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ARTICLE

Clinical Research

3-Year results following treatment with the second generation of the temporary implantable nitinol device in men with LUTS secondary to benign prostatic obstruction

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Abstract

Background To report the 3-year results of a prospective, single arm, multicenter, international clinical study with the second generation of the temporary implantable nitinol device (iTIND; Medi-Tate Ltd®, Israel) on men suffering lower urinary tract symptoms (LUTS) secondary to benign prostatic obstruction (BPO).

Methods Eighty-one men with symptomatic BPO (IPSS ≥ 10, peak urinary flow <12 ml/s, and prostate volume <75 ml) were enrolled in this study between December 2014 and December 2016. Subjects were washed-out 1 month for alpha-blockers and 6 months for 5-ARIs. The implantation was performed under light sedation and the removal 5–7 days later with topical anesthesia. Perioperative results including OR-time, pain (VAS) postoperative complications (Clavien–Dindo-Grading System), functional results (Qmax, IPSS, PVR) and quality of life (QoL) were assessed at 1, 3, 6 months, 1, 2, and 3 years. Sexual and ejaculatory function were evaluated using two yes/no questions.

Results Thirty-six month functional results were available for 50 patients and demonstrated that iTIND efficacy remained stable through 3 years, with averages IPSS, QOL, Qmax and PVR of 8.55 + 6.38, 1.76 + 1.32, 15.2 + 6.59 ml/s and 9.38 + 17.4 ml, improved from baseline by −58.2, −55.6, +114.7, and −85.4% (all significantly different from their corresponding baseline values, $p < 0.0001$). Even considering the Intention to Treat analysis (ITT), the 36-month results confirmed significant improvements of the functional outcomes if compared with baselines values (all $p < 0.0001$). No late post-operative complications were observed between 12 and 36 months. Sexual function was stable through 3 years, with no reports of sexual or ejaculatory dysfunctions. No patients underwent alternative treatments between 24 and 36 months.

Conclusion Treatment of BPO-related LUTS with iTIND demonstrated a significant and durable reduction in symptoms and improvement of functional parameters and quality of life at 3 years of follow-up. No late post-operative complications, ejaculatory dysfunction or additional treatment failures were observed between 24 and 36 months.

Introduction

Lower urinary tract symptoms (LUTS) secondary to benign prostatic obstruction (BPO) is one of the most common conditions which can negatively impact the quality of life of men in their lifetime. Prevalence of benign prostatic hyperplasia (BPH) that can lead to BPO starts at age 40–45 years, reaches 60% by age 60, and can be as much as 80% by age 80 [1].

Treatment for reducing LUTS secondary to BPO often begins with watchful waiting and implementation of lifestyle changes, and then progresses to pharmaceutical therapy with the use of selective alpha-blockers, with or without 5-alpha reductase inhibitors [2, 3]. Despite pharmaceutical therapy being considered the first line of treatment, many

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patients are unhappy with the level of symptomatic relief it offers, or are bothered by treatment-induced side effects, such as dizziness and sexual dysfunction. For this reason, treatment compliance is low, with only ~29–30% of patients adhering to treatment during the first 12 months [3, 4].

The gold standard surgical treatment for BPH today is trans-urethral resection of the prostate (TURP), which offers a significant and durable reduction in symptoms and increase in urinary flow. However, TURP is also associated with a 20% morbidity rate, including urinary incontinence (3%), bleeding requiring blood transfusion (2.9%), urethral stricture (7%), TUR syndrome (1.4%), erectile dysfunction (10%) and retrograde ejaculation (65%) [5–7].

New, laser-based ablative techniques, while also effective in providing relief of BPH-related symptoms, still present complications similar to those seen with TURP [7–9].

The temporary implantable nitinol device was developed to offer an effective and minimally invasive alternative for treating LUTS due to BPO through the use of a temporarily implanted device. The device, left in place for only 5–7 days, remodels the prostatic urethra and bladder neck through ischemic pressure, effectively relieving the obstruction to the bladder outlet without ablating or resecting tissue, and without leaving a permanent implant in the body.

In the first-in-man, 3-year clinical study of the first-generation device (TIND; Medi-Tate Ltd., Israel), and in the multicenter, prospective analysis of the 1 and 2 years performance of the second-generation device (iTIND), this minimally invasive approach demonstrated safety and effectiveness leading to significant and stable relief of BPO-associated LUTS as measured by IPSS, QoL, and improved functional results [10–13].

The aim of the present study is to report on the outcomes of patients 3 years after treatment with iTIND.

Patients and methods

In this prospective, single arm, multi-center international study, men with lower urinary tract symptoms secondary to BPO were treated and followed annually for 3 years. Subjects were enrolled at 9 centers in Italy, Switzerland, Belgium, the UK, Spain and Hong Kong between December 2014 and December 2016. The study was approved by the institutional ethics committee at each participating study site and conducted in accordance with Good Clinical Practice guidelines, in compliance with the World Health Organization guidelines, and was registered at www.clinicaltrials.gov (ID: NCT02145208). Written informed consent was obtained from all participants included in this study. Enrollment was limited to men with an International Prostate Symptom Score (IPSS) ≥ 10, a prostate volume <75 ml, a maximum urinary flow rate (Qmax) of <12 ml/s, a measured pos-void residual (PVR) urine <250 ml, normal urinalysis, complete blood count and biochemistry values. Excluded from enrollment were patients with obstructive median lobe, previous prostate surgery, prostate or bladder cancer, neurogenic bladder and/or sphincter abnormalities, or confounding bladder pathologies based on medical history, recent cystolithiasis or hematuria, active urinary tract infection, compromised renal function, active antithrombotic or antiplatelet treatment, cardiac disease, including arrhythmias and uncontrolled diabetes mellitus. Participants were required to undergo a washout and discontinue the use of any medications for LUTS secondary to BPH prior to treatment, 1 month for alpha-blockers and 6 months for 5α-Reductase inhibitors. Baseline patient's information including medical history, BPH-related medications, uroflowmetry, IPSS, PVR, and quality of life (QoL) assessment was collected up to 40 days before the procedure. Peri- and postoperative results including OR-time, pain (VAS), complications (modified Clavien–Dindo-Grading System) and adverse events were recorded. Functional results (PVR, Qmax, IPSS) and quality of life (QoL) were evaluated at 1, 3, and 6 months, and 1, 2 and 3 years. Sexual and ejaculatory function were considered with two yes/no questions: (1) are you capable of performing sex? (2) Do you ejaculate upon orgasm?

Device design, mechanism of action, and surgical procedure

The design of the iTIND device, the differences between the first TIND and second-generation iTIND devices, the mechanism of action, and implantation and removal procedures have already been outlined in previous publications [10–13].

In brief, the second-generation iTIND device is comprised of 3 nitinol "struts", and an anti-migration anchoring leaflet. Placed at the bladder outlet, within the prostatic urethra and bladder neck, for 5–7 days, it expands and exerts radial force on the tissue, causing ischemic incisions at the 12, 5, and 7 o'clock positions (Fig. 1).

The device is implanted under direct vision through a standard rigid 19F-22F cystoscope under light intravenous sedation, and removed in outpatient setting through an open-ended 22F Foley catheter with topical anaesthesia. Catherization is not required after either implantation or after removal of the device.

Statistical analysis

Feasibility and safety of the procedure and functional, sexual, and ejaculatory function were assessed up to 36 months. Treatment failure was defined as any surgical treatment for recurrent/persistent LUTS during follow-up.

Data were expressed as means and standard deviations (SDs) for continuous variables, and as frequencies and proportion along with corresponding confidence interval for categorical variables. The means of continuous variables were compared by using the paired Student's *t*-test after verifying that the variables to be analyzed were approximately normally distributed.

The analysis up to 36 months of follow-up was performed on intention-to-treat basis (ITT). For IPSS, QOL, Qmax and PVR, change from baseline was evaluated using general estimating equation model (GEE) with baseline value and visit as predictors. Exchangeable correlation structure and identity link were used. In addition, to avoid the misleading artifact of the attrition of participants from the study imputation of missing values was done using last observation carried forward (LOCF). A $P < 0.05$ was considered to indicate statistical significance. SAS® (Cary, NC, USA), version 9.4 for Windows was used for all statistical analyses.

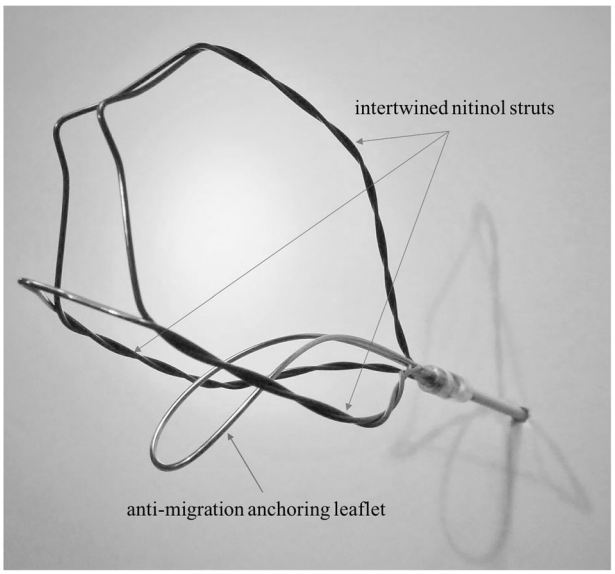

Fig. 1 Structure of the iTIND device. The device is composed of 3 intertwined nitinol struts (red arrows) and an anchoring leaflet (blu arrow).

Results

A total of 81 patients were recruited into the study with a mean age of 63.94 and an average prostate volume of 40.5 (12.25) ml. At baseline mean IPSS was 22.5 (5.6), Qmax was 7.3 (2.6) mL/s, and the median (interquartile range) IPSS QoL score was 4 (2–5) (Table 1). All iTIND implantations were successful with no intraoperative complications and a median (range) VAS pain score of 4 (0–10). All patients were discharged on the same day as the surgery without a catheter. Devices were retrieved at a mean (SD) of 5.7 (0.9) days after implantation. All procedures were uneventful, with a mean (range) VAS pain score after device removal of 2 (0–10).

All perioperative complications were self-resolving and graded as I or II according to the Clavien–Dindo system: haematuria (12.3%), micturition urgency (11.1%), pain (9.9%), dysuria (7.4%), and UTI (6.2%) and occurred in the short-term (54.7% ≤7 days; 30.2% 8–20 days; 15.1% 20–30 days). Eight cases of urinary retention were recorded (9.9%), five while the device was in place, and three after device removal (Table 2).

At 3 years of follow-up, data were available for 50 patients. Only 1 subject was lost between the 24 and 36 months follow-up, withdrawing consent following emigration to his home country (Fig. 2).

Functional results demonstrated that iTIND efficacy remained stable through 3 years, with averages in IPSS, QOL, Qmax, and PVR of 8.55 ± 6.38, 1.76 ± 1.32, 15.2 ± 6.59 ml/s,

Table 1 Baseline and perioperative parameters in both ITT and PP populations.

Patients	Enrollment (ITT) Baseline values $N = 81$	3-year follow-up (PP) Baseline values $N = 50$
Age (median, IQR, years)	65 (45.5–84.5)	62.79 (45.5–83.74)
BMI (median, IQR, kg/m2)	26.1 (18.5–35.1)	26.1 (18.5–35.1)
PSA level (mean, SD, ng/ml)	1.7 ± 1.4	1.8 ± 1.3
Prostate volume (median, IQR, ml)	40 (16–69)	37 (16–65)
PVR (mean, SD, ml)	77.25 ± 55.17	68.84 ± 39.06
Qmax (ml/sec)	7.3 ± 2.6	7.64 ± 2.25
IPSS score (mean, SD, pt.)	22.5 ± 5.6	20.60 ± 4.58
QoL score (median, IQR, pt.)	4 (2–5)	4 (2–5)
Capable of performing sex (erectile function), *n* (%)	74 (91.3)	48 (96.0)
Ejaculate upon orgasm, *n* (%)	72 (88.8)	48 (96.0)
Median lobe, *n* (%)	10 (12.3)	0 (0)

Table 2 Treatment-related adverse events stratified by Clavien–Dindo classification grade.

AE	No. patients (%)			
	0–1 month	1–12 months	12–24 months	24–36 months
Clavien–Dindo grade I				
Hematuria	10 (12.3%)			
Dysuria	6 (7.4%)			
Urgency	9 (11.1%)			
Pain	8 (9.9%)			
Clavien–Dindo grade II				
UTI	5 (6.2%)			
Clavien–Dindo grade IIIa				
AUR	8 (9.9%)			
Failed voiding trial after implantation; resolved before discharge	5 (6.2%)			
Clavien–Dindo grade IIIb				
Stricture	0 (0%)			
Device migration	0 (0%)			
Secondary treatment (TURP, Laser)	2 (2.5%)	5 (6.2%)		

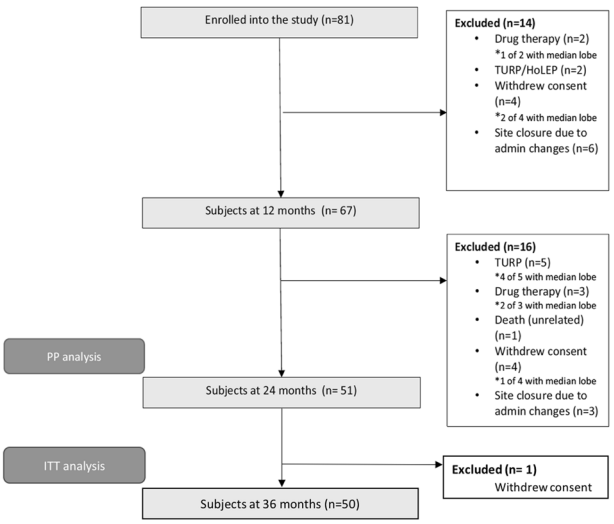

Fig. 2 Study enrollment flowchart. From enrollment to 36-month follow-up.

and 9.38 ± 17.4 ml, improvements from baseline of −58.2%, −55.6%, +114.7%, and −85.4%, respectively (Table 3a). All these variables were significantly different from their corresponding baseline values ($p < 0.0001$).

Even considering the ITT–LOCF analysis set (Table 3b), the 36-month results showed statistically significant improvements ($p < 0.0001$) of the functional outcomes when compared with baselines values (averages IPSS, QOL, Qmax, and PVR of 12.05 ± 6.38, 2.22 ± 1.44, 13.43 ± 8.41 ml/s and 42.6 ± 71.1 ml, improved from baseline by −46.1%, −43.3%, +101.1%, and −36.1%).

Of note, the ITT patient population includes those patients who were identified as having median lobes which was found to be a predictor for treatment failure between 12 and 24 months of follow-up [13].

Figure 3 shows the values of IPSS, IPSS QoL, and Qmax at every time point from baseline to 3 years follow-up (both via PP analysis with no imputation and ITT analysis with LOCF imputation).

No adverse events were recorded between 12 and 36 months, and none of the patients who were previously sexually active reported a deterioration in sexual or ejaculatory abilities according to the yes/no questions during follow-up.

From baseline to 24 months, 5 (6.2%) patients required drug therapy and 8 (8.6%) patients underwent surgical retreatment. No additional patients underwent alternative treatments (either medical and surgical) between 24 and 36 months.

Discussion

Benign prostatic hyperplasia (BPH) is a common problem among older men and can have a significant impact on their quality of life. International guidelines for BPH suggest that patients with moderate-to severe LUTS are best managed initially with drugs [14]. Invasive treatments are delayed until either patients fail a trial of medical therapy, the degree of bother to the patient is significant, or there is a risk of complications due to disease progression [5–7]. However, in daily practice adherence to drug therapy is low, with only 29–30% of patients continuing treatment at 12 months [3, 4]. Additionally, despite the low rates of patient compliance with drug therapy, very few patients chose to undergo surgery; with only ~3% of patients undergoing

Table 3 (a) Outcome measures after iTIND—4 weeks to 36 months PP Analysis Set; (b) outcome measures after iTIND—4 weeks to 36 months (ITT–LOCF Imputation Analysis Set).

a	4 weeks	3 months	6 months	12 months	24 months	36 months
IPSS						
N	78	75	70	67	51	50
Baseline	22.22 ± 5.62	22.41 ± 5.72	21.99 ± 5.48	21.70 ± 5.56	20.51 ± 4.58	20.69 ± 4.58
Follow-up	11.72 ± 7.99	9.77 ± 6.69	9.75 ± 7.10	8.78 ± 6.41	8.51 ± 5.51	8.55 ± 6.38
Change	−10.50 ± 8.32	−12.63 ± 7.40	−12.23 ± 6.79	−12.92 ± 6.92	−12.00 ± 6.12	−12.14 ± 6.95
% change	−46.3 ± 33.2	−55.0 ± 29.3	−56.4 ± 27.5	−59.1 ± 26.3	−56.7 ± 25.6	−58.2 ± 32.1
(95% CI)	(−54.0%, −38.5%)	(−61.9%, −48.1%)	(−63.0%, −49.8%)	(−65.7%, −52.5%)	(−64.1%, −49.4%)	(−67.4%, −49.0%)
P value	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
QOL						
N	78	75	70	67	51	50
Baseline	4.00 ± 0.84	3.97 ± 0.84	3.97 ± 0.84	3.97 ± 0.87	3.96 ± 0.87	3.96 ± 0.87
Follow-up	2.08 ± 1.35	1.83 ± 1.30	1.81 ± 1.30	1.59 ± 1.29	1.76 ± 1.32	1.76 ± 1.32
Change	−1.92 ± 1.50	−2.14 ± 1.48	−2.16 ± 1.44	−2.38 ± 1.60	−2.20 ± 1.46	−2.20 ± 1.46
% change	−45.8 ± 34.4	−51.7 ± 34.9	−53.3 ± 32.5	−56.9 ± 38.5	−54.0 ± 38.5	−55.6 ± 37.0
(95% CI)	(−53.8%, −37.8%)	(−59.9%, −43.5%)	(−61.1%, −45.5%)	(−66.5%, −47.3%)	(−64.8%, −43.2%)	(−66.2%, −45.0%)
P value	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Qmax (ml/s)						
N	78	75	70	67	51	50
Baseline	7.28 ± 2.49	7.44 ± 2.43	7.58 ± 2.43	7.61 ± 2.25	7.62 ± 2.25	7.71 ± 2.26
Follow-up	11.23 ± 5.66	12.40 ± 7.52	13.69 ± 6.26	14.91 ± 8.06	16.00 ± 7.43	15.20 ± 6.59
Change	3.94 ± 5.22	4.96 ± 6.96	6.12 ± 6.22	7.30 ± 8.20	8.38 ± 7.93	7.49 ± 6.86
% change	79.4 ± 167.7	75.4 ± 105.2	95.6 ± 106.5	111.7 ± 147.1	130.8 ± 132.2	114.7 ± 108.5
(95% CI)	(41.1%, 117.7%)	(50.7%, 100.1%)	(70.1%, 121.2%)	(74.3%, 149.0%)	(93.3%, 168.4%)	(83.2%, 146.2%)
P value	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Post-void residual urine (ml)						
N	78	75	70	67	51	50
Baseline	76.17 ± 55.52	73.96 ± 52.89	78.70 ± 56.11	73.54 ± 49.54	65.84 ± 38.46	68.58 ± 39.53
Follow-up	49.84 ± 57.27	46.75 ± 53.21	48.84 ± 47.59	34.03 ± 54.13	14.26 ± 24.05	9.38 ± 17.43
Change	−26.33 ± 57.59	−27.21 ± 57.04	−29.86 ± 60.89	−39.51 ± 57.46	−51.58 ± 36.68	−59.21 ± 37.75
% change	−26.9 ± 60.5	−26.6 ± 79.2	−13.8 ± 105.9	−47.8 ± 72.5	−75.7 ± 45.1	−85.4 ± 30.7
(95% CI)	(−41.3%, −12.6%)	(−45.9%, −7.3%)	(−39.9%, 12.2%)	(−66.7%, −28.9%)	(−88.9%, −62.4%)	(−94.6%, −76.3%)
P value	0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

b	4 weeks	3 months	6 months	12 months	24 months	36 months
IPSS						
N	81	81	81	81	81	81
Baseline	22.34 ± 5.73	22.34 ± 5.73	22.34 ± 5.73	22.34 ± 5.73	22.34 ± 5.73	22.34 ± 5.73
Follow-up	13.12 ± 8.68	11.18 ± 7.59	11.29 ± 7.82	11.17 ± 7.79	12.21 ± 7.61	12.05 ± 8.13
Change	−9.22 ± 8.53	−11.16 ± 8.00	−11.05 ± 7.48	−11.17 ± 7.71	−10.13 ± 7.37	−10.29 ± 7.79
% change	−41.2 ± 34.5	−49.4 ± 32.1	−50.0 ± 31.1	−49.9 ± 31.4	−45.3 ± 30.8	−46.1 ± 34.4
(95% CI)	(−48.8%, −33.6%)	(−56.5%, −42.4%)	(−56.8%, −43.1%)	(−56.8%, −43.1%)	(−52.1%, −38.6%)	(−53.7%, −38.6%)
P value	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
QOL						
N	81	81	81	81	81	81
Baseline	4.00 ± 0.85	4.00 ± 0.85	4.00 ± 0.85	4.00 ± 0.85	4.00 ± 0.85	4.00 ± 0.85
Follow-up	2.32 ± 1.45	2.05 ± 1.42	2.07 ± 1.39	1.94 ± 1.42	2.23 ± 1.43	2.22 ± 1.44

Table 3 (continued)

b	4 weeks	3 months	6 months	12 months	24 months	36 months
Change	−1.68 ± 1.54	−1.95 ± 1.55	−1.93 ± 1.49	−2.06 ± 1.62	−1.77 ± 1.56	−1.78 ± 1.50
% change	−40.8 ± 35.5	−47.5 ± 36.1	−47.2 ± 34.1	−49.2 ± 38.9	−42.2 ± 39.6	−43.3 ± 39.1
(95% CI)	(−48.6%, −33.0%)	(−55.4%, −39.5%)	(−54.6%, −39.7%)	(−57.7%, −40.6%)	(−50.9%, −33.5%)	(−51.9%, −34.7%)
P value	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Qmax (ml/s)						
N	81	81	81	81	81	81
Baseline	7.28 ± 2.55	7.28 ± 2.55	7.28 ± 2.55	7.28 ± 2.55	7.28 ± 2.55	7.28 ± 2.55
Follow-up	11.91 ± 10.72	11.66 ± 7.37	12.56 ± 6.47	13.25 ± 7.97	14.10 ± 8.96	13.43 ± 8.41
Change	4.63 ± 10.49	4.38 ± 6.76	5.28 ± 6.18	5.97 ± 7.88	6.82 ± 9.10	6.15 ± 8.40
% change	73.8 ± 163.9	68.9 ± 102.6	84.3 ± 104.3	96.3 ± 142.3	112.7 ± 163.1	101.1 ± 150.3
(95% CI)	(37.6%, 110.1%)	(46.2%, 91.6%)	(61.3%, 107.4%)	(64.8%, 127.8%)	(76.6%, 148.8%)	(67.9%, 134.4%)
P value	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Post-void residual urine (ml)						
N	81	81	81	81	81	81
Baseline	78.72 ± 56.39	78.72 ± 56.39	78.72 ± 56.39	78.72 ± 56.39	78.72 ± 56.39	78.72 ± 56.39
Follow-up	57.27 ± 68.78	53.14 ± 63.99	57.17 ± 59.80	51.02 ± 69.24	45.85 ± 70.79	42.60 ± 71.08
Change	−21.44 ± 61.20	−25.58 ± 63.57	−21.54 ± 64.26	−27.69 ± 68.91	−32.86 ± 68.14	−36.11 ± 69.61
% change	−24.2 ± 60.9	−26.0 ± 77.4	−8.6 ± 103.4	−29.0 ± 91.1	−43.0 ± 85.8	−49.0 ± 84.5
(95% CI)	(−38.2%, −10.2%)	(−43.8%, −8.2%)	(−32.4%, 15.1%)	(−50.0%, −8.0%)	(−62.8%, −23.3%)	(−68.4%, −29.5%)
P value	0.0008	<0.0001	0.0005	<0.0001	<0.0001	<0.0001

Imputation of missing values was done using last observation carried forward (LOCF). For IPSS, QOL, Qmax and PVR, change from baseline was evaluated using general estimating equation model (GEE) with baseline value and visit as predictors. Exchangeable correlation structure and identity link were used.

Missing values were not imputed. For IPSS, QOL, Qmax and PVR, change from baseline was evaluated using general estimating equation model (GEE) with baseline value and visit as predictors. Exchangeable correlation structure and identity link were used.

TURP, the gold-standard for surgical intervention, per year [3, 4, 15].

The side effects associated with drugs, and potential risks inherent in invasive surgery are of a great concern to many patients and may deter them from adhering to, or pursuing treatment for BPH [16]. For this reason, a number of minimally invasive treatment options have emerged in order to provide a more effective alternative to drug therapy, while also avoiding the potential risks associated with invasive surgery [17]. Among these, the temporary implantable nitinol device has shown to be a valid option for the treatment of LUTS secondary to BPO. The understandable concern, however, is that these new, less invasive treatments are indeed able to deliver on their promise of a reduced risk of adverse events, while still ensuring satisfactory results in terms of long-term efficacy [10–13]. The results of this prospective, single arm, multi-center study confirms that the treatment with the second-generation iTIND is effective out to 3 years, well tolerated by patients, and does not carry any late procedure-related complications.

Initial experience with the first-generation device was reported by Porpiglia et al. in a single arm, single center prospective study including 32 patients. At 12 months of follow-up a statistically significant improvement in IPSS and Qmax was demonstrated (45% and 67%, respectively) [10]. At 36 months of follow-up, the same patient cohort reported a durable improvement in Qmax and maintained symptomatic relief with mean IPSS symptoms scores and QoL of 12 and 2, respectively [11]. Similar results were found with the use of second-generation device [12, 13].

The current report on the second-generation iTIND further supports that the treatment offers significant and durable improvements in objective and subjective parameters to 36 months. IPSS, QoL, and Qmax were improved by −46%, −44.5%, and +84%, respectively, in the ITT–LOCF base, despite the fact that it includes patients with obstructive median lobes, which was identified as a predictor of treatment failure in a previous report [13]. Excluding those patients, improvement in IPSS, QoL and Qmax were shown to be −58%, −55%, +114%, respectively. All results were statistically significant ($p < 0.0001$).

The procedure itself seems to have been well tolerated by patients, with low mean VAS pain scores of 4 and 2 (0–10), respectively. No intraoperative complications were

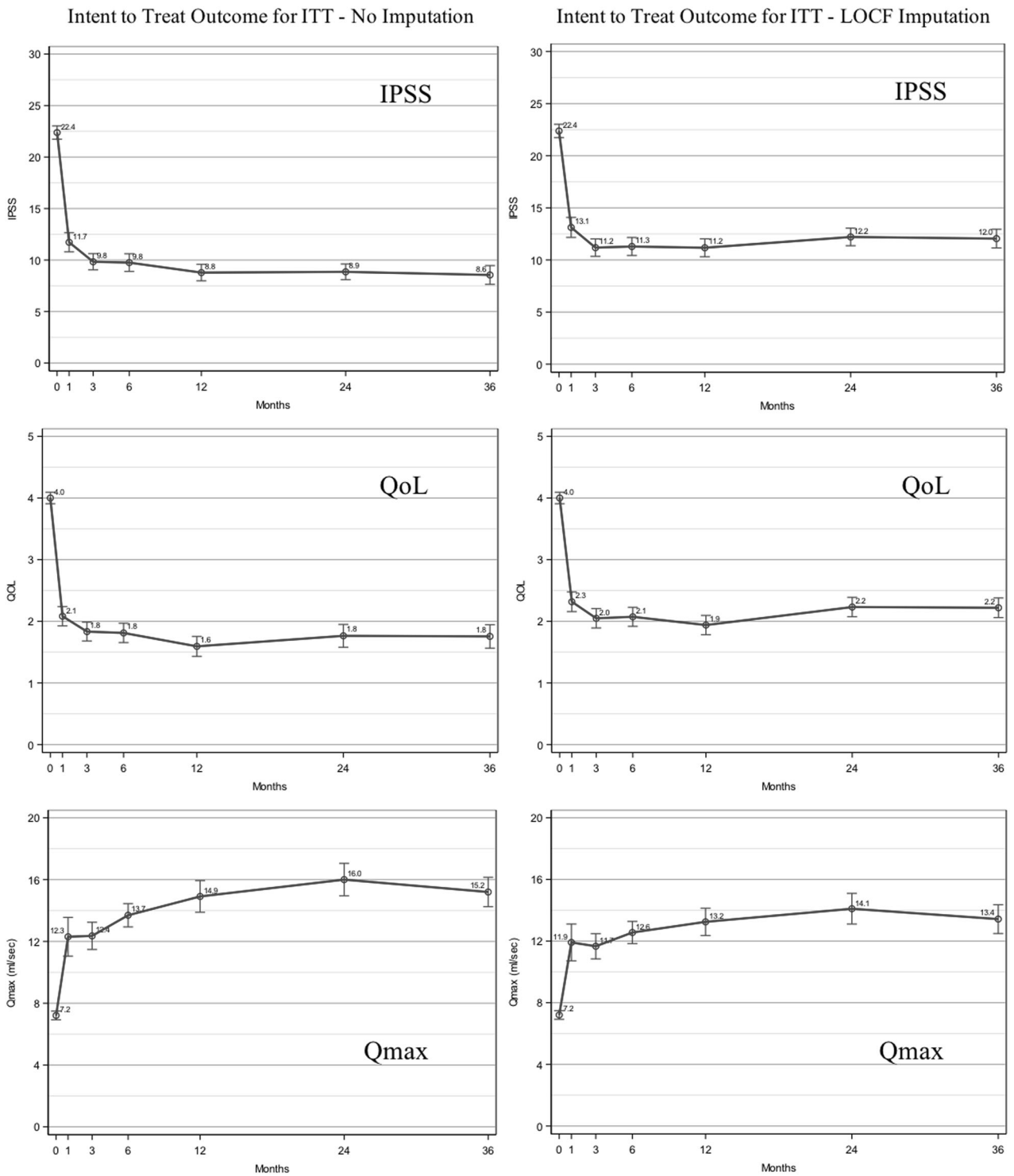

Fig. 3 Functional postoperative outcomes. Improvements from baseline to 36 month follow-up of IPSS, QoL and Qmax (observed values on per protocol patient population and Intent to treat outcome for ITT - LOCF Imputation).

reported, and all patients were discharged without a catheter on the same day of the procedure. All devices were successfully removed at a mean (SD) of 5.9 (1.1) days after implantation. The rate of post-operative adverse events was low, with all complications graded as I or II according to the Clavien–Dindo system, self-limiting and resolved within 30 days. Of note, the rate of procedure-related adverse events was low even when compared to other minimally invasive procedures; with 6.2% UTI versus up to 12.5% with Urolift [18] and 21.5% with Rezum [19]; 12.3%

hematuria versus up to 41% with Urolift [20] and 13.8% with Rezum [19]; and 9.9% reports of pain versus up to 17.9% [21] with Urolift and 17% with Rezum [19]. No new procedure or device related adverse events were reported at any of the other follow-up points out to 3 years. This finding is in line with the 3-year follow-up of the previous study on the first-generation TIND. The very low rate of early post-procedural adverse events, and the absence of any late or ongoing treatment-related complications or side effects may be attributed to the non-permanent implantation of the device and is a significant benefit to patients.

In addition, rapid symptomatic relief was demonstrated, with a mean reduction of 46% in both IPSS scores and IPSS QoL at the 4-week assessment, which was maintained and even improved at 36 months. Similarly, objective functional parameters also showed prompt improvement after surgery (4 weeks after iTIND removal, Qmax increased 79% from baseline).

A total cumulative surgical re-intervention rate of 8.6% at 3 years was demonstrated, which is in line with other minimally invasive treatments for BPH and TURP and laser: 10.7% for UroLift; [21, 22] 2.3–4.3% at 1 year, 5.8–9.7% at 5 years for TURP; [23, 24] 6.7% at 2 years, 6.8–34% at 5 years for Laser [25–27]. Finally, none of the previously sexually active patients reported a deterioration in sexual or ejaculatory function at any of the follow-up visits according to two yes/no questions. This finding demonstrates that the procedure appears to preserve sexual function. The limitation of these questionnaires has already been discussed in a previous publications [12, 13]. Among the other limitation, as previously declared, the study suffers from a lack of a control arm, such as a "sham" procedure. Finally, only 62% of the enrolled patients (50/81) completed the 36 months of follow-up and this may weaken the results of the study. To overcome this issue, the ITT–LOCF analysis was performed in addition, showing comparable results.

Notwithstanding these limitations, the results of this prospective multi-centre study confirm the safety and efficacy that iTIND implantation, even 36 months after surgery, with a low treatment failure rate and satisfactory functional outcomes.

Conclusion

Treatment of BPO-related LUTS with the second-generation temporary implantable nitinol device demonstrated a significant and durable reduction in symptoms and improvement in functional parameters and quality of life at 3 years of follow-up. As for the first-generation device, no late post-operative complications were observed between 12 and 36 months. No impact on ejaculatory function, and a low, total and cumulative (8.6%) treatment failure rate from baseline to 3 years was recorded.

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

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