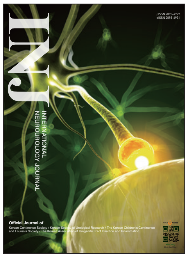

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Risk Factors for Transurethral Coagulation for Hemostasis During Holmium Laser Enucleation of the Prostate

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Purpose: We aimed to identify risk factors for transurethral coagulation (TUC) using bipolar electrocautery for hemostasis during holmium laser enucleation of the prostate (HoLEP) surgery for benign prostatic hyperplasia (BPH).
Methods: We analyzed the clinical outcomes of HoLEP surgery performed by a single surgeon between January 2010 and April 2020 at the Seoul National University Hospital. Patient characteristics and perioperative parameters were used to identify the risk factors for TUC. The TUC group was defined as a case of conversion to hemostasis using electrocautery during the hemostasis step after enucleation.
Results: Of 1,563 patients, 357 underwent TUC (TUC group; 22.8%) as an adjuvant (n = 299, 19.1%) or salvage (n = 58, 3.7%) therapy. Patients in the TUC group were older (mean ± standard deviation, 70.6 ± 7.3 years vs. 69.3 ± 7.0 years; P = 0.002), had more 5-alpha reductase inhibitor (5-ARI) use (35.6% vs. 25.9%, P < 0.001), higher serum prostate-specific antigen (PSA) (5.4 ± 4.8 ng/mL vs. 3.8 ± 4.5 ng/mL, P < 0.001), larger total prostate volume (TPV) (89.5 ± 44.7 mL vs. 66.0 ± 32.6 mL, P < 0.001), and larger transitional zone volume (TZV) (57.3 ± 34.9 mL vs. 37.7 ± 24.2 mL, P < 0.001) than those who did not undergo TUC (non-TUC group). In univariate logistic regression analysis, age, 5-ARI use, PSA, TPV, and TZV correlated with TUC, whereas in multivariate logistic regression analysis, only TZV was associated with TUC. The odds ratios (ORs) of TUC were analyzed per TZV quartile. Compared to TZV < 22.3 mL, the OR was 2.42 in 34.1 mL ≤ TZV < 53.5 mL (95% confidence interval [CI], 1.58–3.72; P < 0.001), 5.17 in ≥ 53.5 mL (95% CI, 3.44–7.77; P < 0.001).
Conclusions: The risk of TUC during HoLEP surgery increases in patients with TZV > 35 mL. Therefore, TUC may be potentially necessary in patients with a large transition zone volume in patients with BPH.

Keywords: Transurethral resection of prostate; Endoscopic hemostasis; Holmium; Laser coagulation; Prostatectomy

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- **Research Ethics:** This study reviewed a patient cohort at Seoul National University Hospital (SNUH). The Institutional Review Board (IRB) of SNUH approved this study (IRB No. H2111-180-1277).
- **Conflict of Interest:** No potential conflict of interest relevant to this article was reported.

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INTRODUCTION

Benign prostatic hyperplasia (BPH) is a disease that causes lower urinary tract symptoms, especially in older men. Treatment modalities for BPH include watchful waiting, medical therapy, and surgical treatment. Regarding surgical treatment for BPH, holmium laser enucleation of the prostate (HoLEP) surgery has proven to be a safe and effective surgical method that could replace transurethral resection of the prostate (TURP) [1,2].

HoLEP surgery has less bleeding, shorter Foley catheter stay, and shorter hospital stay than TURP. In addition, HoLEP is an effective surgery that can be performed, replacing open prostatectomy, even in patients with large prostate [3,4]. HoLEP has a lower recurrence rate concerning long-term follow-up and is more cost-effective than TURP [5-9]. The outcome of HoLEP surgery is generally excellent in improving lower urinary tract symptoms [10-12], and patient satisfaction is also high [13].

Intraoperative hemostasis is critical for successful HoLEP surgery. Hemostasis must be performed adequately during the enucleation step to ensure good visibility of the endoscope during morcellation [14-16]. Securing good endoscopic visibility allows safe morcellation to be performed. In the case of uncontrolled arterial bleeding or obscure bleeding in challenging locations, hemostasis may be difficult with holmium laser coagulation. In such cases, transurethral coagulation (TUC) using bipolar electrocautery is inevitable for controlling the bleeding. To the best of our knowledge, there are no studies on the risk factors that make intraoperative hemostasis difficult during HoLEP surgery. This is the first study to address this issue.
We analyzed the clinical characteristics of patients who underwent TUC during HoLEP surgery and sought to determine the risk factors.

MATERIALS AND METHODS

Study Design

This study reviewed a patient cohort at Seoul National University Hospital (SNUH). The Institutional Review Board of SNUH approved this study (IRB No. H2111-180-1277). We analyzed the clinical factors of patients who underwent HoLEP surgery performed by a single surgeon (SJO) among patients from January 2010 to April 2020.

The participants in this study were patients aged >45 years who were diagnosed with BPH and underwent HoLEP surgery. Patients with neurogenic bladder or neuropathy were excluded from the study. In patients whose preoperative serum prostate-specific antigen (PSA) was >than 3 ng/mL or nodules were palpated during a digital rectal examination, we performed transrectal ultrasound-guided prostate needle biopsy to rule out prostate cancer. Patients who were taking anticoagulants discontinued the therapy 4–7 days prior to surgery after consulting either cardiologists or neurologists. The same clinical protocol for HoLEP including baseline and postoperative follow-up evaluation schedules were applied to all patients after 2009 in SNUH. A set order was made to optimize the patient management pathway. Therefore, the data of the patient cohort followed by a prospectively designed protocol were analyzed retrospectively in this study.

We analyzed various clinical parameters before, during, and after surgery. Preoperative parameters included age, body mass index, medication history, underlying disease, International Prostate Symptom Score (IPSS), quality of life (QoL) scores, PSA, maximum flow rate (Qmax), postvoid residual (PVR) volume, total prostate volume (TPV), and transition zone volume (TZV). Intraoperative parameters included operation time, enucleation time, morcellation time, enucleation weight, and intraoperative complications (prostate capsule perforation). Postoperative parameters included IPSS, QoL scores, Qmax, and PVR at 2 weeks, 3 months, and 6 months after surgery.

Patients were divided into 2 groups: patients who underwent TUC (TUC group) and those who did not (non-TUC group). The clinical characteristics of the 2 groups were compared. The case of conversion to hemostasis using electrocautery during the hemostasis step after enucleation of the prostate was defined as the TUC group. The TUC group included all patients who underwent adjuvant TUC and salvage TUC. Adjuvant TUC was defined as cases where hemostasis was primarily possible with the laser; however, electrocautery TUC was performed additionally to facilitate later morcellation when hemostasis for more than 10 minutes was considered to be necessary due to abundant small bleeding vessels in the prostatic fossa bed. Salvage TUC was defined as a procedure performed when electrocautery TUC was inevitable due to bleeding that was difficult to control with laser coagulation.

Surgical Procedures

All surgeries were performed by a single surgeon (SJO) using a 3-lobe surgical technique [17]. Prostate enucleation was performed using a 26F resectoscope (Karl Storz, Tuttlingen, Germany) with a 550-μm end-firing laser fiber (SlimLine, Lumenis

Ltd., Yokneam, Israel). An 80W Ho:YAG laser machine (VersaPulse Power-Suite, Lumenis Ltd.) was used, and the energy power was usually set to 2.0 J and 40 Hz.

After enucleation, the energy power was lowered to 0.5 J and 35 Hz for routine laser hemostasis. Hemostasis was performed simultaneously during enucleation to secure good visibility of the endoscopic surgical field and proceed with the operation. After enucleation was completed, adequate hemostasis was ensured including controlling the bleeding in all small blood vessels in the prostatic fossa (hemostasis step). Regarding hemostasis, after defocusing at a distance of approximately 2 mm from the tip of the laser fiber, the laser was applied to the bleeding vessel or the proximal source of the blood vessel for more than 3 seconds. Most of the tissue surrounding the bleeding vessels also turned white with hemostasis.

Before morcellation, electric hemostasis for either adjuvant or salvage purpose was performed using either bipolar mode (27040EB, Karl Storz) or monopolar mode (27050E, Karl Storz) if necessary. Since this study protocol was conducted prospectively, it was decided at the time of surgery whether it was adjuvant TUC or salvage TUC. Immediately after each operation, the type of TUC was recorded in the electronic medical record. Morcellation was performed using a VersaCut mechanical morcellator (Lumenis Ltd.) with a 0° rectangular nephroscope (Karl Storz). After complete morcellation, a 22F 3-way urethral catheter was inserted for continuous irrigation with normal saline.

Statistical Analysis

Independent Student t-test and chi-square test were used to compare the means and proportions of the 2 groups according to different categories based on preoperative, intraoperative, and postoperative parameters.

The risk analysis of TUC was performed using univariate and multivariate logistic regression. The dependent variable was the presence of TUC. Statistical significance was set at $P < 0.05$. Statistical analyses were performed using IBM SPSS Statistics ver. 25.0 (IBM Co., Armonk, NY, USA).

RESULTS

Among the 1,563 patients, 357 (22.8%) underwent TUC (TUC group) and 1,206 (77.2%) did not (non-TUC group). In the TUC group, 299 patients (83.8%) underwent adjuvant TUC, while 58 patients (16.2%) underwent salvage TUC.

Table 1 shows the patient demographics including basic characteristics, medication use, and comorbidities. The TUC group

Table 1. Patient's demographics

Variable	TUC group (n = 357)	Non-TUC group (n = 1,206)	P-value
Basic characteristics			
Age (yr)	70.6 ± 7.3	69.3 ± 7.0	0.002
Body mass index (kg/m^2)	24.2 ± 2.9	24.4 ± 2.9	0.351
Duration of LUTS (mo)	64.8 ± 60.7	58.8 ± 58.5	0.106
Previous TURP	19 (5.3)	59 (4.9)	0.743
Medical treatments			
Anticoagulants	100 (28.0)	344 (28.5)	0.850
α-blocker	273 (76.5)	877 (72.7)	0.158
Anticholinergics	38 (10.6)	176 (14.6)	0.057
5-ARI	127 (35.6)	312 (25.9)	< 0.001
Desmopressin	16 (4.5)	58 (4.8)	0.798
Comorbidities			
Hypertension	170 (47.6)	580 (48.1)	0.875
Diabetes mellitus	65 (18.2)	260 (21.6)	0.170
Cerebrovascular disease	12 (3.4)	35 (2.9)	0.655
Neurologic disease	3 (0.8)	11 (0.9)	1.000
Parkinson disease	7 (2.0)	13 (1.1)	0.188

Values are presented as mean ± standard deviation or number of patients (%).
LUTS, lower urinary tract symptoms; TURP, transurethral resection of the prostate; 5-ARI, 5-alpha reductase inhibitor.

had a higher mean age (70.6±7.3 years vs. 69.3±7.0 years, P=0.002), and more 5-alpha reductase inhibitor (5-ARI) use (35.6% vs. 25.9%, P<0.001) than the non-TUC group.

The preoperative and intraoperative parameters are shown in Table 2. Among the preoperative factors, there were significant differences between the two groups in PSA, TPV, and TZV. The TUC group had higher PSA (5.4±4.8 ng/mL vs. 3.8±4.5 ng/mL, P<0.001), larger TPV (89.5±44.7 mL vs. 66.0±32.6 mL, P<0.001), and larger TZV (57.3±34.9 mL vs. 37.7±24.2 mL, P<0.001) than non-TUC group. Except for intraoperative capsule perforation, all intraoperative parameters, including operative time, enucleation time, morcellation time, and enucleation weight were significantly larger in the TUC group than in the non-TUC group (P<0.05).

Postoperative outcomes are shown in Table 3. During the 2-week postoperative follow-up, PVR was significantly higher in the TUC group (28.0±41.5 mL vs. 19.4±35.0 mL, P=0.001), but there was no significant difference between the 2 groups in total IPSS, QoL score, and Qmax (P>0.05). Regarding the postoperative follow-up results at 3 months and 6 months, none of the postoperative factors showed any significant difference between the 2 groups (P>0.05).

Table 4 shows the results of univariate and multivariate logistic regression analyses concerning risk factors for TUC. In univariate logistic regression analysis, age, 5-ARI use, PSA, TPV, and TZV correlated with TUC. In the multivariable logistic regression analysis, only TZV was associated with TUC. The odds ratios (ORs) of TUC were analyzed by quartile of TZV (first quartile: 0 to 22.2 mL, second quartile: 22.3 to 34.0 mL, third quartile: 34.1 to 53.4 mL, fourth quartile: ≥53.5 mL). Compared to TZV<22.3 mL, OR was 2.42 in 34.1 mL≤TZV<53.5 mL (95% confidence interval [CI], 1.58–3.72; P<0.001), 5.17 in ≥53.5 mL (95% CI, 3.44–7.77, P<0.001).

Regarding risk factors for adjuvant TUC, univariable logistic regression analysis showed that age, 5-ARI use, PSA, TPV, and TZV correlated with adjuvant TUC. In the multivariable logistic regression analysis, only TZV was associated with adjuvant TUC. Concerning risk factors for salvage TUC, univariate logistic regression analysis showed that PSA, and TZV correlated with salvage TUC. Multivariable logistic regression analysis showed that only TZV correlated with salvage TUC.

The results of comparison of the TZV between the group taking 5ARI and the group not taking it are shown in Table 5. The TZV in the group taking 5-ARI was significantly larger than that in the group not taking 5-ARI (52.9±33.2 mL vs. 37.9±24.8 mL, P<0.001).

Table 2. Comparison of pre- and intraoperative parameters

Variable	TUC group (n=357)	Non-TUC group (n=1,206)	P-value
Preoperative parameters			
Total IPSS	19.5±8.0	18.7±7.8	0.116
QoL score	4.2±1.1	4.1±1.2	0.111
PSA (ng/mL)	5.4±4.8	3.8±4.5	<0.001
Qmax (mL/sec)	9.0±4.4	9.6±4.9	0.052
Postvoid residual volume (mL)	68.8±91.3	67.5±90.5	0.848
Total prostate volume (mL)	89.5±44.7	66.0±32.6	<0.001
Transition zone volume (mL)	57.3±34.9	37.7±24.2	<0.001
Intraoperative parameters			
Operation time (min)	74.9±36.6	49.1±23.9	<0.001
Enucleation time (min)	41.0±18.3	32.1±15.0	<0.001
Morcellation time (min)	14.5±11.4	8.8±6.9	<0.001
Enucleation weight (g)	37.1±29.1	21.4±26.6	<0.001
Intraoperative capsule perforation	2 (0.6)	5 (0.4)	0.662

Values are presented as mean±standard deviation or number of patients (%).
TUC, transurethral coagulation; IPSS, International Prostate Symptom Score; QoL, quality of life; PSA, prostate-specific antigen; Qmax, maximum flow rate.

Table 3. Comparison of postoperative parameters

Variables	TUC group (n = 357)	Non-TUC group (n = 1,206)	P-value
Postoperative parameters at 2 weeks after surgery			
Total IPSS	10.5 ± 6.6	10.9 ± 6.7	0.464
QoL score	2.3 ± 1.5	2.4 ± 1.6	0.612
Qmax (mL/sec)	20.9 ± 9.7	20.5 ± 9.8	0.543
Postvoid residual volume (mL)	28.0 ± 41.5	19.4 ± 35.0	0.001
Postoperative parameters at 3 months after surgery			
Total IPSS	7.1 ± 5.4	7.7 ± 5.8	0.112
QoL score	1.5 ± 1.3	1.6 ± 1.4	0.156
Qmax (mL/sec)	23.6 ± 11.5	22.1 ± 10.9	0.048
Postvoid residual volume (mL)	17.5 ± 36.2	15.2 ± 32.0	0.312
Postoperative parameters at 6 months after surgery			
Total IPSS	5.5 ± 5.1	5.7 ± 5.1	0.578
QoL score	1.1 ± 1.2	1.2 ± 1.2	0.163
Qmax (mL/sec)	23.1 ± 10.3	22.1 ± 12.1	0.281
Postvoid residual volume (mL)	15.0 ± 41.4	13.0 ± 31.4	0.404

Values are presented as mean ± standard deviation.
TUC, transurethral coagulation; IPSS, International Prostate Symptom Score; QoL, quality of life.

Table 4. Univariable and multivariable logistic regression analysis for transurethral coagulation

Variable	Univariable analysis		Multivariable analysis	
	Unadjusted OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
Age	1.03 (1.01–1.04)	0.002	-	-
5-ARI	1.58 (1.23–2.04)	< 0.001	-	-
PSA	1.07 (1.04–1.10)	< 0.001	-	-
TPV	1.02 (1.01–1.02)	< 0.001	-	-
TZV				
Q1 (0–22.2)	1.00	-	1.00	-
Q2 (22.3–34.0)	1.44 (0.91–2.27)	0.117	1.42 (0.90–2.25)	0.132
Q3 (34.1–53.4)	2.45 (1.60–3.76)	< 0.001	2.42 (1.58–3.72)	< 0.001
Q4 (≥ 53.5)	5.19 (3.45–7.79)	< 0.001	5.17 (3.44–7.77)	< 0.001

OR, odds ratio; CI, confidence interval; 5-ARI, 5-alpha reductase inhibitor; PSA, prostate-specific antigen; TPV, total prostate volume; TZV, transition zone volume; Q1, first quartile; Q2, second quartile; Q3, third quartile; Q4, fourth quartile.

Table 5. Comparison of transition zone volume according to taking 5-ARI

Variable	TZV (mL)	P-value
5-ARI		< 0.001
Yes (n = 439)	52.9 ± 33.2	
No (n = 1,124)	37.9 ± 24.8	

Values are presented as mean ± standard deviation.
5-ARI, 5-alpha reductase inhibitor; TZV, transition zone volume.

DISCUSSION

HoLEP surgery consists of 2 steps: enucleation to remove the enlarged prostate and morcellation to remove the enucleated prostate [17]. During HoLEP surgery, adequate bleeding control is an important step in reducing clot formation and thus, the resulting urinary retention [18]. Successful morcellation requires good endoscopic visibility during the procedure [14-16].

If the visual field is obscured during morcellation, there is a risk of iatrogenic bladder injury, and the morcellation time is extended. Therefore, we sought to perform hemostasis meticulously during HoLEP surgery.

Our previous study on endoscopic anatomy during HoLEP surgery demonstrated that the risk of bleeding increases with larger prostate volume [19]. Marshall and Narayan [20] reported that prostatic bleeding increased due to friable hypervascularity as prostate size increased. Foley and Bailey [21] reported that bleeding in prostatic hyperplasia is related to the microvascular density of the prostate. Evidently, the risk of bleeding increases as the prostate volume increases because the larger the prostate, the more blood supply is required, and thus, the blood vessel density increases. Currently, the cost of TUC in HoLEP surgery, including costs for disposable electrode, irrigation fluid, depreciation cost of electrocautery equipment, surgeon's time and efforts, are not covered by insuranceset in most countries. This data will be used as a basic data for initiation of proper cost estimation by the insurance authorities.

Univariate logistic regression showed that TPV and TZV had a significant correlation with TUC. However, multivariate logistic regression analysis demonstrated that TPV did not correlate with TUC, whereas only TZV correlated with TUC. As the TZV increases, the TPV also increases [22]. Therefore, in general, TZV is closely correlated with TPV. Considering this point, it is difficult to accurately explain why TPV did not correlate with TUC in this study.

Univariable and multivariable logistic regression analyses for adjuvant TUC showed similar results to those of TUC. This is because the majority of patients (83.8%) in the TUC group underwent adjuvant TUC. Additionally, TZV third quartile (≥ 34.1 mL) showed a significant correlation with salvage TUC in multivariable logistic regression analysis.

As shown in the results, the average age, TPV, TZV, and PSA values were higher in the TUC group than in the non-TUC group. In a study analyzing resected prostate cancers over 50 years, Berry et al. [23] reported that prostate volume increased with age. Rhode et al. [24] reported that in a 5-year study examining the size of the prostate in adult men over 40 years of age, the growth rate of the prostate tended to increase with age, and the average growth rate was 1.6% per year and that the larger the prostate size, the higher the growth rate. Roehrborn et al. showed that serum PSA levels were strongly correlated with prostate volume in men with BPH without prostate cancer and that the correlation was influenced by the patient's age [25]. Summarily, prostate volume is closely correlated with age and serum PSA, and our results reflect this fact.

Our previous study on endoscopic anatomy during HoLEP surgery demonstrated that bleeding often occurs in the 2–5 and 7–10 positions of the proximal prostate [19]. Therefore, we paid more attention to hemostasis during enucleation in these directions. Most cases of bleeding could be sufficiently controlled using holmium laser coagulation. However, adjuvant TUC after holmium laser coagulation was performed when better visibility was required for performing adequate morcellation. Hemostasis using holmium laser coagulation only may be problematic when extensive arterial bleeding occurs during HoLEP surgery. In such cases, salvage TUC was performed to achieve fast and adequate hemostasis. TUC remains superior to holmium laser coagulation in terms of hemostasis and rapidity. Thus, it is thought that the hemostasis performance of the holmium laser is limited.

The primary mechanism of the holmium:yttrium-aluminum-garnet (Ho: YAG) laser is the photothermal effect [26]. To effectively perform lithotripsy or soft tissue incision using a Ho:YAG laser, the laser fiber must directly be in contact with the stone or soft tissue. However, for hemostasis, the fibers are not directly in contact with the tissue. In other words, the Ho:YAG laser was not developed primarily for hemostasis when considering its mechanism. Therefore, the Ho:YAG laser needs to be improved to achieve more effective hemostasis, such as the addition of a hemostatic mode, or to develop a new laser with different energy transfer characteristics.

Postoperative IPSS, QoL score, Qmax, and PVR were not significantly different between the 2 groups. Therefore, whether TUC was performed did not affect the therapeutic effect of HoLEP surgery. The use of 5-ARI was higher in the TUC group than that in the non-TUC group. Previous studies have shown that patients taking 5-ARI experience reduced prostatic bleeding during BPH-related surgeries [27-29]. Several studies have suggested that 5-ARI can reduce the risk of bleeding by affecting the microvessel density [27,28]. However, our study did not show similar results to other observations [27-29]. This could be due to the fact that the average TZV in the group taking 5-ARI was significantly larger than that in the group not taking 5-ARI. TZV is considered a more important factor in determining bleeding risk in HoLEP surgery than 5-ARI use.

As mentioned in the Materials and Methods section, all patients included in this study were subjected to the same prospectively designed protocol for baseline and postoperative follow-up. Although this study is a retrospective study, it has the advantage of being able to minimize the possibility of selection bias because all patients during a given period were included in this study. On the other hand, in prospective patient enrollment studies, patients who did not consent to the registry before surgery were excluded from the study data, which could lead to unwanted selection bias.

This study has some limitations. The criteria for performing TUC are not completely objective. Although there is a criterion for performing adjuvant TUC when hemostasis is not sufficient even with the laser for more than 10 minutes, our subjective experience is inevitably included. However, the surgeon did not routinely apply TUC to all patients. A single surgeon applied the same criteria for both the TUC and non-TUC groups. This study is significant because it is a prospectively conducted study in a real clinical practice environment.

In conclusion, TZV is the most critical risk factor for performing adjuvant or salvage TUC after the routine HoLEP procedure. In particular, when the TZV is more than 35 mL, the risk of TUC increases. Therefore, TUC may be potentially necessary in patients with a large TZV in patients with BPH.

AUTHOR CONTRIBUTION STATEMENT

· Conceptualization: *MSC*, *SJJ*, *SJO*
· Data curation: *HSY*, *MHK*, *JSP*
· Formal analysis: *HSY*
· Funding acquisition: *SJO*
· Methodology: *HSY*, *SJO*
· Project administration: *SJO*
· Visualization: *HSY*
· Writing-original draft: *HSY*
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