1 Transurethral minimally invasive procedures

1.1 TEMPORARY IMPLANTABLE NITINOL DEVICE (TIND)

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Introduction

Benign prostate hyperplasia (BPH) is a disease of ubiquity in the aging male. The progressive enlargement of the prostate gland usually correlates with worsening lower urinary tract symptoms (LUTS), the holistic burden of which can affect the individual's health-related quality of life (HRQL) and lead to a deterioration in social functioning and mental health.[1–3] The prevalence of the disease is estimated to be over 30 million men in Europe and the USA.[4] Medical therapy consisting of α-blockers and/or 5α-reductase inhibitors is usually the first option for the management of these patients, even if it provides only modest symptom relief. This limited symptom relief, together with the incidence of side effects, leads to more than 25% of patients discontinuing/stopping the drug therapy. Some of these patients opt for surgical intervention.[5]

For decades transurethral resection of the prostate (TURP) has been the gold-standard surgical technique, typically reserved for severe or pharmacologically refractory cases.[7, 8] While it offers excellent functional results, it has the drawback of short and long-term complications, including perioperative and postoperative morbidity (20%), ejaculatory dysfunction (65%), erectile disorders (10%) and urethral strictures (7%).[6] New attractive laser-based therapies allow relief of PBH-related symptoms, but present complications, including ejaculatory dysfunction similar to that seen with TURP.[7–11]

Based on these findings, many men seek more significant symptomatic improvement than is offered by the drugs but are not willing to face the risk of surgery. In the past, many minimally invasive procedures have been introduced with the aim of reducing TURP morbidity, such as transurethral needle ablation (TUNA), transurethral microwave thermotherapy (TUMT), and alcohol injections. None of these, however, brought about a safe, quick, and durable relief of symptoms, and none has been routinely used in clinical practice.[12–15]

Recently, the continuous pursuit of minimally invasive alternatives, to address non-advanced disease, has given rise to several new approaches which aim to reduce the morbidity of treatment for BPH such as PUL (NeoTract Inc, USA) or Rezum (NxThera Inc, USA) procedures.[16, 17]

With the goal of further minimizing the invasiveness of interventional BPH therapy, the temporary implantable nitinol device is another effective technique (Medi-Tate®; Medi-Tate Ltd., Or Akiva, Israel). TIND is a crimped prostatic device bearing nitinol struts, which exert radial force, inducing incisions and remodelling of the bladder neck, and prostatic urethra. The purpose of the present chapter is to offer a narrative synthesis of the available literature and to take a look to the ongoing studies.

Rationale

The premise behind the TIND procedure is that tissue can be incised and remodelled through pressure. By exerting mechanical pressure greater than the vascular blood pressure in tissue, cells will be starved of oxygen, leading to a gradual necrosis of successive cell layers over a period of time. This mechanism of action is commonly used in general surgery for a number of applications, such as rubber band ligation for treatment of internal haemorrhoids, and for non-surgical adult male circumcision. Therefore, placement of a large, self-expanding nitinol device at the site of the bladder neck, and between the obstructed prostatic lobes, will create longitudinal incisions and remodel the prostatic urethra to allow increased urinary flow.

The temporary implantable nitinol device

First generation device

The TIND is comprised of elongated struts and an anchoring leaflet all made of nitinol, a biocompatible super elastic shape-memory alloy widely used in the manufacture of medical devices (Figure 1.1.1). The total length of the device is 50 mm and its outer diameter is 33 mm, designed to cover the entire length of the prostatic urethra, from the bladder neck to a point proximal to the external urinary sphincter. The struts are designed in order to create prostate incisions anteriorly, at the five and seven o'clock positions. An anchoring leaflet prevents retromigration of the device. The tip of the device is covered by a soft plastic material in order to avoid any bladder injury while the tail of the device is anchored to a nylon wire for retrieval. This first-generation device was discontinued in 2014.

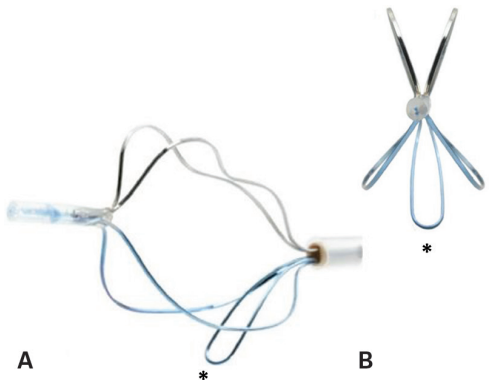

FIGURE 1.1.1 The Medi-Tate TIND (first generation device) in its expanded configuration. Note the four nitinol struts, the anchoring leaflet (*) and plastic cover create to reduce bladder mucosa injury. A) Longitudinal view; B) frontal view.

Second generation device

The second generation device has been called "iTIND". It is currently available on the market. iTind is equal to the first-generation one in size, but with some structural differences. First, only three struts are used, with double intertwined nitinol wires configured in a tulip shape. The struts formed are located at 12, five, and seven o'clock positions. In addition, the three intertwined wires connect together in the upper part of the device allowing it to exert action on the urethral mucosa at the bladder neck, avoiding potential injuries of the bladder mucosa and removing the need for a soft plastic cover. Other features of the second-generation device are similar to the previous version, including the anchoring leaflet, as well as the distal nylon wire for removal of the device (Figure 1.1.2).

Mechanism of action

The radial force exerted by the struts cause ischaemic necrosis of the tissue, leading to bladder neck and prostatic urethra incision. The hypothesis is that these incisions "reshape" the prostatic urethra and the bladder neck,

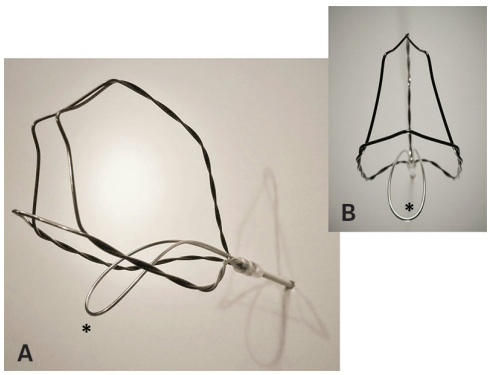

FIGURE 1.1.2 The Medi-Tate iTIND (second generation device) in its expanded configuration. Longitudinal view. Note that this device has only three nitinol struts. A) Longitudinal view; B) frontal view.

and reduce urinary flow obstruction caused by the prostatic tissue.

Current indications

Based on the current literature, patients presenting symptomatic BPH with an IPSS ≥10, Q_{max} ≤12 mL/s, prostate volume <60–75 mL, were eligible for TIND implantation. Main contraindications are haemostatic disorders, neurogenic bladder and/or sphincter abnormalities, comprised renal function, history of urethral strictures, post-void residual (PVR) volume >250 mL, urinary bladder stones, bladder cancer, active urinary tract infection and previous prostate surgery. Due to the characteristics of the device and the need of anchoring leaflet stay at six o'clock at the bladder neck, obstructive median lobe is also a contraindication for the TIND implantation.

Surgical procedure

TIND implantation

The procedure is performed under light IV sedation. In addition, an antibiotic prophylaxis is administered. The patient is placed in a lithotomy position. A 22 F standard cystoscope is gently inserted into the urethral meatus, and a urethro-cystoscopy is performed. The device, preloaded on a dedicated delivery system, is advanced into the bladder through the cystoscope sheath, and deployed inside the bladder. The device is then further manipulated under direct visualisation, until the anchoring leaflet slides to its position at six o'clock distal to the bladder neck and the device is securely positioned within the bladder neck and the prostatic urethra (Figure 1.1.3). Finally, the bladder is emptied and the cystoscope is removed. No catheterisation is required.

TIND removal. At five to seven days after placement, the TIND is retrieved in an outpatient setting. The patient is placed in a lithotomy position and 20 mL lidocaine gel is applied to the urethral meatus. Urethroscopy is performed with a standard 22-F cystoscope, and the TIND is identified, retracted into the cystoscope sheath under visualisation, and then removed.[18]

The second-generation device can be retrieved in an ambulatory setting under topical anesthesia with lidocaine gel. A 22 F open-ended catheter is used to remove the device. The retrieval suture is inserted into the catheter lumen with the aid of a dedicated metallic semirigid double wire (Snare; Medi-Tate Ltd., Israel). Then, the catheter is advanced up the urethra, while the retrieval suture is held taut. When the catheter reaches the distal end of the device, the suture is pulled back, retracting the device into the lumen of the catheter. The catheter is then removed.[19]

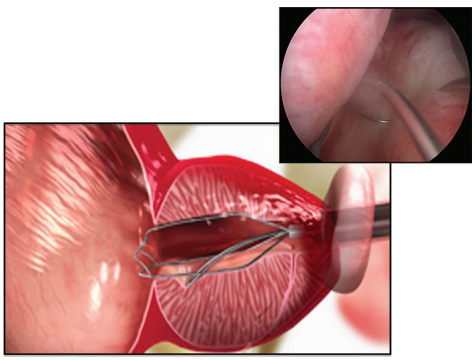

FIGURE 1.1.3 The device in place, in its expanded configuration. The leaflet is cranially to the veru montanum. Left: scheme; right: endoscopic view. The device will be removed after 5 days.

Clinical results

First generation device

Our group reported the first clinical experience with TIND (MT 01 study) on 32 patients and showed that the implantation of the device is feasible and safe in the treatment of LUTS related to BPH.[18] Mean age of the patients was 69 years old and mean prostate size was 29.5 cc. All the procedures included in the prospective case series were successfully completed under light sedation and required only a few minutes to perform. Neither intraoperative complications nor technical difficulties were reported. In this first report, all but one patient was able to void the same day of surgery, with no need of unplanned post-operative visits. During follow-up (one year), no changes in sexual function or ejaculation in sexually active patients were reported. Median IPSS was reduced from 19 at baseline to nine after 12 months (-45%),

while the mean Qmax increased from 7.6 mL/s to 11.9 mL/s (+67%) (P<0.05). No patients required further treatment with medical therapy or surgery. Notably, this improvement was recorded early, within three weeks of the procedure, demonstrating an important positive aspect of this procedure, as the vast majority of other minimally invasive techniques can require several weeks before improvement.[13–15] EPIC score, at 12 months after surgery, showed that 26 patients (82%) were 'satisfied' or 'extremely satisfied' with the intervention, five (15%) patients were uncertain about their satisfaction and only one (3%) patient was 'dissatisfied'. The QoL scores followed the same trend as the IPSS, with patients reporting a significant improvement, which remained stable at scheduled follow-ups over time.

These data suggested that TIND implantation positively affected the QoL of the patients, a key factor when assessing a new technology. After one year, the results were comparable, if not superior, to those of other minimally invasive procedures, even the most novel ones.

The same patients were followed until three years after surgery.[20] Qmax decreased not significantly compared to the 12 month analysis, with an increase equal to 41% (+3 mL/s) with respect to baseline. IPSS increased at 24 and 36 months after treatment but was still significantly lower than baseline values. After the 36 month observation period, only 9% of patients reinitiated their discontinued pharmacological therapy, and no patient needed additional surgery. Statistical analysis revealed an IPSS of >8 after six weeks as a predictor of higher long-term QoL, for which the score was one after 12 months and two after 36 monoths. 19 of the 32 patients were sexually active, none of whom reported ejaculatory dysfunction after TIND implantation.[20, 21]

Second generation device

The interim results of MT02 study, a one-arm, multi-center, international prospective study to assess the efficacy of second generation of Medi-Tate (i-TIND), were recently presented at the EAU annual meeting in Copenaghen, Denmark.[22] Eighty-one patients with urinary symptoms due to BPH were enrolled; mean age was 63.9 years old, and mean prostate volume was 35 cc. At the baseline, median IPSS score, QoL (median, range) and mean Qmax were 22 mL/s, and 8.46 mL/s, respectively. All the implantations and removals of devices were successfully concluded with no intraoperative complications. All the postoperative-reported complications were graded I or II according to the Clavien Dindo classification. Three months after implantation median IPSS score, median QoL and mean Qmax were 8.2 two, 2 and 12.48 mL/s (P<0.05 for all the evaluated variables). Twelve months after surgery IPSS score was 7(-65% with respect to the baseline), 1 and 14.72 mL/s (+100% with respect to the baseline) respectively. No patients reported ejaculatory dysfunction during follow-up. Only one patient underwent surgery for BPH during the one year follow-up. The authors concluded that, like the first-generation device, second generation iTIND implantation is a safe and effective minimally invasive option for the treatment of BPH-related lower urinary tract symptoms (LUTS) until one year follow-up. Table 1.1.I. shows baseline characteristics of 70 patients treated with second generation device at San Luigi Hospital, Orbassano, Turin. (unpublished data). Figures 1.1.4, 1.1.5 and 1.1.6 summarize functional results over one year follow-up.
In this data series, no grade >2 complications were recorded, no patients had ejaculatory dysfunction after treatment.

Outlook on the future: ongoing studies

Several studies are ongoing involving hundreds of patients worldwide. The MT03 study is a prospective randomized controlled trial wherein i-TIND is compared 2:1 to the sham procedure (IDE study for US FDA approval). The number of patients included is 175, recruitment was completed in September 2017 and results will be available soon. The primary endpoints of the study are the safety of the surgical treatment and the IPSS improvement of i-TIND *vs.* the sham procedure at three months, then IPSS again *vs.* baseline in the arm receiving the device at 12 months. The MT04 study aims to clarify the role of iTind in a setting of acute urinary retention (AUR). This is a prospective randomized controlled trial 1:1 comparing i-TIND *vs.* the standard of care (alpha blockers + Foley) for patients with AUR. Five different sites in the

1.2 AQUABLATION: THE NEW WATER JET ABLATION TECHNOLOGY FOR THE TREATMENT OF BPH

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Introduction

Transurethral resection of the prostate (TURP) is the historic gold standard for treatment of BPH for smaller glands <80 cc and open prostatectomy for larger glands >80 cc.[1] More modern surgical approaches include ablative treatments such as transurethral laser photo-vaporization (PVP), transurethral laser prostatectomy (Greenlight, holmium, thulium, diode) as well as non-tissue ablative techniques such as prostatic stents (iTind; Medi-Tate, Or Akiva, Israel), Urolift (Neotract, Pleasanton, CA, USA), and Rezum water vapor therapy (NxThera, Maple Grove, MN, USA).[2] Laser prostatectomy (enucleation technique), was developed to minimise bleeding complications and mimic open prostatectomy, while Urolift, Rezum, and iTind were developed to minimize postoperative sexual dysfunction and encourage same day discharge. Prostate artery embolization (PAE) also been advocated as a radiological non-invasive treatment for large prostates. However, long term follow-up data is not available yet for these modern non-ablative techniques.

Even with wide modalities of treatment available, some of these options are limited when treating large (>80 cc) and very large (>100 cc) prostates. While some of these are recommended, a few are not currently recommended per the British, American or European guidelines.[3-6] For patients with large prostate volumes, effective surgical approaches include open and laser enucleation techniques such as holmium, thulium or green light laser enucleation of the prostate. These approaches are likely to have better safety profiles compared to open simple prostatectomy with regard to transfusion and complication rates.[7] However, there is a considerable learning curve and longer operating time associated with these modalities which precludes their widespread adoption.[8]

For that reasons, there is a need for a novel surgical approach that is safe and effective with smooth learning curves in the context of BPH treatment. More recently, aquablation (AquaBeam®, Procept BioRobotics, Redwood Shores, CA, USA), also termed water-jet ablation, has emerged as the latest surgery of interest in this area. Aquablation also represents one of the latest applications of robotic technology in urology.[9]

Technique

Aquablation technique was first described for liver resection with selective dissection of liver parenchyma leaving the bile ducts and blood vessels unharmed.[10, 11] The feasibility of this technology for open and laparoscopic treatment of organs such as the brain, kidney and lung parenchyma has also been demonstrated.[12-15] Similar hydro-dissection and water jet technology has been utilised and its safety and efficacy confirmed in the transurethral setting for resection of bladder tumors.[16] Simulated use and testing of the device has been completed in both animal and human cadavers and also confirmed the effectiveness, speed and reasonable haemostasis achieved by this device.[17]

The Aqua Beam systems have three main elements; the conformal planning unit (CPU), robotic hand-piece and a console.[18] The bi-planar transrectal ultrasound (TRUS) device is mounted into position with the patient placed in the dorsal lithotomy position under a general/spinal anesthesia. The bladder is then accessed using the 24-Fr hand-piece, which accommodates the scope. Transrectal ultrasound is used throughout the procedure. The robotic handpiece with an integrated cystoscope and ablation probe is inserted through the urethra and into the bladder. Positioning is confirmed by using visual markers on a computer screen, and the

urologist is able to plan the depth and angle of resection using the system software. Once the surgical mapping is complete, a high-speed jet of saline is delivered to the prostate at various flow rates, according to the depth of penetration needed. The ablated tissue is aspirated through ports in the handpiece and can be used for histological analysis. Haemostasis can be achieved by cautery or by inflating a Foley balloon catheter inside the prostatic cavity. The average resection time is typically about 3 to 5 minutes. After the procedure, a 3-way Foley catheter is placed under traction and continuous bladder irrigation is started. The Traction is removed 2 hours after the procedure and irrigation is progressively decreased. The catheter is removed before the patient is discharged from hospital, usually the day after the procedure.

Evidences and outcome measurements on current literature

There are only few studies on a small number of patients that have published the outcomes to assess the efficacy of this technology, and till date Level 1 evidence is still poor (Tables 1.2.I, 1.2.II). To measure the efficacy of Aquablation the studies looked at International Prostate symptom score (IPSS), Quality of life (QOL), sexual function, maximum urinary flow rate, Post void residual volume (PVR), urinary incontinence and Prostate volume reduction. While discontinuation of BPH medication was also considered, the safety aspects looked at were – bleeding, retrograde ejaculation, urinary retention, urethral stricture or adhesions or other damage, bladder spasm, urinary tract infection, dysuria, urinary urgency, frequency, leakage of urine, pain and these complications were reported as per the Clavien-Dindo grading.

Only one randomised controlled trial (WATER trial) compared the efficacy of Aquablation with TURP.[22] This showed, similar efficacy as TURP at a 1-year follow-up, but had a quicker resection time and was found to be better in preventing erectile dysfunction. Another recent study also compared the efficacy of Aquablation on <100 cc, >100 cc volume of prostate.[24]

Advantages

Aquablation holds a number of advantages. It is associated with a shorter resection time of less than 10 min which has been consistently achieved across multiple studies.[19] This can potentially avoid resection time related complications. The key anatomical structures such as the verumontanum and bladder neck can be spared by detailed radiographic mapping (using constant ultrasound) and by establishing a precise resection plane.[18] Moreover, there have been no cases of retrograde ejaculation, erectile dysfunction or incontinence reported in the literature so far. The potential for preservation of sexual function and urinary continence represent the key strengths for this novel surgery. However, only long-term results will confirm if this is truly the case. Its heat-free status is considered as the fundamental reason for a reduction in irritative urinary symptoms, which can be associated with alternative BPH surgeries. No major complications (>III Clavien-Dindo grading) have been reported in any of the human trials. The implementation of a CPU and integrated software has allowed for the learning curve to be reduced in comparison to counterparts such as holmium laser, which will support its uptake accordingly. The use of ultrasound guidance avoids exposure to ionising radiation and importantly, specimens can be collected for histological analysis.[25]

Disadvantages

The lack of long term follow up and the requirement for inpatient hospital admission are discussed as disadvantages in the literature. Similarly, its role in large prostate size is still evolving. But as the techniques to improve haemostasis gets better, it might help in doing this procedure as a day case.

Future improvements

Perhaps the technique can address its currently limitation on the role of aquablation for treatment of large prostates, large median lobes or patients with urinary retention.

TABLE 1.2.I Clinical outcomes from human trials.

Studies	Number (N)	RST (min)	↑IPSS	↑Qmax (mL/s)	↑PVR (mL)	Complications
Gilling *et al.*[19]	15	8	-14.5	10	-61	5 UR, 3 dysuria, 3 pelvic discomfort,1 bladder spasm; 1 cardiac arrhythmia
Anderson *et al.*[20]	9	5	-18.1	9.6	NA	NA
Desai *et al.*[21]	20	4	-19.5	8.3	-66	NA
Gilling *et al.*[2]	21	5	-16	9.6	-82.4	3 UR; 1 dysuria; 1 haematuria; 1 UTI; 1 bladder spasm; 1 meatal stenosis
WATER [22]						3-months primary safety endpoint:
Aquablation Trial	114	4	-17	10.9	-55	26% in Aquablation and 42% in
TURP	62	35.5	-15.4	8.9	-64	TURP
Deasi *et al.*[23]	47	4	-19.4	9.4	-76	6 UR; 1 hematuria requiring transfusion; 1 infection, 2 stricture
Bhojani *et al.*[24]	101				More in	6 BT- 2 in <100 cc and 4 in >100 cc.
<100cc					<100cc	-Clavien–Dindo grade 2 and higher
>100 cc		31	-16.5	8	group	adverse events were similar in both
		41	-10.6	11		groups

RST: resection time; IPSS: International Prostate Symptom Score; Qmax: maximum urinary flow; PVR: postvoid residual urine; UR: urinary retention; NA: not applicable; UTI: urinary tract infection; TURP: transurethral resection of the prostate; BT: blood transfusion

TABLE 1.2.II Demographics with follow-up on published studies on Aquablation.

Study	Type	Country	Time	Number (N)	Age	Volume (mL)	Key findings	Follow-up periods
Gilling *et al.*[22]	RCT	Australia, NZ, UK USA (17 sites)	2015-2016	184	66	30-80	Less MRT and LOS	6 months
Desai *et al.*[23]	Case series	India	NR	47	66	48	MRT- 4 min	3 months
Gilling *et al.*[19]	Case series	NZ	2013-14	15	73	54	MOT-48 min	6 months
Gilling *et al.*[2]	Case series	AUS, NZ	2013-14	21	70	57	MOT-45 min	1 year
Bhojani *et al.*[24]	Multi-centre trial	Canada USA	2017	101	45-80	80-150	MOT-(31-41), LOS-<2 days	6 months

MRT: mean resection time; MOT: mean operating time; LOS: length of stay; NR: not recorded; RCT: randomised controlled trial

Bhojani *et al.* and Chugtai *et al.*[24, 26] have recently published results of aquablation on large (>100 cc prostate) on 101 patients at 13 US and 3 Canadian centers (WATER II trial) between September and December 2017 and concluded that aquablation clinically normalises outcomes of patients with prostate size of <100 cc and >100 cc. It was found to be safe and effective in patients with large prostate glands with a smoother learning curve. Future work with aquablation will probably also emphasize the approaches to achieve hemostasis, as it has been variable and involved choices such as traction devices,