



Voiding Dysfunction

Intraprostatic and Bladder-Neck Injection of Botulinum A Toxin in Treatment of Males with Bladder-Neck Dyssynergia: A Pilot Study

Sey Kiat Lim*, Pearlyn L.C. Quek

Department of Urology, Changi General Hospital, Singapore

Article info

Article history:

Accepted October 2, 2007

Published online ahead of
 print on October 15, 2007

Keywords:

Botulinum A toxin
 Primary bladder-neck
 obstruction
 Bladder outlet obstruction
 Bladder-neck dyssynergia

Abstract

Objectives: To determine if intraprostatic and bladder-neck injection of botulinum toxin A (BoNTA) in patients with bladder-neck dyssynergia (BND) is a feasible alternative therapy.

Methods: Males diagnosed with BND on video-urodynamics showing delayed and incomplete bladder-neck opening during voluntary voiding were recruited. Eight consenting patients had 100 U of BoNTA injected transurethraly into the bladder neck and proximal prostatic urethra laterally (10 U/ml × 10 sites). Patients were assessed at preinjection, at 1, 6, and 2 wk, and at 4 weekly intervals thereafter by means of uroflometry, 3-d frequency–volume chart, and International Prostate Symptom Score (IPSS)-Quality of life (QoL) questionnaire. Urodynamic studies were done at screening and 6 wk postprocedure.

Results: The mean age was 36.9 yr. Mean duration of symptoms was 6.5 yr. At 6 wk, 7 of 8 (87.5%) patients had > 50% reduction of IPSS from baseline. Overall mean reduction was 50% (19.9 ± 2.7 vs. 9.9 ± 1.7 , $p = 0.036$). Six of 8 (75.0%) patients had > 3 ml/s increase in peak urinary flow rate with overall mean peak urinary flow rates improving from 11.6 to 17.2 ($p = 0.048$) at 6 wk. Micturition frequency decreased 46% (13.6 vs. 7.6 , $p = 0.036$) and IPSS-QoL scores improved 47% (4.9 ± 0.2 vs. 2.6 ± 0.6 , $p = 0.048$). None reported any adverse effects or ejaculation dysfunction. Three of 8 patients had recurrence of symptoms after a mean of 8 mo.

Conclusion: These results are encouraging. Larger, randomized, placebo-controlled trials could be worthwhile to verify these results.

© 2007 European Association of Urology. Published by Elsevier B.V. All rights reserved.

* Corresponding author. 2 Simei Street 3, Changi General Hospital, Department of Urology, Singapore 529889. Tel. +065 81230946.
 E-mail address: smurferoos@hotmail.com (S.K. Lim).

1. Introduction

Bladder-neck dyssynergia (BND) is characterized as an inadequate opening of the bladder neck during micturition, resulting in obstruction to urinary flow in the absence of other anatomical obstruction [1]. BND has also been termed Marion's disease, dysfunctional bladder neck, and primary bladder-neck obstruction. It commonly occurs in men younger than 50 yr and accounts for 33–54% of diagnoses made on videourodynamics studies (VUDS) in young men with lower urinary tract symptoms (LUTS) [2,3].

Exact etiology of BND is unclear. Studies thus far suggest abnormal morphological arrangement of the detrusor or trigonal musculature [4]; a higher density of neuropeptide Y immunoreactive nerves, which increase the sympathetic tone of the bladder neck and cause a functional obstruction [5]; or an extension of functional striated sphincter to the bladder neck, causing an ineffective voiding pattern [6].

Treatment options include pharmacotherapy with α -blockers and transurethral incision of the bladder neck. α -Blockers have a success rate of only 54–70% [2,3,7] and has poor long-term compliance rates of 13–30% [2,3,7,8]. In fact some studies reported no significant benefits with α -blockers [4,8].

TUIBN is curative in 82–100% [4,7–10] but causes retrograde ejaculation in 11–27% [7,9,11]. Some have advocated that a single incision will suffice and result in a lower retrograde ejaculation rate of 0–16% [4,8,11]. However Kochakarn et al. [10] found a 70% decrease in sperm counts without a decrease in ejaculatory volume pre- and post-unilateral incision of the bladder neck. In this study, two patients became azoospermic.

BoNTA has established applications in treating skeletal muscle spasms and off-label use in neurogenic detrusor overactivity and nonneurogenic voiding dysfunction [1,12–15]. BoNTA inhibits acetylcholine release into the neuromuscular junction of both presynaptic motor and autonomic neurons [16] including efferent neurons innervating exocrine glands and smooth muscles, such as gastrointestinal and urogenital sphincters. Thus BoNTA has been used for focal hyperhidrosis, hypersalivation, hyperlacrimation, achalasia, and sphincter of Oddi dysfunction [17].

In studies employing the same principle of a presynaptic neuromuscular blockade, reports of BoNTA's use in treating detrusor external sphincter dyssynergia in spinal cord-injured patients, detrusor overactivity, and benign prostatic obstruction have largely been positive [12–15,18–22].

Given that the main theories of BND revolve around increased smooth muscle tone, this pro-

spective study aims to investigate the effect of BoNTA when injected into the bladder neck and prostate of males with BND.

2. Methods

From July 2005 to November 2006, males diagnosed with BND on VUDS who had failed a trial of bladder training and α -blockers with or without anticholinergics for a minimum period of 3 mo were recruited in this nonblinded, uncontrolled prospective study. All patients were older than 18 yr, had moderate to severe LUTS (IPSS > 15) and maximum urinary flow rate < 15 ml/s. Diagnosis of BND was made on VUDS when narrowing at the vesicle neck was noted during voluntary micturition. This diagnosis was confirmed by Whiteside "trapping of contrast" when patients were asked to momentarily stop micturition during voluntary voiding. Care was taken to exclude bladder outlet obstruction due to a narrowed prostatic channel, which has a very different appearance. No voiding pressure criteria were used; however, the opening pressure, voiding pressure at peak flow, and obstruction status on Abrams-Griffiths curve were noted. Approval by the institutional review board and ethics committee, and informed consent from patients were obtained.

Patients with previous pelvic, urethral, prostate, bladder or bladder-neck surgeries or pathologies, or central or peripheral neurological disorders or neuromuscular conditions were excluded. Patients with benign prostatic enlargement (BPE) on subsequent flexible cystoscopy were also excluded. Finally patients unable or unwilling to complete a 3-d frequency-volume chart, IPSS-QoL questionnaire, or repeat VUDS at 6 wk postprocedure, or to comply with the study protocol were excluded.

Those who agreed to participate were reevaluated with a history, physical examination, and a screening protocol, which included a urinalysis and urine culture, a kidney-ureters-bladder (KUB) X-ray, uroflowmetry, and postvoid residual (PVR) volume scan, a 3-d frequency-volume chart, a preprocedure IPSS-QoL questionnaire, a flexible cystoscopy, and a VUDS.

A 22F rigid cystoscope was inserted under general anesthesia and the bladder was surveyed; prostatic lobe enlargement was again excluded. BOTOX[®] (Allergan) diluted at 10 U/ml with preservative-free saline was injected transurethraly at 10 sites into the patients' bladder necks and lateral lobes of their prostates. All patients were discharged the same day after voiding without problems.

Patients were reviewed at 1, 6, and 12 wk and at 4-wk intervals thereafter by means of a 3-d frequency-volume chart, free uroflowmetry, PVR volume scan, and IPSS-QoL questionnaire. Pressure flow studies were repeated at 6 wk postprocedure. Adverse events if any were also documented at each visit. Patients whose symptoms recurred were offered a repeat injection.

Successful outcome was defined as a reduction of IPSS score of > 50% from baseline and improvement of peak urinary flow rate of \geq 3 ml/s.

The nonparametric Wilcoxon signed rank test with multiple comparison corrections by the Bonferroni adjustment

Table 1 – Results

	Screening	1 week	6 weeks	16 weeks	32 weeks N = 6
IPSS					
IPSS (total) ± SEM	19.9 ± 2.7	8.9 ± 1.9 <i>p</i> = 0.012 A = 0.036	9.9 ± 1.7 <i>p</i> = 0.012 A = 0.036	8.4 ± 2.5 <i>p</i> = 0.011 A = 0.033	11.2 ± 2.4 <i>p</i> = 0.026 A = 0.078
IPSS (storage) ± SEM	8.6 ± 1.5	4.1 ± 0.8 <i>p</i> = 0.012 A = 0.036	4.0 ± 0.7 <i>p</i> = 0.011 A = 0.033	4.0 ± 1.2 <i>p</i> = 0.011 A = 0.033	4.5 ± 1.3 <i>p</i> = 0.027 A = 0.081
IPSS (voiding) ± SEM	11.3 ± 1.5	4.8 ± 1.6 <i>p</i> = 0.011 A = 0.033	5.9 ± 1.2 <i>p</i> = 0.012 A = 0.036	4.4 ± 1.5 <i>p</i> = 0.011 A = 0.033	6.7 ± 1.5 <i>p</i> = 0.027 A = 0.081
IPSS-QoL ± SEM	4.9 ± 0.2	2.9 ± 0.5 <i>p</i> = 0.015 A = 0.045	2.6 ± 0.6 <i>p</i> = 0.016 A = 0.048	1.9 ± 0.6 <i>p</i> = 0.016 A = 0.048	2.7 ± 0.6 <i>p</i> = 0.042 A = 0.13
Bladder diary					
Daytime frequency ± SEM	13.6 ± 0.9	—	7.6 ± 0.9 <i>p</i> = 0.012 A = 0.036	10.5 ± 1.0 <i>p</i> = 0.044 A = 0.13	12.0 ± 0.9 <i>p</i> = 0.34
Night frequency ± SEM	2.9 ± 0.8	—	1.3 ± 0.4 <i>p</i> = 0.075	2.0 ± 0.4 <i>p</i> = 0.34	1.0 ± 0.4 <i>p</i> = 0.14
Total frequency ± SEM	16.2 ± 1.5	—	8.8 ± 1.2 <i>p</i> = 0.012 A = 0.036	12.2 ± 1.2 <i>p</i> = 0.043 A = 0.13	13.0 ± 1.1 <i>p</i> = 0.10
Mean voiding volume ± SEM (ml)	192 ± 60	—	238 ± 35 <i>p</i> = 0.40	187 ± 23 <i>p</i> = 0.46	186 ± 38 <i>p</i> = 0.18
Largest voiding volume ± SEM (ml)	334 ± 78	—	355 ± 48 <i>p</i> = 0.71	315 ± 37 <i>p</i> = 0.88	550 ± 50 <i>p</i> = 0.18
Mean voiding interval ± SEM (min)	78 ± 16	—	167 ± 31 <i>p</i> = 0.012 A = 0.036	133 ± 20 <i>p</i> = 0.028 A = 0.084	84 ± 17 <i>p</i> = 0.50
Uroflometry					
Peak flow ± SEM (ml/s)	11.6 ± 1.1	—	17.2 ± 2.4 <i>p</i> = 0.016 A = 0.048	16.5 ± 2.4 <i>p</i> = 0.17 A = 0.051	17.7 ± 4.6 <i>p</i> = 0.11
PVR volume ± SEM (ml)	24 ± 16	—	47 ± 12 <i>p</i> = 0.18	42 ± 14 <i>p</i> = 0.027 A = 0.081	36 ± 6 <i>p</i> = 0.29
Urodynamics					
First sensation of bladder filling ± SEM (ml)	124 ± 38	186 ± 27	Change +50% <i>p</i> = 0.069	—	—
Strong desire to void ± SEM (ml)	256 ± 46	306 ± 28	+20% <i>p</i> = 0.33	—	—
Mean PdetQ _{max} ± SEM (cm H ₂ O)	39.0 ± 3.0	33.7 ± 1.7	-14% <i>p</i> = 0.07	—	—
Mean opening pressure ± SEM (cm H ₂ O)	40.0 ± 3.4	31.0 ± 4.5	-23% <i>p</i> = 0.05	—	—
Mean maximum voiding pressure ± SEM (cm H ₂ O)	67.3 ± 20.4	39.1 ± 3.3	-42% <i>p</i> = 0.012	—	—
Maximum voided volume ± SEM (ml)	320 ± 44	361 ± 33	+ 13% <i>p</i> = 0.33	—	—
IPSS, International Prostate Symptom Score; SEM, standard error of the mean; QoL, quality of life; P _{det} , detrusor pressure; Q _{max} , maximal flow rate; PVR, postvoid residual. A = <i>p</i> value after correction with Bonferroni adjustment method.					

method was used for statistical analysis. Statistical significance was considered at *p* < 0.05 after adjustment.

3. Results

Thirteen patients met our study criteria and 8 patients consented for the study. Mean age was

36.9 yr (range, 20–52). Mean duration of symptoms was 6.5 yr (range, 1–25) before diagnosis. Mean follow-up period was 10.4 mo (range, 5–19); 6 of 8 patients have exceeded 32 wk of follow-up.

Overall, a 55% reduction in mean IPSS was observed at week 1. All 8 patients had > 7 points reduction in IPSS with 7 of 8 (87.5%) achieving > 50%

Table 2 – Urodynamic results for individual patients

Patient	1	2	3	4	5	6	7	8
FS								
Pre	88	62	387	102	68	118	89	80
Post	213	156	301	115	135	147	301	120
SD								
Pre	164	138	468	301	132	241	422	180
Post	436	260	361	263	246	236	390	250
PdetQ_{max}								
Pre	41	44	47	44	24	38	46	28
Post	34	38	42	32	28	35	28	31
OP								
Pre	39	56	42	36	24	32	47	44
Post	29	42	52	12	20	31	35	26
MVP								
Pre	48	206	78	50	27	38	52	42
Post	34	49	48	45	20	37	40	40
MVV								
Pre	289	206	500	315	183	287	520	260
Post	529	348	381	376	305	240	436	270
Q_{max}								
Pre	13.4	14.7	11.7	7.9	5.9	13.4	13.0	12.6
Post	15.2	31.2	15.0	14.3	9.8	12.4	22.7	16.8
AGN (O/N/E)								
Pre	E	E	E	E	E	E	E	E
Post	N	N	E	N	E	E	N	N

Pre, pretherapy; post, 6 wk posttherapy; FS, first sensation of bladder filling (ml); SD, strong desire to void (ml); PdetQ_{max}, voiding pressure at maximum flow rate (cm H₂O); OP, opening pressure (cm H₂O); MVP, maximum voiding pressure (cm H₂O); MVV, maximum voided volume (ml); Q_{max}, maximum flow rate (ml/s); AGN (O/N/E), Abrams-Griffiths nomogram (obstructed/not obstructed/equivocal).

reduction of IPSS from baseline. These improvements were maintained at 4 mo but showed a slight uptrend at 8 mo, although these levels did not reach pretreatment levels. QoL scores improved by > 40% (Table 1).

Six of 8 (75.0%) patients had > 3 ml/s increase in maximum urinary flow rate with overall mean maximum urinary flow rates improving from 11.6 to 17.2 ($p = 0.048$) at 6 wk. These results were maintained beyond 32 wk in terms of absolute values despite their failing to achieve statistical significance after 16 wk.

Daytime frequency and mean voiding interval were significantly reduced at 6 wk but failed to maintain statistical significance at 16 wk after adjustment. These symptoms appeared to recur at 8 mo. No significant changes were noted in the mean voided volume and largest voided volume (Table 1).

Individual urodynamics results are shown in Table 2.

Opening pressures decreased by 23% and mean maximum voiding pressure decreased by 41% on repeat urodynamics. A 14% reduction was

observed in voiding pressure at maximum flow rate (PdetQ_{max}) although this value did not achieve statistical significance (Table 1). Five of 8 patients shifted from the equivocal to the unobstructed region on the Abrams-Griffiths nomogram (Table 2).

Three of 8 (37.5%) patients had recurrence of symptoms at a mean of 8 mo (range, 6–10) posttherapy. All of them had further relief of symptoms after a second BoNTA injection (mean IPSS improved by 40.6%). Five patients had no recurrence of symptoms until a mean of 10.8 mo. Two of 8 patients actually remained symptom-free despite being 1 yr posttherapy.

All patients tolerated treatment well. No patient withdrew from the study. Potential side effects like urinary retention, urinary incontinence, gross hematuria, urinary tract infection, or systemic weakness were not reported. In addition, no patient reported any decrease in ejaculatory volume or ejaculatory dysfunction.

4. Discussion

BND is an underdiagnosed condition in younger men presenting with LUTS. Diagnosis is made on VUDS when delayed and incomplete bladder-neck opening is seen during voluntary voiding. The opening pressures and PdetQ_{max} in our cohort are only minimally raised by established criteria for bladder outlet obstruction, implying that high obstructive voiding pressures are not mandatory for diagnosis. In fact all our patients were in the equivocal rather than the obstructed region of the Abrams-Griffiths nomogram. Indeed, Nitti [1] has commented that voiding pressures may range from 20 to 200 cm H₂O. Furthermore, Nitti [2] classified BND into three distinct types: classic high pressure low flow, normal pressure low flow with bladder-neck narrowing, and delayed opening of the bladder neck. Although cystoscopic appearance of a high bladder neck is not a stated requirement, it was observed in all our patients.

Case series of BoNTA use in BPE reported variable success with reduction in prostate volumes ranging from 13–55% [18,19–22]. The exact mechanism for volume reduction is unclear but is likely related to a reduced neurotropic influence on the prostate. One postulation suggests that denervation alters growth factor expression in the prostate, causing programmed cell death and glandular atrophy [20,23].

Because the two main theories of BND revolve around an extension of the external sphincter and increased sympathetic tone at the bladder neck, we postulated that BoNTA might result in a similar

relaxation or even atrophy of the bladder neck, reducing the delay in bladder-neck opening and improving flow.

The mechanism behind the concomitant reduction of storage symptoms can only be speculated. The action of BoNTA does not seem to be restricted to efferent autonomic neurons but may also affect afferent autonomic neurons and ganglionic neurons [24]. A recent review of the use of BoNTA in overactive bladder by Apostolidis [15] proposed that BoNTA inhibits the release of excitatory neurotransmitters such as acetylcholine, adenosine triphosphate, and substance P, and reduces axonal expression of capsaicin and purinergic receptors, resulting in central desensitisation, thus improving storage symptoms.

Our dosing aliquots and method of injection were extrapolated from case series of BoNTA in treatment of BPE, overactive bladder, and idiopathic detrusor overactivity [13,14,19] because there were no reports of BoNTA use in BND from our literature review. Chuang et al. [19] and Park et al. [22] injected 100 U of BoNTA into smaller prostates (<30 g) of Asian men, and Kuo [20] injected BoNTA into 10 sites in separate Asian studies. All studies showed good results without any reported adverse effects. Hence we chose to inject our cohort of young Asian men with small prostates with 100 U of BoNTA into 10 sites.

Our definitions of success were based on use of α -blockers for BPE in placebo-controlled trials because this is a pilot study with no precedent in our literature reviews. Success is defined by > 50% drop in IPSS and > 3 ml/s increase in maximum flow. In placebo-controlled α -blockers trials [25,26], use of placebos resulted in a 0.7–1.4 ml/s increase in mean maximum flow and 17–33% decrease in IPSS, whereas use of α -blockers resulted in a 2.2–3.6 ml/s increase in mean maximum flow and 39–49% decrease in IPSS. In another placebo-controlled BoNTA trial [18], use of BoNTA in BPE patients resulted in an increase of mean maximum flow of 6.8 ml/s and a 54% decrease in IPSS, whereas use of placebo resulted in minimal changes in mean maximum flow and IPSS. Our results of a 5.6 ml/s increase in mean maximum flow and 55% decrease in IPSS are greater than those achieved with placebos and comparable with those achieved with α -blockers and BoNTA in these trials.

Opening pressures and mean maximum voiding pressures were significantly improved on urodynamics. If delayed bladder-neck opening resulted in true BND, improved bladder-neck relaxation may explain this finding. Most patients reported subjective improvements in their symptoms. Although other urodynamics parameters showed

some improvements, they failed to reach statistical significance, probably because of our small sample size.

BND is not characterized by high voiding pressures and patients can have slightly increased or even normal voiding pressures [2,3,8]. It is therefore unclear if a significant reduction in voiding pressures should be expected although there was a clear trend of improvement noted in our patients.

Many studies involving BoNTA for various voiding dysfunction conditions showed that the mean duration of action of BoNTA is about 8–11 mo [12,14,15], which largely concurred with our finding. Maria et al. [18] reported improvement of maximum flow rates that were maintained beyond 12 mo after injection of 200 U of BoNTA diluted in 4 ml and injected into each lobe of the prostate. This prolonged effect might be due to glandular atrophy. Skeletal muscle atrophy from BoNTA is well described and has even been exploited for cosmetic purposes [27,28]. It can only be speculated that the prolonged effect in two of our patients is due to bladder-neck atrophy.

Our mean duration of effect implies that repeat injections can be performed about three times in 2 yr. Our three patients with recurrence of symptoms showed resolution of symptoms following a second BoNTA injection.

In our nonblinded, uncontrolled study with a small sample size, many parameters showed improvements but failed to achieve statistical significance. Although it might not be possible for this pilot study to prove the efficacy or evaluation of the safety of BoNTA in treatment of patients with BND, nevertheless it shows promising results.

5. Conclusion

Placebo-controlled trials and larger studies exploring higher doses and differing dilutions of BoNTA are required. It is possible that early repeat injections in partial responders or an increase in the dose may prove more effective.

Conflicts of interest

The authors have nothing to disclose.

References

- [1] Huckabay C, Nitti VW. Diagnosis and treatment of primary bladder neck obstruction in men. *Curr Urol Rep* 2005;6:271–5.
- [2] Nitti VW, Lefkowitz G, Ficazzola M, et al. Lower urinary tract symptoms in young men: videourodynamic findings

- and correlation with noninvasive measures. *J Urol* 2002;168:135–8.
- [3] Yang SS, Wang CC, Hsieh JH, et al. Alpha1-adrenergic blockers in young men with primary bladder neck obstruction. *J Urol* 2002;168:571–4.
- [4] Norlen LJ, Blaivas JG. Unsuspected proximal urethral obstruction in young and middle-aged men. *J Urol* 1986;135:972–80.
- [5] Crowe R, Noble J, Robson T, Soediono, Milroy EJG, Burnstock G. An increase of neuropeptide Y but not nitric oxide synthase-immunoreactive nerves in the bladder neck from male patients with bladder neck dyssynergia. *J Urol* 1995;154:1231–7.
- [6] Yalla SV, Resnick NM. Initiation of voiding in humans: the nature and temporal relationship of urethral sphincter responses. *J Urol* 1997;157:590–5.
- [7] Trockman BA, Gerspach J, Dmochowski R, Haab F, Zimmern PE, et al. Primary bladder neck obstruction: urodynamic finding and treatment results in 36 men. *J Urol* 1996;156:1418–20.
- [8] Kaplan SA, Te AE, Jacobs BZ. Urodynamics evidence of vesicle neck obstruction in men with misdiagnosed chronic bacterial prostatitis and the therapeutic role of endoscopic incision of the bladder neck. *J Urol* 1994;152:2063–5.
- [9] Sirils LT, Ganabathi K, Zimmern PE, et al. Transurethral incision of the prostate: an objective and subjective evaluation of long term efficacy. *J Urol* 1993;150:1615–21.
- [10] Kochakarn W, Lertsithichai P. Unilateral transurethral incision for primary bladder neck obstruction: symptom relief and fertility preservation. *World J Urol* 2003;21:159–62.
- [11] Katz PG, Greenstein A, Ratliff JE, et al. Transurethral incision of bladder neck and prostate. *J Urol* 1990;144:694–6.
- [12] Patel AK, Patterson JM, Chapple CR. Botulinum toxin injections for neurogenic and idiopathic detrusor overactivity: a critical analysis of results. *Eur Urol* 2006;50:684–710.
- [13] Werner M, Schmid DM, Schussler B. Efficacy of botulinum-A toxin in the treatment of detrusor overactivity incontinence: a prospective nonrandomized study. *Am J Obstet Gynecol* 2005;192:1735–40.
- [14] Schmid D, Sauer mann P, Werner M, et al. Experience with 100 cases treated with botulinum-a toxin injections in the detrusor muscle for idiopathic overactive bladder syndrome refractory to anticholinergics. *J Urol* 2006;176:177–85.
- [15] Apostolidis A, Dasgupta P, Fowler CJ, et al. Proposed mechanism for the efficacy of injected botulinum toxin in the treatment of human detrusor overactivity. *Eur Urol* 2006;49:644–50.
- [16] MacKenzie I, Burnstock G, Dolly JO. The effects of purified botulinum neurotoxin type A on cholinergic, adrenergic and non-adrenergic, atropine-resistant autonomic neuromuscular transmission. *Neuroscience* 1982;7:997–1006.
- [17] Dressler D, Saberi FA, Barbosa ER. Botulinum toxin: mechanisms of action. *Arq Neuropsiquiatr* 2005;63:180–5.
- [18] Maria G, Brisinda G, Civello IM, et al. Relief by botulinum toxin of voiding dysfunction due to benign prostatic hyperplasia: results of a randomized, placebo-controlled study. *Urology* 2003;62:259–65.
- [19] Chuang YC, Chiang P, Huang C, et al. Botulinum toxin type A improves benign prostatic hyperplasia symptoms in patients with small prostates. *Urology* 2005;66:775–9.
- [20] Kuo HC. Prostate botulinum A toxin injection—an alternative treatment for benign prostatic obstruction in poor surgical candidates. *Urology* 2005;65:670–4.
- [21] Guercini F, Giannantoni A, Bard RL, et al. Intraprostatic botulinum toxin injection in patients with severe benign prostatic hyperplasia: a multicenter feasibility study. *J Urol* 2005;173:376–7.
- [22] Park DS, Cho TW, Lee YK, et al. Evaluation of short term clinical effects and presumptive mechanism Botulinum type A toxin as a treatment modality of benign prostatic hyperplasia. *Yonsei Med J* 2006;47:706–14.
- [23] Doggweiler R, Zermann DH, Ishigooka M, Schmidt RA. Botox induced prostatic involution. *Prostate* 1998;37:44–50.
- [24] Kim HJ, Seo K, Yum KW, Oh Y-S, Yoon TG, Yoon SM. Effects of botulinum toxin type A on the superior cervical ganglia in rabbits. *Auton Neurosci* 2002;102:8–12.
- [25] Kirby RS, Roehrborn C, Boyle P, et al. Efficacy and tolerability of doxazosin and finasteride, alone or in combination, in treatment of symptomatic benign prostatic hyperplasia: the prospective European doxazosin and combination therapy (PREDICT) trial. *Urology* 2003;61:119–26.
- [26] Andersen M, Dahlstrand C, Hoye K. Double-blind trial of the efficacy and tolerability of doxazosin in the gastrointestinal therapeutic system, doxazosin standard, and placebo in patients with benign prostatic hyperplasia. *Eur Urol* 2000;38:400–9.
- [27] Kim NH, Chung JH, Park RH, Park JB. The use of botulinum toxin type A in aesthetic mandibular contouring. *Plast Reconstr Surg* 2005;115:919–30.
- [28] Lee HJ, Lee DW, Park YH, et al. Botulinum toxin a for aesthetic contouring of enlarged medial gastrocnemius muscle. *Dermatol Surg* 2004;30:867–71.

Editorial Comment on: Intraprostatic and Bladder-Neck Injection of Botulinum A Toxin in Treatment of Males with Bladder-Neck Dyssynergia: A Pilot Study

Robert Pickard

*School of Surgical and Reproductive Sciences,
Newcastle University, Newcastle upon Tyne NE2 4HH,
United Kingdom
r.s.pickard@ncl.ac.uk*

This paper reports an uncontrolled phase 2 study investigating the effectiveness of botulinum toxin A (BTX-A) injected into prostatic urethral tissue for eight younger men with bothersome lower urinary tract symptoms (LUTS) [1]. It adds to a number of similar studies involving varying groups of men with LUTS treated with BTX-A using a variety of doses and methods of administration [2]. In common with this preceding literature the present study found a rapid improvement in symptoms, which persisted during the follow-up period and was not associated with troublesome side-effects. Unlike previous studies, possible decreases in prostate volume or prostate-specific antigen were not assessed. As with all such studies, the cause of LUTS within each individual is unclear with both filling and voiding abnormalities identified on urodynamic testing. The mode of action of BTX in achieving symptom reduction is therefore unknown with much speculation of possibilities outside its known effect on cholinergic neurotransmission [3]. At present, evidence is insufficient to allow routine clinical use of this drug for such men and this will only be rectified by an

adequately powered controlled trial with defined dosage and route of administration. It appears from this and other studies that prior categorisation using urodynamic or other measures is unnecessary and that inclusion criteria should be broadly similar to those used for trials of oral therapy. Scientifically, the lack of differential effect in various urodynamic groups is concerning because it is difficult to conceive of a single common mode of action, although some may argue that this is irrelevant as long as it works and does no harm. However, given the likely need for repeated injections, the specific short- and long-term effects of BTX on different cells and tissues within the genitourinary tract should be explored using appropriate methodology.

References

- [1] Lim SK, Quek PLC. Intraprostatic and bladder-neck injection of botulinum A toxin in treatment of males with bladder-neck dyssynergia: a pilot study. *Eur Urol* 2008;53:620-7.
- [2] Antunes AA, Srougi M, Coelho RF, Freire G-C. Botulinum toxin for the treatment of lower urinary tract symptoms due to benign prostatic hyperplasia. *Nat Clin Pract Urol* 2007;4:155-60.
- [3] Chuang Y-C, Chancellor MB. The application of botulinum toxin in the prostate. *J Urol* 2006;176:2375-82.

DOI: [10.1016/j.eururo.2007.10.002](https://doi.org/10.1016/j.eururo.2007.10.002)

DOI of original article: [10.1016/j.eururo.2007.10.001](https://doi.org/10.1016/j.eururo.2007.10.001)

Editorial Comment on: Intraprostatic and Bladder-Neck Botulinum A Toxin in Treatment of Males with Bladder-Neck Dyssynergia: A Pilot Study

Martin Michel

*Department of Pharmacology and Pharmacotherapy,
AMC, University of Amsterdam, Amsterdam,
The Netherlands
M.C.Michel@amc.uva.nl*

Lim and Quek report the results of a pilot study on the use of botulinum toxin (BTX) in men with bladder-neck dyssynergia [1]. This adds to a

growing list of conditions of lower urinary tract dysfunction that may be susceptible to BTX treatment and includes neurogenic and idiopathic detrusor overactivity [2], painful bladder syndrome [3], benign prostatic enlargement [4], and chronic prostatic pain. It almost looks as if BTX may be the magic bullet for nonmalignant diseases of the lower urinary tract. Hence, BTX has found its way into the clinical practice of many urologists despite a lack of regulatory approval for such use. Although studies such as the one by Lim and Quek [1] are of value, and insight into the underlying mechanism of action is emerging [5], it is

striking that the field of clinical BTX research is dominated by a large number of relatively small open-label studies [2]. This may be explained by the fact that clinical BTX research is much more driven by investigators than by pharmaceutical companies. Nevertheless, despite requiring administration by injection, at the end of the day BTX in principle does not differ from other medical treatments. Hence, it needs to undergo the same scrutiny of efficacy and tolerability as any other type of medication, particularly because wrongly administered BTX can be lethal. Therefore, this field does not need more small-scale single-centre studies, but rather adequately powered, double-blind, controlled trials on its efficacy and safety. These need to include dose-finding studies with regard to the total dose required, the number of injection sites over which this needs to be spread, and treatment intervals. Given that direct injections generally tend to cause greater placebo effects than oral treatment, placebo-controlled studies are indispensable. Moreover, direct comparisons with other medications such as muscarinic antagonists (eg, by a double-dummy design) also appear very desirable.

References

- [1] Lim SK, Quek LCP. Intraprostatic and bladder-neck injection of botulinum A toxin in treatment of males with bladder-neck dyssynergia: a pilot study. *Eur Urol* 2008;53:620–7.
- [2] Patel AK, Patterson JM, Chapple CR. Botulinum toxin injections for neurogenic and idiopathic detrusor overactivity: a critical analysis of results. *Eur Urol* 2006;50:684–710.
- [3] Giannantoni A, Costantini E, Di Stasi SM, Tascini MC, Bini V, Porena M. Botulinum A toxin intravesical injections in the treatment of painful bladder syndrome: a pilot study. *Eur Urol* 2006;49:704–9.
- [4] Silva J, Silva C, Saraiva L, et al. Intraprostatic botulinum toxin type A injection in patients unfit for surgery presenting with refractory urinary retention and benign prostatic enlargement. Effect on prostate volume and micturition resumption. *Eur Urol* 2008;53:153–9.
- [5] Apostolidis A, Dasgupta P, Fowler CJ. Proposed mechanism for the efficacy of injected botulinum toxin in the treatment of human detrusor overactivity. *Eur Urol* 2006;49:644–50.

DOI: [10.1016/j.eururo.2007.10.003](https://doi.org/10.1016/j.eururo.2007.10.003)

DOI of original article: [10.1016/j.eururo.2007.10.001](https://doi.org/10.1016/j.eururo.2007.10.001)