



Review

Botulinum toxin and benign prostatic hyperplasia

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Abstract Benign prostatic hyperplasia (BPH) is a clinical condition where lower urinary tract symptoms are caused by both a physically obstructing prostate as well as tight smooth muscles around the bladder outlet. Treatment of this condition with botulinum toxin has been used since 2003, but this interest has somewhat died down after two large randomized controlled trials (RCTs) showing equivalence of results between their treatment and placebo arms. However, with review of animal studies and unexplained exaggerated effect of the placebo arms of the two RCTs, together with recent data of sustained benefits after 18 months of treatment, the place of botulinum toxin in the BPH field is probably still present.

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1. Introduction

Lower urinary tract problems resulting from benign prostatic hyperplasia is a very common clinic problem encountered in the urology outpatient. Treatment algorithm includes conservative management, medications, surgery and in recent years, minimally invasive treatment methods such as injection with Botulinum toxin. In this review, we attempt to review the management of benign prostatic hyperplasia (BPH) with the use of botulinum toxin.

2. BPH

BPH is a condition caused by an enlarging prostate which causes lower urinary tract symptoms (LUTS). This can be due to a fixed mechanical obstruction from physically enlarged prostate especially with a large intravesical protrusion. It can also be due to a dynamic component related to tight smooth muscles around the bladder neck and in the stroma of the prostate, which can cause obstruction despite a relatively small prostate. This is also the mechanism of action of α 1-blockers that has been first line treatment for patients with LUTS secondary to BPH.

The prostate is controlled mainly by the autonomic nervous system, through the adrenergic and muscarinic receptors. Parasympathetic stimulation mainly affects growth and secretion of the prostate epithelium. Sympathetic stimulation results in smooth muscle contraction,

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and further studies have shown that sympathetic stimulation induces epidermal growth factors and has trophic function on prostate growth [1].

3. Botulinum toxin (BoNT) and its mechanism of action

It is well known that BoNT is derived from the Gram-positive rod shaped anaerobic bacteria, *Clostridium botulinum*. There are seven serotypes of BoNT (A–G) [2] out of which only types A and B have been available to commercial use. The three commercially available BoNT are Botox (onabotulinum toxin A; Allergan, Irvine, CA, USA), Dysport (abobotulinum toxin A; Ipsen, Berkshire, UK), and Myobloc (Elan Pharmaceuticals, Inc., Princeton, NJ, USA). The initial two are BoNT-A and the latter is BoNT-B. The doses are expressed in Units of activity and are not interchangeable in doses.

BoNT enters the neurons by binding to the synaptic vesicle protein 2 (SV2), during exocytosis of the neurotransmitter. With endocytosis of this toxin, it combines with synaptosomal-associated proteins (SNAP 25) protein and inhibits exocytosis of the neurotransmitters within the vesicles. Hence the affected neuromuscular junctions become paralyzed. The affected neurotransmitters include acetylcholine, noradrenaline and sensory neuropeptides such as adenosine triphosphate (ATP), substance P, neurokinin A, nitric oxide etc. [3].

The mechanism of action of BoNT on the prostate has been extensively studied. With the blockade of release in acetylcholine, marked atrophy and diffused apoptosis is found in canine models treated with BoNT-A [4]. Other studies on the dynamic contractions of canine prostates injected with BoNT-A 100 U, 200 U and control with saline showed significantly less contraction on electrostimulation and intravenous norepinephrine in the 200 U group compared with 100 U or saline group [5]. Hence it can be deduced that effect of BoNT works on both the structural as well as dynamic component of BPH.

4. BoNT and BPH

Use of BoNT-A on BPH was first reported in 2003 in a randomized placebo-controlled trial by Maria et al. [6], where 30 patients were randomized to 200 U of onabotulinum toxin A injection or saline. It was reported that 13 of 15 in the treated arm vs. 3 in the placebo arm had beneficial effects of drop in International prostate symptom score (IPSS) scores (65% reduction) and prostate specific antigen (PSA) levels (51% reduction). The participants were followed for 19 months. This brought about an explosion of reports of the use of BoNT-A on BPH [7–12], albeit most of these reports were case series. Most studies reported improvement in IPSS scores starting after 1 week [7] to 1 month [12] of administration, with reduction of total prostate size and improvement in maximal flow rate (Q_{max}) and post void residual urine sustaining between 6 and 18 months.

5. Route of administration

Other aspects of interest in this area include the route of administration. There are three possible routes in

administering BoNT-A into the prostate, namely transperineal, transurethral and transrectal. The original randomized controlled trial by Maria et al. [6] was done via the transperineal route. Other authors like Kuo [7] reported using the transurethral route although this requires some form of anaesthesia or sedation. Besides familiarity, transurethral route has the advantage of focusing on the lateral as well as the median lobe which can be injected separately. Transrectal route is the most popular route for urologists due to the transrectal ultrasound and biopsy of prostate that all urologists are familiar with. This route has the advantage of ability to be done without anaesthesia, but does harbour a higher risk of infection than the other two routes. The transperineal route has not been very popular due to unfamiliarity, but with more and more transperineal prostate biopsies being done, urologists are becoming more familiar with the anatomical views of the prostate through this route and are more likely to adopt this in future.

It is described that the BoNT-A is reconstituted with normal saline to about 10%–14% [13,14] of the prostate volume. Injection is done with 2% lignocaine or general anaesthesia, into the transition and peripheral zones. This is done under transrectal ultrasound guidance, either through transperineal (two separate injections) or transrectal approach (two injections per lobe, four injections total), with the needles as deep as possible but without traversing the bladder mucosa. The patients are covered with 3 days of broad spectrum antibiotics. The commonest dosage for onabotulinum toxin A is 200 U.

6. Adverse events (AEs)

AEs appear to be mainly related to the needle injections. Most frequent AEs were haematuria (11.3%, 9.8%) and haemospermia (7.2% and 8.6%) in BoNT and placebo groups respectively in the pooled results [15] of the three randomized controlled trials (RCTs). Other AEs include urgency, dysuria, retention of urine, urinary tract infection (UTI), prostatitis PSA elevation etc. There was no difference in incidence of adverse events between the two groups.

7. Clinical data

The enthusiasm of using BoNT-A in treatment of BPH stems from the minimally invasive nature and potentially, for treatment of poor surgical candidates [7,12]. Both studies reported ability to remove long term indwelling catheters in 80% of patients with significantly reduced prostate volumes. The other potential group are patients who failed medical therapy but are not keen for surgical treatment.

In 2013, a large randomized double-blind placebo-controlled trial by Marberger et al. [16], had 94, 95, 94 and 97 participants in placebo, 100 U, 200 U and 300 U of onabotulinum toxin A, respectively. It was found that LUTS/BPH symptoms improved in all groups including the placebo, with no significant difference between groups. This has been attributed to the placebo effect of the act of injection. Of note there was no change in the PSA levels of the treatment group over the 72 weeks duration. In a *post hoc* analysis in men previously treated with α blockers

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