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Enucleation vs. Resection: A matched-pair analysis of TURP, HoLEP and bipolar TUEP in medium-sized prostates

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Key words: benign prostatic hyperplasia; lower urinary tract symptoms; holmium laser enucleation of the prostate (HoLEP); transurethral resection of the prostate (TURP); bipolar transurethral enucleation of the prostate (bTUEP)

Running Head: HoLEP and bTUEP show a trend towards overall superiority compared to TURP in medium-sized prostates

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ABSTRACT

Objective: To evaluate efficacy and safety of holmium laser enucleation of the prostate (HoLEP), bipolar enucleation of the prostate (bTUEP) and transurethral resection of the prostate (TURP) in medium-sized prostates (50cc).

Methods: We present a retrospective analysis of 2230 patients treated for lower urinary tract symptoms. We analysed perioperative parameters, short-term clinical outcomes and adverse events in matched-pair cohorts.

Results: Both HoLEP and bTUEP were superior in terms of efficacy compared to TURP (surgery time: 51min and 50min vs. 60min; $p < 0.001$; tissue retrieval percentage: 71.4% and 70% vs. 50%; $p < 0.001$) and showed stronger improvement of LUTS (change IPSS: -15 and -14 vs. -10; $p = 0.008$). Furthermore, urodynamic parameters (Qmax: +15 ml/s and +19 ml/s vs. +12 ml/s; $p < 0.001$; PVR: -100 ml and -95 ml vs. - 80ml; $p < 0.008$) were significantly more improved after enucleation than after TURP. All techniques showed an equally low complication rate (6.9% and 6.9% vs. 10.3%; $p = 0.743$). No relevant difference of clinical outcomes was identified between HoLEP and bTUEP.

Conclusions: Both resection and enucleation are efficient and safe procedures in patients with medium-sized prostates (50cc), but irrespective of the technical approach, transurethral enucleation is superior to TURP in terms of perioperative and functional outcomes.

Introduction

In recent years the portfolio of surgical treatment modalities of lower urinary tract symptoms (LUTS) due to benign prostatic obstruction (BPO) has been constantly evolving. On the one hand, emerging novel minimally invasive approaches strive for equal efficiency to standard resection, but with a more favourable safety profile (1, 2). On the other hand, novel ablative techniques anticipate the potential to outdo the standards on various technical and functional aspects. Laser-based approaches in combination with modified enucleation techniques such as holmium laser enucleation of the prostate (HoLEP) have been introduced with success and the efficacy and safety of this size-independent procedure has led to the integration into several international guidelines (3). However, enucleation itself is also possible in bipolar technique using a button-shaped electrode or specially designed loops. First results resemble those reported for HoLEP. Bipolar transurethral enucleation of the prostate (bTUEP) was at least equally effective, but showed better hemostatic control, less complications and both shorter catheterization and hospital stay (4-8). Some data suggest that the underlying laser physics of HoLEP offer superior outcomes compared to bTUEP (9, 10). A direct comparison between TURP, HoLEP and bTUEP in medium-sized prostates (50cc), where TURP has set the benchmark for decades, is lacking. This prompted us to investigate the true benefits of the enucleation procedure as performed with two different technical approaches compared to the current standard.

Patients and Methods

Study design and surgical procedures

We conducted a retrospective, single-centre analysis of 2230 men treated for LUTS due to BPO from 2014 to 2018 at the Department of Urology of the Ludwig-Maximilians-University of Munich, Germany (HoLEP: n=1137; TURP: n=691; bTUEP:

n=402). All three cohorts were matched for prostate size (50cc ± 5), which was determined by transrectal ultrasound (TRUS). We analysed perioperative parameters, clinical outcomes and adverse events. Patients outside the matching limits, without complete datasets or missing follow-up data were excluded from final evaluation. In order to reduce a potential selection bias, the investigator who searched for matching patients was blinded to the procedure. A second investigator analysed the data and the datasets were finally allocated to the correct procedure by a third supervising investigator. For the final analysis 261 patients were eligible for inclusion (each cohort n=87). HoLEP was performed in one-lobe technique with the VersaPulse® 100W Holmium Laser (Lumenis Ltd., Yokneam, Israel) at a frequency of 53 Hz and a power setting of 1.2 J. Morcellation was carried out using the Piranha morcellator system (Richard Wolf GmbH, Knittlingen, Germany). TURP was executed with the Gyrus ACMI PlasmaKinetic SuperPulse™ Generator (Gyrus Medical Ltd., Cardiff, United Kingdom) at a setting of 280 W for cutting and 140 W for coagulation. For bTUEP we used the same equipment as for standard TURP. No specially designed loop or electrode was used. The procedure was executed in one-lobe technique. The enucleation was conducted as a combination of mainly gentle mobilization with the tip of the resectoscope and cutting whenever necessary. A first incision was placed proximal to the verumontanum in order to get access to the plain. Using the tip of the resectoscope the apical part of the adenoma was mobilized and then followed by the early apical dissection in order to protect the sphincter region from further traction during the enucleation manoeuvres. In this en bloc approach the entire adenoma is developed until reaching the bladder outlet. Here, it was left attached to the prostatic fossa and finally resected. Three senior surgeons with great expertise with endoscopic techniques performed all interventions. Three surgeons performed all TURPs and two among them executed also the enucleation procedures.

Parameters

In the present study we evaluated prostate volume (PV; cc), International Prostate Symptom Score (IPSS), quality of life (QoL), peak urinary flow rate (Qmax; ml/s), postvoid residual urine volume (PVR; ml), total surgical time (min; defined as the time between start of the procedure and placement of the catheter after intervention), resected prostatic adenoma (g and %), haemoglobin drop (g/dl) and efficiency (g/min; weight of resected adenoma relative to the total surgery time). The short-term LUTS improvements and functional outcomes were determined 4 weeks after surgery, whereas the perioperative technical parameters were measured in the operating room directly after surgery. The drop in haemoglobin levels was studied 24 hours after the intervention. The tissue retrieval percentage (%) was defined as the proportion of removed tissue relative to the prostate volume as determined by TRUS prior to surgery. Demographic parameters included age (yr), BMI, total serum prostate-specific-antigen (PSA; ng/ml; Elecsys® Assay, Roche Diagnostics GmbH, Mannheim, Germany) and PSA density (ng/mL/cc). Treatment-related adverse events (AEs) were graded according to the Clavien-Dindo classification.

Statistical analysis

The matching process of 2230 patients resulted in three cohorts with 87 patients each for final analysis. For descriptive statistics, continuous variables were presented as the median (interquartile range, IQR) and categorical variables were given as percentages or absolute numbers. Normal distribution of variables was calculated based on the Shapiro-Wilk test. Univariate analyses were performed using Fisher's exact test, *T* test and Mann-Whitney *U* test for categorical variables and continuous variables, respectively. A p-value < 0.05 was considered statistically significant. All calculations were carried out using SPSS Statistics software, version 25.0 (SPSS, Chicago, IL, USA).

Results

Patient characteristics were equivalent between cohorts (Table 1). No differences were identified for age, BMI and prostate volume (PV). All subjects presented with severe LUTS as quantified by a median IPSS score of 21 points for TURP, 21 points for HoLEP and 19 points for bTUEP (p=0.819). The median quality of life (QoL) subscore was 4 in all three cohorts (p=0.529). No difference was determined for total

PSA (2.4 ng/ml vs. 2.3 ng/ml vs. 2.5 ng/ml; *p*=0.397). The median Qmax was 9 ml/s in all groups (*p*=0.185) and the median postvoid residual urine volumes (PVR) for TURP, HoLEP and bTUEP were 100 ml, 80 ml and 100 ml, respectively (*p*=0.5). Perioperative parameters and early functional outcomes 4 weeks after surgery are depicted in table 2. In terms of efficacy the enucleation techniques were always superior to TURP. The median total surgery times for HoLEP, bTUEP and TURP were 51 min, 50 min and 60 min, respectively (*p*<0.001). With regard to tissue removal the enucleation procedures were always more efficient than TURP as determined by the net weight of removed tissue (30 gr and 29 gr vs. 20 gr; *p*<0.001), the tissue retrieval percentage (71.4% and 70% vs. 50%; *p*<0.001) and the efficacy rate (0.47 g/min and 0.46 g/min vs. 0.31 g/min; *p*<0.001). The perioperative haemoglobin drop was low in all three cohorts with a median reduction ranging from 0.5 g/dl to 0.6 g/dl (p>0.05). No difference between groups was observed for hospitalization and catheterization time (all *p*>0.05). The early clinical outcomes favoured again the enucleation techniques. The improvement of LUTS as determined by the median changes of IPSS (15 and 14 vs. 10; *p*<0.05) and the Qol subscore (4 and 3 vs. 2; *p*=0.001) were good in all cohorts, but the outcomes were significantly more pronounced after HoLEP and bTUEP than after TURP. Correspondingly, urodynamic results revealed both a significantly stronger increase of Qmax (19 ml/s and 15 ml/s vs. 10 ml/s; *p*=0.001) and a stronger reduction of PVR (100 ml and 95 ml vs. 80 ml; *p*<0.05) after enucleations. The oncological evaluation revealed no striking difference between groups. The detection rate of incidental prostate cancer (iPCa) was 16.1% for TURP and HoLEP and 14.9% for bTUEP (p>0.05). In the majority of iPCa cases low-grade disease was diagnosed. Of note, no differences of perioperative parameters and clinical outcomes between HoLEP and bTUEP were identified in the final analysis (Table 2, always p>0.05). The safety assessment according to the Clavien-Dindo grading confirmed a good safety profile of all techniques with overall low complication rates of HoLEP, bTUEP and TURP (6.9% and 6.9% vs. 10.3%; *p*=0.743). Complications grade >2 were also equally low with a rate of 3.4% in all cohorts.

Discussion

The field of surgical treatment options for LUTS due to BPO is a vivid, constantly evolving area of interest striving for the best solutions to offer our patients. The debates about energy sources and techniques are still ongoing among urologists worldwide. Nevertheless, the convincing body of evidence of procedures such as HoLEP proved that the reference methods like open prostatectomy for large prostates and TURP for small and medium sized prostates can still be optimized. The success of HoLEP actually paved the way for upcoming approaches that followed the principle of *anatomical enucleation* (11). Apart from technical variations of the enucleation procedure itself, a plethora of energy sources including Thulium:YAG (12), diode laser (13) or Lithium-Borate "*greenlight*" (14) were introduced and confirmed the clinical benefits. Common findings favouring transurethral enucleation techniques over monopolar/bipolar TURP are a more efficient removal of the adenoma, shorter catheterization and hospitalization, less complications and a lower re-intervention rate (3, 8, 15, 16).

This implies that the principle of *anatomic enucleation* is the main cornerstone for the superior outcomes compared to TURP. However, the question about the contribution of the energy source still remains elusive. A recent randomized trial of bipolar TURP vs. HoLEP vs. Greenlight laser Vapo-Enucleation (GL.PVEP) confirmed superiority of the enucleation procedures over TURP (17). Between the enucleation techniques, GL.PVEP showed longer operation time compared to HoLEP (mean 92 min vs. 73 min) and a higher re-treatment rate at 3 years (4.7% vs. 0%). Results on the comparison between HoLEP and thulium laser enucleation of the prostate (ThuLEP) suggest that both procedures are equally effective and safe for the treatment of bothersome LUTS, with only slight differences in perioperative parameters such as operation time (18, 19). In the meta-analysis by Wroclawski et al on the safety and efficacy of endoscopic enucleation and non-enucleation procedures, authors also compared laser-based and non-laser based enucleation techniques including plasmakinetic and bipolar enucleation of the prostate (16). In this regard, the laser-based approaches were found to provide a higher tissue retrieval and better hemostatic control.

Current guideline recommendations acknowledge these developments, but the heterogeneous body of evidence, the "real world" quality of supply, urologists' varying proficiencies and the patients' demands make it difficult to highlight a *one fits all* procedure. Despite the well-documented clinical benefits of enucleation techniques like HoLEP, in the real-life scenario they only constitute 4%-5% of all performed surgeries for the treatment of LUTS due to BPO (20). Main reasons for this development comprise the economic burden for the technical equipment, the steep learning curve and reimbursement issues.

The current study was not only designed to reveal the true benefits of enucleation techniques but also to demonstrate, that even with our standard TURP equipment, we are able to achieve those goals following the principles of *anatomic enucleation*. Our results in concert with published data clearly confirmed the quality features of the reference method TURP, but here we showed that these outcomes could still be optimized using refined surgical techniques (21, 22). This trend is mirrored by current guideline recommendations, which integrated enucleation techniques as surgical options for prostate sizes ranging from 30cc to 80cc (23). Most importantly, the surgeons' proficiency must be assured to accomplish the clinical benefits reported for techniques like HoLEP. Once the surgeon is comfortable with an enucleation technique, it seems that the energy source is of secondary matter. A growing body of clinical evidence suggests that the enucleation in expert hands is the key factor. To our knowledge, our results are the first to show in a matched-pair analysis of common LUTS patients, that enucleation as a general principle offers better results than resection in medium-sized prostates. We have to emphasize that in the current study no special equipment was used for surgery. Enucleation was executed mainly with the tip of the resectoscope without any technical modification. Energy was only applied when necessary. Nevertheless, the outcomes are equivalent to the laser-based approach.

The retrospective single-centre design with the short-term follow-up needs to be acknowledged as shortcoming of our study. However, the presented data clearly pinpoints towards the enucleation principle as the crucial factor for superior outcomes. In the end, the success is not exclusively depending on the energy source, but foremost on the surgical precision of a correct enucleation procedure. The presented outcomes demonstrated the benefits for medium-sized prostates, but for the complete appraisal additional studies are warranted to confirm the trend for larger prostates >80cc. Long-term prospective randomized controlled trials are necessary to answer the question about the most complete technique.

Conclusion

The convincing body of clinical evidence proves that the technique of endoscopic enucleation has come of age. Both resection and enucleation are efficient and safe procedures in patients with LUTS due to BPO with medium-sized prostates, but irrespective of the technical approach, transurethral enucleation is superior to TURP in terms of perioperative and functional outcomes. No relevant differences of perioperative parameters, clinical outcomes and the safety profile were identified between HoLEP and bTUEP. Performing a successful enucleation with the standard equipment as used for TURP showcases the importance of the technical principle.

Compliance with ethical standards

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

For this type of study formal consent is not required.

This article does not contain any studies with human participants or animals performed by any of the authors.

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Table 1: Demographic parameters

Characteristics				
	TURP (n=87)	**HoLEP (n=87)**	**bTUEP (n=87)**	***p*-value**
Age (yr)				
Median	71	70	71	0.886
IQR	62 – 77	61 - 76	61 - 77	
BMI				
Median	26.6	24.5	25	0.69
IQR	23.5 – 29.2	22.3 - 29	24 – 27	
IPSS				
Median	21	21	21	0.819
IQR	15.5 – 26.5	16 – 26	17 – 25	
QoL				
Median	4	4	4	0.529
IQR	3.5 – 5	4 – 5	4 – 5	
PV (cc)				
Median	50	50	50	0.883
IQR	45 – 54	46 – 55	45 – 52	
Total PSA (ng/ml)				
Median	2.4	2.3	2.5	0.397
IQR	0.7 – 4.1	1.4 – 4.2	1.3 – 4.2	
Qmax (ml/s)				
Median	9	9	9	0.185
IQR	8 – 12.5	5 – 13	8 – 10	
PVR (ml)				
Median	100	80	100	0.5
IQR	45 – 195	39.5 – 190	50 – 150	
Indwelling catheter n (%)	19 (21.8%)	14 (16.1%)	17 (19.5%)	0.625

TURP = bipolar transurethral resection of the prostate; HoLEP = holmium laser enucleation of the prostate; bTUEP = bipolar transurethral enucleation of the prostate; IQR = interquartile range; BMI = body mass index; IPSS = International Prostate Symptom Index; QoL = quality of life; PV = prostate volume; PSA =

prostate-specific-antigen; Qmax = peak urinary flow rate; PVR = postvoid residual urine;

Bold values indicate statistical significant *p* values (*p*<0.05)

Table 2: Perioperative and clinical outcomes

Outcomes	TURP[a] (n=87)	HoLEP[b] (n=87)	bTUEP[c] (n=87)	*p*-value a - b	*p*-value a - c	*p*-value b - c
Time (min)						
Median	**60**	**51**	**50**	**< 0.001**	**< 0.001**	0.211
IQR	**53 - 69**	**45 - 59**	**42 - 58**			
Tissue removal (g)						
Median	**20**	**30**	**29**	**< 0.001**	**0.001**	0.07
IQR	**15 - 25**	**27 - 35**	**24 - 33**			
Tissue removal (%)						
Median	**50**	**71.4**	**70**	**< 0.001**	**< 0.001**	0.331
IQR	**44– 61**	**69 – 75**	**60 - 73**			
Efficiency (g/min)						
Median	**0.31**	**0.47**	**0.46**	**< 0.001**	**< 0.001**	0322
IQR	**0.2 – 0.3**	**0.4 – 0.6**	**0.4 – 0.6**			
ΔHb (g/dl)						
Median	**0.5**	**0.5**	**0.6**	0.345	0.942	0.382
IQR	**0.1 – 1.1**	**0.1 - 1**	**0.2 – 0.9**			
ΔIPSS						
Median	**10**	**15**	**14**	**0.008**	**< 0.001**	0163
IQR	**4 - 17**	**10 – 21**	**11 - 19**			
ΔQoL						
Median	**2**	**4**	**3**	**0.001**	**0.001**	0.794
IQR	**1 - 4**	**3 - 4**	**2 - 4**			
ΔQmax (ml/s)						
Median	**12**	**19**	**15**	**< 0.001**	**0.002**	0.317
IQR	**3 - 23**	**12 - 26**	**14 - 18**			
ΔPVR (ml)						
Median	**80**	**100**	**95**	**0.008**	**0.018**	0.643
IQR	**46 - 101**	**50 - 185**	**50 - 150**			
Catheterization (d)						
Median	**2**	**2**	**2**	0.667	0.456	0.716
IQR	**2 - 2**	**2 - 2**	**2 - 2**			
Hospitalisation (d)						
Median	**3**	**3**	**3**	0.975	0.821	0.483
IQR	**3 - 3**	**3 - 3**	**3 - 3**			
Histopathology (%)						
BPH	**83.9**	**83.9**	**85.1**	1.0	1.0	1.0
iPCa	**16.1**	**16.1**	**14.9**			
Gleason score (%)						
≤6	**92.9**	**92.9**	**84.6**	1.0	0.666	0.666
7	**7.1**	**7.1**	**15.4**			

TURP; a = bipolar transurethral resection of the prostate; HoLEP; b = holmium laser enucleation of the prostate; bTUEP; c = bipolar transurethral enucleation of the prostate; IQR = interquartile range; Hb = haemoglobin drop; IPSS = International Prostate Symptom Index; QoL = quality of life; Qmax = peak urinary flow rate; PVR = postvoid residual urine; BPH = benign prostatic hyperplasia, iPCa = incidental prostate cancer

Bold values indicate statistical significant *p* values ($p<0.05$)

Table 3: Treatment related adverse events (AEs) according to the Clavien-Dindo classification

Adverse events (AEs)				
	bTURP	**HoLEP**	**bTUEP**	***p*-value**
Overall AEs; *N* (%)	**9** (10.3%)	**6** (6.9%)	**6** (6.9%)	0.743
Clavien Dindo I	**3** (3.4%)	**2** (2.3%)	**2** (2.3%)	0.616
Urinary retention	3	2	2	
Clavien Dindo II	**3** (3.4%)	**1** (1.1%)	**1** (1.1%)	0.624
Clot retention	2	1	1	
Fever	1			
Clavien Dindo III	**3** (3.4%)	**3** (3.4%)	**3** (3.4%)	1.0
Urinary retention	1	2	1	
Clot retention	1	1	2	
Bleeding	1			

Bold values indicate statistical significant *p* values ($p<0.05$)