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Holmium laser enucleation of the prostate: a paradigm shift in benign prostatic hyperplasia surgery

Tevita F. Aho

Abstract: Holmium laser enucleation (HoLEP) was developed in the 1990s as a more efficient and cost effective method of benign prostatic hyperplasia surgery than laser vaporization and resection techniques. As a true anatomical enucleation it mimics open prostatectomy and is as durable. There is a significant body of level 1 evidence in support of HoLEP, including 2 meta-analyses and 14 randomized trials which compare HoLEP with a number of other procedures. This review describes the development of and summarizes the evidence for HoLEP.

Keywords: HoLEP, holmium laser enucleation of the prostate, benign prostatic hyperplasia, prostate, lower urinary tract symptoms

Correspondence to:
Tevita F. Aho
Department of Urology, Cambridge University, Addenbrookes Hospital, Hills Rd, Cambridge, CB22 5AN, UK
tevita.aho@addenbrookes.nhs.uk

Introduction

In 1926 when transurethral resection of the prostate (TURP) was introduced by McCarthy, it represented a paradigm shift in benign prostatic hyperplasia (BPH) surgery. However, not everyone was convinced of its merits, and some found it difficult to learn. In 1935 Nathaniel G. Alcock proclaimed that TURP 'cannot be taught and can be learned only by hard, tedious experience' [Hawtrey and Williams, 2008]. Nevertheless, with time, TURP became the gold standard for the surgical management of small to moderate sized obstructive BPH. There are similarities between the TURP story and that of holmium laser enucleation (HoLEP) which, as the first endoscopic enucleation technique for obstructive BPH, is the most recent paradigm shift in BPH surgery. Like TURP initially, there is a perception that HoLEP is difficult to learn. Many aspects of HoLEP, including the learning curve, have been investigated. The aim of this paper is to describe the development of and summarize the published evidence for HoLEP.

History

The limitations and potential complications of TURP and open prostatectomy (OP) are well documented, and have stimulated the search for better surgical techniques [Roos *et al.* 1989; Mebust *et al.* 1989; Rassweiler *et al.* 2006].

Many alternatives to TURP have been investigated in the search for a less morbid, more generally applicable and durable, yet cost-effective procedure. Until the evolution of HoLEP the alternatives consisted exclusively of variations on coagulation, vaporization and resection. Many of these procedures simply shifted morbidity from the perioperative to the postoperative period. None were shown to be more durable than TURP and all were limited by prostate size.

In 1994 Gilling and coworkers, who recognized the shortcomings of Nd:YAG vaporization for BPH [Reek *et al.* 2001; Keoghane *et al.* 2000], realized that the holmium:YAG laser was better suited to endoscopic BPH surgery. They developed holmium laser ablation of the prostate (HoLAP) using a 60 W holmium:YAG laser via a side-firing fibre [Gilling *et al.* 1995]. Although very haemostatic, with little need for postoperative irrigation, short hospital stay and excellent improvements in subjective and objective outcomes when used for small prostates [Mottet *et al.* 1999]; 60 W HoLAP was a slow procedure and the need for single-use side-firing fibres made it expensive.

In order to decrease costs, Gilling and colleagues cut the ends off used side-firing fibres, converting them to end-firing fibres that could then be used multiple times. The end-firing fibres proved to be useful for resecting small pieces of prostate which was faster than vaporizing it. This technique was called holmium laser resection of the prostate (HoLRP) and was the first laser resection technique [Westenberg *et al.* 2004].

Soon, it was appreciated that the tissue plane between prostate adenoma and capsule could be recognized endoscopically, and that the end-firing fibre could be used like a finger in OP to enucleate each lobe of the prostate [Tan and Gilling, 2003]. A tissue morcellator was developed to remove the prostatic lobes from the bladder, and HoLEP was born.

Level 1 evidence

Meta-analyses

In a meta-analysis of 23 randomized, controlled trials (RCTs) comparing monopolar-TURP (M-TURP) or OP with other surgical techniques [bipolar techniques, HoLEP, greenlight photoselective vaporization of the prostate (PVP)], data from 2245 patients was analysed [Ahyai *et al.* 2010]. HoLEP was the only procedure with a statistically significant greater international prostate symptom score (IPSS) reduction (p = 0.005) compared with TURP. HoLEP was also the only procedure with a statistically greater increase in maximal flow rate (Q_{max}) compared with TURP (p = 0.012). There were no statistically significant differences in improvement in quality of life scores (QoL) and postvoid residual volume (PVR) between the procedures.

This meta-analysis also reported on complication rates. There was no TUR syndrome with any of the minimally invasive procedures. Although there were some significant bleeding complications with the bipolar techniques there were few reported for HoLEP (0–5% required secondary coagulation revision), and greenlight PVP (0–3% had secondary haemorrhage). HoLEP was the only procedure that did not require reintervention for recurrent benign prostatic enlargement. Mucosal bladder injury occurred in 0–18% of HoLEP patients and capsular perforation in 0–2%.

A more recent meta-analysis included six HoLEP *versus* M-TURP RCTs. The Q_{max} and IPSS scores were reported to be significantly better for HoLEP at 12 months (p < 0.0001 and p = 0.01, respectively). There were statistically significant benefits for HoLEP in terms of blood loss (p = 0.001), duration of catheterization (p < 0.001), hospital stay (p = 0.001) and transfusion rates (p = 0.04). However, there was a longer operating time (p = 0.001) and more postoperative dysuria (p = 0.003) [Yin *et al.* 2013].

RCTs

There are 14 published RCTs comparing HoLEP with a variety of other procedures [Tan *et al.* 2003; Kuntz *et al.* 2004; Montorsi *et al.* 2004; Gupta *et al.* 2006; Mavuduru *et al.* 2009; Fayad *et al.* 2011; Chen *et al.* 2013; Neill *et al.* 2006; Zhang *et al.* 2012; Elmansey *et al.* 2012; Naspro *et al.* 2006; Kuntz *et al.* 2008; Zhang *et al.* 2007; Aho *et al.* 2005].

M-TURP. All five RCTs comparing HoLEP with M-TURP found HoLEP to have less blood loss, need for irrigation and blood transfusions, shorter duration of catheterization and hospital stay, and at least equivalent improvements in IPSS, Q_{max} and PVR (Table 1) [Tan *et al.* 2003; Kuntz *et al.* 2004; Montorsi *et al.* 2004; Gupta *et al.* 2006; Mavuduru *et al.* 2009]. Tan and colleagues reported superior urodynamic relief of bladder outlet obstruction (BOO) for HoLEP at 6 months (Table 2), whereas Montorsi and colleagues found no significant difference in urodynamic results at 12 months. TUR syndrome has never been reported for HoLEP.

Bipolar-TURP (B-TURP). In a trial of HoLEP *versus* B-TURP it was reported that there were no significant differences in terms of change in serum haemoglobin and sodium, catheter time, hospital time, IPSS, Q_{max} and PVR to 6 months [Fayad *et al.* 2011]. The operative time for HoLEP was longer (110.5 *versus* 76.5 min). Despite the preoperative prostate volumes being similar (76.5 and 80.6 g) for HoLEP and B-TURP, respectively, the weight of tissue removed was significantly greater in the B-TURP group (66 *versus* 56 g). This is in contrast to the M-TURP *versus* HoLEP RCT data for prostates of this size [Tan *et al.* 2003; Kuntz *et al.* 2004; Montorsi *et al.* 2004], which raises a question as to how complete an enucleation was performed in the HoLEP group in this study.

Another study included 280 patients who were randomized to either plasmakinetic TURP or HoLEP. Despite more tissue being removed in HoLEP, it caused less bleeding and, therefore,

Table 1. Outcomes from HoLEP *versus* M-TURP randomized, controlled trials.

	Post-op Irrigation		Transfusion (%)		Catheter time (h)		Hospital stay (h)		IPSS (% change)		Q_{max} (% change)		PVR (% change)	
	HoLEP	TURP	HoLEP	TURP	HoLEP	TURP	HoLEP	TURP	HoLEP	TURP	HoLEP	TURP	HoLEP	TURP
Tan *et al.* [2003]	7%	70%	0	3	17.7	44.9	27.6	49.9	83	79	160	122	70	59
Kuntz *et al.* [2004]	N/A		0	2	27.6	43.4	53.3	85.8	92	82	469	369	98	88
Montorsi *et al.* [2004]	N/A		0	2	31.0	57.8	59.0	85.8	81	82	206	217	N/A	
Gupta *et al.* [2006]	4.2 l	9.1 l	0	2	28.6	45.7	N/A		78	76	387	427	82	76
Mavuduru *et al.* [2009]	19 h	30 h	0	7	46.4	78.2	N/A		81	84	393	302	53	65

HoLEP, holmium laser enucleation; IPSS, international prostate symptom score; N/A, not applicable; PVR, postvoid residual volume; TURP, transurethral resection of the prostate

there was less need for postoperative bladder irrigation, shorter catheter time and shorter length of stay for HoLEP. There were no significant differences in IPSS, QoL, and Q_{max} to 2 years. The authors noted that in their opinion, 'HoLEP should be proposed as a potential new gold standard surgical therapy instead of TURP for patients with BPH' [Chen *et al.* 2013].

Bipolar enucleation. Theoretically, endoscopic enucleation could be performed using any source and an interesting question is: "Which is the best energy source for enucleation?". To date there are two RCTs comparing HoLEP with other energy sources for enucleation [Neill *et al.* 2006; Zhang *et al.* 2012]

In a study of HoLEP *versus* bipolar plasmakinetic enucleation (PkEP) [Neill *et al.* 2006], HoLEP was superior in terms of operative time (mean = 44 *versus* 61 min), postoperative recovery room time (47 *versus* 66 min) and need for postoperative irrigation (5% *versus* 35%). The two energy sources were equivalent in all other perioperative and postoperative outcomes. The three surgeons, who all used both energy sources, felt that visibility was poorer with PkEP due to vaporization bubbles and that it was less haemostatic than the holmium laser.

Thulium laser enucleation of the prostate. In this study, endoscopic enucleation with the holmium and thulium lasers in men with relatively small prostates (mean prostate volume for all patients = 44.7cc) was compared [Zhang *et al.* 2012]. The only statistically significant differences reported were that thulium laser enucleation of the prostate (ThuLEP) took longer to perform (72.4 *versus* 61.5 min), and that HoLEP resulted in greater blood loss (166.6 *versus* 130.1ml). However, there was no significant difference in change in serum haemoglobin (−0.5g/dl for both groups). IPSS, Q_{max} and PVR were followed to 18 months and no differences were noted at any time point.

The authors suggested that the tissue charring and consequent difficulty in recognizing the correct tissue plane that occurs with ThuLEP, and necessitates more blunt dissection than HoLEP, might account for its longer operative time.

Greenlight PVP. Although individually they are the most widely investigated current laser techniques for BPH, HoLEP and greenlight PVP have only been compared head to head in a single RCT

Table 2. Mean urodynamic outcomes HoLEP *versus* TURP [Tan *et al.* 2003].

	Baseline		6 months post-op	
	HoLEP	TURP	HoLEP	TURP
PdetQ_{max} (cmH_2O)	76.2	70.0	20.8	40.7
Schafer grade	3.5	3.7	0.2	1.2

HoLEP, holmium laser enucleation; PdetQ_{max}, detrusor pressure at maximal flow rate; TURP, transurethral resection of the prostate

Table 3. Outcomes from HoLEP *versus* OP randomized, controlled trials.

	Operating time (min)		Specimen weight (g)		Transfusion (%)		Duration of catheterization		Hospital stay (days)	
	HoLEP	OP	HoLEP	OP	HoLEP	OP	HoLEP	OP	HoLEP	OP
Naspro *et al.* [2006]	72.1	58.3	59.3	87.9	5	18	1.5 day	4.1 day	2.7	5.4
Kuntz *et al.* [2008]	135.9	90.6	83.9	96.4	0	13	30.8 h	194.4 h	69.6	251.0

HoLEP, holmium laser enucleation; OP, open prostatectomy

[Elmansey *et al.* 2012]. In this study of men with prostates larger than 60 cm³, the 120 W greenlight High Performance System (HPS) was used.

A total of 22% of PVPs were converted to TURP or HoLEP intraoperatively due to bleeding or inadequate tissue removal. None of the HoLEPs were converted.

Clavien grade 1 complications (analgesics or pelvic floor exercises needed for transient stress incontinence) occurred in 14% of PVP and 26% of HoLEP patients. Clavien grade 3 complications (recatheterization after failed trial without catheter, clot retention or reoperation due to recurrent BPH) were noted in 7% of HoLEPs and 14% of PVPs.

Significantly more tissue was removed by HoLEP (78 *versus* 52% decrease in TRUS volume and 88% *versus* 60% decrease in PSA). This might explain why HoLEP resulted in significantly higher Q_{max} and lower PVR at all follow up points to 1 year, and why retrograde ejaculation (RGE) was more common after HoLEP (88% *versus* 29%).

A median of one fibre per patient was used for PVP, however two fibres were necessary in 33% of patients. For HoLEP, one fibre was used for approximately 20 patients. This has significant cost implications in favour of HoLEP. Whilst HoLEP has been found to be cost effective in a British study [Armstrong *et al.* 2009], greenlight PVP was considered not to be cost effective.

Open prostatectomy. Three RCTs compared HoLEP with OP [Naspro *et al.* 2006; Kuntz *et al.* 2008; Zhang *et al.* 2007].

The study by Naspro and colleagues included patients with prostates >70 cm³ and the trial by Kuntz and colleagues included patients with prostates >100 cm³. Both reported longer operating time for HoLEP, but less blood loss, fewer blood transfusions, and shorter catheter and hospital time (Table 3). Naspro and colleagues reported equivalent improvements in pressure-flow studies at 12 months and no significant differences in IPSS, QoL and Q_{max} to 2 years. Kuntz and colleagues reported equivalent IPSS, Q_{max} and PVR and no reoperations due to recurrent benign prostatic obstruction (BPO) in either group at 5-year follow up.

One RCT was in Chinese and has not been reviewed [Zhang *et al.* 2007].

HoBNI. In a small RCT comparing HoLEP with holmium laser bladder neck incision (HoBNI) for prostates less than 40 g, 79% of patients having

HoLEP were discharged on the day of surgery [Aho *et al.* 2005]. The mean (range) operative time, duration of hospitalization and duration of catheterization for HoLEP *versus* HoBNI were 30 min (18–43 min) *versus* 7 min (2–17 min), 12 h (7–28 h) *versus* 14 h (7–28 h) and 23 h (12–48 h) *versus* 23 h (17–25), respectively. There were no differences in IPSS, QoL or Q_{max} to 12 months, however HoLEP achieved better relief of BOO based on pressure-flow studies at 6 months, and HoLEP was more durable (0 *versus* 20% reoperation for persistent/recurrent BOO at 12 months).

Urinary retention. It has been reported that the proportion of men having BPH surgery for urinary retention has increased over the last two decades [Izard and Nickel, 2010], and that TURP for men in urinary retention is associated with significant morbidity [Gujral *et al.* 2000; Chacko *et al.* 2001]. A recent American study reported a rise in the prevalence of BPH-associated acute renal failure of >400% between 1998 and 2008 [Stroup *et al.* 2011]. A safe and effective procedure for men in urinary retention is therefore a necessity.

HoLEP for acute and chronic retention is as safe as HoLEP for LUTS and allows 98% to remain catheter free at a mean follow up of 5 years with a mean IPSS score of 3.5 and a mean QoL score of 0.8 [Finch *et al.* 2012]. HoLEP for retention has low morbidity [Elzayat *et al.* 2005; Peterson *et al.* 2005].

Large prostates. Men having bladder outlet surgery in the modern era have larger prostates than those undergoing surgery previously [Mayer *et al.* 2012].

A number of studies have shown that HoLEP is safe and effective for men with prostates of any size [Shah *et al.* 2008; Seki *et al.* 2007; Elzayat and Elhilali, 2006]. There is no upper size limit for HoLEP. This is best illustrated by Mandeville and colleagues [Mandeville *et al.* 2012]: in 58 patients with prostate volumes greater than 200 cm^3, 29% of whom were in retention, mean enucleation and morcellation efficiency were 2.8 and 6.3 g/min, respectively. The mean weight of tissue enucleated was 213g, with a mean catheter time of 19.9 h and mean hospital stay of 26 h. One patient required cystostomy to remove the prostate lobes from the bladder due to the lobes filling the bladder. His catheter was successfully removed 48 h later. One developed clot retention and returned to theatre but no bleeding point was found and following clot evacuation the bleeding stopped. One returned at 48 h for completion of morcellation and two patients received blood transfusions. Two patients had perineal urethrostomy to allow the instruments to reach far enough to perform the procedure, and another had a minor bladder mucosal injury from the morcellator which did not alter his management. All were able to urinate postoperatively and there were no secondary procedures at 1-year follow up.

Anticoagulation. Oral anticoagulant (OAC) use is increasing. Descazeaud and colleagues reported that 33% of men listed for bladder outlet surgery were taking an OAC [Descazeaud *et al.* 2011]. Although most urologists would recommend stopping these agents perioperatively, this is not without risk, and even if they are stopped there remains a significant risk of bleeding with M-TURP [Tyson and Lerner, 2009].

HoLEP can be safely performed in fully warfarinized patients or those who are transitioned to low molecular weight heparin, albeit with a higher blood transfusion rate. Elzayat and colleagues reported a transfusion rate of 14% in patients who underwent HoLEP whilst warfarinized or on bridging heparin, which is significantly higher than transfusion rates for HoLEP in those with normal coagulation [Elzayat *et al.* 2006].

In another study that included 13 patients on warfarin with a mean (range) international normalized ratio (INR) of 1.5 (1.2–2.2), 23% required postoperative continuous bladder irrigation but none had intraoperative bleeding problems or required transfusion [Descazeaud *et al.* 2011].

Durability. HoLEP is the most durable endoscopic procedure for BPH. Kuntz *et al.* reported no reoperations for recurrent BPH at 5 years in men with prostates >100g who had HoLEP [Kuntz *et al.* 2008].

At 7-year follow up of a RCT of HoLEP *versus* TURP for prostates 40–200 cm^3, with 51% of patients assessable: none required re-operation for BPH in the HoLEP group *versus* 18% in the TURP group [Gilling *et al.* 2011] .There were no significant differences between groups in terms of IPSS, QoL, Q_{max}, International Index of Erectile Function (IIEF) score, BPH impact index (BPHII) or International Continence Society Short Form Male questionnaire (ICSmale-SF) at 7 years.

The longest published follow up for HoLEP is at 10 years [Elmansy *et al.* 2011]. A total of 10% of the original cohort completed 10-year follow up: mean IPSS, QoL, Q_{max} and PVR were 3.6, 0.7, 26.9 and 20.7, respectively. The re-operation rate due to recurrent BPO was 0.7% during 10 years of follow up.

Sexual function. In a systematic review of RCTs for BPH procedures [Frieben *et al.* 2010], six out of eight RCTs for HoLEP provided erectile function (EF) data without using validated questionnaires, and two of eight used the IIEF. Overall, 7.5% (3.9–11.2%) and 7.7% (0–17%) reported decreased EF after HoLEP and TURP, respectively; and 7.1% (1.7–20%) and 6.2% (0–19%) reported increased EF, respectively. RGE was common after both HoLEP (50–96%) and TURP (50–86%).

In a cohort study of 108 HoLEP patients who completed the Danish Prostate Symptom Score Sexual Function questionnaire preoperatively and at 6 months postoperatively, HoLEP did not significantly affect satisfaction with libido, erections or sex life, or the percentage who were fully impotent [Meng *et al.* 2007]. The occurrence of early morning erections increased from 45% preoperatively to 62% postoperatively. A total of 70% had RGE 6 months post-HoLEP.

The IIEF-15 questionnaire was administered preoperatively and during the first year of follow up in a longitudinal study of 191 sexually active men undergoing HoLEP, holmium laser ablation of the prostate (HoLAP) and greenlight PVP [Elshal *et al.* 2012]. In those having HoLEP, there were significantly improved mean overall scores, erectile function, desire and intercourse satisfaction domains. In HoLAP and PVP there were no significant changes in preoperative to postoperative scores. The incidence of new onset RGE occurred in 77% in the HoLEP group compared with 31% and 33% in the HoLAP and PVP groups, respectively.

HoLEP after previous BPH surgery. Two recent studies compare perioperative parameters and postoperative outcomes for patients who have had previous BPH surgery with those who have not [Jaeger and Krambeck, 2013; Elshal *et al.* 2012]. There were no significant differences in operative efficiency, complication rates or improvements in symptom scores, flow rates and PVRs in either study. Both concluded that HoLEP in those who have had previous BPH surgery seems to be as safe, efficient and effective as HoLEP in *de novo* cases.

Learning curve. Like any surgical technique, the most effective and safest manner in which to learn HoLEP is by mentorship or formal training [Al-Hakim and Elhilali, 2002]. Training programmes for consultants exist in Europe, North America and Asia and it is highly recommended that formal training takes place.

Several authors have published their own self-taught learning curve experiences [Seki *et al.* 2003; Shah *et al.* 2007; Placer *et al.* 2009; Hwang *et al.* 2010]. Despite a lack of mentorship, Placer and colleagues achieved operative efficiencies comparable with TURP at around case 50 and found HoLEP to be a well-standardized and reproducible procedure. The overall results of their first 125 patients in terms of IPSS, QoL, Q_{max} and PVR showed improvements; the transfusion rate of 0.8% and day 1 discharge rate of 89% are equivalent to those of experts. The only significant complication they felt was directly related to the self-taught learning curve was stress urinary incontinence (SUI). At 12-month follow up, six patients (4.8%) still had mild to moderate SUI. Five of these six were amongst the first 40 procedures performed and their mean prostate volume was 98 cm^3 (48–123 cm^3). In the authors' view the most difficult part of HoLEP is the incision of the anteroapical mucosal attachments of the lateral lobes, especially in large prostates. A mishap in this area could result in sphincteric injury. The authors therefore recommend avoiding large prostates in the first stages of the learning curve, and to arrange mentorship for the first cases.

Similar observations were made by Seki and colleagues, Shah and coworkers and Hwang's group, who reported that with regard to patient outcomes and operative efficiency, the self-taught learning curve begins to plateau around case 50.

Lerner and colleagues reported that the major associated risk for SUI during the HoLEP learning curve was time between cases. In their experience, the more frequently HoLEP was performed during the learning curve, the lower the incidence of SUI [Lerner *et al.* 2010].

Conclusion

As the first endoscopic enucleation procedure for BPH, HoLEP is a paradigm shift in BPH surgery.

There is a significant level 1 evidence base to support it, and it is the only BPH procedure to have demonstrated better symptom relief, greater urodynamic improvement and greater durability than TURP. It is safe and effective for prostates of all sizes, men in urinary retention and those who are anticoagulated or have bleeding disorders. HoLEP, therefore, is a valuable addition to the modern BPH surgery armamentarium.

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Conflict of interest statement

The author has given lectures, attended workshops and been a proctor for Lumenis, given lectures for American Medical Systems and Olympus.

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