Meta-analysis

Meta-analysis of holmium laser enucleation *versus* transurethral resection of the prostate for symptomatic prostatic obstruction

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Background: **Holmium laser enucleation (HoLEP) is an alternative to transurethral resection (TURP) of the prostate for symptomatic prostatic obstruction.**

Methods: **Randomized controlled trials comparing HoLEP and TURP were identified systematically using Medline, Embase and The Cochrane Library. Primary outcomes were peak urinary flow rate (Qmax), postvoid residual volume, symptom score and quality of life. Secondary outcomes were duration of operation, hospital stay, blood loss, catheterization time and adverse events.**

Results: **There was no statistically significant difference between HoLEP and TURP in terms of Qmax at 6 and 12 months' follow-up. HoLEP was associated with significantly less blood loss, a shorter catheterization time and a shorter hospital stay. TURP was associated with reduced operating time. The techniques were similar in terms of urethral stricture, stress incontinence, transfusion requirement and rate of reintervention.**

Conclusion: **HoLEP and TURP provide a similar improvement in Qmax. HoLEP, however, has several advantages over TURP, despite requiring more operating time. It is at least as safe as TURP in terms of adverse events.**

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Introduction

Transurethral resection of the prostate (TURP) is the 'gold standard' surgical treatment for bladder outlet obstruction due to prostatic disease. A large body of evidence supports its therapeutic efficacy in improving urinary flow rates and alleviating obstructive voiding symptoms, with success rates of 85–90 per cent[1]. Nevertheless, 15–20 per cent of patients develop a significant complication, such as bleeding, transurethral resection syndrome, bladder neck stricture formation or sexual dysfunction, and 10–15 per cent require a second intervention within 10 years[2,3]. In addition, a mortality rate of 0·2–2·5 per cent has been reported[2–7]. In the light of this, alternative treatments have been sought in the hope of minimizing these adverse effects while maintaining therapeutic efficacy. Holmium laser enucleation of the prostate (HoLEP) represents one such alternative treatment.

The first combined holmium and neodymium:yttrium–aluminium–garnet laser technique for prostatectomy was reported in 1995 by Chun and colleagues[8] and Gilling and co-workers[9]. Clinical experience since then has shown that HoLEP offers an efficient alternative to TURP. A variety of techniques exists but the preferred method for the removal of prostatic adenoma has evolved from ablation or vaporization[10,11] through resection[12,13] to the currently preferred method of enucleation[14,15]. This new method achieves equivalence with TURP in terms of efficacy, with improvement in perioperative morbidity in some randomized controlled trials (RCTs)[16–18]. Recent studies have compared the outcome and side-effect profiles of HoLEP and TURP, with varying results, probably because of variability in study design, different inclusion–exclusion criteria, and different methods of outcome measurement. This means that the magnitude of the surgical effect remains unknown and so far there has been no meta-analysis to compare the two approaches.

Methods

Objectives, search strategy, study selection criteria, methods for determining eligibility, data elements, methods for abstraction and methods for study quality assessment were defined. Two independent reviewers completed each step in this protocol and resolved disagreements by consensus.

Literature search

All relevant RCTs that compared HoLEP with TURP for symptomatic prostatic obstruction were identified. A RCT was defined as a trial in which participants were assigned prospectively to one of two interventions by random allocation. To identify all relevant studies, the electronic databases Medline, Embase and The Cochrane Library were used systematically to search for all articles from 1990 to 2007 in any language that included the following terms in their titles, abstracts or keyword lists: holmium laser enucleation (or HoLEP), transurethral resection (or TURP), the prostate (*Fig. 1*). This search strategy was performed iteratively until no new potential citations could be found on review of the reference lists of retrieved articles.

Study selection

The reference lists of all traced articles and general reviews of this topic were examined manually; reviews and commentaries were excluded. Citations selected from this initial search were subsequently screened for eligibility using the follow criteria: (1) contained patients with symptomatic prostatic obstruction at baseline, (2) compared HoLEP with TURP and (3) RCT.

Data extraction

Two reviewers (A.T. and C.L.) abstracted data independently and reached consensus on all items. The following variables were recorded: authors, journal and year of publication, geographical region, number of patients, age, international prostate symptom score (IPSS), postvoid residual volume (PVR), quality of life (QOL), duration of operation, intraoperative irrigant, blood loss, catheterization time, hospital stay, urethral stricture, stress incontinence, blood transfusion and reintervention. If necessary, the primary authors were contacted to retrieve further information.

Data analysis

A formal meta-analysis was made of all RCTs comparing the efficacy and safety of HoLEP and TURP. The outcomes used for this study were objective measures of obstruction, as defined by peak urinary flow rate (Qmax), and perioperative variables (duration of operation, catheterization time, hospital stay and blood loss) and adverse events (urethral stricture, stress incontinence, blood transfusion and reintervention). Pooled estimates

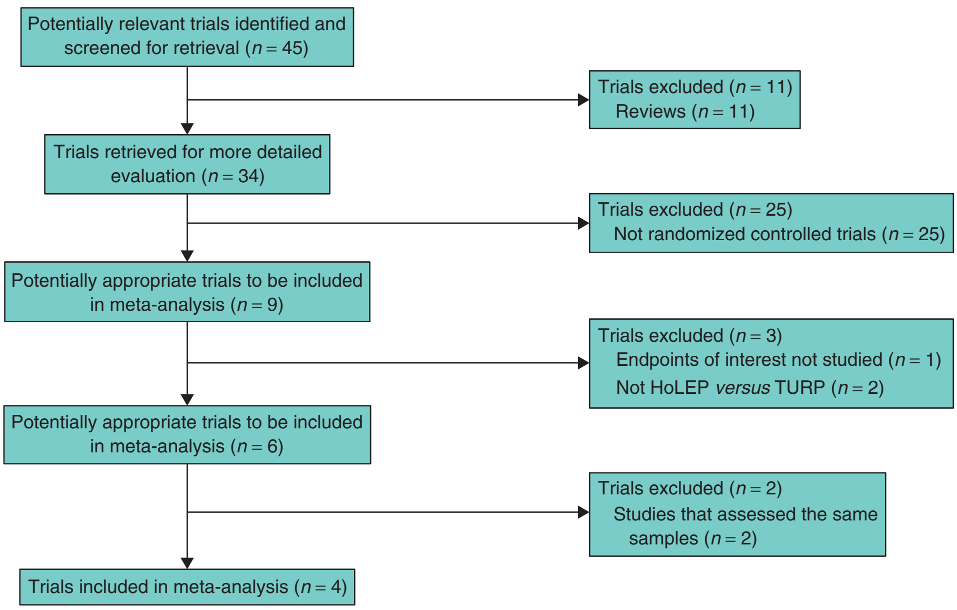

Fig. 1 Process of selection of randomized controlled trials for analysis. HoLEP, holmium laser enucleation of the prostate; TURP, transurethral resection of the prostate

of efficacy were calculated using a fixed-effects model[19] but a randomized-effects model was used according to heterogeneity. A test for heterogeneity, defined as variation among the results of individual trials for a given treatment (HoLEP or TURP) beyond that expected from chance, was used to assess whether the magnitude of a given treatment effect varied between the trials. The method described by Cochran[20] was used for continuous variables and that by Yusuf *et al.*[21] for binary outcomes. Bias was studied using the weighted regression tests described by Egger and colleagues[22]. In addition, sensitivity analysis was applied by removing individual studies from the data set and analysing the effect on the overall results[19]. Data analysis was performed using Stata® version 9.0 (Stata Corporation, College Station, Texas, USA).

Assessment of study quality

The methodological quality of the studies included in the meta-analysis was scored using the Jadad composite scale[23,24]. This is a five-point scale, with low-quality studies having a score of 2 or less and high-quality studies a score of at least 3[24,25].

Results

Seven RCTs were identified[26–32]. One study[26] was excluded because of failure to address measures of clinical outcome, such as Qmax, perioperative variables and adverse events. In addition, two studies that assessed the same samples as another two studies (and provided fewer measures of clinical outcome) were also omitted[27,28]. The literature search and study selection process therefore identified four RCTs[29–32] and these examined a total of 460 participants having either HoLEP (232) or TURP (228). The median follow-up was 12 months and the four studies all provided a year of follow-up data. One[32] has a related further study[28] that reported results at 2 years. It was decided to use the data obtained within the first year after randomization for the meta-analysis.

The mean Jadad score of the studies included was 3 (*Table 1*). The main study limitations pertained to justification of sample size, randomization and the procedure for concealing the treatment allocation. For example, only one study[32] described how the random allocation sequence was generated and only two[30,32] estimated the sample size before initiating the study as part of a calculation of statistical power. In addition, outcome measures, such as PVR, QOL and IPSS, varied. Not all the four studies included presented outcomes as a mean(s.d.), which was considered a minimum requirement for any meta-analysis, and this limited the analysis of these outcomes to trials providing complete information.

Table 1 Jadad score calculation for included studies

	Gupta *et al.*[29]	Tan *et al.*[32]	Kuntz *et al.*[30]	Montorsi *et al.*[31]
Was the study described as randomized (this includes words such as randomly, random and randomization)?	1	1	1	1
Was the method used to generate the sequence of randomization described and appropriate (table of random numbers, computer-generated, etc.)?	1	1	1	1
Was the study described as double blind?	0	0	0	0
Was the method of double blinding described and appropriate (identical placebo, active placebo, dummy, etc.)?	0	0	0	0
Was there a description of withdrawals and dropouts?	1	1	1	1
Total	3	3	3	3

Baseline characteristics of patients in the included trials are summarized in *Table 2* and results for various outcome measures at 6 and 12 months after surgery are shown in *Table 3*. Data for Qmax, perioperative variables and adverse events were included in meta-analyses.

Peak urinary flow rate

At baseline, the Qmax of patients randomized to HoLEP or TURP appeared similar (*Table 3*), with a minimal pooled difference estimate of −0·027 ml/s. There was no statistically significant difference in the two groups at either 6 months (weighted mean difference (WMD) 1·06 (95 per cent confidence interval (c.i.) −0·16 to 2·27) ml/s) (*Fig. 2a*) or 12 months (WMD 0·59 (95 per cent c.i. −0·04 to 1·23) ml/s) (*Fig. 2b*). However, there was significant heterogeneity between individual trials at the 6-month ($I^2 = 97·0$ per cent) and 12-month ($I^2 = 90·3$ per cent) follow-up. Sensitivity analysis showed that the significant heterogeneity of outcome between reported trials could be attributed mainly to the trial reported by Kuntz and colleagues[30].

Perioperative variables

Table 4 summarizes the results of meta-analysis of perioperative outcomes. The statistically significant differences in pooled estimates suggest a benefit of HoLEP over TURP for catheterization time (17·7–31·0 *versus* 43·4–57·8 h

Table 2 Baseline characteristics

	No. of patients	Age (years)	Qmax (ml/s)	PVR (ml)	PdetQmax (cmH_2O)	IPSS	Prostate size (g)	Schäfer grade
Gupta *et al.*[29]								
HoLEP	50	65·8(10·1)	5·2(4·4)	112·0(155·9)	n.r.	23·4(4·5)	57·9(17·6)	n.r.
TURP	50	65·7(7·5)	4·5(4·7)	84·0(129·7)	n.r.	23·3(3·9)	59·8(16·5)	n.r.
P		n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
Tan *et al.*[32]								
HoLEP	30	71·7(1·1)	8·4(0·5)	113·5(15·5)	76·2(4·4)	26·0(1·1)	77·8(5·6)	3·5(0·2)
TURP	30	70·3(1·0)	8·3(0·4)	126·7(21·3)	85·8(5·4)	23·7(1·2)	70·0(5·0)	3·7(0·2)
P		n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
Kuntz *et al.*[30]								
HoLEP	100	68·0(7·3)	4·9(3·8)	238(163)	83·5(34·9)	n.r.	53·5(20·0)	3·8(1·1)
TURP	100	68·7(8·2)	5·9(3·9)	216(177)	87·3(31·4)	n.r.	49·9(21·1)	4·0(1·1)
P		0·52	0·08	0·08	0·65	n.r.	0·15	0·62
Montorsi *et al.*[31]								
HoLEP	52	65·1(7·3)	8·2(3·2)	n.r.	77·3	21·6(6·7)	70·3(36·7)	n.r.
TURP	48	64·5(6·4)	7·8(3·6)	n.r.	81·8	21·9(7·2)	56·2(19·4)	n.r.
P		0·21	0·61	n.r.	0·67	0·83	< 0·050	n.r.

Values are mean(s.d.). HoLEP, holmium laser enucleation of the prostate; TURP, transurethral resection of the prostate; Qmax, peak urinary flow rate; PVR, postvoid residual volume; PdetQmax, detrusor pressure at Qmax; IPSS, international prostate symptom score; n.r., not reported.

Table 3 Urodynamic measurements, quality of life and symptom scores before and at 6 and 12 months after treatment

	Baseline		6 months		12 months	
	HoLEP	TURP	HoLEP	TURP	HoLEP	TURP
Qmax (ml/s)						
Gupta *et al.*[29]	5·2(4·4)	4·5(4·7)	23·1(1·2)	20·7(1·3)	25·1(1·1)	23·7(1·6)
Tan *et al.*[32]	8·4(0·5)	8·3(0·4)	26·4(1·8)	20·8(2·3)	21·8(2·1)	18·4(2·8)
Kuntz *et al.*[30]	4·9(3·8)	5·9(3·9)	25·1(6·9)	25·1(9·4)	27·9(9·9)	27·7(12·2)
Montorsi *et al.*[31]	8·2(3·2)	7·8(3·6)	23·1(8·6)	26·5(15·5)	25·1(7·2)	24·7(10·0)
PVR (ml)						
Gupta *et al.*[29]	112·0(155·9)	84·0(129·7)	< 20	< 20	< 20	< 20
Tan *et al.*[32]	113·5(15·5)	126·7(21·3)	33·7(5·5)	51·8(14·5)	n.r.	n.r.
Kuntz *et al.*[30]	238(163)	216(177)	4·8(12·5)	16·7(16·9)	5·3(15·3)	26·6(60·4)
Montorsi *et al.*[31]	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
QOL						
Gupta *et al.*[29]	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
Tan *et al.*[32]	4·8(0·2)	4·7(0·2)	1·6(0·3)	1·5(0·2)	1·5(0·5)	1·4(0·3)
Kuntz *et al.*[30]	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
Montorsi *et al.*[31]	4·6(1·1)	4·7(1·0)	1·0(0·8)	0·6(0·2)	1·4(0·9)	0·8(1·3)
IPSS						
Gupta *et al.*[29]	23·4(4·5)	23·3(3·9)	5·2(0·3)	6·1(0·4)	5·2(0·2)	5·6(0·3)
Tan *et al.*[32]	26·0(1·1)	23·7(1·2)	6·0(1·0)	4·8(0·7)	4·3(0·7)	5·0(0·9)
Kuntz *et al.*[30]	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
Montorsi *et al.*[31]	21·6(6·7)	21·9(7·2)	3·9(2·9)	2·9(2·6)	4·1(2·3)	3·9(3·6)

Values are mean(s.d.). HoLEP, holmium laser enucleation of the prostate; TURP, transurethral resection of the prostate; Qmax, peak urinary flow rate; PVR, postvoid residual volume; QOL, quality of life; IPSS, international prostate symptom score; n.r., not reported.

respectively; $P < 0{\cdot}001$), hospital stay (27·6–59·0 *versus* 48·3–85·5 days; $P = 0{\cdot}001$) and blood (haemoglobin) loss (1·30–1·32 *versus* 1·29–1·80 mg/dl; $P = 0{\cdot}022$). In contrast, pooled estimates of the difference favoured TURP over HoLEP for duration of operation (33·1–73·8 *versus* 62·1–94·6 h respectively; $P = 0{\cdot}001$). Once again there was significant heterogeneity for most outcomes variables. Sensitivity analysis identified the study reported by Kuntz and colleagues[30] as the main source of heterogeneity for duration of operation, catheterization time and hospital stay.

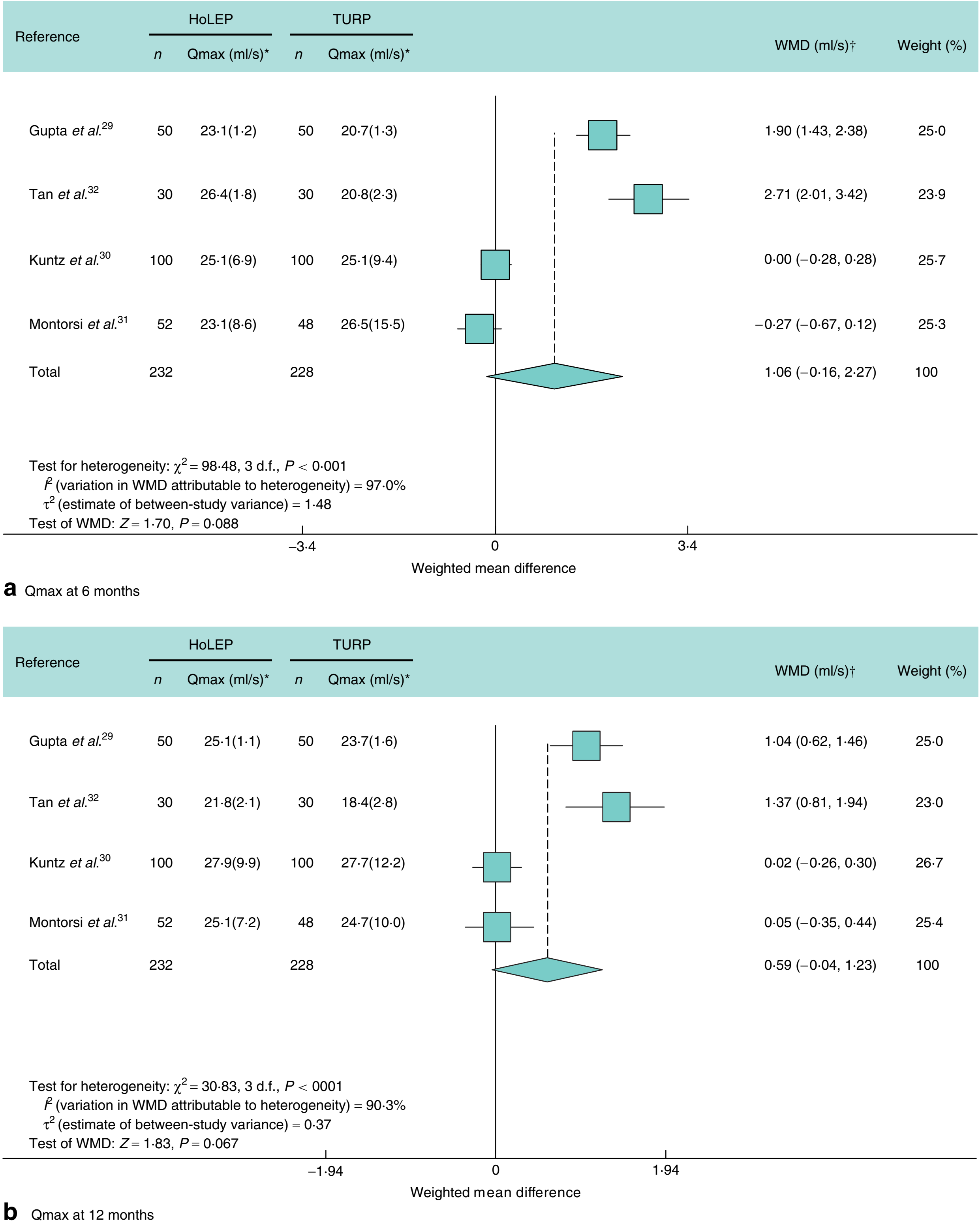

Fig. 2 Meta-analysis of peak urinary flow rate at 6 and 12 months after treatment. *Values are mean(s.d.); †values in parentheses are 95 per cent confidence intervals. HoLEP, holmium laser enucleation of the prostate; TURP, transurethral resection of the prostate; WMD, weighted mean difference; Qmax, peak urinary flow rate

Table 4 Meta-analysis of perioperative data and adverse events

	No. of patients		Pooled difference estimate	*P*	I^2 (%)*	Difference in favour of
	HoLEP	TURP				
Perioperative data						
Duration of operation (h)	232	228	1·81 (0·73, 2·90)	0·001	95·8	TURP
Catheterization time (h)	232	228	− 1·79 (− 2·65, −0·93)	<0·001	93·1	HoLEP
Hospital stay (days)	182	178	− 2·39 (− 3·82, −0·95)*	0·001	96·1	HoLEP
Blood (haemoglobin) loss (mg/dl)	152	148	− 0·27 (− 0·50, 0·04)	0·022	66·7	HoLEP
Adverse events						
Urethral stricture	232	228	0·59 (0·22, 1·58)	0·944	0·6	None
Stress incontinence	202	198	0·97 (0·20, 4·76)	0·980	0	None
Blood transfusion	180	180	0·27 (0·05, 1·64)	0·140	0	None
Reintervention	232	228	0·50 (0·24, 1·03)	0·059	0	None

Values in parentheses are 95 per cent confidence intervals. *Test for heterogeneity. HoLEP, holmium laser enucleation of the prostate; TURP, transurethral resection of the prostate.

Adverse events

Table 4 shows the adverse events after treatment. No statistically significant differences between pooled estimates were noted between HoLEP and TURP for urethral stricture (2·6 *versus* 4·4 per cent; $P = 0{\cdot}944$), stress incontinence (1·5 *versus* 1·5 per cent; $P = 0{\cdot}980$), blood transfusion (0 *versus* 2·2 per cent; $P = 0{\cdot}140$) and reintervention (4·3 *versus* 8·8 per cent; $P = 0{\cdot}059$). However, the composite complication rates were 19 of 232 in the HoLEP group and 37 of 228 in the TURP group, with a statistically significant difference in the pooled estimates ($P = 0{\cdot}019$). Funnel plots detected no obvious publication bias ($P = 0{\cdot}170$, Egger's test).

Discussion

Meta-analysis showed that HoLEP was as effective as TURP in improving subjective symptoms and urodynamic measurements at 6 and 12 months after treatment. The baseline characteristics of the patients enrolled in the studies were similar to those of patients in other trials of surgical intervention for prostate-related bladder outlet symptoms (such as TURP *versus* laser ablation of the prostate[33]), suggesting that the patient population was representative.

Although this study shows HoLEP to have similar therapeutic efficacy to TURP, the former seems superior from a clinical perspective, especially blood loss. This result may be attributed to the haemostatic nature of the holmium wavelength[34]. Bleeding points are coagulated with the defocused beam as they are encountered. The decrease in bleeding with HoLEP results in a decreased transfusion requirement. Based on a subset of 180 patients having HoLEP and 180 having TURP for whom the appropriate information was available, the mean TURP-related transfusion rate in this meta-analysis was 2·2 per cent compared with zero in the HoLEP group. This TURP transfusion rate is lower than that of 5·2 per cent reported by Mebust and co-workers[3], based on a retrospective review of the outcomes of 3885 TURP candidates. Although TURP-related transfusion rates in contemporary series may be lower[35], a recent retrospective study reported no transfusion requirement for patients treated by HoLEP[36]. As the catheter placed at the end of a transurethral surgical procedure is not usually removed until haematuria has decreased significantly, the duration of catheterization in the HoLEP group was significantly less than that in the TURP group.

The mean duration of operation was longer for HoLEP. There are probably two reasons. First, it requires additional time for fragmentation of the prostatic lobes into pieces small enough to be evacuated through the resectoscope sheath[30]. However, a significant decrease in operating time can be achieved by using a mechanical soft tissue morcellator[13,17]. Second, more tissue is removed with HoLEP[31,32]. In some recent series that included large glands of up to 100 g[37,38], the resected weight with HoLEP was much greater, and closer to that retrieved at open surgery. Furthermore, when the efficiency of the two techniques was compared, in terms of weight removed per minute of energy source use, HoLEP was significantly more efficient than TURP[30]. As intraoperative bladder irrigant use is related to the length of the operation[36] – the longer the operation the more irrigant – significantly more irrigant is used during operation with HoLEP than with TURP[29].

This pooled analysis of the literature has also shown that HoLEP reduces the risk of complications. Still, a drawback of the technique is its associated learning curve; substantial skill in endoscopic techniques is needed as well as a precise knowledge of the anatomy and morphology of the bladder neck and prostatic urethra. It has been estimated that trainees must perform 20 to 30 cases on moderately sized glands (50 ml) before they can consistently reproduce good outcomes[39]. Nevertheless, this is probably not much different from the initial learning curve for TURP.

The heterogeneity of some variables in this study is worthy of comment. Four of nine variables exhibited significant heterogeneity (I^2 more than 70 per cent). Explanations may include the following. First, the procedures were performed by different surgeons in each hospital. Second, the trials had different inclusion–exclusion criteria and sample sizes. Third, various different holmium laser enucleation devices, energy sources and power settings were used, potentially affecting outcomes. Finally, there were differences in study design and operative techniques.

To this must be added the fact that the number of the RCTs included is small, which has limited the ability to compare the relative efficacy of the treatments. Prostate size is known to be an important predictor of complications after TURP[3,40] and this varied significantly among studies. Generally patients were included only if they had a relatively large prostate (over 40 ml). Three of the four studies set upper limits for prostate size as part of their inclusion–exclusion criteria. As far as the authors are aware, the selected thresholds for prostate size were arbitrary. In addition, the lack of extended follow-up is an important limitation of this meta-analysis. Only one study[28] provided data at 2 years; this showed no significant difference between the two groups with respect to IPSS, QOL or Qmax, but two patients in the TURP group required reoperation. In general, the data were not adequate to allow assessment of the durability of any observed improvement in urinary flow rates.

This study suggests that HoLEP is a safe and minimally invasive technique that produces results at 1-year follow-up similar to those of TURP in terms of relief of symptoms. Although HoLEP takes longer to perform than TURP, it is associated with significantly less blood loss, and shorter hospital stay and catheterization time. Moreover, the overall rate of complications appears lower after HoLEP. Nevertheless, the conclusions from this study remain somewhat limited by the short follow-up and small sample size.

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