

Botulinum toxin in low urinary tract disorders - over 30 years of practice (Review)

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Abstract. Botulinum toxin is a substance produced by *Clostridium Botulinum* and is responsible for human botulism. This substance is a poison, a neurotoxin, but used in limited quantities it can be a cure for some diseases. It is well connected to a large variety of medical applications. The mechanism of action relies on blocking the acetylcholine at the neuromuscular junction, which blocks the transmission of the nervous impulse with secondary flaccid paralysis. In urology, its role in idiopathic overactive bladder and neurogenic bladder is well known. We performed a thorough review using PubMed and other databases, revising the mechanisms of botulinum toxin action in urologic pathology, treatment procedures and other options. Botulinum toxin is a well-studied substance with a large number of applications in medicine. In urologic pathology, overactive bladder and neurogenic bladder are backed by robust studies that support the therapeutic role of this substance. The toxin has multiple effects, such as inhibition of the nerve growth factor, blocking the bladder sensory afferent pathway and apoptotic effect on the prostate tissue, by inhibiting the substance P, altering the nociceptive pathways. Interstitial cystitis and other rare pathologies show promising results, but further studies are needed. The role of botulinum toxin in benign prostatic hyperplasia is still not elucidated.

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1. Introduction

The first medical use of botulinum toxin dates back to 1988, when Dykstra *et al* used it in detrusor external sphincter dyssynergia (1). Since then, this poison began to be widely used in medical practice for chronic migraines, chronic pain, head and neck dystonias, strabismus, hyperhidrosis and anal fissures (2). Botulinum toxin is a poison, a neurotoxin, but used in limited quantities it can be a cure for some diseases. The first medical use of this neurotoxin dates back to 1981, when Scott used it to correct strabismus (3). American Urological Association (AUA) recommends this type of treatment for refractory overactive bladder. Federal Drug Administration (FDA) officially approved the usage of botulinum toxin in August 2011.

As of general recommendations, botulinum toxin is the third line of treatment option for overactive bladder. Although it has clear benefits, there are also side effects that can not be ignored including urinary tract infections and elevated post-void residual volume.

There are eight different strains of toxin: A, B, C1, C2, D, E, F and G. The most widely used in medicine is the A subtype. This strain has much longer lasting effects than all the others, which is a great advantage given the fact that the instillation is an invasive procedure. The B subtype is also used, but it has a shorter duration of action and there are not many studies on it.

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2. Materials and methods

PubMed and Scopus databases were searched for reviews and original articles regarding Botulinum toxin overactive bladder and neurogenic bladder. Morphopathology and the clinical use were envisaged. Side effects were taken to consideration.

3. Results

Botulinum toxin has many medical uses. Its effect on overactive bladder and neurogenic bladder were searched. These two pathologies have many common characteristics, but also some differences. Overactive bladder, so-called idiopathic bladder, reunites all the causes that can not be included in the neurogenic bladder category, so it is an exclusion diagnosis. Overactive bladder (OAB) is defined by the International Continence Society as urgency with or without urinary incontinence (UI), usually associated with frequency and nocturia. It is a multifactorial and common disease, associated with detrimental effects on the quality of life and a great economic burden. Neurogenic detrusor overactivity (NDO) is defined as a special type of OAB, when there is a relevant underlying neurological condition, such as spinal cord injury or multiple sclerosis (4-6).

4. The mechanism of action

Botulinum toxin is one of the most potent neurotoxins. It has been calculated that 1 g of this purified substance can kill over 1 million people (7). It is a 150 kDa polypeptide with three separate domains: N, middle and C. The C domain binds to the pre-synaptic membrane, the N domain is a specific polypeptidase and the middle domain facilitates the L chain into the cytosol. The most remarkable aspect is the affinity of this substance for the most active synapses.

The mechanism of action relies on blocking the acetylcholine at the neuromuscular junction, which blocks the transmission of the nervous impulse with secondary flaccid paralysis.

The toxin has multiple effects such as inhibition of the nerve growth factor, it blocks the bladder sensory afferent pathway, it has apoptotic effect on the prostate tissue, by inhibiting the substance P, altering the nociceptive pathways (8-10). This type of paralysis lasts from 3 to 6 months when injected into the neuromuscular junction of the skeletal muscle and more than one year if the injection is made into the smooth muscle.

There are many commercially available products, starting with Botox (onabotulintoxin), Dysport (abobotulintoxin) and Xeomin (incobotulintoxin). There is no direct equivalency between doses, but it is generally accepted that one unit of onabotulinum is equivalent to 3-5 units of abobotulinum. There is still no equivalency with incobotulintoxin (11-13).

Its usage is accepted for overactive bladder, in fact both European and American guidelines recommend this type of treatment as a third line therapy. There are numerous studies that compare the effectiveness of botulinum toxin against oral therapies.

5. Studies of efficiency

One of the most comprehensive meta-analysis was carried out by Drake *et al* (14). In the study, 56 randomized controlled

trials were revised comparing onabotulinum toxin to oral medication, including mirabegron and anticholinergics. They used network meta-analysis and network meta regression for comparison and adjusted the baseline for severity symptoms. The set period was 12 weeks, the span of the review ranged from 2007 to 2014 and only studies in English were eligible. All medications had higher efficiency than placebo, with onabotulinumtoxin being superior to oral medication in every aspect of micturition, urgency, urinary incontinence episodes. Regarding side effects, onabotulinumtoxin led to urinary tract infection, urinary retention, bacteriuria, increased residual urine volume and haematuria. Onabotulinumtoxin had also the best results in relieving the overactive bladder symptoms.

One suggestive example of the superiority of this toxin over oral medication was presented by Ferreira *et al* (15). Their small study included 61 patients who were randomly selected to oral or toxin medication. Of the patients 23.5% with oral medication and 11.8% from the onabotulinum group were non-responders. Macroscopic haematuria was present in 28% of the onabotulinum patients and dry mouth in 72% of the patients with oral medication. The study reported the superiority of onabotulinum toxin to oral medication in almost all aspects of urodynamics, continence and quality of life. Most important, all patients were from the neurogenic bladder group, not from the overactive bladder group. Schurch *et al* (16) also reported an improvement in quality of life. Karsenty *et al* (17) reported urinary continence in 40-80% of the cases.

There are other studies that compared the toxin to placebo. One of the most recent reviews is by Zhou *et al* (18). Using many databases, they searched for the efficacy and safety of botulinum toxin in the treatment of neurogenic bladder. They identified four articles including 932 patients, from whom 450 were included in the botulinum group and 482 in the control group. The authors found that onabotulinum toxin is very efficient in comparison to placebo, regardless of the dosage. Also, treatment complications are mostly related to urinary tract and include urinary infection, urinary retention, and haematuria (19).

One of the most important issues of overactive and neurologic bladder is the high pressure inside the bladder during voiding. There are many discussions regarding the need of urodynamics in patients following treatment for overactive or neurologic bladder. Koschorke *et al* (20) evaluated the need for urodynamics in patients with neurologic overactive bladder under treatment with onabotulinum toxin. Their study group included 148 patients who were evaluated before and 6 weeks after receiving the treatment. High intravesical pressure leads to renal failure later, so it is mandatory to evaluate the patient carefully. The authors determined a pressure higher than 40 mmH₂O before receiving the treatment indicates a poor prognosis for urodynamic outcomes. Even if 66% of the patients became continent, one out of five had high intravesical pressure, putting the upper urinary tract at risk. After repeating the treatment, 10 out of 18 patients achieved normal vesical pressure. There were still 8 patients out of 148 who did not achieve a normal intravesical pressure status. Thus, these authors underlined the need for urodynamics (20).

Another debated problem was the dosage of the substance. Every pharmaceutical company that produces some form of the toxin has its own measure, there is no a standardized one. Moreover, there is still debate on what quantity of the same

toxin has greater efficiency. Zhang *et al* (21), tried to elucidate this subject. Participants (1,879) from eight studies were included in their analysis. Besides the good efficiency of the drug, the authors emphasize the differences that appear with varying doses. Their comparison between 200 and 300 units did not find any significant differences, but the Cochrane review has some interesting findings: lower doses of the drug appear to have beneficial effects, but higher doses have better efficiency (and also a higher rate of side effects), suburothelial injection seems to have the same effect as intradetrusor injection, and the effect is dose and toxin type-dependant (22).

Many authors considered that single dose treatment is the optimal medical approach, but there are studies that have found that repeat treatment can be used in the same patient. Denys *et al* (23) proved that patients with neurogenic bladder can be treated with repeated injections of botulinum toxin. Moreover, even patients who do not achieve a good performance status after the first dose can respond better after repeated treatment. Other studies also concluded that there is no refractory response with repeated treatment.

The first study that investigated this toxin in the treatment of neurogenic bladder dates back to 2005. Schurch *et al* (24) evaluated 59 patients with neurogenic bladder who received a single dose of toxin (200 or 300 units) or placebo. The results were spectacular, a significant improvement in all aspects was observed.

Another aspect is the place of injection. As yet, there is no standardized recommendation for injection site. There are studies that compared trigone versus outside the trigone and concluded that trigonal injection is superior (25,26).

The side effects of this substance in pregnancy are less studied. FDA put botulinum toxin in category C for pregnant women, indicating a major teratogen. Moreover, great care must be taken in elderly patients or those aged under 18 years.

The follow up is another debated problem. There are no guidelines regarding the follow-up of these patients, but given the fact that these diseases are progressive, the patients should be monitored.

There are studies that tried to link this medication to other neurological disorders such as Parkinson's disease, multiple sclerosis, spinal cord injury, cerebrovascular accident and myelomeningocele. Some of the results were promising, but there are no standardized recommendations.

Cheng *et al* (27), in their review, evaluated the efficacy and safety of the toxin in the treatment of neurogenic bladder. In the same study, they evaluated the differences regarding the dosage. They found out that there are no differences between 200 and 300 units. Patients (1,915) from six studies were included in their review, with great improvements in the toxin group regarding urinary incontinence, maximum detrusor pressure and maximum cystometric capacity.

Some authors have tried to expand the use of this medication. Trinh *et al* (28) evaluated the efficacy of botulinum toxin in a small group of patients with failed sacral modulation. The results were encouraging, but far inferior to the patients with no sacral modulation treatment.

New applications of this medication include benign prostatic hyperplasia and chronic prostatitis, with contradictory results (29,30). Jhang and Kuo (31), in their study, reviewed all current applications of this medication.

There are studies that evaluated botulinum toxin injections in patients with severe comorbidities (32,33). Liao *et al* (34) concluded that it is safe, but caution should be taken. Post voiding residue is a very important complication that needs to be monitored and also the success of this procedure is relatively lower in frail patients.

6. Conclusions

Evidence for the use of botulinum toxin in overactive bladder and neurogenic bladder continues to accumulate. This type of treatment offers a reasonable alternative to neural stimulation. It has limited side effects, generally related to the surgical procedure.

One severe possible complication is the post voiding residue. The elderly and neurological patient should be treated carefully. Another complication is the high intravesical pressure, which may lead in time to renal failure. Urodynamics in this type of patients is mandatory, pre- and post-injecting the medication. Patients with multiple sclerosis have increased risk of urinary infections, so particular attention is recommended.

Novel applications of botulinum toxin may be benign prostatic hyperplasia, interstitial cystitis, and chronic pelvic pain, but there are no standardised approaches. There is still no consensus regarding the injection pattern or a regular dose. Repeated treatment seems to offer good results in selected cases. One possible application of this treatment could be for patients who have undergone augmentation cystoplasty for the same disease. Also, there is no standardised follow-up for this type of patients, and no guidelines. There are still many questions and many fields in which botulinum toxin can be used. For some diseases, such as overactive bladder and neurologic bladder, the indications are clear, and these indications may be expanded to other urologic diseases in the future.

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Authors' contributions

AMAS, SB, OF and RB collected, analyzed and interpreted the patient data regarding the metabolic and cardiovascular benefits of GLP-1 agonists. ADS, DLDM, OGB and CCD substantially contributed to the conception of the work and interpretation of data; also, they drafted the manuscript and were major contributors in writing the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

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Competing interests

The authors declare that they have no competing interests.

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