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ORIGINAL ARTICLE

Urinary and sexual function after treatment with temporary implantable nitinol device (iTind) in men with LUTS: 6-month interim results of the MT-06-study

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Abstract

Purpose To evaluate the functional outcomes as they relate to the preservation of urinary continence and sexual function after treatment with the temporarily implanted nitinol device (iTind; Medi-Tate Ltd, Israel); a novel minimally invasive treatment for lower urinary tract symptoms (LUTS) secondary to benign prostatic hyperplasia (BPH).

Methods Men with symptomatic BPH (IPSS ≥ 10, Q_{max} < 12 ml/s, and prostate volume (PV) < 120 ml) were invited to participate in this single-arm, prospective multicenter study (MT06). Patients were not washed out of BPH medications before the procedure. The iTind was implanted through a 22F rigid cystoscope under intravenous sedation and was removed 5–7 days later through a 22F Foley catheter under local anesthesia. Post-operative VAS and complications (Clavien Dindo-Grading System) were recorded. Preservation of urinary continence and erectile and ejaculatory function were assessed according to ISI, MSHQ-EjD and SHIM questionnaires. Post-operative IPSS, QoL, Q_{max} and PVR were also assessed at 1, 3, and 6 months post-operatively.

Results This interim report includes data out to 6 months on the first 70 patients enrolled in the study. The median age was 62.31 years, and the mean prostate volume was 37.68 ml (15–80 ml). Baseline and follow-up data are reported in Table 1. No intraoperative complications were observed, the average post-operative VAS score was 3.24 ± 2.56. On average patients returned to daily life after 4.3 days following the retrieval procedure. Sexual function and urinary continence were preserved in all subjects according to the ISI, SHIM and MSHQ-EjD questionnaires and significant improvements ($p < 0.0001$) from baseline levels were recorded in IPSS, QoL and peak flow.

Conclusion iTind is a well-tolerated, minimally invasive treatment for BPH-related LUTS which preserves sexual function and urinary continence, offers a rapid recovery and return to daily life, and a significant improvement of symptoms and urinary flow at 6-month follow-up.

Keywords iTind · LUTS · BPH · Functional · Outcomes

Introduction

Lower urinary tract symptoms (LUTS) secondary to benign prostatic hyperplasia (BPH) are highly prevalent in adult men [1]. Since the quality of life of these patients can be significantly impaired by the associated bothersome symptoms, several treatments have been proposed, such as lifestyle changes, pharmacological therapy, and surgical procedures [2–4]. Transurethral prostatic resection (TURP) is still considered the gold standard when surgery is indicated in LUTS/BPH patients, even though this procedure is associated with significant morbidity. TURP is associated with a 2.5–4.2% risk of blood transfusion, a 5.5% risk of

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clot retention and a 2–3% risk of TUR syndrome due to an electrolytic imbalance. Other complications that have been reported in more than 5% of patients include sexual dysfunction, including retrograde ejaculation and erectile dysfunction persistent storage symptoms bladder neck contracture, urethral stricture, the need for blood transfusion, and urinary tract infection [5–7]. A variety of minimally invasive surgical therapies have been developed to address the limitations and shortcomings of surgery for the management of LUTS/BPH with emphasis on reducing the risk of post-procedural morbidity, specifically those pertaining to urinary incontinence and erectile and ejaculatory function [8–11]. The risk of experiencing one or more of these complications is a concern for many patients, and avoidance of these perceived risks is often one of the predominant factors discouraging them from undergoing an invasive treatment or beginning some medical therapies [12]. Moreover, there is an increasing population of men with bothersome LUTS that is not responsive to pharmacotherapy and also not fit for surgery as the result of concomitant comorbidities which may increase their risk of bleeding or undergoing anesthesia [13, 14]. The temporarily implanted nitinol device (iTind® Medi-Tate Ltd., Or Akiva, Israel) is a device consisting of nitinol struts which is positioned endoscopically into the prostatic urethra to remodel the bladder neck and prostatic urethra and provide relief from bothersome LUTS secondary to BPO [13, 15, 16] Although several studies have evaluated the safety and efficacy of iTind in patients with LUTS with excellent results in terms of symptoms relief and improvement in flow, no studies have been published evaluating the impact of this new device on urinary continence and sexual function using the validated tools. The aim of our study was to evaluate the preservation of urinary continence, erectile and ejaculatory function after treatment with the second generation iTind in patients with LUTS/BPH.

Materials and methods

From June 2018 to September 2019, a consecutive series of patients with moderate/severe LUTS/BPH looking to conserve their ejaculatory function were enrolled. The study protocol was approved by the Ethics Committee and was in accordance with the principles of the Declaration of Helsinki. All patients signed a dedicated informed consent to be included in the study. The study is a single-arm, prospective multicenter study (MT-06). This interim report includes the 6-month follow-up of the first 70 patients enrolled in the first 5 centers in Italy and Spain.

The study's inclusion criteria were IPSS ≥ 10; $Q_{max} < 12$ ml/s; prostate volume (PV) < 120 ml; normal urinalysis and urine culture. Exclusion criteria included previous prostate surgery; prostate cancer; urethral stricture; bladder stones; urinary tract infections (UTI); obstructing median lobe (considered > 1.2 cm); and neurological conditions potentially affecting voiding function.

Patients were not washed out of drug therapy for BPH (alpha-blockers and/or 5-alpha reductase inhibitors) and did not stop anti-coagulation or anti-platelet therapy before the procedure.

Collected data

At baseline, patients' clinical history was evaluated, and a physical examination including digital rectal examination (DRE), uroflowmetry, evaluation of prostatic specific antigen (PSA), transrectal ultrasound (TRUS), urinalysis and urine culture was carried out. Moreover, validated questionnaires were used to assess urinary symptoms: International Prostate Symptoms Score (IPSS), sexual function (Sexual Health Inventory for Men questionnaire (SHIM)), ejaculatory function (Male Sexual Health Questionnaire—(MSHQ-EjD)) and incontinence (Incontinence Symptom Index questionnaire (ISI)).

Surgical technique

The patient is positioned in the lithotomy position and a 22F rigid cystoscope with continuous irrigation is introduced. The iTind is then pushed into the bladder through the cystoscope sheath. The cystoscope is then re-introduced and the device is retracted into the prostatic urethra and positioned under direct vision so that the anchoring the leaflet is at the 6 o'clock position behind the bladder neck and the distal end of the device is protruding into the bladder. The end of the guidewire is cut, completing the deployment of the device, and the positioning is verified with a second urethra-cystoscopy. All procedures were performed in an outpatient setting under local anesthesia and light sedation. No post-operative catheterization is required [4, 17, 18]. Device retrieval was performed through a 22F silicone Foley catheter under local anesthesia 5–7 days after the procedure, as previously described. All patients discontinued drug therapy for BPH after device retrieval.

Follow-up

Follow-up visits were carried out at 4 weeks, 3 and 6 months from device retrieval. Patients completed IPSS, SHIM, MSHQ-EjD, ISI and QoR questionnaires and question 32 of the EPIC questionnaire. VAS pain scores (Visual Analogic Scale) were recorded directly following the implantation and retrieval procedures. Complications were evaluated according to the modified Clavien–Dindo classification system [19].

Statistical analysis

Statistical analysis was performed using SPSS 24.0 software (SPSS Inc, Chicago, IL, USA) and STATA 24.0 software (Stata Corp LLC). Evaluation of data distribution confirmed a not normal distribution of the study dataset. Differences in peak flow rate, post-void residual (PVR), IPSS, QoL, MSHQ-EjD, SHIM and ISI before and after iTind implantation were assessed using the Wilcoxon test. An alpha value of 5% was considered as the threshold for significance. Data are presented as median with inter-quartile range (IQR).

Results

Overall, 70 patients were included in this analysis, with a median age of 62.3 years (IQR 45/75), and a mean prostatic volume (PV) of 37.68 ml (IQR 15–80 ml). Of them, 31% were previously under drug therapy for BPH (Table 1). All patients successfully completed the procedure and no intraoperative complications were observed. The average VAS score recorded after the implantation procedure was 3.2 ± 2.6. VAS scores were also recorded over the implantation period until device removal and showed a gradual decrease to 2.6 ± 2.0 by day 3, 2.1 ± 1.9 by day 5, and 1.5 ± 2.2 by day 7. The average VAS score recorded following the removal procedure was 3.4 ± 2.7. Overall, 75 complications were detected in 70 patients.

Table 1 Baseline characteristics of the study population (N = 70 patients)

Demographic characteristics	Mean (SD)
Age (years)	62.3 (9.5)
BMI (Kg/m^2)	26.3 (3.3)
Non-invasive investigations	Mean (SD)
IPSS Urinary symptoms	21.2 (6.0)
QoL	4.1 (1.0)
Q_{max} (ml/s)	7.3 (2.2)
PVR (ml)	69.3 (86.8)
Prostate volume (ml)	37.68
LUTS medications	Numbers (%)
Alpha blockers	20 (28.5%)
5-ARIs	2 (2.8%)
Chronic anti-coagulant/platelet medications	Numbers (%)
Anti-coagulant therapy	6 (8.6%)
Anti-platelet therapy	11 (15.7%)
Dual anti-platelet therapy	3 (4.3%)
Comorbidities	Numbers (%)
Diabetes	7 (10%)
Hypertension	37 (52.8%)
High cholesterol	12 (17%)
Heart disease	19 (27%)

All complications except for one were graded as I or II according to the Clavien–Dindo system and were self-limiting, with 75% of patients recovering from all their AEs within 7 days (Table 2). The most common complication was transient hematuria (18%) which was recorded postoperatively and when the device was in place. Of note, 20 of the 70 patients (28.5%) were on active anti-coagulant (6) or anti-platelet therapy (14) and only 4 of them experienced transient hematuria. In six patients (9.6%), we observed transient incontinence which resolved after device removal. Three patients (4.2%) had a temporary AUR (acute urinary retention), two with the device in situ and one 12 h after device removal. All patients in AUR were treated with the temporary placement of a 10–12F Tiemann catheter. Only one patient presented a Clavien 3 complication (1.4%), specifically gross haematuria presenting a few days following iTind removal in a patient with a large prostate (80 g), requiring endoscopic fulguration. On average, patients returned to daily life 4.3 days following the retrieval procedure.

At 6 months, erectile and ejaculatory function and urinary continence were preserved in all 70 cases and even improved according to the MSHQ-EjD questionnaire (Table 3). Moreover, statistically significant improvements in symptoms (IPSS 21.2 ± 6.0–8.3 ± 6.7; $p < 0.0001$), quality of life (IPSS $Q8$ 4.13 ± 1.01–1.96 ± 1.45, $p < 0.001$) and uroflowmetry (Q_{max} 7.34 ± 2.22–12.08 ± 5.35; $p < 0.0001$) were recorded (Table 3). No significant changes in PVR were recorded ($p > 0.05$). Data at 4 weeks and 3 months were not statistically significant vs 6 months ($p > 0.05$) (Table 3).

Table 2 Reported complications according to modified Clavien–Dindo classification

	N	%
Clavien–Dindo Grade1		
Transient haematuria	13	18.6%
Dysuria	12	17%
Urgency	9	12.8%
Frequency	5	7%
Pain	8	11.4%
Transient urinary incontinence (device in situ)	6	8.4%
Clavien–Dindo Grade > 3°		
Acute urinary retention	3	4.2%
Clavien–Dindo Grade 3b		
Gross haematuria	1	1.4%

Table 3 Summary of functional results up to 6 months of follow-up

	4 Weeks $N = 70$	3 Months $N = 70$	6 Months $N = 70$
IPSS URINARY SYMPTOMS			
Baseline	21.2 ± 6.0	21.2 ± 6.0	21.2 ± 6.0
Follow-up	9.5 ± 6.8	7.8 ± 5.4	8.3 ± 6.7
Change	− 11.7 ± 8.3	− 13.4 ± 6.4	− 12.7 ± 6.9
p	< 0.01	< 0.01	< 0.01
IPSS-QoL			
Baseline	4.1 ± 1.0	4.1 ± 1.0	4.1 ± 1.0
Follow-up	1.8 ± 1.4	1.6 ± 1.3	2.0 ± 1.4
Change	− 2.4 ± 1.5	− 2.5 ± 1.6	− 2.2 ± 1.6
P	< 0.01	< 0.01	< 0.01
Peak flow rate (ml/s)			
Baseline	7.3 ± 2.2	7.3 ± 2.2	7.3 ± 2.2
Follow-up	13.2 ± 5.5	11.8 ± 5.1	12.0 ± 5.4
Change	5.8 ± 5.5	4.5 ± 5.2	4.6 ± 5.5
P	< 0.01	< 0.01	< 0.01
Post-void residual (ml)			
Baseline	69.3 ± 86.8	69.3 ± 86.8	69.3 ± 86.8
Follow-up	49.2 ± 74.5	33.4 ± 46.2	48.1 ± 72.7
Change	− 19.4 ± 95.4	− 37.4 ± 90.5	− 22.6 ± 77.3
P	0.13	0.11	0.12
SHIM: total score			
Baseline	16.1 ± 7.7	16.1 ± 7.7	16.1 ± 7.7
Follow-up	18.0 ± 7.6	18.7 ± 7.7	18.2 ± 8.2
Change	1.9 ± 4.8	2.3 ± 6.9	2.2 ± 7.4
P	0.09	0.07	0.06
ISI: total score			
Baseline	1.1 ± 1.9	1.1 ± 1.9	1.1 ± 1.9
Follow-up	0.6 ± 1.4	0.9 ± 1.7	0.8 ± 1.6
Change	− 0.5 ± 1.7	− 0.3 ± 1.5	− 0.3 ± 1.4
P	0.21	0.14	0.14
MSHQ-EJD: total score			
Baseline	9.2 ± 4.9	9.2 ± 4.9	9.2 ± 4.9
Follow-up	10.7 ± 4.6	11.1 ± 4.9	11.2 ± 4.8
Change	1.5 ± 5.1	1.8 ± 5.2	2.0 ± 4.4
P	< 0.01	< 0.01	< 0.01

Discussion

The interim results of the present multicenter prospective single-arm study demonstrate that the iTind procedure preserves urinary continence and erectile and ejaculatory function as measured by the accepted tools. Moreover, the short-term efficacy of iTind in patients with LUTS/BPH is also demonstrated with a statistically significant improvement in symptoms, quality of life and uroflowmetry recorded at 6 months. Finally, the procedure may be considered safe (only one Clavien–Dindo 3 complication was recorded). In our experience, iTind is of particular benefit to LUTS/BPH patients seeking a minimally invasive treatment associated with a significant improvement in symptoms with no side effects in terms of erectile or ejaculatory function. Nowadays, there is a growing interest in minimally invasive surgical therapies for male LUTS/BPH [20]. The hallmarks of a successful minimally invasive surgical treatment include a rapid and durable relief of symptoms, a fast recovery, minimal adverse events and an ambulatory procedure with minimal anesthesia requirements [13, 21–23]. All these characteristics are evident for the iTind which is a novel device used to alleviate symptoms by creating incisions in the prostate via mechanical stress [24]. One of its principal advantages, especially compared to other minimally invasive intraprostatic permanent implants, is its temporariness, which can prevent the potential complications associated with a permanent device. The possibility of preserving sexual function, in particular antegrade ejaculation, which can be negatively influenced by most of the available LUTS/BPH medical and surgical treatments represents another significant benefit of the iTind.

To date, one single-center, single-arm prospective study has evaluated the first-generation TIND and another multicenter, international single-arm study has evaluated the second-generation iTind in LUTS/BPH patients. Porpiglia et al. [18] evaluated the first-generation TIND in a study including 32 patients with an IPSS ≥ 10, Q_{max} < 12 ml/s, and a prostate volume < 60 ml. As in the current study, no intraoperative complications were recorded. Four post-operative complications (4/32; 12.5%) were recorded, including urinary retention, transient incontinence due to device displacement, prostatic abscess, and urinary tract infection. No late complications were recorded. Patients were followed for 1, 2 and 3 years. No patients required adjunctive surgical treatments during the 3-year follow-up period and it was concluded that TIND implantation is a feasible, safe and minimally invasive option for the treatment of BPH-related LUTS with results durable to 36 months. This study did not actively evaluate sexual outcomes, although no patients who were sexually active at baseline reported a deterioration of sexual function following the procedure.

Later, Porpiglia et al. [15] presented their experience with the second generation iTind. Overall, 81 patients were enrolled with similar baseline characteristics to the current study (mean patient age was 65 years, mean prostate volume was 40.5 ml, and mean preoperative Q_{max} was 7.3 ml/s, mean preoperative IPSS was 22.5). Most of the complications were low grade and self-limiting: haematuria (12.3%), urgency (11.1%), pain (9.9%) and dysuria (7.4%). UTIs were recorded in five cases (6.2%). As in our experience at the 6-month follow-up, 85.2% of the treated patients reported a ≥ 3 points improvement in IPSS, and at 12 months, the average reduction in IPSS was 60% from baseline. This improvement in symptoms and functional results continued to be demonstrated in these patients out to 2 years.

Our study is clearly in line with these experiences and confirms the efficacy and safety of iTind for the treatment of patients with LUTS/BPH. In addition, about 30% of the study population were successfully treated without discontinuing their anti-coagulant or anti-platelet medication, which highlights the possible role of the iTind in these groups of patients.

In the previous studies, preservation of erectile and ejaculatory function was either self-reported or evaluated using two non-validated questions: (1) Are you capable to perform sex? (2) Do you have ejaculation upon orgasm? Our study has the merit to specifically focus on erectile and ejaculatory function and urinary continence with validated questionnaires.

Ejaculation disorders still remain a major concern when dealing with BPH treatments. Recently Cacciamani et al. [25] showed in a systematic review that the new treatment modalities such as Greenlight laser vaporization, Aquablation and prostatic artery embolization (PAE) are associated with a reduced, but still present, risk of ejaculatory function when compared to TURP. Their study also confirmed the lack of well-designed studies evaluating ejaculatory dysfunction using dedicated questionnaires as the MSHQ in LUTS/BPH patients, especially considering that ejaculation disorders are known to affect patients' quality of life and that this remains a major outcome measure when dealing with LUTS/BPH surgery. Furthermore, a reduced quality of life is the primary factor that motivates patients to seek medical advice. Recently, it has been highlighted that when considering treatments for LUTS/BPH patients are willing to trade a degree of efficacy for a lower risk of ejaculation disorders [17]. For this reason, when discussing surgical options with patients, postoperative ejaculatory disorders should always be considered. According to the current EAU guidelines, the only approved ejaculatory sparing technique is the prostatic urethral lift, while prostatic embolization, convective water vapor energy ablation (Rezum), image guided robotic waterjet ablation (Aquabeam) and the iTind are still considered investigational. In the near future, RCTs comparing these different minimally invasive techniques will better clarify their role in patients looking to spare ejaculatory function.

We must also acknowledge some limitations to our study. First of all, a possible limitation is the single-arm design of the study and the limited reported follow-up. However, although a 6-month follow-up could be considered a limitation, it is an adequate time to evaluate functional outcomes. Recruitment of patients to this study is still on-going and a longer follow-up (up to 3 years) will ensue to evaluate the efficacy and durability of the procedure. These results will be available in the near future. Furthermore, patients' characteristics and clinical outcomes are similar in the different centers and so far, the multicentre fashion of the study should also be considered as a merit. Another possible limitation is that we have not used the full MSHQ questionnaire to assess the different domains of male sexual function. However, in our study, ejaculatory and erectile function was assessed with the MSHQ-EJD and SHIM questionnaires, which are validated tools to assess sexual dysfunction in male BPH patients. A study including the complete MSHQ questionnaire is also planned and the results will be available in the near future. The lack of urodynamic data is another important limitation. Urodynamic data would better highlight the effect of iTind on bladder outlet obstruction, even in patients with a concomitant detrusor underactivity. However, as stated by the EAU guidelines, urodynamic investigation in LUTS/BPH patients is recommended only in selected cases, which were not included in our series [1].

Finally, the results of our study clearly showed that iTind is effective in a selected group of patients (moderate/severe LUTS/BPH patients looking to preserve their ejaculatory function) although it cannot be extended to all patients with LUTS/BPH. It takes more than one study to prove a hypothesis and future RCTs are needed to confirm the short- and long-term safety and efficacy of iTind or to compare the iTind to TURP or other minimally invasive treatments which are proven to reduce the risk of ejaculatory dysfunction. Our findings certainly need further confirmation in different populations, however notwithstanding all these limitations, our study is the first multi-center study that confirms the efficacy and safety of iTind in terms of erectile and ejaculatory function and urinary continence evaluated with validated questionnaires.

Conclusions

The iTind is a well-tolerated, minimally invasive treatment for LUTS/BPH, offering a rapid recovery and return to daily life, preservation of erectile and ejaculatory function and urinary continence as well as a significant improvement of symptoms, quality of life and urinary flow at 6-month follow-up. Further studies are necessary to assess the durability of these results and to compare the iTind with other minimally invasive treatments with a proven minimal impact on ejaculatory function.

Author contributions CDN: project development, data management, data analysis, manuscript writing and editing. FC: project development, data management, data analysis, manuscript writing and editing. CF: data collection and management and manuscript editing. FC: data collection and management, and manuscript editing. PT: protocol development, data management, data analysis, manuscript writing and editing. DA: protocol development, data management and manuscript editing. VB: protocol development, data management and manuscript editing. JRE: protocol development, data management, manuscript writing and editing. FGS: protocol development, data management,

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The article does not contain any studies with animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study.

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