

PROSTATIC DISORDERS
REVIEW

Holmium laser enucleation versus simple prostatectomy for treating large prostates: Results of a systematic review and meta-analysis



Patrick Jones^{a,*}, Laith Alzweri^b, Bhavan Prasad Rai^c, Bhaskar K. Somani^d,
Chris Bates^e, Omar M. Aboumarzouk^f

^a Blackpool Victoria Hospital, Blackpool, Lancashire, UK

^b Sandwell and West Birmingham Hospitals NHS Trust, Birmingham, West Midlands, UK

^c Lister Hospital, Stevenage, Hertfordshire, UK

^d University Hospital Southampton NHS Trust, Southampton, Hampshire, UK

^e St. Joseph's Hospital, Newport, South Wales, UK

^f Islamic University of Gaza, College of Medicine, Gaza, Palestine

Received 22 July 2015, Received in revised form 27 September 2015, Accepted 17 October 2015

Available online 26 November 2015

KEYWORDS

HoLEP;
Holmium;
Lasers;
Prostatectomy;
BPH

ABBREVIATIONS

OP, open prostatectomy;
HoLEP, holmium enucleation of the prostate;

Abstract Objective: To compare and evaluate the safety and efficacy of holmium laser enucleation of the prostate (HoLEP) and simple prostatectomy for large prostate burdens, as discussion and debate continue about the optimal surgical intervention for this common pathology.

Materials and methods: A systematic search was conducted for studies comparing HoLEP with simple prostatectomy [open (OP), robot-assisted, laparoscopic] using a sensitive strategy and in accordance with Cochrane collaboration guidelines. Primary parameters of interest were objective measurements including maximum urinary flow rate (Q_{max}) and post-void residual urine volume (PVR), and subjective outcomes including International Prostate Symptom Score (IPSS) and quality of life (QoL). Secondary outcomes of interest included volume of tissue retrieved, catheterisation time, hospital stay, blood loss and serum sodium decrease. Data on baseline characteristics and complications were also collected. Where possible, comparable data were combined and meta-analysis was conducted.

* Corresponding author at: Blackpool Victoria Hospital, Whinney Heys Road, Blackpool, Lancashire FY3 8NR, UK

E-mail address: patrick.jones1@nhs.net (P. Jones).

Peer review under responsibility of Arab Association of Urology.



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LASP, laparoscopic simple prostatectomy; MeSH, Medical Subject heading; Q_{\max} , maximum urinary flow rate; PVR, post-void residual urine volume; QoL, quality of life; RASP, robot-assisted simple prostatectomy; RCT, randomised controlled trial; WMD, weighted mean difference

Results: In all, 310 articles were identified and after screening abstracts (114) and full manuscripts (14), three randomised studies (263 patients) were included, which met our pre-defined inclusion criteria. All these compared HoLEP with OP. The mean transrectal ultrasonography (TRUS) volume was 113.9 mL in the HoLEP group and 119.4 mL in the OP group. There was no statistically significant difference in Q_{\max} , PVR, IPSS and QoL at 12 and 24 months between the two interventions. OP was associated with a significantly shorter operative time ($P = 0.01$) and greater tissue retrieved ($P < 0.001$). However, with HoLEP there was significantly less blood loss ($P < 0.001$), patients had a shorter hospital stay ($P = 0.03$), and were catheterised for significantly fewer hours ($P = 0.01$). There were no significant differences in the total number of complications recorded amongst HoLEP and OP ($P = 0.80$).

Conclusion: The results of the meta-analysis have shown that HoLEP and OP possess similar overall efficacy profiles for both objective and subjective disease status outcome measures. This review shows these improvements persist to at least the 24 month follow-up point. Further randomised studies are warranted to fully determine the optimal surgical intervention for large prostate burdens.

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Introduction

BPH is a condition, which affects $\approx 28\%$ of men aged > 70 years [1]. The progressive nature of this disease has been confirmed by landmark studies, such as the Olmstedt County Study [2] and Baltimore Longitudinal Study of Aging [3]. The search for the optimal surgical treatment for large prostate burdens (> 80 mL) is unremitting and remains the subject of continued conjecture and debate [4]. Before the advent of endoscopic approaches, simple open prostatectomy (OP) surgery was the prerogative and still is the only option in certain developing countries [5]. Despite a decline in the number of open procedures carried out each year in western countries, it remains a core component of the urologist's therapeutic arsenal [6].

Holmium laser enucleation of the prostate (HoLEP) is an efficient, laser-based, transurethral alternative, which is both minimally invasive and has been cited as 'size independent' [7]. Its application has achieved diffusion across centres worldwide with 10-year outcome data now available. While there has been increased attention towards the efficacy of HoLEP vs its endourological alternatives such as TURP and photo-selective vapourisation of the prostate, formal evaluation of HoLEP compared with simple prostatectomy [OP, laparoscopic simple prostatectomy (LASP), and robot-assisted simple prostatectomy (RASP)] remains under reported.

The objective of the present study was to systematically review the evidence and compare the efficacy and safety between HoLEP and simple prostatectomy.

Materials and methods

A systematic search was conducted according to Cochrane Collaboration guidelines and the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) checklist [8]. The search strategy was devised to retrieve studies from electronic databases including Medline, Web of Science, Embase, and the Cochrane Central Register of Registered Trials (CENTRAL), and Scopus. The search was performed on 24 May 2015.

Specific search terms included, but were not limited to: 'holmium', 'enucleation', 'laser surgery', 'open prostatectomy', 'laparoscopy', 'minimally invasive', 'robotic', 'benign prostate hyperplasia', and 'lower urinary tract symptoms'. Medical Subject heading (MeSH) phrases included: 'prostatectomy' [MeSH], 'laser therapy' [MeSH], 'laparoscopy' [MeSH], 'robotic surgical procedures' [MeSH], 'prostatic hyperplasia' [MeSH]. Phrases were combined using Boolean operators ('AND', 'OR') to augment the search. References from suitable studies were also hand searched.

Data extraction and analysis

The pre-defined inclusion criteria were for randomised controlled trials (RCTs) comparing HoLEP with any form of simple prostatectomy. The list of potentially relevant studies generated by the search was reviewed by two of the authors independently (P.J. and O.A.). The extraction of data from selected studies was performed in the same manner.

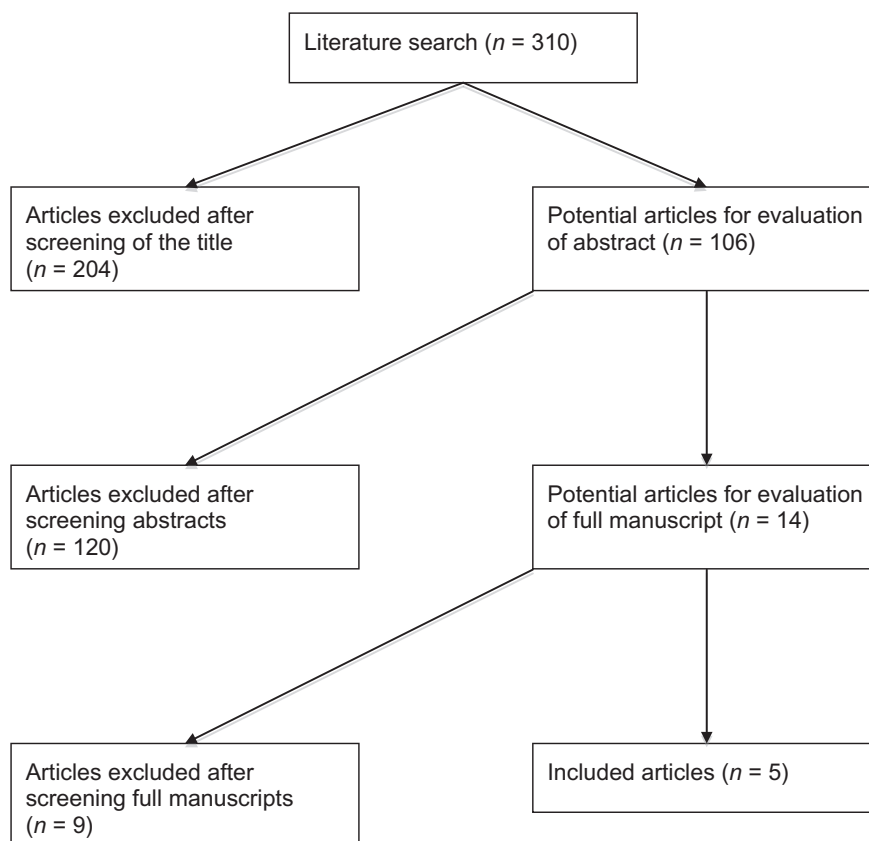


Figure 1 PRISMA flowchart of literature search.

Data on baseline characteristics and complications were also collected.

Outcome measures

Primary outcomes were maximum urinary flow rate (Q_{\max}) and post-void residual urine volume (PVR), and subjective outcomes included IPSS and quality of life (QoL).

Secondary outcomes of interest included: operative time, volume of prostate tissue retrieved, drop in haemoglobin and serum sodium levels, catheterisation time, hospital stay, and complications. Complications were grouped according to their estimated Clavien–Dindo system grade, as none of the studies implemented a formal tool for

classifying complications [9]. The Martin Criteria, a validated tool for accurate and comprehensive reporting of surgical complications, was also incorporated into our evaluation [10]. Articles were analysed and labelled with a level of evidence in accordance with the Oxford Centre for Evidence Based Medicine (CEBM) [11].

Where possible, comparable data were combined and meta-analysis was performed using Cochrane software Review Manager version 5.3. Results for continuous outcomes were displayed as the mean difference with 95% CIs, where $P < 0.05$ was considered to indicate statistical significance. Heterogeneity was analysed using a chi-squared test and with the I^2 test where I^2 values of 75%, 50% and 25% correspond to high, medium and low levels of heterogeneity, respectively.

Table 1 Study characteristics for HoLEP vs OP.

References	Level of evidence	Country	Journal	Sample size, n	Mean (SD) age, years	Mean (SD) TRUS volume, mL
Naspro et al. [12]	2	Italy	<i>Eur. Urol.</i>	41 vs 39	66.26 (6.55) vs 67.27 (6.27)	113.27 (35.33) vs 124.21 (38.52)
Salonia et al. [13]	2	Italy	<i>Urology</i>	34 vs 29	67.4 (6.7) vs 68 (6.4)	113.8 (37.0) vs 121.0 (34.9)
Kuntz et al. [14–16]	2	Germany	<i>J. Urol.</i> , <i>J. Endourol.</i> , <i>Eur. Urol.</i>	60 vs 60	69.2 (8.4) vs 71.2 (8.3)	114.6 (21.6) vs 113.0 (19.2)

Table 2 Objective outcomes for HoLEP vs OP.

Variable, mean (SD)	Naspro et al. [12]	Salonia et al. [13]	Kuntz et al. [16]
Q_{\max} , mL/s			
Before procedure	7.83 (3.42) vs 8.32 (2.37)	8.9 (4.2) vs 8.4 (2.4)	3.8 (3.6) vs 3.6 (3.8)
At 12-month follow-up	22.32 (3.8) vs 24.21 (6.49)	NR	27.4 (9.7) vs 28.3 (7.5)
At 24-month follow-up	19.19 (6.3) vs 20.11 (8.8)	NR	26.7 (8.3) vs 27.4 (6.8)
At \geq 36-month follow-up	NR	NR	27 (9.8) vs 25.3 (6.8)
PVR, mL			
Before procedure	NR	87.4 (83.5) vs 106.3 (71.8)	280 (273) vs 292 (191)
At 12-month follow-up	NR	NR	5.8 (16.7) vs 6.4 (12.3)
At 24-month follow-up	NR	NR	1.7 (6.5) vs 2.4 (6.7)
At \geq 36-month follow-up	NR	NR	6.1 (12.1) vs 4.4 (10.5)

Results

In all, 310 articles were screened, from which five publications were identified, which met our pre-defined inclusion criteria (Fig. 1) [12–16]. Three studies were duplicate publications of the same trial [14–16]. This resulted in a total of three trials to analyse. Each trial compared HoLEP with OP. No studies were identified, which compared HoLEP with LASP or RASP.

Characteristics of included studies

All studies were conducted in Europe and published between 2002 and 2008. They included 263 patients, 135 and 128 underwent HoLEP and OP, respectively. The mean age of the patients was 67.6 years in the HoLEP group and 68.8 years in the OP group. The mean TRUS volume was 113.9 mL in the HoLEP group and 119.4 mL in the OP group (Table 1).

Primary outcomes

Clinical efficacy

- Q_{\max}

This parameter was recorded in the three studies; however, follow-up occurred in only two of these (Table 2) [12,14–16]. Meta-analysis at 12 and 24 months showed no significant differences [12 months $P = 0.11$, weighted mean difference (WMD) -1.53 , 95% CI -3.40 to 3.4 ; 24 months $P = 0.65$; WMD 0.49 , 95% CI -1.63 to 2.6 ; Fig. 2).

- PVR

PVR follow-up data were available for one study (Table 2). (12 months $P = 0.82$, WMD -0.60 , 95% CI -5.85 to 4.65 ; 24 months $P = 0.41$, WMD 1.7 , 95% CI -2.35 to 5.75 ; Fig. 2) [14–16]. This revealed no significant difference between HoLEP and OP.

- IPSS

Data on IPSS were retrieved from all studies; however, follow-up data were only available for two of the studies (Table 3) [12,14–16]. Meta-analysis of the 12 and 24 month IPSS revealed no significant differences at 12 or 24 months postoperatively (12 months $P = 0.99$, WMD 0.00 , 95% CI -0.64 to 0.65 ; 24 months $P = 0.76$, WMD -0.11 , 95% CI -0.78 to 0.56 ; Fig. 3).

- QoL

Two studies recorded QoL data (143 patients) [12,13]. Of them, only one reported QoL in the follow-up (Table 3) [2]. This did not show any significant difference at 12 and 24 months (12 months $P = 0.72$, WMD -0.07 , 95% CI -0.46 to 0.32 ; 24 months $P = 0.38$, WMD -0.16 , 95% CI -0.52 to 0.2 ; Fig. 3).

Secondary outcomes

- Operative time

The operative time for OP was significantly shorter than for HoLEP ($P = 0.01$; WMD 24.86 , 95% CI 5.8 – 43.92).

- Tissue retrieved

For the volume of tissue retrieved, the results from the meta-analysis favoured OP, as this technique retrieved significantly greater volumes of tissue compared to HoLEP ($P < 0.001$; WMD -13.16 , 95% CI -20.31 to -6.00) (Table 4).

- Decrease in haemoglobin

Two studies provided data on haemoglobin loss. Meta-analysis showed HoLEP to result in a significantly smaller drop in haemoglobin ($P < 0.001$; WMD -0.95 , 95% CI -1.35 to -0.56) [12,14–16] (Table 4).

- Decrease in serum sodium

One study supplied a decrease in serum sodium data, which showed no significant difference ($P = 0.13$; WMD -0.5 , 95% CI -0.15 to 1.15) [14–16].

- Catheterisation time

Two studies reported catheterisation time in hours and meta-analysis showed it to be significantly shorter in HoLEP ($P = 0.01$; WMD -117.36 , 95% CI -208.11 to -26.62) [13–16]. Naspro et al. [12] measured catheterisation time in days and the results also favoured HoLEP over OP ($P < 0.001$; WMD -2.60 , 95% CI -2.96 to -2.24).

- Hospital stay duration

For the two studies that reported the duration of hospital stay in hours, it was significantly less for HoLEP vs OP ($P = 0.03$; WMD -123.85 , 95% CI -236.55 to -11.16) [13–16]. Naspro et al. [12] reported hospital stay in days, with no significant difference found ($P = 0.11$; WMD -2.73 , 95% CI -6.11 to 0.65).

Complications

There were no significant differences in the total number of complications recorded amongst HoLEP and OP ($P = 0.80$). The commonest Clavien–Dindo Grade I complication in the HoLEP group was dysuria (27.7%) and in the OP group it was transitory urge incontinence (23.2%) (Table 4). In the sub-analysis of complications according to Clavien–Dindo Grade, the only statistically significant difference was seen amongst Grade II complications, where the results of the meta-analysis favoured HoLEP ($P = 0.02$; WMD 0.35 , 95% CI 0.15 – 0.82). For Grade I complications, the results favoured OP; however, this was not statistically significant. For Grade III, IV and V complications, the trend in results favoured HoLEP, but again this superiority was not statistically significant. There was one death in the OP group, with none in the HoLEP group.

Discussion

The results of the present meta-analysis suggest that HoLEP and OP possess similar overall efficacy profiles for both objective and subjective disease status outcome measures. The present review shows these improvements persist to at least the 24-month follow-up point. However, in the perioperative period, patients undergoing HoLEP spend significantly fewer hours in hospital and are catheterised for a significantly shorter period.

Efficacy and safety

While OP retrieves greater tissue volumes and carries the advantage of a shorter operative time, it is associated with a significantly greater drop in haemoglobin. Elshal et al. [17] reported that 24.5% of patients had required a blood transfusion after OP in a retrospective analysis of 163 patients at their institution. Such are the haemostatic advantages associated with HoLEP, Tyson et al. [18] determined it to be a safe alternative to TURP for patients on oral anticoagulation therapy.

The lower volumes of tissue retrieved by HoLEP may well be confounded by the effects of tissue vapourisation [19], which has been estimated to equate to an $\approx 10\%$ tissue loss. Elkoushy et al. [19] recently published findings from a single-centre large series of 1216 HoLEP procedures conducted between 1998 and 2013, and recorded a re-operation-free probability of 95% at 10 years.

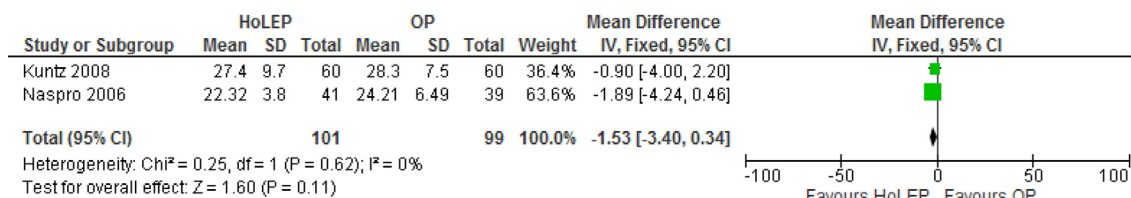
Complications

There were no differences in the total number of complications between the two interventions. This lack of difference in the overall complication rate may be compounded by insufficient power amongst the included studies. Across the studies, the mean rating according to Martin Criteria was 4.3/10 (Table 5). Reasons for a low score included poor evidence of risk stratification and poor indication of the method used in the studies. None of the included studies used a grading system to classify the severity of complications. Of note, Salonia et al. [13] did not report on complications at all. None of the studies recorded sexual function as an outcome measure, an important marker of disease burden and a strong determinant for patient choice of intervention. None of the studies included in the present review provided data on re-intervention for symptom recurrence.

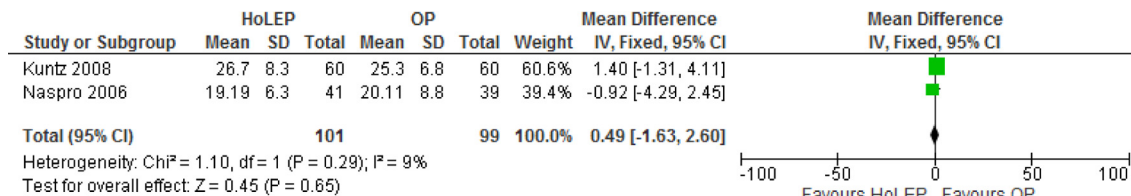
Cost efficacy

With the heavy economic burden of healthcare, the net cost of a surgical procedure is an important consideration. Salonia et al. [13] compared the perioperative costs for OP vs HoLEP (\$3556.3 vs \$2919.4). Overall, there was a percentage net cost saving of 9.6% in favour of HoLEP. HoLEP may yield financial advantages for an institution over time, especially given the potential use of the holmium: yttrium aluminium garnet (YAG) laser as a lithotripter and cost savings achieved through shorter length of stays. However, the cost burden of the initial set up is high [6]. This, as well as the specialist training required has already proved to be a barrier to the implementation of laser therapies across less developed countries [6].

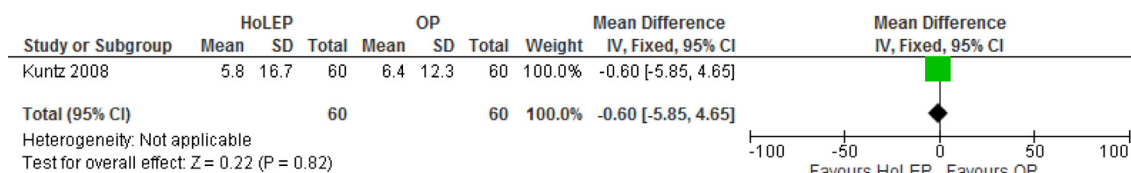
Q_{max}: 12 months postoperative



Q_{max}: 24 months postoperative



PVR: 12 months postoperative



PVR: 24 months postoperative

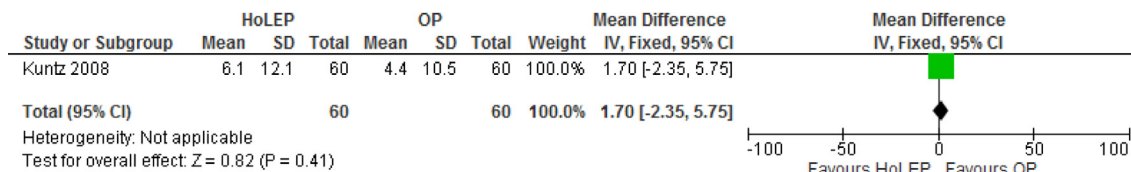


Figure 2 Comparisons of objective outcomes.

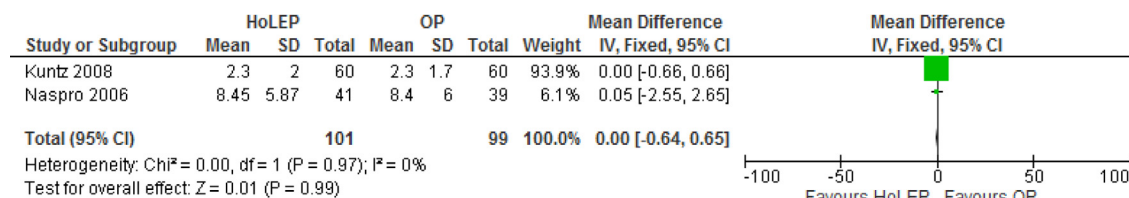
Learning curve

Dialogue continues amongst urologists about the true learning curve associated with HoLEP [20]. Gilling et al. [21] have advised dissemination of formal mentorship programmes, which should incorporate elements of focused preparation, observation in theatre, and formal supervision. These tutored courses are typically only delivered by specialist centres and made possible through financial support from companies marketing HoLEP technology. Lack of such didactic opportunities has led to many surgeons adopting a self-taught method for HoLEP, which is thought to be one of the principle reasons the learning curve has been reported by many as protracted. Vincent et al. [22] have proposed that mentorship initiatives can allow the HoLEP technique to be learnt safely after 10 cases.

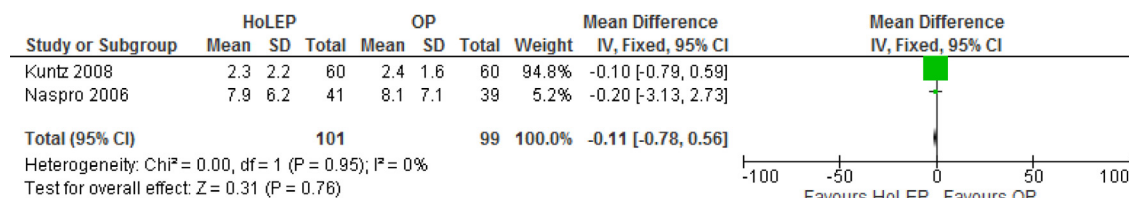
Strengths and limitations of the review

The main limitation of the present review was the small number of included studies. However, these were all RCTs and each with a low overall risk of bias. A further limitation is the time at which these studies were performed, which was as early as 2002. Given HoLEP was still evolving at this time and associated with a steeper learning curve compared with now, the recorded HoLEP outcomes are likely to be limited accordingly. For example, advances in morcellation technique(s) have resulted in shorter operative times. Such technology was not available for Kuntz et al. [14] at the beginning of their study; therefore the enucleated adenoma was resected using traditional techniques. Unfortunately, Kuntz et al. do not state after how many cases the morcellator was introduced. This represents the

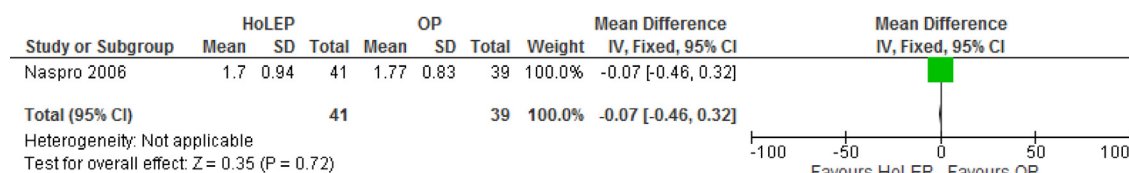
IPSS improvement: 12 months postoperative



IPSS improvement: 24 months postoperative



QoL: 12 months postoperative



QoL: 24 months postoperative

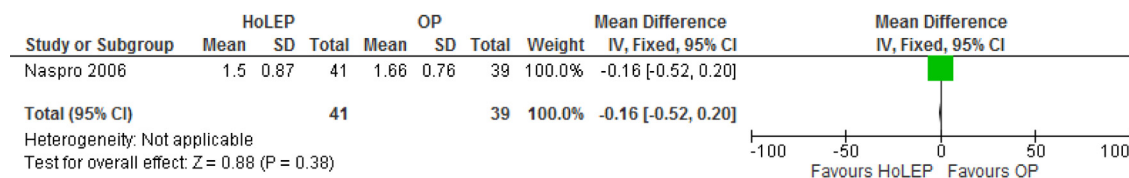


Figure 3 Comparisons of subjective outcomes.

Table 3 Subjective outcomes for HoLEP vs OP.

Variable, mean (SD)	Naspro et al. [12]	Salonia et al. [13]	Kuntz et al. [16]
IPSS			
Before procedure	20.11 (5.84) vs 21.6 (3.24)	19.6 (7) vs 21.6 (3.5)	22.1 (3.3) vs 21 (3.6)
At 12-month follow-up	8.45 (5.87) vs 8.4 (6)	NR	2.3 (2) vs 2.3 (1.7)
At 24-month follow-up	7.9 (6.2) vs 8.1 (7.1)	NR	2.3 (2.2) vs 2.4 (1.6)
At ≥ 36 -month follow-up	NR	NR	3 (3.1) vs 2.8 (1.6)
QoL			
Before procedure	4.07 (0.93) vs 4.44 (0.96)	4.6 (1) vs 4.4 (1)	NR
At 12-month follow-up	1.7 (0.94) vs 1.77 (0.83)	NR	NR
At 24-month follow-up	1.5 (0.87) vs 1.66 (0.76)	NR	
At ≥ 36 -month follow-up	NR	NR	

Table 4 Assumed Clavien–Dindo grading of reported complications.

Complication	Clavien–Dindo Grade	Procedure, <i>n</i> (%)	
		HoLEP	OP
UTI	I	–	–
Dysuria	I	28	16
Bladder mucosal injury (superficial)	I	3	–
Transitory urge incontinence	I	19	23
Stress incontinence	I	1	1
AUR	II	8	5
Urosepsis	II	–	–
Bleeding requiring blood transfusion	II	3	11
Bladder neck stenosis	IIIb	–	2
Urethral stricture	IIIb	2	2
Surgical intervention for bleeding	IIIb	1	–
Capsular perforation	IIIb	–	–
Myocardial infarction	IVa	–	1
Death	V	–	1
Total, <i>n/N</i> (%)		65/101 (64.3)	62/99 (62.6)

AUR, acute urinary retention.

Table 5 Martin Criteria.

Martin Criteria	Naspro et al. [12]	Salonia et al. [13]	Kuntz et al. [16]
Method of accruing data defined	Yes	No	Yes
Duration of follow-up indicated	Yes	No	Yes
Outpatient information included	Yes	No	Yes
Definitions of complications provided	Yes	No	No
Mortality rate and causes of death listed	No	No	Yes
Morbidity rate and total complications indicated	Partially	No	Yes
Procedure-specific complications included	Yes	No	Yes
Severity grade used	No	No	No
Length-of-stay data	Yes	Yes	Yes
Risk factors included in the analysis	No	No	No
Total criteria, <i>n</i>	5	1	7

major technical difference across the studies. Moreover, information on technical points is limited across the three studies. Each study referenced the surgical technique for HoLEP described by Gilling et al. [23,24]; however, the authors of the respective studies have provided little additional information thereafter. Only Naspro et al. [12] commented that they adopted the traditional transvesical approach for OP, the other two studies did not mention any details on it at all.

A recent matched pair analysis of 92 HoLEP and 91 transvesical OP procedures, published by Elshal et al. [25] has confirmed many of the advantages of HoLEP identified by these early randomised studies. The authors reported a median hospital stay of 2 days in the HoLEP group vs 9 days in the OP group ($P < 0.001$).

No studies were identified, which compared HoLEP with minimally invasive simple prostatectomy (LASP/RASP). Although clinical equipoise persists for OP and HoLEP, randomisation of open vs minimally inva-

sive therapies is difficult to justify and is likely the principal reason the number of RCTs identified in this review was low. For the same reasons, it is likely to remain this way in the future. Whether the urology community settles with this or goes on to carry out formal randomisation of RASP or LASP vs OP for large prostate burdens remains to be determined. The method itself of true blunt enucleation performed during HoLEP is comparable to that of OP using finger enucleation. However, it carries the advantages of augmented visual control of bleeding allowing for fewer complications and overall shorter hospital stay.

The present review was strengthened through its systematic approach and using methodology based on Cochrane review standards. Indeed, we think this is the first systematic review to compare simple OP and HoLEP.

Further randomised studies are warranted to fully determine the optimal surgical intervention for large prostate burdens. These should be conducted in

accordance with the Consolidated Standards of Reporting Trials (CONSORT) statement and standardised grading of complications [26].

Conclusion

OP and HoLEP are both effective and durable surgical interventions for the treatment of LUTS secondary to BPH. Given the clinically relevant advantages associated with HoLEP, such as shorter catheterisation time and hospital stay, the ascendance of this viable laser therapy is likely to continue amongst the urology community. Nonetheless, over a century in clinical practice, OP remains a valuable intervention in the urologist's armamentarium. However, with growing economic pressures and the evolution of minimally invasive therapies, its presence will potentially fade.

Conflicts of interest

None declared.

Source of funding

None.

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