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Original Article

Efficacy of botulinum toxin-A injection versus oral anticholinergic medications following transurethral resection of the prostate to manage bladder outlet obstruction with overactive bladder: a prospective randomized clinical trial study

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Abstract: Background: To compare the effect of botulinum toxin-A (BoNT-A) injection versus oral anticholinergic agents following transurethral resection of the prostate (TURP) in patients with benign prostatic hyperplasia (BPH) and Overactive Bladder. Materials and methods: In this randomized clinical trial from February 2021 till May 2022 data of patients with obstructive urinary symptoms and urgency incontinence were analyzed. The intervention group consisted of 35 patients who were injected with 300 units of BoNT-A (Dysport®) into the detrusor muscles at the same time as TURP. 38 participants in the control group were treated with solifenacin 5 mg (Urinacin®) daily after TURP. Results: In the evaluation of 73 included patients (mean age: 67.54±6.3), IPSS score change (first month, P=0.777; 6th month, P=0.761) and storage irritative symptoms change score (first month, P=0.995; 6th month, P=0.962) were decreased and Qmax was increased (first month, P=0.195; 6th month, P=0.174) similarly in 2 groups. Lower number of patients experienced urgency incontinence during follow up time in intervention group, significantly (first month, 18 versus 5, P=0.002; 6th month, 20 versus 6, P=0.002). PVR was also decreased more in first month and 6th month follow up in patients of intervention group (1th month, P=0.012; 6th month, P=0.033). Conclusion: Anticholinergic agents or intradetrusor BoNT-A injection would improve the storage symptoms in patients with BPH and detrusor overactivity following TURP. In contrast to IPSS score, storage irritative score and Qmax, which improve similarly in both groups, the PVR and urgency incontinence episodes will improve more in patients receive intradetrusor BoNT-A injection.

Keywords: Transurethral resection of prostate, benign prostate hyperplasia, botulinum toxins, cholinergic antagonists, overactive detrusor

Introduction

Benign prostatic hyperplasia (BPH) is a common condition in older men and is seen in more than half of men over the age of 60 and almost all men over the age of 80 [1, 2]. Men with BPH can develop bladder outlet obstruction (BOO) and lower urinary tract symptoms (LUTS) [3]. Detrusor muscle overactivity (DO) as one of the most well-known causes of LUTS, associated with bladder storage symptoms (including frequent urination, urgency, stress urinary incontinence) and increases with age [4]. DO can only be detected by urodynamic examination, which is due to involuntary contractions of the detrusor muscle or is spontaneous or excitatory during bladder filling in cytometry [5]. Cystometric studies in men with BPH have shown that DO is present in 50 to 75% of cases, and meta-analysis has shown the average prevalence of 60.2% [6].

TURP is known as the gold standard treatment for medium sized prostates in patients with BPH and obstructive LUTS who are resistant to medical treatment [7]. Oral anticholinergic

agent and intravesical botulinum A toxin injection are two standard method in treatment of DO [8]. Following TURP in patients with both obstructive and irritative LUTS caused by BPH and DO, some physicians prefer to use long time oral anticholinergic agents to eradicate irritative LUTs while others offer the patients intravesical botulinum A toxin injection during the same session of the surgery. But to our best knowledge, there is no randomized clinical trial in the literature that compares these two methods of treatment. Therefore, this study was designed to evaluate the outcomes of oral anticholinergic agent versus intravesical botulinum A toxin injection following TURP in patients suffer from simultaneous obstructive and irritative LUTS due to DO and BPH.

Materials and methods

Study design and participants

The present randomized clinical trial was performed on 45-84 years old men referred to the Urology Clinic of Shohada Tajrish Hospital, Tehran, Iran who were diagnosed as symptomatic BPH went under TURP treatment by simple randomized sampling. The study was registered at http://www.irct.ir (Identifer: IRCT20201225049827N1). All volunteer patients are treated with an alpha-blocker for at least one month. The inclusion criteria were obstructive and irritative symptoms defined by International Prostate Symptom Score (IPSS) and enlarged prostate on DRE examination, satisfaction to enter the study, history of OAB and persistence of DO and leakage (OAB type III and IV) and bladder outlet obstruction index (BOOI) > 40 on urodynamics and prostate volume less than 80 cc. OAB defined as a condition with characteristic symptoms of urinary urgency, usually accompanied by nocturia and frequency, with or without urgency incontinence, in the absence of any obvious pathology including urinary tract infection, metabolic disorders or urinary stress incontinence (updated in 2010 by the International Continence Society) [9, 10]. We diagnosed OAB with a detailed history, physical exam, asking about voiding diaries and urine analysis to rule out other pathologic causes. We included patients with OAB and urine leakage in this study. The patients with neurological diseases such as Parkinson's or stroke, CVA, diabetes mellitus, spinal disease or history of spinal surgery, prostate or bladder cancer, bladder or prostate surgery in the past, dissatisfaction with entering the study, hypersensitivity to the drug solifenacin or botulinum toxin, history of bladder stones, bladder diverticulum, PSA > 4 ng/ml, history of pelvic radiotherapy, history of urethral stricture, candidates for open prostate surgery (> CC 80), history of urinary retention in the last 12 months, urinary tract infection, post void residual (PVR) > 200 CC, and history of permanent catheterization or CIC were excluded.

Data gathering

In the initial evaluation of patients, demographic information including age, sex, BMI, and IPSS, patients' quality of life were assessed and recorded using a questionnaire, smoking, alcohol, and underlying disease were also documented. Uroflowmetry was performed to determine the peak flow rate for each patient, and the residual volume after urination was determined by trans-abdominal ultrasound for each patient. PSA was assessed for each patient through blood samples. Trans-abdominal ultrasound was performed for each patient to determine prostate volume. OAB classification and extent of obstruction were determined in the Pressure Flow Study.

Patients eligible for the study were divided into two groups using a random computer block. Group A patients have treated with solifenacin 5 mg (VSOL) daily after TURP surgery. In group B, 300 units of Botulinum toxin (Dysport) diluted with 10 cc of normal saline was injected into the bladder wall in the operating room at the same time as TURP, injection was performed through the cystoscope at 20 detrusor points away from the ureteral orifice and trigon. Follow-up of patients was performed at intervals of 1, 3, and 6 months using the desired outcomes.

IPSS, PVR, urgency incontinence after 1, 3, and 6 months are examined in both groups.

In group A (control-solifenacin), 42 patients were included in the study, of which 38 were provided with the possibility of follow-up (4 did not refer for follow-up).

In group B (case-Botox Disport), 42 people were included in the study, which allowed 35 people to follow up (7 people did not apply for follow-up).

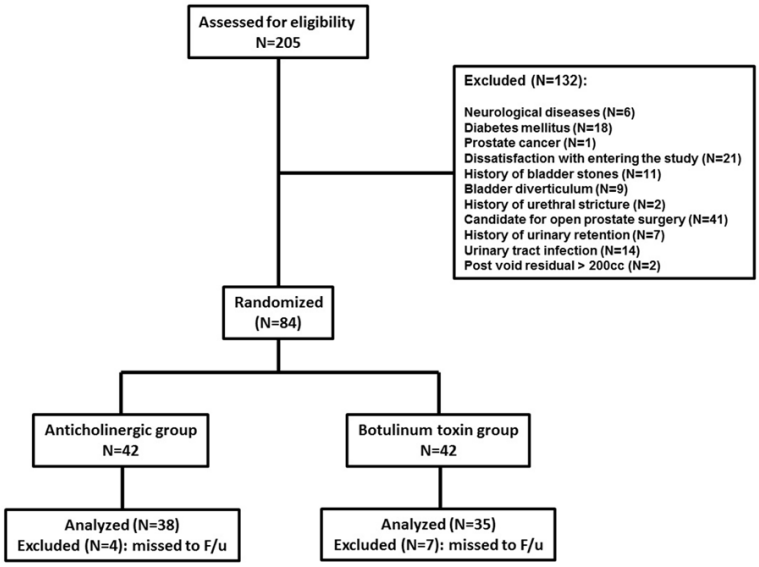

Figure 1. The CONSORT diagram shows the flow of participants.

Table 1. Characteristics and pre-operative data of patients in group 1 and 2, separately

	Group 1	Group 2	*P*-value
Number	38	35	
Age	69.39±5.4	72.7±7.7	0.153
BMI	26.99±1.2	26.09±1.2	0.466
Smoking	7	6	0.742
Alcohol	1	1	0.865
Ischemic heart disease	3	3	0.841
Preoperative PSA	3.17±0.16	3.22±0.12	0.85
Prostate volume	53.4±9.7	56.3±3.5	0.365
PVR	86.44±27.9	93.79±15.59	0.174
Preoperative IPSS	25.04±4.6	25.11±3.1	0.939
Storage irritative score	4.27±0.57	4.17±0.61	0.447
Preoperative PFR	10.97±2.15	11.06±0.91	0.832
DO type			0.92
3	29	28	
4	9	7	
Mean ± SD BOO index	58.26±6.21	56.80±7.5	0.644

BMI, body mass index; PSA, prostate specific antigen; IPSS, International Prostate Symptom Score; PFR, peak flow rate; PVR, post-void residual; DO, detrusor overactivity; BOO, bladder outlet obstruction.

Statistical analysis

Data was analyzed with SPSS software (Version 26). Quantitative variables described with Mean ± SD (standard deviation), and frequency was used to describe qualitative variables. Normality test was don for quantitative variables by Shapiro-Wilks test. Independent sample t-test and paired t-test was performed for comparing between and within group, respectively. Repeated measure ANOVA was done for examine change over the time between two groups. Chi-Square test was applied for comparing qualitative variables.

Ethical consideration

The ethics committee approved all the processes of the present study of Shahid Beheshti University of Medical Sciences, Tehran, Iran, and received the ethics code IR.SBMU.RETECH.REC.1400.1060.

Before the presence of patients in the study, the informed consent form was completed for each of them.

Results

Participants

The CONSORT diagram in **Figure 1** shows the flow of participants. Two hundred five patients were assessed for eligibility and 73 patients met our inclusion criteria.

Demographics

The mean age was 67.54±6.3 year. The mean BMI was 26.54±1.1. Thirteen (17.8%) and 2 (2.73%) patients used alcohol and smoked cigarette, respectively. Six (8.21%) patients suffered from underlying disease. The mean PSA was 3.19±0.14 and 57 (78.08%) and 16 (21.91%) patients suffered from OAB type 3, 4 with urgency incontinence, respectively. The mean size of the prostate was 54.85±6.3, the mean peak flow rate, IPSS score, residual volume and BOO index, were 11.01±1.7, 25.07±3.4, 90.11±20.4 and 57.53±6.9, respectively.

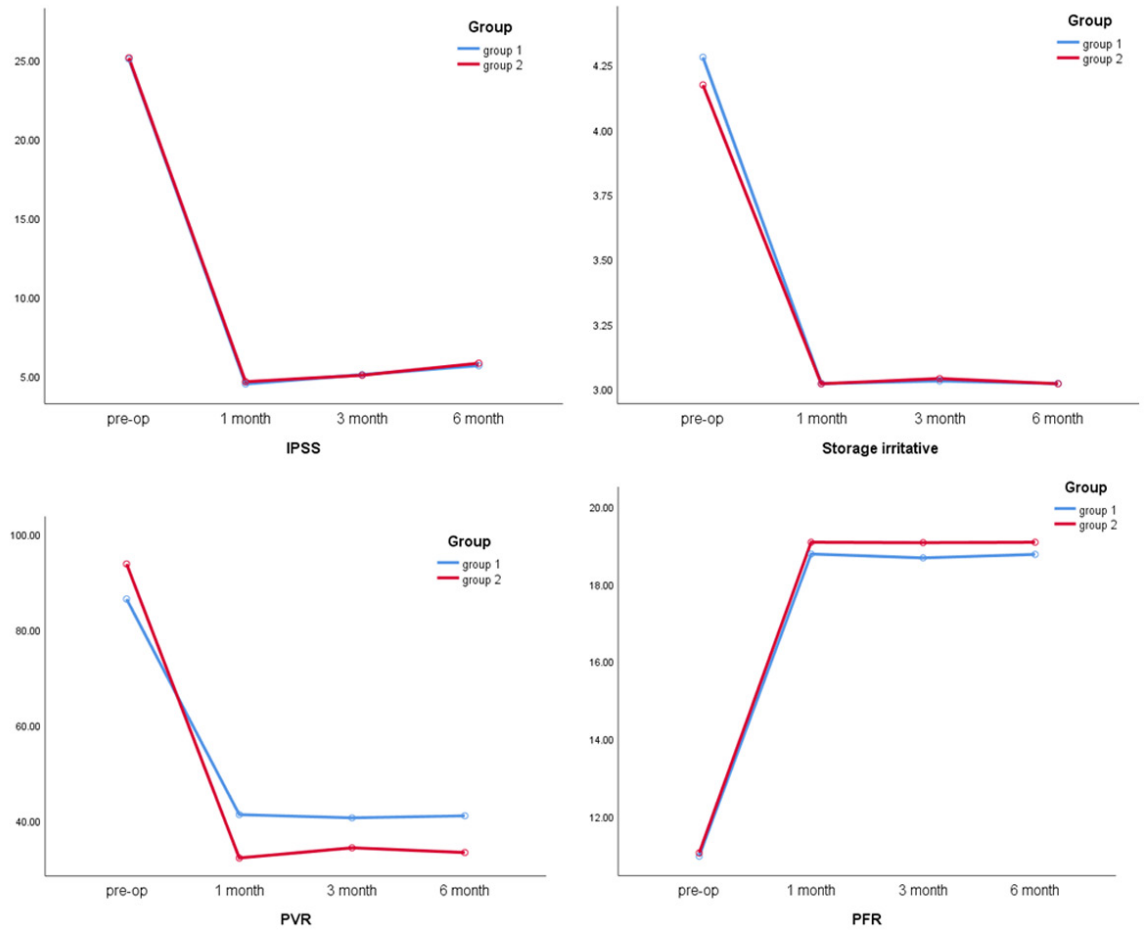

Figure 2. The mean trend of IPSS, Storage irritative, PVR, PFR in two groups.

Follow up

In the one, three and six month follow up and compared to preoperative values, the mean IPSS score (P=0.006), BOO index (P=0.0001) and PVR (P=0.003) decreased and the mean PFR (P=0.000) increased, significantly in both groups. All these data of two groups are shown in **Table 1**, separately and plotted in **Figure 2**.

The mean IPSS and Storage irritative were reduced significantly in both groups, this comparison between pre-operation and all three follow up was significant (*P*-value < 0.05) but after first follow up no significant change was observed in other follow-up for IPSS and Storage irritative in each group. The mean PVR was reduced in both groups in first follow-up, but after 1 month no significant change were observed. The mean reduction in group 1 is more than group 2 significantly.

The mean PFR was increased significantly in both groups, this increase was significant between pre-operation and all follow-up (*P*-value < 0.05) but between three follow-up no significant change was observed. Comparing number of Urgency incontinence between pre-operation and all follow up in group 2 was more reduced than group 1 significantly (**Table 2**).

Discussion

Urgency urinary incontinence, as a disease which creates a debilitating condition for a patient, could affect the quality of life. Oral anticholinergic would be the first choice treatment for this situation but may have minimal to modest efficacy. Lack of complete symptom improvement, the need to use medication every day and associated drug side effects including constipation and dry mouth would be three reasons why the patient does not tolerate this kind

Table 2. Changes in patients' symptoms at 1, 3 and 6 months follow-up in group 1 and 2

	Pre-op	1 month	3 months	6 months	*P* value
IPSS score					
Group 1	25.04±4.6	4.50±2.1	5.09±2.1	5.66±2.1	< 0.001
Group 2	25.11±3.1	4.65±2.1	5.06±2.1	5.82±2.1	< 0.001
P value	0.939	0.777	0.943	0.761	
Storage irritative					
Group 1	4.27±0.57	3.02±0.64	3.03±0.64	3.03±0.64	< 0.001
Group 2	4.17±0.61	3.01±0.56	3.03±0.56	3.01±0.56	< 0.001
P value	0.447	0.995	0.949	0.962	
PVR (cc)					
Group 1	86.44±27.9	41.29±16.34	40.61±16.34	41.04±16.34	< 0.001
Group 2	93.79±1559	32.20±1364	34.33±1364	33.35±1364	< 0.001
P value	0.174	0.012	0.08	0.033	
Urgency incontinence (n)					
Group 1	38	18	20	20	0.866
Group 2	35	5	6	6	0.798
P value		0.002	0.002	0.002	
PFR (ml/sec)					
Group 1	10.97±2.15	18.76±0.98	18.67±0.98	18.77±0.98	< 0.001
Group 2	11.06±0.91	19.06±0.96	19.05±0.96	19.07±0.96	< 0.001
P value	0.832	0.195	0.098	0.174	

IPSS, international Prostate Symptom Score; PVR, post void residue; PFR, peak flow rate.

of medicine [11, 12]. In a population based study in terms of perceptions and behaviors about bladder control problems Diokno et al [13] found that only 56% of patients found this medicine useful in improvement of their symptoms and half of them didn't continue their medication. Many studies approved the efficacy of intradetrusor BoNT-A injection in treatment of urgency incontinence and refractory detrusor overactivity [12, 14]. Usually it is not to be used as a first treatment but in patients with refractory symptoms. Incomplete bladder emptying and need to clean intermittent self-catheterization may be a problem [15] but other studies did not confirm these worries [16, 17].

Betterment of quality of life is the main goal of prostate surgery in patients suffering BPH [18]. Storage symptoms remain in a significant number of patients following TURP and affect the quality of life [19]. Today, use of oral anticholinergic agent or intra bladder botulinum injection become more popular to improve urinary urgency and storage symptoms following prostate surgeries. This trial was designed if using intra bladder botulinum injection as a periodic office-based procedural approach would be superior to oral anticholinergic drugs as a daily pharmacologic therapy.

In 2020 in a case control study [20], we compared 25 patients underwent TURP and solifenacin 5 mg daily, subsequently to 25 patients underwent TURP and BoNT-A injection in the bladder wall in the same session. We follow the patients in 3 months and 6 months postoperatively and finally concluded that improvement of IPSS score, storage symptoms, PVR, urgency and nocturia was more significant in second group. According to the interesting results, we designed a prospective randomized clinical trial in this regard. All the mentioned parameters were improved in both groups (the patients with BPH and detrusor overactivity simultaneously) significantly. In this study we didn't find any significance in improvement of IPSS score, peak flow rate (Qmax) and storage irritative score including urgency, frequency and nocturia between two groups. But we observed a significance improvement in PVR and urgency incontinence rate in intervention group.

There are many studies which evaluated the effects intradetrusor BoNT-A injection [21, 22] and oral anticholinergic medications [23-25] on

men with lower urinary tract symptoms. Huang et al [26] evaluated the efficacy of botulinum toxin injections plus TURP in men with BPH and concluded that it would be an effective treatment in such patients. Kuzmenco et al [27] also showed the safety and efficacy of oral anticholinergic following TURP and persisted LUTS. But to the best of our knowledge, there is a lack in studies about the comparison of intradetrusor BoNT-A injection and oral anticholinergic medications following TURP in patients with BPH and overactive bladder. Prospectiveness and randomization in this trial were the strengths of this study but it would be better to include larger sample size with longer follow up.

Conclusion

Anticholinergic agent or intradetrusor botulinum injection would improve the storage symptoms in patients with BPH and detrusor overactivity following TURP. In contrast to IPSS score, storage irritative score and peak flow rate, which improve similarly in both groups, the post-void residue and urgency incontinence episodes will improve more in patients receive intradetrusor BoNT-A injection.

Disclosure of conflict of interest

None.

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