REVIEW

The Minimally Invasive Treatments for Benign Prostrate Hyperplasia

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ABSTRACT

The prevalence of benign prostatic hyperplasia (BPH) increases with age, affecting more than 50% of men above the age of 50 to varying degrees. As it enlarges, it compresses onto the urethra causing bladder outlet obstruction. This can cause a spectrum of problems ranging from irritative and obstructive lower urinary tract symptoms (LUTS) to retention of urine with obstructive uropathy. Transurethral resection of prostate (TURP) is the standard for surgical intervention, however with the advent of an ageing population, there is an increasing number of patients who have ischaemic heart disease who require long-term anticoagulation and have multiple co-morbidities that put them at an increased risk of general anaesthesia. This review aims to critically appraise the effectiveness and evidence for use of these minimally invasive techniques.

Both PubMed and Ovid were used to search for randomised control trials (RCT) comparing the various minimally invasive techniques against TURP. In cases where there were no RCTs, the results of the respective trial were compiled. This was later compiled in a summary table.

An effective minimally invasive treatment modality will play a complimentary role to TURP which remains the standard of surgical treatment for BPH. Technologies progressing towards rapid re-creation of prostatic channel, minimal blood loss and non-urethral instrumentation will bridge the divide between pharmacotherapy and surgery.

Keywords: Benign prostate enlargement, BPE, Benign prostate hyperplasia, BPH, Minimally invasive surgery, Transurethral resection of prostate, TURP

INTRODUCTION

Benign prostatic hyperplasia (BPH) is benign enlargement of the prostate gland. Its prevalence increases with age, affecting more than 50% of men above the age of 50[1]. BPH occurs in the transition zone of the prostate through which the urethra passes through. As it enlarges, it compresses on the urethra, causing bladder outlet obstruction. This leads to a spectrum of clinical consequences; ranging from lower urinary tract symptoms (LUTS) such as urinary hesitancy, slow stream, retention of urine, recurrent urinary tract infection; bladder stone formation and obstructive uropathy.

The management of BPH is dependent on the severity of the disease. In the early stage, when patients' LUTS are mild, monitoring is sufficient. As it progresses, medical therapy with alpha-blockers or 5-alpha-reductase inhibitors are appropriate. In the advanced cases, surgical intervention is necessary.

Transurethral resection of prostate (TURP) is the standard for surgical intervention[2]. The transurethral access provides immediate removal of obstructing prostate tissue without the need for skin incision as required in open prostatectomy. Long term studies have also shown lasting effects of prostate debulking[3].

The major intra-operative complication of TURP remains haemorrhage requiring blood transfusion. Mebust[4] et al reported in a series of 3885 patients treated at 13 participating centres from 1978 to

Table 1. Complication rates of patients in TURP studies.

Study	Study size	Transfusion rate	TUR syndrome	UTI	Repeat TUR
Reich et al	9197	2.9%	1.4%	3.6%	
Tasci et al	3589	0.25%	0%	6.5%	4.4%
Mebust et al	3885	2.5%	2%		

TURP: Transurethral resection of prostrate

1987, a transfusion rate of 2.5%. Reich[5] et al reported a similar transfusion rate of 2.9% in 9197 patients who were treated at a collection of 44 mainly non-academic centres from 2002 to 2003. However the transfusion rate was improved when performed by a single surgeon at a specialised centre — Tasci[6] et al reported a transfusion rate of 0.25% for 3589 patients from 2000 to 2008. Improved resectoscopes and electrosurgical equipment can reduce bleeding and optimise the endoscopic view for better-controlled haemostasis.

Transurethral resection (TUR) syndrome, is a condition in patients with dilution hyponatraemia from absorption of irrigation fluid, experiencing mental confusion, nausea, vomiting and increased blood pressure. This gradually disappears through improved irrigation fluids, and improved surgical techniques and equipment. Table 1 describes the common complication rates reported in various TURP studies. Mebust et al reported 2% incidence of TUR syndrome between 1978 and 1987, Reich et al 1.4% and Tasci et al 0% incidence.

With the advent of an ageing population, there is an increase in the number of patients who have ischaemic heart disease, long-term anticoagulation and other multiple co-morbidities that puts them at increased risk of general anaesthesia and surgical complications. It is also precisely this group of older patients that are more frequently afflicted with BPH.

A number of new minimally invasive therapies have been developed in order to meet the challenge of treating BPH while minimising the invasiveness and complications of treatment. In this review we aim to critically appraise the effectiveness and evidence for use of these minimally invasive techniques.

Minimally Invasive Treatments Modalities

Contact-based Prostate Ablation

There are the catheter based techniques such as the transurethral microwave therapy (TUMT) and water-induced thermotherapy (WIT). These two deliver thermal energy to the prostate gland via a special catheter that is inserted through the urethra. The thermal energy from these techniques cause coagulation necrosis of the prostate tissue.

Transurethral Microwave Thermotherapy

Transurethral microwave thermotherapy is a non-surgical technique that uses microwave energy to deliver heat to the prostate. A special catheter (size 22 Fr) with a microwave antenna is introduced into the urethra. The antenna is positioned and adjusted according to the length of the prostate urethra. Microwave energy is then applied, heating the prostate tissue to 42°C. The temperature is maintained in a narrow range by the urethral coolant system within the catheter. It is monitored using a rectal probe that measures rectal temperature and feeds back to the control unit to adjust the energy level. The high temperature causes coagulation necrosis of the prostate tissue which is absorbed and reorganised resulting in the creation of a cavity.

The duration of this procedure ranges from 28.5 to 60 minutes[7] depending on the system used. This treatment may be performed in an outpatient clinic setting with oral analgesia and sedation.

Due to the size of the catheter (22 Fr), patients with abnormal anatomy following pelvic radiation therapy or have a urethral stricture may not be able undergo TUMT. Another limitation of TUMT is therapy induced oedema increasing the risk of urinary retention, resulting in the need for a

Table 2. Comparative Studies between TUMT and TURP

Study	Follow up period	Modality	Study size	Mean Age (years)	Mean Prostrate size (ml)	Mean IPSS		Mean Qmax (ml/s)		Mean PVRU (ml)	
						Base line	Post op	Base line	Post op	Base line	Post op
De la Rosette 2003	36 months	TUMT	78	67	51	20	11.5	9.2	11.7	65	94
		TURP	66	66	52	20	2.6	8.0	22.8	91	35
Mattiasson 2007	60 months	TUMT	62	67	49	21.0	7.4	7.6	11.4	106	70
		TURP	34	69	53	20.4	6.0	7.8	13.6	94	51

TUMP: Transurethral microwave therapy; TURP: Transurethral resection of prostrate

catheter for two to four weeks after the procedure. Tissue is also not available for histology as the coagulated tissue gradually sloughs off. The failure rate is about 20.5% at three years and 33.2% at eight years. Uroflometry results at five years record a maximum flow 11.4 ml/s, post-void residual volume was 60 ml and an International prostate symptom score (IPSS) of 7.4. Table 2 describes two randomised controlled trials comparing TUMT and TURP.

The currently available brand names include: Targis™, Prostatron™, TherMatrx™ dose-optimized thermotherapy system, Urowave™, Prolieve ™ system, and ProstaLund™.

Water-induced Thermotherapy

Water-induced thermotherapy (WIT) is another catheter based therapy. It uses a smaller catheter size of 18 Fr catheter to deliver the thermal energy to the prostate. Unlike TUMT, the conducting agent is water heated to 60°C. This water is heated outside the body and delivered directly to the prostate through the insulated catheter. This ensures the delivery of a constant and safe thermal energy source. The duration of therapy is 45 minutes. The failure rate is 11.2% at three years [8]. Uroflometry results at two years [9] record a maximum flow 16.4 ml/s, post-void residual volume was 89 ml and IPSS 11.3

Table 3 demonstrates the improvement in symptoms, flow rate and residual urine volume in the bladder following water thermotherapy.

Intra-Prostatic Ablation

Transurethral Needle Ablation

Transurethral needle ablation (TUNA) uses radiofrequency (RF) energy transmitted through prostate tissue between two needle electrodes. The prostate cells resist the passage of the current and thermal energy is produced. TUNA generates coagulation necrosis at temperatures of 70–110°C.

TUNA is administered under mild sedation. The TUNA catheter is advanced and positioned in the prostate under direct fibre-optic vision. The shaft is rotated to deploy the two RF needles probes into the selected prostatic area, both lateral lobes are treated in 2–3 planes, beginning at 1 cm from the bladder neck to 1 cm proximal to the verumontanum. The failure rate is 23.3% at

Table 3. Water-induced Thermotherapy

Study	Follow up period	Modality	Study size	Mean Age (years)	Mean Prostrate size (ml)	Mean IPSS		Mean Qmax (ml/s)		Mean PVRU (ml)	
						Base line	Post op	Base line	Post op	Base line	Post op
Muschter 2000	12 months	WIT	112	67.4	40.1	24	12	8.7	15	59.1	29.2

WIT: Water-induced thermotherapy

Table 4. Comparing TUNA and TURP

Study	Follow up period	Modality	Study size	Mean Age (years)	Mean Prostrate size (ml)	Mean IPSS		Mean Qmax (ml/s)		Mean PVRU (ml)	
						Base line	Post op	Base line	Post op	Base line	Post op
Hindley 2001	24 months	TUNA	19	Not recorded	Not recorded	25	8	8.5	8.6	66	89
		TURP	19			25	3	9.1	18.1	71	32

TUNA: Transurethral needle ablation; TURP: Transurethral resection of prostrate

five years[10]. Table 4 demonstrates a randomised controlled trial comparing TUNA with TURP.

Earlier cases of intraurethral injections were performed using a straight needle. In 2000, the Prostaject™ device was available for use. This was a modification of the TUNA radio-frequency delivery device. The radiofrequency coupler was removed and creation of a detente system for graduated needle deployment. This curved needle that passively deflects in an axial plane allowed for deeper prostatic injection[11].

Interstitial Laser Coagulation

Interstitial laser coagulation (ILC) utilises the Neodymium laser (Nd:YAG) or Diode laser system Indigo 830. The optical fibres are inserted directly into the prostate and coagulation necrosis followed by atrophy is achieved of the prostate tissue with preservation of the urethra mucosa. This procedure can be performed under local or spinal anaesthesia. A catheter is usually inserted for one week to avoid urinary retention due to tissue oedema following treatment. There has also been no reported retrograde ejaculation associated with ILC. Table 5 demonstrates two randomised control trials that compare ILC treatment against TURP. Uroflometry at two years[12] recorded a maximum flow 10.3 ml/s and a post-void residual volume 94 ml.

Transurethral Ethanol Ablation of Prostate

Transurethral ethanol ablation of prostate (TEAP) procedure uses the ProstaJect™ device to administer deep intraprostatic parenchymal injection. This allows in-situ delivery of pure ethanol to produce chemical ablation and tissue necrosis in the prostate. Ethanol has been shown to ablate all cellular elements within the human prostate including nerves[13]. Immunohistochemical review shows complete destruction of nerve cells and nerve endings. A neurolytic role may also exist when treatment with TEAP by improving BPH urinary symptoms[13].

Analgesia in the form of peri-prostatic block or regional anaesthesia is used. No tissue sloughing

Table 5. Comparing ILC and TURP

Study	Follow up period	Comparison	Study size	Mean Age (years)	Mean Prostrate size (ml)	Mean IPSS		Mean Qmax (ml/s)		Mean PVRU (ml)	
						Base line	Post op	Base line	Post op	Base line	Post op
Kursh 2003	24 months	ILC	37	68	41	24	4.5	9.2	13.9	81	57.7
		TURP	35	69	40	23	5.0	9.1	16.5	87	44.0
Donovan 2007	7.5 months	ILC	117	67	41	19.1	8.3	10.4	16.2	124	50.6
		TURP	117	66	38	19.2	6.9	10.3	20.0	104	30

ILC: Interstitial laser coagulation; TURP: Transurethral resection of prostrate

Table 6. Transurethral ethanol ablation of prostrate results

Study	Follow up period	Technology	Study size	Mean Age (years)	Mean Prostrate size (ml)	Mean IPSS		Mean Qmax (ml/s)		Mean PVRU (ml)	
						Base line	Post op	Base line	Post op	Base line	Post op
Sakr[15] 2009	48 months	TEAP	35	64	52.7	22	9.9	5.9	16.9	68.6	36

TEAP: Transurethral ethanol ablation of prostrate

was observed and no retrograde ejaculation[14] reported. Table 6 demonstrates the results of TEAP. Uroflometry results at four years[15] recorded a maximum flow of 16.8 ml/s, post-void residual volume 36 ml, IPSS 9.85

The patients are commonly discharged for home with an in-dwelling catheter for seven days. The common complications are urinary tract infections and epididymo-orchitis occurring in 14.3% and 5.7% respectively.

Botox

Botulinum toxin-type A (Botox) is injected into the prostate through the transperineal, transrectal or transurethral approach. It has been observed from animal studies that Botox injection in the rat prostate showed apoptosis of glandular elements and a decrease in prostate weight[16].

These findings have subsequently been confirmed in human subjects[17] resulting in a 30–50% reduction[18] in prostate weight. Prostate biopsies obtained from human prostates after Botox injection revealed numerous apoptotic cells in glandular and stromal tissue[18]. The maximum effect of reduction in prostate weight is observed between the first and second month, and the duration of the effect last between three months to one year. Uroflometry results[19] at six months recorded a maximum flow of 11.6 ml/s, post-void residual volume 36.8 ml and IPSS 11.4.

A literature review of studies found that there were more studies performed using the transperineal approach for injection of Botox[20] compared to the transurethral approach, however the outcomes were comparable. Table 7 demonstrates two studies involving the use of botulinum toxin to treat BPH. One with trans-urethreal Botox, and another with trans-perineal Botox.

Some studies preferred the transperineal approach as it only required trans-rectal ultrasound guidance and did not require cystoscopy and the accompanying general anaesthesia required for transurethral injections. There have been no reports of local or systemic complications following intra-prostatic Botox injections.

Table 7. Intra-prostatic injection of botulinum toxin results

Study	Follow up period	Modality	Study size	Mean Age (years)	Mean Prostrate size (ml)	Mean IPSS		Mean Qmax (ml/s)		Mean PVRU (ml)	
						Base line	Post op	Base line	Post op	Base line	Post op
Kuo[17] 2005	12 months	Transurethreal Botox	10	75.2	65.5	-	-	7.6	11.6	243	36.8
Park[21] 2006	6 months	Transperineal Botox	23	66.3	47.5	24.0	14.7	7.4	9.4	108.7	59.4

Table 8. High intensity focused ultrasound treatment results

Study	Follow up period	Modality	Study size	Mean Age (years)	Mean Prostrate size (ml)	Mean IPSS		Mean Qmax (ml/s)		Mean PVRU (ml)	
						Base line	Post op	Base line	Post op	Base line	Post op
Lu[24] 2007	12 months	Transrectal HIFU	150	75.2	65	-	-	6.0	17.2	75	30.3
Uchida[25] 1998	12 months	Transrectal HIFU	35	68.5	33.9	20.6	11.7	10.7	11.0	40	41

Extracorporeal Ablation

High Intensity Focused Ultrasound

The Sonablate-500™ High intensity focused ultrasound (HIFU) treatment delivers ultrasound beams in a tight focus achieving temperatures of 80–90°C. This causes coagulation necrosis similar to the earlier mentioned techniques. However the benefit of HIFU is that the targeted area can be treated at a distance, it does not need to be in direct contact with the probe. The duration of HIFU treatment ranged between 25 to 90 min and the indwelling catheter duration post-procedure ranged from three to 19 days. Sullivan[22] et al report complications following HIFU include hematospermia (13%), hematuria (9%), acute retention of urine (4%), perineal pain (11%) and epididymitis (9%). Madersbacher[23] et al reported from their study in 1995 of 98 men, that 43.8% of the 98 men had to undergo a TURP within four years. Table 8 demonstrates the results of HIFU treatment on BPH.

Histotripsy

Histotripsy is a therapy that focuses short-duration, high-amplitude pulses of ultrasound to incite a localized cavitation cloud that mechanically breaks down tissue[26]. Unlike HIFU, Histotripsy does not create heat within the prostate gland. It's delivery of energy is the athermal mechanical breakdown of targeted tissue using focused sound pulses. This technology has been proven in animal laboratories and has yet to be introduced into human subjects.

Mechanical Separation of Prostatic Lobes

Prostatic Urethral Lift

The UroLift® System is a minimally invasive device designed to open the urethra directly by retracting the obstructing prostatic lobes without applying incisions, surgical resection or thermal injury to the prostate. It can be performed under local or general anaesthesia. Chin et al reported an overall failure rate of 20%[27] at two years. Table 9 demonstrates the early results of the prostatic urethral lift system. Figure 1 contains diagrams to describe the effect of the prostatic urethral lift system.

Urethral stents

The first urethral stent system was described in 1980. It was a temporary stent, described as the Fabian spiral[28]. There were many problems

Table 9. Prostatic urethral lift system results

Study	Follow up period	Modality	Study size	Mean Age (years)	Mean Prostrate size (ml)	Mean IPSS		Mean Qmax (ml/s)		Mean PVRU (ml)	
						Base line	Post op	Base line	Post op	Base line	Post op
Chin[27] 2012	24 months	UroLift® System	64	66.9	51	21.8	12.6	7.4	10.3	89	89

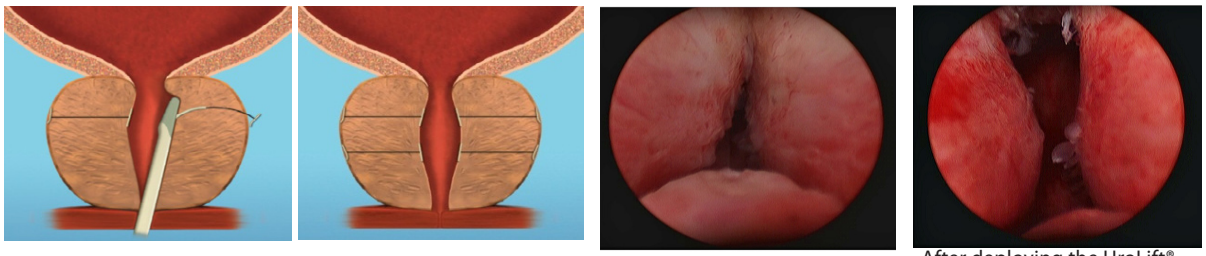

Fig 1. Diagram describing the prostatic urethral lift system

associated with the use of this temporary stent such a stent dislocation, incrustation, recurrent urinary tract infections and the impossibility of cystoscopy after insertion because of the small diameter of the Fabian spiral.

In 1990, the first permanent urethral stent system[29] was introduced for clinical use. Table 10 demonstrates the results of one permanent urethral stent, the Memotherm urethral stent. The mesh structure of the permanent stents allow complete epithelialisation. Permanent stents were also associated with fewer side effects. The other problems such as dislocation and incrustation were minimised, allowing for long-term use. However recurrent urinary tract infections still affected about half (45.5%) of patients, urothelial hyperplasia affected 27.6% of patients, and urethral stricture affect 10.6% of patients[30]. Another disadvantage of stent therapy is the high number of re treatments which can be reduced by optimising stent positioning. In view of the disadvantages of almost half of patients being affected by recurrent urinary tract infection, the urethral stent should be reserved for the selected group of high surgical risk patients with benign prostate hyperplasia.

DISCUSSION

The ideal minimally invasive BPH treatment is one that re-creates the prostatic urethral channel in the shortest period of time, with minimal blood loss and does not require urethral instrumentation. In this review, we describe the various technologies which have been developed with this goal in mind. We also assess their clinical progress in achieving this goal.

Most of the reviewed modalities (TUMT, TUNA, ILC, HIFU) employ the use of coagulative necrosis of the prostatic tissue as the main mechanism for the re-creation of prostatic channel. This is achieved by thermal energy. The coagulated tissue is absorbed and reorganised over time by inflammatory reaction. However, the sloughing of the overlying mucosa results dysuria and urinary obstruction in treated patients and the duration of these symptoms are unpredictable.

Other mechanisms include chemical induced prostatic tissue atropy, which can be in the form of

Table 10. Memotherm urethral stent results

Study	Follow up period	Modality	Study size	Mean Age (years)	Mean Prostrate size (ml)	Mean IPSS		Mean Qmax (ml/s)		Mean PVRU (ml)	
						Base line	Post op	Base line	Post op	Base line	Post op
Gasenberg[30] 1998	48 months	Memotherm stent	123	77.6	40.2	24.0	6.1	7.4	16.1	153	26

Table 11. Comparison of various modalities

Study	Follow up period	Modality	Study size	Change in IPSS	Change in mean Qmax (ml/s)	Change in mean PVRU (ml)	Failure rate
Tasci 2011	42 months	TURP	3589	-19.9	+12.9	-116.6	4.4%
Mattiass 2007	60 months	TUMT	62	-13.6	+3.8	-36	10%
		TURP	34	-14.4	+5.8	-43	4.3%
Hindley 2001	24 months	TUNA	19	-17	+0.1	-23	10%
		TURP	19	-22	+9	-39	-
Kursh 2003	24 months	ILC	37	-19.5	+4.7	-23.3	16%
		TURP	35	-18	+7.4	-43	-
Muschter 2000	12 months	WIT	112	-12	+6.3	-29.9	5.6%
Sakr 2009	48 months	TEAP	35	-12.1	+11	-32.6	NR
Kuo 2005	12 months	Transurethreal Botox	10	-	+4	-206.2	10%
Uchida 1998	12 months	Transrectal HIFU	35	-8.9	-0.3	-1	NR
Chin 2012	24 months	UroLift® System	64	-9.2	-2.9	0	20%

ethanol or botulinium toxin. Histotripsy offers the promise of mechanical tissue lysis and sloughing in order to create a prostatic channel. However, these series are small and have not been compared to the gold standard TURP in a randomised manner.

While these modalities have shown promising improvements in symptomatic relief, retreatment rate is high, and TURP is still the modality that consistently produces reduction in IPSS, improvement in peak urinary flow and reduction in post-void residual urine. This is clearly demonstrated in Table 11 which compares TURP with various modalities of treatment. This may be due to the immediate creation of the channel in TURP whereas with the exception of prostatic urethral lift and urethral stent, none of other modalities is able to replicate this effect.

CONCLUSION

An effective minimally invasive treatment modality will play a complementary role to TURP, which remains the standard of surgical treatment for BPH. The three key requirements are rapid re-creation of prostatic channel, minimal blood loss and non-urethral instrumentation. Technologies are progressing towards these goals and the victor will bridge the great divide between pharmacotherapy and surgery.

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