The impact of preoperative lower urinary tract symptoms medication on the functional performance of holmium laser enucleation of the prostate

Alexander Tamalunas, Thilo Westhofen, Melanie Schott, Patrick Keller, Michael Atzler, Christian G. Stief, Giuseppe Magistro

Department of Urology, University Hospital, LMU Munich, Munich, Germany

Citation: Tamalunas A, Westhofen T, Schott M, et al. The impact of preoperative lower urinary tract symptoms medication on the functional performance of holmium laser enucleation of the prostate. Cent European J Urol. 2021; doi: 10.5173/ceju.2021.130 [Epub ahead of print]

Article history
Submitted: April 21, 2021
Accepted: June 30, 2021
Published online: Aug. 13, 2021

Corresponding author
Alexander Tamalunas
ORCID iD: 0000-0002-4659-2262
Ludwig-Maximilians University
University Hospital
Department of Urology
15 Marchioninistr
81377 Munich
phone: +49 89 44000
alexander.tamalunas@med.uni-muenchen.de

Introduction Medical treatment of lower urinary tract symptoms (LUTS) secondary to benign prostatic obstruction (BPO) targets prostate size, to prevent disease progression, and prostate smooth muscle tone for rapid relieve of LUTS. Holmium laser enucleation of the prostate (HoLEP) is a size-independent method for surgical treatment of LUTS/BPO in medication-refractory patients and offers durable long-term results with reduced perioperative morbidity. As up to 50% of patients receive medical treatment for LUTS/BPO prior to surgery, we analyzed the impact of alpha-blockers and 5-alpha-reductase-inhibitors (5-ARI) on outcomes and perioperative morbidity in patients undergoing HoLEP for LUTS.

Material and methods We retrospectively gathered data of 1,057 patients, who underwent HoLEP for LUTS/BPO from 2013–2018, and divided patients into group 1 (no medication), group 2 (α-blockers), and group 3 (5-ARI and α-blockers). Perioperative parameters, short-term functional outcomes and safety were assessed and statistical analysis was performed using SPSS V26.0 software.

Results Even though preoperative LUTS profile was significantly different between groups, all patients improved significantly after HoLEP, irrespective of preoperative LUTS medication. Median improvement of IPSS was 9, 8 and 7 points, of Q_{max} was 10, 12 and 9.5 ml/s, with significant improvement of QoL and reduction of PVR for for groups 1–3, respectively, 30 days after surgery. With only 4.0% (42/1,057) of patients experiencing a Clavien-Dindo grade ≥II complication, there was no difference in prevalence of perioperative complications between groups (p = 0.943).

Conclusions Although preoperative LUTS medication does not impair efficacy of HoLEP with acceptable perioperative morbidity, the time gap between medical therapy and surgical treatment may favor an earlier response.

Key Words: holmium laser enucleation of the prostate ‹› alpha-blockers ‹› 5-alpha reducatse inhibitors ‹› benign prostatic hyperplasia ‹› benign prostatic enlargement ‹› medical treatment ‹› lower urinary tract symptoms

INTRODUCTION

Voiding symptoms caused by bladder outlet obstruction (BOO) due to benign prostatic enlargement (BPE) and increased smooth muscle tone characterize lower urinary tract symptoms (LUTS) suggestive of benign prostatic obstruction (BPO) [1, 2]. Medical treatment includes α_1-blockers for rapidly inhibiting prostate smooth muscle contraction to facilitate voiding, and 5α-reductase inhibitors (5-ARI) for preventing disease progression and even reducing prostate size [1, 3]. With over 600 million men affected worldwide by LUTS/BPO in 2018, annual costs add up to five billion USD for medical treatment alone [4]. Although α1-adrenoceptor antagonists are the gold standard of medical therapy in LUTS/BPO,

improvement of prostate symptom scores (IPSS) and urinary flow rates (Q_{max}) is limited to 30–50% [5]. Insufficient current medications show an unfavorable balance between efficacy and side effects, leading to high discontinuation rates and patient non-compliance [6]. Typically, the urologic patient seeking treatment for LUTS/BPO is 65 years of age or above, bringing with them a higher prevalence of multiple comorbidities combined with polypharmacy, i.e. taking ≥5 medications simultaneously [7, 8]. By the year 2040, 25 % of all Americans will be over the age of 65, most likely leading to a higher incidence of LUTS secondary to BPO [9]. However, up to 49% of patients who receive surgical treatment for LUTS/BPO have had or are actively being treated with LUTS medications prior to surgery [10].

Since the introduction of holmium laser enucleation of the prostate (HoLEP) in 1996, transurethral resection of the prostate (TURP) has constantly been challenged as the reference method for surgical relieve of LUTS/BPO [11, 12]. HoLEP is equal in efficacy when compared to TURP, and even superior regarding perioperative morbidity [13, 14]. HoLEP is a size-independent technique for surgical relief of LUTS and its efficacy is comparable to open prostatectomy (OP) with shorter catheterization time, hospital stay and less blood loss [15, 16].

Considering this, together with the age-dependent prevalence of LUTS/BPO and the expected demographic shift in Western countries, improved understanding of the influence of LUTS medications on the functional outcome of surgical treatment options for LUTS/BPO is mandatory.

With major progress in the safety and efficacy of endoscopic laser techniques, analyzing the impact of LUTS medications on postoperative functional outcomes and perioperative morbidity of patients undergoing HoLEP for LUTS/BPO seems mandatory [11, 12, 17].

MATERIAL AND METHODS

Patient population and study design

We included 1,057 patients who underwent HoLEP for LUTS secondary to BPO between 2013 and 2018. A computerized database containing information about prior LUTS medications and clinical information, as well as perioperative data and follow-up information, was used for this study. We retrospectively analyzed this database and included patients, who had been taking α_1-blockers for at least 4 weeks and 5-ARI for at least 3 months prior to HoLEP without wash-out phase. We only included patients in groups 2 and 3 who were on active treatment within 4 weeks of surgery. Furthermore, patients attributed to group 1 (no medication) had to be off treatment for at least 3 months. In total, 1,057 patients were evaluated, in which all the information was available, and subdivided into three groups. HoLEP for LUTS/BPO was indicated in accordance with current EAU guidelines on management of non-neurogenic male LUTS [1]. All patients were screened for urinary tract infections (UTI) before surgery and, if UTI was found, treated accordingly and only referred to surgery after no evidence of UTI could be found. Patients with diverticula or calculi were rare and statistical analysis underpowered in such a large patient cohort. Therefore, those patients were omitted in the final analysis.

Table 1. *Demographic parameters*

Variables	Group 1 n = 697	Group 2 (α-blocker) n = 224	Group 3 (α-blocker + 5-ARI) n = 136	p-value
Age (years)				
Median	72	71	**73**	**0.458**
IQR	66–76	65–76	**67–76**	
BMI				
Median	25.8	26.1	25.9	0.598
IQR	24.0–28.0	24.3–28.4	23.8–28.4	
IPSS				
Median	19	19	17	**<0.02**
IQR	15–24	13–24	13–23	
QoL				
Median	4	4	4	0.609
IQR	3–5	3–5	3–5	
Q_{max} (ml/s)				
Median	11.0	10.5	11.0	0.524
IQR	8.5–15.0	8.0–14.3	8.0–15.0	
PVR (ml)				
Median	80	90	80	0.986
IQR	38–165	35–170	34–175	
Hb (g/dl)				
Median	14.6	14.8	14.9	0.116
IQR	13.7–15.5	13.9–15.5	14.2–15.6	
Total PSA (ng/ml)				
Median	5.8*	5.8**	4.1	*<0.001
IQR	3.4–10.9	3.4–8.9	2.4–6.7	**<0.01
PSA density (ng/ml/cc)				
Median	0.07*	0.06**	0.05	*<0.001
IQR	0.04–0.12	0.04–0.10	0.03–0.08	**<0.01
Prostate volume (cc)				
Median	85	80	83	0.815
IQR	65–110	65–109	69–106	
ASA score ≥III vs <III (%)	35.9 % (297)	27.7 % (62)	27.3 % (36)	**<0.03**
IDC (%)	39.0% (194)	22.4% (50)	22.8% (31)	**<0.001**

IQR – interquartile range; BMI – body mass index; IPSS – International Prostate Symptom Index; QoL – quality of life; PVR – postvoid residual urine; Q_{max} – peak urinary flow rate; Hb – haemoglobin; PSA – prostate-specific-antigen; ASA – American Society of Anaesthesiologists; IDC – indwelling urinary catheter. Bold values indicate statistically significant p-values (p <0.05)

Only two experienced surgeons performed all HoLEPs. We used the VersaPulse® 100W Holmium Laser (Lumenis Ltd., Yokneam, Israel) with a frequency of 53 Hz and a power setting of 1.2 kJ. Morcellation was performed using a mechanical tissue morcellator (R. Wolf, Piranha, Knittlingen, Germany). According to our standard protocol a 24 F three-way foley catheter was inserted after surgery and followed by 12 hours of continuous bladder irrigation with normal saline.

Patients were stratified into three groups. Group 1 included patients who did not receive any LUTS medication (n = 697), group 2 included patients who only received α_1-blockers (n = 224) and group 3 included only patients who received a combination of α_1-blockers and 5α-reductase inhibitors (n = 136). Clinical and pathological information as well as perioperative data were used to describe the patient cohorts. Perioperative complications were analyzed in all groups. They were defined as any adverse event within 30 days of surgery and classified using the modified Clavien-Dindo scale [18].

Statistical analysis

Statistical analysis was performed using SPSS V26.0 software (IBM SPSS Statistics, Version 26.0. Armonk, NY). Results are given as median and interquartile range (IQR) for continuous variables and as percentage for categorial variables. Univariate analyses were performed using Fisher's exact test, T test and Mann-Whitney U test for categorical variables and continuous variables, respectively. For analyses, in which three groups were compared, we used univariate analysis of variation (ANOVA). All reported p-values were two-sided and considered statistically significant if $p < 0.05$.

RESULTS

Patient characteristics

Table 1 displays the demographic parameters of patient groups 1, 2 and 3, respectively. In total, 1,057 patients underwent HoLEP for LUTS secondary to BPO. LUTS profile was significantly different between the patient cohorts (Table 1). Patients in group 3 presented with significantly lower international prostate symptom score (IPSS) of 17 points (IQR 13–23) compared to group 1 with 19 (IQR 15–24) ($p < 0.02$) with no significant difference to group 2 with 19 points (IQR 13–24). Obviously, median PSA was significantly different in all three groups with a median of 4.1 ng/ml (IQR 2.4–6.7) in group 3, i.e. treated with 5α-reductase inhibitors, versus groups 1 and 2 with 5.8 ng/ml (IQR 3.4–10.9) and 5.8 (IQR 3.4–8.9) with $p < 0.001$ and $p < 0.01$, respectively. Preoperative assessment of an American Society of Anesthesiologists (ASA) score ≥III was significantly higher in group 1 compared to the other patient groups, with 35.9 % in group 1 and 27.7 % and 27.3 % for groups 2 and 3, respectively ($p < 0.03$). Also, an indwelling urinary catheter at time of surgery was significantly more prevalent in group 1 with 39.0% versus 22.4% and 22.8% for groups 2 and 3, respectively ($p < 0.001$). Apart from that, patient characteristics were comparable between all three cohorts and groups 1, 2 and 3 showed no statistically significant difference in age, BMI, preoperative quality of life (QoL), maximum flow rate (Q_{max}), post

Table 2. *Perioperative and clinical outcomes 4 weeks after surgery*

Variables	Group 1 n = 697	Group 2 (α-blocker) n = 224	Group 3 (α-blocker + 5-ARI) n = 136	p-value
Enucleation time (min)				
Median	37	34	37	0.436
IQR	28–55	26–47	30–43	
Operating speed (g/min)				
Median	1.54	1.54	1.65	0.595
IQR	1.01–2.23	1.08–2.28	1.22–2.38	
Resected tissue (g)				
Median	65	60	65	0.084
IQR	45–88	43–80	50–86	
Catheterization time (days)				0.143
Median	2.0	2.0	2.0	
IQR	2.0–3.0	2.0–2.0	2.0–2.3	
Hospitalization time (days)				0.509
Median	3.0	3.0	3.0	
IQR	3.0–4.0	3.0–4.0	3.0–4.0	
Δ Hb (g/dl)				
Median	0.7	1.3	1.5	**<0.001**
IQR	0.0–1.7	0.6–2.1	0.7–2.3	
Δ IPSS				
Median	9	8	7	0.481
IQR	3–15	2–15	0–16	
Δ QoL				
Median	3	2	3	0.529
IQR	1–4	1–4	1–3	
Δ Q_{max} (ml/s)				
Median	10	12	9.5	0.385
IQR	5–20	7–21	4–18	
Δ PVR (ml)				
Median	50	68	67	0.061
IQR	0–30	6–150	8–160	

IQR – interquartile range; BMI – body mass index; IPSS – International Prostate Symptom Index; QoL – quality of life; PVR = postvoid residual urine; Q_{max} – peak urinary flow rate; Hb – haemoglobin

Bold values indicate statistically significant p-values (p <0.05)

void residual (PVR), preoperative hemoglobin (Hb) or prostate volume (PV) prior to surgery.

Perioperative assessment and functional outcomes

The analysis of the perioperative outcomes showed no difference in surgery time or operating speed (Table 2). Also, there was no difference in total resected tissue (g), but in median tissue retrieval percentage with 75 % (IQR 62–88) in group 1 versus group 2 with 71 % (IQR 58–84) ($p < 0.03$), but no difference versus group 3 with 76 % (IQR 65–85).

There was a statistically significant difference in the overall median haemoglobin drop between the three groups with 0.7 g/dl (IQR 0.0–1.7) in group 1 versus 1.3 (IQR 0.6–2.1) and 1.5 (IQR 0.7–2.3) in groups 2 and 3, respectively with $p < 0.001$ for both groups.

Four weeks after surgical treatment LUTS improved in all three patient cohorts. The median IPSS decreased by 9 points (IQR 3–15), 8 (IQR 2–15) and 7 (0–16) for groups 1–3, respectively ($p = 0.481$). We observed a relevant improvement in QoL for all three groups with no significant difference between groups. The early functional outcomes four weeks after surgery showed no significant difference between all groups, with a difference in Q_{max} of 10.0 ml/s (IQR 5–20), 12 ml/s (IQR 7–21) and 9.5 ml/s (IQR 4–18), respectively ($p = 0.385$). A median PVR reduction of 50 ml (IQR 0–130), 68 (6–150) and 67 (8–160) was observed for groups 1–3, respectively ($p = 0.061$). Furthermore, we observed no difference between the three groups in duration of hospital stay or catheterization time.

Perioperative complications

Complications seen are listed in detail in table 3. In total, 67 (67/1,057, 6.3 %) patients of the entire cohort experienced at least one perioperative complication. We report 34 (4.9%), 19 (8.5%) and 14 (10.3%) patients that had at least one perioperative complication for groups 1–3, respectively, with no significant difference between groups ($p = 0.943$). There was no difference in severity of perioperative complications, which were reported according to the modified Clavien-Dindo-Score in Table 3, and divided into minor (Clavien I) and major complications (Clavien II to V), with no difference in frequency between groups ($p = 0.93$).

Preoperative lower urinary tract symptoms medication

Table 4 gives an overview of preoperative LUTS medications. Patients included in our study had taken α-blockers for at least 4 weeks, and 5-ARI for at least 3 months prior to HoLEP. Predominantly, tamsulosin was prescribed in both groups with 87.5% and 88.9% for groups 2 and 3, respectively. The use of other α-blockers was rare with 9.4% using alfuzosin and silodosin in 3.1%. While 5-ARI were most often prescribed in combination with tamsulosin, use of other α-blockers was also rare in group 3. Finasteride was prescribed in 83.8% of patients, and Dutasteride was most often administered in combination with tamsulosin (Duodart®) and prescribed in 16.2% of patients. All medications were prescribed

Table 3. *Perioperative adverse events according to the Clavien-Dindo classification*

Adverse events (AEs)	Group 1 n = 697	Group 2 (α-blocker) n = 224	Group 3 (α-blocker + 5-ARI) n = 136	p-value
Overall AEs; N (%)	**34** (4.9 %)	**19** (8.5 %)	**14** (10.3 %)	0.943
Clavien Dindo I	**12** (1.7 %)	**6** (2.7 %)	**6** (4.4 %)	
Clavien Dindo II	**3** (0.4 %)	**1** (0.4 %)	**0** (0.3 %)	
Clavien Dindo III	**14** (2.0 %)	**10** (4.5 %)	**7** (5.1 %)	
Clavien Dindo IV	**4** (0.6 %)	**2** (0.9 %)	**1** (0.7 %)	
Clavien Dindo V	**0** (0.0 %)	**0** (0.0 %)	**0** (0.0 %)	
CDC ≥II vs <II	**21** (3.0 %)	**13** (5.8 %)	**8** (5.9 %)	0.930
Grade	Complication		Management	
I	Hematuria ± blood clot retention (n = 12)		(Prolonged) bedside bladder irrigation ± clot evacuation	
	Acute urinary retention after catheter removal (n = 12)		Bedside recatheterization	
II	Indwelling suprapubic catheter (n = 4)		Bladder training post-surgery	
III	Persistent hematuria (n = 17)		Coagulation	
	Urethral flap (n=13)		Urethral resection (TURP)	
	Injury of right ureteral ostium (n = 1)		Double J-stent placement	
IV	Aspiration pneumonia (n = 2)		Admission to intensive care unit	
	Urosepsis (n = 2)		Admission to intensive care unit	
	Stroke (n = 1)		Admission to intensive care unit	
	Pulmonary embolism (n = 1)		Admission to intensive care unit	
	Myocardial infarction (n = 1)		Admission to intensive care unit	

The following adverse events (AEs) were identified and consecutive management is given in the table. Bold values indicate statistically significant p-values ($p < 0.05$).

Table 4. *Preoperative lower urinary tract symptoms medication*

Variables	Group 1 n = 697	Group 2 (α-blocker) n = 224	Group 3 (α-blocker + 5-ARI) n = 136
Tamsulosin	0	196 (87.5 %)	121 (88.9 %)
Alfuzosin	0	21 (9.4 %)	10 (7.4 %)
Silodosin	0	7 (3.1 %)	5 (3.7 %)
Finasteride	0	0	114 (83.8 %)
Dutasteride*	0	0	22 (16.2 %)

Tamsulosin 0.4 mg q.d.; Alfuzosin 5.0 mg q.d.; Silodosin 4.0 mg q.d.; Finasteride 5.0 mg q.d.; Dutasteride 0.5 mg q.d; *most often administered as compound drug Duodart® Dutasteride 0.5 mg + Tamsulosin 0.4 mg q.d.

according to their respective approval by European Medicines Agency (EMA) and in accordance with EAU guidelines [1]: patients with moderate to severe LUTS were treated with α-blockers as monotherapy, and 5-ARI were offered to patients with moderate to severe LUTS and a higher risk of disease progression (prostate volume >40 ml).

DISCUSSION

Bothersome LUTS become more prevalent with age. The histological diagnosis of benign prostatic hyperplasia is age-dependent and present in at least 40% of 50–60-year-old men and peaks up to 80% in 80-year-old men with half of them becoming symptomatic [1]. LUTS secondary to BPO considerably affect quality of life in the elderly male population. Currently, we observe a demographic shift in western societies. Patients presenting at a higher age bring with them the risk of multiple comorbidities and the prevalence of polypharmacy in those individuals is significantly increased [7, 8]. Side effects of LUTS medications include orthostatic hypotonia, retrograde ejaculation, dizziness, heat sensations and increased risk of adverse events, i.e. a tendency to fall [19]. Ineligibility for LUTS medications is contrasted by an unfavorable balance between side effects and efficacy [6]. Thus, often warranting surgical relief of symptoms. With up to 49% of patients using LUTS medication one year prior to surgical intervention, assessing their impact on preoperative LUTS profile, perioperative morbidity and postoperative functional results becomes self-evident [10]. We report that 34.1% of patients (360/1,057) were on active treatment with LUTS medication at time of surgery. Contrary to Strope et al, we did not only aim for prevalence of LUTS medication use 12 months prior to surgery, but at being actively treated with α-blockers for at least 4 weeks, and 5-ARI for at least 3 months prior to HoLEP to evaluate the impact of LUTS medications on the functional performance after HoLEP.

While our patient cohorts did not differ in age, BMI or Q_{max}, however, they were different in LUTS profile and ASA score (Table 1). Patients receiving both α-blockers and 5-ARI presented with significantly lower preoperative IPSS of 17 points vs 19 points in patients without previous LUTS medications ($p < 0.02$). This may reflect efficacy of LUTS medications, while simultaneously showing the limitations of current medications with only a difference of 2 points between groups, mandating a surgical approach for – in the current setting – medication-refractory LUTS. Previous studies have shown that decrease in IPSS of ≥3 must be achieved for LUTS/BPS medications to be considered effective and satisfying by the patient [20]. Corroborating this hypothesis, we observed an unsatisfying QoL score of 4 points throughout our patient cohort with no difference between groups ($p = 0.609$) as well as a clinically relevant, and equally dissatisfying, median PVR of 80, 90 and 80 ml for groups 1–3, respectively ($p = 986$). However, and with no difference in Q_{max} between groups prior to surgery, patients in group 1 did not receive any LUTS medication, which may be attributed to Q_{max} not being impaired enough to decrease quality of life or increase PVR to a medically relevant level.

As anticipated, we observed a significantly lower median PSA value in patients treated with 5-ARI and α-blockers in group 3 with 4.1 ng/ml versus 5.8 ng/ml in groups 1 and 2 with $p < 0.001$ and $p < 0.01$, respectively. At the same time, we observed no significant difference in prostate volume ($p=0.815$), resulting in a significantly different median PSA density between group 3 with 0.05 ng/ml/cc versus groups 1 and 2 with 0.07 and 0.06 with $p < 0.001$ and $p < 0.01$, respectively. Thus, showing that median total PSA does not arise from prostate size, but decrease in group 3 is dependent on 5-ARI use. With that, our results corroborate the findings of Naslund et al., who was able to show a decrease in PSA of up to 50% during the use of 5-ARI [21]. Furthermore, prostate volume may be a predictor of LUTS, but – and according to current literature – prostate volume alone does not correlate with the severity of LUTS [22]. Thus, patients of the same median prostate sizes may have received different medical treatment, or none at all.

Typically, the urologic patient seeking treatment for LUTS/BPO is 65 years of age or above, bringing with them a higher prevalence of multiple comorbidities combined with polypharmacy, i.e. taking ≥5 medications simultaneously [7, 8]. While age alone may not be an indicator for frailty and, thus, a contrain-

dication for various LUTS medications, pharmacotherapy may be chosen carefully in light of increased risk for polypharmacy and increased toxicity. In addition, we observed a significantly higher proportion of patients presenting with ASA score ≥III in group 1 (35.9% versus 27.7% and 27.3% in groups 2 and 3, respectively; $p < 0.03$), while there was no difference in age between all groups [9, 23, 24]. It therefore seems possible, that age-independent frailty or polypharmacy in group 1 patient cohort may be the reason for not administering any LUTS medications. LUTS profile cannot only be assessed via IPSS and QoL scores, but also by necessity of an IDC prior to surgery. While 39% of patients in group 1 presented with an IDC at date of surgery, we observed this in only 22.4% and 22.8% in groups 2 and 3, respectively ($p < 0.001$). Again, this supports our hypothesis of a frailer patient cohort in group 1, where an IDC poses a more favorable risk profile than LUTS medications.

While there was no significant difference in preoperative haemoglobin value, there was a statistical difference in postoperative haemoglobin drop with 0.7 g/dl in group 1 versus 1.3 g/dl and 1.5 g/dl for groups 2 and 3, respectively ($p < 0.001$). However, there was no need for perioperative blood transfusion. This corresponds well to the data we gathered on the favorable perioperative safety profile of performing HoLEP in octogenarians [25]. In a recent prospective randomized placebo-controlled trial, Bansal et al. could show that short-term preoperative treatment with 5-ARI significantly reduced perioperative bleeding and the need for blood transfusions for patients undergoing TURP for LUTS/BPO. They even suggested 4-week prior treatment with 5-ARI for TURP in order to decrease prostatic microvessel density (MVD). However, the ability of 5-ARI to decrease blood loss during TURP or HoLEP remains controversial [26]. Even though reduction of MVD through finasteride seems feasible, we cannot corroborate the favorable effect of preoperative 5-ARI use on perioperative blood loss discovered by Bansal et al. [26, 27]. Therefore, we are reluctant in stating protective effects of 5-ARI before prostate surgery.

All patients in our study cohort showed significant improvement in functional outcomes after HoLEP. Patients in group 1 had the greatest improvement in postoperative IPSS with 9 versus 8 and 7 points for groups 2 and 3, respectively (Table 2). Although not statistically significant, patients in group 3 had a less pronounced improvement in Q_{max} of 9.5 ml/s compared to the other groups. When looking at LUTS/BPO we see a multifactorial disease, in which LUTS arise from a combination of obstructive voiding symptoms due to increased prostate smooth muscle tone and prostate growth [1, 2]. While prostate smooth muscle tone is relieved by α-blockers, progression of prostate size is chronic and may become more dominant in a later stage of LUTS/BPO. Patients in group 3 may have suffered from LUTS/BPO for an extended period of time, and less improvement of Q_{max} may be due to an increased prevalence of detrusor underactivity, contrasted by decline of bladder outlet obstruction and therefore may explain the less pronounced effect in patients in group 3 [25, 28]. As we hypothesized in a patient cohort ≥80 years of age, the modest initial improvement of Q_{max} and IPSS in group 3 may be due to prolonged recovery of the patients' detrusor secondary to prolonged medical treatment [25]. However, we did not perform urodynamic assessment pre-HoLEP, due to the invasive nature and limited benefit of this diagnostic procedure [29].

As patients receiving combination therapy of α-blockers and 5-ARI may suffer from longer-lasting LUTS/BPO, detrusor contractility may need to be assessed over an extended follow-up period. However, Elshal et al report no difference between short-term postoperative functional outcomes (30 days) compared to follow-up after one year [30]. Furthermore, there was no difference in preoperative QoL, patients showed similar improved after HoLEP.

Mamoulakis et al aimed at modifying the Clavien-Dindo classification (CDC) system for reporting and defining perioperative complications following transurethral resection of the prostate [18]. Overall 67 patients (67/1,057, 6.3%) suffered a postoperative complication according to the CDC (grade I–IV; Table 3). Our population had very modest perioperative complications when compared to the study by Mamoulakis et al, where overall CDC rate was 15.7% [18]. Most of our complications were found to be CDC grade III (42/67, 62.7%) with persistent hematuria or obstruction by a urethral flap requiring surgical reintervention as the most common grade III complications (30/1,057; 2.8%). There were seven CDC grade IV complication due to life-threatening aspiration pneumonia, urosepsis, stroke, pulmonary embolism and myocardial infarction, accounting for 0.7% of all complications in our patient cohort and therefore corresponding well with the complication rate of 0.7% for CDC grade IV reported by Elshal et al. [30]. There was no statistical difference in ≥grade II CDC between all groups. Also, there was no CDC grade V in our patient cohort within the first 30 days of surgery. In our present study, HoLEP was performed by a small number of high-volume experienced surgeons, which may account for lack of grade V complications associated with the surgical procedure. Furthermore, one of the many advantages of

HoLEP includes using physiologic saline as an irrigant. We found no life-threatening transurethral resection (TUR-) syndrome in our patient cohort.
Based on our data we could show that, regardless of preoperative LUTS profile and medication use, HoLEP is a feasible, effective and safe surgical treatment option in LUTS/BPO.
Our study is clearly limited by the retrospective design. We did not include and compare patients undergoing TURP or other laser treatment options for LUTS/BPO. We did not include patients receiving phosphodiesterase-5 (PDE5) inhibitors even though tadalafil was approved for treatment of LUTS secondary to BPO in Germany in 2013 [31]. Patients rarely received tadalafil 5 mg q.d. as generic drugs were only available after 2017 significantly reducing the cost of PDE5 inhibitor therapy. Naturally, including such a small group in our study would have limited the power of our analysis. Also, we did not use objective outcome measures to assess frailty scores. As medical therapy was mostly initiated by the patients' treating urologists and in accordance with EAU guidelines, we as a tertiary referral center are mostly not able to initiate and screen patients for medical therapy of LUTS/BPO, therefore preventing a more detailed gathering of preoperative data. Following up the patient for a longer period of time is difficult as we are a tertiary referral center, preventing the complete collection of data for more cases. However, a longer follow-up may be required for complete appraisal of functional outcomes and the safety profile in certain cases. However, we could show that there are no limitations to using HoLEP even in patients suffering from various degrees of LUTS/BPS, presenting with different LUTS profiles and prolonged medication use prior to surgery. HoLEP shows exceptionally low morbidity and non-existent perioperative mortality in our analysis. However, HoLEP should be considered as a surgical treatment in LUTS/BPO at an even earlier stage to prevent disease progression and offer patients optimum functional results.

CONCLUSIONS

Patients seeking relieve for LUTS/BPO may present at various stages of the disease. Many of whom may have already profited from medical therapy but are either dissatisfied by the results or unable to receive LUTS medications due to an unfavorable risk profile. Regardless of preoperative LUTS medications, HoLEP is a safe procedure, which therefore can be offered to a large variety of patients. However, 5-ARI may not have the suspected protective properties in preventing perioperative blood loss. Furthermore, postoperative functional parameters have improved throughout our patient cohorts, although the time gap between medical therapy and surgical treatment may favor an earlier response. In conclusion, HoLEP provides a favorable safety profile and efficient functional outcomes for all patients, regardless of prior LUTS medications.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

STATEMENT OF ETHICS

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required. All data were collected and analyzed anonymously.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

References

1. Gravas S, Cornu JN, Drake MJ, et al. Management of Non-neurogenic Male LUTS. EAU Guidelines. Edn. presented at the EAU Annual Congress Copenhagen 2018. ISBN 978-94-92671-01-1
2. Hennenberg M, tief CG, Gratzke C. Prostatic alpha1-adrenoceptors: new concepts of function, regulation, and intracellular signaling. Neurourol Urodyn. 2014; 33: 1074-1085.
3. Fusco F, Creta M, De Nunzio C, Gacci M, Li Marzi V, Finazzi Agrò E. Alpha-1 adrenergic antagonists, 5-alpha reductase inhibitors, phosphodiesterase type 5 inhibitors, and phytotherapic compounds in men with lower urinary tract symptoms suggestive of benign prostatic obstruction: A systematic review and meta-analysis of urodynamic studies. Neurourol Urodyn. 2018; 37: 1865-1874.
4. Irwin DE, Kopp ZS, Agatep B, Milsom I, Abrams P. Worldwide prevalence estimates of lower urinary tract symptoms, overactive bladder, urinary incontinence and bladder outlet obstruction. BJU Int. 2011; 108: 1132-1138.
5. Michel MC, Mehlburger L, Bressel HU, Goepel M. Comparison of tamsulosin efficacy in subgroups of patients with lower urinary tract symptoms. Prostate Cancer Prostatic Dis. 1998. 1: 332-335.
6. Cindolo L, Pirozzi L, Fanizza C, et al. Drug Adherence and Clinical Outcomes for Patients Under Pharmacological Therapy for Lower Urinary Tract Symptoms Related to Benign Prostatic Hyperplasia: Population-based Cohort Study. Eur Urol, 2015; 68: 418-425.
7. Michel MC, Mehlburger L, Bressel HU, Schumacher H, Schäfers RF, Goepel M. Tamsulosin treatment of 19,365 patients with lower urinary tract symptoms: does

co-morbidity alter tolerability? J Urol. 1998; 160 (3Pt1): 784-791.

8. Becher KF, Madersbacher S, Michel MC, Olbert P. Management of geriatric patients with benign prostatic hyperplasia. Urologe A. 2020; 59: 1195-1203.

9. Gazala S, Tul Y, Wagg A, Widder SL, Khadaroo RG; Acute Care and Emergency Surgery (ACES) Group. Quality of life and long-term outcomes of octo- and nonagenarians following acute care surgery: a cross sectional study. World J Emerg Surg. 2013; 8: 23.

10. Strope SA, Vetter J, Elliott S, Andriole GL, Olsen MA. Use of Medical Therapy and Success of Laser Surgery and Transurethral Resection of the Prostate for Benign Prostatic Hyperplasia. Urology. 2015; 86: 1115-1122.

11. Gilling PJ, Cass CB, Cresswell MD, Fraundorfer MR. Holmium laser resection of the prostate: preliminary results of a new method for the treatment of benign prostatic hyperplasia. Urology. 1996; 47: 48-51.

12. Suardi N, Gallina A, Salonia A, et al. Holmium laser enucleation of the prostate and holmium laser ablation of the prostate: indications and outcome. Curr Opin Urol. 2009; 19: 38-43.

13. Ahyai SA, Gilling P, Kaplan SA, et al. Meta-analysis of functional outcomes and complications following transurethral procedures for lower urinary tract symptoms resulting from benign prostatic enlargement. Eur Urol. 2010; 58: 384-397.

14. Magistro G, Westhofen T, Stief CG, Weinhold P. A matched-pair analysis of patients with medium-sized prostates (50 cc) treated for male LUTS with HoLEP or TURP. Low Urin Tract Symptoms. 2020; 12: 117-122.

15. Kuntz RM, Lehrich K, Ahyai SA. Holmium laser enucleation of the prostate versus open prostatectomy for prostates greater than 100 grams: 5-year follow-up results of a randomised clinical trial. Eur Urol. 2008; 53: 160-166.

16. Humphreys MR, Miller NL, Handa SE, Terry C, Munch LC, Lingeman JE. Holmium laser enucleation of the prostate--outcomes independent of prostate size? J Urol. 2008; 180: 2431-2435.

17. Niţă G, Georgescu D, Mulţescu R, et al. Prognostic factors in laser treatment of upper urinary tract urothelial tumours. J Med Life. 2012; 5: 33-38.

18. Mamoulakis C, Efthimiou I, Kazoulis S, Christoulakis I, Sofras F. The modified Clavien classification system: a standardized platform for reporting complications in transurethral resection of the prostate. World J Urol. 2011; 29: 205-210.

19. Becher E, Roehrborn CG, Siami P, Gagnier RP, Wilson TH, Montorsi F. The effects of dutasteride, tamsulosin, and the combination on storage and voiding in men with benign prostatic hyperplasia and prostatic enlargement: 2-year results from the Combination of Avodart and Tamsulosin study. Prostate Cancer Prostatic Dis. 2009; 12: 369-374.

20. Barry MJ, Williford WO, Chang Y, et al. Benign prostatic hyperplasia specific health status measures in clinical research: how much change in the American Urological Association symptom index and the benign prostatic hyperplasia impact index is perceptible to patients? J Urol. 1995; 154: 1770-1774.

21. Naslund MJ, Miner M. A review of the clinical efficacy and safety of 5alpha-reductase inhibitors for the enlarged prostate. Clin Ther. 2007; 29: 17-25.

22. Loeb S, Kettermann A, Carter HB, Ferrucci L, Metter EJ, Walsh PC. Prostate volume changes over time: results from the Baltimore Longitudinal Study of Aging. J Urol. 2009; 182: 1458-1462.

23. Steinmeyer Z, Delpierre C, Soriano G, et al. Hemoglobin concentration; a pathway to frailty. BMC Geriatr. 2020; 20: 202.

24. Donoghue TJ. Assessing Frailty and Its Implications on Anesthesia Care and Postoperative Outcomes in Surgical Patients. AANA J. 2019; 87: 152-159.

25. Tamalunas A, Westhofen T, Schott M, et al. The clinical value of holmium laser enucleation of the prostate in octogenarians. Low Urin Tract Symptoms. 2021; 13: 279-285.

26. Zhu YP, Dai B, Zhang HL, Shi GH, Ye DW. Impact of preoperative 5alpha-reductase inhibitors on perioperative blood loss in patients with benign prostatic hyperplasia: a meta-analysis of randomized controlled trials. BMC Urol. 2015; 15: 47.

27. Bansal A, Arora A. Transurethral Resection of Prostate and Bleeding: A Prospective, Randomized, Double-Blind Placebo-Controlled Trial to See the Efficacy of Short-Term Use of Finasteride and Dutasteride on Operative Blood Loss and Prostatic Microvessel Density. J Endourol. 2017; 31: 910-917.

28. Lee KH, Kuo HC. Recovery of Voiding Efficiency and Bladder Function in Male Patients With Non-neurogenic Detrusor Underactivity After Transurethral Bladder Outlet Surgery. Urology. 2019; 123: 235-241.

29. Lewis AL, Young GJ, Selman LE, et al. Urodynamics tests for the diagnosis and management of bladder outlet obstruction in men: the UPSTREAM non-inferiority RCT. Health Technol Assess. 2020; 24: 1-122.

30. Elshal AM, Elmansy HM, Elhilali MM. Transurethral laser surgery for benign prostate hyperplasia in octogenarians: safety and outcomes. Urology. 2013; 81: 634-639.

31. Cantrell MA, Baye J, Vouri SM. Tadalafil: a phosphodiesterase-5 inhibitor for benign prostatic hyperplasia. Pharmacotherapy. 2013; 33: 639-649. ■