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Review article

Botulinum toxin A treatment for lower urinary tract symptoms/benign prostatic hyperplasia☆

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ABSTRACT

Botulinum toxin A (BoNT-A) has been widely used in the treatment of overactive bladder and neurogenic detrusor overactivity. Recently, prostatic injection of BoNT-A had been tried to reduce the prostate volume and relieve lower urinary tract symptoms (LUTS) in patients with benign prostatic enlargement (BPE) due to benign prostatic hyperplasia (BPH). However, the efficacy of BoNT-A on BPE is still controversial. Traditionally, male LUTS have been considered as synonym of BPE because most male LUTS developed in aging men. Recent investigations have revealed that bladder dysfunction and bladder outlet dysfunction other than BPE contribute equally in male LUTS. Injecting BoNT-A into the prostatic urethra and bladder neck yielded improvement of LUTS, but not reduction of the prostatic volume, especially in men with small prostatic volume. The therapeutic effects of BoNT-A on LUTS might not be due to prostatic volume reduction, but through inhibiting the adrenergic hyperactivity in men with LUTS/BPH. This article discusses the current consensus and controversy of BoNT-A treatment on LUTS/BPH.

1. Introduction

Benign prostatic enlargement (BPE) due to benign prostatic hyperplasia (BPH) is a common cause of voiding dysfunction in the elderly men. The traditional treatment for patients with BPE and lower urinary tract symptoms (LUTS) may include medication with α_1 adrenergic antagonists, combining α_1 adrenergic antagonists and 5-α reductase inhibitors (5ARI), or transurethral resection of the prostate (TURP).[1–3] Surgical treatment might not be suitable for younger patients who are afraid of postoperative urinary incontinence or erectile dysfunction, or older patients with poor cardiopulmonary conditions, bleeding tendency, or debilitating diseases. Some patients still experience clinical BPH progression or limited improvement in LUTS after combined medical treatment.[4] Such patients may have a low quality of life (QoL) and may convert to surgical intervention.

Botulinum toxin A (BoNT-A) has been widely used in treatment of skeletal muscle spasticity,[5] and recently been used for neurogenic or non-neurogenic detrusor overactivity with excellent outcome.[6,7] The mechanism of action is its inhibitory effect on the acetylcholine release from nerve terminals, causing paralysis of muscles at the injection sites. The prostatic epithelium receives a cholinergic innervation while the stroma receives a predominantly noradrenergic innervation.[8,9] BoNT-A has been shown to block the release of neurotransmitters from the presynaptic nerve terminal including acetylcholine, norepinephrine, calcitonin gene related peptides, substance P, and glutamate.[10,11] Injection of onabotulinumtoxinA (BOTOX; Allergan, CA, USA) in the prostate provides an alternative treatment for patients with symptomatic BPE, especially those who are at high surgical risks.[12,13]

2. Effects of BoNT-A on the prostate

BPE is a nonmalignant enlargement of the prostate and is regarded as a major cause of voiding dysfunction in aging men.[14,15] Excessive growth (static component) and contraction (dynamic component) are the two main components in BPE. Recent evidence suggested that BPE could be originated from neural dysregulation of the prostate and alterations in local neuropeptides.[8,16] It is widely believed that the prostatic epithelium receives a cholinergic innervation while the stroma receives a predominantly noradrenergic innervation.[8] Thus, the secretion and growth of prostate epithelial is under parasympathetic influence, while the stromal contractile component is under sympathetic control. Therefore, the regulation of neural control could be an attractive option for the

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management of BPE. Previous animal studies showed that intraprostatic injection of onabotulinumtoxinA induces selective denervation and subsequent apoptosis and atrophy of the glands,[17,18] and causing prostate atrophy through impairment of sympathetic nerves and decrease of adrenergic stimulation of the prostate.[19] Lin et al.[20] reported that 200 U onabotulinumtoxinA injection into the canine prostate significantly reduced the prostate urethral pressure response to intravenous norepinephrine and electrostimulation, suggesting onabotulinumtoxinA might attenuate the dynamic contraction of BPE. In humans, increases in apoptotic activity at both epithelial and stromal components were noted after onabotulinumtoxinA injection, and thus reduce the bulk or anatomic obstructive component of BPE in humans.[21] These evidence support the therapeutic efficacy of onabotulinumtoxinA treatment in human BPE.

3. Clinical therapeutic efficacy of BoNT-A on BPH/LUTS

However, the therapeutic efficacy of BoNT-A on BPH has been controversial in recent decade. Intraprostatic injection of 100 U–200 U onabotulinumtoxinA had been shown effective in patients with BPE and poor surgical risk,[12,13] and the reported effect sustained for 12 months.[22] The first report of BoNT-A treatment on BPH was from Maria et al.,[23] in that study they showed the LUTS was significantly improved and total prostatic volume was reduced to 50% of baseline at 1 month and to one third at 2 months after intraprostatic injection of 200 U onabotulinumtoxinA. Prostatic volume reduction by 12.7%–25% had also been observed in the other small series trial.[13,24,25] However, other studies failed to confirm these therapeutic effects.[12,22] In another study by Chuang et al.,[26] the prostatic volume was not reduced although LUTS and maximum flow rate (Q_{max}) showed improvement in patients with small BPE of smaller than 30 mL. Silva et al.[27] injected 200 U onabotulinumtoxinA into the prostate of patients with BPH and refractory urinary retention and found 81% of them could resume voiding at 3 months. The mean prostate volume decreased from 70 mL to 57 mL at 1 month and to 47 mL at 3 months. The duration of prostatic volume reduction lasted for 18 months after intraprostatic injection of 200 U onabotulinumtoxinA.[28] Risinda et al.[25] found 55 (71%) of 77 patients had subjective symptomatic improvement after intraprostatic injection of 200 U onabotulinumtoxinA with only 12.7% reduction of the prostatic volume.

Kuo[12] reported dramatic therapeutic efficacy of transurethral injection of 200 U onabotulinumtoxinA on 10 elderly men with BPE and urinary retention who were at high surgical risk. All patients could have catheter removal and the prostatic volume was significantly reduced. The therapeutic effects lasted for a mean of 9 months and no one had recurrence of urinary retention. Hamidi Madani et al.[13] also reported transurethral intraprostatic BoNT-A injection provided efficient treatment effect for men with BPH refractory to current medical therapy and in poor surgical candidates. These evidence showed that intraprostatic injection of onabotulinumtoxinA may rapidly reduce the prostatic volume, decrease the bladder outlet resistance and relieve bladder outlet obstruction and urinary retention. In men who are at surgical risk of prostatectomy, intraprostatic onabotulinumtoxinA injection might be an alternative surgical procedure.

However, in another study in 60 men with total prostatic volume of more than 60 mL and refractory to combined α_1 adrenergic antagonists and 5-ARI, Kuo and Liu[29] found the therapeutic effects of improvement of LUTS and reduction of prostatic volume at 12 months was similar to continuing combined medical treatment.[29] The results of this study did not support previous reports and showed add-on BoNT-A treatment provides limited clinical effect in patients with LUTS and BPE larger than 60 mL. An enlarged prostate consists of variable proportion of the glandular component, fibrous tissue and smooth muscles.[30] The glandular component comprises only 20%–40% of the total prostate volume.[31] Whether intraprostatic injection of onabotulinumtoxinA can reduce the prostatic volume by more than 20% is still questionable. Using 5-ARI to reduce prostatic hyperplasia, the total prostatic volume reduction was estimated to be 15%–20% in long-term treatment.[2] If BoNT-A has effect on glandular apoptosis, the reduction of total prostate volume will be at most the same extent of that by 5-ARI.

A recent clinical trial revealed transrectal intraprostatic injections of 100 U or 300 U onabotulinumtoxinA insignificantly decreased AUA symptom scores and increased Q_{max} at 3 and 12 months after treatment.[32] The patient reported satisfaction rate to 200 U onabotulinumtoxinA injection at 3 months was 67% and 68% of patients judged the treatment was effective.[33] Although the pilot studies seem promising, the other studies did not consistently show the same results.[29,34] The main reason for the negative results might be heterogeneous distribution of patients with BPH. Patients with LUTS due to BPE might have different composition of glandular and stroma tissue. Although onabotlinumtoxinA can reduce the glandular component, the bladder outlet resistance might not be affected by a fixed dose of onabotulnumtoxinA. A high placebo effect noted in a phase 2 trial might also contribute to the improvement in symptom scores after treatment.[35]

4. Dose and administration of BoNT-A on BPE

Intraprostatic injections of BoNT-A can be carried out through transperineal, transrectal or transurethral routes.[12,22] Among these three ways, transperineal injection provides the best way of approach and free of risk of urinary tract infection.[22,36] However, transurethral intraprostatic injection is the procedure that urologists are most familiar and BoNT-A can be injected to the desire sites.[12,13] During treatment, onabotulinumtoxinA 200 U is usually reconstituted by normal saline to a volume of 20% of total prostate volume and is injected transperineally or transurethrally to the transition zone and peripheral zone under 2% lidocaine local anesthesia at outpatient clinic or under intravenous general anesthesia in the operation room.[12] The injection needle should be inserted as deep as possible but not penetrating into the urinary bladder. Under transrectal sonography guidance, the prostatic gland is adequately distributed by the injecting solution with the volume. BoNT-A solution should be injected equally distributed to bilateral lobes including the median lobe. Broad spectrum antibiotics should be routinely prescribed for 3 days to prevent prostatic infection after injections.

5. Are we treating BPE or LUTS by BoNT-A?

The pathophysiology of male LUTS is multifactorial. In addition to BPE, the hyperactivity of the bladder neck, urethral smooth muscle, and external sphincter may also result in voiding dysfunction.[37] Injection of 100 U onabotulinumtoxinA into the prostatic urethra and bladder neck provided significant improvements in symptom scores, Q_{max} and postvoid residual (PVR) in patients with primary bladder neck dysfunction and videourodynamically proven obstruction.[38–40] These preliminary results highlight that onabotulinumtoxinA might effect on lower urinary tract dysfunction (LUTD) by modulating the adrenergic nerves or sensory pathways. Previous studies of BoNT-A effect on men with small BPE have shown durable effect on LUTS improvement without remarkable decrease of prostate volume.[27] In fact, the prostatic volume is not well correlated with urethral resistance, ageing men with a small prostate might have a high bladder outlet resistance and LUTS.[15] On the other hand, LUTS in men are not solely caused by BPE and obstruction. The causes for non-BPE LUTS