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ORIGINAL RESEARCH

Clinical Efficacy of Transurethral Resection of the Prostate Combined with Oral Anticholinergics or Botulinum Toxin – A Injection to Treat Benign Prostatic Hyperplasia with Overactive Bladder: A Case–Control Study

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Farzad Allameh[1]
Abbas Basiri[1]
Mohammadreza Razzaghi[2]
Amir reza Abedi[3]
Morteza Fallah-karkan[2,3]
Saleh Ghiasy[3]
Seyyed Mohammad Hosseininia[3]
Saeed Montazeri[3]

[1]Urology and Nephrology Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran; [2]Laser Application in Medical Sciences Research Center, Shohada-e-Tajrish Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran; [3]Department of Urology, Shohada-e-Tajrish Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Introduction: Recent investigations showed that anticholinergic drugs could use for the management of storage symptoms after transurethral resection of the prostate (TURP). The use of intravesical botulinum toxin-A (BTX-A) for the management of overactive bladder is rapidly increasing. In this research, we assess the efficacy of BTX-A vs solifenacin in men suffering from bladder outlet obstruction–over active bladder (BOO-OAB) managed with TURP.

Methods: In this case–control study, 50 men with BOO-OAB randomized into two groups. The control group (A) underwent TURP and subsequently managed by solifenacin 5 mg daily, and the case group (B) underwent TURP and BTX-A injection in the bladder wall in the same session. Treatment success was the primary outcome and defined as post-injection improvement in the storage score of the International Prostate Symptom Score (IPSS) from baseline.

Results: The IPSS, post-void residual volume, frequency, incomplete emptying, nocturia and urgency subscores considerably ameliorated after 12 weeks and 36 weeks for both groups, but it was more significant in the case arm. The quality of life (QoL) scores significantly improved after the treatments in both groups. Intervention group showed significant reductions regarding urgency incontinence compared with the solifenacin group at 12th and 36th weeks.

Conclusion: BTX-A is an effective and well-tolerated treatment in patients with benign prostatic hyperplasia (BPH) who are candidates of TURP and simultaneously suffer from OAB symptoms.

Keywords: anticholinergic drug, benign prostatic hyperplasia, botulinum toxin-A, over active bladder, solifenacin, TURP

Introduction

One of the treatment challenges for general practitioners and urologists is the lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH).[1–4]

In men, bladder outlet obstruction (BOO) may be accompanied by Detrusor Overactivity (DO) due to BPH, or secondary to obstruction. BOO leads to DO by BPH-induced physiological alterations in the bladder wall, denervation caused by ischemia and changes in neuronal mechanisms that control the bladder contraction.[5,6]

The storage symptoms are the most distressing symptoms of BPH. These symptoms include over active bladder (OAB) symptoms, which consist of:

Correspondence: Saeed Montazeri
Urology Resident, Shohada E Tajrish Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
Tel +98 21 22749221
Email saeed.montazeri89@gmail.com

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frequency, urgency, and urge incontinence and voiding symptoms such as intermittency, slow stream and hesitancy are more common. Thus, an essential goal in the management of concomitant symptoms of DO and BPH is to treat these bothersome symptoms.[7]

The most effective treatment for the amelioration of LUTS presented in BPH is transurethral resection of the prostate (TURP), but despite this treatment, a higher percentage of storage symptoms in comparison with voiding symptoms tend to remain.[8–11] Moreover, long term follow-up of patients who underwent TURP showed that symptoms related to OAB tend to reoccur in more than 60%,[12,13] which has led to an assumption of a direct association between DO and BPH; however, this association has been disputed.[14]

Some investigations have recommended that administering anticholinergic drugs could treat the storage symptoms, regardless the presence of BOO.[15] Recently, a meta-analysis suggested that administering anticholinergic drugs did not increase the acute urinary retention rates, but there were no significant alterations in neither the International Prostate Symptom Score (IPSS) nor the maximum urinary flow.[16] On the other hand, BPH is a disease that presents in older men, so an important point is considering the possibility of subjects taking medications for other disorders.[10]

BTX-A injection has been used in several urological disorders, such as voiding dysfunction, including OAB.[17] An increasing trend emerged in using intravesical BTX-A for the treatment of overactive bladder. On the other hand, an increasing evidence demonstrates this technique to be well-tolerated, effective and with minimal or no adverse effects.[18,19] In the present study, the effects of BTX-A vs solifenacin in men with BOO-OAB who managed with TURP were evaluated.

Methods

Population

This was a case–control study that took place from November 2015 to May 2018. Twenty-five men of 50 years and older diagnosed with BOO-OAB completed the investigation in Shohadaye-Tajrish Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran. The control group consisted of 25 patients as well, which for the management of the selection bias, matched according to demographic and clinical features of the case arm.

Eligible subjects were required to have urinary frequency (micturition≥ 8/24 hrs), urgency, urge incontinence (1 or more experience/24 hrs). Also, subjects required to have the following criteria: volume to the first contraction less than 350 mL, urodynamically confirmed DO (Involuntary detrusor contraction ≥ 10 cm H2O), IPSS of 18 or higher (administered once at the first screening and again after BPH drug washout when pertinent), Qmax ≤15 mL per second, voided volume of 125 mL or less and undergoing washout period for any BPH medication.

Subjects with a history of prostate/bladder cancer, bladder stones or bladder diverticulum, an elevated serum prostate-specific antigen level (>4 ng/mL), pelvic radiotherapy, neurological diseases, history of urethral Stenosis/stricture, patients who needed open prostatectomy due to significant high prostate volume (≥80 cc), acute urinary tract infection, previous outpatient BOO procedures, post-void residual (PVR) ≥ 400 mL, urinary retention in the last 12 months, clean intermittent catheterization/indwelling catheter, bladder training (within ten days) and cases with a history of adverse reaction to anticholinergic or BTX-A were excluded.

Study Protocol

At initial presentation, all cases evaluated by a complete urologic physical examination and history. The diagnosis of BOO-OAB based on the history, IPSS, Urodynamic Study (UDS) and transabdominal Ultrasonography for prostate volume and residual volume measurement. Urine culture, renal function test, and coagulative status tests done for all the cases before the procedure, and if needed, appropriate antibiotics prescribed.

The control group (A) underwent TURP and managed by solifenacin 5 mg daily (which started immediately after surgery and continued for a duration of 6 months) and the case intervention group (B) underwent TURP and Dysport injection in bladder wall in the same session (300 units diluted in 10 ccs normal saline injected into 20 points of the bladder wall. The dosage of 300 U in the study protocol is based on the lower optimum dose of BTX-A and also the fact that the suggestive conversion ratio for Dysport compared to Botox is 2.5:1. The injection in the trigonum and near the ureteral ostium was avoided to inhibit any injury to the upper urinary tract).

Outcomes

Treatment success, which was the primary efficacy outcome defined as improvement in the storage score of IPSS

by at least 30% before injection. All cases undertake uroflowmetry to calculate the maximum flow rates. All subjects were examined for a 2-day frequency volume chart (FVC) with a graduated cylinder (the number of voids during the daytime and nighttime) before and after the intervention according to revisit time. Post-void residual (PVR) volume measured using transabdominal Ultrasonography before and after management. Follow-up sessions done at 6 and 9 months post-operatively. Any symptoms of serious adverse events or urinary retention reported on the basis of case-by-case.

Statics

For statistical analysis, SPSS software (IBM corp., Chicago, IL, USA; version 20.0) used. Quantitative variables reported as mean ± standard deviation and qualitative variables reported as frequency and percentage. All nonparametric comparisons with Chi-Square tests. A P value of less than 0.05 considered to be statistically significant.

Ethics

This study was conducted in accordance with the declaration of Helsinki. The approval of the Shahid Beheshti University of Medical Sciences' ethical committee and The Institutional Review Board of Tajrish Hospital obtained. After explaining the benefits, risks, and options of treatment, written informed consent acquired from all patients. The gathered information was considered confidential and used anonymously throughout the survey.

Results

Of the 50 men who entered the research, data acquired from 39 subjects. Four subjects in the case and seven in the control group who did not make the follow-up visits excluded from all analyses.

Table 1 presents the demographic and baseline characteristics. Comparison between the treatment groups was generally feasible.

Of the 18 cases treated with solifenacin, six patients experienced short-run constipation, rash, and dry mouth. One patient in the case group starts to develop voiding difficulty and urinary retention, which needed catheterization. After four days, the patient could urinate spontaneously.

The total IPSS, PVR volume, frequency, nocturia, incomplete emptying and urgency subscores improved significantly after 12 weeks and 36 weeks for both groups but more significantly in case arm. In both groups, the scores of QoL significantly ameliorated after the intervention. Notably, urgency incontinence rates significantly reduced in case group patients at the 12th and 36th week. Table 2 shows changes in storage symptoms at 6 and 9 months in the case arm and comparison with baseline. Table 3 illustrates changes in storage symptoms at 6 and 9 months in the control arm and comparison with baseline. And finally, Table 4 shows changes in the storage symptoms at 6 and 9 months in the case and control groups.

At the 12th week, daytime frequency in the case group reduced from 7.5±2.6 before treatment with BTX-A to 6.1 ±2.00 after treatment ($P < 0.001$) and nighttime frequency reduced from 2.5 ±1.6 before treatment to 2.1 ±1.03 after treatment ($P < 0.003$), all of which were statistically significant. On the other hand, also at 12th week, in the control group, daytime frequency showed reduction from 7.7 ±2.1 before treatment with solifenacin to 6.9 ±2.3 ($P < 0.031$) after treatment and nighttime frequency showed reduction from 2.5 ±1 before treatment with solifenacin to 2 ±1.2 after treatment ($P < 0.039$) which were also statistically significant. At 36th week, daytime frequency reached 6.7 ± 2.3 ($P < 0.014$) and nighttime frequency reached 2.8 ±1.2 ($P < 0.002$) in case group; while in the control group daytime frequency was 7.1 ±2.1 ($P < 0.001$) and nighttime frequency was 2.2 ±1.01 ($P < 0.004$).

Discussion

LUTS, which are suggestive of BPH accounts for one of the most common urological complaints that affect the quality of life. However, storage symptoms reduce QoL more significantly and are more vexing.[20] Both storage and voiding symptoms co-exist in male LUTS, and the OAB is presented in 50% to 70% of patients.[21] BOO results in functional and morphological modifies in the bladder wall (eg: ischemia, partial denervation, neurotransmitter imbalance, changes in electrical characteristics of detrusor smooth muscle cells, spinal micturition reflex reorganization).[3,22]

OAB Treatments include pelvic floor muscle training, behavioral therapy, intravesical treatments, anti-muscarinic drugs, clean intermittent catheterization, and occasionally bladder open surgery.[23–25] Prostate Surgery in some of these cases can normalize the OAB-cystometric responses and in others, causes urge incontinence. Generally, after treatment with TURP, storage symptoms tend to remain more than voiding symptoms (storage symptoms remain in 40% of patients at some levels for mean duration of 3 months), thus having a negative impact on the QoL.[8,12,26]

Table 1 Baseline and Demographic Characteristics

Variables	TURP+Solifenacin N=18		TURP+Dysport N=21		P
Age, year	68.50±6.51		71.71±7.47		0.164
Prostate Volume, mL	53.03±11.23		57.10±03.07		0.231
Qmax	11.01±2.05		11.07±1.12		0.218
BCI*	164±17.01		161±16.06		0.103
OAB type	III: 14	IV:4	III:17	IV:4	0.558
PVR	86.6±23.31		87.02±19.07		0.127
IPSS	24.5±6.75		24.86±5.16		0.853
Urgency	4.22±0.64		4.24±0.70		0.942
Frequency	4.08±0.31		4.03±0.55		0.921
Nocturia	4.17±0.08		4.11±0.10		0.948
QoL	4±1		4±1		0.901

Note: *Bladder contractility index.

Table 2 Changes in Storage Symptoms at Months 6 and 9 in the Case Arm and Comparison with Baseline

Variables	TURP+Dysport N=21			P	
	Baseline	6 Months	9 Months	6 Months	9 Months
PVR	87.02±19.07	33.41±13.28	42.07±18.02	0.000	0.000
IPSS	24.86±5.16	5.1±2.07	8.2±1.19	0.000	0.000
Urgency	4.24±0.70	1.67±1.27	2±1.86	0.000	0.001
Frequency	4.03±0.55	2.01±0.06	2.15±1.13	0.000	0.000
Nocturia	4.11±0.10	2.00±0.86	2.93±0.43	0.000	0.01
Incontinence	15	3	4	0.000	0.000
QoL	4±1	2±0.07	2±1.07	0.000	0.001

Injection of BTX-A has been used in several urological disorders, such as voiding dysfunctions, including OAB.[27] Moreover, in patients with detrusor overactivity, injection of BTX-A in detrusor muscle can inhibit contractions and thus improving urinary continence.[28] Many investigations present the period of induced detrusor paralysis after BTX-A injection to be approximately nine months.[10,19,28–31]

Table 3 Changes in Storage Symptoms at Months 6 and 9 in the Control Arm and Comparison with Baseline

Variables	TURP+Solifenacin N=18			P	
	Baseline	6 Months	9 Months	6 Months	9 Months
PVR	86.6±23.31	41.07±18.09	66.26±10.22	0.000	0.001
IPSS	24.5±6.75	7±3.23	11±1.02	0.000	0.003
Urgency	4.22±0.64	3.78±1.39	4.64±1.91	0.02	0.3
Frequency	4.08±0.31	2.51±1.22	2.91±1.09	0.001	0.01
Nocturia	4.17±0.08	2.76±1.09	2.9±2.36	0.001	0.01
Incontinence	17	9	12	0.000	0.008
QoL	4±1	2±0.3	3±1.04	0.002	0.01

Table 4 Changes in the Storage Symptoms at Months 6 and 9 in Case and Control Groups

Variables	TURP+Solifenacin N=18		TURP+Dysport N=21		P	
	6 Months	9 Months	6 Months	9 Months	6 Months	9 Months
PVR	41.07±18.09	66.26±10.22	33.41±13.28	42.07±18.02	0.01	0.005
IPSS	7±3.23	11±1.02	5.1±2.07	8.2±1.19	0.033	0.01
Urgency	3.78±1.39	4.64±1.91	1.67±1.27	2±1.86	0.000	0.001
Frequency	2.51±1.22	2.91±1.09	2.01±0.06	2.15±1.13	0.05	0.01
Nocturia	2.76±1.09	2.9±2.36	2.00±0.86	2.93±0.43	0.01	0.33
Incontinence	9	12	3	4	0.003	0.000
QoL	2±0.3	3±1.04	2±0.07	2±1.07	0.4	0.06

Three action mechanisms that explain the clinical effects of BTX-A are as follows: inducing a flaccid paralysis of detrusor muscle by blocking acetylcholine released at the neuromuscular junction,[30] inhibition the release of other neurotransmitters such as norepinephrine (that has a significant physiologic effect on the functional modulation of the lower urinary tract.),[32] and the inhibition of afferent neurotransmission.[10]

An alternative treatment of anticholinergic therapy is injection into the detrusor muscle. First trials with BTX-A suggested favorable results respecting the urodynamic and clinical and advantages of this novel treatment. The neurotoxin injection into the bladder wall results in neuromuscular junction blocking and thus relaxation of the detrusor muscle.[33,34]

Previous researches mentioned BTX-A effects on reduced DO and urine leakage to be comparable to placebo.[17–19,28,30,35,36] However, the surgical management of BPH with simultaneous BTX-A injection for management of BOO-OAB has not investigated yet.

In the present study, subjects who had clinical BPH managed by TURP plus anticholinergic medication or simultaneous BTX-A injection in bladder detrusor muscle were included. Our results presented that the PVR, total IPSS, QoL scores, nocturia, frequency, and urgency significantly improved after 12 weeks and 36 weeks for both groups but more significantly in the BTX-A injection group. Also, significant reduction seen in the case group compared to the solifenacin group regarding urgency incontinence.

Conclusion

BTX-A is an effective and well-tolerated treatment in patients with benign prostatic hyperplasia (BPH) who are candidates of TURP and simultaneously suffer from OAB symptoms.

Limitation and Recommendations

A limitation of our study was low number of patients which became more problematic when four subjects in the case and seven in the control group excluded from the study due to loss of follow-up visits. Future studies with larger number of patients are needed to elucidate the efficacy of BTX-A injection in male subjects with concomitant BPH and OAB using randomized clinical trials for the long-term periods compared to placebo or other medications.

Informed Consent

According to Research involving Human Participants, written informed consent acquired from all patients.

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Author Contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors have no conflicts of interest to declare.

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