticoagulation. Curr Urol Rep 2017; 18: 77.