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Review Article

Review of simultaneous treatment with intradetrusor onabotulinumtoxinA injections during transurethral prostate surgery for men with bladder outlet obstruction and overactive bladder

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Abstract

Bladder outlet obstruction (BOO) is common in males with benign prostate enlargement (BPE) and often presents with different lower urinary tract symptoms. Overactive bladder (OAB) has been reported to be related to BOO, although it can also be idiopathic. The storage symptoms of BOO are often similar to those of OAB. The etiology and pathophysiology of both BPE and OAB are multifactorial with metabolic syndrome known as one of the factors. As of today, transurethral prostate surgery remains the gold standard for treating BOO associated with BPE. Intradetrusor onabotulinumtoxinA (BoNT-A) injections have been shown to be effective in treating OAB. However, they are usually administered after transurethral prostate surgery. In view of the strong therapeutic effects of both surgery and injections, the feasibility of combining them in one setting to increase patient comfort, convenience, and possibly results while decreasing costs is appealing to physicians. However, patient safety and possible complications have to be considered. In this article, we review available studies of concurrent intradetrusor BoNT-A injections during transurethral prostate surgery. Although there is no definitive evidence supporting the concurrent use of intradetrusor BoNT-A during transurethral prostate surgery, there are no reports of increased complications too. Further large-scale randomized controlled trials would be necessary to validate the feasibility of combining the treatments in one setting and observe for possible complications.

Keywords: *Bladder outlet obstruction, OnabotulinumtoxinA, Overactive bladder, Transurethral resection of the prostate, Treatment*

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Introduction

Men with bladder outlet obstruction (BOO) caused by benign prostate enlargement (BPE) often present with lower urinary tract symptoms (LUTS). In addition to voiding symptoms, storage symptoms are common too, which may significantly reduce the quality of life (QoL) [1-3]. These symptoms include overactive bladder (OAB) symptoms, such as urgency, usually with urinary frequency and nocturia, and with or without urinary incontinence [4,5]. Therefore, management of BOO with concomitant OAB symptoms is imperative [6].

Transurethral resection of the prostate (TURP) remains one of the most effective treatments capable of directly improving LUTS caused by BPE with BOO. However, storage symptoms tend to persist post-TURP as compared to voiding symptoms [7,8]. Moreover, OAB symptoms have been reported in more than half of the patients who had undergone TURP during long-term follow-up [9]. As for oral drugs, antimuscarinics are preferred in treating males with LUTS. Antimuscarinic monotherapy has been shown to significantly improve frequency, urgency, and urge urinary incontinence (UUI) in men with OAB in the absence of BOO [2]. However, antimuscarinics have also been associated with increased post-void residual (PVR) levels even though acute urinary retention is rare. Therefore, it is unsuitable for men with a PVR volume of >150 mL [2]. On the other hand, studies combining mirabegron and antimuscarinics have reported better treatment effects but lower patient compliance [10]. Intradetrusor onabotulinumtoxinA (BoNT-A)

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injections are the next step in treating refractory urinary incontinence after oral therapies and offer a new treatment option for males with LUTS [2,11]. Patients with BOO caused by BPE with concomitant OAB symptoms are indicated to receive TURP and intradetrusor BoNT-A injections to improve their voiding and storage symptoms. However, there are currently no guidelines on the concurrent implementation of these two treatments in one setting for this specified condition. This article reviews current studies for the feasibility of concurrent implementation of TURP and intradetrusor BoNT-A injections in one setting, so as to provide physicians with a summarized outlook of the current situation and the occurrence of reported adverse effects.

Bladder outlet obstruction and overactive bladder

The pathophysiology of OAB with or without BOO may vary. OAB is characterized by urinary urgency, usually with frequency and nocturia. In general, the pathophysiology of OAB is multifactorial and can be divided into myogenic, neurogenic, urothelial mechanisms, and other conditions, such as metabolic syndrome, diabetes, benign prostate hypertrophy, and psychological disorders [12,13]. Deterioration of or damages to the nerve pathway in the micturition reflex, alterations of the muscle cells of the bladder, and the impact of urothelium on the bladder afferent signaling pathway can lead to bladder overactivity and the clinical presentation of OAB [12,13]. OAB patients can be further divided into having or not having detrusor overactivity (DO) through urodynamic studies. Fan *et al*.[14] reported that 60.2% of OAB patients are diagnosed with DO through urodynamic studies. The only difference between people with and without DO was the presence of nocturia, no differences were observed in other variables and symptom scores.

LUTS are common in male patients with BOO. Physiological alterations in the detrusor muscle, such as hypertrophy, denervation due to ischemia, and changes in neuronal mechanisms, caused by obstruction may lead to OAB [15]. Progression from BOO to OAB involves biochemical, histological, and structural factors. Oxidative stress in the bladder detrusor muscle has been reported to be related to bladder change secondary to BOO in animal studies. BOO can lead to an initial inflammatory response and ischemia, which may eventually progress to smooth muscle hypertrophy [16]. Detrusor ischemia-reperfusion, which is associated with BOO, leads to increased oxidative stress in the bladder wall [17,18]. This increased oxidative stress further increases reactive oxygen species and/or decreases the antioxidant defense ability of the muscle cell, which may cause cell apoptosis. In animal studies, timely medical therapy appears to improve detrusor blood flow [17], but there is a lack of evidence for humans.

In the human bladder, smooth muscle cells show upregulation of hypoxia-inducible factor (HIF)-1α and vascular endothelial growth factor (VEGF) after exposure to hypoxia, which is a time-dependent event [19]. HIF-1α is expressed mainly in stromal cells between muscle bundles and in the connective tissue beneath the mucosal layer, whereas no immunoreactivity is observed in the urothelium and the detrusor muscle. The probability of HIF-1α immunoreactivity was four times greater in men with BOO for <10 years than in those with BOO for >10 years, with a high odds ratio of 4.25, suggestive of deterioration of adaptive response despite initiation compensation by the bladder. Moreover, the likelihood of high expression of HIF-1α was four times higher in men with urinary retention [20]. Similarly, patients with severe BOO due to BPE showed statistically significant overexpression of VEGF compared to age-matched controls [21].

In a chronic BOO animal model, changes in the detrusor muscle were different from skeletal muscles. Smooth muscle cell hypertrophy and increased deposition of the extracellular matrix are determining factors in the increase in bladder wall thickness and loss of compliance, which may lead to decompensation of bladder function [22-24]. Extracellular matrix deposition results from imbalanced collagen production and degradation. In clinical studies of bladder tissue from patients with nonmuscle-invasive bladder cancer (NMIBC) and BOO, collagen deposition was higher in patients with BOO than in those with NMIBC (48% vs. 17%; $P < 0.001$) [25]. Bladder wall thickening in patients with BOO has been attributed mainly to smooth muscle cell hypertrophy and collagen deposition [26,27]. Several studies have shown that bladder wall thickness is significantly different between patients with and without BOO. The degree of obstruction, prostate volume, and international prostate symptom score (IPSS) seem to be positively correlated with bladder wall thickness [28,29].

OAB symptoms should have been resolved after TURP if they are entirely caused by BOO and would have persisted if otherwise [30,31]. Studies have shown that approximately one-third of patients will develop storage symptoms after TURP. Although the obstructive symptoms disappear after surgery, persistent OAB symptoms may still cause postoperative dissatisfaction and decrease the QoL [32]. The development of LUTS after TURP is a complex and multifactorial process that is still not fully understood. Possible reasons include hypoxic insult, changes in neuroplasticity, and/or progressive detrusor hypertrophy from chronic obstruction [33-35]. Abnormal bladder distention caused by BOO may alter gene expression and protein synthesis in the bladder epithelial and detrusor muscle cells, which further affects the structure and physiological performance of these cells. The final result is a thickened bladder wall with reduced compliance and low contractility. Similarly, nerve growth factor may also be increased in the bladder, to overcome the increased bladder outlet resistance to maintain acceptable urination. Therefore, following the resolution of BOO, these hyperactive neural pathways may persist and progress to OAB symptoms [33-35].

Current clinical evidence supporting the performance of onabotulinumtoxinA injections during transurethral prostate surgery

The evidence for performing intradetrusor BoNT-A injections during TURP is limited. Most studies focused on treatments for OAB, such as drugs and BoNT-A injections,

after TURP [36,37]. Table 1 lists some of the relevant studies. In these studies, two surgical techniques, resection of the prostate and enucleation of the prostate, were used, as well as different brands of BoNT-A, which may cause variations and affect comparison analysis. In addition, the study durations are short, with 9 months being the maximum duration. This is probably because the effectiveness of BoNT-A injections decreases over time. Other notable issues include biases due to outcome evaluation based on subjective reporting of symptoms by patients and inadequate follow-up with urodynamic parameters.

Allameh *et al*. [38,39] explored the effectiveness of combining TURP with intradetrusor BoNT-A injections in one session and TURP with postoperative antimuscarinics. Although their results showed that both groups achieved significant improvement in clinical symptoms, the intradetrusor BoNT-A injections group performed better. The peak flow rate was reported in one of the studies only, and it may be because both treatments improve the storage function of the bladder, which leads to an improved flow rate. However, objective data for bladder capacity are lacking [39]. Huang *et al.*'s [40] study is the only study on BoNT-A injections during enucleation of the prostate, which showed that combining intradetrusor BoNT-A injections and surgery in one setting led to a significant reduction in incontinence scores without increasing operation duration, hospital days, and complications.

Adverse events such as symptomatic urinary tract infections (UTIs), dysuria, *de novo* urinary retention, gross hematuria, and increased residual urine volume have been reported [41]. Unfortunately, current evidence has not been discussed in depth or observed adverse effects or complications. Huang *et al*. [40] reported a transient postoperative retention in three patients (7%) after concurrent performance of transurethral enucleation of the prostate and intradetrusor BoNT-A injections, but it was not statistically significant. There were no post-operative 90-day complications, such as blood transfusions, urethra strictures, or bladder neck contractures reported. A recent phase IV prospective, interventional, multiple-center study (Restore Study) has reported the adverse events of BoNT-A injections in patients with neurogenic detrusor overactivity (NDO) and OAB. *De novo* urine retention was observed only in NDO patients and not OAB patients [42]. Although current evidence is limited, performing intradetrusor BoNT-A injections during transurethral prostate surgery appears to be safe and effective, improving clinical symptoms in patients with LUTS/BOO and OAB without increasing the incidence of complications.

Transurethral prostate surgery for bladder outlet obstruction

Surgical treatments are important in LUTS/BOO management. In accordance with the guidelines of the European Association of Urology [2], monopolar TURP has long been regarded as the reference technique for treating LUTS/BOO caused by BPE. However, rapid technological advances have provided safer and more effective alternatives to TURP. Here, we will briefly introduce the two main surgical methods, resection and enucleation of the prostate.

Table 1: Summary of studies performing intradetrusor onabotulinumtoxinA injections during transurethral prostate surgery

Article	First author	Publication year	Type of study	Area/country	Number of patients (*n*)	Mean age (years)	Inclusion criteria	Treatment modality	Follow-up period	Clinical parameters	Urodynamic parameters	Adverse events
1	Allameh *et al*.	2020 [38]	Prospective case–control study	Iran	TUR-P + BoNT-A: 21 TURP + solifenacin: 18	TUR-P + BoNT-A: 71.5±7.5 TURP + solifenacin: 68.5±6.5	Men >50 years old, diagnosed with BOO-OAB	TURP + BoNT-A (Dysport) injection (300 units diluted in 10 cc of normal saline injected into 20 points of the bladder wall)	3, 6, and 9 months	IPSS, incontinence, QoL	PVR	NR
2	Allameh *et al*.	2023 [39]	Prospective randomized controlled study	Iran	TUR-P + BoNT-A: 35 TURP + solifenacin: 38	TUR-P + BoNT-A: 72.7±7.7 TURP + solifenacin: 69.4±5.4	Men with obstructive and irritative symptoms defined by IPSS, enlarged prostate on DRE examination, history of OAB and persistence of DO and leakage, BOOI >40 on urodynamics, and prostate volume <80 cc	TURP + BoNT-A (Dysport) injection (300 units diluted in 10 cc of normal saline injected into 20 points of the bladder wall)	1, 3, and 6 months	IPSS, incontinence	PVR, peak flow rate	NR
3	Huang *et al*.	2023 [40]	Retrospective cohort study	USA	HoLEP + BoNT-A: 41 HoLEP: 41	HoLEP + BoNT-A: 73 (69–78) HoLEP: 74 (65–77)	Men with severe storage symptoms were identified and consented to have simultaneous intradetrusor BoNT-A injection at the time of HoLEP	HoLEP + BoNT-A (Botox) injection (200 units diluted in 20 cc of normal saline injected into 40 points of the bladder wall)	1 week, 3, and 6 months	M-ISI, AUASS	NR	Emergency department visits, UTIs

AUASS: American urology association symptom score, BoNT-A: onabotulinumtoxinA, BOO: Bladder outlet obstruction, BOOI: BOO index, DO: Detrusor overactivity, DRE: Digital rectal examination, HoLEP: Holmium laser enucleation of the prostate, IPSS: International prostate symptom score, M-ISI: Michigan incontinence symptom index, NR: Not reported, OAB: Overactive bladder, PVR: Postvoid residual urine, QoL: Quality of life, TURP: Transurethral resection of the prostate, UTIs: Urinary tract infections

Transurethral resection of the prostate

Traditional TURP can be performed using either a monopolar (M-TURP) or a bipolar (B-UTR-P) method. The safety and effectiveness of M-TURP have been well studied. Patients' clinical symptoms, for example, IPSS and QoL score, and objective urodynamic parameters, for example, maximum flow rate and PVR urine are significantly improved after surgery, with no reoccurrence of symptoms [43,44]. Failures are associated with detrusor underactivity rather than re-growth of the prostate. The annual rate of a second prostatic operation, usually repeat TURP, is approximately 1%–2% and has remained constant [45]. Perioperative mortality and morbidity (0.1% and 11.1%) following M-TURP have decreased, but morbidity remains considerable [32]. The common short-to mid-term complications include transfusion due to bleeding (0%–9%), transurethral resection syndrome (TUR-syndrome; 0%–5%), acute urinary retention (AUR; 0%–13%), blood clots obstruction (0%–39%), and UTIs (0%–22%) [43]. Long-term complications include urinary incontinence, urinary retention, UTIs, bladder neck contracture, urethral stricture, retrograde ejaculation, and erectile dysfunction [46].

Bipolar TURP is a widely used alternative to M-TURP. A meta-analysis has confirmed that B-TURP's effectiveness in improving clinical symptoms shows little to no difference when compared to M-TURP (IPSS, QoL score, and flow rate) [47,48]. In B-TURP, energy is confined between an active and a passive pole at the tip of the resectoscope, thus avoiding the use of distilled water and preventing TUR syndrome [49]. Another consideration would be the efficiency of hemostasis. Rühle *et al.* [50] evaluated the safety of B-TURP for patients taking oral anticoagulation (phenprocoumon) or undergoing antiplatelet drug therapy (acetylsalicylic acid or clopidogrel), without stopping or bridging the anticoagulants. Patients under oral anticoagulation therapy showed longer catheterization and hospitalization time and a higher rate of AUR but had the same blood transfusion rate as the control group. Blood transfusion and re-hospitalization rates were higher for patients receiving antiplatelet therapy.

M-TURP or B-TURP is still the preferred surgical procedure for men with LUTS/BOO secondary to BPE currently [2]. The upper limit in prostate size for M-TURP is recommended to be 80 mL in accordance with guidelines, although there have been studies exploring the optimal cutoff value [2]. This is because complication rates increase with surgical duration, which is related to prostate size [32,51]. In general, the choice of M-TURP or B-TURP should be based on the availability of equipment, expertise of the surgeon, and preference of the patient.

Transurethral enucleation of the prostate

Enucleation of the prostate can be performed by different types of laser procedures. However, holmium laser enucleation of the prostate (HoLEP) is the only method with reported concurrent use of intradetrusor BoNT-A injections [40]. The following section will focus on the current evidence of HoLEP in the treatment of male LUTS/BOO secondary to BPE.

Compared to M-TURP, HoLEP has been reported to show higher short-term efficacy, in terms of IPSS and maximum flow rate (Qmax), and similar efficacy at 24-month follow-up [48,52,53]. Compared to B-TURP, HoLEP did not show significant differences in short-term and mid-term (24-month follow-up) efficacy (IPSS, QoL score, and Qmax) [48,54]. In the case of long-term follow-up, functional results were comparable for HoLEP, M-TURP, and B-TURP [55,56]. However, the overall re-treatment rate, such as continuous oral therapies and reoperations, was significantly lower after HoLEP [56].

HoLEP is thought to be a safer procedure for patients undergoing anticoagulation or antiplatelet therapies. However, this observation is derived by comparing with patients not taking anticoagulant or antiplatelet medications. The lack of large prospective randomized controlled trials and observations for long-term complications makes it difficult to ascertain the effectiveness of HoLEP [57]. In real-world practice, the human factor, exemplified in the experience of the surgeon, is the most important factor related to the occurrence of complications [58]. The choice of surgery depends on joint decision-making between the surgeon and the patient.

The effect of transurethral resection of the prostate in treating bladder storage symptoms

As mentioned earlier, OAB symptoms should be resolved after transurethral prostate surgery if they are caused by BOO only. Gharib *et al.* [59] reported the predictors of improvement in storage symptoms after TURP. In their study, patients who had postoperative persistent storage symptoms were significantly older. Terminal DO and higher peak flow rate were also found in those with persistent storage symptoms. In addition, those with higher maximum cystometric capacity tend to have better improvement of storage symptoms after TURP. In a more recent study, Mostafa *et al.* [60] reported significant improvement in subjective parameters, such as IPSS, frequency, urgency, nocturia, and urinary incontinence at 3 and 6 months postoperatively of BPE patients with OAB symptoms and who had undergone either TURP, HoLEP, or vaporization of the prostate. Among these symptoms, frequency has the most improvement at 3-month follow-up, whereas nocturia has the most improvement at 6-month follow-up. Interestingly, the rate of postoperative need for anticholinergics in their study is low (6.9%) [60]. Unfortunately, follow-up data of longer duration remains lacking, which may be related to the increase in factors that may affect urination and bladder function of patients as they age.

Intradetrusor onabotulinumtoxina injections for overactive bladder

BoNT-A inhibits signal transmission at the neuromuscular junction by inhibiting acetylcholine release, therefore interfering with the binding of neurotransmitters to postsynaptic receptors [37,61]. In addition, BoNT-A inhibits bladder afferent nerve firing and provides anti-inflammatory effects to manage bladder disorders. Injections of BoNT-A into the bladder wall can reduce UUI by 50% in OAB-wet patients, who had shown inadequate responses to anticholinergics, therefore implying a higher probability of these patients becoming completely dry when compared to the saline injections control group [62]. However, in some patients with NDO caused by central neurological disease, such as Parkinson's disease and post-stroke spasticity, the clinical benefit is limited due to a higher rate of urinary retention [63].

In post-prostatectomy refractory OAB, intradetrusor BoNT-A injections can significantly improve clinical symptoms and QoL [64]. Similar results have been reported for non-obstructed patients with refractory OAB [65]. In a retrospective study of BoNT-A treatment for OAB, patients who had previously undergone de-obstructive prostate surgery were less likely to require postoperative catheterization [66], which indicates that prostate surgery can reduce the likelihood of complications that may occur after intradetrusor BoNT-A injections.

Compared to oral therapies for OAB (such as solifenacin and mirabegron), BoNT-A was associated with a decrease in frequency and UUI episodes [67,68]. On the other hand, BoNT-A injections have a higher rate of complications for urinary retention and UTIs [68]. Despite these higher complication rates, intradetrusor BoNT-A injections are recommended for men with refractory OAB, as its effectiveness is superior to those of oral therapies.

Conclusions

Current evidence and clinical practices have established the effectiveness and safety of transurethral prostate surgery for male LUTS/BOO and intradetrusor BoNT-A injections for male OAB. However, evidence for the combined use of transurethral prostate surgery and intradetrusor BoNT-A injections in one setting remains limited. No report of increased rate of complications or incidence of adverse effects is seen too. Therefore, we propose that the simultaneous performance of intradetrusor BoNT-A injections during transurethral prostate surgery is clinically feasible. We do note that there is a lack of long-term follow-up and detailed reporting of complications, as well as subgroup analysis of patients. The optimal timing and patient population for this treatment method remain unclear. Further large-scale randomized controlled trials would be necessary to validate the feasibility of combining the treatment in one setting and observe the possible complications.

Data availability statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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Conflicts of interest

There are no conflicts of interest.

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