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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.

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.

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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 α1-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 habour 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 sudies 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 onbotulinum 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

showed significant improvement in IPSS in the 200 U group compared to placebo at week 12. This was attributed to the fact that men previously treated with medications may have memory of its effect hence improving their ability to discern between treatment and placebo.

As a response to the above, McVary et al. [17] embarked on another multicenter, randomized, double blind placebo-controlled study of men with LUTS/BPH symptoms previously treated with oral medications with 200 U of onabotulinum toxin A *vs.* placebo. In order to minimize the placebo effect, a pretreatment sham procedure was done with transrectal ultrasound rectal probe insertion for 2 min. Participants with response to this sham procedure were excluded. Again, results showed that both treatment groups and placebo groups had responses in terms of IPSS, and Q_{max}, total prostate volume (TPV), post void residual urine (PVRU) and increase in PSA levels, with no significant difference between the groups.

Again the improvement in symptoms after saline injection is attributed to placebo response. The reason for such high level of placebo effect is not known. However, TPV, Q_{max} and PVRU levels are relatively objective measurements, and the reason for such changes in the placebo arm is not explained. On the same note, most case series reported significant decline in PSA levels [6, 11,12] after injection with BoNT. However, Marberger's group [16] reported no change and McVary's group [17] reported a rise in PSA levels after treatment. The reason for this difference is also unknown.

The original RCT reported by Maria et al. [6] was done with BoNT administered via a transperineal route. Marberger's group [16] had the initial 63 patients administered via a transperineal route, but later converted to transrectal route due to urologists' familiarity. McVary's study [17] was done via the transrectal route. Although the pathophysiology cannot be explained at this juncture, the difference in results appears to be the difference in route of administration. Further studies paying attention to the effect of saline injection transrectally may be needed.

A large randomized trial [18] comparing intraprostatic injection of onabotulinum toxin A 200 U to optimized medical therapy in the treatment of LUTS/BPH (PROTOX study) was done in France, consisting of 127 participants. Among the BoNT group, 73% could interrupt their medical treatment from day 30—120. Change in international prostate symptom score (ΔIPSS) between the study groups at day 120 was 0.04. The authors concluded non inferiority between BoNT-A 200 U *vs.* optimized medical therapy.

In a follow-up study [19] of this cohort of patients, it was noted that at 18 months, 37 out of 62 (58%) of the BoNT group are still able to enjoy a good result with no additional treatment. Mean IPSS score did not differ between groups (BoNT-A and continuous medical treatment), but is still significantly decreased between inclusion and at 18 months. This is consistent with the clinical findings reported by Silva et al. [12] where a single 200 U injection of BoNT is found to have sustained effect on prostate volume reduction up to 18 months. This sustained effect observed over 18 months suggest that a real biological effect is present rather than placebo. Although a cost effective study has not been done, it may be more economical for patients to undergo one injection of BoNT-A than take medications continuously for 18 months.

8. Conclusion

In conclusion, use of BoNT-A on patients with LUTS secondary to BPH has been shown repeatedly to have a sustained effect to reduce prostate size and improve symptoms. Although large scale RCTs have not shown superiority to placebo, it may still have a place in specific groups of patients such as those who do not want to take long-term oral medications or patients who are poor surgical candidates.

Conflicts of interest

The authors declare no conflicts of interest.

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