iTIND: the second-generation temporary implantable nitinol device for minimally invasive treatment of benign prostatic hyperplasia

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Abstract: iTIND is the second-generation version of the temporary nitinol implantable device (TIND), which has emerged over the past decade as one of the latest additions to the library of minimally invasive surgeries now available to treat bothersome lower urinary tract symptoms (LUTS) caused by benign prostate enlargement. While the key procedural steps remain the same, it now carries specific modifications designed to improve its efficacy and safety profile further. With the option to perform implantation under local anaesthesia, it can be delivered on an ambulatory basis and in the office setting. While the formal position of iTIND in current guidelines is yet to be determined, 12-month data demonstrates that it can improve both objective and subjective outcome measures, which are sustained at short-term follow up.

Keywords: alternative therapies, BPE, BPH, iTIND, LUTS, minimally invasive, TIND

Introduction
Bothersome lower urinary tract symptoms (LUTS) caused by benign prostate enlargement (BPE) is a condition of prevalence, which has been confirmed by a number of community-based, longitudinal studies. It is estimated to affect over one-third of men over 60 years of age to a moderate or severe extent. The sequelae are far reaching, and the burden of this disease can be both psychological and socio-economic. Management initially includes lifestyle advice and medical therapies such as α-blockers and 5α-reductase inhibitors. However, side-effects associated with pharmacotherapy, including postural hypotension and sexual dysfunction, can lead to reduced patient tolerance, poor compliance and early discontinuation accordingly. Approximately 25% of men over 50 years who develop LUTS due to BPE will require surgical intervention. While transurethral resection of the prostate (TURP) has served as the gold standard surgical treatment for many years, efforts have always been going on to develop alternatives that deliver high efficacy rates while sustaining sexual function and minimising morbidity. Minimally invasive alternatives include laser-based methods such as holmium laser enucleation of the prostate (HoLEP), greenlight photo-vaporisation of the prostate and thulium laser enucleation of the prostate. Newer treatment options also include prostate artery embolisation, UroLift® (PUL), aquablation and rezum.

iTIND is the second-generation version of the temporary implantable nitinol device, TIND (TIND; Medi-Tate, Or Akiva, Israel), which has undergone a number of improvements. This mechanical device has now undergone a number of changes as part of its evolution. The aim of this article is to provide an overview of this modified version of the device.

What is the device?
The iTIND serves to re-model the bladder neck and the prostatic urethra. The device comprises of three elongated struts, which are configured at 12, 5, and 7 o’clock positions using interlaced

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The size of the newer device is the same (5 cm × 3.3 cm) as the first-generation model and is intended to match the dimensions from the bladder neck to the external urinary sphincter. In addition to the extra strut, which the first-generation device had, the tip was pointed and covered by a soft plastic material. This cover was designed to help avoid bladder injury. However, in order to minimise risk of damage to mucosa, this tip has now been removed and the resultant, open-end appearance is often described as being similar to that of a tulip flower. There remains an anchoring leaflet, which is attached to a nylon wire. The procedural steps are the same for the first- and second-generation devices. The device itself is left in situ for approximately 5 days. Maximal expansion of the structure is reached by this point and, through a process of localised ischemic necrosis from where the struts have compressed the encroaching tissue, longitudinal channels are created. From this remodelling process and channel formation, improved urinary outflow is established.

The procedure
The patient is given a single dose of antibiotic prophylaxis and lies in the lithotomy position. The mainstay of cases can be achieved with use of local anaesthetic only but light, intravenous sedation can be used to support this as required. In a similar method to PUL, the device is pre-loaded into a custom system (14Fr) and then passed through the cystoscopic sheath (19-22 Fr). Once routine inspection of both bladder and urethra has been performed, the device can be deployed into a full bladder. Under endoscopic vision, it can then be carefully manipulated into the desired position. The anchoring leaflet should be orientated to the 6 o’clock position, under the bladder neck and cranial to verumontanum. With this secured, the device can be carefully retracted so that the nitinol, longitudinal struts are in contact with the encroaching prostatic tissue. Once this has been performed to the surgeon’s satisfaction, the plastic sheath covering the nylon wire can be taken off and the wire itself can be shortened. To complete the procedure, the bladder is emptied, and no catheter is required. The total procedural time is less than 10 min. With continuous pressure and resultant ischaemia, the prostatic urethra and bladder neck is remodelled, which creates new channels via which urine can flow. While it is yet to be formally assessed, surgeon observation and experience suggests that this procedure carries a short learning curve.

Patients can be discharged on the same day with a regime of simple analgesia. After 5–7 days, patients return to have the device removed. This is achieved via retrieval of the nylon wire, using a snare to pull the device into either a cystoscope sheath or an open-ended silicone catheter (20-22Fr).

Patient selection
Based on studies to date, patients require prostate size less than 60cc (Table 1). It has yet to be carried out in patients with previous prostate cancer, prominent median lobe, urethral stricture, concomitant bladder stones or previous prostate surgery. Of note, no published study has performed it in a population sample where the mean prostate size exceeds 40cc.18

Current evidence for iTIND
The initial clinical experience with the first-generation version of this mechanical device was reported in a sample of 32 patients by Porpiglia et al. in 2015.19 At 1 year follow up, the international prostate symptom severity score (IPSS) and maximum urinary flow rate (Qmax) scores had improved by −45% and +67% respectively. The early complications were prostate abscess (n = 1), urinary tract infection (n = 1), transient urinary incontinence caused by device displacement (n = 1) and urinary retention (n = 1). Extended follow up to 3 years

| Inclusion | Exclusion |
|-----------|-----------|
| Size <60 cc | History of prostate cancer |
| Age >50 years | Previous prostate surgery for example, TURP |
| IPSS >12 | History of urethral stricture |
| Qmax >12 ml/s | Bladder stones |
| | Active infection |
| | Urinary retention |

IPSS, international prostate symptom severity score; iTIND, second-generation temporary implantable nitinol device; Qmax, maximum urinary flow rate; TURP, transurethral resection of the prostate.
was later published. No further adverse events were recorded; however, three cases had required re-intervention within 24 months of the initial operation. The final improvement in IPSS and Qmax was −19% and +41%, respectively.

A single-arm, prospective, multi-centre study (MT-02) was performed to report the clinical experience of patients managed with the second-generation version for the treatment of bothersome LUTS due to BPE. A total of 81 patients were involved in this study and follow-up assessments were conducted at 1, 3, 6 and 12 months post-operatively. Study sites included Italy, the United Kingdom (UK), Switzerland, Belgium and Hong Kong. All patients enrolled in this study had an IPSS $\geq 10$, Qmax $< 12$ ml/s, and prostate volume $< 75$ cc. The mean patient age was 65 years. The devices were retrieved at a mean of 5.9 days after implantation, typically under topical anaesthesia. The results of this study showed the mean Qmax at 1 month follow-up was 11.2 ml/s and continued to improve thereafter, reaching 14.9 ml/s and 16 ml/s at the 12 months and 24 months, respectively. The mean IPSS was 11.7 after 1 month, and this improved further to 8.7 and 8.5 (−60%) at 12 months and 24 months, respectively. No major complications (>ClavienIII) were recorded. All the implantations were successful, and all patients were discharged on the same day of surgery. However, during the 12-month period, two patients required subsequent surgery (TURP/HoLEP). In the second year, a further five patients required additional surgery (TURP). Four of these patients who required re-treatment were found to have prominent median lobes. Failure analysis was carried out, and the presence of prominent median lobe was associated with a significantly higher rate of treatment failure ($p < 0.0001$). At the 2-year follow-up mark, no patients reported de novo sexual dysfunction.

While the European Association of Urology guidelines acknowledge the emerging role of this device, no specific recommendation is given, and its formal role is therefore yet to be defined.

**Comparison with similar treatment(s)**

The modus operandum of this device is mechanical rather than ablative or cavitating, and therefore the alternative that is most similar is arguably UroLift. Elterman et al. reported 3 year clinical and economic outcomes from their single-arm, prospective study. The authors directly compared their findings using the first-generation device with the 3-year outcomes published from the L.I.F.T. study (Luminal Improvement Following Prostatic Tissue Approximation for the Treatment of LUTS secondary to BPE). The latter, a randomised controlled multicentre trial, compared PUL with a sham procedure. In the L.I.F.T study, 5.2 implants were used on average and the authors calculated an overall cost at $4160 CAD ($800 CAD/implant). In comparison, the cost of iTIND per device was reported as $2500 CAD (single implant only). The authors reported superior results associated with iTIND, with regards to IPSS ($p = 0.033$), Qmax ($p = 0.033$) and quality of life (QoL) ($p = 0.192$). However, the sample size was small ($n = 32$) and the study was completely separate, non-matched and non-randomised. Future comparative studies are required to be able to truly validate these early findings by Elterman et al. Both do offer strong profiles with respect to preservation of sexual function and are widely accepted as similar in this regard. However, the efficacy, safety and durability of PUL has been studied more extensively to date. A meta-analysis by Cacciamani et al. determined that preservation of antegrade ejaculation is sparse among endoscopic treatments such as TURP compared with the newer treatments such as iTIND and PUL. The potential role of these alternatives is therefore of great interest to both clinicians and patients alike.

**Advantages and disadvantages**

This mechanical device offers a number of potential advantages (Table 2). Requirement for general anaesthesia is obviated and therefore it can be delivered in an office or ambulatory setting. Given the short procedural time, a high number of cases can be performed in an operating session. While yet to be determined and published formally, it would be estimated that cost savings would follow accordingly. A urinary catheter is not required at end of the procedure, which is anticipated to increase patient satisfaction. The modified design, principally the removal of the cranial tip, should also minimise risk of tissue injury on deployment of the device. The mechanism of action allows for preservation of sexual function, which is supported by the clinical studies to date.
However, there is a lack of long-term data available for the new device and therefore, the durability of this procedure is yet to be established at this time. It is also yet to be demonstrated in larger prostate volumes or those with obstructive median lobes. Future studies with broader inclusion and exclusion criteria will help delineate the generalisability and reproducibility of this novel surgery.

Future research
At present, the authors know of four registered studies that are currently ongoing. These exist in the UK [ClinicalTrials.gov identifier: NCT03239951], Germany [ClinicalTrials.gov identifier: NCT03994263], North America [ClinicalTrials.gov identifier: NCT02506465] and a multi-centre study across Europe [ClinicalTrials.gov identifier: NCT03395522]. However, these all represent one-arm trials and while such research will augment the available evidence to support this novel procedure, Level 1 evidence in the form of randomised trials would complement this the most. Future studies should aim to include measurement of cost and learning curve as these two elements have yet to be addressed.

Conclusion
The second generation iTIND is a novel and minimally invasive surgery, which can now be offered in the ambulatory setting. While at present, only limited evidence exists to support its use, early results of this modified version are very promising. Key advantages include a strong safety profile and preservation of existing sexual function. Future studies are awaited to help delineate its formal role in current treatment algorithms.

Conflict of interest statement
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References
1. Soler R, Gomes CM, Averbeck MA, et al. The prevalence of lower urinary tract symptoms (LUTS) in Brazil: results from the epidemiology of LUTS (Brazil LUTS) study. Neurourol Urodyn 2018; 37: 1356–1364.
2. Sarma AV, Wei JT, Jacobson DJ, et al. Comparison of lower urinary tract symptom severity and associated bother between community-dwelling black and white men: the Olmsted county study of urinary symptoms and health status and the flint men’s health study. Urology 2003; 61: 1086–1091.
3. McVary KT. BPH: epidemiology and comorbidies. Am J Manag Care 2016; 15 (Suppl. 5): 122–128.
4. Djavan B, Margreiter M and Dianat SS. An algorithm for medical management in male lower urinary tract symptoms. Curr Opin Urol 2011; 21: 5–12.
5. Bachmann A, Muir GH, Wyler SF, et al. Surgical benign prostatic hyperplasia trials: the future is now! Eur Urol 2013; 63: 677–679; discussion 679–680.
6. Rassweiler J, Teber D, Kuntz R, et al. Complications of transurethral resection of the prostate (TURP): incidence, management, and prevention. Eur Urol 2006; 50: 969–979.
7. Krambeck AE, Handa SE and Lingeman JE. Experience with more than 1,000 holmium laser prostate enucleations for benign prostatic hyperplasia. J Urol 2013; 189(Suppl. 1): S141–S145.

8. Rapisarda S, Russo GI, Osman NI, et al. The use of laser as a therapeutic modality as compared to TURP for the small prostate < 40 ml: a collaborative review. Minerva Urol Nefrol 2019; 71: 569–575.

9. Yamada Y, Furusawa J, Sugimura Y, et al. Photoselective vaporization of the prostate: long-term outcomes and safety during 10 years of follow-up. J Endourol 2016; 30: 1306–1311.

10. Nettleton J, Jones P, Pietropaolo A, et al. The industrial revolution for the management of benign prostate obstruction: worldwide publication trends for surgical and medical therapies over the past two decades. Cent European J Urol 2019; 72: 149–155.

11. Jones P, Rai BP, Nair R, et al. Current status of prostate artery embolization for lower urinary tract symptoms: review of world literature. Urology 2015; 86: 676–681.

12. Jones P, Rai BP, Aboumarzouk O, et al. Prostatic urethral lift versus prostate arterial embolisation: novel non-ablative strategies in the management of LUTS secondary to BPH. Urology 2016; 87: 11–17.

13. Roehrborn CG, Teplitsky S and Das AK. Aquablation of the prostate: a review and update. Can J Urol 2019; 26(Suppl. 4): 20–24.

14. Nguyen D, Misrai V, Bach T, et al. Operative time comparison of aquablation, greenlight PVP, ThulLEP, GreenLEP, and HoLEP. World J Urol. Epub ahead of print 2 March 2020. https://doi.org/10.1007/s00345-020-03137-8.

15. McVary KT, Rogers T and Roehrborn CG. Rezum water vapor thermal therapy for lower urinary tract symptoms associated with benign prostatic hyperplasia: 4-year results from randomized controlled trials. Urology 2019; 126: 171–179.

16. Marcon J, Magistro G, Stief CG, et al. What’s New in TIND? Eur Urol Focus 2018; 4: 40–42.

17. Amparore D, De Cillis S, Volpi G, et al. First- and second-generation temporary implantable nitinol devices as minimally invasive treatments for BPH-related LUTS: systematic review of the literature. Curr Urol Rep 2019; 20: 47.

18. Bertolo R, Fiori C, Amparore D, et al. Follow-up of temporary implantable nitinol device (TIND) implantation for the treatment of BPH: a systematic review. Curr Urol Rep 2018; 19: 44.

19. Porpiglia F, Fiori C, Bertolo R, et al. Temporary implantable nitinol device (TIND): a novel, minimally invasive treatment for relief of lower urinary tract symptoms (LUTS) related to benign prostatic hyperplasia (BPH): feasibility, safety and functional results at 1 year of follow-up. BJU Int 2015; 116: 278–287.

20. Porpiglia F, Fiori C, Bertolo R, et al. 3-Year follow-up of temporary implantable nitinol device implantation for the treatment of benign prostatic obstruction. BJU Int 2018; 122: 106–112.

21. Porpiglia F, Fiori C, Amparore D, et al. Second-generation of temporary implantable nitinol device for the relief of lower urinary tract symptoms due to benign prostatic hyperplasia: results of a prospective, multicentre study at 1 year of follow-up. BJU Int 2019; 123: 1061–1069.

22. Kadner G, Valero M, Giannakis I, et al. Second generation of temporary implantable nitinol device (iTind) in men with LUTS: 2 year results of the MT-02-study. World J Urol. Epub ahead of print 2 March 2020. DOI: 10.1007/s00345-020-03140-z.

23. Gravas S, Cornu N, Rai BP, et al. EAU guidelines on non-neurogenic male lower urinary tract symptoms (LUTS), including benign prostatic obstruction (BPO). European Association of Urology, 2017, pp.129–146.

24. Jones P, Rajkumar GN, Rai BP, et al. Medium-term outcomes of Urolift (minimum 12 months follow-up): evidence from a systematic review. Urology 2016; 97: 20–24.

25. Elterman DS. The temporary implantable nitinol device (iTind) for the minimally invasive treatment of benign prostatic hyperplasia: comparison of three-year outcomes and cost in Canada. In: 72nd Annual Meeting of the Canadian Urological Association, Canada. Can Urol Assoc J 2017; 11(Suppl. 4): S228.

26. Roehrborn CG, Gange SN, Shore ND, et al. The prostatic urethral lift for the treatment of lower urinary tract symptoms associated with prostate enlargement due to benign prostatic hyperplasia: the L.I.F.T. study. J Urol 2013; 190: 2161–2167.

27. Cacciamani GE, Cuhna F, Tafuri A, et al. Anterograde ejaculation preservation after endoscopic treatments in patients with bladder outlet obstruction: systematic review and pooled-analysis of randomized clinical trials. Minerva Urol Nefrol 2019; 71: 427–434.

28. Speakman MJ, Cornu JN, Gacci M, et al. What is the required certainty of evidence for the implementation of novel techniques for the treatment of benign prostatic obstruction? Eur Urol Focus 2019; 5: 351–356.

29. Burns PB, Rohrich RJ and Chung KC. The levels of evidence and their role in evidence-based medicine. Plast Reconstr Surg 2011; 128: 305–310.