Minimally Invasive Therapy for BPH

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Benign prostatic hyperplasia (BPH), a nonmalignant enlargement of the prostate, is one of the most common conditions affecting aging men. Although there is debate regarding its exact definition, the fundamental aspects of the disease include interaction between the prostatic hyperplasia, bladder outlet obstruction, and lower urinary tract symptoms (LUTS) [1,2]. The LUTS associated with BPH can be categorized into voiding symptoms and storage symptoms. The degree to which the symptoms bother the patient and impair quality of life is the key factor for seeking medical treatment from an urologist.

Most men 50 to 80 years old will develop some degree of benign prostatic hyperplasia (BPH). Many who experience lower urinary tract symptoms (LUTS) will be treated medically. Medical therapies widely used today for treating BPH are targeted at relaxing prostate smooth muscle tone, such as α-blockers, or at reducing prostate volume, such as 5-α reductase inhibitors [3]. However, these drugs are not without side effects, such as postural hypotension, retrograde ejaculation and impotence. Transurethral resection of the prostate (TURP) has been a gold standard for treatment of BPH. Nevertheless, there have been concerns about the safety of TURP, with associated long-term morbidity including retrograde ejaculation, bladder neck contracture, and impotence [3,4]. Approximately 15%-25% of patients who undergo surgery do not have satisfactory long-term outcomes. Consequently, there has been much interest in the development of minimally invasive treatments for BPH.

There have been many innovations in the development of minimally invasive therapies for BPH over the last decade [5]. These may be imagined on a continuum between pharmacotherapy and TURP. Among them, injection therapies and laser therapies for BPH have received wide attention in recent years [6-10]. Many studies on injection therapy provide evidence that it may relieve LUTS, but there is less urodynamic evidence for its relief of obstruction. These techniques may also have higher retreatment rates than TURP, indicating a need for repeated therapy. Patients, however, are willing to accept a one-time method if it reduces risks, avoids hospitalization, and has a reliable efficacy. Until recently, laser prostatectomy has not been widely used due to its difficulty and slow resection/vaporization. However, the newly developed neodymium: yttrium aluminum garnet (Nd: YAG), potassium-titanyl-phosphate (KTP) laser therapy reduces anatomic obstruction and relieves LUTS with a degree of efficacy comparable to TURP [9]. In this article we review the results of injection therapy and KTP-YAG laser therapy for BPH.

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INJECTION THERAPY FOR BPH

Intraprostatic injection therapy to reduce prostate volume has been explored since the early 1900s. Indications for treatment have evolved toward LUTS associated with various prostate sizes [6,9].

ROUTE OF INJECTION

Intraprostatic injection therapy can be performed using transperineal, transurethral, or transrectal approaches. The transperineal and transrectal routes avoid the need for cystoscopy and can even be performed without local anesthesia and temporary urethral catheter drainage. However, some backflow along the needle tract outside the prostatic capsule has been known to occur using the transperineal approach. Transurethral injection using a cystoscopically-adapted needle provides a direct view of the prostate, but regional or general anesthesia is needed. Transurethral injection using a chemo-ablation agent like ethanol offers a safer method than transrectal and transperineal injection.

ETHANOL INJECTION — EFFECTS OF COAGULATIVE NECROSIS

Ethanol is a widely used agent for in situ tissue ablation, for example, intralesional treatment of hepatocellular carcinoma by percutaneous injection. Recently, intraprostatic ethanol injection has attracted attention from urological societies [6-8]. Ethanol induces some degree of inflammation with eventual coagulative necrosis, subsequent shrinkage of the enlarged gland volume and restoration of varying degrees of voiding function. Use of ethanol for chemo-ablation of prostate tissue reveals negligible systemic absorption, but temporary Foley catheter drainage is needed due to focal inflammation and tissue swelling.

The volume of ethanol used for injection has been reported to range from 15% to 45%. Improvements have been consistently observed without an apparent dose effect. Grise reported that statistically significant improvements were seen, with International Prostate Symptom (IPSS) and Quality of Life (QoL) scores decreasing by more than 50%. Peak flow rates (Q(max)) improved by 35% by the three-month evaluation and these results were sustained through to the 12-month follow-up [8]. The average prostate volume reduction was 16%. Adverse events included discomfort or irritative voiding symptoms in 26% of patients and hematuria in 16%, with retrograde ejaculation, and erectile dysfunction reported in less than 3% of patients. Two patients experienced serious adverse events (bladder necrosis) and underwent open surgery that included a urinary diversion and a ureteral implantation. At the one-year follow- up, 7% of patients required a transurethral resection of the prostate (TURP). Other studies have yielded

similar results [7]. However, some mild to moderate degree of adverse events, including hematuria (42.9%), irritative voiding symptoms (40.3%), pain/discomfort (25.6%) and urinary retention (22.1%) should be cautioned again. Although ethanol can safely ablate prostate tissue, some adverse events may still occur. Further studies are necessary before it receives widespread clinical application.

BOTULINUM TOXIN A (BONT-A) INJECTION — EFFECTS OF CHEMICAL DENERVATION

The human prostate is innervated by sympathetic and parasympathetic efferents, as well as by sensory afferents. The prostatic epithelium receives a cholinergic innervation, while the stroma receives a predominantly noradrenergic innervation. Cholinergic innervation of the prostate gland has an important role in regulation of the functions of the prostate epithelium, affecting growth and secretion, while the noradrenergic innervation has been implicated in the contraction of smooth muscle and the etiology of outflow obstruction accompanying BPH [9]. In addition, excessive sympathetic activity stimulates epidermal growth factor in the prostate, which has a resulting trophic effect on prostate growth. BoNT-A acting at the nerve terminals, blocking vesicle transport of neurotransmitters, including acetylcholine, noradrenalin, and sensory neuropeptides, can alter neural control of the prostate. In some animal studies, injection of BoNT-A has been demonstrated to induce marked atrophy and diffuse apoptosis of the prostate gland associated with decreased cell proliferation, decreased epinephrine-induced prostate contraction and inhibited inflammatory reaction and pain sensation. In addition, one recent study using a canine model also demonstrated that BoNT-A inhibits norepinephrine and electrostimulation induced contraction of prostate smooth muscle [11]. Therefore, BoNT-A represents an alternative option for the treatment of symptomatic BPH.

Therapeutic doses of BoNT-A have been reported from 100 units to 300 units of Botox® in volumes ranging from 4 cc to 20 cc. We performed BoNT-A prostate injections using a transperineal approach under TRUS guidance. A 21 gauge, 20 cm long needle (Chiba, Denmark) was placed in the adapter of the transrectal linear 7.5 MHz endosonic multiplane transducer (BK, type 8551, B-K medical, Denmark) and was inserted 1 cm to the left and 1 cm to the right of the median raphe and 1-3 cm above the anal sphincter. The transverse

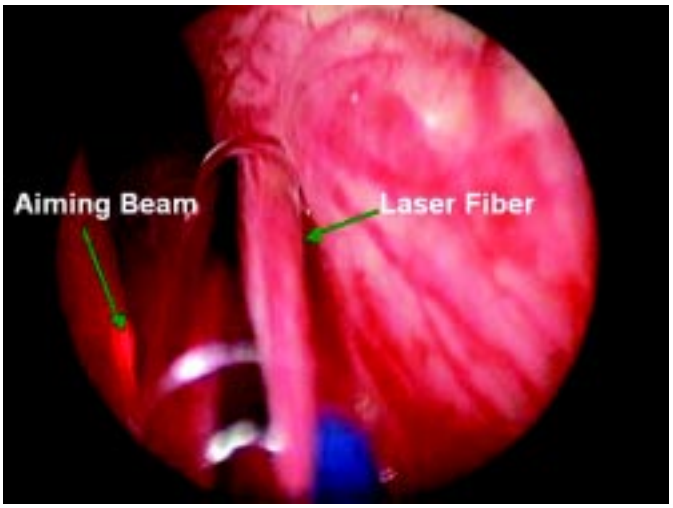

Fig. 1. KTP laser fiber.

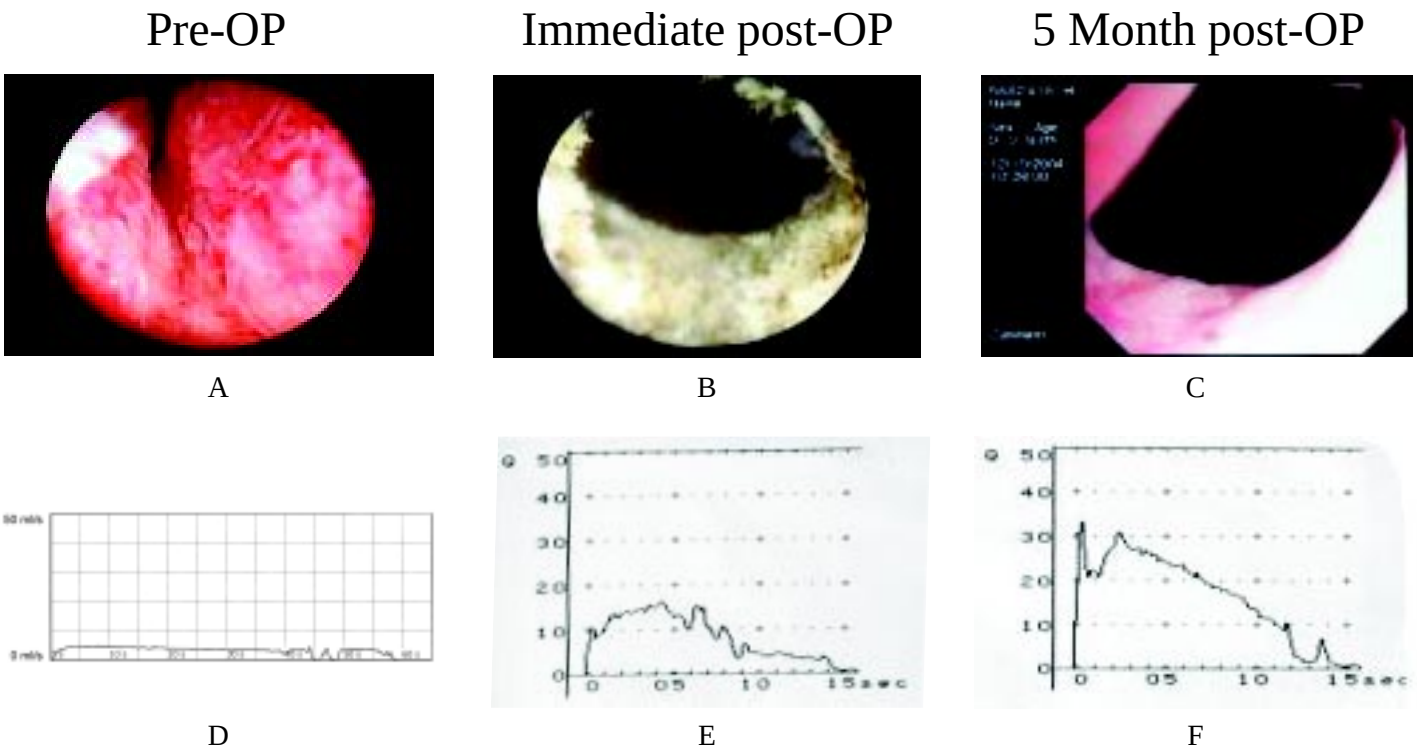

Fig. 2. Clinical result of KTP laser prostatectomy.

view was used to insure proper placement of the needle as a bright spot in the center of the transitional zone. The scanning plane was changed to longitudinal and the needle was further advanced until it was 0.5 to 1.0 cm from the bladder neck. BoNT was injected at the cranial, middle, and caudal aspect of lateral lobe. Diffusion of hyperechoic BoNT over the lateral lobe of the prostate was noted by TRUS monitoring.

The application of BoNT-A for BPH was pioneered by Maria et al in a report published in 2003 [9]. In patients treated with BoNT-A (200 units in 4 mL saline) sshowed significant improvement in maximum flow rates (52%), post void residual (PVR) decreased by 83%, and an improvement of 65% was seen on the AUA symptom score. Of particular interest is the reduction of prostate volumes from 52.6 mL to 16.8 mL (68%) and of PSA levels from 3.7 ng/mL to 1.8 ng/mL (51%). These results can be considered similar to resection and have a duration as long as 12 months. There were no local complications or systemic side effects observed over an average of 19.6 months follow-up. Kuo reported on 10 patients with BPH and urinary retention or large residual urine volume who received Botox (200 units in 20 mL normal saline) injection into 10 sites of the transitional zone of the prostate via cystoscopy. The results were encouraging, with significant in improvements; maximum flow rate increased by 30.3%, PVR decreased by 77.8%, prostate volumes decreased by 29.9%, voiding detrusor pressure by 16.8%, and the quality of life index improved by 48.9% at 3-month follow-up.

We performed BoNT prostate injections by mixing one vial (100 units) of Botox with 4 cc of saline just prior to injection. The total amount of Botox used by our group ranged from 100 to 200 units, dependent on the prostate size. In patients with smaller prostates, (i.e. <30 mL), we selected 100 units and for those with larger prostates (>30 mL), we selected 200 units. In our study series, 31 out of 41 patients (75.6%) showed more than 30% improvement on LUTS and QOL indices. Four out of five patients (80%) with urinary retention for more than one month could void spontaneously from one week to 1 month after the BTX/A injection. Twelve of 41 patients (29.2%) did not experience a change in prostate volume, however 7 out of the 12 patients (58.3%) still showed more than 30% improvement in maximal flow rate, LUTS, and QOL. The results suggest BoNT/A may beneficially affect the dynamic component of BPH. Translational research suggests novel mechanisms of action for botulinum toxin in the prostate. Since the use of botulinum toxin in the prostate is currently off-label and, in support of evidence-based medical practice, caution should be used until larger randomized clinical studies are completed to guide physicians making decisions about the use of botulinum toxin in the prostate.

LASER PROSTATECTOMY

Laser prostatectomy has been developing since 1986. The ideal type of laser for treatment of symptomatic BPH is one that has a high degree of vaporizing properties and vessel coagulating effects [10]. Previous laser therapies for BPH, like visual laser ablation of the prostate and interstitial laser coagulation, cause coagulative necrosis with secondary ablation. Long postoperative catheterisation, unpredictable outcomes, and high reoperation rates have restricted the use of these techniques. However, newly developed, high-powered 80-W KTP lasers with excellent ablative/vaporising capacities have meant the procedure has regained some popularity. The KTP: YAG laser is based on the principle of passing Nd: YAG laser light through a KTP crystal, which emits a green light at a wavelength of 532 nm which is absorbed by hemoglobin. The tissue penetration of KTP: YAG laser is 0.8 mm, leading to thermal ablation of the surface tissue through vaporization and immediately removing obstructive tissue. In addition, the high rate of absorption by hemoglobin causes heat-induced coagulation of the superficial blood vessels and consequently reduces the chance of bleeding.

The KTP laser is applied through a side-firing fiber that emits a divergent beam with a spot size of 1.2 mm at a distance of 2mm from the fiber tip. The small spot size allows efficient vaporization, characterized by continuous formation of bubbles. Hemostasis is achieved by distancing the fiber 3-4 mm away from the tissues or reducing the power to 30-40 W. The technique of high power KTP laser vaporization has been shifted from the 60 W setting in 1997 to the recent 80 W setting producing greater efficiency. The efficacy and safety of photoselective vaporization of the prostate (PVP) have been demonstrated in multiple trials with more than 50% improvement in IPSS, and more than 100% improvement in maximal flow rate. Prostates of all sizes can be operated on. It is at least as safe and effective as transurethral resection of the prostate, with significantly lower morbidity.

The effects are immediate and can persist as long as 5 years, according to current reports. The greatest impact this technology has may be on special high-risk surgical populations with symptomatic BPH. Studies have demonstrated that high-power KTP laser prostatectomy is safe and effective for patients with symptomatic BPH and large prostates, coagulopathies, and platelet disorders, as well as for those considered to be high cardiopulmonary surgical risks. This approach could possibly challenge TURP to become the gold standard surgical treatment for BPH.

CONCLUSION

Minimally invasive therapy for BPH is an ongoing story. New methods will develop, but few will stand with time. Urologists should first know the importance of pharmacotherapy and master the skills required for TURP before becoming experts in minimally invasive therapy.

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