Prognostic Factors Predicting Bleeding After Discharge Requiring Readmission After Thulium Laser Enucleation of the Prostate (ThuLEP)

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Abstract

Objectives Postoperative haematuria is a feared complication following prostate enucleation, and it may occur even weeks after discharge. We evaluated the risk of bleeding after discharge and its predictive factors in patients who underwent Thulium laser enucleation of the prostate (ThuLEP).

Methods Between January 2015 and December 2018, patients with surgical indication for benign prostatic hyperplasia underwent ThuLEP in 4 urology departments. All procedures were performed by experienced urologists. Postoperative haematuria was defined as macroscopic haematuria occurring 7 days after discharge. Readmission rate due to macroscopic haematuria was assessed. Logistic regression models tested for predictors of postoperative bleeding requiring readmission.

Results Overall, 748 patients were included, and 52 (6.9%) of them were readmitted after discharge because of macroscopic haematuria. No cases of deep venous thrombosis or pulmonary embolism were diagnosed. Mean length of stay for surgical treatment was 2.1 days, and mean hospitalization for readmission was 5.6 days. None of the readmitted patients required reintervention, while 46.1% of them required blood transfusions. Diabetes mellitus ($P < 0.05$), a long bridge of oral anticoagulant drugs with low molecular weight heparin (LMWH) ($P < 0.05$) and history of constipation ($P < 0.05$) were significant predictors of readmission after discharge due to macroscopic haematuria.

Conclusions Patients with a clinical history of diabetes mellitus or constipation and patients who undergo a long bridge of oral anticoagulant therapy with LMWH are at higher risk of bleeding requiring readmission after ThuLEP.

Introduction

Lower urinary tract symptoms (LUTS) due to benign prostatic hyperplasia (BPH) are common in aging men. Studies found that 56% of men aged 50 to 79, 70% of men aged 80 to 89, and 90% of men aged 90 or older reported experiencing LUTS[1]. Transurethral resection of the prostate (TURP) remains the gold standard surgical treatment according to European Association of Urology guidelines, especially for prostates of 30 to 80 mL, while open prostatectomy

Key Words

Bleeding, complication, haematuria, prostate enucleation, thulium laser

Competing Interests

None declared.

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Abbreviations

BPH benign prostatic hyperplasia
LMWH low molecular weight heparin
LUTS lower urinary tract symptoms
TURP transurethral resection of the prostate
OP open prostatectomy
ThuLEP thulium laser enucleation of the prostate

(OP) is still recommended for larger prostates. However, the use of laser devices has increased during recent decades, becoming a valid alternative to TURP and OP, showing comparable efficacy and safety[2–6]. The Holmium:YAG (Ho:YAG) and Thulium:YAG (Tm:YAG) lasers are the most commonly used devices, allowing treatment of prostates > 80 mL[7–10]. A decreased bleeding risk compared with TURP and OP has been described, even in patients with bleeding disorders or on anticoagulant treatment[4,5,9,10]. Specifically, some studies showed Thulium laser enucleation of the prostate (ThuLEP) provided better haemostasis, a lower overall complication rate, and shorter catheterization time than traditional TURP[11,12]. Nevertheless, the risk of bleeding after discharge is still a major concern and sometimes requires readmission of the patient, blood transfusion, and surgical haemostasis. Evidence on bleeding after discharge following laser treatment for BPH is lacking in the literature. Therefore, the aim of this study is to evaluate the risk of bleeding after discharge and its predictive factors in patients who have undergone ThuLEP.

Materials and Methods

The study included patients with surgical indication for BPH who were treated with ThuLEP between January 2015 and December 2018. Four urology departments were involved: Busto Arsizio Hospital (Busto Arsizio, Varese, Italy), University of Modena and Reggio Emilia (Modena, Italy), Marco Pasquali Institute (Latina, Rome), and Hospital Universitario HM Montepríncipe (Madrid, Spain). Four experienced surgeons performed all the procedures. Laser settings were 120 W for ablation and 35 W for coagulation. Enucleation was performed according to the most familiar technique for each surgeon, and in no case was a mono/bipolar resectoscope used for haemostasis. Guidelines appropriate for the study type were followed[13]. Ethical committee approval for this prospective study was obtained in February 2013 (ASLMI2 n°39/2013). Exclusion criteria were patients aged < 18 or > 90 years, the presence of acute infection or preoperative positive urine culture and concomitant urethral stenosis or prostate cancer. Patients with a positive urine culture underwent antibiotic therapy until they tested negative. For patients with an indwelling catheter, antibiotic therapy was started soon after change of the catheter, and the surgery was performed after they tested negative. Chronic kidney disease was an additional exclusion factor, because impaired renal function may alter drug bioavailability. Any patient on anticoagulant therapy was evaluated by a cardiologist to determine the indication for perioperative bridging.

In all cases, bridge therapy was started 5 to 7 days before surgery with a protocol based on the half-life of the anticoagulant drug taken by the patient. Bridge of anticoagulant therapy was defined as long if continued after discharge and short if the oral anticoagulant drug was reintroduced during hospitalization 2 or 3 days post surgery. The dosage of LMWH varied according to patient's weight following cardiological indications. Patients receiving antiplatelets underwent ThuLEP without stopping this treatment if based on secondary prevention. If antiplatelets were taken as a primary prevention, the therapy was stopped 7 days before the operation and reintroduced 5 days after. A standardized follow-up was applied for the first month after surgery, and patients were readmitted in case of severe postoperative macroscopic haematuria (grade 4 according to Droller grading [14]) occurring at least 7 days after discharge. Patients who needed a readmission for haematuria occurring during the first 7 days after surgery were not included in the analysis. Patients with postoperative bleeding requiring only catheterization were managed in an outpatient regimen and discharged home without hospitalization. These patients were therefore not included in the analysis. The following variables were considered and analysed as potential predictors of postoperative bleeding requiring readmission: age > 75 years[15], body mass index (BMI) > 30[16], prostate size > 150 mL according to previous evidence[17], hypertension, diabetes mellitus, history of constipation according to the Rome IV criteria[18], use of 5-alpha-reductase inhibitors (5-ARIs), short or long bridge of anticoagulant therapy with low-molecular-weight heparin (LMWH), antiplatelet therapy, previous transfusions in the clinical history of the patient, American Society of Anesthesiologists score ≥ 3[19], and preoperative indwelling bladder catheter.

Median and interquartile range (IQR) versus numbers and proportions were used to describe continuous and categorical variables, respectively. Logistic regression models tested for predictors of postoperative bleeding requiring readmission. Data were analysed with R software for statistical computing and graphics version 3.4.1 (R Foundation for Statistical Computing, Vienna, Austria). All statistical tests were 2-sided with a level of significance set at $P < 0.05$. The sample size was calculated with a confidence level of 95% and a confidence interval of 5%.

Results

Overall, 748 patients were included. Preoperative features are reported in Table 1. Mean age was 71.1 years (SD 12.4). Mean prostate volume was 85.9 mL (SD 77.2). Among patients taking anticoagulant therapy (180, 24.1%), the most commonly taken drug was warfarin (104, 13.9%), followed by rivaroxaban (23, 3.1%), dabigatran (19, 2.5%), acenocumarolum (14, 1.9%), apixaban (11, 1.5%), edoxaban (9, 1.2%). Overall, 120 patients (16.0%) took antiplatelets, of which 108 took Cardioaspirin (14.4%) and 12 clopidogrel (1.6%). Intra- and postoperative outcomes are shown in Table 2. Mean operative time was 68.1 min (SD 51.7). A haemoglobin decrease of 1.97 g/dl (SD 1.63) was observed on the first postoperative day. Mean hospital stay was 2.2 days (SD 1.7) with a mean catheterization time of 2.1 days (SD 1.3) (Table 2).

Readmission after discharge because of macroscopic haematuria was required in 52 cases (6.9%). Mean duration of hospitalization at the readmission was 5.6 days (SD 1.3). None of the readmitted patients required reintervention, whereas blood transfusions were performed in 24 cases (46.1%) (Table 2). No cases of deep venous thrombosis or pulmonary embolism were diagnosed.

Postoperative bleeding requiring readmission was significantly correlated with diabetes mellitus (OR 2.1 [1.02 to 5.2]; $P = 0.01$), a long bridge of oral anticoagulant therapy with LMWH (OR 2.4 [1.05 to 5.3]; $P = 0.03$) or history of constipation (OR 4.3 [2.8 to 9.7]; $P = 0.02$) (Table 3).

TABLE 1.

Descriptive characteristics of 748 patients treated with ThuLEP for benign prostatic hyperplasia

Variables	Mean (SD)
Age, years	71.1 (12.4)
Prostate volume, mL	85.9 (77.2)
Preoperative PSA, ng/mL	2.9 (5.2)
Preoperative Hb, g/dL	12.8 (4.8)
IPSS	16.9 (5.8)
Qmax, mL/s	6.2 (7.1)
PVR, mL	150.7 (61.2)
	n (%)
Anticoagulant therapy	**180 (24.1)**
Anticoagulant drug	
warfarin	104 (13.9)
acenocoumarolum	14 (1.9)
apixaban	11 (1.5)
rivaroxaban	23 (3.1)
dabigatran	19 (2.5)
edoxaban	9 (1.2)
Antiplatelets therapy	**120 (16.0)**
Anticoagulant drug	
Cardioaspirin	108 (14.4)
clopidogrel	12 (1.6)

SD: standard deviation; PSA: prostate-specific antigen; Hb: haemoglobin; IPSS: International Prostatic Symptoms Score; Qmax: maximum flow rate; PVR: post-void residual

Discussion

The Tm:YAG laser has a 2010 nm wavelength with a continuous wave output and a shallow penetration in the prostatic tissue (< 0.2 mm). Its continuous wave output allows a lower mechanical stress on the tissue than Ho:YAG laser and good haemostatic property. Tm:YAG laser seems to provide better haemostasis, lower overall morbidity, shorter catheterization time, and shorter hospital stay compared with TURP[4,5,11]. Haemostatic properties have also been shown in patients with an increased haemorrhage risk (anticoagulation/antiplatelets therapy, bleeding disorders)[20,21]; however, the retrospective nature of many studies and the inclusion of prostate sizes only between 50 mL and 110 mL make it difficult to come to strong conclusions[22]. Some studies have investigated factors potentially linked to postoperative bleeding, showing a

TABLE 2.

Intraoperative and postoperative characteristics of 748 patients treated with ThuLEP for benign prostatic hyperplasia

Variables	Mean (SD)
Operative time, min	68.1 (31.7)
Hb drop, g/L	1.9 (1.6)
Catheterization time, days	2.1 (1.3)
Irrigation volume, L	31.6 (18.6)
Hospital stay, days	2.2 (1.7)
Enucleated prostate volume, mL	67.3 (58.9)

SD: standard deviation; Hb: haemoglobin

TABLE 3.

Logistic regression models testing for predictors of postoperative bleeding requiring readmission of 748 patients treated with ThuLEP for benign prostatic hyperplasia

Variables	Patients readmitted for bleeding n (%)	Patients with no bleeding n (%)	OR	CI	*P*
Age > 75 years	8 (4.3)	179 (95.7)	1.3	0.91–3.8	0.34
BMI > 30	5 (3.7)	129 (96.3)	1.5	0.79–1.9	0.24
Prostate size > 150 mL	4 (4.5)	84 (95.5)	1.4	0.69–1.7	0.12
Hypertension	27 (5.5)	460 (94.5)	1.3	0.81–1.8	0.06
Diabetes mellitus	30 (10.5)	255 (89.5)	2.1	1.02–5.2	0.01
Constipation	15 (13.3)	98 (86.7)	4.3	2.8–9.7	0.02
Use of 5-ARIs	18 (3.6)	479 (96.4)	0.9	0.78–1.4	0.26
Short bridge	5 (5.3)	89 (94.7)	1.2	0.89–1.4	0.32
Long bridge	19 (22.1)	67 (77.9)	2.4	1.05–5.3	0.03
Antiplatelets therapy	4 (3.3)	116 (96.7)	1.56	0.84–1.6	0.18
Previous transfusions	2 (4.9)	39 (95.1)	1.34	0.74–1.5	0.09
ASA score ≥ 3	1 (1.5)	64 (98.5)	0.78	0.61–1.9	0.58
Indwelling bladder catheter	6 (4.5)	128 (95.5)	0.86	0.65–1.3	0.67

BMI: body mass index; 5-ARIs: 5-alpha-reductase inhibitors; ASA: American Society of Anesthesiologists

higher rate in patients with larger prostate size[17], and those on anticoagulation[23] or who underwent multiple manual irrigations shortly after operation[24]. In this study we report our analysis of the risk of bleeding after discharge and its predictive factors in patients undergoing ThuLEP.

According to our results, diabetes mellitus significantly correlates with the risk of postoperative macroscopic haematuria. Diabetes mellitus is characterized by hyperglycaemia, insulin-resistance, and altered lipid profile. Biochemical and cellular changes lead to endothelial dysfunction, impaired endothelial repair, inflammatory state, and impaired micro- and macro-circulation. Diabetes mellitus is also correlated with platelet dysfunction[25]. Moreover, hyperglycaemia predisposes to immunosuppression, increasing the risk of infections[26]. Postoperative urinary tract infections can lead to irritative symptoms and consequently to macroscopic haematuria[27]. Although the present study could not demonstrate the exact mechanism relating diabetes mellitus to a higher rate of postoperative bleeding, statistical analysis showed that diabetic patients had a significantly higher risk of bleeding compared with non-diabetic patients. It would be interesting to investigate the pathophysiological factors responsible for this association.

Constipation is a common gastrointestinal problem, with a multifactorial pathogenesis including genetic predisposition, socioeconomic status, low fibre consumption, lack of adequate fluid intake, lack of mobility, altered hormone balance, and side effects of medication[28]. Constipation is correlated with a higher risk of urinary tract infections[29] and increased abdominal pressure during defecation, which favours the fall of eschar and consequently macroscopic haematuria.

In populations with higher life expectancy, cardiovascular diseases requiring anticoagulant or antiplatelet therapy are common. According to a review

published by the American Urological Association, there is still not enough evidence to determine the best time to resume anticoagulant/antiplatelet therapy after surgery in patients bridged to LMWH other than that it should be resumed as soon as the risk of bleeding has decreased[30]. According to European Association of Urology guidelines, laser devices for the endoscopic treatment of BPH seem to be safe in patients on anticoagulant/antiplatelet therapy. Elzayat et al. published a study of 81 patients taking anticoagulant therapy who underwent HoLEP. Only 3 of them (3.6%) had clot retention and required readmission after surgery[31]. Moreover, there is evidence in the literature that patients receiving bridge therapy after anticoagulant interruption experience a higher bleeding rate and no benefits in thromboembolism prevention. In the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy with Dabigatran Etexilate) trial, 15.4% of dabigatran-treated patients were bridged to LMWH. Increased rate of major bleeding was registered in the bridged group compared with the non-bridged group (6.5% vs. 1.8%, OR 3.68) and no significant difference in the rate of thromboembolism (0.5% vs. 0.3%) was reported[32]. Therefore, our study supports the evidence that the risk of macroscopic haematuria after endoscopic laser enucleation of the prostate is higher in patients who undergo a long bridge to LMWH. Further, a short bridge with reassumption of anticoagulant therapy during hospitalization would allow a better management of these patients by monitoring the correct intake of drugs and the colour of urine.

Daily surgical practice shows that a rapid rise in blood pressure may cause or increase bleeding from any surgical site. Despite pharmacological therapy, patients with hypertension may have altered pressure values in the postoperative period. Therefore, a rise in blood pressure may occur even on specific therapy. Despite these factors, no statistical correlation was observed between bleeding and hypertension. Additionally, larger prostates are commonly thought to be more inclined to bleeding[17]; however, a significant correlation was not observed (**Table 3**).

The use of 5-ARIs was not a significant protective factor against bleeding after discharge (**Table 3**), and our results agree with those of previously published studies. Some evidence showed benefit from the preoperative use of 5-ARIs in reducing perioperative bleeding[23], but conflicting studies exist, reporting a non-significant association between 5-ARIs use before treatment and the risks of blood transfusion and blood clot evacuation[33]. The use of 5-ARIs after endoscopic prostate resection/enucleation is common, but their efficacy has not been proven. A randomized trial did not show any benefit in reducing the rate of bleeding[34]. Other studies have suggested that the benefit of 5-ARIs during the initial period after surgery is inconsistent[23,35]. Similarly, Welk et al. did not find that 5-ARI use among men with an episode of macroscopic haematuria post-TURP reduced the rate of repeat episodes. Therefore, they stated that the evidence for macroscopic haematuria reduction in operation-naive patients and during treatment should not be automatically extrapolated to the postoperative period[36].

Despite its strengths, the limitations of our study need to be taken into account. Firstly, all procedures were performed by experienced endourologists. With less experienced surgeons, the risk of bleeding could be higher, due, for example, to residual prostatic adenoma. Secondly, the enucleation technique was not exactly the same for each surgeon, and haemostasis was not performed through a resectoscope. A comparison with a cohort of patients in which haemostasis is performed using a mono/bipolar loop or ball electrode should be of interest. Thirdly, preoperative cardiological evaluation was performed by different cardiologists from different centres. Indications to the time of bridge therapy may differ between cardiological units. Fourthly, all patients underwent ThuLEP. A similar study comparing HoLEP and ThuLEP would be interesting. Fifthly, patients with an impaired renal function, which is common among aging males, were excluded to prevent bias. Lastly, there are no data regarding the surgical time spent on haemostasis.

Conclusions

A significant correlation was observed between patients readmitted for macroscopic haematuria after ThuLEP and diabetes mellitus, history of constipation, or long bridge of oral anticoagulant therapy with LMWH. According to our results, a good glycemic control in diabetic patients and regularization of bowel function should be preoperatively assessed. Moreover, short anticoagulation bridge seems to be safer when needed, but a preoperative cardiological evaluation is recommended. These precautions might prevent bleeding after ThuLEP. Further studies are needed to confirm our findings.

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