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Anesthetic Technique (Spinal vs. General Anesthesia) in Holmium Laser Enucleation of the Prostate (HoLEP)

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Table of Contents

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Dear Dr. Gild

We are pleased to inform you that your manuscript ANESTHETIC TECHNIQUE (SPINAL VS. GENERAL ANESTHESIA) IN HOLMIUM LASER ENUCLEATION OF THE PROSTATE (HoLEP) - RETROSPECTIVE ANALYSIS OF PROCEDURAL AND FUNCTIONAL OUTCOMES AMONG 1,159 PATIENTS has been accepted for publication and passed on to our Production Editing Department. You will hear from a production editor in due course.

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ANESTHETIC TECHNIQUE (SPINAL VS. GENERAL ANESTHESIA) IN HOLMIUM LASER ENUCLEATION OF THE PROSTATE (HoLEP) - RETROSPECTIVE ANALYSIS OF PROCEDURAL AND FUNCTIONAL OUTCOMES AMONG 1,159 PATIENTS

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Abstract

Objective: To compare procedural efficacy, early- and late functional outcomes in Holmium Laser Enucleation of the Prostate (HoLEP) under spinal (SA) vs. general anesthesia (GA).

Methods: We retrospectively reviewed patients undergoing HoLEP at our institution between 2012-2017. Standard pre-, peri- and postoperative characteristics were compared according to anesthetic technique. Multivariable logistic regression analyses (MVA) were employed to study the impact of SA on procedural efficacy and postoperative complications.

Results: Our study cohort consisted of 1,159 patients, of whom 374 (32%) underwent HoLEP under SA. While a medical history of any anticoagulation/antiplatelet therapy exempt low-dose AsA was significantly more common among patients undergoing GA (16% vs. 10%,p=0.001), no other significant differences in preoperative characteristics were noted including age, body mass index (BMI), American Society of Anesthesiologists Classification (ASA), prostate size, or International Prostate Symptom (IPSS), and Quality of Life (QoL) scores. Patients under SA exhibited shorter times of enucleation (42 min (interquartile range (IQR):27-59 vs. 45 min (IQR:31-68),p=0.002), and combined time of enucleation/morcellation/coagulation (57 min (IQR:38-85) vs 64 min (IQR:43-93),p=0.002), as well as fewer complications (Clavien-Dindo ≥3) (12 (3.2%) vs. 55 (7%), p=0.013). These associations were confirmed in MVA. Patients did not differ significantly with regard to early micturition including post-void residual volume and maximum flow-rate improvement. At a median follow-up of 33 months (IQR:32-44), patients with SA had a lower IPSS score (median 3 (IQR:1-6) vs. 4 (IQR:2-7),p=0.039). However, no significant differences were observed with respect to any UI, urge symptoms, and postoperative pain.

Conclusion: In this large retrospective series, HoLEP under SA was a safe and efficacious procedure with comparable early and long-term functional outcomes.

Introduction

Lower urinary tract symptoms (LUTS) due to benign prostate hyperplasia (BPH) frequently affect elderly men with prevalence rates ranging between 50-75% among men greater than 50 years to 80% among men 70 years and older[1,2]. Consequently, desobstructive surgery in patients failing or not tolerating medical LUTS treatment represents a common reason for surgery in elder men[3]. Because the risk of perioperative complications is generally greater in elderly patients, even without underlying medical conditions[4], regional or spinal anesthesia (SA) poses an attractive alternative to general anesthesia (GA) in order to minimize such risk[5]. Importantly, while this applies to a number of surgeries, past studies have failed to show convincing differences for SA vs. GA in various endpoints including morbidity and mortality, myocardial ischemia, cognitive function, and haemodynamic disturbances when undergoing transurethral resection of the prostate (TURP)[5,6]. SA may, however, reduce postoperative pain, sore throat, and nausea[6] and potentially offer superior cost effectiveness[7,8]. Past studies have focused almost exclusively on anesthetic features of SA, while none have evaluated functional urological outcomes. Additionally, the existing literature stems from the transurethral resection of the prostate (TURP) era, where a salient feature of SA was neurological monitoring and early identification of TUR syndrome. Currently, enucleation techniques such as Holmium Laser Enucleation of the Prostate (HoLEP) have proven superior efficacy, safety, and cost effectiveness over TURP with reliable long-term data and have become guideline endorsed treatments in the last decade[9]. While reports of TUR syndrome are anecdotal under HoLEP and other enucleation techniques due to the use of saline as irrigation fluid, differences in the surgical approach i.e. closer proximity to the prostate capsule and external sphincter, the use of morcellation and longer operation time may leave the patient prone to injury during SA and thereby affect functional outcome.

Against this backdrop, we aimed to assess the impact of anesthesia, namely GA or SA, on procedural and perioperative characteristics as well as short- and long- term functional outcomes of patients undergoing HoLEP at our institution.

Materials and Methods

Study population & covariates

This was a local ethics committee (No. PV5633) approved observational study with written consent obtained from all patients. HoLEP was introduced at our institution in 2006 and a retrospective database maintained as of 2012. Given that a variable for anesthesia (GA vs. SA) was introduced in 2012, our analysis focused on patients that consecutively underwent the procedure between 2012-2017. No patient was excluded from analysis. *Baseline patient characteristics* recorded included patient age, body mass index (BMI), Charlson Comorbidity Index (CCI), American society of Anesthesiologists (ASA) Score, transrectal ultrasound determined prostate size (ml), Prostate Specific Antigen (PSA) (mg/dl), concurrent medication (Alpha blockers, 5-Alpha Reductase Inhibitors (5ARI), low-dose Acetylsalicylic Acid (AsA), any anticoagulation/antiplatelet therapy (exempt low-dose AsA), preoperative post-void residual volume (PVR, ml), maximum urinary flow (Qmax, ml/s), International Prostate Symptom Score (IPSS) and Quality of life score. *Procedural and perioperative characteristics* included surgeon volume, enucleated specimen weight (Gramm (g)), enucleation and morcellation time in min, enucleation and morcellation rate (g/min), total time (enucleation/morcellation/transurethral coagulation, min), difference in pre- vs. postoperative Haemoglobin nadir (ΔHb), receipt of blood transfusion, postoperative complications (recorded and graded according to the Clavien-Dindo Classification (CDC)[10]), length of catheterization and hospitalization (days). Postoperative voiding characteristics included pre- vs. postoperative post voiding residual volume (ΔPVR), pre- vs. postoperative Qmax (ΔQmax), discharge with indwelling catheter.

Intervention

The choice of anesthetic technique relied on the discretion of the treating physicians as well as patients' personal preference. For spinal anesthesia, lumbar puncture was performed with a 25 G pencil point needle and 10mg of isobaric 0.5% bupivacaine (2mL) mixed with 5 µg of sufentanil (1mL for a total volume of 3 mL) injected at L3-L4 level block; sedation was avoided unless clinically indicated. All prostatic adenomas were completely enucleated in 3-lobe technique as has been reported previously[11] and cases performed or supervised by expert surgeons (caseload >50/year), totaling 7 surgeons. The 100W holmium laser generator (Versa Pulse 100, Lumenis, Palo Alto, CA, USA) was used at 70W with settings of 1,4J and a frequency of 50 Hz via a 550- µm end-firing laser fibers (Lumenis, Palo Alto, CA, USA). For enucleation a 27 French (Fr) continuous flow resectoscope with a laser bridge adapter and an endoscopic camera (Olympus) was used. The enucleated tissue was removed with the Lumenis morcellator device over a 26-Fr nephroscope. All specimens were histopathologically evaluated by a pathologist with urogenital expertise. The weight of the removed tissue was routinely measured and documented. All patients received perioperative antibiotic prophylaxis. After the intervention, the patients received a 22-Fr irrigation catheter and the bladder was irrigated for 24 hours with saline solution, while the catheter was removed 48 hours after the procedure according to our institutional standard. After removal of the catheter, uroflowmetry outcomes and residual urine measurement were recorded for all patients.

Our institutional standard for management of anticoagulation/antiplatelet therapy was as follows: Patients receiving direct oral anticoagulants (DOAC) discontinued therapy 48 hours prior to surgery. All patients on Coumarins paused medication seven to ten days prior to surgery. These patients were bridged via bodyweight adapted low-molecular-weight heparin (LMWH) based on their individual international normalized ratio (INR) threshold and CHA_2DS_2-VASc Score based thromboembolic risk. LMWH was seized 24h prior to surgery. With regard to platelet inhibitors, patients continued low dose Acetylsalicylic Acid (AsA), while ADP antagonists, whenever possible were exchanged for low-dose AsA. In select cases (i.e. presence of artificial heart valves, coagulation disorders), blood-thinning agents were managed individualized after consultation with our institutional cardiology and a coagulation specialist. In any case, Coumarins, DOAC and ADP antagonists were restarted after 14 days of LMWH.

Follow-up

Follow-up was performed cross-sectionally via postal mail and included self-administered validated questionnaires, namely IPSS and QoL, as well as a non-validated institutional questionnaire. The latter included questions exploring the presence of any urinary incontinence (UI), the use of pads, as well as presence and duration of postoperative pain. UI was defined as the use of zero or a maximum of 1 safety pad/24h; contrary urinary incontinence was defined as the regular use of more than 1 pad/24h.

Statistical analysis

Descriptive statistics were reported using medians and interquartile ranges (IQR) or means and standard deviations (SD) for continuous variables, and frequencies and proportions for categorical variables. The Pearson's chi-squared as well as Students t-test and Mann-Whitney U-test were used as appropriate for comparison of categorical and continuous variables between the groups. First, the cohort was stratified according to anesthesia into SA or GA. Second, preoperative, procedural and perioperative, as well as early functional voiding and follow-up data were compared between the cohorts. Third, multivariable logistic regression models, adjusted for established confounders were employed to study the impact of SA on procedural efficacy (total time below group median) and postoperative complications CDC ≥3. All statistical testing was two-sided with a level of significance set at $p < 0.05$. Analyses were performed using Stata v.14.0 (StataCorp, College Station, TX, USA).

Results

Preoperative characteristics

Preoperative characteristics are displayed in **Table 1**. Our study cohort consisted of 1,159 patients with a median age of 71 years (interquartile range [IQR]: 66-76), median prostate volume of 80 ml (IQR: 60-110) and median PSA of 5.4 ng/ml (IQR: 2.9-11). The majority of patients (62%) were healthy or exhibited mild systemic disease (ASA 1-2). 1,074 (93%) were on Alphablockers and/or 5ARI, any anticoagulation/antiplatelet therapy was present in 165 (14%). The median IPSS and QoL scores were 19 (IQR: 13-24) and 4 (IQR: 3-5).

374 (32%) and 785 (68%) patients underwent HoLEP in SA and GA, respectively. While any anticoagulation/antiplatelet therapy was more common among GA patients (16% vs. 10%; *p*=0.01), no other significant differences were observed between the strata, including age (p=0.07), prostate size (p=0.4) and ASA scores (p=0.7).

Procedural and perioperative characteristics

Procedural/perioperative characteristics can be taken from **Table 2**. Overall, the median enucleated specimen weight was 55 grams (IQR: 34-83), enucleation and morcellation time were 44 min (IQR: 29-65) and 10 min (IQR: 6-17), respectively. 24 patients (2.1%) received a blood transfusion; complications (CDC ≥3) occurred in 67 (5.8%) of cases, the median length of catheterization was 2 days (IQR: 2-2).

Stratification by anesthesia revealed significant differences in favor of SA. Specifically, enucleation time was shorter (42 min (IQR: 27-59) vs. 45 min (31-68), p=0.002), and enucleation rate superior (1.3 g/min (IQR: 0.8-1.9) vs. 1.1 g/min (IQR: 0.71-1.7), p=0.009) in patients undergoing spinal block. Similarly, ΔHb was lower (1.1 mg/dl (IQR: 0.5-1.8) vs. 1.3 mg/dl (IQR: 0.7-2.1), p=0.007), and complications (CDC ≥3) less common (12 (3.2%) vs. 55

(7%), p=0.013) in patients receiving SA. No significant differences were observed with respect to enucleated specimen weight, morcellation time/rate, receipt of blood transfusions, and lengths of catheterization and hospitalization.

Multivariable analyses predicting procedural efficacy and postoperative complications

On multivariable logistic regression analysis, SA (odds ratio (OR) 1.7, 95% confidence interval (CI) 1.3-2.3, p<0.001) and surgeon volume (OR 1.004, 95% CI 1.0-1.0, p<0.001) were associated with superior procedural efficacy, while BMI (OR 0.96, 95% CI 0.93-1.0, p=0.035), and preoperative prostate volume (OR 0.98, 95% CI 0.97-0.98, p<0.001) were associated with lower procedural efficacy. Similarly, SA was associated with lower odds of CDC ≥3 complications (OR 0.5, 95% 0.3-0.9, p=0.033), while age (OR 1.1, 95% CI 1.0-1.1, p=0.019) and any anticoagulation (OR 4.0, 95% CI 2.25-7.18, p<0.001) were associated greater odds of such event (**Table 3**).

Early functional and follow-up characteristics

Early voiding characteristics are displayed in **Table 4A**. The cohorts' median ΔPVR and ΔQmax were 90ml (IQR: 40-155) and 12 ml/s (IQR: 5-20.7), respectively. 34 (2.9%) of patients failed to void and were discharged with an indwelling catheter. No significant differences were observed among the strata (all p>0.6).

Follow-up was available in 484 (42%) of patients with a median time of follow-up of 33 months (IQR: 23-44) (**Table 4B**). At the time of follow-up the median IPSS and QoL were 3 (IQR: 2-7) and 1 (IQR: 0-2), respectively. Permanent UI was reported in 16 (3.3%) of cases. 388 (80.2%) of patients reported no postoperative pain, whereas 5 (1%) reported of chronic pain.

Stratification by anesthesia revealed significant differences with regard to time of follow up, which was shorter among GA patients (30 months (IQR: 22-42) vs. 39 months (IQR: 28-48), $p<0.001$). Moreover, patients under SA had a lower IPSS score (3 (IQR: 1-6) vs. 4 (IQR: 2-7), $p=0.039$). No other significant differences were observed between GA and SA, including Qol, presences of UI, and postoperative pain.

Discussion

To the best of our knowledge, this is the first study to compare SA and GA in patients undergoing HoLEP. Our main findings in a cohort of >1,159 patients, of which 374 (32%) received SA, were superior procedural characteristics, namely faster operating time and enucleation efficiency, as well as fewer postoperative complications, both in favor of SA. Importantly, no clinically relevant differences were observed with respect to early and late functional outcomes including failure to void, postoperative pain and urinary incontinence. Several of our findings merit further discussion.

First, the demographic and preoperative features of our cohort were equally distributed, exempt a history of any anticoagulation, which was significantly more common among patients receiving GA, as it constitutes a contraindication of SA in certain scenarios (such a as patients on a therapeutic bridging LMWH regimen). Similarly, comparative studies from the TURP era - which have predominantly concluded on equal outcomes of SA and GA - did not observe significant differences with respect to preoperative patient characteristics[6]. The fact that patient age and comorbidities were equally distributed suggests that the choice of anesthesia was driven by patients´ preferences and not comorbidities precluding GA. While few studies have elucidated determinants of anesthesia in transurethral surgery, this notion is supported by data from the ambulatory setting. Capdevila et al. in a cohort of 592 patients undergoing ambulatory orthopedic and urologic surgeries found that the deciding factors to undergo SA were patient preference (60%) and comfort, whereas ASA Status (9%) and age (2%) were only minor drivers[12]. Of note, only a few HoLEP series have reported on their mode of anesthesia [13,14]. For example, Humphreys et al in a series of 507 patients reports of GA in more than 90% of cases[13], whereas Placer among 125 cases reports of only 4%[14], which compares to 68% of GA in our series. Notably, both studies are single surgeon reports from academic centers. The observed sizeable heterogeneity in anesthetic choice may solely reflect local preferences of operation processes.

Second, the differences we observed in procedural characteristics and complications were meaningful and in support of a decision towards anesthesia in SA[6,12]. For example, the total time of surgery (enucleation, morcellation, transurethral coagulation) differed by a median of 7 minutes, whereas severe postoperative complications occurred more than twice as often (3.2% vs. 7%) among patients in GA. Except for any anticoagulation/antiplatelet medication, which was significantly more common in the GA cohort, patients did not differ with respect to measurable preoperative characteristics. Further, surgeon volume was significantly greater in patients under GA. Thus, one explanation of our finding would be the presence of blood thinning agents. Indeed, previous reports demonstrate that complications are significantly more common in patients with a medical history of anticoagulation or antiplatelet therapy, undergoing HoLEP[15]. Importantly, previous studies also indicate, that procedural characteristics do not differ significantly between therapy naive and patients on anticoagulation (it is therefore unlikely, that presence of anticoagulation explains the superior procedural efficacy of SA in our cohort)[16]. Lastly, and with respect to early- and long-term functional outcomes, we did not observe significant differences aside a slightly better IPSS in SA patients. As from a surgeon’s perspective, a major concern of SA would be the possibility of a detrimental impact on functional outcomes, we are glad to reject this hypothesis based on our data.

Third, our finding of non-inferior functional outcomes of SA merits further notice under an economical consideration. Interestingly there is a dearth of urological studies on the topic. A look at orthopedic trauma and joint replacement surgery however supports an absolute reduction in staff and supply costs that range in between 5-40% under SA [7,8,17]. In this context it should be noted that inherent differences in procedures, institutions, countries and ultimately reimbursement systems would hinder comparison to HoLEP at our hospital. Nevertheless, in a study from our institution, Schuster et al. among 466 patients undergoing orthopedic and trauma procedures demonstrated reduced anesthesia related costs of approximately 13% for a 50 min case. Further, a direct impact of reduced case duration on anesthesia costs was shown, where a 10% reduction in surgically controlled time (which is similar to the reduction observed in our cohort), equals to a 7% reduction in costs[8]. Taken together, should these findings similarly apply to HoLEP, SA may pose a more cost-effective alternative to GA, yet with equal functional outcomes.

Our study has several strengths that include its cohort size, detailed assessment of procedural and perioperative features as well as short- and long-term functional follow-up, which allow for a thorough comparative analysis of SA vs. GA. Despite these strengths there are some limitations that should be noted. First, this study was a retrospective single center study, by default prone to non-measurable selection bias. This includes the decision to administer either form of anesthesia, which was based on patients´, surgeons´, and anesthetists' individual preferences. Second, aside its relatively large size, our cohort may have been underpowered to detect further differences between the strata. Third, as follow-up was performed cross-sectionally and using a self-administered questionnaire, information on postoperative pain and urinary incontinence are prone to recall bias.

Fourth, while our response rates are comparable to the literature, the may have introduced non-response bias[18]. Fifth, while all cases were operated on or supervised by expert surgeons, the individual surgeons´ learning curve may have impacted our findings. Lastly, study focused on Holmium Laser as energy source, while over the last decade a number energy sources have become available for endoscopic enucleation of the prostate including Thulium Laser or bipolar energy. However, as a growing body of literature has pointed to comparable outcomes of enucleation - irrespective of energy source - our findings may well be applicable to these settings[19].

Conclusions

Our findings indicate that HoLEP in SA versus GA offers at least equal procedural efficacy and safety. Importantly, short- and long-term outcomes of the two techniques, including failure to void, postoperative pain, quality of life, and urinary incontinence do not differ significantly. Therefore, our data support the decision to undergo either form of anesthesia on an individual basis taking into account a joint decision of patient, anesthetist, and surgeon.

Statement of Ethics: Informed consent was obtained from all individual participants included in the study. All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and national research committees and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Conflict of Interest Statement: The authors declare that they have no conflict of interest.

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Table 1 Preoperative characteristics of 1,159 patients undergoing Holmium Laser Enucleation of the Prostate (HoLEP) stratified by mode of anesthesia (spinal anesthesia vs. general anesthesia).

	Overall	Spinal anesthesia	General anesthesia	*p*-value
Number of Patients; n (%)	1,159 (100)	374 (32)	785 (68)	
Age (years), median (IQR)	71 (66-76)	71 (66-76)	71 (66-75)	0.07
BMI, median (IQR)	26 (24-29)	26 (24-29)	26 (24-29)	0.07
CCI, n(%)				0.9
0	729 (63)	238 (64)	491 (63)	
1	237 (21)	75 (20)	162 (21)	
≥2	191 (17)	60 (16)	131 (17)	
Unknown	2 (0.74)	1 (0.30)	1 (0.13)	
ASA, n(%)				0.7
1-2	722 (62)	229 (61)	493 (63)	
3-4	422 (36)	141 (38)	281 (36)	
Unknown	15 (1.3)	4 (1.1)	11 (1.4)	
PSA (mg/dl), median (IQR)	5.4 (2.9-11)	5.6 (2.7-11)	5.3 (3.0-10)	0.8
Prostate size (ml), median (IQR)	80 (60-110)	80 (60-110)	80 (60-109)	0.4
Medication, n(%)				
Alpha Blocker	839 (72)	270 (72)	569 (73)	0.2
5-ARI	235 (20)	80 (21)	155 (20)	0.1
Low dose AsA	282 (24)	94 (25)	188 (24)	0.1
Any anticoagulation/antiplatelet therapy[#]	165 (14)	39 (10)	126 (16)	**0.01**
Indwelling catheter, n(%)	320 (28)	103 (28)	217 (28)	0.8
Preoperative post-void residual urine (ml), median (IQR)	91 (44-180)	100 (50-170)	90 (40-200)	0.7
Preoperative Q_{max} (ml/s), median (IQR)	10 (7-14)	10 (6.6-15)	10 (7.3-14)	0.5
Preoperative IPSS, median (IQR)	19 (13-24)	19 (13-24)	19 (13-24)	0.8
Preoperative QoL, median (IQR)	4 (3-5)	4 (3-5)	4 (3-5)	0.3

BMI: Body Mass Index; IQR: Interquartile range; CCI: Charlson Comorbidity Index; ASA: American Society of Anesthesiologists classification; PSA: Prostate Specific Antigen; 5-ARI: 5-Alpha Reductase Inhibitor; AsA: Acetylsalicyclic Acid; Q_{max}: Maximum flow rate; IPSS: International Prostate Symptom Scores; QoL: Quality of Life
#: History of either Coumarins, ADP-Antagonists, Direct Oral Anticoagulants (DOAC), therapeutic low-molecular-weight Heparin (LMWH)
Percentages may not add up to 100%, as they are rounded.

Table 2 Perioperative characteristics of 1,159 patients undergoing Holmium Laser Enucleation of the Prostate (HoLEP) stratified by mode of anesthesia (spinal anesthesia vs. general anesthesia).

	Overall	**Spinal anesthesia**	**General anesthesia**	***p*-value**
Number of Patients; n (%)	1,159 (100)	374 (32)	785 (68)	
Surgeon volume; median (IQR)	115 (46-204)	98 (39-184)	123 (50-210)	**0.012**
Enucleated specimen weight (g); median (IQR)	55 (34-83)	54 (32-82)	55 (34-83)	0.7
Enucleation time (min); median (IQR)	44 (29-65)	42 (27-59)	45 (31-68)	**0.002**
Enucleation rate (g/min); median (IQR)[1]	1.2 (0.74-1.8)	1.3 (0.80-1.9)	1.1 (0.71-1.7)	**0.009**
Morcellation time (min); median (IQR)	10 (6-17)	10 (6-17)	10 (6-17)	0.6
Morcellation rate (g/min); median (IQR)[2]	5.2 (3.5-7.4)	5.3 (3.7-7.4)	5.1 (3.5-7.4)	0.8
Total time (min); median (IQR)[3]	62 (40-90)	57 (38-85)	64 (43-93)	**0.002**
ΔHb (mg/dl); median (IQR)	1.2 (0.6-2)	1.1 (0.5-1.8)	1.3 (0.7-2.1)	**0.007**
Perioperative blood transfusion; n(%)	24 (2.1)	4 (1.1)	20 (2.6)	0.08
Postoperative complications (CDC ≥3); n (%)	67 (5.8)	12 (3.2)	55 (7)	**0.013**
Length of catheterization (days); median (IQR)	2 (2-2)	2 (2-2)	2 (2-2)	0.07
Length of hospitalization (days); median (IQR)	4 (4-5)	4 (4-5)	4 (4-6)	0.8

IQR: Interquartile Range; ΔHb: difference in pre- vs. postoperative nadir hemoglobin level; CDC: Clavien-Dindo Classification

1: Enucleated specimen weight/enucleation time; 2: Enucleated specimen weight/morcellation time; 3: Enucleation time + morcellation time + coagulation time

Percentages may not add up to 100%, as they are rounded

Table 3 Multivariable logistic regression analyses predicting procedural efficacy[%] and postoperative complications (CDC ≥3)[*] among 1,159 patients undergoing Holmium Laser Enucleation of the Prostate (HoLEP).

Variables	*Procedural efficacy*			*Postoperative complications*		
	OR	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
Spinal anesthesia (vs. general anesthesia)	1.7	1.3-2.3	**<0.001**	0.5	0.3-0.9	**0.033**
BMI (continuous)	0.96	0.93-1.0	**0.035**	1.0	0.93-1.1	1.0
Age (continuous)	0.99	0.97-1.0	0.3	1.1	1.0-1.1	**0.019**
ASA						
1-2	Ref			Ref		
3-4	0.83	0.62-1.1	0.2	0.93	0.52-1.6	0.8
Unknown	0.56	0.15-2.1	0.4	1.0	0.11-9.4	1.0
Prostate Size	0.98	0.97-0.98	**<0.001**	1.0	1.0-1.0	0.4
Any Anticoagulation/Antiplatelet therapy (vs. none)	1.2	0.79-1.7	0.5	4.0	2.25-7.18	**<0.001**
Surgeon volume (continuous)	1.004	1.0-1.0	**<0.001**	1.0	1.0-1.0	0.081

[%]defined as being below the groups median (62 min) of total surgical time (n=584 events)
[*]CDC: Clavien-Dindo Classification, n=67 events
OR: Odds Ratio; 95% CI: 95% confidence interval

Table 4 Early functional voiding characteristics **A**) among 1,159, and long-term follow-up data **B**) of 484 available patients undergoing Holmium Laser Enucleation of the Prostate (HoLEP), stratified by mode of anesthesia (spinal anesthesia vs. general anesthesia).

A)

	Overall	**Spinal anesthesia**	**General anesthesia**	***p*-value**
Number of Patients; n (%)	1,159 (100)	374 (32)	785 (68)	
ΔPVR (ml), median (IQR)	90 (40-155)	90 (40-150)	90 (40-160)	0.6
ΔQ_{max} (ml/s), median (IQR)	12 (5-21)	12 (4.1-20)	11 (5.2-21)	0.6
Failure to void, n (%)	34 (2.9)	11 (2.9)	23 (2.9)	0.9

B)

	Overall	**Spinal anesthesia**	**General anesthesia**	***p*-value**
Number of Patients; n (%)	484 (100)	181 (37)	303 (63)	
Median F/u (months), median (IQR)	33 (23-44)	39 (28-48)	30 (22-42)	**<0.001**
IPSS, median (IQR)	3 (2-7)	3 (1-6)	4 (2-7)	**0.039**
QoL, median (IQR)	1 (0-2)	1 (0-2)	1 (0-2)	0.08
Urinary incontinence >3 months, n(%)	16 (3.3)	5 (2.8)	11 (3.6)	0.2
Urge symptoms >3 months	27 (5.6)	6 (3.3)	21 (6.9)	0.2
Postoperative pain, n(%)				0.8
No pain	388 (80)	149 (82)	239 (79)	
1st week	34 (7.0)	11 (6.1)	23 (7.6)	
≤2 weeks	22 (4.6)	9 (5.0)	13 (4.3)	
≤3 months	12 (2.5)	3 (1.7)	9 (3.0)	
>3 months	5 (1.0)	1 (0.6)	4 (1.3)	
Unknown	23 (4.8)	8 (4.4)	15 (5.0)	

ΔPVR: pre- vs. postoperative post voiding residual volume; ΔQ_{max}: pre- vs. postoperative maximum urinary flow rate; IQR: Interquartile Range; Q_{max}: maximum flow-rate; F/u: follow-up; IPSS: International Prostate Symptom Score; QoL: Quality of life
Percentages may not add up to 100%, as they are rounded.

II. Presentation of the publication

1. Introduction

Benign prostatic hyperplasia (BPH), the nonmalignant enlargement of the prostate gland, is one of the most common conditions affecting elderly men. Approximately 50% of men >50 years of age will have evidence of BPH, and this number will increase to 80% as men reach their eighth decade of life and older (Chughtai et al., 2016). BPH is a pathological diagnosis, and histologically refers to the proliferation of smooth muscle and epithelial cells within the prostatic transition zone according to current guidelines (Parsons et al., 2020, S. Gravas, 2021). Although many potential risk factors have been associated with the development and progression of BPH over the past decades, the definite etiology is still unclear. Forty years ago, the concept of “embryonic reawakening” of inductive potential in stromal cell was first proposed by McNeal et al, characterizing BPH as an age-related reinitiation of benign neoplastic growth in the transitional periurethral zone (McNeal, 1978, Cunha et al., 1983). In addition, the increase in cell number may be due to epithelial and stromal proliferation or impaired programmed cell death leading to cellular accumulation (Wein et al., 2016). Regardless, many other potential factors, such as metabolic anomalies, sex hormones (androgen and estrogen), neurotransmitters, stromal-epithelial interactions, growth factors, inflammation and diet have also been suggested to play a role (Chughtai et al., 2016).

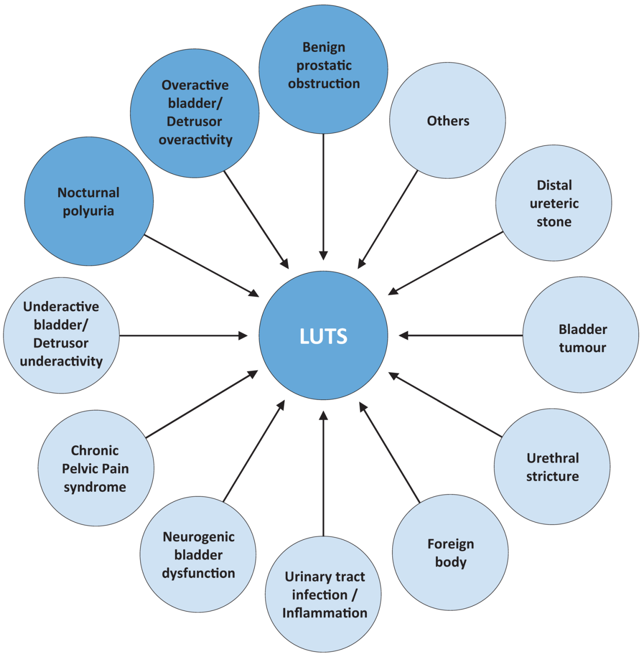

Figure 1. Causes of male LUTS (S. Gravas, 2021)

The presence of BPH is strongly associated with the development of lower urinary tract symptoms (LUTS). BPH in many men leads to the morphologic enlargement of the prostate, termed benign prostatic enlargement (BPE). Such enlargement may cause obstruction at the level of bladder neck, which is termed as benign prostatic obstruction (BPO), subsequently resulting in bladder outlet obstruction (BOO) and corresponding symptoms (Parsons et al., 2020). However, it is important to realize that LUTS could result from various causes and BPH is just one of them (Figure 1). Conversely, not all men with BPH will develop BPE or BPO (Figure 2). LUTS are

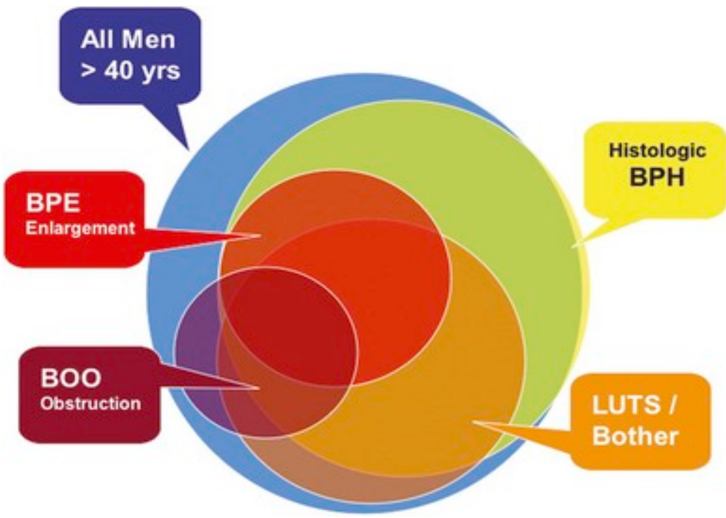

Figure 2. The partial overlap between different disease definitions (Wein et al., 2016)

classified as three categories, that is storage, voiding and post-micturition symptoms (Gratzke et al., 2015). Storage symptoms include urinary frequency, nocturia, urgency. Voiding symptoms include urinary hesitancy, delay in initiating micturition, intermittency, weak urinary stream and dysuria. Post micturition symptoms include sensation of incomplete voiding, and/or postmicturition dribbling (Abrams et al., 2002). LUTS due to BPH represent a substantial disease burden, cause bother and impact quality of life (QoL) (Kupelian et al., 2006). As the prevalence of BPH/LUTS is associated with ageing, with an estimated longer life expectancy, a potential further rise in BPH/LUTS diagnosis would be expected in the next a few decades.

The treatment modalities for LUTS attributed to BPH usually include watchful waiting or lifestyle modification, pharmacological treatment and surgical intervention. Conventionally, the main focus of treatment is mainly to alleviate the bother of LUTS, and more recently, treatment has also been focused on the alteration of disease progression and prevention of complications (Parsons et al., 2020). When patients present with LUTS, for those with mild symptoms or International Prostate Symptoms Score (IPSS) ≤7, or non-bothersome moderate to severe symptoms, watchful waiting or lifestyle change is usually suggested. This should be tailored to meet the individualized needs. Pharmacological treatment is usually a primary option for patients with moderate to severe LUTS. There are a number of pharmaceutical options, including α1-blockers, 5α-reductase inhibitors, anticholinergics, vasopressin analogs, PDE-5 inhibitors and phytotherapy, as single use or in combination (Parsons et al., 2020, S. Gravas, 2021). However, when conservative management is no longer adequate, or patients are not tolerating medical therapy, surgical intervention should be considered. These can be categorized as open, minimal invasive and endoscopic techniques. Historically, transurethral resection of the prostate (TURP) has been the gold standard of care for the surgical treatment of LUTS attributed to BPH. Currently, enucleation techniques such as Holmium Laser Enucleation of the Prostate (HoLEP) have proven superior efficacy, safety, and cost-effectiveness over TURP with reliable long-term data and have become guideline endorsed treatments in the last decade (S. Gravas, 2021). As early as 1995 holmium laser resection of the prostate (HoLRP) technique was first described by Gilling et al (Gilling et al., 1995, Gilling et al., 1996). This technique later evolved into HoLEP with the advent of intravesical morcellation (Gilling et al., 1998). During HoLEP the prostatic tissue is enucleated from the surgical capsule in a retrograde manner and displaced into the bladder followed by removal with an intravesical soft-tissue morcellator. This technique takes advantage of the distinct anatomical planes to remove the entire prostatic transition zone, resulting in removing more tissue than TURP and less retreatment rate (Das et al., 2019). Over the years, numerous emerging head-to-head comparative studies continue to demonstrate HoLEP a safe and effective treatment for LUTS due to BPH with excellent durable long term efficacy (Large and Krambeck, 2018, Das et al., 2020).

Patients undergoing HoLEP may be offered either spinal anesthesia (SA) or general anesthesia (GA). GA has been considered a safe and well tolerated option at all age groups (Dodds, 1999). However, administering GA to elderly patients requires consideration of the evolving physiological and pathophysiological changes that may come with age, and which may leave them frailer at various levels, thereby increasing the odds of perioperative complications in cardiovascular, respiratory, hepatorenal and neurological system (Deiner and Silverstein, 2011, Caruselli and Michel, 2020). Indeed, it has been long recognized that the risk of perioperative complications or morbidity is generally greater in elderly patients, especially those with underlying medical conditions (Rix and Bates, 2007, Aubrun et al., 2012). However, elderly patients who are eligible for surgery should not be denied based only on age, especially since they constitute the main population for desobstructive prostate surgery. While surgical technique will normally only marginally be changed in the elderly, the main limitation comes from fitness for anesthesia. Regional or spinal anesthesia (SA) poses an attractive alternative to general anesthesia (GA) in order to mitigate perioperative risks in the elderly (Rodgers et al., 2000). Although comparative studies have been largely carried out in a variety of surgeries, none have exhibited convincing differences between SA and GA in various endpoints including morbidity and mortality, myocardial ischemia, cognitive function and hemodynamic disturbances et al, in TURP (Rodgers et al., 2000, Reeves and Myles, 1999). SA may be advantageous with no airway instrumentation, adequate analgesia, stable hemodynamics, reduced blood loss, less pulmonary vascular and neurological complications, better control postoperative nausea and vomiting (Liu et al., 2005), and potentially offer superior cost effectiveness (Gonano et al., 2006, Schuster et al., 2005). However, SA may also bring several disadvantages such as intraoperative anxiety, cough, hiccups and movement (Meng et al., 2017). Past studies in desobstructive prostatic surgery have focused almost exclusively on anesthetic features of SA, while none have evaluated functional urological outcomes. In addition, the existing literatures mostly stem from TURP era, where a salient feature of SA was neurological monitoring and early identification of TUR syndrome. HoLEP has considerable differences in anatomical approach, tissue extraction (morcellation), which may leave patients prone to adverse outcomes with SA.

Against this backdrop, we retrospectively assessed the impact of spinal vs. general anesthesia, on procedural and perioperative characteristics as well as short- and long- term functional outcomes of patients undergoing HoLEP at our institution.

2. Material and methods

2.1 Study population and covariates

2.1.1 Study population

This observational study was approved by the local ethics committee (No. PV5633) with written consent obtained from all patients. We retrospectively reviewed the medical records of 1,159 patients who consecutively underwent HoLEP at our institution between 2012-2017. No patient was excluded from analysis.

2.1.2 Covariates

(1) Baseline patient characteristics: patient age, body mass index (BMI), Charlson Comorbidity Index (CCI), American society of Anesthesiologists (ASA) Score, transrectal ultrasound determined prostate size (ml), Prostate Specific Antigen (PSA) (mg/dl), concurrent medication (Alpha blockers, 5-Alpha Reductase Inhibitors (5ARI), low-dose Acetylsalicylic Acid (AsA), any anticoagulation/antiplatelet therapy (exempt low-dose AsA), preoperative indwelling catheter, preoperative post-void residual volume (PVR, ml), maximum urinary flow (Qmax, ml/s), International Prostate Symptom Score (IPSS) and Quality of life (QoL) score.

(2) Procedural and perioperative characteristics: surgeon volume, enucleated specimen weight (Gramm (g)), enucleation and morcellation time in min, enucleation and morcellation rate (g/min), total time (enucleation/morcellation/transurethral coagulation, min), difference in pre- vs. postoperative Hemoglobin nadir (ΔHb), receipt of blood transfusion, postoperative complications (recorded and graded according to the Clavien-Dindo Classification), length of catheterization and hospitalization (days). Surgeon volume was defined as the total amount of procedures performed by a surgeon at the time of the surgery one performed. This variable was used to adjust for in the multivariable model.

(3) Postoperative voiding characteristics: pre- vs. postoperative post voiding residual volume (ΔPVR), pre- vs. postoperative Qmax (ΔQmax), discharge with indwelling catheter.

2.2 Intervention

2.2.1 Anesthesia

The choice of anesthetic technique relied on the discretion of the treating physicians as well as patients' personal preference. For spinal anesthesia, lumbar puncture was performed with a 25 G pencil point needle and 10mg of isobaric 0.5% bupivacaine (2mL) mixed with 5 µg of sufentanil (1mL for a total volume of 3 mL) injected at L3-L4 level block; sedation was avoided unless clinically indicated. For general anesthesia, most patients received a balanced anesthesia with isoflurane, sevoflurane, or desflurane as volatile anesthetic and sufentanil or remifentanil as opioids. A portion of patients received total IV anesthesia with propofol in combination with sufentanil or remifentanil. Propofol or etomidate were used to induce anesthesia, and rocuronium, cisatracurium, and succinylcholine were used as neuromuscular blocking drugs. Airway management was achieved by intratracheal intubation or laryngeal masks (Schuster et al., 2005).

2.2.2 HoLEP technique

All prostatic adenomas were completely enucleated in 2-lobe or 3-lobe technique as has been reported previously (Gilling, 2008) and cases performed or supervised by expert surgeons (caseload >50/year), totaling 7 surgeons. The 100W holmium laser generator (Versa Pulse 100, Lumenis, Palo Alto, CA, USA) was used at 70W with settings of 1,4J and a frequency of 50 Hz via a 550- µm end-firing laser fibers (Lumenis, Palo Alto, CA, USA). For enucleation a 26 French (Fr) continuous flow resectoscope with a laser bridge adapter and an endoscopic camera (Olympus) was used. The enucleated tissue was removed with the Lumenis morcellator device over a 26-Fr nephroscope. All specimens were histopathologically evaluated by a dedicated uro-pathologist. The weight of the removed tissue was routinely measured and documented.

2.2.3 Management of anticoagulation/antiplatelet therapy

Patients receiving direct oral anticoagulants (DOAC) discontinued therapy 48 hours prior to surgery. All patients on Coumarins paused medication seven to ten days prior to surgery. These patients were bridged via bodyweight adapted low-molecular-weight heparin (LMWH) based on their individual international normalized ratio (INR) threshold and CHA2DS2-VASc Score based thromboembolic risk. LMWH was paused 24h prior to surgery. With regard to platelet inhibitors, patients continued low dose Acetylsalicylic Acid (AsA), while ADP antagonists, whenever possible, were exchanged for low-dose AsA.

2.3 Follow-up

Follow-up was performed cross-sectionally via postal mail and included self-administered validated questionnaires, namely IPSS and QoL, as well as a non-validated institutional questionnaire. The latter included questions exploring the presence of any urinary incontinence (UI), the use of pads, as well as presence and duration of postoperative pain.

2.4 Statistical analysis

First, the cohort was stratified according to anesthesia into SA or GA. Second, preoperative, procedural and perioperative, as well as early functional voiding and follow-up data were compared between the strata. Third, multivariable logistic regression models adjusted for established confounders were employed to study the impact of SA on procedural efficacy (total time below group median) and postoperative complications CDC≥3. Analyses were performed using Stata v.14.0 (StataCorp, College Station, TX, USA).

3. Results

3.1 Preoperative characteristics

Preoperative characteristics are displayed in **Table 1**. Our cohort consisted of 1,159 patients, of which 374 (32%) patients underwent HoLEP in SA and 785 (68%) in GA. Except for anticoagulation/antiplatelet therapy (GA 16% vs. SA 10%; p=0.01), no other significant differences were observed between strata, including age (p=0.07), prostate size (p=0.4) and ASA scores (p=0.7).

3.2 Procedural and perioperative characteristics

Procedural and perioperative characteristics are shown in **Table 2**. Stratification by anesthetic modality revealed significant differences in favor of SA. Specifically, enucleation time was shorter (42 min (IQR: 27-59) vs. 45 min (31-68), p=0.002), and enucleation rate higher (1.3 g/min (IQR: 0.8-1.9) vs. 1.1 g/min (IQR: 0.71-1.7), p=0.009) in patients undergoing SA. Besides, ΔHb was lower (1.1 mg/dl (IQR: 0.5-1.8) vs. 1.3 mg/dl (IQR: 0.7-2.1), p=0.007), and severe postoperative complications (CDC ≥3) were less (12 (3.2%) vs. 55 (7%), p=0.013) in patients receiving SA. No significant differences were observed among other parameters.

3.3 Multivariable analyses predicting procedural efficacy and postoperative complications

On multivariable logistic regression analysis (**Table 3**), SA (odds ratio (OR) 1.7, 95% confidence interval (CI) 1.3-2.3, p<0.001) and surgeon volume (OR 1.004, 95% CI 1.0-1.0, p<0.001) were associated with superior procedural efficacy (below median (62 min) of total surgical time), while BMI (OR 0.96, 95% CI 0.93-1.0, p=0.035), and preoperative prostate volume (OR 0.98, 95% CI 0.97-0.98, p<0.001) were associated with lower procedural efficacy. Similarly, SA (OR 0.5, 95% CI 0.3-0.9, p=0.033) was associated with lower CDC≥3 complications, while age (OR 1.1, 95% CI 1.0-1.1, p=0.019) and any anticoagulation (OR 4.0, 95% CI 2.25-7.18, p<0.001) were associated with greater odds of such events.

3.4 Early functional and follow-up characteristics

Early voiding characteristics are displayed in **Table 4A**. There were no significant differences with regard to early voiding parameters (all p>0.6). Follow-up was available in 484 (42%) patients with a median follow-up of 33 months (**Table 4B**). Patients under SA had a lower IPSS score (3 (IQR: 1-6) vs. 4 (IQR: 2-7), *p*=0.039). No other significant differences were observed between GA and SA, including QoL (*p*=0.08), presences of UI (*p*=0.2), and postoperative pain (*p*=0.8).

3.5 Perioperative, early- and long-term functional outcomes of patients with large prostates (≥100 mL)

Subgroup analysis of patients with large prostate are shown in **Table S1** and **Table S2**. Similarly, enucleation time was shorter (51 min (IQR:37-72) vs. 55 min (IQR:41-79), *p*=0.03), and enucleation rate was higher (1.9 g/min (IQR:1.3-2.5) vs. 1.7 g/min (IQR:1.1-2.2), *p*=0.03) in patients under SA. Severe postoperative complications (CDC≥3) were less common (3.2% vs. 9.7%, *p*=0.03) in patients receiving SA. No significant differences were observed with respect to early voiding features and long-term functional outcomes.

Table S1. Procedural and perioperative characteristics of patients with large prostate (≥100mL) undergoing HoLEP stratified by anesthesia mode

	Overall	**Spinal anesthesia**	**General anesthesia**	***p*-value**
Number of Patients, n (%)	386(33)	128(33)	258(67)	
Enucleated specimen weight (g), median (IQR)	90(66-110)	90(66-110)	89(70-106)	0.8
Enucleation time (min), median (IQR)	55(40-77)	51(37-72)	55(41-79)	**0.03**
Enucleation rate (g/min), median (IQR)	1.7(1.1-2.3)	1.9(1.3-2.5)	1.7(1.1-2.2)	**0.03**
Morcellation time (min), median (IQR)	16(10-26)	17(10-25)	17(12-27)	>0.9
Morcellation rate (g/min), median (IQR)	5.4(3.7-7.5)	5.3(3.6-7.2)	5.1(3.5-7.2)	>0.9
Total time (min), median (IQR)	82(60-114)	75(55-103)	81(60-113)	0.08
ΔHb (mg/dl), median (IQR)	1.6(1-2.4)	1.5(0.9-2.1)	1.6(1.1-2.5)	0.2
Perioperative blood transfusion, n (%)	12(3.1)	2(1.6)	10(3.9)	0.2
Postoperative complications (CDC ≥3), n (%)	29(7.6)	4(3.2)	25(9.7)	**0.03**

Length of catheterization (days), median (IQR)	2(2;2)	2(2;2)	2(2;2)	0.8
Length of hospitalization (days), median (IQR)	4(4;5)	4(4;5)	4(4;5)	0.9

Table S2. Early and long-term functional outcomes of patients with large prostate (≥100mL) undergoing HoLEP stratified by anesthesia mode

a)

	Overall	**Spinal anesthesia**	**General anesthesia**	***p*-value**
Number of Patients, n (%)	386(33)	128(33)	258(67)	
ΔPVR (ml), median (IQR)	80(50-150)	75(40-150)	80(50-150)	0.5
ΔQ_{max} (ml/s), median (IQR)	11(5-20)	12(7-21)	11(45-19)	0.4
Failure to void, n (%)	13(3.4)	3(2.3)	10(3.9)	0.8

b)

	Overall	**Spinal anesthesia**	**General anesthesia**	***p*-value**
Number of Patients, n (%)	173 (100)	66(38)	107(62)	
Median F/u (months), median (IQR)	34(22-44)	40(25-48)	31(22-42)	**0.01**
IPSS, median (IQR)	3(1-6)	3(1-4)	4(2-7)	0.3
QoL, median (IQR)	1(0-1)	1(0-1)	1(0-1)	0.4
Urinary incontinence >3 months, n (%)	23(13)	2(3)	4(3.7)	0.2
Urge symptoms >3 months, n (%)	4(2.3)	1(1.5)	3(2.8)	0.6
Postoperative pain, n (%)				0.5
No pain	136(79)	52(79)	84(79)	
1st week	11(6.4)	3(4.5)	8(7.5)	
≤2 weeks	8(4.6)	4(6.1)	4(3.7)	
≤3 months	5(2.9)	1(1.5)	4(3.7)	
>3 months	1(0.6)	0(0)	1(0.9)	
Unknown	12(6.9)	6(9.1)	6(5.6)	

4. Discussion

We critically analyzed the impact of spinal vs. general anesthesia in a cohort of 1,159 patients with LUTS secondary to BPO treated with HoLEP at a single institution. We found that HoLEP under spinal anesthesia exhibited superior procedural characteristics, i.e. faster operating time and enucleation efficiency, lower ΔHb as well as fewer severe (CDC≥3) postoperative complications. Importantly, with regard to early voiding features and long-term functional outcomes, no clinically relevant differences were observed between SA and GA. Several points merit further discussion.

The demographic and preoperative characteristics in both groups were equally distributed except for a history of any anticoagulation/antiplatelet therapy, which was significantly more often in patients receiving GA since it constitutes a contraindication for SA in certain scenarios (such as patients on therapeutic bridging LMWH regimen). This corresponds to a previous study in TURP era, which concluded on equal outcomes of SA vs. GA and did not observe significant differences among preoperative characteristics (Reeves and Myles, 1999). The fact that patients' age and comorbidities were equally distributed suggests that the choice of anesthesia was driven by patients' preference, certainly together with anesthetists and surgeons, however not by comorbidities precluding general anesthesia. This point of view is supported by data from the ambulatory setting. Capdevila et al. (Capdevila et al., 2020) in a cohort of 592 patients undergoing ambulatory orthopedic and urologic surgeries, found that the determining factors to undergo SA were patient preference (60%) and comfort, whereas ASA score (9%) and patient's age (2%) were only minor drivers. In fact, there has been a large number of studies investigating the impact of anesthetic techniques in different types of surgery, however, only few HoLEP series have reported on their mode of anesthesia. Humphreys et al. (Humphreys et al., 2008) in a cohort of 507 patients reported more than 90% of cases received GA, whereas Placer et al. (Placer et al., 2009) reported only 4% of patients with GA in 125 patients, which was in contrast to 68% of patients receiving GA in our cohort. Both studies were single surgeon reports from academic centers. The observed high heterogeneity in anesthetic choice may solely reflect local preferences of operation processes.

In perioperative characteristics and complication analysis, we observed significant and meaningful differences in support of a decision towards SA. For example, the enucleation time was shorter, leading to a higher enucleation efficiency (1.3 g/min vs. 1.1 g/min). The total operation time (enucleation, morcellation, coagulation) was faster, differed by a median of 7 min in favor of SA. Additionally, while seldom, severe postoperative complications (CDC≥3) occurred more than twice as often (3.2% vs. 7%) among patients receiving GA. This was corroborated in earlier studies (Reeves and Myles, 1999), where GA patients had higher incidence of adverse events postoperatively, even though those events were mostly minor. In our present study, except for any anticoagulation/antiplatelet therapy, which was more common in the GA cohort, patients did not differ with respect to measurable preoperative characteristics. Therefore, one explanation of our findings on procedural efficiency and complications could be the presence of anticoagulation/antiplatelet (AC/AP) therapy. Firstly, regarding postoperative complications, previous studies demonstrated that complications were significantly more common in patient with a medical history of AC/AP therapy, especially intra- and postoperative bleeding, when undergoing HoLEP (Becker et al., 2019, Romero-Otero et al., 2020). Secondly, regarding procedural efficacy, one previous study with conflicting results exhibited shorter enucleation time, higher enucleation rate and morcellation rate for patients under AC/AP therapy vs. no AC/AP (El Tayeb et al., 2016). To the contrary, another study revealed that procedural characteristics do not differ between therapy naïve and patients on AC/AP therapy (Becker et al., 2019). Therefore, it is less likely that the presence of anticoagulation/antiplatelet therapy could properly explain the superior procedural efficacy of SA in our cohort. Furthermore, surgeon volume was significantly greater in patients under GA, which eliminated surgeon volume as an confounding factor on superior procedural efficiency in SA. In such context, possible explanations could be some other non-measurable confounders, such as the surgeon (and staff) being influenced by the patients presence and feedback during SA.

Lastly, with respect to early and long-term functional outcomes, we did not observe significant differences including failure to void, QoL, incontinence, urge and postoperative pain, aside a slightly better IPSS in patients receiving SA. In subgroup analysis among patients with large prostate (≥100mL), similar outcomes were observed, in that patients under SA exhibited superior enucleation efficiency and fewer severe (CDC≥3) complications. Besides, no significant differences were observed regarding early and long term functional outcomes between SA and GA. Previous studies exhibited that prostate size (>100 mL vs. <100mL) did not influence safety and efficacy outcomes of HoLEP (Becker et al., 2018, Romero-Otero et al., 2020). In our subgroup analysis, we further demonstrated that the choice of anesthesia did not impact functional outcomes in patients with large prostates.

Our study is not devoid of limitations. First of all, the nature of this retrospective single center study may be prone to non-measurable selection bias. This includes the decision to administer either form of anesthesia, which was based on patients', surgeons', and anesthetists' individual preferences. Second, despite its relatively large size, our cohort may have been underpowered to detect further differences between the strata. Third, as follow-up was performed cross-sectionally and using a self-administered questionnaire, information on postoperative pain and urinary incontinence are prone to recall bias. Fourth, while our response rates are comparable to the literature, non-response bias may still have been introduced (Nakash et al., 2006). Fifth, although all cases were operated by or supervised by expert surgeons, the individual surgeons' learning curve may have impacted our findings. Lastly, our study focused on Holmium Laser as energy source, while over the last decade a number of energy sources have become available for endoscopic enucleation of the prostate including Thulium Laser or bipolar energy. However, as a growing body of literature has pointed to comparable outcomes of enucleation - irrespective of energy source - our findings may well be applicable to these settings (Kyriazis et al., 2015).

5. Conclusions

Our findings indicate that HoLEP in SA versus GA offers at least equal procedural efficacy and safety. Importantly, short- and long-term outcomes of the two techniques, including failure to void, postoperative pain, quality of life, and urinary incontinence do not differ significantly. Therefore, our data support the decision to undergo either form of anesthesia on an individual basis as a joint decision of patient, anesthetist, and surgeon.

6. Zusammenfassung

Diese Studie zielte darauf ab, die prozedurale Effektivität sowie die frühen und späten funktionellen Ergebnisse der Holmium-Laser-Enukleation der Prostata (HoLEP) unter Spinalanästhesie (SA) mit der Vollnarkose (GA) zu vergleichen. Wir untersuchten retrospektiv Patienten, die sich zwischen 2012 und 2017 an unserer Institution einer HoLEP unterzogen. Standardmäßige prä-, peri- und postoperativen Charakteristika wurden gemäß der Anästhesietechnik verglichen. Multivariable logistische Regressionsanalysen (MVA) wurden eingesetzt, um die Auswirkungen von SA auf die prozedurale Wirksamkeit und die postoperative Komplikationen zu untersuchen. Unsere Studienkohorte bestand aus 1,159 Patienten, von denen sich 374 (32%) einer HoLEP unter SA unterzogen. Während das Vorhandensein jeglicher Antikoagulation/Thrombozytenaggregationshemmung - ausschließlich niedrig dosierten ASS - bei Patienten mit GA signifikant häufiger war (16% gegenüber 10%, *p*=0.001), wurden keine weiteren signifikanten Unterschiede in den präoperativen Merkmalen festgestellt, einschließlich Alter, Body Mass Index (BMI), Klassifikation der American Society of Anesthesiologists (ASA), Prostatagröße oder International Prostate Symptom (IPSS) und Lebensqualität (LQ). Patienten unter SA wiesen kürzere Enukleationszeiten (42 Minuten (Interquartilsbereich (IQR): 27-59) vs. 45 Minuten (IQR: 31-68), *p*=0.002) und kombinierte Zeit von Enukleation / Morcellation / Koagulation (57 Minuten (IQR: 38-85) vs. 64 min (IQR: 43-93), *p*=0.002), sowie weniger Komplikationen (Clavien-Dindo ≥3) (12 (3.2%) vs. 55 (7%), *p*=0.013) auf. Diese Assoziationen wurden in der MVA bestätigt. Die Patienten unterschieden sich nicht signifikant in Bezug auf die frühe Miktion einschließlich der Verbesserung des Restharns und der maximalen Flussrate in der Uroflowmetrie. Bei einer medianen Nachbeobachtungszeit von 33 Monaten (IQR: 32-44) hatten die Patienten mit SA einen niedrigeren IPSS-Score (Median 3 (IQR: 1-6) gegenüber 4 (IQR: 2-7), *p*=0.039). Es wurden jedoch keine signifikanten Unterschiede in Bezug auf jegliche Harninkontinenz, Drangsymptome und postoperative Schmerzen beobachtet. Zusammenfassend lässt sich sagen, dass die HoLEP unter SA ein sicheres und wirksames Verfahren mit vergleichbaren frühen und langfristigen funktionellen Ergebnissen in dieser großen retrospektiven Serie war.

Abstract

This study aimed to compare procedural efficacy, early- and late functional outcomes in Holmium Laser Enucleation of the Prostate (HoLEP) under spinal (SA) vs. general anesthesia (GA). We retrospectively reviewed patients undergoing HoLEP at our institution between 2012-2017. Standard pre-, peri- and postoperative characteristics were compared according to anesthetic technique. Multivariable logistic regression analyses (MVA) were employed to study the impact of SA on procedural efficacy and postoperative complications. Our study cohort consisted of 1,159 patients, of whom 374 (32%) underwent HoLEP under SA. While a medical history of any anticoagulation/antiplatelet therapy exempt low-dose AsA was significantly more common among patients undergoing GA (16% vs. 10%, *p*=0.001), no other significant differences in preoperative characteristics were noted including age, body mass index (BMI), American Society of Anesthesiologists Classification (ASA), prostate size, or International Prostate Symptom (IPSS), and Quality of Life (QoL) scores. Patients under SA exhibited shorter time of enucleation (42 min (interquartile range (IQR): 27-59) vs. 45 min (IQR: 31-68), *p*=0.002), and combined time of enucleation/morcellation/coagulation (57 min (IQR: 38-85) vs 64 min (IQR: 43-93), *p*=0.002), as well as fewer complications (Clavien-Dindo ≥3) (12 (3.2%) vs. 55 (7%), *p*=0.013). These associations were confirmed in MVA. Patients did not differ significantly with regard to early micturition including post-void residual volume and maximum flow-rate improvement. At a median follow-up of 33 months (IQR: 32-44), patients with SA had a lower IPSS score (median 3 (IQR: 1-6) vs. 4 (IQR: 2-7), *p*=0.039). However, no significant differences were observed with respect to any urinary incontinence, urge symptoms, and postoperative pain. In conclusion, In this large retrospective series, HoLEP under SA was a safe and efficacious procedure with comparable early and long-term functional outcomes.

7. Reference

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III. Authors’ contribution

Own contribution:

- Literature search: comparative study of anesthesia methods in urological area and other surgical field, management of lower urinary tract symptoms, complications and outcomes of HoLEP.
- Acquisition of data: anesthesia method.
- Statistical analysis and evaluation of the results.
- Drafting the original manuscript.

Contribution of co-authors:

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- Analysis and interpretation of data: Philipp Gild
- Manuscript writing: Philipp Gild
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06/2018-Present	University Medical Center Hamburg-Eppendorf Department of Urology M.D. Student, Supervisor: Prof. Michael Rink and Prof. Margit Fisch

Publication

1. **Yu, H.**; Gild, P.; et al. Anesthetic technique (Spinal vs. General anesthesia) in Holmium Laser Enucleation of the Prostate(HoLEP) -Retrospective analysis of procedural and functional outcomes among 1,159 patients (Accepted by Urologia Internationalis 2021)
2. Janisch, F.; **Yu, H.**; et al. Do Younger Patients with Muscle-Invasive Bladder Cancer have Better Outcomes? J Clin Med 2019, 8(9).
3. Soave, A.; Kluwe, L.; **Yu, H.**; et al. Copy number variations in primary tumor, serum and lymph node metastasis of bladder cancer patients treated with radical cystectomy. Sci Rep. 2020 Dec 9;10(1):21562.
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VI. Eidesstattliche Versicherung

Ich versichere ausdrücklich, dass ich die Arbeit selbständig und ohne fremde Hilfe verfasst, andere als die von mir angegebenen Quellen und Hilfsmittel nicht benutzt und die aus den benutzten Werken wörtlich oder inhaltlich entnommenen Stellen einzeln nach Ausgabe (Auflage und Jahr des Erscheinens), Band und Seite des benutzten Werkes kenntlich gemacht habe.
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