Botox – an option for treatment of male lower urinary tract symptoms?

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Abstract

Benign prostatic hyperplasia (BPH) is a highly prevalent nonmalignant condition which occurs commonly in men over the age of 60. Botulinum toxin type A (BoNT-A) used selectively can be a therapeutic solution for those patients. This paper aims to update the knowledge referring to the effects of BoNT-A on the prostate.

Intramuscular injection of BoNT-A induces inhibition of acethylcholine release at the neuromuscular junction and causes temporary chemodenervation with paralyzing effects and atrophy of striated muscle as well as the smooth muscle fiber. BoNT-A also causes inhibitory effects on the autonomic nervous system affecting the glandular tissue, action responsible for diffuse atrophy and apoptosis of nasal and prostate glands.

BoNT-A injected at the prostatic level induced: increase of the urinary flow, decrease of the prostatic volume, of the residual volume, of the IPSS symptom score, as well as of PSA. The effects maintained for 6-12 months and no side effects were reported in any patient.

BPH is an important issue of public health and any new treatment option is good news for the patient population as well as for the urological community. Although the clinical series demonstrates efficacy at 30 months more studies are necessary in order to identify the mechanisms by which BoNT-A affects the prostate, the ideal dose and the duration of effect.

Key words: botulinum toxin; prostate; BPH; minimal invasive therapies

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Introduction

Benign prostatic hyperplasia (BPH) is a highly prevalent nonmalignant condition which occurs commonly in men over the age of 60 [1,2,3]. While it is not known what causes BPH, it is believed that the condition may be related to hormone changes that occur during the aging process. BPH is not life threatening, but can cause bothersome urinary symptoms, including difficult urinating, the need to urinate quite frequently, or awaking during the night which have a bad impact on the quality of life. It is a condition that affects more than half of men in their sixties and nearly 90 percent of those over the age of seventy, so new treatment options and greater awareness are needed to help support people suffering from this condition [4].

History and structure

Botulinum toxin (BoNT), first identified in 1897, is produced by Clostridium Botulinum [5]. From the seven serotypes of BTX only five are pharmacologically active in humans: A, B, E, F, G. In clinical use are A (BoNT-A) (Botox® (Allergan, Irvine, USA), Dysport® (Ipsen-Biotech Ltd. Berkshire, UK) and Neuronox® (Medy-Tox, Coreea de Sud)) and B (BoNT-B) (Myobloc® tradename for USA and Neurobloc® tradename for European Union (Elan Pharmaceuticals, Princeton, USA). First studied in British and American military laboratories and isolated in 1946, only in 1977 Alan Scott injected the first patient with BoNT-A to correct a strabismus [6]. The first urological use was described by Dykstra *et al.* in the late eighties [7].

BoNT serotypes synthesized as a single-chain, inactive polypeptide in order to be activated must be cleaved into a 100kDa heavy chain, responsible for the specificity of each serotype and a 50 kDa light chain, responsible for the pharmacological action [8,9,10,11].

Mechanism of action

In BPH, bladder outlet obstruction results from a mechanical component caused by an enlarged gland and from a dynamic component caused by the stromal smooth muscle. Another therapeutic option besides surgery is medical therapy. It consists of: 5 alpha-reductase inhibitors and alpha-blockers. The alpha adrenergic antagonists have as primary target the dynamic component of BPH mediated mainly through alpha-adrenoceptor stimulation. Neither the surgical treatment nor the medical one is without side-effects. Between 15 and 25 percent of patients who undergo surgical treatment do not have satisfactory long term results [12]. The medical treatment also has side-effects such as: dizziness, asthenia, orthostatic hypotension, retrograde ejaculation, impotence and decreased libido. [13,14].

Intramuscular injection of BoNT-A induces inhibition of acethylcholine release at the neuromuscular junction and causes temporary chemodenervation with paralyzing effects and atrophy of striated muscle as well as the smooth muscle fiber [10]. BoNT-A also causes inhibitory effects on the autonomic nervous system affecting the glandular tissue, action responsible for diffuse atrophy and apoptosis of nasal and prostate glands [15,16,17]. Fig 1, 2

Chuang *et al.* have demonstrated a significant increase in apoptotic cells, and decrease in proliferative cells after BoNT-A injection in rats prostate. They also described no change in the androgen receptor, and decrease in in α_{1A} adrenergic receptor [18].

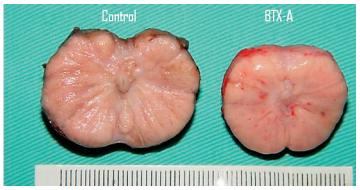

Fig. 1: Canine prostate one month after injection of saline respectively BoNT-A

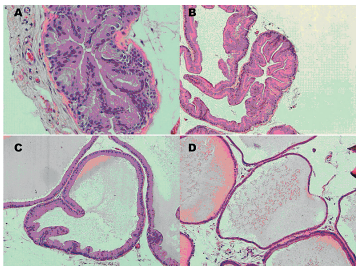

Fig. 2: Significant glandular proliferation was seen in the saline injected rat (A). Atrophy change of glandular component was seen in the BoNT-A treated rat (B - 5U, C – 10U, D – 20U).

Chuang *et al.* demonstrated that injection of 100U Botox® into the canine prostate induced marked atrophy and diffuse apoptosis of glands associated with decreased cell proliferation. The effect persisted for at least 3 months without any notable side effects [19]. (Fig. 1)

Clinical studies

The clinical studies come from a few urological centers worldwide. Professor Chancellor and Professor Chuang have been studying the effect of BoNT-A in BPH and published three clinical studies. Table 1. In one of those, on 8 men with symptomatic BPH and

relatively large prostates, at one month follow-up, IPSS score was significantly reduced from 19.0±1.8 to 5.1±2.0 (73.1%, p<0.05), Qmax increased from 7.5±1.8 to 12.9±0.5 ml (72%, p<0.05). PV was significantly reduced from 61.6±8.7 to 50.0±5.9 ml (18.8%, p<0.05), QoL (Quality of Life) index from 3.9±0.3 to 1.5±0.2 (61.5%, p<0.05) and PVR from 177.6±71.7 to 24.5±4.5 (86.2%, p=0.06). The effects were maintained at three months follow-up [17].

Chuang *et al*. also reported symptomatic improvement in 16 patients with BPH and PV<30ml, starting at one week and maintained for a mean follow-up of ten months (Table 1) [20]. The maximal flow rate was significantly increased by 39.8% (7.3±0.7 ml/sec to 11.8±0.8 ml/sec, p<0.0001) and the IPSS score was significantly reduced by 52.6% (from 18.8±1.6 to 8.9±1.9, p<0.0001) [20].

Chuang *et al.* reported in a third study on 41 men treated with 100U (for prostates<30 ml) or 200U (for prostates>30 ml) of BoNT-A [21] improvement of LUTS and QoL indices by over 30% in 31 out of 41 patients (76%). The efficacy was mantained at 12 months. Four out of five men (80%) with urinary retention for more than one month could void spontaneously after BoNT-A injection. Seven patients did not have change of PV but had more than 30% improvement in Qmax, LUTS and QoL scores. This is due to the fact that the mechanisms of LUTS relief through intraprostatic BoNT-A injection may not totally depend on the volume shrinkage but also on the inhibitory effect on the smooth muscle tone and sensory nerve function [21].

Maria *et al.* published the first prospective, randomized double-blind, placebo-controlled trial, evidence level 1b, in 30 patients, with a mean follow-up of 19.6 months (Table 1). 11 respectively 13 patients out of 15 had symptomatic relief at one month respectively at two months, AUA (American Urological Association) score was reduced by 54%(p=0.00001) and 65% (p=0.00001) [22].

Six years later, in 2009, the same authors came with an open-label study, 77 patients with BPH, were injected with 200 U BoNT-A. 41 patients had symptomatic relief at 1 month, AUA score reduced from 24.1 ± 4.6 to 12.6 ± 2.9 (p=00001). At 2 months AUA score was reduced by 63.9% (p=0.00001). Mean peak urinary flow increased significantly at 1 month as well as at 2 months. A rescue treatment with 200U BoNT-A was proposed to the 22 patients who reported no symptomatic improvement after toxin injection. At 30 months all 77 patients had good voiding, AUA symptom score was 11.1 ± 2.7 points (p=0.02 vs. 2 month value) and the peak urinary flow was 14.5 ± 2.0 mL/s (p=0.03 vs 2 month value). [23]

Twenty-one men (mean age 80±2 years) with BPH, on chronic indwelling catheter for at least 3 months, with poor general condition received 200U BoNT-A in a 3 months follow-up study published by Sylva *et al* [24]. 16 (76%) patients could resume voiding at one month, with a mean Qmax of 9.0±1.2 ml/s. At three months, 17 patients (81%) voided with a mean Qmax of 10.3±1.4ml/s [24].

The same results are also supported by the studies of Kuo [25, 26], Park *et al*. [27], Guercini *et al.* [28], Larson *et al*.[29]

One case of acute epidydimitis was reported [29]. Dysuria and occasional minor hematuria were noted in three patients but the symptoms resolved by the next day [20].

The procedure is considered safe [30]. The doses used in intraprostatic injection of BoNT-A are well below the presumed fatal dose and only minute quantities reach the systemic circulation.

Conclusion

BPH is an important issue of public health and any new treatment option is good news for the patient population as well as for the urological community. Although the clinical series demonstrates efficacy at 30 months more studies are necessary in order to identify the mechanisms by which BoNT-A affects the prostate, the ideal dose and the duration of effect.

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Table 1

Study	PSA(ng/ml)	PVR(ml)	PV (ml)	Qmax (ml/s)	QoL	IPSS	PI		FU
Maria et al; [43]	3.7 to 1.8 51%, p=0.00001	126.3 to 21 83%, p=0.00001	52.6 to 16.8 68%, p<0.00001	8.1 to 15.4 p<0.00001		23.2 to 8 65%, p=0.00001	13(15)		2
Chuang et al; [34]	NA	177.6 to 24.5 86.2%, p=0.064	61.6 to 50 18.8%, p<0.05	7..5 to 12.9 72%, p<0.05	3.9 to 2.1 61.5%, p<0.05	From 19 to 5 (73%, p<0.05)	8(8)		1
Chuang et al; [44]	0.8 to 0.72 NA	67.7 to 25.1 63%, NA	19.6 to 17 13.3%, p<0.0014	7.3 to 11.8 39.8%, p<0.001	3.8 to 2.1 44.7%, p<0.0001	18.8 to 8.9 52.6%, p=0.0001	16(16)		1
Chuang et al; [45]	NA	64.2 to 35.7 44%, p=0.3	21.1 to 18 15%, p<0.001	7.9 to 12 62%, p<0.001	3.9 to 2.1 46%, p<0.001	18.7 to 9.8 48%, p<0.001	100U	31(41)	1
	NA	161.7 to 45.2 72%, p=0.02	54.3 to 46.3 15%, p<0.001	7 to 10.3 47%, p<0.001	4.1 to 2 51%, p<0.001	19.3 to 9.5 51%, p<0.001	200U		1
Kuo; [46]	NA	243.5 to 36.8 p=0.005	65.5 to 49.6 p=0.009	7.6 to 11.6 p=0.05	4.5 to 2.1 p<0.0001	NA	10(10)		6
Park et al; [47]	2.6 to 2.4 NA	122.7 to 84.7 34%, p<0.05	47.2 to 42 13.1%, p<0.05	9.6 to 11.1 15.5%, p<0.05	NA	24.3 to 16.9 30.3%, p<0.05	39(52)		3
Silva et al; [48]	6 to 5 p=0.04	0 to 92	70 to 47 p<0.001	0 to 10.3	NA	NA	10(10)		3
Guercini et al; [49]	9.5 to 2.5 p<0.05	295 to 85 p<0.05	NA	8.2 to 18.1 p<0.05	NA	24 to 9 p=0.002	16(16)		6
Larson et al; [50]	NA	NA	NA	10.4 to 13.3	4.1 to 1.7	21.2 to 11.4	17(21)		3
Kuo et al; [51]	35.4%, p<0.05	NA	NA	By 2.9 ml/s	NA	47%	NA		NA
Brisinda et al; [Urology]	6.2 to 4.8 p=0.03	92.1 to 80.3 P=0.01	54.1 to 47.2 p=0.01	8.6 to 13.1 p=0.01	NA	AUA 24.1 to 12.6 p=0.00001	41(77)		1
	6.2 to 3.0 p=0.00001	92.1 to 40.6 p=0.002	54.1 to 30.9 p=0000.1	8.6 to 16.5	NA	24.1 to 8.7 P=00001	55(77)		2
	3.0 to 3.1 p=0.7	40.6 to 27.1 p=0.03	30.9 to 26.9	16.5 to 14.5 p=0.03	NA	8.7 to 11.1 p=0.02	55+22(77)		30

Abbreviations: PI, patients improved, FU, follow-up (months); IPSS, International Prostate Symptoms Score; QoL, quality of life; Qmax, maximum urinary flow rate; PV, prostate volume; PVR, post-void residual volume; NA, not available.

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