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A Review of Laser Treatment for Symptomatic BPH (Benign Prostatic Hyperplasia)

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Abstract Benign prostatic hyperplasia (BPH) is the predominant cause of bladder outflow obstruction and is associated with significant morbidity. Surgical removal of adenoma has been a key treatment principle for alleviation of obstruction. Lasers have been used as an alternative to transurethral resection of the prostate (TURP), due to the higher complications of the latter procedure, since the early 1990s. Early generations of lasers utilized coagulative and ablative techniques to dis-obstruct the bladder. Ablative techniques have remained popular with the resurgence of 532-nm vaporization (commonly known as GreenLight). Enucleation techniques especially with the holmium laser have shown durable efficacy in randomized controlled trials whilst new modalities such as thulium still require long-term data. This review examines the most common types of laser technology used in BPH surgery, with a focus on efficacy and side effect profile.

Keywords Benign prostatic hyperplasia · Laser · Enucleation · Ablation · Efficacy · Complications

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Introduction

Transurethral Resection of the Prostate (TURP) has been regarded as the 'gold standard' for the transurethral treatment of symptomatic bladder outflow obstruction secondary to benign prostatic hyperplasia (BPH). However, TURP carries the risk of significant complications such as bleeding and TUR syndrome in addition to a long learning curve for the surgeon. The advent of laser technology has led to several therapies that rival, and potentially even surpass the efficacy of TURP with fewer complications [1–3]. Amongst these laser therapies, Holmium Laser Enucleation of the Prostate (HoLEP) appears to be the laser technique that rivals and exceeds TURP, with an extensive body of supporting literature that has confirmed both durable and reproducible clinical results, with few adverse effects [1–5]. In addition, there are several laser wavelengths for which evidence is being compiled, namely the thulium and diode systems and vaporization using the 532-nm device (KTP, LBO). Nd-YAG will also be discussed briefly, as one of the early prostatic laser therapies; however, it has been superseded by the other laser methods mentioned. Each laser has unique properties resulting in a variety of possible techniques, ranging from vaporization to resection and enucleation. The aim of this review is to outline and evaluate current laser therapies which have been proposed as alternatives to TURP for the surgical treatment of BPH, using the most recent evidence available.

Current Laser Wavelengths

Holmium:YAG

Mechanism of Action

The holmium laser is delivered through small flexible low-water content quartz fibres and releases energy in short pulses.

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The absorbing chromophore for holmium laser energy is water, and with a wavelength of 2140 nm and penetration depth in prostate tissue of 0.5 mm means that beyond this distance, energy is dissipated in cellular and extracellular water and has no deep thermal effect on tissue [6]. Due to the high water content of prostatic tissue, which leads to excellent thermal conductance, the holmium laser allows the operating surgeon to either coagulate or ablate. The pulsed nature of the wavelength also contributes to its ability to vaporize tissue and aids in the dissection necessary for enucleation. Furthermore, haemostasis is independent of the patient's coagulative state making it ideal for use in patients on anticoagulant therapy [6].

Use and Effect in BPH Surgery

Holmium energy was first used in the prostate in conjunction with Nd:YAG in 1994. Following coagulation with the Nd:YAG wavelength (1064 nm), holmium was used to create a channel using vaporization and incision. The procedure was termed Combination Endoscopic Laser Ablation of the Prostate (CELAP). The neodymium component was omitted in favour of a holmium-only approach using a side-firing fibre in the technique named Holmium Laser Ablation of the Prostate (HoLAP) [7]. This was subsequently modified to enable direct resection of adenomatous tissue using an end-fire fibre resulting in the procedure known as Holmium Laser Resection of the Prostate (HoLRP). With the introduction of a mechanical soft-tissue morcellator, Holmium Laser Enucleation of the Prostate (HoLEP) evolved from the resection experience. HoLEP has continued to grow in popularity as different holmium lasers and morcellators have been produced but also due to its continued favourable outcomes from a range of authors [8, 9].

During HoLEP, the laser fibre is stabilized in the end of the endoscope using a modified inner sheath and a ureteric catheter which enables the surgeon to control both the laser and endoscope at the same time (Fig. 1). Formerly, the initial incisions were made at the 5 o'clock and 7 o'clock and enucleation of the middle lobe preceded that of the lateral lobes [6, 10] however a two-lobe technique is now favoured in our opinion. After haemostasis, the enucleated tissue is morcellated and evacuated.

Efficacy

The efficacy of HoLEP is well established with consistent, statistically significant results across a range of studies, including multiple randomized controlled trials. Promising early outcomes were first reported by Gilling et al in 1998, in a prospective study of 64 patients with a mean prostate size of 75.3 cm^3, with statistically significant improvements in Qmax (8.9 to 23.4 ml/s at 1 month) and AUASA (23 to 8.6) [7]. This has subsequently been reproduced in both prospective and retrospective studies, the largest of which is a retrospective study with a sample size of 1065 [11]. Qmax improvements range from increases of 157 to 470 %, whilst PVR is reduced by at least 80 % [11–17]. More importantly, HoLEP has shown efficacy using validated symptom scores such as IPSS and AUASA, with reductions of greater than 70 %, as well as more than 60 % improvement in QoL or HRQL scores [5, 11–18]. These improvements have been sustained in long-term studies, including an RCT by Gilling et al. with a 7-year follow-up period, as well as the large retrospective analysis from Elmansy et al which had a 10-year follow up [5, 12].

Several studies have also looked at the efficacy of HoLEP based on patient factors such as prostate size and age. The safety and efficacy of HoLEP in large prostates (>100 g) was confirmed as early as 2000, with comparable efficacy to open prostatectomy (OP) and lower perioperative morbidity [19–22]. In 2007, 5-year follow-up results from the initial RCT comparing HoLEP to OP in large prostate sizes showed sustained benefits in AUASA, Qmax and PVR with no difference in complication rates [20]. More recently, Kim et al performed a retrospective analysis looking at the use of HoLEP in extremely large prostate sizes (>200 g), and although IPSS and Qmax showed beneficial 6-month results comparable to outcomes in smaller and moderate sized prostates (<100 ml, 100–200 ml, respectively), the sample size for patients with prostate size > 200 g was small ($n = 6$) [kim 2015]. Extremely large prostates also had longer operative time, higher rates of

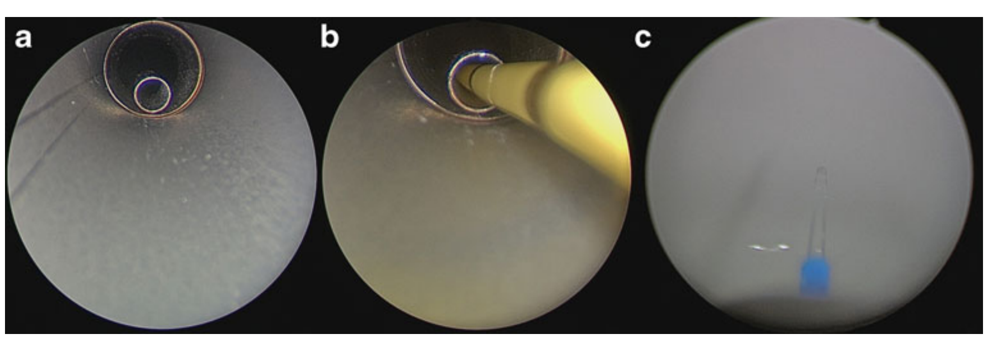

Fig. 1 The Karl Storz resectoscope is used for holmium enucleation (Catalogue number 27040 XAL). The inner sheath of the resectoscope has a metal insert (**a**) which allows a ureteric catheter to be placed through it (**b**). This protects the laser fibre from damage and the final view is unobscured by the ureteric catheter (**c**)

transient dysuria, longer postoperative recatheterization and hospitalization [23]. However, as in previous studies, there was no increase in significant complications such as bleeding requiring transfusion, reoperation or conversion to TURP; leading to the conclusion that HoLEP can be performed safely and effectively in extremely large prostates with the caveat that sufficient experience is recommended due to the technical difficulties associated with navigating the large prostate [20–24].

A meta-analysis by Yin et al comparing HoLEP to TURP confirmed that HoLEP is superior to TURP with greater improvements in IPSS and Qmax at 12 months [4]. There was no statistically significant difference in complication rates between the two procedures. Although TURP had a slightly more favourable operative time and postoperative dysuria profile, hospital stay, catheterization and perioperative blood loss all favoured HoLEP making it overall, a highly competitive alternative to TURP [4].

When compared to OP, HoLEP is even more favourable with two key RCTs confirming benefits at up to 5 years of follow-up [20, 21]. Both studies showed that HoLEP has equivalent efficacy to OP with lower perioperative morbidity, shorter hospital stays and shorter catheterization duration, in even large prostates [20, 21].

Complications

In the largest retrospective study available with a sample size of 1065 patients, the most common adverse effect reported was transient urinary incontinence – both stress and urgency – at a prevalence of 11-12 % [11]. Following this, bladder neck contracture occurred at rates of up to 6 % and urethral stricture at 1.3 %.

One of the significant benefits of laser energy on the prostate tissue is the ability to thermally coagulate the tissue. This leads to immediate sealing of the blood vessels which also decreases the fluid absorption. In addition, the use of normal saline with lasers markedly reduces incidence of TUR syndrome. This is especially significant when treating large volume BPH (>150 g), as an adequate TURP with a monopolar energy source would be difficult.

Further to the issue of TUR syndrome, significant complications such as significant bleeding, conversion to open procedure, bladder injury and sepsis were very low occurring at a rate of less than 1 % [11]. Risk factors for subsequent urinary incontinence include bladder injury, diabetes mellitus, greater prostate volumes (> 81 g) and greater degree of serum PSA reduction (>84 %) [18, 25]. Early studies have suggested that HoLEP has no statistically significant impact on sexual function; however, these studies have tended not to use validated tools such as the International Index of Erectile Function (IIEF), and it is only relatively recently that sexual function outcomes have been a focus for HoLEP [26]. The largest retrospective cohort study to date looking at sexual function outcomes by Klett et al in 2014 showed that HoLEP has no adverse long-term effects on sexual function [27]. Mean baseline IIEF score of 13.3 did not differ significantly at up to 36 months of follow-up (11.8) [27]. In addition, previous RCTs showed that there was no difference in sexual function related side effects when HoLEP was compared to both TURP and OP [5, 12, 20, 21]. Several studies have also shown that HoLEP has a distinct learning curve, and these complications tend to most commonly occur in this period which is generally agreed to be within the first 30–50 cases of the operating surgeon [28, 29]. Strategies such as the use of simulators in HoLEP training and starting with prostate sizes <80 g have been recommended to minimize the risks associated with the learning curve period [22, 30].

The current body of evidence for HoLEP has validated endoscopic enucleation with fewer complications when compared to both TURP and OP. It is an increasingly widely utilized alternative to TURP which has the potential for superseding it as the gold standard in BPH surgery [9, 31].

Thulium

Mechanism of Action

The thulium (Tm) laser has a wavelength of 2013 nm and a penetration depth of 0.25 mm, using water as the absorbing chromophore [2]. Unlike holmium, energy is released in a visible continuous wave [2]. Two forms of thulium lasers are currently used in clinical practice—Tm-YAG (Revolix) and Tm-fibre (Vela XL) [31].

Use and Effect in BPH Surgery

Similar to holmium, the thulium laser can be used for vaporization, resection or enucleation. First used for BPH in 2005 by Xia et al, a Tm:YAG laser was used for a procedure known as thulium laser resection of the prostate (TmLRP-TT) in which thulium laser is used to resect the prostate into small tissue chips [32]. Another version is known as thulium vaporesection of the prostate (ThuVARP), referring to a combination of vaporization and resection [33, 34]. In 2009, Bach et al then adopted enucleation which became Thulium VapoEnucleation of the prostate (ThuVEP) initially, analogous to HoLEP. Recently, this has been further refined to become thulium laser enucleation of the prostate (ThuLEP), in which the incision is apical rather than the original three-lobe HoLEP/ThuVEP, and blunt enucleation is used more, for dissection to the surgical capsule [34, 35].

Efficacy

Bach et al performed a systematic review in 2010 which pooled data from all thulium laser prostatectomy methods and included 11 studies with an average follow-up period of 16 months. Their review reported mean improvements of: IPSS 14.2 points; QoL 3.2 points; Qmax +14.5 ml/s and PVR 82.8 % [34]. In terms of individual thulium laser techniques, there has been a recent meta-analysis by Tang et al to assess the efficacy of TmLRP (or ThuVARP) specifically. Nine trials which included retrospective, prospective and RCTs, were included. They showed no significant difference in Qmax, PVR, QoL and IPSS at 12 months of follow-up compared to TURP [36]. There are currently no systematic reviews of either of the enucleation techniques.

ThuVEP has been studied in a large case series with a sample size of 1080 patients showing good perioperative and efficacy profile [37]. A follow-up was limited to the immediate postoperative period and improvements in Qmax (+9.5 ml/s) and PVR (-100 ml) were noted on discharge [37]. A subsequent case series in 207 patients with a 12-month follow-up, confirmed these improvements were sustained with QoL 3.2 points; IPSS 16.8 points; Qmax +14.1 ml/s and PVR 132.5 ml [38].

A recent systematic review looking at the use of ThuLEP in BPH has been performed by Kyriazis et al, which included four studies in their final analysis (after one trial was excluded as it was not in English) [39]. The final sample of studies included two RCTs comparing ThuLEP to either TURP or HoLEP, and two prospective cohort studies with follow-up periods of 3 to 24 months. As ThuLEP is still evolving, the main limitations of the review are a lack of studies and the subsequent heterogeneity of the studies included [39]. Early outcomes though are promising, with up to 87 % reduction in prostate volume, comparable Qmax and IPSS improvements when compared to both HoLEP and TURP and reductions in PVR ranging from 69 to 91 % [39–42]. Mean postoperative IPSS ranged from 3.9 to 6.57 with improvements reaching clinical significance (> 4-point difference), and mean postoperative Qmax ranged from 23 to 28.6 ml/s. [39].

Complications

TmLRP has a reduced risk of TUR syndrome, blood transfusion and urethral stricture compared to TURP [36]. Other reported complications include recatheterization, transient urinary incontinence, UTI and retrograde ejaculation; however, rates were comparable to TURP [36]. Complications from ThuVEP are similar as expected; however, postoperative irritative symptoms and bladder neck contracture have also been reported [37, 38]. In terms of sexual dysfunction, although retrograde ejaculation is known to be common, no significant difference in erectile function scores has been seen pre- and postoperatively, or compared to TURP [43]. However, there have been few studies which have included sexual function-related complications in their outcome measures.

ThuLEP has had an encouraging safety profile so far. Reported complications include bleeding requiring transfusion (0.9–2.7 %) in two studies in which large prostate sizes and a more elderly and comorbid sample size, respectively, were noted, bladder wall injuries limited to studies where a mechanical morcellator was used (1.3–5.6 %), recatheterization (1.4–6.8 %), surgical capsule perforation (1.4 %), irritative symptoms (6.7–18.5 %), transient urinary incontinence (0.5–6.7 %), urethral/bladder neck strictures (0–5.6 %) and reoperation (1.7–3.7 %) [39].

Photoselective Vaporization (GreenLight: KTP, LBO)

Mechanism of Action

Photoselective vaporization (PVP) is the collective term referring to the process of ablation used mainly by 532-nm wavelength lasers. Initially, these only included potassium-titanyl-phosphate (KTP) lasers, which are a crystal laser developed from the Nd:YAG laser; however, photoselective vaporization now also refers to the lithium triborate (LBO) lasers which were developed to improve on the performance of the KTP [44, 45]. Both KTP and LBO lasers are marketed as the GreenLight system (formerly called the Niagara system) but other companies also make this wavelength, and thus, PVP is often referred to as GreenLight in the literature but applies to the 532-nm wavelength [44]. As both KTP and LBO lasers have wavelengths of 532 nm, penetration depth for both is 0.8 mm and the absorbing chromophore is haemoglobin [2]. Energy is released in a quasi-continuous wave and ablation is achieved by vaporization [45].

Use and Effect in BPH Surgery

First used in 1998, photoselective vaporization was performed using the 60-W KTP laser, which has undergone a relatively rapid evolution since its introduction [46]. Subsequent developments have led to a range of PVP systems and have been marketed successively by three different companies. These include the 80-W KTP laser, the 120-W high-performance system (HPS) KTP laser (resulting from the addition of LBO crystals) and most recently, the "Xcelerated Performance System" (XPS) or 180-W KTP laser [47]. Whilst the safety and efficacy of the 80-W KTP laser has been established, it has yet to surpass TURP as the gold standard, largely owing to the greater operative time required for 80-W KTP despite comparable improvements in clinical outcomes and minimal complications [47]. It does show particular promise in the treatment of high-risk patients on therapeutic anti-coagulation. Despite an improvement in operative time, the 120-W HPS KTP laser has unfortunately failed to show superiority to TURP in both functional outcomes, as well as reoperation rates; therefore, the role of 120-W HPS KTP has yet to be confirmed, although, like its predecessor, has been shown to have a good safety profile in select patient populations such as high-risk patients [47]. The newest addition to the GreenLight system, the 180-W KTP laser, has just completed a phase IV trial which will be discussed below [48].

Efficacy

The progression of PVP from the initial 80-W KTP laser to the 120-W HPS KTP and subsequently, the 180-W XPS KTP laser has resulted in a large heterogeneous evidence base. Therefore, although PVP refers to all 532-nm laser systems, the change in power settings can lead to different clinical outcomes. Naturally, a need to evaluate each laser system individually is required. A meta-analysis by Thangasamy et al in 2012 sought to evaluate the efficacy of 80-W and 120-W PVP systems against TURP [49]. However, their meta-analysis looked at results from 80-W and 120-W lasers collectively, and did not assess each laser as a separate entity [49]. A total of nine trials were included—five on 80-W lasers, four on 120-W lasers—with sample sizes of 20 to 155 and follow-up periods ranging from 6 to 36 months [49]. In terms of perioperative outcomes, PVP had shorter catheterization time and length of hospital stay but TURP had a shorter mean operative time [49]. Only three studies had 12-month follow-ups so were included in the meta-analysis for Qmax and IPSS outcomes, which showed no significant difference compared to TURP. Seven of the nine studies showed the same result, with varying final follow-up periods [49]. Similar results were published in the meta-analysis performed by Zhang et al, with no significant difference in improvements in IPSS and Qmax compared to TURP. Again, the analysis was performed with studies using either 80 W or 120 W [50]. The most recent meta-analysis by Cornu et al which looked at all transurethral procedures, chose to include only 120 W in their meta-analysis for PVP and again showed no significant difference in IPSS or Qmax compared to TURP. It did, however, have a better perioperative profile with shorter catheterization times, hospital stays and reduced risk of postoperative transfusion [51]. Finally, the most current form of PVP, the 180-W Greenlight XPS laser system, has just completed a phase IV clinical trial in small prostates (19-g resection weight in the TURP arm), with 12-month follow-up data having just been published for the randomized, multicentre noninferiority study known as the GOLIATH study [48]. Using a final sample of 256 patients (130 PVP, 126 TURP), the GOLIATH study showed that a 180-W XPS is non-inferior to TURP with 66.98 % decrease in IPSS, 142 % increase in Qmax and 60.9 % reduction in PVR at 12 months of follow-up [48].

Complications

Perioperative outcomes for 80-W and 120-W PVP are more favourable compared to TURP, with lower risks of postoperative transfusion, clot retention and the complete avoidance of TUR syndrome due to a saline fluid medium rather than glycine [49–51]. No difference in urethral stricture or bladder neck contracture rates was seen between TURP and 80-W and 120-W PVP; however, reoperation rates were significantly higher in PVP [49–51]. The GOLIATH study showed no significant difference in treatment-related adverse events at 12 months, and although reoperation rate in PVP was higher (11.8 vs 15 %), the difference was not statistically significant [48]. Similar to its predecessors, early perioperative outcomes of the 180-W PVP were more favourable than TURP [48]. There is no significant difference in sexual function outcomes in any of the PVP systems when compared to TURP [48–51].

Diode

Mechanism of Action

Diode lasers refer to a group of lasers that function through a semiconductor bar that uses electronic energy to generate laser light and cause tissue ablation through vaporization [2, 31, 52]. Although the absorbing chromophore is haemoglobin and water for all diode lasers, there is a range of wavelengths and, therefore, the penetration depths achieved [2, 31, 52, 53]. For laser prostatectomy, current wavelengths available for clinical application are 940, 980 or 1470 nm with varying penetration depths depending on wavelength [2].

Use and Effect in BPH Surgery

Diode laser prostatectomy can be performed under spinal or general anaesthesia, under cystoscopic guidance and continuous bladder irrigation [chen 2010]. Power settings usually range between 80–200 W and vaporization is achieved without direct tissue contact using a side-firing fibre [54]. After the lateral and median lobes are ablated, the laser is used for haemostasis if required [54]. More recently, diode laser enucleation of the prostate (DiLEP) has been developed, based on a modified HoLEP technique [55]. A 980-nm diode laser is used with a flexible firing fibre and resectoscope, and enucleation is achieved using the 4-U incision technique used in the early HoLEP procedure [7, 55]. Again, similar to HoLEP, a tissue morcellator is used to collect enucleated tissue for histological analysis [55].

Efficacy

Several retrospective studies and case series confirming the safety and efficacy of diode laser vaporization of the prostate have been published; however, we have only found one RCT comparing diode laser vaporization (980 nm) to TURP. This showed that although improvements in Qmax, IPSS and PVR were comparable to TURP at 6 months, the difference could not be sustained and TURP was superior to 980-nm diode laser vaporization at 24 months of follow-up in a sample of 115 patients [56]. Most of the literature is based on this 980-nm diode laser prostatectomy; however, DiLEP seems to be gaining popularity [2, 55, 57, 58]. In a retrospective analysis, Yang et al found perioperative outcomes for DiLEP were more favourable as compared to TURP with shorter postoperative catheterization time and hospital stays [55]. In addition, improvements in IPSS (21.8 to 5), Qmax (6.9 to 16 ml/s) and PVR (103.2 to 36.6 ml) were all comparable to TURP and sustained to up to 12 months of follow-up [55]. When comparing DiLEP to plasmakinetic enucleation and resection of the prostate (PKERP), Xu et al found in their RCT that there was no statistically significant difference in functional outcomes such as IPSS, Qmax, QoL and PVR at 12 months of follow-up in a sample size of 80 patients [57]. The DiLEP group did, however, have significantly shorter operative time, postoperative irrigation and catheterization time compared with the PKERP group. The drop in haemoglobin levels were also less than the DiLEP group. More RCTs and long-term efficacy studies are required to confirm the role of diode laser vaporization.

Complications

The main adverse effects which particularly affect diode laser therapy are irritative symptoms and retrograde ejaculation [2, 55, 57]. Other reported complications include bleeding requiring transfusion, capsule perforation and urinary incontinence; however, there was no statistically significant difference in the frequency of these complications compared to other treatments such as TURP and PKERP [2, 55, 57].

Nd-YAG

Mechanism of Action

Neodymium-yttrium-aluminium-garnet (Nd-YAG) laser is a crystal laser with water and haemoglobin as the absorbing chromophore, a wavelength of 1064 nm and a penetration depth of 10 mm. Tissue ablation occurs via pulsed or continuous coagulation—the basis of initial contact laser prostatectomy procedures [2]. However, due to its low absorption coefficient and tissue penetration depth, Nd-YAG has a greater risk of thermal injury, particularly deep coagulative necrosis which can take up to 3 months to heal completely but form the basis of its effect. [2, 59].

Use and Effect in BPH Surgery

Studies had shown considerable promise in procedures such as visual laser ablation of the prostate (VLAP) and interstitial laser coagulation (ILC) with functional outcomes comparable to TURP [60, 61]. However, more recent studies including long-term randomized controlled studies with follow-up of up to 10 years have resulted in Nd-YAG-based procedures being largely abandoned after TURP was shown to be both superior in functional outcomes, as well as ongoing issues with persistent dysuria [61, 62]. Another significant disadvantage of Nd-YAG, like all ablation procedures, is its inability to obtain tissue for histological analysis, which is likely another reason for its redundancy [2].

Efficacy

Nd-YAG laser prostatectomy has been shown to result in improvements in symptom scores, with a Cochrane review in 2000 approximating a 66 % improvement in symptom score at 12 months, compared to 78 % in TURP [63]. Similarly, Hoekstra et al, confirmed improvements in IPSS of 57.5 % and QoL of 75 % at 10 years of follow-up [63]. However, what Nd-YAG has consistently failed to show has been any significant improvement in Qmax across a range of studies [2, 47, 61, 63]. Despite early promising results, Nd-YAG has failed to rival TURP in the treatment of BPH, and has been effectively superseded by other non-contact laser procedures.

Conclusion

Multiple laser therapies have been developed as less invasive options compared to TURP for the treatment of symptomatic BPH. Currently, the most widely used and well-established laser therapies/techniques are HoLEP and 532-nm ablation. Both have good safety profiles and efficacy equivalent to TURP. The main disadvantage of HoLEP is the well-known learning curve that must be overcome, and PVP is limited by its long operative duration and the variable tissue removal. ThuLEP, ThuVEP and DiLEP are promising new modalities, but require more high-quality RCTs and long-term efficacy studies to compete and compare with TURP. Nd-YAG has been abandoned for its lack of long-term efficacy and variable clinical efficacy.

Compliance with Ethical Standards

Conflict of Interest Shiva Madhwan Nair, Marie Adrianne Pimentel, and Peter John Gilling each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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