

Research Paper:

# Transurethral Intraprostatic Botulinum Toxin-a Injection in Patients with Benign Prostatic Hyperplasia: A Case Series and Literature Review



Mahmoud Tavakkoli<sup>1</sup>, Hamidreza Ghorbani<sup>1</sup>, Amin Nobahar<sup>1</sup>, Maryam Emadzadeh<sup>2</sup>, Atena Aghae<sup>3</sup>, Mahdi Mottaghi<sup>1</sup>, Salman Soltani<sup>1\*</sup>

1. Department of Urology, Kidney Transplantation Complications Research Center, Mashhad University of Medical Sciences, Mashhad, Iran.
2. Clinical Research Development Unit, Ghaem Hospital, Mashhad University of Medical Sciences, Mashhad, Iran.
3. Nuclear Medicine Research Center, Mashhad University of Medical Sciences, Mashhad, Iran.



**How to cite this paper** Tavakkoli M, Ghorbani HR, Nobahar A, Emadzadeh M, Aghae A, Mottaghi M, et al. Transurethral Intraprostatic Botulinum Toxin-a Injection in Patients with Benign Prostatic Hyperplasia: A Case Series and Literature Review. Iranian Journal of Toxicology. 2022; 16(1):9-16. <http://dx.doi.org/10.32598/IJT.16.1.851.1>

<http://dx.doi.org/10.32598/IJT.16.1.851.1>



## Article info:

**Received:** 13 Jul 2021

**Accepted:** 06 Oct 2021

**Online Published:** 01 Jan 2022

## \* Corresponding author:

**Salman Soltani, MD.**

**Address:** Department of Urology, Kidney Transplantation Complications Research Center, Mashhad University of Medical Sciences, Mashhad, Iran.

**E-mail:** [soltanis@mums.ac.ir](mailto:soltanis@mums.ac.ir)

## ABSTRACT

**Background:** We aimed to assess the efficacy of Intraprostatic Onabotulinumtoxin-A (BTA) on the International Prostate Symptom Score (IPSS) and other objective measures of patients with Benign Prostatic Hyperplasia (BPH).

**Methods:** Fifteen patients were included in this study. The drug (BTA; 150 IU) was reconstituted in 20 mL of 0.9% saline before administration to the patients. After providing urethral anesthesia, 20 intraurethral injections were made to lateral lobes of the prostate, 10 injections in each lobe. Follow-up visits were planned 3 and 12 months after the intervention. Pre- and post-interventional IPSS, Prostate-Specific Antigen (PSA), Prostate Volume (PV), Post-Void Residue (PVR), and maximum urinary flow rate (Qmax) compared via paired t-test. Finally, we reviewed the Pubmed database to provide a more precise conclusion.

**Results:** The Mean±SD age of patients was 69±8.24 years, and the mean IPSS score decreased significantly from 24.3±3.3 to 14.6±3.7 (P<0.001) and 16.86±3.06 (P<0.009) on the 3<sup>rd</sup> and 12<sup>th</sup> months, respectively. The Mean±SD PSA, PVR, Qmax, and PV were 3.26±1.38, 82.33±35.55, 8.56±1.76, and 47.86±8.93, respectively at baseline. These factors significantly improved to 2.72±1.33 (P<0.000), 71.33±30.55 (P<0.000), 9.5±1.33 (P<0.011), and 42.86±6.04 (P<0.000), respectively, on the 12<sup>th</sup> month follow-up.

**Conclusion:** Although the overall results support the efficacy of BTA for BPH, the best route of administration, the most effective dose, the optimal number, and the volume of injections need further investigations. The probable placebo effect and underlying medical conditions (e.g., insulin resistance) should be considered as the confounding factors.

**Keywords:** Benign prostatic hyperplasia, Benign prostatic hypertrophy, Botox, Onabotulinumtoxin-A, Botulinum toxin A

## Introduction

**B**enign Prostatic Hypertrophy (BPH) is a common condition affecting at least 50% of men after age 50 [1]. Treatment for mild cases of BPH is only observation

and moderate symptoms are managed pharmacological interventions [2]. Due to its high complication rate, surgery is reserved for severe cases of BPH after poor response to pharmacological treatments [2]. The Transurethral Resection of the Prostate (TURP) is the gold standard therapy [3]. In some cases, however, several

underlying conditions, such as cardiovascular diseases, coagulopathies, and certain disabling conditions are the obstacles that may deprive the patient of the TURP advantage [4].

Additionally, since 15%-25% of patients who undergo TURP are not satisfied with the long-term clinical outcomes, younger patients prefer less invasive interventions to save their sexual and urinary functions from being endangered by unwanted complications of TURP [2, 5]. In such circumstances, the alternative options may be LASER prostatectomy, photoselective prostate vaporization, bipolar transurethral enucleation, prosthetic arterial embolization, and intraprostatic alcohol injection. Newer minimally invasive procedures can also be considered by urologists, such as aquablation, convective water vapor treatment, and Botox injection [6]. Intraprostatic onabotulinumtoxin-A (BTA) injection is another alternative option with satisfactory results. Although a meta-analysis proposed a potent placebo effect, it is still worth attention because several studies have shown improvement in objective measures, such as Prostate Volume (PV), maximum urinary flow rate (Qmax), and Post-Void Residue (PVR). Progress in these factors has been declared by several studies that rule out the placebo effect. In this study, we aimed to investigate these factors in patients with BPH in response to BTA injection.

## Materials and Methods

Eighty six patients with previously diagnosed BPH were referred to our tertiary clinic, between September 2018 and March 2019, after their poor response to pharmacological therapy or refusal to undergo TURP. The inclusion criteria were: a) age <60 years; b) patients with confirmed BPH, based on symptoms, ultrasound and rectal examination; c) persistent symptoms despite proper medical treatment based on the American Urology Association guideline; d) non-compliance with TURP or underlying medical conditions, which exclude TURP as an option for the treatment. The exclusion criteria were: a) patients with active UTI; b) nephrolithiasis; c) malignancies; d) PVR > 250 mL; e) previous prosthetic or bladder surgery; and, f) history of BTA hypersensitivity. We also searched the PubMed database by titles and/or abstract. The search words were as follows: botox; onabotulinumtoxin; botulinum; onabotulinumtoxin-A; vistabel; vistabex; oculinum; meditoxin; neuronox; prostatic hyperplasia; prostatic hypertrophy; prostatic adenoma; and prostatic enlargement strategy. Marchal, et al. have reviewed studies on this subject up to 2012, and we summarized the studies after that data onward [7].

**Procedures:** Fifteen male patients were included voluntarily in this study. A written and signed informed consent was obtained from each of the participants before being enrolled in the study. We reconstituted 150 IU BTA (Dysport™) in 20 mL normal saline. Urethral anesthesia was achieved by the injection of 15 mL Lidocaine 2% gel and waited 10 minutes. With a 22-Fr cystoscope (Storz, Germany) and a 23-gauge needle, 20 injections were made (10 in each lobe) to the lateral lobes of the prostate with the patients in lithotomy position. The depth of the injections was 0.5-1 cm. Patients were administered ciprofloxacin 500 twice daily for five days, starting 12 hours before the procedure. We measured pre-interventional Prostate-Specific Antigen (PSA), International Prostate Symptom Score (IPSS), PVR, PV, and Qmax and followed up the clinical changes at 3 and 12 months post procedure.

**Statistical analyses:** The data were analyzed on SPSS, v. 20, and paired t-test, and the results were compared pre-and post-operative measures. A  $P < 0.05$  was considered statistically significant.

## Results

The Mean±SD patients' age was 69.00±8.24 years. The post-operative visits were carried out 6-12 hours after the surgical procedure. No complications occurred during the surgery. Also, patients did not complain of any adverse events at the follow-up visits 3-12 months after the treatment. The results are summarized in Table 1. The Mean±SD values of IPSS decreased significantly from the baseline score of 24.3±3.32 to 14.6±3.7 and 16.9±3.1 at 3-month ( $P < 0.001$ ) and 12-month ( $P = 0.009$ ), respectively. Similarly, the Mean±SD values of PSA, PVR, and PV declined significantly by 0.75±0.82, 20.5±11.4, and 8.7±3.8, respectively. The P-value for all measures were <0.001. The mean primary Q-max volume increased by 2.8±1.48 and 0.9±1.37 at 3-month ( $P < 0.001$ ) and 12-month ( $P = 0.02$ ), respectively.

## Discussion

**Pathophysiology and animal studies:** The prostate is innervated mainly by the autonomic nervous system [8]. Cholinergic fibers regulate the growth and secretion of the prostate epithelium, while stroma and smooth-muscle cells predominantly receive sympathetic fibers [8]. Thus, autonomic denervation of the prostate by the BTA can limit or even decrease glandular growth and smooth-muscle contraction. These effects have been detected in animal studies whereby BTA caused glandular atrophy and apoptosis of the cells as compared to the effect by

**Table 1.** Laboratory and clinical variables at baseline, 3-month and 12-month followup

Time Point	Mean±SD				
	IPSS	PSA	PVR	Qmax	PV
Baseline	24.3±3.3	3.3±1.4	82.3±35.5	8.6±1.8	47.9±8.9
3-mon. followup	14.6±3.7	2.5±1.1	61.8±28.8	11.3±1.8	39.1±6.1
	P=0.0001	P=0.0001	P=0.0001	P=0.0001	P=0.0001
	9.7±1.4	0.7±0.8	20.5±11.4	-2.8±1.5	8.7±3.8
12-mon. followup	P=0.0001	P=0.003	P=0.0001	P=0.0001	P=0.0001
	16.9±3.1	2.7±1.3	71.3±30.5	9.5±1.3	42.9±6.0
	P=0.009	P=0.0001	P=0.0001	P=0.011	P=0.0001
	7.4±2.7	0.5±0.8	1.1±14.7	-0.9±1.4	5.0±4.6
	P=0.0001	P=0.024	P=0.012	P=0.020	P=0.001

IPSS: International Prostate Symptom Score; PSA: Prostate-specific Antigen; PVR: Post-Void Residue; Qmax: Maximum Urinary Flow Rate; PV: Prostate Volume.

normal saline injection [9, 10]. Four experiments on adult male Sprague-Dawley rats showed atrophy and apoptosis of the prostate gland [10-13]. Two studies on Wistar rats also showed the same results [14, 15]. Also in previous studies on canine models, researchers have shown decreases in the prostate size, but significant atrophy was shown in only one study [9, 16].

**Injection routes:** Three main routes of BTA injection are transrectal, transperineal, and transurethral. Most urologists use the transrectal approach because of its similarities with the transrectal biopsy of the prostate, and it does not need general anesthesia. However, it increases the risk of prostatitis. Transperineal access is relatively uncommon. One study changed this route to transrectal through the trial [17]. The transurethral technique is more familiar for the urologists, gives better access to the lateral and medial lobes, and carries a lower risk of prostatitis; however, it requires general anesthesia. Studies that use the transperineal method found relatively similar outcomes in terms of improvement of Qmax and PVR, which are the objective measures and immune to the placebo effect [2]. To gain a better understanding, we summarized clinical trials that used no control groups in Table 2. The IPSS score, PVR volume, and PV declined in all studies, but the significance of such findings varies in different studies. PSA values are more heterogeneous among these studies.

**Endocrine status:** Vikram, et al. have shown that the prostate of insulin-resistant rats is less likely to undergo

apoptosis and atrophy in response to BTA injection [13]. Another study has demonstrated that Metformin treatment in rats decreases the androgen-induced prostatic hyperplasia [18]. Rahman, et al. provided rats with a high-fat diet and concluded that hyperlipidemia is associated with an increased rate of prostatic hypertrophy [19]. However, human studies have shown that hyperlipidemia alone does not increase the risk of BPH, unless one of the other components of metabolic syndrome is present [20]. These findings suggest that the studies which are conducted on the effects of BTA on BPH should consider the underlying endocrine status of patients as a confounding factor.

**Complications:** Reported adverse events are hematuria, prostatitis, urgency, increase in PSA, erectile dysfunction, urinary retention, UTI, and pollakiuria, frequent, abnormal urination during the day [17, 21-25]. Erectile function was more likely to be preserved in the BTA group in comparison to the TURP group in the study conducted by El-Dakhkhny, et al. [21].

**Clinical data:** We found six clinical trials that assessed the efficacy of BTA on BPH symptoms since 2003. Four of them compared BTA efficacy with saline injections, one compared it to TURP, and one used standard pharmacological therapy as a control group. We have summarized these studies in Table 3. Shim, et al. conducted a meta-analysis in 2015, which analyzed three eligible clinical trials of BTA versus saline injection [25]. They concluded that improvements in IPSS were mostly a

**Table 2.** Clinical and lab variables from six previous studies versus those of the current research

Study Ref.	Patients (I/P)	Dose (IU)	Injection	Injection Volume	Injection Route	Mean Difference [Post-Interventional Minus Baseline] Intervention/Placebo (Follow-Up Period by Month)				
						IPSS	PSA (ng/mL)	PVR (mL)	Qmax (mL/Sec)	PV (mm <sup>3</sup> )
[1]	45	100	2	10(1)	Rectal	-7.69* (3)		-24.96* (3)	+2.36* (3)	
						-7.53* (2)	-0.21 (3)	-25.34† (2)	+2.32† (2)	-1.4* (3)
						-6.69* (1)		-20.8† (1)	+1.76† (1)	
[28]	23	100	4	8(1)	Rectal	-9.00* (24)			+2† (24)	
						-10.4† (18)			+1.5† (18)	
						-10.4† (12)	N/A	-2.2† (24)	+2.7† (12)	N/A
						-10.8† (6)		-25.4† (6)	+2.3† (6)	
						-10.6† (3)			+4† (3)	
[26]	32	200	5	5(1)	Supra-pubic	-9.4* (12)	-1.3* (12)	-68.0* (12)	+2.9 (12)	-11.8* (12)
						-11.5* (6)	-1.6* (6)	-80.9* (6)	+4.8* (6)	-30.1* (6)
						-10.2* (3)	-1.5* (3)	-66.3* (3)	+4.1* (3)	-17.9* (3)
[4]	10	100-200-300	10	2-4-6(+)	Urethral	-8.3* (1)	-0.6 (1)	-38.2* (1)	+1.7 (1)	-5.5 (1)
						-11.1* (7.5)	-1.4* (7.5)	-11.1 (7.5)	+8.32* (7.5)	-11.1* (7.5)
[3]	15	200	4	Rectal	Rectal	-9* (12)	-0.4 (12)		+2.3 (12)	0.0 (12)
						-9* (9)	-0.4 (9)	-90* (12)	+2.3 (6)	-5 (6)
						-7* (6)	-0.3 (6)	-100* (3)	+2.3 (3)	-1 (1)
						-4 (3)	+0.2 (3)			
[27]	10	100-200	2	4(2)	Rectal	-8* (1)	+0.7 (1)			
						-6.9* (12)		-27.1 (12)	+0.9 (12)	-6.8 (12)
						-10* (9)		-13.2 (9)	-0.1 (9)	-4.9 (9)
						-10* (6)	+0.05 (12)	-46.6* (6)	+0.5 (6)	-7.6* (6)
						-8.9* (3)	-0.55 (6)	-34.2* (3)	+2.5* (3)	-8.6* (3)
Our study	15	150	20	20(1)	Urethral	-7.5* (1)		-14.6 (1)	-0.8 (1)	-7.6* (1)
						-7.40* (12)	-0.54* (12)	-11.00* (12)	+0.94* (12)	-5.00* (12)
						-9.66* (3)	-0.75* (3)	-20.53* (3)	+2.77* (3)	-8.73* (3)

\* Statistically significant difference; † Statistical significance not mentioned.

placebo effect, based on pooled data from 522 subjects. However, it is essential to consider improvements in Qmax in two robust studies of Marberger and McVary [17, 23]. Improvement in Qmax as an objective measure raises the suspicion that whether the saline injection itself affects the pathophysiology of the BPH or not. Furthermore, studies that are used in the above-mentioned meta analysis are not similar. The route of administration, volume of saline in which the BTA vial was reconstituted, the number of injections, and the volume of each injection varied in these studies.

**IPSS scores:** All studies unanimously reported improvement based on IPSS [2-4, 17, 21-25, 26-29]. This reduction in the IPSS score ranges from 4.8 to 14.6 among various studies. Robert, et al. compared the BTA to pharmacological therapy and declared that BTA is not inferior to optimal drug treatment [24]. On a 4-month IPSS follow-up declined by 4.8 and 3.9 in BTA and medical treatment groups, respectively [24]. El-Dakhkhny, et al. reported a 7.1 and 9.5 decreases in IPSS scores among BTA and TURP groups on a 12-month follow-up [21]. Marberger, et al. [17] and McVary, et al. [23] have reported IPSS improvements among the BTA and

**Table 3.** Clinical data from previous studies on the efficacy of BTA on BPH symptoms

Study Ref.	Placebo	Patient (I/P)	Injection /Dose	Injection Volume/ Route	Mean (monthly follow-up) [Post-intervention Minus Baseline]					
					IPSS	PSA (mL)	PVR (mL)	Qmax (mL/Sec)	PV (mm <sup>3</sup> )	
[21]	TURP	92 (46/46)	2(200)	3(1)/IP	BTA	7.1*(12)				
						-7.8*(9)				
						-6.4*(6)	-1.40*(12)	-45.5*(12)	+7.3*(12)	-17.9*(12)
					TURP	-4.8*(3)	-1.45*(9)	-49.2*(9)	+5.1*(9)	-16.2*(9)
						9.5*(12)	-1.50*(6)	-51.3*(6)	+4.5*(6)	-11.1*(6)
						-9.7*(9)	-1.25*(3)	-33*(3)	+3.7*(3)	-8.2*(3)
[24]	Medical treatment	127 (64/63)	4(200)	10(2.5) / Rectal	BTA	-4.8*(4)	+0.2(4)	+4.2(4)	+2.0(4)	-4.1(4)
					Control	-3.9(4)	-0.5(4)	+4.2(4)	+1.1(4)	-1.1(4)
[2]	Saline	20 (10/10)	6Ω (200-300)	6-8(1)/IP	BTA	12.9*(3)	-0.83(3)	-79.4*(3)	+4.9*(3)	-30%*
					Saline	-8.8*(1)		-76.6*(1)	+2.9*(1)	
						0.0(3)	-0.06(3)	+15.6(3)	+1.22(3)	.
[23]	Saline	313 (156/157)	4 (200)	4(+)/ Rectal	BTA	-6.3(6)	(6)	+4.7(6)	+2.5(6)	-1.1(6)
					Saline	-6(6)	(6)	-11.7(6)	+1.9(6)	-2.5(6)
[17]	Saline	380 (95-94-97/94)	6 (100, 200, 300)	4-9φ/ Rectal; IP	BTA 100	-6(12)	N/A	+0(3)	+2.7(3)	-3.5(3)
					BTA 200	-5(12)	N/A	+10(3)	+2(3)	-3.7(3)
					BTA 300	-5(12)	N/A	+8(3)	+1.9(3)	-3.34(3)
					Saline	-5(12)	N/A	+2(3)	+2.7(3)	-4.5(3)
					[22]	Saline	30 (15/15)	2(200)	4(2)/IP	BTA
					Saline	0(2)	-0.1(2)	-1.3(2)	-0.1(2)	-2(2)

\*Statistically significant; †Statistical significance not mentioned; IPSS: International Prostate Symptom Score; PSA: Prostate-specific Antigen; PVR: Post-Void Residue; Qmax: Maximum Urinary Flow Rate; PV: Prostate Volume; BTA: Botulinum Toxin-A group; TURP: Transurethral Resection of the Prostate; LUTS: Lower Urinary Tract Symptoms; IP: Intraperitoneal; I/P: Intervention vs Placebo; Ω=8 injections if middle lobe was present; φ=12% of the total prostate volume.

normal saline injection groups. The latter two studies strongly suggest placebo effects, but as mentioned earlier, the exact impact of normal saline injection on the prostate is not fully elucidated.

**PSA levels:** The PSA values decreased in most studies. The denervation-induced apoptosis of prostate cells may explain this finding. Also, our study showed similar results. Robert, et al. [24] and Yokoyama, et al. [27] have

reported increases in PSA of 0.2 and 0.05, respectively. An increase in the PSA levels is only reported in studies with the transrectal approach. The PSA levels in de Kort, et al. study showed an increase in the first month of follow-up but a decrease after that point [3]. Additionally, comparing the route of injection and PSA levels show a smaller decrease or even an increase in the PSA level compared to those for transurethral and transperineal routes. We found no study which compared differ-

ent routes of injection. The transrectal route is widely used by urologists because of its convenience. It also poses a higher risk of prostatic infection. Transurethral injection allows for focusing on both lateral and medial lobes separately. Other choices are transperineal and suprapubic approaches.

**Prostate volume:** The prostate Volume (PV) decreases in all of the reviewed studies. This decrease was almost equal among BTA and saline injection in McVary and Marberger studies [21, 23]. The PV decreased by 4.1 mm<sup>3</sup> in the BTA group and 1.1 mm<sup>3</sup> among medical treatments in the study of Robert, et al. [24], although the differences were not significant. Meanwhile, El-Dakhakhny's group [21] showed a significant progressive PV decrease among the BTA group during the 12-month follow-up. In the present study, a reduction in PV was detected, which was significant compared to the data collected at baseline.

**Post-void residue:** In terms of PVR, studies are not conclusive. Marberger, et al. [17] reported an increase in PVR for the placebo group, BTA 100, and BTA 300. The same increase in PVR was reported by Robert, et al. [24] for BTA and medical treatment groups. Almost all other reviewed studies have reported a decline in PVR. Due to the heterogeneity of the methods used in these studies, it is hard to determine a single factor to explain this finding. Meanwhile, the increases in PVR reported by the two studies, observed in both intervention and placebo groups, implying that the same factor affected both groups. Moreover, a possible short-term washout period of previous medical treatments may cause a rebound increase in PVR.

**Maximum urinary flow rate:** The Q<sub>max</sub> increased in all of the reviewed studies. In the studies conducted by Yokoyama, et al. and Ding, et al., an increase in Q<sub>max</sub> was significant after 6 and 3 months, respectively [26, 27]. El-Dakhakhny, et al. [21] showed the same progressive increase in Q<sub>max</sub> during the 12-month follow-up. However, this study showed a rise in Q<sub>max</sub> was mostly in the third month of the follow-up. This discrepancy might be due to the concentration of each injection. We reconstituted 150 IU BTA in 20 mL saline, while in other studies they used 200 IU vial with a lower volume of saline for reconstitution.

**Follow-up intervals:** Studies with frequent follow-ups, such as El-Dakhakhny, et al. [21] and Yokoyama, et al. [27] showed that different measures caused the reported improvement at various time points. For example, the most increases in the PVR detected occurred at the sixth month in both studies, while IPSS reached its nadir

at the 9<sup>th</sup> month. Extender follow-up periods, together with more frequent checkpoints, may improve the certainty about the true effect of BTA.

**Limitations of the study:** This study had the following limitations: a) small sample size; b) lack of control groups; c) few follow-up points; and d) underlying confounders not considered, e.g., insulin resistance, hyperlipidemia, and hyper-androgenism.

**Recommendations for future research:** We recommend having more frequent follow-up visits to assess the confounding factors that impair the Botox effects on prostate. We also suggest that the effect of intraprostatic saline injections be explored on the BPH and/or the Lower Urinary Tract Symptoms (LUTS).

## Conclusions

Intraprostatic Botox injection improved the Q<sub>max</sub> and decreased the IPSS scores, PSA, PV, and PVR values significantly among the patients. The IPSS was the only subjective factor in the reviewed studies, and improvements in the objective measures (PSA, PV, Q<sub>max</sub>, and PVR) make it less likely to be claimed as the placebo effects. Furthermore, BPH is not malignant; therefore, if intraprostatic injections may improve the quality of life, it is worth considering it even with the likelihood of the placebo effect. We suggest that future studies should report the exact injection sites, number and the volume of injections, the volume of the saline which is used to reconstitute the BTA vial, and determining the washout period of previous pharmacological treatment. Assessment of the endocrine status in patients (components of metabolic syndrome) in future studies can be helpful to determine the exact impact of the BTA on the prostate status.

## Ethical Considerations

### Compliance with ethical guidelines

The Ethical Committee approved the methodology of the present study of the Mashhad University of Medical Sciences (Code: IR.MUMS.MEDICAL.REC.1397.521). All ethical principles are considered in this article. The participants were informed about the purpose of the research and its implementation stages. They were also assured about the confidentiality of their information. They were free to leave the study whenever they wished, and if desired, the research results would be available to them.

## Funding

This research did not receive any grant from funding agencies in the public, commercial, or non-profit sectors.

## Authors' contributions

Conceptualization and supervision: Salman Soltani; Methodology: Mahmoud Tavakkoli, Hamidreza Ghorbani; Investigation, writing – original draft, and writing – review & editing: All authors; Data collection: Amin Nobahar, Mahdi Mottaghi, Atena Aghaee; Data analysis: Maryam Emadzadeh.

## Conflict of interest

The authors declared no conflict of interest.

## Acknowledgments

We also acknowledge the support of the management, clinicians, academicians, and the staff of Mashhad University of Medical Sciences. We also thank the Clinical Research Development Unit of Ghaem Hospital for their contribution to this study.

## References

- [1] Moussa AS, Ragheb AM, Abdelbary AM, Ibrahim RM, El Adawy MS, Aref A, et al. Outcome of Botulinum Toxin-A intraprostatic injection for benign prostatic hyperplasia induced lower urinary tract symptoms: A prospective multicenter study. *Prostate*. 2019; 79(11):1221-5. [DOI:10.1002/pros.23805] [PMID]
- [2] Totaro A, Pinto F, Pugliese D, Vittori M, Racioppi M, Foschi N, et al. Intraprostatic botulinum toxin type "A" injection in patients with benign prostatic hyperplasia and unsatisfactory response to medical therapy: A randomized, double-blind, controlled trial using urodynamic evaluation. *Neurourol Urodyn*. 2018; 37(3):1031-8. [DOI:10.1002/nau.23390] [PMID]
- [3] de Kort LMO, Kok ET, Jonges TN, Rosier PFWM, Bosch JLHR. Urodynamic effects of transrectal intraprostatic Ona botulinum toxin A injections for symptomatic benign prostatic hyperplasia. *Urology*. 2012; 80(4):889-93. [DOI:10.1016/j.urology.2012.06.004] [PMID]
- [4] Madani AH, Enshaei A, Heidarzadeh A, Mokhtari G, Farzan A, Mohiti Asli M, et al. Transurethral intraprostatic Botulinum toxin-A injection: A novel treatment for BPH refractory to current medical therapy in poor surgical candidates. *World Journal of Urology*. 2013; 31(1):235-9. [DOI:10.1007/s00345-012-0851-z] [PMID]
- [5] Lombardo R, Andersson KE, Tubaro A, Nunzio CD. Intraprostatic injections for lower urinary tract symptoms/benign prostatic enlargement treatment. *Minerva Urol Nefrol*. 2018; 70(6):570-57. [DOI:10.23736/S0393-2249.18.03233-2] [PMID]

- [6] Chung AS, Woo HH. Update on minimally invasive surgery and benign prostatic hyperplasia. *Asian J Urol*. 2018; 5(1):22-7. [DOI:10.1016/j.ajur.2017.06.001] [PMID] [PMCID]
- [7] Marchal C, Perez JE, Herrera B, Machuca FJ, Redondo M. The use of botulinum toxin in benign prostatic hyperplasia. *Neurourol Urodyn*. 2012; 31(1):86-92. [DOI:10.1002/nau.21142] [PMID]
- [8] Ng LG. Botulinum toxin and benign prostatic hyperplasia. *Asian J Urol*. 2018; 5(1):33-6. [DOI:10.1016/j.ajur.2017.11.003] [PMID] [PMCID]
- [9] Chuang YC, Tu CH, Huang CC, Lin HJ, Chiang PH, Yoshimura N, et al. Intraprostatic injection of botulinum toxin type-A relieves bladder outlet obstruction in human and induces prostate apoptosis in dogs. *BMC Urol*. 2006; 6:12. [DOI:10.1186/1471-2490-6-12] [PMID] [PMCID]
- [10] Chuang YC, Huang CC, Kang HY, Chiang PH, Demiguel F, Yoshimura N, et al. Novel action of botulinum toxin on the stromal and epithelial components of the prostate gland. *J Urol*. 2006; 175(3 Pt 1):1158-63. [DOI:10.1016/S0022-5347(05)00318-6] [PMID]
- [11] Nishiyama Y, Yokoyama T, Tomizawa K, Okamura K, Yamamoto K, Matsui H, et al. Effects of purified newly developed botulinum neurotoxin type A in rat prostate. *Urology*. 2009; 74(2):436-9. [DOI:10.1016/j.urology.2009.01.047] [PMID]
- [12] Xu YP, Yu X, Ye ZQ, Pan TJ, Wen HD, Wang T. [Effects of intraprostatic injection of botulinum toxin A (BTX-A) on benign prostatic hyperplasia (Chinese)]. *Zhonghua Nan Ke Xue*. 2010; 16(10):905-10. [PMID]
- [13] Vikram A, Jena G, Ramarao P. Insulin-resistance reduces botulinum neurotoxin-type A induced prostatic atrophy and apoptosis in rats. *Eur J Pharmacol*. 2011; 650(1):356-63. [DOI:10.1016/j.ejphar.2010.09.066] [PMID]
- [14] Silva J, Pinto R, Carvallho T, Coelho A, Avelino A, Dinis P, et al. Mechanisms of prostate atrophy after glandular botulinum neurotoxin type a injection: An experimental study in the rat. *Eur Urol*. 2009; 56(1):134-41. [DOI:10.1016/j.eururo.2008.07.003] [PMID]
- [15] Ergün O, Koşar PA, Onaran İ, Darici H, Koşar A. Lysozyme gene treatment in testosterone induced benign prostatic hyperplasia rat model and comparison of its' effectiveness with botulinum toxin injection. *Int Braz J Urol*. 2017; 43(6):1167-75. [DOI:10.1590/s1677-5538.ibju.2016.0677] [PMID] [PMCID]
- [16] Mostachio GQ, Apparicio M, Motheo TF, Alves AE, Vicente WRR. Intra-prostatic injection of botulinum toxin type A in treatment of dogs with spontaneous benign prostatic hyperplasia. *Anim Reprod Sci*. 2012; 133(3-4):224-8. [DOI:10.1016/j.anireprosci.2012.06.024] [PMID]
- [17] Marberger M, Chartier-Kastler E, Egerdie B, Lee KS, Grosse J, Bugarin D, et al. A randomized double-blind placebo-controlled phase 2 dose-ranging study of onabotulinumtoxinA in men with benign prostatic hyperplasia. *Eur Urol*. 2013; 63(3):496-503. [DOI:10.1016/j.eururo.2012.10.005] [PMID]
- [18] Mosli HH, Esmat A, Atawia RT, Shoieb SM, Mosli HA, Abdel-Naim AB. Metformin attenuates testosterone-induced prostatic hyperplasia in rats: A pharmacological perspective. *Sci Rep*. 2015; 5:15639. [DOI:10.1038/srep15639] [PMID] [PMCID]
- [19] Rahman NU, Phonsombat S, Bochinski D, Carrion RE, Nunes L, Lue TF. An animal model to study lower urinary tract symptoms and erectile dysfunction: The hyperlipidaemic rat. *BJU Int*. 2007; 100(3):658-63. [DOI:10.1111/j.1464-410X.2007.07069.x] [PMID]

- [20] Russo GI, Castelli T, Urzi D, Privitera S, La Vignera S, Condorelli RE, et al. Emerging links between non-neurogenic lower urinary tract symptoms secondary to benign prostatic obstruction, metabolic syndrome and its components: A systematic review. *Int J Urol*. 2015; 22:982-90. [DOI:10.1111/iju.12945] [PMID]
- [21] El-Dakhakhny AS, Gharib T, Issam A, El-Karamany TM. Transperineal intraprostatic injection of botulinum neurotoxin A vs transurethral resection of prostate for management of lower urinary tract symptoms secondary to benign prostatic hyperplasia: A prospective randomised study. *Arab J Urol*. 2019; 17(4):270-8. [DOI:10.1080/2090598X.2019.1662214] [PMID] [PMCID]
- [22] Maria G, Brisinda G, Civello IM, Bentivoglio AR, Sganga G, Albanese A. Relief by botulinum toxin of voiding dysfunction due to benign prostatic hyperplasia: Results of a randomized, placebo-controlled study. *Urology*. 2003; 62(2):259-64. [DOI:10.1016/S0090-4295(03)00477-1] [PMID]
- [23] McVary KT, Roehrborn CG, Chartier-Kastler E, Efros M, Bugarin D, Chen R, et al. A multicenter, randomized, double-blind, placebo controlled study of onabotulinumtoxinA 200 U to treat lower urinary tract symptoms in men with benign prostatic hyperplasia. *J Urol*. 2014; 192(1):150-6. [DOI:10.1016/j.juro.2014.02.004] [PMID]
- [24] Robert G, Descazeaud A, Karsenty G, Saussine C, Azzouzi AR, de la Taille A, et al. Prostatic injection of botulinum toxin is not inferior to optimized medical therapy in the management of lower urinary tract symptoms due to benign prostatic hyperplasia: Results of a randomized clinical trial. *World J Urol*. 2018; 36(6):921-9. [DOI:10.1007/s00345-018-2193-y] [PMID]
- [25] Shim SR, Cho YJ, Shin IS, Kim JH. Efficacy and safety of botulinum toxin injection for benign prostatic hyperplasia: A systematic review and meta-analysis. *Int Urol Nephrol*. 2016; 48(1):19-30. [DOI:10.1007/s11255-015-1153-3] [PMID]
- [26] Ding XD, Chen HX, Xiao HQ, Wang W, Ding ZG, Zhang GB, et al. Treatment of benign prostatic hyperplasia by ultrasound-guided botulinum toxin type A injection. *Cell Biochem Biophys*. 2015; 73(2):357-9. [DOI:10.1007/s12013-015-0606-8] [PMID]
- [27] Yokoyama T, Yamamoto Y, Suzuki T, Oguma K, Nagai A. Intraprostatic botulinum neurotoxin type a injection for benign prostatic hyperplasia: Preliminary results with a newly purified neurotoxin. *Acta Medica Okayama*. 2012; 66(4):291-7. <https://ousar.lib.okayama-u.ac.jp/en/48668>
- [28] de Carvalho TGR, Pinto R, Cruz F, Silva J. Effect of onabotulinum toxin type a intraprostatic injection on the outcome of Benign Prostatic Hyperplasia patients refractory to medical therapy: A 2-year follow-up study. *Arch Esp Urol*. 2016; 69(10):719-26. [PMID]
- [29] Sacco E, Bientinesi R, Marangi F, Totaro A, D'Addressi A, Racioppi M, et al. Patient-reported outcomes in men with Lower Urinary Tract Symptoms (LUTS) due to Benign Prostatic Hyperplasia (BPH) treated with intraprostatic OnabotulinumtoxinA: 3-month results of a prospective single-armed cohort study. *BJU Int*. 2012; 110(11 Pt C):E837-44. [DOI:10.1111/j.1464-410X.2012.11288.x] [PMID]