Factors Influencing Intraoperative Blood Loss in Patients Undergoing Holmium Laser Enucleation of the Prostate (HoLEP) for Benign Prostatic Hyperplasia: A Large Multicenter Analysis

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OBJECTIVE To assess blood loss during holmium laser enucleation of the prostate (HoLEP) and investigate the factors influencing it.

PATIENTS AND METHODS Analysis of patients with benign prostatic hyperplasia (BPH) treated with HoLEP at 3 centers. Hemoglobin and hematocrit were measured before surgery and hospital discharge. All blood transfusions performed during and after HoLEP were recorded. Blood loss outcomes were analyzed regarding antithrombotic (antiplatelet/anticoagulant) therapies and drug treatments for BPH and other conditions.

RESULTS The analysis included 963 patients with a mean age of 72 years. Mean (range) prostate size was 102 (40-316) g; 28% of patients were receiving antiplatelets and 11% anticoagulants. Mean (range) prostate-specific antigen was 6.0 (0.3-43.5) ng/dL. Mean (range) operation time was 77 (28-178) minutes. Bladder calculi were found in 54 (5.6%) patients; all of them were successfully treated with cystolitholapaxy. Forty-eight (5%) patients required blood transfusion during or immediately after the HoLEP procedure. Overall, mean (SD) hemoglobin decreased from 14.6 (1.5) g/dL to 12.3 (2.1) g/dL (P <.001), and mean (SD) hematocrit decreased from 44.3% (4.7) to 37.7% (6.5) (P <.001). Neither hemoglobin nor hematocrit decreases were significantly different between patients receiving and not receiving antithrombotic therapy or BPH therapy.

CONCLUSION HoLEP is safe and has no remarkable impact on blood loss. Patients at high risk, such as those receiving antithrombotic therapy, had the same outcome than the rest regarding blood loss, although showed a higher transfusion rate. Operating time may influence hemoglobin decrease; therefore, it should be considered in patients with higher risk of bleeding. UROLOGY 132: 177−182, 2019. © 2019 Elsevier Inc.

Benign Prostatic Hyperplasia (BPH) is one of the most common urologic diseases in men. Its prevalence is approximately 60% for men in their 60s, and can reach 80%-90% for men in their 70s and 80s, constituting an important health and economic issue that grows with population ageing.[1,2]

Patients not responding to medical treatment and those who developed BPH-related complications such as hematuria, bladder stones, recurrent urinary tract infections, chronic urinary retention or renal insufficiency, often require surgical treatment of BPH. Historically, transurethral resection of the prostate (TURP) and open prostatectomy (OP) are considered standard surgical treatments for small-to-medium prostates (<80 g) and large prostates (>80 g), respectively.[3] Although considered overall safe, both TURP and OP are associated with excessive bleeding, which may require prolonged catheterization, continuous bladder irrigation, and blood transfusions.[4-7] Intraoperative blood loss may vary among centers, and transfusion rates of

Conflicts of Interest: *The authors declare no conflict of interest.*

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Submitted: May 5, 2019, accepted (with revisions): June 17, 2019

https://doi.org/10.1016/j.urology.2019.06.024
0090-4295

up to 22% and 19% have been reported for TURP and OP, respectively.[5,7] Besides intraoperative bleeding, TURP and OP include other disadvantages that can negatively impact patients' quality of life, including urethral stricture, bladder neck contracture, stress urinary incontinence, erectile dysfunction, and retrograde ejaculation.

In recent years, various surgical approaches have been developed as alternatives to TURP and OP to minimize these complications. Holmium laser enucleation of the prostate (HoLEP) was developed as an effective and minimally invasive alternative to traditional surgical techniques.[8] Since its introduction in the late 1990s, HoLEP has shown equal or better outcomes than TURP or OP, with a lower risk of intraoperative bleeding and blood transfusion.[9-11] These results have been confirmed in patients receiving anticoagulant/antithrombotic therapy. However, due to the prolonged learning curve of the technique, HoLEP has barely entered the urological community, thus limiting the data available on the daily use of this technique. One of the unmet needs regarding the use of HoLEP for BPH is the identification of factors influencing intraoperative blood loss.

In 2007, 3 centers in Madrid (Spain) initiated an enucleation program. Since the beginning a prospective database has been build up including these patients. This study analyses this cohort of patients with BPH treated in our program with the aim to identify factors influencing hematological outcomes.

PATIENTS AND METHODS

Study Design and Patients

This was a critical analysis of a prospectively built database of patients treated with HoLEP surgery between December 2007 and December 2016 at 3 different centers in Madrid: *Hospital Universitario 12 de Octubre, Hospital Universitario Montepríncipe, and Hospital La Luz*.

Patients were included if they were over 18 years of age, had a positive preanaesthesia assessment and gave consent for the surgery. Any patient with suspected prostatic neoplasia at the transitional zone or a bladder tumour, as well as patients presenting bladder diverticulum, urethral stones or urethral stricture requiring other concomitant operations during the same procedure, were excluded from the study. Other exclusion criteria were previous history of urethral stricture or prostatic surgery and active hematuria. When prostatic neoplasia was suspected due to prostate-specific antigen (PSA) levels and/or by digital rectal examination, a biopsy was performed prior to surgery. If negative, the patient was scheduled for HoLEP and included in the analysis. Those patients done during the learning curvature were also included and no limit regarding prostate size was stablished.

The study protocol was approved by the Ethics Committee of *Hospital 12 de Octubre*.

Surgical Procedures

Two surgeons performed all HoLEP procedures as described by Gilling et al[8] and modified by Kuntz et al.[12] The equipment included a 100 W holmium laser (Lumenis Inc, Palo Alto, CA) with a reusable 550-nm laser fibre, a 26-Fr continuous flow resectoscope (Storz), a 27-Fr nephroscope with a 5-mm working channel, a morcellator (Versacut, Lumenis Inc), normal saline irrigation, and a video system.

When bladder stones were observed, cystolitholapaxy was performed at the time of HoLEP with the same instrument used to remove prostatic adenoma.

Variables and Endpoints

Demographic and clinical characteristics included age, International Prostate Symptom Score, presence of preoperative urinary catheterization, and comorbidities, such as diabetes mellitus and arterial hypertension. Other data collected before surgery were the American Society of Anesthesiologists score, maximal flow rate (Qmax), prostate-specific antigen concentration, and prostate size either measured by abdominal or transrectal ultrasound. Intraoperative variables included total time in surgery, time required for enucleation and morcellation, weight of resected tissue as provided by the pathologist, length of hospital stay, catheterization time, and whether a transfusion and/or a concomitant bladder lithiasis treatment was needed. Hemoglobin and hematocrit levels were measured before surgery (as recorded in the anesthesia report) and after surgery (last blood sample collected before discharge) by routine blood tests. Antithrombotic (antiplatelet/anticoagulant) therapies (if any) were also recorded, as well as different medical treatments for BPH: α-blockers, 5-α-reductase inhibitors, anticholinergics, and phytotherapics. Blood loss was measured by the decrease in hemoglobin and hematocrit levels as a result of HoLEP surgery and also by transfusion rates. All blood transfusions performed after surgery were recorded in the dataset.

Statistics

Quantitative variables are described as mean and standard deviation (SD) and/or range, whereas categorical variables are presented as frequencies and percentages. To investigate factors with potential influence on blood loss, patients were grouped according to clinical characteristics (eg, age, prostate size, antithrombotic treatment, BPH treatment) or intraoperative variables (eg, operating time, concomitant cystolitholapaxy). Mean differences (pre- and postoperative values) in hemoglobin and hematocrit between groups were compared using a paired-samples *t* test. When considered clinically relevant, between-group differences in pre- and postoperative mean values were compared using an independent sample *t* test. All variables that were clinically relevant or showed significant differences in the bivariate analysis were included in 2 multiple regression models to predict hematocrit and hemoglobin decreases. The threshold for statistical significance was established at a 2-sided alpha value of 0.05. All statistical analyses were performed using the SAS software.

RESULTS

Characteristics of Study Patients

Between 2007 and 2016, 1152 patients underwent HoLEP surgery for BPH at the participating sites. Of these, 189 were excluded from the analysis for not meeting the selection criteria: 73 were lost to follow-up, 3 required concomitant diverticulectomy, 62 had been previously operated on for BPH using another surgical technique, 11 required concomitant urethrotomy, 27 needed concomitant TURb, 3 required concomitant ureterorenoscopy, and 10 were excluded for other reasons. Data from 963 patients were therefore used in the analysis.

The age of the study sample ranged from 48 to 91 years old (mean of 72). Table 1 summarizes the main clinical characteristics of study patients at admission. Hypertension was the most frequent comorbidity, occurring in 55% of the study population, and 39% of patients received antithrombotic therapy (either antiplatelet or anticoagulant drugs). Regarding BPH medical treatment, most patients received α-blockers, 5-α-reductase inhibitors, or both to manage symptoms. At the moment of undergoing HoLEP surgery, 343 (35.7%) patients had a urinary catheter.

Surgical Outcomes

Mean (range) operation time was 77 (28-178) minutes; mean enucleation and morcellation times were 40 (SD of 13, range of 21-130) minutes and 25 (SD of 13, range of 5-117) minutes, respectively. Mean weight of resected tissue was 73 (SD of 19, range of 11-258) g. Patients remained catheterized for a mean of 1.3 (SD of 2.7 range of 1-21) days. Mean length of hospital stay was 4 (SD of 2, range of 2-41) days. Both hematocrit and hemoglobin concentrations significantly decreased during surgery. Pre- and postoperative mean (SD) hematocrit was 44.3% (4.7) and 37.7% (6.5), respectively (P <.001). Hemoglobin dropped from a preoperative mean (SD) of 14.6 (1.5) g/dL to a postoperative 12.3 (2.1) g/dL (P <.001). Forty-eight (5%) patients required a blood transfusion during or immediately after the HoLEP procedure. A surgical hemostatic review was needed in 17 patients (1.8%). As it is a small amount of patients we found no correlation with any other variable.

Table 1. Demographic and clinical characteristics of the study population

Urinary catheter, *n (%)*	343 (35.7)
Hypertension, *n (%)*	530 (55)
Diabetes mellitus, *n (%)*	173 (18)
Neuropathy, *n (%)*	67 (7)
Vasculopathy, *n (%)*	39 (4)
Antiaggregants, *n (%)*	270 (28)
Anticoagulants, *n (%)*	106 (11)
BPH medical treatments, *n (%)*	
α-blockers	181 (18,7)
5ARIs	5 (0,5)
α-blockers + 5ARIs	472 (49)
Anticholinergics	48 (5)
Phytotherapics	34 (3.5)
ASA Score, *n (%)*	
1	57 (5.9)
2	544 (56.5)
3	332 (34.5)
4	28 (2.9)
IPSS, *median (range)*	23.2 (14-30)
PSA (ng/dL), *median (range)*	6.02 (0.3-43.5)
Qmax (mL/s), *median (range)*	7.2 (0-16)
Prostate size (external ultrasound) (g), *median (range)*	102 (40-316)
Prostate size (transrectal ultrasound) (g), *median (range)*	91 (35-247)

ASA, American Society of Anesthesiologists; IPSS, International Prostate Symptom Score; PSA, prostate-specific antigen; Qmax, maximal flow rate; 5ARIs, 5-α-reductase inhibitors.

Bladder calculi were found in 54 (5.6%) patients during the HoLEP procedure, all of which were successfully treated with cystolitholapaxy.

FACTORS INFLUENCING BLOOD LOSS

Demographic and Clinical Characteristics

No significant correlations were found between age and decrease in hemoglobin (P = .45) or hematocrit (P = .52). Mean (SD) age of patients with and without blood transfusions during HoLEP was 73 (11) and 71 (18) years, respectively (P = .61). Likewise, prostate volume (measured by external ultrasound) showed no significant correlations with the decrease in hemoglobin (P = .49) or hematocrit (P = .35). No significant differences regarding prostate volume were found between patients with and without transfusion: mean (SD) of 101 (21) g vs 104 (32) g (P = .83).

Antithrombotic Therapy

Regarding antithrombotic therapy, no significant differences were observed in hemoglobin and hematocrit decrease in patients treated and not treated with antiplatelet/anticoagulant drugs (Table 2). Mean hemoglobin concentration decreased 1.94 g/dL in patients treated with antiplatelet drugs and 2.27 g/dL in patients not treated with antiplatelet drugs. The corresponding decreases in hematocrit for patients receiving antiplatelet treatment and those not receiving it were 5.37% and 6.75% respectively. Patients not receiving anticoagulant drugs experienced a hemoglobin decrease of 2.24 g/L, while hemoglobin levels in patients treated with anticoagulants dropped 2.14 g/L. The corresponding decreases in hematocrit for patients receiving anticoagulant treatment and those not receiving it were 6.12 % and 6.28%, respectively.

Of 48 patients who received blood transfusions, 10 (21%) were being treated with anticoagulants and 8 (17%), with antiplatelets. Anticoagulant treatment had a significant influence on blood transfusion rates, being 9.4% and 4.4% for patients treated and not treated with anticoagulants, respectively (P <.001). This trend was not significant in patients treated with antiplatelet drugs, where transfusion rates were 2.9% and 5.7% for patients receiving and not receiving antiplatelet treatment, respectively (P = .320).

Table 2. Mean decreases of hemoglobin and hematocrit levels (pre- and postoperative differences) in patients receiving antiplatelet or anticoagulant treatment

	Hemoglobin decrease (g/dL) *Mean (SD)*	*P*	Hematocrit decrease (%) *Mean (SD)*	*P*
Antiplatelet				
Yes	1.94 (1.52)	0.520	5.37 (5.13)	0.400
No	2.27 (1.79)		6.75 (6.63)	
Anticoagulant				
Yes	2.24 (1.50)	0.500	6.12 (5.31)	0.800
No	2.14 (1.74)		6.28 (6.31)	

Regarding prostate size, no significant relationships were found between antiplatelet treatment and blood loss ($P = .430$ for hemoglobin and $P = .090$ for hematocrit) nor for anticoagulant therapy and blood loss ($P = .500$ for hemoglobin and $P = .170$ for hematocrit).

Treatment for BPH

Blood loss was also assessed in patients being treated for BPH. Overall, changes in hematocrit and hemoglobin were not significantly different in patients treated and not treated with α-blockers, 5-α-reductase inhibitors, anticholinergics, or phytotherapics (Table 3). Moreover, pre- and postoperative hemoglobin and hematocrit values showed no differences between treated and nontreated patients, except for 5-α-reductase inhibitors. In this case, while no significant differences were observed in preoperative hemoglobin and hematocrit of patients treated and not treated with 5-α-reductase inhibitors (mean [SD] preoperative hemoglobin was 14.5 [1.5] g/dL vs 14.7 [1.40] g/dL; $P = .50$ and mean [SD] preoperative hematocrit was 44.5 [4.3] % vs 44.2 [4.4] %; $P = .70$), those treated with 5-α-reductase inhibitors had significantly higher postoperative values of both hemoglobin (12.61 [1.71] g/dL vs 11.94 [1.82] g/dL; $P = .02$) and hematocrit (39.03 [6.27]% vs 36.56 [6.10]%; $P = .01$). No significant differences were found in transfusion rates for patients treated and not treated with each of the analyzed BPH treatments.

Intraoperative Variables

Operating time significantly influenced the change in hemoglobin concentration, which decreased 0.01 g/dL per each additional minute of surgery ($P = .04$). Conversely, no significant correlation was observed between operating time and hematocrit decrease ($P = .11$). Mean operating time was similar in patients requiring a blood transfusion and those that did not: mean (SD) operating time was 72 (18) and 79 (23) minutes for patients receiving a transfusion and those that did not, respectively ($P = .43$).

Table 3. Mean decreases of hemoglobin and hematocrit levels in patients undergoing different BPH medical therapies

	Hemoglobin decrease (g/dL) Mean (SD)	*P*	Hematocrit decrease (%) Mean (SD)	*P*
α-blockers				
Yes	2.11 (1.68)	0.510	6.26 (5.89)	0.930
No	2.26 (1.77)		6.25 (6.80)	
5-α-reductase inhibitors				
Yes	2.02 (1.73)	0.250	5.98 (6.24)	0.540
No	2.28 (1.67)		6.51 (6.10)	
Anticholinergics				
Yes	1.64 (2.17)	0.310	5.45 (8.44)	0.660
No	2.19 (1.67)		6.30 (6.03)	
Phytotherapics				
Yes	0.93 (1.29)	0.210	5.26 (5.97)	0.630
No	2.19 (1.70)		6.36 (6.09)	

Concomitant treatment of bladder lithiasis did not influence the decrease in hemoglobin and hematocrit during surgery. Mean (SD) hemoglobin decrease was 1.39 (1.87) g/dL and 2.20 (1.68) g/dL for patients with and without concomitant cystolitholapaxy during prostate surgery, respectively ($P = .49$). Mean (SD) hematocrit decrease was 2.38 (6.88) % and 6.50 (6.05) % for patients with and without cystolitholapaxy, respectively ($P = .08$). Of all patients treated for bladder stones, only one required a blood transfusion.

Multivariate Analysis

Although yielding nonsignificant results in univariate analyses, all variables deemed clinically relevant regarding blood loss were included in 2 multiple regression models to predict hemoglobin and hematocrit decrease: age, prostate size, resected tissue weight, surgical time, antiplatelet treatments, and anticoagulant treatments. The model did not significantly predict a decrease in hemoglobin ($R^2 = 6.14$; $P = .45$) or hematocrit ($R^2 = 3.32$; $P = .77$).

DISCUSSION

This analysis of 963 patients undergoing HoLEP surgery for BPH during 10 years found that hemoglobin and hematocrit decreases were not influenced by prostate volume, patients age, antithrombotic therapy, BPH medical treatments or concomitant treatment of bladder calculi. Operating time significantly influenced a decrease in hemoglobin, but not in hematocrit. Transfusion rates were significantly higher in patients treated with anticoagulant drugs, although this treatment did not influence hemoglobin or hematocrit decrease.

Transfusion rates in our cohort (5%) were higher than those reported in previous series of BPH patients undergoing HoLEP surgery (up to 1.9%),[13-16] but lower than those reported for OP (0 to 19%).[4,5,17,18] Although transfusion rates are widely used to measure blood loss during surgery, the low percentage of transfusions often hamper the investigation of factors influencing blood loss. Furthermore, most centers lack transfusion guidelines, this decision falling upon the anesthesiologist and the urologist. Alternatively, we investigated factors influencing blood loss in terms of hemoglobin and hematocrit decrease during HoLEP. Like transfusion rates, hemoglobin decrease observed in our cohort (2.15 g/dL) was higher than that reported in previous HoLEP studies, which ranged from 0.8 to 1.67 g/dL.[13-16] A clinical characteristic that might have contributed to a higher hemoglobin decrease was the larger volume of the prostate in our cohort (mean of 102 g and 91 g, measured by external and transrectal ultrasound, respectively), while the mean volume reported in the aforementioned studies ranged from 54 to 82 g. Although in our cohort prostate volume did not influence any of the variables related to blood loss, a previous study covering a wider range of prostate volumes concluded that patients with prostates over 100 g experienced a significantly higher decrease in hemoglobin when undergoing HoLEP surgery.[19]

Antithrombotic therapies present in many patients requiring BPH surgery, may have an important influence on blood loss during surgery. These patients have a higher risk of haemorrhagia during surgical procedures[20,21] and may experience thromboembolic events in case of treatment discontinuation. Nevertheless, various studies have concluded that HoLEP remains safe in patients receiving antithrombotic therapy, with no significant differences in either hemoglobin decrease or transfusion rates.[22-25] In line with these studies, greater drops in hemoglobin levels of patients receiving antiplatelet or anticoagulant medication were not observed, a trend that was confirmed when analyzing the change in the hematocrit level. Patients receiving anticoagulant treatment had higher transfusion rates. However, as discussed above, this variable may be influenced by operating procedures used at the participating sites. Many times transfusion is a personal decision, and in this kind of patients our anesthesiologist trended to be very conservative and did transfusion sooner than in other population, trying to avoid low level of hemoglobin.

In addition to antithrombotic therapy, the potential influence of BPH treatments on blood loss was explored. These treatments aim to shrink the prostate, in some cases by reducing vascularization. In the case of 5-α-reductase inhibitors, decreased vascularization has been associated with less blood loss during TURP[26,27] and HoLEP.[28] Nevertheless, consistently with previous studies, no differences in either hemoglobin drops or transfusion rates were found.[29] Treatment with 5-α-reductase inhibitors resulted in a postoperative increase of hematocrit and hemoglobin levels in our cohort. Such increases, which cannot be attributed to blood transfusion because transfused patients were excluded from the analysis, suggest better blood outcomes in patients treated with 5-α-reductase inhibitors. However, considering the extent of these dissimilarities and the absence of drops in hemoglobin and hematocrit values, differences were deemed clinically irrelevant.

One of the advantages of the HoLEP operation is the possibility to treat bladder calculi during prostate surgery. This procedure, which increases the complexity of the overall surgery, did not influence transfusion rates in previous studies.[30,31] However, the effects of cystolitholapaxy during HoLEP surgery had not been investigated in terms of hemoglobin and hematocrit decrease. In this regard, our results confirm that cystolitholapaxy during HoLEP surgery is safe and has no influence on blood loss.

We have included the analysis of bladder stones and not other pathologic conditions such as: vesical diverticula, bladder neoplasm, urethral stenosis; because we believe it is relatively common to find bladder stones that are treated in a standardized way with the laser. However, the other conditions mentioned are exceptional and added a lot of variability to the analysis.

The results of this study must be read in the context of some limitations. Firstly, although data were collected prospectively in a specific dataset built for the enucleation program, the analysis was retrospective and, therefore, data accuracy was not monitored in the study setting. Secondly, the measures of hematocrit and hemoglobin decrease were highly variable, thus reducing the reliability of all related analyses. Finally, transfusion rates in our study cohort were low and limiting the analyses regarding factors influencing this outcome. Despite these limitations, our study is strengthened by the large number of subjects included throughout 10-years of experience using this technique. Also, to our knowledge, this was the first study specifically designed to assess blood loss during HoLEP surgery and investigate the factors influencing the hematological outcomes.

CONCLUSION

In summary, our results confirm that HoLEP is a safe procedure with no remarkable concerns regarding blood loss. This blood loss profile applies to patients at high risk, such as those with larger prostates and receiving antithrombotic therapy, although, in our series, the transfusion rate was higher in these patients. Operating time had a significant—albeit moderate—impact on hemoglobin decrease and, therefore, should be considered in patients with a higher risk of bleeding. Based on blood loss outcomes, HoLEP should be considered for all patients with BPH, regardless of their age, prostate size, antithrombotic therapy or need of concurrent bladder lithiasis treatment.

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