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In 2013, Holmium Laser Enucleation of the Prostate (HoLEP) May Be the New 'Gold Standard'

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Abstract In this review article, we assess why holmium laser enucleation of the prostate (HoLEP) has become an important treatment modality for benign prostatic hypertrophy (BPH). Meta-analysis comparing HoLEP with both open prostatectomy (OP) and transurethral resection of prostate (TURP) shows TURP to be as effective with less morbidity. More recently, HoLEP has long-term durability data confirming a very low reoperation rate. This article investigates how previous hurdles to the widespread uptake of HoLEP have been overcome. Recent literature shows that the learning curve is actually similar to many other current urological procedures, and that the efficiency of HoLEP is equal to that of other surgical procedures. HoLEP is also beneficial in the growing population of men on anticoagulation who require treatment for BPH. Finally, HoLEP is the only laser treatment for BPH with level 1 evidence and endorsement in both the American Urological Association (AUA) and European Association of Urology (EAU) guidelines.

Keywords Holmium · Laser therapy · Benign prostatic hypertrophy · BPH · HoLEP · Morcellation · Lower urinary tract symptoms

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Introduction

Benign prostatic hypertrophy (BPH) causing lower urinary tract symptoms (LUTS) is a significant health issue for men as they get older. By their 80s, nearly 50 % of men have moderate to severe LUTS, causing reduction in quality of life and requiring some sort of treatment [1]. The treatment algorithm for the management of this condition has changed dramatically over the last decade. Innovations in medical therapies and also in surgical options have created a variety of choices for patients. This is reflected in the American Urological Association (AUA) 2010 BPH guidelines advising the urologist to discuss the benefits and risks of a wide variety of interventions when planning management [2]. A patient ideally wants a procedure that will cure symptoms long-term with minimal complications, and that provides a short recovery time and immediate relief! Holmium laser enucleation of the prostate (HoLEP) is a procedure that, over the last sixteen years, has proven to have achieved this goal in clinical practice, when compared with other interventions.

A laser's wavelength and characteristics dictate how it can be effectively used for treatment of BPH. The holmium: yttrium-aluminum-garnet (Ho:YAG) laser's pulsed wavelength is 2140 nm; this means it is strongly absorbed by water. Therefore, during an endoscopic procedure with normal saline irrigation and with prostate tissue having a high water content, this absorption produces for a shallow penetration depth and outstanding haemostasis [3•]. This wavelength also provides versatility for the urologist by allowing other uses of the laser, such as treatment of urinary tract stones that are often encountered in patients with BPH.

It is important to understand the many laser acronyms that now abound in the BPH literature as they are not interchangeable. Even if the same laser is used, the procedures themselves are quite different. A laser can essentially be used in four ways to treat BPH: coagulation, non-contact

vaporisation, resection/ vapour-resection, or enucleation. Holmium lasers were first used for treating BPH in 1994 [4], and moved through the various methods of laser treatments described above to what we currently understand as HoLEP. Enucleation was developed, aiming to perform an open prostatectomy endoscopically. The process involves completely resecting the transitional zone of the prostate using anatomical planes and morcellation of this tissue inside the bladder, to enable entirely endoscopic tissue extraction [3•]. Nineteen years after the introduction of holmium prostatectomy, we will address the current advances in this technology and look at where HoLEP is going in the future.

The Evidence from Meta-Analysis

Meta-analysis is important in helping to interpret the surgical literature. Properly carried out, it can contribute high-level evidence to clinical questions, and therefore the results are important. Often a new technology is introduced with much fanfare, but before adopting it, there is the necessity of quality evidence supporting its claims. All too often, for many surgical techniques, the quality of this evidence can be lacking, or of poor quality, consisting mainly of retrospective reviews or expert opinion [5]. It is well understood in the pharmaceutical industry that there is the need to show, with robust evidence, that a product is effective when compared with the current "gold standard". The level of evidence required is usually at least one prospective double-blind randomised controlled trial. However, in general, this study would need to be repeated and then combined with other trials to form a meta-analysis to provide the robust evidence required for a product's use. In establishing the HoLEP technique, we and others have attempted to mirror the pharmaceutical industry's approach, by performing randomised prospective trials comparing HoLEP with the "gold standard" treatments. For prostates less than 100 g, transurethral resection of prostate (TURP) has for many years been seen as the gold standard for surgical treatment of BPH. For glands greater then 80 g, the gold standard treatment has been open prostatectomy (OP) [6]. These comparative trials of HoLEP vs. the "gold standards" have culminated in meta-analyses that provide the most robust level of evidence for HoLEP in the treatment of BPH.

In 2007, Tan et al. published a meta-analysis of HoLEP vs. TURP [7]. Four randomised controlled trials met their inclusion criteria, and included 232 participants in the HoLEP arm and 228 in the TURP arm. At follow-up of 1 year, they found that HoLEP was similar in effectiveness to TURP for improvement in quality of life (QOL) and International Prostate Symptom Score (IPSS). It was also similar in improvement for maximum flow rate and residual volume. Perioperatively, patients in the HoLEP arm had decreased hospital stays and decreased catheter times when compared with TURP, with an increased mean duration of operation noted for the HoLEP procedure. Adverse outcomes were similar between the two groups, with zero blood transfusions in the HoLEP arm vs. 2.2 % for TURP. The stricture rate at one year was 2.6 % for the HoLEP group vs. 4.4 % for the TURP group. The overall complication rate tended to be less in the HoLEP arm. These same results were echoed in another meta-analysis by Ahayi in 2010 [8•], and have also been subsequently published in recent critical review articles discussing laser technology for BPH management [9•].

A criticism of these meta-analyses is that there could always be more trials to increase precision in results and to decrease heterogeneity between studies. However, with HoLEP already performed in so many centers around the world, more randomised control trials of its effectiveness are not required for its acceptance. Instead, the shift has been towards proving its durability and improving the technical aspects of the procedure, particularly with new technologies becoming available. We need to remember HoLEP is the most studied of all laser treatments for BPH management. The meta-analysis results show it to be just as effective as TURP, while providing advantages in perioperative and postoperative morbidity. This is a result that we should discuss with our patients who are searching for the ideal treatment for their LUTS.

Durability is Superior

One of the key criticisms of laser technology for treatment of BPH has been the lack of long-term data to show its durability. If a procedure has decreased morbidity at the time of operation, but a patient requires re-intervention early or often, it will not be accepted as standard treatment. Surfacing in the literature now are a number of papers published showing very low long-term reoperation rates for HoLEP. As discussed earlier, it is important to compare these long-term rates with the "gold standard" of TURP and OP. A recent publication quoted the 8-year reoperation rate for TURP as 7.4 %, and 2–5 % for OP at 5 years [10, 11].

Gilling et al. recently published their 7-year follow-up of a randomised control trial comparing HoLEP with TURP for prostates 40–100 g [12••]. Of the original 61 patients, they were only able to follow up on 31 (17 TURP, 14 HoLEP). No one in the HoLEP group at seven years had required reoperation, while three in the TURP group had. There was a significant drop off in numbers, which reflects how difficult it is to follow up a geographically dispersed elderly population for a long duration. Although these were small numbers, the groups were similar at baseline, and randomised as part of a trial. Other centres have also recently published their long-term data on HoLEP outcomes in

large cohorts. Krambeck et al. recently published their experience of over 1,000 HoLEP procedures from the years 2000–2010 [13]. Being a referral centre taking many patients from out-of-state, they only have greater than five year follow-up data for 83 patients. However, of these 83 patients, only one required surgery for regrowth of adenoma. Krambeck et al. also found low rates of significant stricture formation (2.3 %) and bladder neck stenosis (1.5 %). In this series, they also investigated rates of long-term stress incontinence, as this is a potential concern for any endoscopic procedure. Krambeck et al. showed that although early transient stress incontinence was noted on occasion, the long-term rates of stress incontinence were very low. This compares favourably with other series for TURP and OP [14].

OP is seen as the most durable procedure for large prostates [11], and hence this gold standard was compared with HoLEP by Kuntz in a randomised controlled trial [15]. At 5 years, there were still 74 patients (61 % of the original recruitment) available for analysis. They showed a reoperation rate of 5 % in the HoLEP group and 7.4 % in the OP group. These results reflect the growing evidence from a number of different centres about the long-term durability of HoLEP. This has been presumed by experts in the field for a long time, as the technique actually removes the entire adenoma rather than just opening a channel that is likely to regrow and require further treatment. In 2013, we can say to our patients that HoLEP, unlike other procedures, is indeed durable when compared with TURP and OP.

Learning Curve and Operating Time

Review articles on BPH surgery often describe the perceived steep learning curve of the HoLEP technique [9•]. With modern audit tools and an increased awareness of patient safety, recent surgical literature has focused on learning curves in surgery and perceived number of procedures required for competency for different operations [16]. Gone are the days of a surgeon seeing a new technique and performing it the next day. Instead, mentorships and modular learning have been shown to ensure patient safety while allowing a surgeon to reach competency at a faster rate [17]. This is very true of the HoLEP literature, where unmentored surgeons have published high rates of complications when compared with other series. Shah et al. critically analysed what actual number of HoLEP procedures were required to gain competency, and found this to be 20 when mentored, with a plateau of around 50 cases [18]. When we compare the number of procedures required to become competent in other urological procedures, such as open or robotic radical prostatectomy or laparoscopic nephrectomy, the published numbers for competency is much higher than for HoLEP [19, 20]. Interestingly, there is no literature that clarifies the learning curve for TURP or OP. Schout et al. searched, and were unable to find any references to this in their article investigating the pitfalls of TURP [21]. The so-called "steep learning curve" for HoLEP is often propagated by established urologists who trained in an era when TURP was the only option, and so found crossing over to a new technique to be more difficult initially. Unfortunately (or fortunately!) the urologist in training now is no longer exposed to the large number of TURPs required to master this difficult procedure [22]. From our institution's experience, residents pick up the technique of HoLEP as fast, if not faster than, TURP. HoLEP is often portrayed as the operation of a gifted few. If this was the case, there would not be centers on all continents performing HoLEP, with exponential growth in some regions.

Another argument that is used against HoLEP is a longer operating time when compared with TURP and OP. The first point that needs to be elucidated from papers is whether or not morcellation of tissue has occurred. Morcellation is the current standard of care, but some of the earlier reports of HoLEP involved electrocautery resection of tissue, hence making it a longer operation. The second point is whether the paper reports total operation time or resection efficiency. If you take out more tissue, it would implicitly seem logical that the operation should take longer. This is often found when comparing absolute times between TURP and HoLEP, with total operation time longer for HoLEP, but also more tissue removed by HoLEP [23]. Recent evidence published by Ahyai et al. shows that the efficiency of tissue resection is the same for TURP vs. HoLEP, and actually improves for HoLEP as the gland gets larger (0.61 vs. 0.51 g per minute) [24•]. Their data also looked at OP and showed no difference in the efficiency of tissue removed between HoLEP and OP. As HoLEP,uses saline rather than glycine, as in a traditional TURP, there is no risk of TURP syndrome from hypo-osmotic fluid reabsorption and the operative time factor is less critical. It is interesting that while 1gm/min has been traditionally quoted for TURP, current series calculate it at around half this figure. Other papers have assessed resection efficiency, and have found similar resection speed with HoLEP, confirming that as a surgeon's experience increases, so to does their efficiency [25].

Morcellation

One of the key advantages of HoLEP is its ability to treat any size of prostate. However, as more tissue is enucleated, there is more tissue to be extracted. Therefore, morcellation impacts greatly on the length of surgery, and can range between 18–30 % of the total operating time [25]. If methods of morcellation could be improved, this would decrease total operating time and increase the efficiency of the process. Not only does morcellation need to be efficient, but it

needs to be carried out safely to avoid bladder injury. Currently, there are two models available (produced by Lumenis and R.Wolf). Recent research has attempted to find a model that can be used to compare morcellators for future development. Ritter et al,, using bovine pericardium, compared the current models with two prototype morcellators [26]. There was a difference between the two current models in rates of morcellation, with the Wolf Piranha being faster than the Lumenis VersaCut. Interestingly, one of the prototypes tested had a rate of morcellation per minute that was much faster than all current models. However, Cornu et al. found the opposite result when they used baked chicken meat, with the Lumenis morcellator faster than the Wolf model [27]. This highlights the difficulty of developing a standardized model and using it to compare morcellators. If, in the future, these newer prototype morcellators prove to be safe for use in humans, they may further improve the efficiency and safety of the HoLEP procedure.

Guidelines

With the increased standardization of care of patients in all areas of medicine, guidelines from reputable societies and organizations have become an essential part of clinical practice. Guidelines take the breadth of the medical literature and critically appraise this into concise, clinically appropriate formats. Hence, they have become the primary source of information for many practitioners when approaching clinical decision-making. In the area of BPH and LUTS, both the AUA and EUA have current guidelines for diagnosis and treatment [2, 28]. In the latest update of the guidelines by the AUA in 2010, laser therapy, and specifically HoLEP, is now included as an appropriate surgical management option for men with symptomatic LUTS, even for very large prostates. In the EUA guidelines, the HoLEP literature was judged as Grade A for both effectiveness and long-term durability when compared with TURP and OP. These guidelines confirm that HoLEP is now established as a treatment for BPH, rather then an emerging technology as previously stated. It highlights that this technique can be safely introduced in any appropriate practice, and that patients desiring optimal outcomes with decreased morbidity should choose this approach.

Despite guidelines and their recommendations, new techniques continue to be investigated to optimize patient management of BPH. Interestingly, there have been a number of recent reports of enucleation by robotic simple prostatectomy in the literature [29]. It is obvious that there needs to be a minimally invasive alternative to OP for massive BPH, but HoLEP is already clinically proven for even the largest of prostates. Robotic surgery is widely used for radical prostatectomy; however, proving that it is feasible to transfer the techniques to the management of BPH does not necessarily justify its use. Currently, there is no evidence to show that it is as cost effective as, and less invasive, more efficient, less comorbid or easier to learn than HoLEP. Outside of a trial situation, no guidelines yet endorse this treatment [2]. It does, however, further legitimize enucleation as the standard for the surgical treatment for BPH.

Anticoagulated Patients

A large number of men who require surgery for BPH have comorbidities that require some form of anticoagulation medication [30]. It is becoming more apparent that stopping these even for a short period of time can place these men at significant risk of adverse outcomes. As urologists, we are often unaware of the complications that these patients suffer postoperatively, as they are usually treated by doctors from other specialities. We are all well aware of the dangers of stopping drugs such as warfarin, but quite readily stop aspirin before endoscopic surgery to avoid the risk of haematuria with little thought of the cardiovascular complications. There is growing evidence that this practice should be abandoned. In the Annals of Surgery 2012, Gerstein et al. reviewed the evidence around perioperative aspirin use and concluded that stopping aspirin perioperatively caused a significant increase in cardiovascular events [31•]. This is likely due to the combination of the “aspirin withdrawal syndrome”, the hypercoagulable state of surgery, and these patients being inherently at risk for these events. Adverse bleeding outcomes for those continuing aspirin during surgery when analaysed were minimal. When broken down into specific operations, for ear, eye, spine and brain surgery, stopping aspirin could be justified due to the danger of increased bleeding in a confined space. Interestingly for TURP, Gerstein et al. found that there was justification to stop aspirin due to the increased bleeding rates, which points more to a failing of TURP than a need to stop aspirin prior to surgery for BPH. HoLEP has less blood loss than TURP, and there is now data showing its safety in those on anticoagulation medication [32]. Tyson et al. retrospectively compared 39 patients on anticoagulation medication (warfarin or aspirin) with 36 control patients having HoLEP [33]. There was no increase in bleeding complications, and Tyson et al. concluded it was safe for patients to remain on anticoagulation medication during HoLEP. In our own institution, all patients on aspirin continue this perioperatively, and patients on warfarin are managed on a case-by-case basis, in discussion with the cardiologist. With such strong evidence showing the dangers of stopping aspirin in the perioperative period, we likely do our patients a disservice by stopping this when not required. With so many men with BPH on aspirin and with this number likely to continue to rise, strong consideration could be made for HoLEP to be a standard of care compared with TURP.

Conclusion

Nineteen years after its introduction, holmium prostatectomy, and specifically HoLEP, continues to prove its effectiveness and durability as a treatment for BPH. Meta-analyses also attest to this, and the international guidelines confirm how well established HoLEP has now become. The future is exciting for HoLEP, with continued modification of the technique and development of new supporting technologies. As its popularity continues to grow, the previous arguments against HoLEP have been replaced with an acceptance of its place and an understanding of the high quality evidence underpinning its use.

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- •• Of major importance

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