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Holmium Laser Enucleation of the Prostate in Patients Requiring Anticoagulation

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Abstract
Purpose of Review This is to evaluate and discuss the literature surrounding holmium laser enucleation of the prostate (HoLEP) in patients on anticoagulation.
Recent Findings The relationship of benign prostatic hyperplasia (BPH) to bothersome lower urinary tract symptoms (LUTS) is well established with a majority of men over the age of 60 having significant symptoms. Patients with severe enough symptoms often require surgery and with cardiovascular disease ranking as the primary cause of death in the USA, a growing number will be taking antiplatelet (AP) or anticoagulation (AC) for primary or secondary prevention of disease. A review of the recent literature focusing on patients on AP/AC undergoing HoLEP noted minimal adverse effects in the postoperative course aside from prolonged bleeding requiring catheterization with continuous bladder irrigation.
Summary Although patients with BPH and bothersome LUTS undergoing HoLEP are at a slightly greater risk for prolonged bladder irrigation secondary to bleeding, surgical outcomes are similar to men not on AP/AC. The literature surrounding newer direct oral anticoagulants (DOACs) and HoLEP is limited, and therefore, conclusions regarding continuation of DOACs cannot be drawn. However, HoLEP appears to be a safe and effective procedure for BPH-related LUTS in patients on AP/AC therapy.

Keywords Lower urinary tract symptoms · Benign prostatic obstruction · Holmium laser enucleation of the prostate (HoLEP) · Anticoagulation

Abbreviations

LUTS	Lower urinary tract symptoms
BPH	Benign prostatic hyperplasia
HoLEP	Holmium laser enucleation of the prostate
VTE	Venous thromboembolism
DAPT	Dual antiplatelet therapy
AC	Anticoagulation
AP	Antiplatelet
AUR	Acute urinary retention
DOACs	direct oral anticoagulants
CABG	Coronary artery bypass grafting
ASA	American Society of Anesthesiologists

Introduction

Lower urinary tract symptoms (LUTS) related to benign prostatic hyperplasia (BPH) occur frequently in the aging male, with nearly three quarters of men experiencing symptoms by the age of 70 [1]. Common symptoms include nocturia, weakened urinary stream, stranguria and/or sensation of incomplete emptying, urgency, and even urinary incontinence. More advanced disease can present with acute urinary retention (AUR), obstructive uropathy, recurrent urinary tract infections, hematuria, bladder stones, and even acute renal failure. The advent of medical therapy has been effective at reducing LUTS related to BPH [2,3]. Nonetheless, a significant number of men with bothersome

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LUTS on medical therapy will develop severe enough symptoms or complications requiring them to undergo surgical management. Recent investigation has also noted that episodes of AUR are increasing in incidence in the USA which may be due to the aging population and significant medical comorbidities associated with advanced age [4,5].

The most concerning and life threatening of aging comorbidities is cardiovascular disease, which is the leading cause of death in the USA. Most treatments for cardiovascular disease are used in conjunction with AC and AP medications. Patients with cardiovascular disease, especially those with atrial fibrillation and/or history of thromboembolic events, present to their Urologist on AC or AP [6]. Such complex patients present a management conundrum to the BPH surgeon. A recent survey to the members of the Endourological Society regarding AC and BPH surgery found that, among respondents to the survey, the management preference of the majority of BPH surgeons is to continue at least some AC therapy during a procedure [7].

Holmium laser enucleation of the prostate (HoLEP) represents a safe and effective surgical option for patients with BPH-related LUTS with superior outcomes to traditional transurethral resection [8]. Importantly, HoLEP has been investigated in the anticoagulated patient and found to be a safe and efficacious treatment even when the medication is continued through the surgical period [9•, 10, 11•]. We will discuss our current surgical technique and report on the current evidence surrounding HoLEP in patients taking AC and AP in comparison to other treatment modalities.

Our Current Surgical Technique

After urethral dilation using sequential metal sounds, a 28F continuous flow resectoscope (Karl Storz Endoscopy, Culver City, CA) with a laser bridge that houses a 7F stabilizing catheter (Cook Medical, Spencer, IN) is inserted into the bladder. Enucleation begins with incisions at the 5 and 7 o'clock position if a median lobe is present or at the 6 o'clock position in the absence of a median lobe. We have also adopted a top down approach which begins in a similar fashion as the standard enucleation technique, but after the initial groves are made down to the surgical capsule, the anterior commissure is divided and enucleation continues anteriorly around laterally until the apex is encountered. The mucosal bridge is found apically and divided. We utilize either a 100 or 120 W Ho:YAG laser with a 550 or 1000 μm laser fiber. In all cases, saline is used as the irrigant. Briefly, the enucleation requires laser settings of 2 J and 40 to 50 Hz for the lateral lobes, 2 J and 20 Hz for the apical dissection, and 2 J and 20 Hz to divide the apical mucosal bridges. Throughout the course of enucleation blood vessels are coagulated as they are encountered. Coagulation occurs by defocusing the laser on the blood vessel and moving the laser closer to the bleeding until the tissue has blanched appropriately. Utilizing a longer pulse width with the 120 W laser, the defocusing technique is not required and any bleeding vessel can be touched with the laser fiber to coagulate. At the conclusion of enucleation, excellent hemostasis must be confirmed as this will make morcellation more efficient and safer. Areas of most concern for bleeding are typically the bladder neck. Tissue morcellation is the next performed utilizing a Storz nephroscope. We currently utilize the Wolf Piranha morcellator. The previous excellent visualization afforded by the laser resectoscope is limited during morcellation since suction or continue flow only occurs when the jaws of the morcellator are activated. Thus, control of all bleeding prior to morcellation is of critical importance. Once morcellation is complete, repeat cystoscopy is performed with the laser scope to ensure all tissue has been removed and to again create hemostasis if necessary.

Current Anticoagulants/Antiplatelets

Prior to 2010, there were very few options to the significant number of patients who required anticoagulation. Vitamin K antagonists like warfarin represented the principle therapy for secondary prevention of stroke in patients with atrial fibrillation and prevention of VTE. However, significant interactions with food and other medications mandate intensive monitoring of coagulation levels thus making it challenging for patients who require therapeutic anticoagulation [12].

Treatment options for the patient requiring anticoagulation changed dramatically in 2010 with the introduction of direct oral anticoagulants (DOACs), sometimes referred to as novel ACs. Since 2010, four DOACs have entered the American market. They offer several advantages over traditional vitamin K antagonists (Warfarin), including lack of routine lab monitoring, fewer drug dietary interactions, shorter reversal time, and fewer major bleeding events [13–15]. Dabigatran is a direct thrombin inhibitor with rivaroxaban, apixaban, and edoxaban direct factor Xa

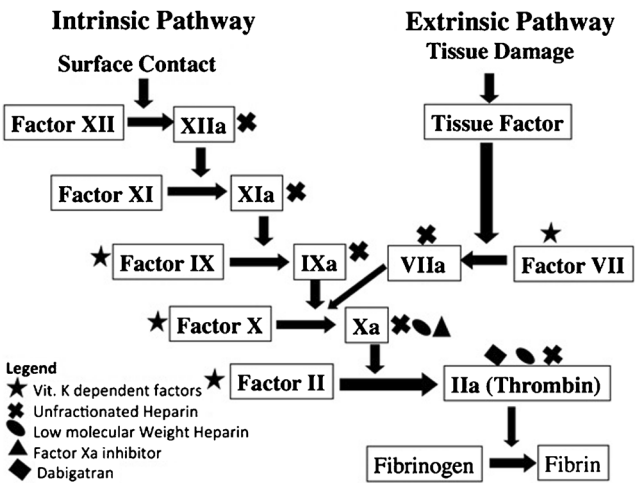

Fig. 1 Coagulation cascade and actions of current anticoagulants

inhibitors (Fig. 1). These medications are not without drawbacks, including a lack of an antidote or reversal agent for the factor Xa inhibitors. Recently, in 2015, the FDA approved idarucizumab for the use of dabigatran reversal [16,17].

Current uses and recommended indications of DOACs include treatment and secondary prevention of non-cancer-related venous thromboembolism (VTE), secondary prevention of embolic stroke in non-valvular atrial fibrillation, and the prevention of VTE after orthopedic surgery [13–15] Table 1.

Antiplatelet therapy remains the mainstay treatment for the primary and secondary prevention of ischemic heart disease with aspirin combined with a P2Y12 inhibitor (i.e., clopidogrel) being utilized as dual AP therapy to reduce thrombosis of coronary stents or coronary bypass grafts (CABG). Recommendations by the American Cardiology College and the American Heart Association include at least 12 months of dual AP therapy for patients with recent acute coronary syndrome who receive percutaneous coronary intervention with bare metal or drug-eluting stents and for those after CABG [18].

HoLEP and Anticoagulation/Antiplatelet Medication

While the literature contains a plethora of investigation regarding surgical management of BPH and various techniques and technologies, there is far less investigation into HoLEP and bleeding prone patients. To date, there have been four studies specifically evaluating patient outcomes while continuing AP/AC medications. Previous investigations into HoLEP have demonstrated similar efficacy with reduced morbidity when compared to suprapubic prostatectomy and superior outcomes when compared to TURP [19–22].

The Holmium laser offers significant advantages over traditional monopolar transurethral resection of the prostate (TURP) when AC/AP is continued. Multiple investigations into TURP when continuing AC/AP compared to TURP controls demonstrated increased rates of transfusion and clot evacuations [23,24]. The observed benefit of HoLEP in maintaining hemostasis even in AC/AP patients is likely a combination of the physics of the Holmium laser and the complete removal of the transitional zone. Introduced commercially in 1991, the Holmium: yttrium aluminum garnet (Ho:YAG) laser is a pulsed, solid-state 2140 nm laser with typical pulse duration of 350 ms [25,26]. Due to the chromophore of water and minimal tissue depth penetration (0.4 mm), the laser achieves rapid vaporization and coagulation of tissue without the disadvantage of deep tissue penetration. This feature of the holmium laser allows for rapid hemostasis, which is beneficial when operating on patients taking AC/APs [27].

The initial small discussion of HoLEP and AC/AP was made by Hochreiter et al., which reported treatment of 19 patients on oral AC with none requiring a blood transfusion; however, two patients did require clot evacuation after going into clot retention [28]. Most recently, a review by El Tayeb and colleagues evaluated 1558 patients at our institution who underwent HoLEP and identified 116 who were on AC/AP medication, including aspirin (325 mg), clopidogrel, aspirin/dipyridamole, dabigatran, enoxaparin, or warfarin, in the perioperative period. All patients on 81 mg aspirin were excluded from the AP/AC group [9•]. Compared to patients not on AP/AC medication, those on AP/AC had a shorter procedure length 51 vs 65 min ($p < 0.001$) and faster morcellation rate, 5 vs 4.5 g/min ($p = 0.02$). Postoperatively, patients on AP/AC had a slightly longer length of stay by 3.8 h and prolonged continuous bladder irrigation by 1.5 h. Transfusion rates were not different between the two groups nor were rates of clot evacuation. Patients were further divided in the AP/AC group as to whether medications were continued or halted in the preoperative period. Within the group of continuous AP/AC patients, 15 were on warfarin; 2, enoxaparin; 10, clopidogrel; 9, aspirin; 1, aspirin/dipyridamole; 2, dabigatran. Interestingly, there were no differences in enucleation or morcellation time, catheterization time, or rates of blood transfusion.

In another report on HoLEP and patients on AP/AC therapy, Bishop et al. noted 52 patients on AP/AC therapy versus 73 not on therapy [11•]. In this retrospective review, medications utilized by patients included aspirin (100–150 mg), clopidogrel, dipyridamole/aspirin, or coumadin. Of the 52 patients that remained on AP/AC medications, 11 patients were on aspirin; 3, on dipyridamole/aspirin; 16, on clopidogrel; and 22, on warfarin with a mean INR of 2.61 at the time of surgery. Patients within the AP/AC group were older with a mean age of 75.1 years compared to 71.7 in the non-AP/AC group. As one would predict, the AP/AC group was also less healthy than the comparison cohort with a mean American Society of Anesthesiologists (ASA) score of 3 compared to 2 in the non-AP/AC group. Resection rates, operative times, and enucleated weights were not different between the two cohorts. Transfusion rates were different in this series with patients AP/AC medications having a 7.7% rate of transfusion ($p = 0.028$) while two patients in the non-AP/AC group required reoperation for bladder repair due to an unrecognized morcellator injury.

In a series evaluating oral AC/AP, specifically aspirin or warfarin therapy, Tyson and Lerner evaluated 76 patients undergoing HoLEP. Of these 38 patients, 25 were on aspirin therapy. The dose of aspirin used was not provided, and the mean INR of patients on warfarin therapy was 1.5 (SD 0.4). Control patients without AC/AP therapy were compared to patients on aspirin or warfarin. There were no differences in prostate volume, average length of hospital stay, duration of catheterization, or rates of transfusion between the three groups. In postoperative follow-up, patients were questioned regarding urinary incontinence requiring pads by 3 months with no difference found between the three groups.

Table 1 Commonly encountered anticoagulants/antiplatelet drugs [30–34]

	Warfarin	Dabigatran (Pradaxa®)	Rivaroxaban (Xarelto®)	Apixaban (Eliquis®)	Edoxaban (Savaysa®)	Clopidogrel (Plavix®)
Target	Vitamin K epoxide reductase	Thrombin	Factor Xa	Factor Xa	Factor Xa	ADP (P2Y12)
Half-life (hours)	20–60	12–17	5–9	9–14	9–11	N/A
Onset time peak effect (hours)	72–96	2	2–3	3	1–2	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 P-plucoprotein transporter	Via cytochrome P450 (15%), and P-glucoprotein transporter	Minimal via cytochrome P450	Via cytochrome P450 (15%), 85% inactive

In the first investigation into HoLEP and patients on AC/AP therapy or with thrombophilia, Elzayat and colleagues evaluated 81 patients on AC/AP and 2 with hemophilia without a control group [29]. A total of 14 patients continued therapeutic AC/AP with 34 bridging with LMWH. A group of 33 held AC including 8 patients on clopidogrel. Mean weight of tissue enucleated was 54.7 g and enucleation time of 86.5 min, catheterization time was 2.2 days with mean hospitalization of 2.5 days. Blood transfusions were required in 7 patients with an additional patient who continued clopidogrel requiring a platelet transfusion due to intraoperative bleeding. Within the group of patients requiring a blood transfusion, 2 were on full AC/AP; 5, on bridging therapy with LMWH; and 1, off of AC/AP therapy. In follow-up, a robust 210% improvement in uroflowmetry, as well as improvement in post void residual and international prostate symptom score was noted.

As reflected by the previous review of the literature, all studies to date have noted that HoLEP appears to be safe in men who continue AC/AP therapy in the perioperative period. However, several of these investigations are historical and are pre-DOAC therapy. Only one investigation included patients on DOAC therapy, and no studies had a patient taking rivaroxaban, apixaban, or edoxaban. Further investigation into the safety of HoLEP in men actively taking DOAC is needed to make definitive conclusions.

Conclusion

HoLEP can be performed safely on patients who require continuous AP/AC therapy during surgery. However, there is limited data surrounding DOACs and bleeding-related complications in HoLEP. Further investigation is warranted as the indications for these newer medications is broadened and will be encountered with increasing frequency by the practicing BPH surgeon.

Compliance with Ethical Standards

Conflict of Interest Marcelino Rivera declares no potential conflicts of interest.

Amy Krambeck reports personal fees from Lumenis, Boston Scientific, and Thermedx.

James Lingeman reports personal fees from Lumenis, Boston Scientific, and Beck Analytical; is an owner and medical directory of Beck Analytical; and owner and investor of Midwest Mobile Lithotripsy.

Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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