3-Year follow-up of temporary implantable nitinol device implantation for the treatment of benign prostatic obstruction

Three-year follow-up of temporary implantable nitinol device (TIND®) implantation for the treatment of benign prostatic obstruction

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Keywords:	BPH, LUTS, minimally invasive techniques, nitinol, urethral implantable device, TIND
Abstract:	Objectives. To report 3-year follow-up results of the first implantations with the Temporary Implantable Nitinol Device (TIND - Meditate®) for the treatment of lower urinary tract symptoms (LUTS) secondary to benign prostatic hyperplasia (BPH). Patients and Methods. Thirty-two patients with LUTS were enrolled in this prospective study. The study was approved by the local Ethics Committee. Inclusion criteria were: age > 50 years, IPSS scores ≥ 10, peak urinary flow (Qmax) < 12 ml/sec, prostate volume < 50 cc. TIND was implanted within the bladder neck and the prostatic urethra under light sedation, and removed 5 days later, in an outpatient setting. Demographics, perioperative results, complications (according to Clavien Dindo classification), functional results and quality of life (QoL) were evaluated. Follow-up assessment was made at 3 and 6 weeks, and 3, 6, 12, 24 and 36 months after the implantation. Student t, ANOVA and Kruskall Wallis tests were used for the statistical analysis.

	Results: At baseline, mean (standard deviation, SD) patient age was 69.4 (8.2) , the mean prostate volume was 29.5 (7.4) mL and the Qmax was 7.6 (2.2) mL/s. The median (interquartile range, IQR) IPSS was 19 (14–23) and QoL score was 3 (3–4). All the implantations were successful, with a mean operative time of 5.8 minutes. No intraoperative complications recorded. Change from baseline in IPSS, QoL score and Qmax was significant at every follow-up time point. After 36 months of follow-up, a 41% rise in Qmax was achieved (mean: 10.1 ml/sec), median IPSS was 12 (6-24) and median IPSS QoL was 2 (1-4). Four early complications (12.5%) were recorded, including 1 case of urinary retention (3.1%), 1 case of transient incontinence due to device displacement (3.1%), and 2 cases of infections (6,2%). No further complications were recoded during the 36 months follow up. Conclusions: The extended follow-up period corroborated our previous findings and suggested that the TIND implantation is safe, effective and well tolerated, for at least 36 months following treatment.

Three-year follow-up of temporary implantable nitinol device (TIND®) implantation for the treatment of benign prostatic obstruction

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Introduction

Lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH), affect approximately 30% of men over the age of 50, including over 30 million men in Europe and the United States [1]. While medical therapy is the first line treatment, in more than one–fourth of the cases, it fails or induces significant side effects, leading many patients to opt for surgical intervention [1,2]. Trans-urethral resection of the prostate (TURP) still remains the gold standard surgical treatment for BPH, but perioperative morbidity and long-term complications, such as postoperative bleeding, urinary retention, incontinence, urethral strictures and sexual dysfunction, are not negligible [3-6]. Alternative laser-based modalities have only partially overcome these drawbacks [7-10]. In light of this, many men seek more significant symptomatic improvement than those provided by drugs, yet are not willing to face the risks associated with the surgery.

In the past, various techniques, including transurethral needle ablation (TUNA), transurethral microwave thermotherapy (TUMT), and transurethral ethanol ablation of the prostate (TEAP), have been proposed to fill this gap, but they did not impose on the clinical practice, being their use very limited today [11-13]. The recently developed prostatic urethral lift (PUL) [14,15] transurethrally delivers permanent implants aimed to separate the prostate lobes and relieve urethral obstruction without cutting, burning, or destroying the tissues. Recent studies have shown that PUL can offer encouraging results 24 months after surgery [16-18].

The temporary implantable nitinol device (TIND; Medi-Tate Ltd., Israel) was designed to create prostate incisions, thereby relieving BPH-related LUTS in a minimally invasive fashion [19]. The TIND is crimped and delivered through a cystoscope sheath, and then, when placed in the urethra, it is released from the cystoscope sheath to assume its expanded configuration, thereby reshaping the urethra and the bladder neck.

In our first experience with this device [20], TIND implantation in 32 patients presenting BPH-related LUTS, was safe and elicited functional improvements and enhanced patient quality of life (QoL) 12 months after surgery.

The aim of the present paper was to report on the 3-year outcomes of the same 32 cases.

Patients and Methods

After the approval from the institutional Ethics Committee, 32 patients were included in this single-arm, prospective study. The study was conducted at the Division of Urology of San Luigi Gonzaga Hospital - University of Turin, Orbassano (Turin). Patients were enrolled between May 2010 and July 2013.

Inclusion criteria. Age >50 years, International Prostate Symptom Score (IPSS) score ≥10, peak urinary flow ≤ 12 ml/sec, prostate volume (as assessed by trans-rectal ultrasound - TRUS) <60 cc. Patients were excluded if they had history of prostate surgery, prostate cancer, urethral stricture, bladder stones, obstructive median lobe, history of significant medical co-morbidities, haemostatic disorders or suspected neurological conditions which could underlie impaired voiding function. All eligible patients were informed about the procedure and signed a detailed consent form.

TIND device. The TIND is comprised of elongated nitinol struts and a nitinol anchoring leaflet. The total length of the device is 50 mm and its outer diameter is 33 mm. When in its expanded configuration, the struts of the TIND exert radial force outwardly on the bladder neck and the prostatic urethra, leading to the incision of the bladder neck and the prostatic urethra. These incisions are thought to "reshape" the prostatic urethra and the bladder neck and reduce the urinary flow obstruction caused by the enlarged prostatic tissue.

Surgical procedure. The procedure for TIND implantation has been previously described [20]. Briefly, with the patient in lithotomy position, under light intravenous sedation, urethrocystoscopy was performed with a standard 22F cystoscope. The TIND, preloaded on a dedicated delivery system, was advanced into the bladder through the cystoscope sheath, and deployed inside the bladder. The device was manipulated under direct vision, until the anchoring leaflet slid into position at 6 o' clock distal to the bladder neck and was securely positioned within the bladder neck

and the prostatic urethra. Finally, the bladder was emptied and the cystoscope was removed. No catheterization was required.

Five days thereafter, a rigid urethroscopy was performed, in an outpatient setting, the TIND was identified and retracted into the cystoscope sheath, under vision, and then removed.

Follow up visits. Patients were visited in an outpatient setting 5 days (removal day), 3 and 6 weeks, and 3, 6, 12, 24 and 36 months after the implantation, for assessment of uroflowmetry, IPSS scoring, and IPSS quality of life (QoL). Sexual dysfunction (i.e., retrograde ejaculation) in sexually-active patients was investigated at 12, 24 and 36 months after the surgery by asking the patient: *"after the intervention, did you record any changes in terms of ejaculation"?*

In addition, patient satisfaction with the surgical intervention was assessed by posing Question 32 of the Expanded Prostate Cancer Index Composite (EPIC) questionnaire [21] to the patients during the follow-up visits: "*Overall, how satisfied are you with treatment you received for your prostate disease intervention?*" (1: extremely dissatisfied; 2: dissatisfied; 3: uncertain; 4; satisfied; 5: extremely satisfied).

During the follow up visits, any need for medical therapy or surgical intervention due to recurrent/persistent LUTS, was recorded too. Complications were recorded during the entire follow-up period. Early complications (<30 days) were classified according to the Clavien system [22].

Statistical analyses. Continuous variables are presented as means and standard deviations; categorical variables are presented as frequencies and proportions or medians and interquartile ranges. The means of continuous variables were compared by using the student's t-test, after verifying that variables to be analyzed were approximately normally-distributed. ANOVA was used to compare the means of more than two groups, whilst statistical comparisons of categorical variables among different subgroups were performed by using the Kruskall Wallis test.

Simple and multiple linear regression models were built aimed to identify independent factors for need of BPH-related medical therapy after intervention, for improvement of maximum peak urinary flow rate (Qmax) and any decrease in IPSS at 36 months after surgery. Clinical characteristics including age, American Society of Anesthesiologists (ASA) score, body mass index (BMI), prostate size, Qmax and IPSS at baseline were used in the regression models. A subgroup analysis of patients with IPSS QoL $\geq$3 at 36 months after surgery was performed.

A p-value < 0.05 was considered statistically significant. Statsoft (Tulsa, OK) Version 8.0 for Windows was used for statistical analyses.

Results

TIND implantation was performed in 32 men of a mean age of 69.4±8.2, with a mean prostate volume of 29.5±7.4 cc and Qmax of 7.6±2.2 ml/sec. All patients were on alpha-blockers therapy at the time of the procedure, with 46% regularly taking 5-ARI inhibitors. Patient demographics and baseline characteristics are summarized in Table 1. All the procedures were performed under light sedation. No intraoperative complications were recorded. Mean operative time was 5.8 (2.5) minutes. Median VAS score 6 hours after the procedure was 2 (2-4). After discharge, no patients required re-admission before device removal. Table 2 summarizes various perioperative parameters. All but one of the devices was removed 5 days after implantation, in an outpatient setting without recording complications.

Functional results. Overall, there was a statistically significant increase in Qmax values over the first 12 months following treatment, peaking at a mean 72% increase by 6 weeks post-treatment and remaining steady over the ensuing 12 months (p value <0.001, see also figure 1). Qmax values slightly declined by 24 and 36 months post-treatment, but the changes from the 12 month follow-up visit were insignificant (p values =0.374 and =0.157, respectively). At the close of the 36-month monitoring period, the mean Qmax volume was 41% higher than the mean baseline recordings (Figure 2). Similary, there was a statistically significant difference between baseline values and the postoperative IPSS and QoL scores (Figure 3; p<0.001). A significant decline in IPSS was noted within 3 weeks of treatment, followed by further reductions peaking at the 3 month follow-up evaluation (55% decline). At the end of follow up IPSS scores were 19% lower that the mean baseline recordings (Figure 2).

All patients were able to discontinue LUTS-related medical therapy three months after the implantation, but three patients (9%) required the therapy again within 12 or 24 months of treatment (Table 3). The multiple regression analysis failed to identify any independent prognostic factors

predictive of the need for BPH-related medical therapy after the TIND implantation, increase of Qmax or decrease of IPSS score.

A comparative analysis of the outcomes of patients presenting IPSS QoL >3 versus IPSS QoL ≤3 at the end of the study period, was performed (Table 4). While no statistically significant differences were found between the baseline measures and demographics of the two subgroups, a multivariable analysis identified IPSS score >8 at 6 weeks after TIND implantation as independent predictor of IPSS QoL ≥3 three years following treatment.

Overall, no patients required any surgical therapy for BPH during the follow-up.

None of the 19 patients reporting preoperative sexual activity (n=19), suffered from ejaculatory dysfunction during the follow-up period.

Patient satisfaction with the surgical intervention. Differences in terms of EPIC score at different time points were not significant (p=0.180, see also figure 3).

Complications. Overall, four patients (12.5%) experienced complications (Table 5). One patient (3.1%) reported urinary incontinence due to device displacement. After its removal (day 1), the patient reported no urine leakage. One patient (3.1%) had urinary retention the same day of the implantation. The bladder was voided via a catheter that was immediately removed; no further complications were recorded in this patient. Finally, two patients (6.2%) developed genito-urinary infections, which resolved following antibiotic therapy. Aside from these early-stage complications, no further complications were recorded during the follow-up period. One patient died 26 months after the TIND implantation, due to causes that were unrelated to the surgical treatment.

Discussion

LUTS are some of the most common medical complaints filed by the aging man [23, 24]. Surgical

intervention is typically the treatment of choice following failed medical therapy, but prostate surgery for BPH still presents significant morbidity including incontinence (3%), urethral stricture (7%), erectile (10%) and ejaculatory dysfunction (65%) [25, 26]. The TIND was developed as a means of minimally invasively treating the symptoms of urinary outflow obstruction secondary to BPH. Our early experience with the device in 32 patients, established an acceptable safety profile and treatment efficacy up to 1 year following treatment [20]. Briefly, from a technical point of view, the procedure was simple, quick (mean operative time: 5.8 minutes), while the patient was under light i.v. sedation. The implantation did not require any special equipment. During the postoperative period, paracetamol (1000 mg, i.v.) was administered to all patients, per local protocol, whilst no patients required adjunctive analgesic drugs, suggesting that the procedure was well tolerated. After the first cases, which were performed with extra surveillance, all the patients were discharged on the same day of the implantation and neither unplanned visits nor re-admissions were required before TIND removal (at day 5). Device removal was uneventful in all the cases and no procedure-related complications were reported. One year functional results were encouraging, with a significant improvement in Qmax, IPSS and IPSS QoL and discontinued medical therapy for BPH by all patients. The present report, summarizing the 3-year outcomes of the same patient cohort, demonstrated continued maintained LUTS relief and safety of the TIND. More specifically, change from baseline in Qmax and IPSS at 24 and 36 months after treatment, were statistically significant. While Qmax began to decline at 24 and 36 months post-treatment, the changes from the 12 month time point were not significant. At 36 months post-treatment, Qmax values were 41% above baseline, a considerable improvement, at least comparable with other minimally invasive novel approaches such as PUL [27]. Similarly, while IPSS began to increase 24 months after surgery, the reduction from baseline was still significant and remained so until the end of the three-year follow-up period. Moreover, none of the patients required more invasive surgeries to treat BPH symptoms in the study period, further demonstrating the efficacy of the procedure even after 36 months.

Whilst all patients discontinued their BPH-related medical therapy after the implantation, three patients (9%) resumed therapy within 12 or 24 months of treatment. Yet, statistical analyses failed to identify any risk factor predictive of medical therapy after the TIND implantation. This could be related to the small number of events recorded in the analysed cohort. Similarly, multivariable regression analysis failed to identify any independent prognostic factor of increased Qmax or decreased IPSS score.

A median QoL score of 2 was recorded at 24 and 36 months post-treatment, suggesting that TIND implantation positively affected the QoL of the patients, a key factor when assessing a new surgical strategy for BPH treatment. No preoperative independent prognostic factor discriminating patients with low (<3) versus high (>3) QoL scores at the close of the study, was identified. However, a dedicated multivariable model identified IPSS scores > 8 at six weeks after the implantation as a predictor of higher QoL.

None of the 19 patients who had sexual activity at enrolment reported ejaculatory dysfunction. Even if we assessed this specific point in a very simple, not standardised way, these findings are of significance, as many men consider ejaculation a basic part of their sexual activity. Thus, we believe these results are worthy of note, especially when compared with the results of other surgical approaches for BPH [28], such as TUR_P or laser-based intervention: these interventions lead to 65% of ejaculatory dysfunction. Aside the early complications, represented by infections (2 cases) and urinary retention (1 case), none of the patient reported procedure - related complications during the whole follow-up. Again, we think that this is an important point in favour of the TIND implantation.

Patients satisfaction. The results of the EPIC question 32 remained stable over the follow-up, thus suggesting that the patients were satisfied with the TIND implantation, further confirming that the procedure was well accepted by the patients.

This study was not devoid of limitations: first, the sample size was small even if the reported cohort represents the first one of patients treated in the entire urologic community and, to date, the data series with the higher number of patients enrolled. Secondly, mean prostate size was small and the effectiveness of the treatment in larger prostates remains to be determined. Thirdly, the duration of follow-up period was still limited. Moreover, the observed trend toward a worsening of functional results after 24 and 36 months, with respect with previous time points, may be a sign of need for reintervention after a certain period of time. For this reason, patients are still being followed-up. Finally, while this study applied the "first generation" TIND, a *second generation* device has since become available and will remains to be assessed. Ongoing, multicentric studies will help us to overcome these limitations.

Conclusions

this extended follow-up of the first cohort of patients undergoing TIND therapy, corroborated our previous findings, which demonstrated that TIND implantation is safe, effective and well tolerated for at least 36 months. Further studies are required in order to assess the durability of TIND results over a longer follow-up, to better define the indications of this approach and to demonstrate the advantages of second-generation device over the first.

Acknowledgments and Conflict of Interest

none

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Figure legends

Figure 1: Maximum peak urinary flow (Qmax) evaluated pre- and postoperatively. The differences between the pre- and postoperative values at every time points were statistical significant.

p.o.= post operatively

Figure 2: Mean Changes (SD) in IPSS score and Qmax at the different time points with respect to baseline values

w.=weeks

mo.=months

Figure 3: Median IPSS, QoL and EPIC score evaluated pre- and postoperatively. The differences between the pre- and postoperative values (IPSS and QoL) at every time points were statistical significant for all the considered variables.

p.o.= post operatively

a) Demographic characteristic and preoperative data	(n=32)
Age, years	69.4 (8.2)
Body mass index (BMI)	26.1 (4.2)
* ASA score	2 (2-3)
* ECOG score	0 (0-1)
PSA level (ng/ml)	1.3 (1.2)
Prostate volume (cc)	29.5 (7.4)
Maximum peak flow (Q_{max}) (ml/sec)	7.6 (2.2)
* Preoperative IPSS score	19 (14-23)
* Preoperative IPSS QoL index	3 (3-4)
Alpha blockers therapy (%)	32 (100)
Alpha blockers + 5 ARI inhibitors therapy (%)	15 (46)
Patients with sexual activity (%)	19 (59)
* Charlson Comorbities Index	1 (0-2)

Table 1: Baseline characteristics of patients. Data are presented as mean (SD) or * median - (interquartiles range).

Perioperative data	**(n=32)**
Operative time (from introduction of the TIND system until withdrawal of the delivery system)	5.8 (2.5)
No. of patients treated by using light sedation (%)	32 (100)
No. of Intraoperative complications (%)	0 (0)
*VAS score, 6 h after the procedure	2 (2-4)
*Paracetamol use (vials)	1 (1-1)
*Hospital stay	1 (1-2)
No. of patients readmitted before device removal (%)	0 (0)
Operative time for TIND removal	2 (1)

Table 2. Perioperative data. Data are presented as percentage (where indicated), mean (SD) or * median - (interquartiles range).

Demographic/preoperative and follow up data	ITA 0113	ITA0124	ITA 0126
Age	68	80	66
BMI	22	21	29
Charlson Index	2	0	0
ASA score	2	3	2
Prostate size	21	31.5	32
Qmax	7	5	10
IPSS	25	17	20
QoL	3	3	3
Months after TIND implantation	24	24	12
Therapy	Silodosin	Tamsulosin	Tamsulosin

Table 3. Patients who required drug therapy for LUTS after TIND implantation.

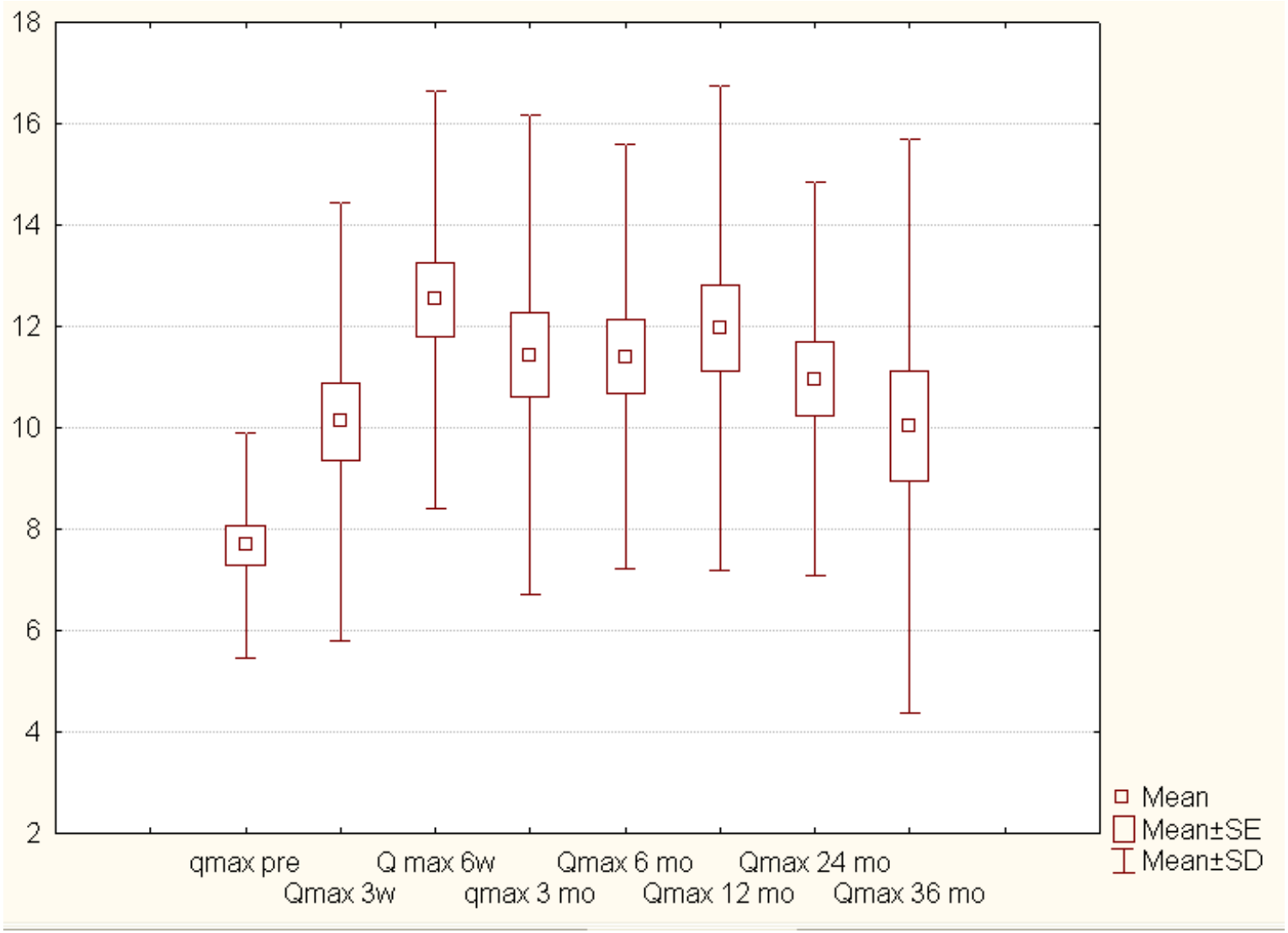
Demographic/preoperative data	QoL ≤3 (36 months after surgery) n=22	QoL >3 (36 months after surgery) n=9	P value
Age	68.40 (9.5)	70.38 (7.2)	0.309
BMI	26.29 (4.4)	27.32 (3.8)	0.277
Charlson Index*	1 (0-2)	1 (1-2)	0.74
ASA score *	2 (2-3)	2 (2-3)	0.611
Prostate size	29.45 (7.7)	31.19	0.364
Qmax	8.1 (2.2)	7.69	0.900
IPSS *	18 (14-23)	19.85	0.758
QoL *	3 (2-4)	4 (2-4)	0.240

Table 4. QoL at the end of follow up period. Patients were divided into two groups based on QoL results. Data from 31 patients were available for the analysis as 1 patient died during follow up. Data are presented as mean (SD) or *= median (IQ range)

Pt. ID and Demographic data	Complication / Grade*	Management
ITA 0101 Age 69 BMI 18.7 Charlson 3 ASA 3 Prostate size 25cc	Prostatic abscess (sepsis, AF, uncontrolled glycaemia) II	Readmission: Antibiotics (i.v.) , amiodarone, insulin Post operative stay of readmission: 10 days
ITA0109 Age 78 BMI 21.9 Charlson 0 ASA 3 Prostate size 27cc	Urinary retention (same day of implantation) II	Catheter positioning (immediately removed)
ITA0119 Age 71 BMI 27.6 Charlson 0 ASA 2 Prostate size 34cc	Transient incontinence due to device displacement III	Early (post operative day 1) removal of device
ITA0123 Age 71 BMI 30.1 Charlson 4 ASA 3 Prostate size 39 cc	UTI II	Antibiotics (given orally)

Table 5. Early (<30 days) complications after TIND implantation. No patients had sequelae after treatment of complications. AF= atrial fibrillation UTI= urinary tract infection i.v.=intra-venous Sc=subcutaneous

*According to Clavien system


18
16
14
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10
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6
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2
qmax pre
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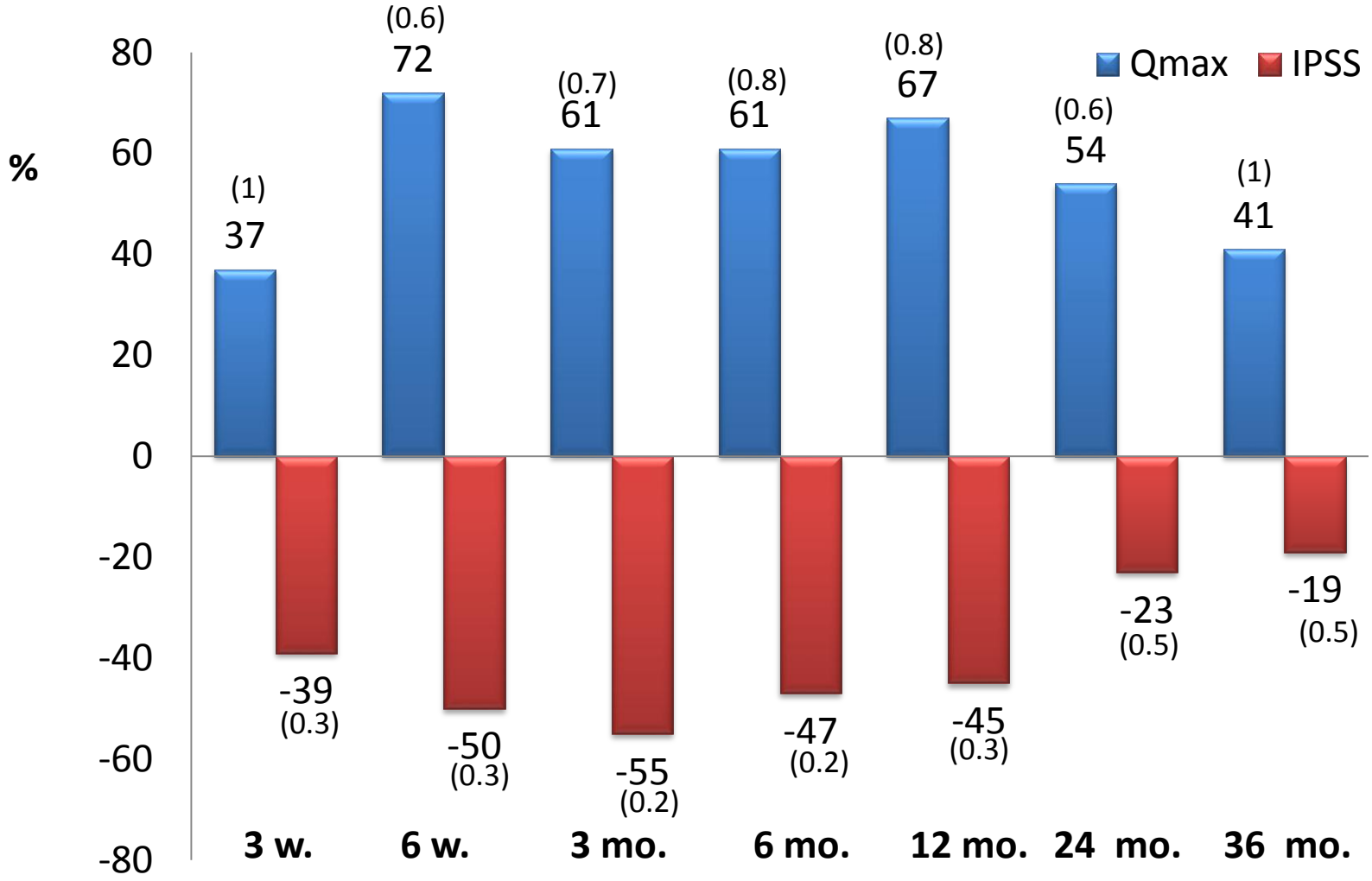
Qmax 12 mo
Qmax 24 mo
Qmax 36 mo
Mean
Mean±SE
Mean±SD

Fig. 1


%
80
60
40
20
0
-20
-40
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-80
Qmax
IPSS
(1)
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-39
(0.3)
(0.6)
72
-50
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61
-55
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-47
(0.2)
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67
-45
(0.3)
(0.6)
54
-23
(0.5)
(1)
41
-19
(0.5)
3 w.
6 w.
3 mo.
6 mo.
12 mo.
24 mo.
36 mo.

Fig. 2

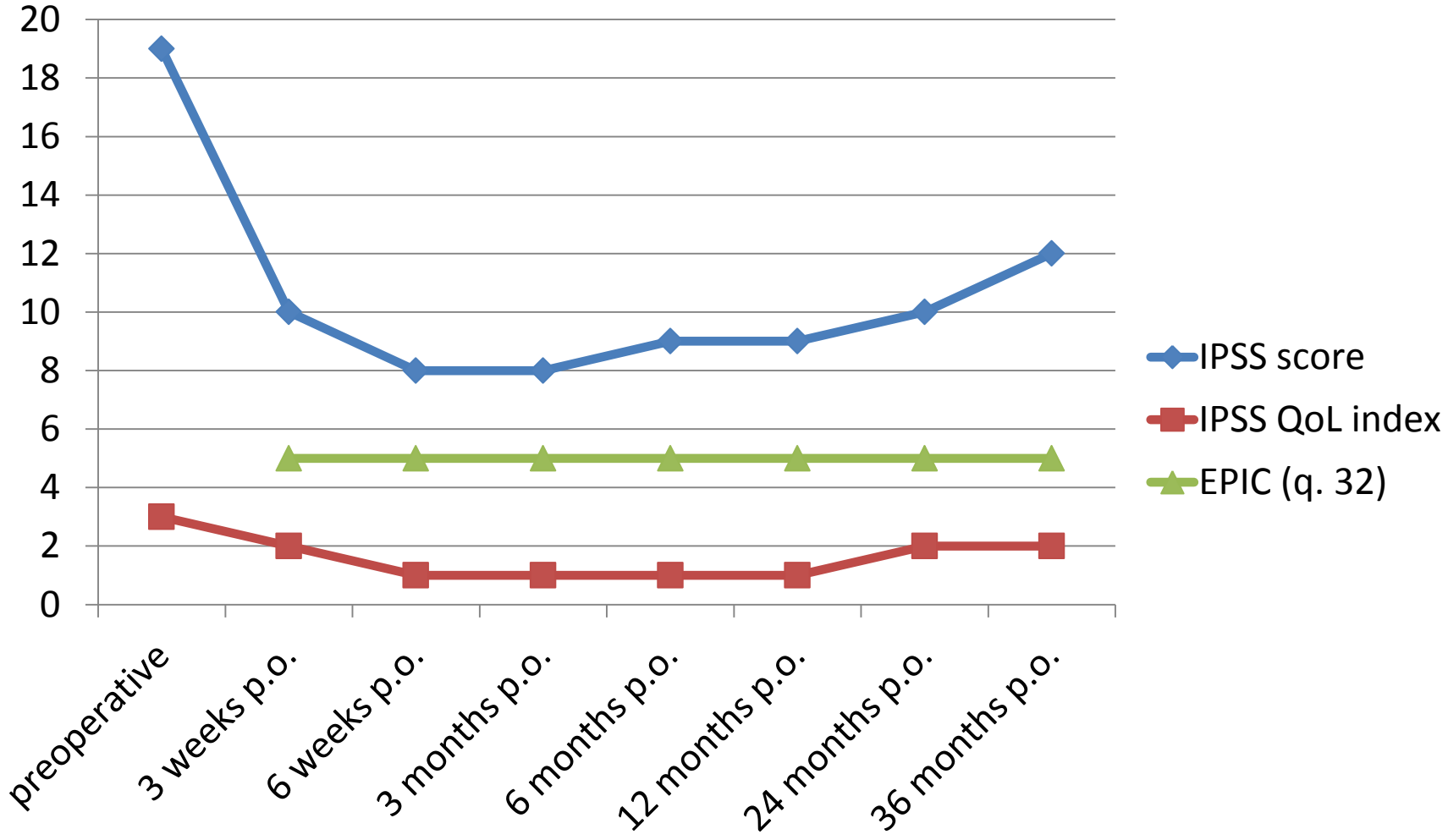
20
18
16
14
12
10
8
6
4
2
0
preoperative
3 weeks p.o.
6 weeks p.o.
3 months p.o.
6 months p.o.
12 months p.o.
24 months p.o.
36 months p.o.
IPSS score
IPSS QoL index
EPIC (q. 32)

Fig. 3