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Comparison of 3 Different Enucleation Techniques of Holmium Laser Enucleation of Prostate (HoLEP)

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ABSTRACT

Purpose:

To evaluate the effect of different enucleation techniques on operation time, enucleation efficacy and postoperative results.

Materials and Methods:

178 HoLEP cases performed by two senior surgeons were evaluated retrospectively. All patients were evaluated for age, IPSS, preoperative PSA, prostate size, maximum flow rate (Qmax) postvoid residual volume (PVR), enucleation time, morcellation time, enucleated tissue weight, enucleation ratio (enucleated tissue weight/prostate volume) and enucleation time efficacy (enucleated weight/enucleation time). Patients were categorized into three groups according to performed enucleation techniques; Retrograde Low Tension (RLT) two-lobe, traditional three-lobe, and en bloc techniques. IPSS, Qmax, PVR and transient urine leakage (TUL) were evaluated during postoperative follow up. All preoperative, intraoperative and postoperative results were compared between 3 groups.

Results:

Mean age was 70.52 (52-85) years. Baseline data were comparable between groups. Enucleation time was significantly shorter in RLT two-lobe (median; 50, 60 and 60 min; RLT two-lobe, traditional three-lobe, and en bloc HoLEP techniques, respectively. (P = .031). Morcellation time was comparable between groups (P = .532). No significant difference was observed between morcellated prostate weights (P = .916) Significant improvements in IPSS, Qmax, and PVR were noted in all groups (P < .001). TUL was significantly increased in en bloc technique (P = .034). Postoperative stricture rates were similar between groups. (P = .769)

Conclusions:

Shorter enucleation time was observed in the RLT HoLEP technique and increased TUL rate was observed in the en bloc technique.

Introduction:

Benign prostate hyperplasia (BPH) is a common cause of lower urinary tract symptoms (LUTS) in aging men. [1] Introduction of lasers for the surgical management of benign prostatic obstruction (BPO) has been a revolutionary step and rapidly adopted by many centers worldwide. Currently, several laser devices with different energy sources are available, but holmium is by far the most commonly used laser.

Holmium laser enucleation of prostate (HoLEP) was first introduced into clinical practice by Gilling et al. in 1998. [2] Many studies have reported the safety and efficacy of HoLEP. Lower morbidity, shorter catheterization time, length of hospital stay and fewer blood transfusions were reported in favor of HoLEP compared to conventional methods such as transurethral resection of prostate (TURP) and open prostatectomy (OP). [3] Several enucleation techniques have been described in the literature. The traditional three-lobe technique was first described by Gilling and Freundorfer. [2] Krambeck et al. and Baazeem et al. proposed the two-lobe technique which involves a single bladder neck incision with one of the lateral lobes excised together with the middle lobe and subsequently the second lateral lobe. [4,5] In our retrograde low tension (RLT) two-lobe HoLEP technique, some alterations were made in the surgical approach to minimize stretching of the external urethral sphincter, to shorten the enucleation time and to fascilitate learning. More recently, Scoffone et al. described the en-bloc technique that provides enucleation the prostate in one piece, without separating the lobes using only a single incision to find the cleavage between prostate capsule and the adenoma. [6]

Studies have reported the safety and efficacy of these techniques however data comparing these three approaches are lacking. [4,6-9] Herein we present our results in patients who underwent HoLEP with our RLT two-lobe, traditional three-lobe HoLEP and en bloc HoLEP techniques and data were compared between three enucleation techniques.

Materials and Methods:

Medical records of 178 patients who underwent HoLEP between October 2015 and June 2017 were evaluated retrospectively. All male patients who underwent HoLEP surgery regardless of patient age, prostate size and PSA level were evaluated in this study. Patients with urethral stricture, neurogenic bladder, prostatic adenocarcinoma, prostatic or pelvic surgeries, and previous pelvic radiotherapy were excluded.

All patients were evaluated for baseline characteristics such as age, preoperative PSA, prostate size, International Prostate Symptom Score (IPSS), maximum flow rate (Qmax) and postvoid residual volume (PVR). All operations were performed by two senior surgeons (Tokatlı Z. and Saglam R.), who had an experience with more than 400 cases of HoLEP including traditional three-lobe and en bloc techniques, previously. 100-watt holmium:yttrium -aluminum-garnet (Ho-YAG) laser device with 550-micron end-firing laser fibers (VersaPulse, Power Suite, Lumenis Medical Systems, Santa Clara, CA) and VersaCut Tissue Morcellator *(Lumenis Medical Systems, Santa Clara, CA)* were utilized in all operations. The morcellator was equipped with single use-disposable blades in all cases. Intraoperative data such as enucleation time, morcellation time, enucleated tissue weight, catheterization time and length of hospital stay were recorded in all patients.

Patients were categorized into three groups according to performed HoLEP technique; RLT two-lobe, traditional three-lobe, or en-bloc techniques. In the traditional three-lobe technique; median lobe was resected first, followed by lateral lobes. Three-lobe enucleation technique was preferred especially in cases with a large median lobe. In our RLT two-lobe technique; an incision is made at 5 or 7 o'clock position and early apical enucleation of one lobe is performed initially. To prevent stretching of the external urethral sphincter (EUS); parasphincteric mucosal strip between prostate adenoma and EUS was cut early after apical dissection. *All of the* dissections *and enucleation were* performed retrogradely. In en-bloc enucleation technique; both lateral lobes and median lobe were enucleated together *without separating the right and left lobes. During the enucleation of the complete prostate adenoma, to reach the bladder neck by pressing the highest place of the prostate adenoma, it is unavoidable to stretch the EUS. One day after removal of the urinary catheter,* patients were asked verbally about any involuntary loss of urine and number of pad use per day and followed at postoperative 1., 3. and 6. months. Transient urine leakage (TUL) was defined as urine leakage persistent more than 24 hours after catheter removal but less than 3 months. Patients who use ≥ 1 pad per day were considered positive for TUL. Spontaneously resolved urine leakage persistent more 3 months was considered as "prolonged incontinence". Patients were evaluated for IPSS, Qmax, and PVR at postoperative 6. months. Further investigations with cystourethroscopies were performed as deemed necessary. Urethral stricture rates and complications were noted. Pelvic-floor muscle exercise was recommended to all patients with postoperative TUL. In addition, duloxetine was recommended to patients with postoperative stress type UI, and anticholinergic drugs were recommended to patients with urge type UI.

Statistical analysis was performed using SPSS software version 21. Variables were investigated using visual (histograms, probability plots) and analytic methods (Kolmogorov-Smirnov/Shapiro-Wilk's test) to determine whether or not they were normally distributed. Kruskal Wallis test was utilized to compare baseline characteristics and intraoperative data among three different enucleation groups. The Mann-Whitney U test was performed to test the significance of pairwise differences using Bonferroni correction to adjust for multiple comparisons. Friedman tests were conducted to test whether there is a significant change between preoperative and postoperative results. Spearman correlation test was used to evaluate correlations between prostate size and enucleation-morcellation times. Chi-square test or Fisher exact test was used to compare proportions between different groups. P-value of less than 0.05 was considered to show a statistically significant result.

Results:

Overall 178 patients who underwent HoLEP between October 2015 to June 2017 were evaluated in the study. Mean age was 70.24±7.50 years. Baseline data were comparable between groups (Table 1). Patients with a wide range of prostate volume (30-224) were included in the study and median prostate volumes were comparable between 3 groups. (P = .425) The urethral catheter was routinely removed on postoperative 2. day and the patient was discharged home. Significant positive correlation was observed between prostate size and enucleation time (correlation coefficient; 0.449, P ≤ .001) and morcellation time (correlation coefficient; 0.513, P ≤ .001). Enucluation time was significantly shorter in RLT two-lobe technique (median 50, 60 and 60 min; RLT two-lobe, En bloc, and three-lobe techniques, respectively, p = .031). Statistically significant difference was found only between RLT two-lobe and three-lobe techniques in pairwise comparisons. (P = .012) Morcellation time was similar between groups (P = 0.532). Enucleated tissue weights were similar between groups. (P = .916) Enucleation ratio (median; 0.40, 0.46 and 0.49; RLT two-lobe, three-lobe, en bloc groups respectively, P = .165) and enucleation time efficacy (median; 0.82, 0.57 and 0.77; RLT two-lobe, three-lobe, en bloc groups respectively, P = .516) were also found similar between groups.

Significant improvements in IPSS, Qmax, and PVR were noted in all groups at postoperative 6. months (P < .001). HoLEP increased Qmax by 283% and reduced PVR by 88% when all patients were evaluated together. Qmax increase and PVR decrease rates were comparable between 3 enucleation groups. Mean follow up duration was 17.9 months. Postoperative results were summarized in Table 2. TUL was observed in 14 (7.9%) patients. TUL rate was

significantly higher in the en-bloc technique (P = .034). Total operation time (median; 72.5 vs 65 mins, P = .033) was significantly longer in patients with TUL. Postoperative bleeding requiring intervention was observed in 2 patients, one in three-lobe technique and one in en bloc technique. There was only one patient with "prolonged" incontinence in en bloc group which became continent 7 months after the surgery. Permanent urinary incontinence was not observed. Postoperative stricture rates were similar between the groups. (P = .769) (Table 2)

Discussion:

HoLEP is a safe and effective treatment for prostates of all sizes, men in retention and those who are anticoagulated or have bleeding disorders. [10] Meta-analyses comparing HoLEP with TURP found comparable and even superior symptom improvement with HoLEP [3,11,12] Shorter catheterization time and hospital stay, reduced blood loss and fewer blood transfusions despite a longer operation time compared with TURP were reported by 3 meta-analyses. [11-13] In a meta-analysis comparing HoLEP with open prostatectomy (OP), HoLEP was found associated with shorter catheterization duration, shorter hospital stay and lower risk of perioperative blood transfusion. [3] Long term complications of HoLEP include retreatment, urinary incontinence, and urethral strictures. [14] A recent retrospective cohort revealed that urinary calculi formation in the prostatic fossa or bladder neck after HoLEP is a rare but possible complication. [15] Reintervention, stress incontinence and urethral stricture rates were similar between TURP and HoLEP.[11] Despite previously reported favorable outcomes and its proven advantages compared to conventional BPH surgeries, HoLEP still comprises only 4-5% of all major BPH surgeries. [16] Three major drawbacks prevent wider adoption of HoLEP; steep learning curve, longer operation time and high transient urinary incontinence rates.

The steep learning curve has always been considered as a major limitation of HoLEP which prevents wide diffusion of the technique. In a prospective study, the learning curve of an experienced endourologist was evaluated from data of the first 160 cases and it was shown that morcellation and enucleation efficacy reached a plateau after the first 50 cases. [17] A retrospective trial also reported that morcellation and enucleation efficacy improved significantly after the first 50 cases. [18] Seki et al. reported that enucleation efficacy increased during the first 70 cases. Gregoire et al. evaluated the learning curve of HoLEP step by step in a multicentric observational trial. Of 9 surgeons participated in the trial, only one achieved the main judgment criterion of four consecutive successful HoLEP procedures in 20 consecutive cases. It was concluded that HoLEP has a steep learning curve exceeding 20 cases. [19] In our

study, the learning curve was not evaluated since both surgeons had high experience with a total of 400 cases of HoLEP.

Postoperative TUL is a bothersome complication, occurring in 1.3%-16.6% of patients. [20-22] Even though most cases recover spontaneously, it was shown to decrease patients' quality of life significantly. [23] There are few studies investigating the factors to predict TUL occurrence. Elmansy et al. reported that presence of diabetes mellitus, prostate volume greater than 81 gm, operative time longer than 96 minutes and reduction in prostate-specific antigen higher than 84% were significantly associated with stress urinary incontinence after HoLEP. [24] In another retrospective study with 391 patients who were treated with HoLEP, TUL was observed in 16.6% of the patients. Increased age and operation time was found the factors significantly associated with the occurrence of postoperative TUL. [20] Kobayashi et al. also found that enucleation time longer than 100 min and blood loss >2.5 g/dL were significant and independent risk factors for postoperative UI. [25] Data related to the effects of different enucleation techniques on postoperative results and operation time is scarce. In our study, TUL rate was significantly higher in the en-bloc technique. Operation time was also significantly longer in patients with TUL, consistent with previous studies. We suggest that one of the most important reasons for TUL is the stretching of the external urethral sphincter, and it is recommended to avoid external urethral sphincter-stretching to decrease TUL rates.

In the traditional three-lobe technique described by Fraundorfer and Gilling, the median lobe is resected first, followed by lateral lobes. [26] In RLT two-lobe technique -a modification of two-lobe enucleation- one lateral lobe was enucleated initially and the remaining lateral lobe and median lobe was enucleated together afterward. In this technique; early cutting of parasphincteric mucosal strip and retrograde 12 o'clock incision results in less stretching of the external urethral sphincter which is probably the reason for the decreased TUL rate in this technique. In 2016, Scaffone et al. reported en-bloc no-touch HoLEP technique, in which both lateral lobes and median lobe are enucleated altogether and they suggested that en bloc technique may improve the learning curve of HoLEP. [6] However, in our study increased TUL rates were observed in the en bloc group. In the en bloc technique; during the enucleation of the whole prostate gland altogether**,** stretching of the EUS is unavoidable while reaching the bladder neck by pressing the highest place of the prostate adenoma it is more important for larger size prostates. In our en bloc group, median prostate sizes were also larger than the other studies, this may explain higher TUL rates. Additionally, enucleation time was significantly shorter in the RLT two-lobe technique. In en bloc technique; it takes more time to push the whole prostate gland into the bladder, and in three-lobe technique, enucleation of both lateral

lobes and the median lobe separately increases the operation time. Late complication rates were similar for all enucleation techniques.

Our study has some limitations. The main limitation of our study is its retrospective design and lack of information about validated symptom scores to evaluate urinary incontinence. On the other hand; to our knowledge, this is the first clinical trial comparing the results of different enucleation techniques. Effect of different enucleation techniques on the learning curve, operation time and postoperative results are issues of great importance and should be investigated with further prospective randomized trials.

Conclusion:

RLT two-lobe, three-lobe, and en bloc techniques are all safe and efficient methods to perform HoLEP with similar postoperative results and late complication rates. Shorter enucleation time was observed in the RLT two-lobe technique and increased TUL rate was observed in en bloc technique.

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Nothing to declare.

CONFLICT OF INTEREST

The authors report no conflict of interest.

REFERENCES:

1. Calogero AE, Burgio G, Condorelli RA, Cannarella R, La Vignera S. Epidemiology and risk factors of lower urinary tract symptoms/benign prostatic hyperplasia and erectile dysfunction. Aging Male. 2019;22:12-9.
2. Gilling PJ, Fraundorfer MR. Holmium laser prostatectomy: a technique in evolution. Curr Opin Urol. 1998;8:11-5.
3. Cornu JN, Ahyai S, Bachmann A, et al. A Systematic Review and Meta-analysis of Functional Outcomes and Complications Following Transurethral Procedures for Lower Urinary Tract Symptoms Resulting from Benign Prostatic Obstruction: An Update. Eur Urol. 2015;67:1066-96.
4. Krambeck AE, Handa SE, Lingeman JE. Experience with more than 1,000 holmium laser prostate enucleations for benign prostatic hyperplasia. J Urol. 2010;183:1105-9.
5. Baazeem AS, Elmansy HM, Elhilali MM. Holmium laser enucleation of the prostate: modified technical aspects. BJU Int. 2010;105:584-5.
6. Scoffone CM, Cracco CM. The en-bloc no-touch holmium laser enucleation of the prostate (HoLEP) technique. World J Urol. 2016;34:1175-81.

7. Glybochko PV, Rapoport LM, Enikeev ME, Enikeev DV. Holmium laser enucleation of the prostate (HoLEP) for small, large and giant prostatic hyperplasia: tips and tricks. Urologia. 2017;84:169-73.
8. Hurle R, Vavassori I, Piccinelli A, Manzetti A, Valenti S, Vismara A. Holmium laser enucleation of the prostate combined with mechanical morcellation in 155 patients with benign prostatic hyperplasia. Urology. 2002;60:449-53.
9. Gu M, Chen YB, Liu C, et al. Comparison of Holmium Laser Enucleation and Plasmakinetic Resection of Prostate: A Randomized Trial with 72-Month Follow-Up. J Endourol. 2018;32:139-43.
10. Aho TF. Holmium laser enucleation of the prostate: a paradigm shift in benign prostatic hyperplasia surgery. Ther Adv Urol. 2013;5:245-53.
11. Tan A, Liao C, Mo Z, Cao Y. Meta-analysis of holmium laser enucleation versus transurethral resection of the prostate for symptomatic prostatic obstruction. Br J Surg. 2007;94:1201-8.
12. Yin L, Teng J, Huang CJ, Zhang X, Xu D. Holmium laser enucleation of the prostate versus transurethral resection of the prostate: a systematic review and meta-analysis of randomized controlled trials. J Endourol. 2013;27:604-11.
13. Lourenco T, Pickard R, Vale L, et al. Alternative approaches to endoscopic ablation for benign enlargement of the prostate: systematic review of randomised controlled trials. BMJ. 2008;337:a449.
14. Davydov DS, Tsarichenko DG, Bezrukov EA, et al. [Complications of the holmium laser enucleation of prostate for benign prostatic hyperplasia]. Urologiia. 201842-7.
15. Lee YJ, Oh SJ. Calculi in the Prostatic Surgical Bed as a complication after Holmium Laser Enucleation of the Prostate. Urol J. 2018;15:238-41.
16. Anderson BB, Heiman J, Large T, Lingeman J, Krambeck A. Trends and Perioperative Outcomes Across Major Benign Prostatic Hyperplasia Procedures from the ACS-NSQIP 2011-2015. J Endourol. 2019;33:62-8.
17. Shah HN, Mahajan AP, Sodha HS, Hegde S, Mohile PD, Bansal MB. Prospective evaluation of the learning curve for holmium laser enucleation of the prostate. J Urol. 2007;177:1468-74.
18. Placer J, Gelabert-Mas A, Vallmanya F, et al. Holmium laser enucleation of prostate: outcome and complications of self-taught learning curve. Urology. 2009;73:1042-8.
19. Robert G, Cornu JN, Fourmarier M, et al. Multicentre prospective evaluation of the learning curve of holmium laser enucleation of the prostate (HoLEP). BJU Int. 2016;117:495-9.
20. Nam JK, Kim HW, Lee DH, Han JY, Lee JZ, Park SW. Risk Factors for Transient Urinary Incontinence after Holmium Laser Enucleation of the Prostate. World J Mens Health. 2015;33:88-94.
21. Shah HN, Mahajan AP, Hegde SS, Bansal MB. Peri-operative complications of holmium laser enucleation of the prostate: experience in the first 280 patients, and a review of literature. BJU Int. 2007;100:94-101.
22. Hwang JC, Park SM, Lee JB. Holmium laser enucleation of the prostate for benign prostatic hyperplasia: effectiveness, safety, and overcoming of the learning curve. Korean J Urol. 2010;51:619-24.
23. Vavassori I, Valenti S, Naspro R, et al. Three-year outcome following holmium laser enucleation of the prostate combined with mechanical morcellation in 330 consecutive patients. Eur Urol. 2008;53:599-604.

24. Elmansy HM, Kotb A, Elhilali MM. Is there a way to predict stress urinary incontinence after holmium laser enucleation of the prostate? J Urol. 2011;186:1977-81.
25. Kobayashi S, Yano M, Nakayama T, Kitahara S. Predictive risk factors of postoperative urinary incontinence following holmium laser enucleation of the prostate during the initial learning period. Int Braz J Urol. 2016;42:740-6.
26. Fraundorfer MR, Gilling PJ. Holmium:YAG laser enucleation of the prostate combined with mechanical morcellation: preliminary results. Eur Urol. 1998;33:69-72.

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Tables

Table 1: Baseline data of three groups

Parameter	RLT two-lobe (n = 60)	Three-lobe (n = 59)	En bloc (n = 59)	p value*
Age (years) (Mean ± SD)	70.14 ± 6.21	70.14 ± 6.06	71.38 ± 6.23	0.904
Pre-op. PSA (ng/dL) [Median (IQR)]	1.69 (0.74-4.12)	2.12 (1.05-3.09)	1.71(0.93-3.03)	0.704
Prostate volume (mL) [Median (IQR)]	106 (74-130.5)	90 (69-121)	86 (65-130)	0.425
Pre-op Qmax (mL/sec) [Median (IQR)]	7 (3-12)	7 (4-11)	6 (4-9)	0.624
Preop PVR (mL) [Median (IQR)]	119.5 (69-367.5)	134 (80-185)	141 (94-259)	0.709
IPSS [Median (IQR)]	16.5 (13-19)	18 (14-23)	19 (14-22)	0.167

mL: mililiters, sec: second.

*Kruskal-Wallis test

Table 2: Intraoperative and postoperative data of 3 different enucleation groups

	RLT two-lobe (n = 60)	Three-lobe (n = 59)	En bloc (n = 59)	p value
Enucleation time (min) [Median (IQR)]	50 (42.5-60)	60 (30-70)	60 (40-60)	†0.031 *
Morcellation time (min) [Median (IQR)]	10 (5-12)	10 (5-15)	10 (5-10)	†0.532
Enucleated prostate weight (g) [Median (IQR)]	40 (26-59)	45 (23-68)	42 (25-51)	†0.916
Enucleation rate [Median (IQR)]	0.40 (0.31-0.49)	0.46 (0.28-0.55)	0.49 (0.32-.60)	†0.165
Enucleation time efficacy [Median (IQR)]	0.82 (0.51–1.03)	0.58 (0.42-1.10)	0.77 (0.43-1.00)	†0.516
IPSS (6. Mo) [Median (IQR)]	8 (5.5-13)	12 (6-15)	11 (5-13)	†0.202
Qmax 6. Mo (mL/sec) [Median (IQR)]	26.2 (17.8-31.8)	26.4 (19.3-30.1)	25.6 (19.8-31.7)	0.904
PVR (6. Mo) mL [Median (IQR)]	19 (10-23.5)	22 (15-27)	17 (11-26)	0.184
Transient urine leakage	2/60	3/59	9/59	¶0.034
"Prolonged" incontinence	0/60	0/60	1/59	na
Urethral stricture	1/59	2/59	1/59	¶0.769

*Pairwise comparisons: RLT two-lobe vs three lobe P = .012, RLT two-lobe vs En bloc P = .050, Two-lobe vs three lobe P = .679 (P < .017; statistically significant due to Bonferroni correction)

na: not applicable, min: minute, mo:months, g: gram, IQR: Interquartile range† Kruskal-Wallis test, ¶ Fisher exact test.