

## Safety of Holmium Laser Enucleation of the Prostate in Anticoagulated Patients

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### Abstract

**Purpose:** Oral anticoagulation (OA) is considered a strict contraindication to transurethral resection of the prostate (TURP). In recent years, however, safe and effective surgical alternatives such as holmium laser enucleation of the prostate (HoLEP) have emerged. Evidence from randomized trials has revealed that HoLEP has fewer bleeding complications than TURP, suggesting that HoLEP in anticoagulated patients is safer than TURP. However, published data evaluating bleeding complications in anticoagulated patients undergoing HoLEP are incomplete. Using a retrospective design, this is the first study to compare the bleeding complication rates of anticoagulated patients undergoing HoLEP to patients not on OA.

**Materials and Methods:** We reviewed the electronic medical records of the first 76 HoLEP patients treated by a single urologist in two New England hospitals from May 2002 to September 2007.

**Results:** Thirty-nine were on OA, and 37 were controls. Thirteen patients were on coumadin (mean international normalized ratio [INR] 1.5), and 25 were on aspirin at the time of their surgery. Among the patients on OA, 8% ( $n = 2$ ) had intraoperative hematuria compared to 14% ( $n = 5$ ) of controls ( $p = 0.25$ ). No patients in either group required blood transfusions. Stratifying the OA population revealed no statistical differences in bleeding complication rates between the coumadin, aspirin, and control groups ( $p = 0.34$ ). Additionally, there were no differences in standard postoperative outcomes.

**Conclusion:** These findings suggest that HoLEP has excellent hemostatic properties in high-risk patients and is a safe surgical alternative to TURP in patients on OA.

### Introduction

**T**RANSURETHRAL RESECTION OF THE PROSTATE (TURP) has remained the gold standard for the surgical relief of bladder outlet obstruction caused by benign prostatic hyperplasia (BPH). Despite its widespread use, TURP is accompanied by significant morbidity with complication rates approaching 15%.<sup>1</sup> Postoperative bleeding complications necessitating blood transfusion have been reported to be as high as 6.4% in the general population. This has in turn led to the emergence of alternative surgical techniques that have challenged the market share of transurethral prostatectomies, especially in patients at higher risk for bleeding complications. Holmium:yttrium aluminum garnet (Ho:YAG) laser is one such alternative that has been shown to be as effective as TURP at relieving urodynamically proven obstruction while having an overall lower complication rate.<sup>2</sup> Evidence from randomized trials in recent years has shown that, compared to TURP, holmium laser enucleation of the prostate (HoLEP) has less blood loss, requires shorter hospitalizations, and has

shorter durations of catheterization despite an increase in operating time.<sup>3–6</sup> This has led many to conclude that HoLEP is safer than TURP in patients at risk of bleeding, such as patients on oral anticoagulation (OA) or patients with inherited coagulopathies.

There are many indications for OA, especially in an aging population of patients with BPH undergoing TURP. Generally, these men tend to have multiple medical comorbidities, such as cardiac arrhythmias, coronary artery disease, deep venous thrombosis, cerebral vascular disease, and prosthetic heart valves. While discontinuing OA in the preoperative period lowers the risk of intraoperative bleeding complications, it has to be weighed against the risk of thrombosis in the intraoperative and postoperative periods. This is especially true in patients undergoing TURP for BPH. Bell and colleagues reported a significant increase in the circulating thrombin-antithrombin complexes 6 hours after TURP as well as a significant decrease in activated partial thromboplastin time, suggesting that TURP is associated with a hypercoagulable, prothrombotic state in the immediate postoperative period.<sup>7</sup>

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While no such study exists for HoLEP, the risks of thrombosis in anticoagulated patients who discontinue their OA in the preoperative period still remains.

Our study attempts to address the question regarding the safety of HoLEP in patients on OA. To our knowledge, this is the first study to compare complication rates in anticoagulated patients undergoing HoLEP to a set of controls with no known risk factors for bleeding. Establishing the safety of HoLEP in patients on OA could have broad implications, especially for patients undergoing endoscopic procedures for BPH.

### Materials and Methods

We retrospectively reviewed data from the first 76 patients with symptomatic BPH who underwent HoLEP by a fellowship-trained urologist practicing in two New England hospitals from May 2002 to September 2007. The review focused on bleeding complications, such as blood transfusion rates and intraoperative hematuria that required termination of the procedure secondary to obscured observation. We also reviewed data related to length of hospitalization, duration of catheterization, acute urinary retention, readmission rates, rates of urinary incontinence, urinary tract infections, and dysuria. All measures, except for urinary retention, were evaluated at 3 months. Acute urinary retention was defined as anyone requiring a Foley catheter or clean intermittent catheterization within 21 days. Incontinence was defined as anyone reporting the use of daily pads at 3 months, regardless of whether the need for a pad was real or perceived.

Preoperative evaluation of patients included a focused history and physical examination, including a digital rectal exam. Lower urinary tract symptoms characterized by international prostate symptom score and symptom complaints. Prostate volume was determined by transrectal ultrasound, when indicated, and serum prostate-specific antigen levels were obtained. The instruments and surgical procedures for HoLEP have been previously described in detail.<sup>8,9</sup> A 20F double lumen Foley catheter was placed in most patients for 1 to 2 days, depending on patient factors such as previous urinary retention and/or catheterization. Occasionally, a 24F three-way was placed. Most patients were discharged on the day of operation or admitted for a 23-hour observation stay.

All statistical calculations were computed using Stata<sup>®</sup> v10.0 for Mac OS<sup>®</sup> X. Categorical data were analyzed using the chi-squared test. The Kruskal-Wallis *H* test was used to compare the three groups of independent nonparametric numerical data. This study received approval from the Committee for the Protection of Human Subjects, which serves as the institutional review board for Dartmouth Medical School.

### Results

A total of 76 patients were included in this study (39 on OA and 37 controls). Of the 39 on OA, 25 patients were on aspirin, 13 were taking coumadin, and 1 was taking clopidogrel in the preoperative period leading up to surgery. The most common indication for coumadin in this cohort was cardiac arrhythmia, while coronary artery disease was the most common indication for aspirin. Since only one patient was on clopidogrel, analysis of this group was not statistically valuable and was therefore dropped from further analysis. Notably, this patient did not have any bleeding complications.

TABLE 1. BASELINE COHORT DATA  
(MEAN ± STANDARD DEVIATION)

	Control	Aspirin	Coumadin	p
Age (years)	65.2 ± 8.7	69.4 ± 7.2	70.6 ± 7.1	0.05
Prostate volume (cc)	49.9 ± 20.6	65.0 ± 31.7	50.3 ± 16.7	0.13
PSA (ng/mL)	4.4 ± 3.9	4.3 ± 6.0	3.9 ± 2.2	0.77
Time spent in OR (minute)	176 ± 69	169 ± 65	150 ± 62	0.32
Irrigation fluids (L)	1.3 ± 0.62	1.5 ± 0.26	1.6 ± 0.50	0.28
IPSS score	23.5 ± 6.7	23.3 ± 4.5	16.5 ± 8.7	0.24
QOL score	3.4 ± 1.4	4.0 ± 0.82	3.6 ± 2.0	0.58
INR	–	–	1.5 ± 0.4	–

PSA = prostate-specific antigen; IPSS = international prostate symptom score; QOL = quality of life; INR = international normalized ratio.

The mean preoperative INR of the 13 patients on coumadin was 1.5 ± 0.4 SD (range, 1.2–2.2; Table 1). All but two patients had INRs below 2.0. Routine preoperative INRs are not obtained on patients at low risk for bleeding, so these data are unavailable for the remainder of the cohort. With respect to all other baseline cohort data (Table 1), there were no significant differences between the three groups regarding prostate volume, preoperative prostate-specific antigen, international prostate symptom scores, or quality of life scores. However, the coumadin and aspirin groups tended to be older ( $p = 0.05$ ).

With regard to bleeding, five patients in the control group (14%) and two patients on aspirin (8%) had persistent intraoperative hematuria that required termination of the procedure secondary to obstructed observation ( $p = 0.34$ ; Table 2). Two of the patients had bleeding secondary to inadvertent resectoscope trauma and perforation of the prostatic capsule. However, no patients required blood transfusions either intraoperatively or in the immediate postoperative period, and of the seven patients who required a second procedure to complete the retrieval of retained prostate fragments, none experienced any bleeding complications during these operations.

With regard to all standard postoperative outcomes evaluated in this study, there were no differences between the three groups (Table 2). The average length of hospitalization for all three groups was approximately 1 day ( $p = 0.99$ ), and the average duration of catheterization was 2 days ( $p = 0.93$ ), although most patients were discharged without an indwelling catheter in place ( $p = 0.94$ ). Regarding the need for continuous bladder irrigation (CBI), there were no differences between the three groups ( $p = 0.29$ ). Among patients who received CBI, there were no differences in the length of time CBI was administered ( $p = 0.87$ ). Readmission rates at 3 months were similar among the three groups with only five patients requiring readmission ( $p = 0.57$ ), and only one of which for hematuria ( $p = 0.59$ ). Notably, the patient who was readmitted for bleeding was in the control group. Rates of incontinence at 3 months were similar between all three groups. When stratified by type (stress, urge, or both), no statistically significant comparison was observed. It should be noted that incontinence was defined as any patient wearing a pad at 3 months, whether they had actual or perceived need was not distinguished. This may have led to an artificially overall high percentage of incontinence in this cohort, but the pad per day values are summarized in Table 2.

TABLE 2. ADVERSE EVENTS IN PATIENTS ON ORAL ANTICOAGULATION COMPARED TO CONTROL GROUP

	<i>Control</i>	<i>Aspirin</i>	<i>Coumadin</i>	p
No. of patients	37	25	13	
Intraoperative				
Hematuria obstructing observation	5 (14%)	2 (8%)	0	0.34
Blood transfusion	0	0	0	–
Postoperative				
Length of hospitalization (days)	1.1 ± 0.5	1.1 ± 0.3	1.2 ± 0.6	0.99
Duration of catheterization (days)	2.6 ± 2.8	2.2 ± 1.8	1.9 ± 1.4	0.93
Presence of catheter on discharge	15 (41%)	9 (36%)	5 (39%)	0.94
Readmission for any cause	3 (8%)	2 (8%)	0	0.57
Readmission for hematuria	1 (3%)	0	0	0.59
Urinary retention	7 (19%)	6 (24%)	3 (23%)	0.88
Dysuria	2 (5%)	2 (8%)	0	0.58
Urinary tract infection	2 (5%)	3 (12%)	1 (8%)	0.88
Incontinence	5 (14%)	6 (24%)	3 (23%)	0.53
Pads per day	0.68 ± 1.8	0.2 ± 0.4	0.46 ± 0.9	0.82
Continuous bladder irrigation (CBI)	4 (11%)	6 (24%)	3 (23%)	0.29
Durations of CBI (days)	1.2 ± 0.4	1.5 ± 1.0	1.7 ± 1.1	0.87
Morcellator issues	5 (14%)	1 (4%)	2 (15%)	0.41
Early revision	5 (14%)	3 (12%)	0	0.38

Incontinence, urinary tract infection, dysuria, urinary retention evaluated at 21 days, and readmission were evaluated at 3 months.

## Discussion

In recent years, several studies have investigated the risk of bleeding in patients undergoing endoscopic procedures while on OA. Some clinicians have suggested that the thromboembolic risk associated with discontinuing the OA in the preoperative period is greater than the risk of significant intraoperative bleeding while fully anticoagulated. In a series of 12 patients fully therapeutic on OA undergoing TURP (mean prothrombin index 2.3), 4 patients (33%) required blood transfusions.<sup>10</sup> For most clinicians, this represented an unacceptably high rate of blood transfusions, leading others to suggest that interruption of coumadin and replacement with intravenous heparin in the preoperative period is safer. In a series of 20 patients who underwent heparin substitution before TURP, 4 patients (20%) required blood transfusions (mean activated partial thromboplastin time was 1.7).<sup>13</sup> Yet, others have suggested that alternative procedures such as HoLEP are altogether safer than TURP in patients with significant risks of bleeding, citing lower blood transfusion rates. Elzayat and colleagues published a series on 14 patients who underwent HoLEP while fully therapeutic on OA (mean INR 2.0) and reported that only 2 patients (14.2%) required blood transfusions in the postoperative period.<sup>14</sup> In the same study, the authors reported that of 34 patients who underwent low-molecular-weight heparin substitution, 5 patients (14.7%) required blood transfusion, while only 1 of 33 patients (3%) who altogether discontinued their OA in the preoperative period required a blood transfusion. It was not determined if these differences were statistically significant, but since the transfusions rates were lower than rates reported in cohort studies done with TURP, the study's authors concluded that HoLEP is safer in patients at high risk of bleeding.

Our study attempts to further assess the safety of HoLEP in patients on OA by comparing bleeding complication rates to patients without any known risk factors for bleeding. Using a case-control study design, we demonstrated that bleeding complication rates were not greater in anticoagulated patients

undergoing HoLEP for BPH. No patients in the cohort required blood transfusions, and while these rates are lower than previously reported by Elzayat (0/13 vs. 2/14), this is likely secondary to a lower mean cohort INR (1.5 vs. 2.0). The only bleeding complication experienced in our cohort was intraoperative hematuria that obscured observation enough to terminate the procedure, but this rate was not significantly different among the three groups. Further, surrogate markers for bleeding such as duration of hospitalization and catheterization were also similar among the three groups. Only one patient required readmission for hematuria, but this patient was in the control group. Based on these findings, it appears as though patients who are on OA preoperatively have similar clinical outcomes to those who are not at increased risk of bleeding, lending additional support to conclusion drawn by Elzayat and colleagues that the hemostatic properties of HoLEP are just as effective in patients with compromised hemostasis.

The hemostatic effects during HoLEP are thought to be related to the physical properties of Ho:YAG laser energy. How the laser energy interacts with the tissue is primarily dependent on three variables: wavelength, time of energy application, and the energy density (fluence). The wavelength and interaction with the target chromophore (water, in the case of Ho:YAG) determine the efficiency with which the energy will heat the tissue.<sup>11</sup> Since the Ho:YAG wavelength has a high absorption in water, efficient thermal conductance in tissue types with high water content, such as the prostate, can be achieved.<sup>12</sup> Second, the amount of time the energy is delivered to the target will determine the amount of thermal conduction introduced into the tissue. The exposure time and conductive heating of the tissue share a direct relationship. As exposure time increases, conductive heating of the tissue will likewise increase, which is a useful relationship that can be manipulated to achieve a desired effect. Finally, the fluence dictates the amount of work done per unit area and defines the reaction of the tissue to the exposure. If the fluence is high enough to heat the tissue to > 100°C, the cellular water will

turn to steam and vaporize the tissue (ablation). At lower fluence with temperatures between 70°C and 100°C, coagulation is achieved. If the fluence is too low, inadequate conductive heating ( $T < 70^\circ\text{C}$ ) will result in thermal injury without vaporization or coagulation. The fiber delivery system can be controlled to produce either ablation or coagulation, that is, decreasing the energy pulse or by pulling the fiber tip away from the tissue. Alternatively, greater conductive heating can be achieved with increasing the energy pulse or by closer proximity of the fiber tip to the tissue, resulting in vaporization. These properties come into effect when treating the prostate and are expected to be true regardless of whether or not the patient is anticoagulated.

A limitation of this study is that all but two patients in this cohort had INRs less than 2.0 and were not therefore fully therapeutic on OA. Most clinicians consider an INR range of 1.2 to 2.0 as elevated, but subtherapeutic. It is possible that some of these patients did not require full anticoagulation in the ambulatory setting or were unintentionally subtherapeutic, while others may have discontinued their OA in the preoperative period despite being informed that this was not necessary. Since the risk of bleeding is directly related to the intensity of anticoagulation, this may have affected the cohort outcomes.<sup>15</sup> It should also be noted that while hemoglobin and hematocrit trends would have been an interesting outcome measure to compare, postoperative complete blood counts were not routinely ordered, preventing this analysis. Another limitation to this study is the design itself. While data from randomized controlled trials represent the best form of clinical evidence, a trial where patients at increased risk of bleeding are randomized to TURP versus HoLEP is unlikely to receive institutional approval. Whereas a retrospective study of patients previously treated with HoLEP is appealing in many ways, the statistics are simply less robust.

## Conclusions

While TURP has remained the gold standard for the surgical correction of BPH, emerging surgical alternatives such as HoLEP are increasing in popularity, especially for patients with compromised hemostasis. Despite the absence of a randomized controlled trial, the results of this study advocate for the safety of HoLEP in patients with compromised hemostasis. Patients who cannot stop their OA and were previously denied TURP for BPH have a safe and efficacious surgical alternative.

## Disclosure Statement

Mark D. Tyson has no competing financial interests.

Lori B. Lerner has the following: Lumenis—preceptor/consultant, and Boston Scientific—preceptor/consultant.

## References

1. Mebust WK, Holtgrewe HL, Cockett ATK, Peters PC. Writing Committee, the American Urological Association: Transurethral prostatectomy: Immediate and postoperative complications. A cooperative study of 13 participating institutions evaluating 3,885 patients. *J Urol* 1989;141:243–247.
2. Tan A, Liao C, Mo Z, Cao Y. Meta-analysis of holmium laser enucleation versus transurethral resection of the prostate for symptomatic prostatic obstruction. *Br J Surg* 2007;94:1201–1208.
3. Tan AH, Gilling PJ, Kennett KM, Frampton C, Westenberg AM, Fraundorfer MR. A randomized trial comparing holmium laser enucleation of the prostate with transurethral resection of the prostate for the treatment of bladder outlet obstruction secondary to benign prostatic hyperplasia in large glands (40 to 200 grams). *J Urol* 2003;170:1270–1274.
4. Montorsi F, Naspro R, Salonia A, Suardi N, Briganti A, Zanoni M, et al. Holmium laser enucleation versus transurethral resection of the prostate: Results from a 2-centre, prospective, randomized trial in patients with obstructive benign prostatic hyperplasia. *J Urol* 2004;172:1926–1929.
5. Kuntz RM, Ahyai S, Lehrich K, Fayad A. Transurethral holmium laser enucleation of the prostate versus transurethral electronically resection of the prostate: A randomized prospective trial in 200 patients. *J Urol* 2004;172:1012–1016.
6. Gupta N, Sivaramakrishna, Kumar R, Dogra PN, Seth A. Comparison of standard transurethral resection, transurethral vapor resection and holmium laser enucleation of the prostate for managing benign prostatic hyperplasia of >40g. *BJU Int* 2006;97:85–89.
7. Bell CR, Murdock PJ, Pasi KJ, Morgan RJ. Thrombotic risk factors associated with transurethral prostatectomy. *BJU Int* 1999;83:984–989.
8. Gilling PJ, Cass CB, Cresswell MD, Fraundorfer MR. The use of the holmium laser in the treatment of benign prostatic hyperplasia. *J Endourol* 1996;10:459–461.
9. Tan AH, Gilling PJ. Holmium laser prostatectomy: Current techniques. *Urology* 2002;60:152–156.
10. Parr NJ, Loh CS, Desmond AD. Transurethral resection of the prostate and bladder tumor without withdrawal of warfarin therapy. *Br J Urol* 1989;64:623–625.
11. Te AE. The development of laser prostatectomy. *BJU Int* 2004;93:262–265.
12. Jansen ED, van Leeuwen TG, Motamedi M, Borst C, Welch AJ. Temperature dependence of the absorption coefficient of water for midinfrared laser radiation. *Lasers Surg Med* 1994;14:258–268.
13. Dotan ZA, Mor Y, Leibovitch I, Varon D, Golomb J, Duvdevani M, et al. The efficacy and safety of perioperative low molecular weight heparin substitution in patients on chronic oral anticoagulation therapy undergoing transurethral prostatectomy for bladder outlet obstruction. *J Urol* 2002;168:610–613.
14. Elzayat E, Habib E, Elhilali M. Holmium laser enucleation of the prostate on anticoagulant therapy or with bleeding disorders. *J Urol* 2006;175:1428–1432.
15. O'Donnell M, Kearon C. Perioperative management of oral anticoagulation. *Clin Geriatr Med* 2006;22:199–213.

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### Abbreviations Used

BPH = benign prostatic hyperplasia  
CBI = continuous bladder irrigation  
HoLEP = holmium laser enucleation of the prostate  
Ho:YAG = holmium:yttrium aluminum garnet  
INR = international normalized ratio  
OA = oral anticoagulation  
TURP = transurethral resection of prostate

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3. Aaron D. Martin, Rafael N. Nunez, Mitchell R. Humphreys. 2010. Bleeding after holmium laser enucleation of the prostate: Lessons learned the hard way. *BJU International* no-no. [[CrossRef](#)]
4. Julien Berger, Gregoire Robert, Aurelien Descazeaud. 2010. Laser Treatment of Benign Prostatic Hyperplasia in Patients on Oral Anticoagulant Therapy. *Current Urology Reports* **11**:4, 236-241. [[CrossRef](#)]
5. Jin Chul Hwang, Sang Myung Park, Jong Bouk Lee. 2010. Holmium Laser Enucleation of the Prostate for Benign Prostatic Hyperplasia: Effectiveness, Safety, and Overcoming of the Learning Curve. *Korean Journal of Urology* **51**:9, 619. [[CrossRef](#)]
6. Jessica Mandeville, Ehud Gnessin, James E. Lingeman. 2010. New Advances in Benign Prostatic Hyperplasia: Laser Therapy. *Current Urology Reports* . [[CrossRef](#)]