A Systematic Review and Meta-analysis of Efficacy and Safety Following Holmium Laser Enucleation of Prostate and Transurethral Resection of Prostate for Benign Prostatic Hyperplasia

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Transurethral resection of prostate (TURP) still remains the "gold standard" surgical treatment for benign prostatic hyperplasia (BPH). In recent years, holmium laser enucleation of prostate (HoLEP) gets more and more popularity in the world. Our objective is to compare the efficacy and safety of HoLEP and TURP for BPH. Eleven studies met our eligibility criteria including 1339 patients. The prostate sizes of the all included studies were smaller than 100 g. Overall, in patients with small to mid-sized prostates, HoLEP offers safer clinical outcomes with less blood drop and potentially better long-term relief of bladder outlet obstruction. UROLOGY 131: 14−20, 2019. © 2019 Elsevier Inc.

Benign prostate hyperplasia (BPH) is the most common cause of lower urinary tract symptoms in older men.[1] Surgery is recommended for patients who have severe urinary retention, recurrent bladder calculus, no satisfactory response to medication therapy and other complications related to BPH.[2] Until now, transurethral resection of the prostate (TURP) remains the gold standard for treatment of BPH due to its safe, effective, and durable outcomes. Nevertheless, the perioperative morbidity from TURP remains considerable,[3] including postoperative bleeding, TUR syndrome, urethral stricture, and so on. Nowadays, holmium laser enucleation of the prostate (HoLEP), first described as one of the alternative treatment options for BPH in 1998,[4] is supposed to replace TURP. Although a number of meta-analyses were previously performed,[5-8] their results may be more or less influenced by the lack of long-term follow-up clinical data. Our purpose was to perform an updated meta-analysis of the comparison of efficacy and safety between the 2 techniques, gathering all the relevant randomized controlled trials (RCTs) available in the literature.

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MATERIALS AND METHODS

Literature Search

A systematic review of literature was conducted, based on a literature search through the PubMed/Medline, Embase, Cochrane Library and Web of Science databases, to identify all published articles from January 1, 1996 to August 1, 2018. The search was performed with the following MeSH headings: "holmium laser enucleation of the prostate (or HoLEP)," "transurethral resection of the prostate (or TURP)," and "prostate." Reference lists of all systematic reviews in the field were also scanned for additional reports.

Study Selection

The criteria used to accept eligible studies were as follows: (1) RCTs comparing the efficacy and safety of HoLEP and TURP for the treatment of BPH; (2) language restricted to English. The excluded criteria were defined as follows: (1) non-RCTs; (2) studies not comparing HoLEP and TURP; (3) duplicated studies and conference abstracts.

Data Extraction and Quality Assessment

The full texts of all included articles were scrutinized by 2 reviewers independently to extract information. Any disagreement was resolved by consensus. The following variables were collected: the first author; year of publication; the country of participants; number of patients; study interval; follow-up duration; baseline characteristics, including age, prostate volume, international prostate symptom score (IPSS), quality of life score (QoL), maximum urinary flow rate (Q_{max}), and postvoid residual urine volume (PVR); American Urological Association Symptom Score (AUA); perioperative and postoperative variables, including bipolar or monopolar resection

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technology used in TURP, operation time, resected prostatic weight, hemoglobin decrease, hospital stay, catheterization time, and bladder irrigation; follow-up data, including Q_{max}, IPSS, QoL, PVR, and AUA; complications including blood transfusion, recatheterization, urethral stricture, transient dysuria, capsular perforation, and transient and persistent urinary incontinence. We estimated the quality of included studies with the Jadad scale.[9] All quality evaluations of the included articles were independently performed by 2 reviewers, and disagreement was resolved by consensus.

Statistical Analysis

The statistical analyses were completed with Rev Man 5.3 software. All the parameters that were available in more than 2 studies were synthesized. Dichotomous variables were presented as the relative risk (RR) with a 95% confidence interval (CI), whereas continuous variables were expressed as weighted mean difference (WMD) or standard mean difference (SMD) with 95% CI. The quantity of the statistical heterogeneity was tested by the chi-squared test and the I^2 statistic; when $P > .05$, $I^2 < 50\%$. In the case of a lack of heterogeneity, the fixed-effects model was performed for the meta-analysis; otherwise, the random-effects model was conducted. Assessment of publication bias was done by funnel plots.

RESULTS

Study and Patient Characteristics

After the search, 470 references were identified, of which 459 were excluded for the reasons shown in Figure 1. Finally, 11 RCTs, comprising 672 cases of HoLEP and 667 cases of TURP, were included in the present study.[10-20] The characteristics of the included studies are summarized in Table 1. Of these 11 RCTs, 9 studies (80%) presented a minimum follow-up of 12 months, whereas 4 studies (40%) reported results collected at 24 months after the operation. The prostate sizes of all the cases in the included studies were smaller than 100 g. Bipolar TURPs were involved in 5 studies, whereas the bipolar or monopolar technique of TURP was not mentioned in the remaining 6 studies.

Perioperative Results

HoLEP was significantly associated with longer operation time (WMD: 16.90; 95%CI: 11.05-22.75; $P< .00001$), but also with less drop in hemoglobin level (WMD: −0.31; 95%CI: −0.48 to −0.13; $P= .0005$), shorter hospital stay (WMD: −20.62; 95%CI: −26.20 to −15.05; $P< .00001$), less catheterization time (WMD: −19.04; 95% CI: −24.32 to −13.76; $P< .00001$), and less bladder irrigation (SMD: −1.36; 95% CI: −1.71 to −1.01; $P< .00001$). The weight of the resected gland was comparable between the 2 groups ($P = .68$). The results appear in Supplement Table 1.

Follow-up Data

Q_{max}. No significant difference was detected between the 2 groups in Q_{max} at 1 month and 6 months after the operation (Supplement Fig. 1). Nevertheless, a higher Q_{max} was detected in HoLEP at 12 months and 24 months after surgery, when compared to TURP at the same periods (Fig. 2).

PVR. The statistically significant differences indicated a benefit of HoLEP over TURP in PVR at 6 and 12 months postoperatively (WMD: −7.56; 95% CI: −11.13 to −3.98; $P< .0001$ and WMD: −15.46; 95% CI: −20.01 to −10.92; $P< .00001$, respectively), as shown in Figure 2.

IPSS. Supplement Table 2 demonstrated that no significant difference was reported between the 2 groups with regard to IPSS at 1, 6, and 24 months after the surgery, but HoLEP showed a superior outcome in IPSS at 12 months postoperatively (WMD: −0.76; 95% CI: −1.25 to −0.27; $P = .002$).

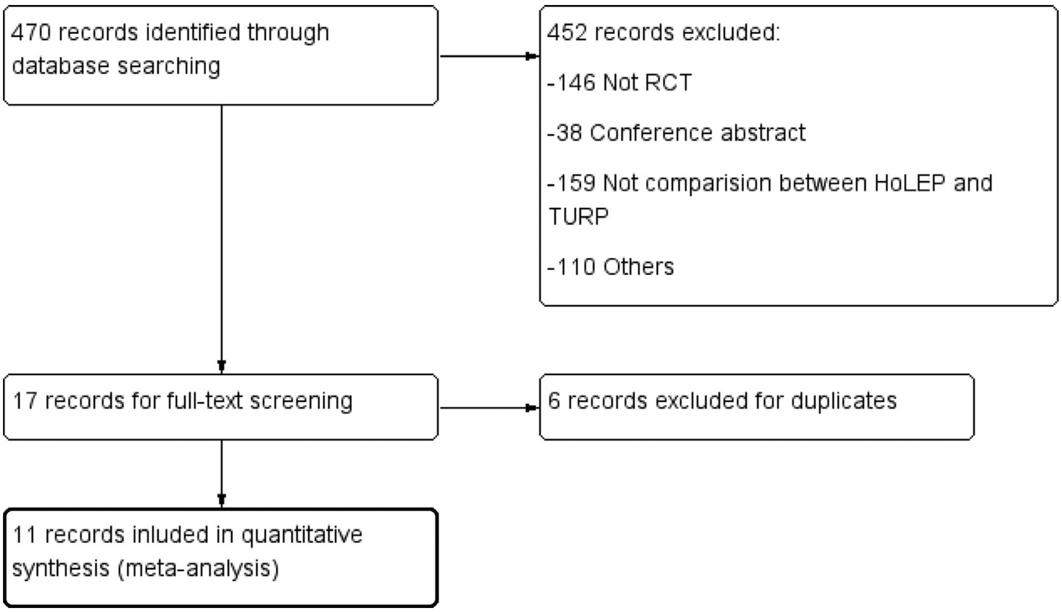

Figure 1. Identification of eligible studies. HoLEP, holmium laser enucleation of the prostate; RCT, randomized controlled trial; TURP, transurethral resection of the prostate.

Table 1. Characteristic of included studies

First Author (Year)	Country	No. of Patients HoLEP/TURP	Follow-up, Months	Age (y) HoLEP/TURP	Prostate Size HoLEP/TURP	Jadad Score
Montorsi 2008	Italy	52/48	12	65.14 ± 7.3/ 64.5 ± 6.4	70.3 ± 36.7/ 56.2 ± 19.4*	2
Fayad 2015	Egypt	60/60	12	60.85 ± 4.0/ 60.35 ± 3.92	68.1 ± 11.2/ 67.2 ± 9.7†	1
Chen 2013	China	140/140	24	73.48 ± 8.8 / 72.11 ± 7.8	56.70 ± 28.41/ 60.31 ± 22.41†	2
Jhanwar 2017	India	72/72	24	67.7 ± 7.44/ 66.78 ± 7.81	75.6 ± 12.84/ 74.5 ± 12.56†	3
Ahyai 2007	Germany	100/100	36	68 ± 7.3/ 68.7 ± 8.2	53.5 ± 20.0/ 49.9 ± 21.1†	3
Gilling 2011	New Zealand	31/30	92	71.7 ± 1.1/ 70.3 ± 1	77.68 ± 32.13/ 70.00 ± 27.78†	3
Mavuduru 2009	India	15/15	9	69.9 ± 9.6/ 66.4 ± 5.8	36.53 ± 12.33/ 36.33 ± 11.4*	2
Fayad 2011	Egypt	30/30	6	60.0 ± 4.5/ 61.2 ± 4.2	76.5 ± 17.22/ 80.6 ± 17.78†	1
Eltabey 2010	Saudi Arabia	40/40	12	67.5 ± 8.1/ 68.3 ± 9.2	62.4 ± 24.1/ 58.5 ± 31.6*	3
Gupta 2006	India	50/50	12	65.88 ± 10.1/ 65.67 ± 7.5	57.9 ± 17.6/ 59.8 ± 16.5*	2
Sun 2014	China	82/82	12	72.1 ± 7.5/ 71.9 ± 7.5	55.1 ± 29.0/ 56.2 ± 30.5*	3

HoLEP, holmium laser enucleation prostatectomy; NA, not available; TURP, transurethral resection of the prostate.
* Presented with measurement unit of gram (g);
† Presented with measurement unit of milliliter (mL);

QoL and AUA. No statistically significant differences were observed in terms of QoL and AUA between the 2 groups at 1, 6, 12, and 24 months after the operation (Supplement Table 2).

Adverse Events

The data about adverse events suitable for meta-analysis are shown in Supplement Table 1. The results showed no significant difference between the 2 groups with respect to recatheterization rate (RR: 0.56; 95% CI: 0.25-1.22; *P*= .14), transient incontinence (RR: 1.40; 95% CI: 0.97-2.03; *P*= .07), persistent incontinence (RR: 0.97; 95% CI: 0.25-3.81; *P*= .97), urethral stricture (RR: 0.51; 95% CI: 0.26-1.02; *P*= .06), and capsular perforation (RR: 3.00; 95% CI: 0.32-27.85; *P*= .33). HoLEP was associated with significantly lower risk of blood transfusion (RR: 0.18; 95% CI: 0.07-0.48; *P*= .0005), but higher risk for transient dysuria (RR: 1.86; 95% CI: 1.31-2.63; *P*= .005), compared to TURP.

Publication Bias Assessment

The results of funnel plots indicated that publication bias in the analysis of our data was not completely excluded. As an example, the funnel plot of catheterization time is presented in Supplement Figure 2.

DISCUSSION

TURP is considered the surgical gold standard therapy for most patients; however, TURP is associated with high morbidity.[3,7,21] In addition, the study reported by Lukacs et al demonstrated that about 30% of patients required pharmacologic treatment for relief of the remaining lower urinary tract symptom after the operation.[22] These disadvantages have facilitated successive searches for less-invasive treatments. By including several long-term studies comparing HoLEP and TURP published recently, we conducted a systematic review and updated meta-analysis focusing on efficacy and safety. HoLEP has been shown to be effective and safe for treating BPH, especially in patients with a large prostate and patients on coagulant therapy.[23] However, none of the included RCTs compared the outcomes after HoLEP or TURP among patients on coagulant therapy, because most of them regarded the coagulant therapy as hemorrhage risk factor in TURP.

According to our results, for small to mid-sized prostate, TURP was superior to HoLEP with respect to operation time. The previous comparison between HoLEP and TURP, published by Ahyai et al, in which the mechanical tissue morcellator was not used, demonstrated that the operation time of HoLEP was much longer than for TURP. This finding led to their assumption that the use of a mechanical morcellator would reduce the operation time of HoLEP to a duration similar to TURP.[19] Nevertheless, their assumption was contradicted by the subsequently published studies, which had routinely performed transurethral morcellation with a tissue morcellator.[10,13,16] Therefore, the long and steep learning curve and rich surgical experience required for HoLEP probably contributed to its longer operative duration.[24,25]

Thereafter, Ahyai et al found that HoLEP was associated with significantly faster tissue resection speed than TURP, and as prostate size increased, the resection speed of HoLEP increased more than that of TURP, which may lead to shorter operation time with HoLEP.[26] Unfortunately, subgroup analysis based on different sizes of

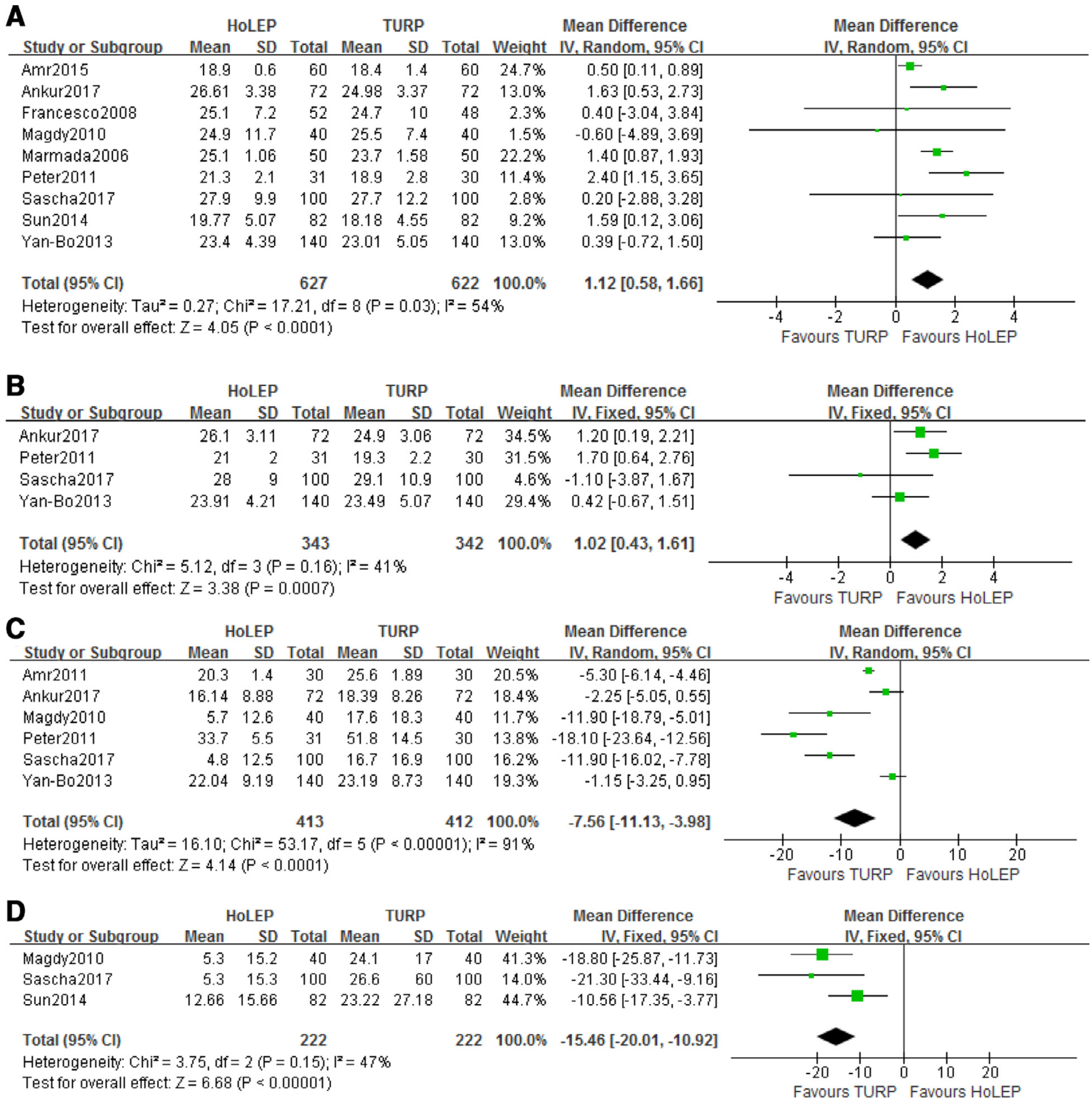

Figure 2. Meta-analysis of Q_{max} and PVR: (**A**) Q_{max} at 12 months after the operation; (**B**) Q_{max} at 24 months after the operation; (**C**) PVR at 6 months after the operation; (**D**) PVR at 12 months after the operation. PVR, postvoid residual urine volume; Q_{max}, maximum urinary flow rate.

prostates was not conducted in our study because our results showed the volume of prostate glands were smaller than 100 g in all included RCTs. Whether operative outcomes after HoLEP or TURP may be confounded by prostatic size should be detected, if more patients with a large prostate size are involved in coming studies.

The study published by Rosenhammer et al demonstrated that HoLEP was associated with a significantly higher incidental prostate cancer detection rate than TURP, even though the majority of cases diagnosed as incidental prostate cancer were at low risk, according to the Gleason score.[27] Therefore, according to the higher incidental prostate cancer detection rate and better long-term outcomes of HoLEP in Q_{max} increase reported in our analysis, it is justified to assume that HoLEP retrieved a greater amount of adenomatous tissue. This hypothesis was in accordance with the results reported by Chen et al[16] and Ankur et al.[15]

However, in our study, the weights of resected tissue were similar between the 2 groups. This can be explained by the different sizes of prostates in the studies included in our article and in the vaporized and desiccated tissue in the enucleation technique.[11,17,28] In addition, the enucleation technique of HoLEP reported by Fayard et al, leaving the apical tissue to be resected at the end of the surgery with the aim to avoid urinary incontinence, may lead to residue of some apical tissue and the decrease of resected tissue.[11] Perhaps we can more accurately assess the amount of resected tissue by the postoperative volume of the prostate (resected prostate volume = preoperative prostate ultrasound volume − postoperative prostate ultrasound volume), but the feasibility of this method needs to be examined with further practice.

In the present meta-analysis, HoLEP was shown to be superior to TURP in terms of hemoglobin loss, bladder irrigation, catheterization time, hospital stay, and blood transfusion. This phenomenon can be explained by 2 reasons. First of all, the holmium laser has been proven to possess excellent hemostatic properties, producing tissue coagulation and necrosis 3-4 mm below the vaporization tissue.[29] Some previous studies demonstrated that in patients taking anticoagulation or antiplatelet therapy and treated by HoLEP, the hemoglobin loss, transfusion rate, and duration of catheterization did not differ from those who did not take the same medication,[23,30] reflecting the outstanding hemostatic properties of HoLEP. For another, opening of the vessels occurred several times while TURP carried down to the capsule.[10] Conversely, the prostate vessels were opened only once at the level of the capsule during HoLEP, leading to a clearer field of vision and smaller transfusion rate.[16] From the clinical point of view, the lower hemoglobin loss and clearer field of operative vision during HoLEP, caused by its excellent hemostatic property, probably contributed to a decrease of bladder irrigation. The shorter catheterization time and hospital duration could make HoLEP a possible option as a day-case surgery in specific patients, proved by Comat et al, but more clinical experience and research are still needed to testify to the safety of day-case HoLEP.[31]

Our results showed that there were significant differences in favor of HoLEP in terms of postoperative Q_{max} and PVR during the 24-month and 12-month follow-ups, respectively. However, no significant differences were detected in terms of subjective score during the follow-up period, except for IPSS 12 months postoperatively, which was in favor of HoLEP. The numerous drop-outs during follow-up played an important role in the negative results of IPSS at 24 months postoperatively in our study. The percentage of more complete glandular volume reduction after HoLEP may lead to the significantly long-term improvement of postoperative Q_{max}.[32] This higher increase of Q_{max} at the 24-month follow-up indicated that a more complete resolution of bladder outlet obstruction could be achieved by HoLEP. The postoperative transrectal ultrasound examination and urodynamic study may help to account for the improvement. However, the 7-15 mL decrease of PVR after HoLEP probably could not lead to the lower IPSS 12 months after HoLEP, from the view of clinical significance. Previous meta-analyses did not assess long-term efficacy and safety, due to a lack of records,[5] but our study did perform an analysis on the long-term information, and the results implied that HoLEP may have better objective, long-term outcomes than TURP. Indeed, the study published by Elmansy et al[32] reported that stable function improvements remained even after 10 years of follow-up.

No significant differences were discovered in recatheterization, transient incontinence, persistent incontinence, urethral stricture, and capsular perforation between the 2 groups, but significant difference was found with respect to postoperative transient dysuria in favor of TURP, and similar findings have been reported by other authors.[5,7] The reason is still unclear. Although urinary incontinence was proved to be the most relevant complication that was influenced by the long learning curve and technical difficulty of HoLEP,[33,34] the comparable incidence of urinary incontinence in our study suggested the durable safety of HoLEP compared to TURP. Because of the absence of data relevant to perioperative sexual function and persistent dysuria, we did not evaluate the sexual function changes and persistent dysuria in the current study. Overall, according to our study, postoperative complications from HoLEP were comparable to TURP.

This method of analysis has a number of limitations. First, high heterogeneity was detected in perioperative parameters among the included studies, even under the condition of sensitivity analysis. Reasons may include different techniques the different surgeons used. For example, a mechanical morcellator was not used in the HoLEP procedure published by Ahyai et al,[19] whereas the morcellator was involved in the vast majority of the included studies. Another reason for high heterogeneity was that HoLEP was performed by different surgeons, whose experience could significantly affect the perioperative parameters, according to Shigemura et al.[35] To minimize the effect of heterogeneity, we used the random-effects model in those cases. Second, publication bias was not excluded in this present study. More RCTs with greater sample size should be used to decrease publication bias in the future.

CONCLUSION

Compared to TURP, among patients with small to mid-sized prostates, although HoLEP is associated with longer operation time, it offers less blood drop, less blood transfusion, shorter hospital stay, shorter catheterization duration, and potentially better long-term results in Q_{max} at the 24-month follow-up and in PVR and IPSS at the 12-month follow-up. Further randomized clinical studies with rigorous design, large sample size, large prostate volume, and long follow-up period are still needed to support our conclusions.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urology.2019.03.034.

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EDITORIAL COMMENT

While the armamentarium available to urologists for managing bladder outlet obstruction due to benign prostatic hyperplasia (BPH) continues to grow, this meta-analysis of 11 randomized controlled trials (RCTs) again demonstrates the excellent outcomes of holmium laser enucleation of the prostate (HoLEP), a procedure established more than 20 years ago. The authors present objective and subjective data demonstrating superior or equivalent perioperative and postoperative outcomes with HoLEP compared to the "gold standard" transurethral resection of prostate (TURP) for prostates <100 g in almost all categories that were evaluated, including decreased blood loss and transfusion rates. Indeed, the authors were unable to assess for differences among patients on anticoagulation as this is typically considered a contraindication for TURP, but not HoLEP.[1]

Some are concerned that men undergoing HoLEP are at a higher risk of postoperative incontinence, possibly related to superior rates of apical tissue removal. However, in this study, no difference was found between TURP and HoLEP with respect to rates of transient or persistent incontinence. In addition, while sexual side effects were not evaluated in this meta-analysis, a prior review suggested that HoLEP may have a proerectile effect,[2] though retrograde ejaculation is a well-established side effect. One area in which TURP was found to be superior in this study was operative time, and this may be related to variability in surgeon experience and the steep learning curve of HoLEP, a concept that has been previously documented.[3]

As the authors noted, 2 of the great benefits of HoLEP, ability to treat very large prostates and long-term efficacy, could not be compared to TURP in the present analysis due to a lack of data and should be assessed in future RCTs. While less than half the RTCs utilized in this study included follow-up ≥24 months, others have published outcomes up to 18 years after HoLEP, consistently showing low reoperation rates for BPH regrowth (<1%-1.5%[4,5] vs ≥9% with TURP[4,6]). Regarding prostate size, HoLEP is a size-independent option per the AUA and recommended specifically for prostates >80 g by the EAU.

Despite the overwhelming evidence supporting use of HoLEP for BPH, HoLEP only accounted for an estimated 5% of all outlet procedures in the United States as recently as 2015,[7] with the majority being performed at a small number of centers. A lack of equipment, a steep learning curve, and limited training opportunities are typically cited as the reasons for why HoLEP is not more widely disseminated in the United States. However, the majority of urology practices use a holmium laser for stone treatment, and it has been demonstrated that HoLEP can be successfully performed with a standard 30W laser.[8] Furthermore, HoLEP may be a more cost-effective option compared to some outlet procedures.[9] With respect to the learning curve, multiple groups are working toward improving HoLEP training through simulation and mentoring.[10] The findings of the current study support these ongoing efforts to increase HoLEP access to more patients with symptomatic BPH.

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