REVIEW ARTICLE

Botulinum-A Toxin's efficacy in the treatment of idiopathic overactive bladder

Marius Alexandru Moga,[1] Simona Banciu,[2] Oana Dimienescu,[3] Nicusor-Florin Bigiu,[4] Ioan Scarneciu[5]

Abstract

The systematic literature review was carried out to point out the efficacy of botulinum type A toxin (BTX-A) intra-detrusor injections in adults with idiopathic overactive bladder (OAB) and urgency urinary incontinence (UUI). A PubMed search for clinical studies with BTX-A intra-detrusor injections in adults with OAB was performed. The studies showed improvements in quality of life by relieving symptoms (decreased urinary frequency, urgency episodes, incontinence and nocturia). Randomised controlled trials conducted in the preceding two years showed complete continence in patients treated with BTX-A in 22.9% to 55% cases. Following treatment, most studies showed an increase in post-void residual volume, a fact that may lead to urinary tract infections (UTIs) and urinary retention requiring catheterisation. BTX-A is an effective treatment for OAB and results in a significant improvement in the quality of life of patients.

Keywords: Botulinum A toxin, Idiopathic overactive bladder, Urgency urinary incontinence.

Introduction

Overactive bladder is defined as urinary urgency with or without urge incontinence frequently associated with urinary frequency and nocturia. Overactive bladder and urge incontinence are often associated with detrusor over-activity (involuntary detrusor contractions during bladder filling).[1] Overactive bladder may have a negative effect on quality of life, productivity and mental health, urinary urgency being particularly troublesome for the patient.

Anticholinergic drug therapy (oxybutynin, tolterodine, solifenacin) have low efficacy and entail unpleasant side effects (dry mouth, constipation, blurred vision).[2]

Injection of botulinum toxin into the bladder is more commonly used in the treatment of persistent or refractory urge urinary incontinence treatment. Efficacy of botulinum toxin type A (BTX-A) injections made in the intra-detrusor muscle was initially reported in 2000 for neurogenic overactive bladder.[3]

Some studies have confirmed the efficacy of BTX-A used in the treatment of neurogenic bladder. In 2011, the US Food and Drug Administration (FDA) approved the medical indication of botox in the treatment of neurogenic overactive bladder, especially in urinary incontinence because of the over-activity of the detrusor associated with neurological pathology refractory to anticholinergic therapy.[4]

For the treatment of idiopathic overactive bladder (OAB), there have been in recent years randomised, placebo-controlled studies. In 2013, the FDA indicated the use of botox to treat idiopathic OAB and urinary incontinence in adults.[5]

Methods

We included clinical trials using the following criteria: the study must be a prospective randomised controlled trial (RCT), a prospective non-randomised controlled trial, a randomised double-blinded placebo controlled trial. Besides, the study was designed to show the efficacy of BTX-A used in the treatment of idiopathic OAB. The outcome measurements partially reported included urodynamic parameters, doses of BTX-A toxin.

The review was conducted in February 2014 using PubMed database and abstracts. The review search used a complex search strategy, including both Medical Subject Heading (MeSH) and 'free text' protocols. Specifically, MeSH search was conducted by combining the following terms retrieved from the MeSH browser: botulinum A toxin (BTX-A), idiopathic overactive bladder (OAB), urgency urinary incontinence (UUI). Subsequently, the searches were pooled and the following limits were used: humans, gender (female), and temporal (from 2005-2013). No language limits were used.

For the purpose of the present review, attention was focused only on the the efficacy of BTX-A toxin used in the treatment of idiopathic OAB. In addition, reference lists of relevant textbooks, review articles and abstracts of scientific meetings were also searched. Two authors independently developed an electronic database search strategy to identify studies that met the eligibility criteria.

[1,4,5]Faculty of Medicine, Nicolae Balcescu Str., [2,3]Clinic Hospital of Obstetrics and Gynaecology "Dr. I. A. Sbarcea", Gheorghe Baritiu Str., Brasov, Romania.
Correspondence: Marius Alexandru Moga. Email: moga.og@gmail.com

Initial searches yielded a total of 104 potentially relevant studies. After screening the abstracts of these preliminary results, we excluded 72(69%) of them that were not related to the efficacy of using BTX-A toxin in the treatment of idiopathic OAB. We read through the full texts of the remaining articles after which 18(17.3%) were excluded as they were narrative reviews or case reports, providing insufficient numerical results or were not controlled clinical trials. Finally, 14(13.5%) trials met the inclusion criteria and were finally included in our meta-analysis[6-19] (Table).

Discussions

Botulinum toxin is a neurotoxin produced by clostridium botulinum that is a gram-negative anaerobic bacteria. Botulinum toxin acts by inhibiting the release of acetylcholine from pre-synaptic neuromuscular junction, resulting in temporary flaccid muscle paralysis. The heavy chain component determines the specificity of the toxin for cholinergic nerve endings. The mechanism of action is a process in two steps. In the first mechanism, the membrane of the neuronal cell binds the molecule with the heavy chain and as a result of this mechanism, the molecule is being internalised. The second mechanism is related to a disulphide reaction that separates the heavy chain from light chain. The light chain connects to the vesicles of acetylcholine, acting as an endopeptidase zinc-dependent; cleaving a number of proteins needed for the fusion of the vesicles of neurotransmitter with the cell area, preventing exocytosis of acetylcholine and also is blocking the neuromuscular end-plate.[20]

Botulinum can disrupt and modulate neurotransmission efficient and selective in striated muscle. In both striated and smooth muscles, BTX-A is internalised by presynaptic neurons by binding to an extracellular receptor. In the neuronal cytosol, BTX-A disrupts the fusion of vesicles that contains acetylcholine with the wall of neuron by splitting the Soluble (N-ethylmaleimide-sensitive fusion-attachment proteins (SNAP-25) in the synaptic fusion compounds. The real effect is the selective paralysis of the weak contractions of the unstable detrusor, while allowing high-quality contractions that initiates micturition. In addition, BTX-A appears to have an effect by modulating the release of adenosine triphosphate (ATP) from urothelium, the effect being seen on afferent nerve activity. The mechanism is the blockage of releasing the substance P and also calcitonin gene peptide (CGRP) and also glutamate from afferent nerves and also is decreasing the levels of nerve growth factor (NGF). These effects on sensory feedback help explaining the BTX-A mechanism in improving symptoms of OAB.[21]

While the flaccid paralysis caused by the botulinum toxin injection it was initially thought to be a permanent paralysis, return of muscle function was noted. The axonal re-arborisation over the nerve endplates at the level of neuromuscular junction and the replacement of toxin-affected nerves with new ones appears to be responsible for the gradual return of function after the treatment with toxin. Most of the patients require repeated injections of toxin into the bladder every 6-12 months.[20]

The botulinum toxin serotype A is the most common form used to treat OAB. In the US, BTX-A is available as Botox and in Europe as Dysport. Dose of 100-300 U of botulinum toxin is reconstituted in 20-30ml sterile saline and is injected into the detrusor muscle, below the bladder mucosa, avoiding the trigone. To inject the toxin, a rigid or flexible cystoscope can be used. A total of 15 to 30 injections may be needed, usually at intervals of approximately 1cm from each other.[4,20]

The effect is not observed immediately after the injection, and muscle paralysis occurs slowly in the following days, with a maximum effect at 7-10 days after the injection. The effects of the toxin last 6 to 12 months, but may vary depending on the dose injected. Higher doses tend to have a longer period of effects, but with associated higher rates of urinary retention.[20]

The most common side effects of botulinum toxin intra-detrusor injections are:

- pain at the injection site
- urinary tract infections due to the procedure
- haematuria (mild)
- augmentation in the volume post-void residual (PVR) that can also lead to urinary retention and catheterisation.

Systemic side effects are rarely observed, occurring due to paralytic mechanism, being possible to appear dysphagia, generalised weakness, blurred vision and diplopia.[20]

Since 2005, a large number of trials identified the efficacy and safety of intra-detrusor BTX-A for the treatment of idiopathic OAB.

In prospective non-randomised studies[6,7] all patients underwent intra-detrusor muscle injections at 30 sites under cystoscopic guidance with a dose of 100U of BTX-A. Improvement in continence was noticed at 4 weeks in one study[6] wherein 26 women became continent, while in the other study,[7] improvement was noticed after 4 to 12 weeks, and 88% patients had significant improvement of the bladder function. They evaluated also the urodynamic

Table: Studies examining the Botulinum type A toxin efficacy used in the treatment of idiopathic overactive bladder.

	Author	Year	Study design	N	Dose of BTX-A	Sites of intra-detrusor injection	Outcome
1	Werner M.[8]	2005	Prospective Non-randomized	26	100 U BTX-A	30	Continence was achieved in most women after 4, 12 and 36 weeks. The adverse effects that occurred were temporarily self-catheterization (2 cases) and urinary tract infections (9 cases).
2	Schmid D.M. et al.[9]	2006	Prospective Non-randomized	100	100 U BTX-A	30	88% of the patients showed significant improvement of bladder function after 4 and 12 weeks. Urodynamic parameters were improved. 4 cases of temporary urine retention. Efficacy duration was at least 6 months.
3	Sahai A. et al.[10]	2007	Randomized Double-blind Placebo controlled	34	200 U BTX-A (16) Placebo (18)	10	Improved clinical symptoms: decreased frequency and urgency urinary incontinence episodes. Improved urodynamic parameters. Post-void residual increased at 4 weeks but was insignificant by 12 weeks and 6 patients required intermittent self-catheterization; Significant improvements in quality of life; The beneficial effects of BTX-A was maintained 24 weeks.
4	Jeffery S. et al.[11]	2007	Prospective	25	500 U Dysport	20	63% of patients were continent from 1 week after treatment and 32% remains continent at 3 months and 6 months after treatment; The volume at first desire to void increased (177 ml to 251 ml at 3 months);35% of patients required catheterization at 6 weeks and at 3 months, 22% at 6 months and only one at 9 months.
5	Brubaker L, Richter H.E. et al.[12]	2008	Randomized Double-blind Placebo controlled	43	200 U BTX-A (28) Placebo (15)	15-20	60% of women had significant improvements in symptoms. Beneficial effect remained 12 months;12 of 28 women (43%) had a significant increase of post-void residual urine and UTIs occurred in 9 of 12 women (75%)
6	Mohanty N.K. et al.[13]	2008	Prospective	39	200 U BTX-A	20	85,7% (30 patients) had improvements in clinical symptoms. Urodynamic parameters were also improved. Beneficial effect was at mean 7 months. There were no adverse effects.
7	Flynn M.K. et al.[14]	2009	Randomized Placebo controlled 1st stage of study	22	200 U BTX-A 300 U BTX-A (15 BTX-A - blind to the doses); Placebo (7)	8-10	50% improved in incontinence episodes, 12% in frequency and 24% in nycturia; 4 subjects had a PVR volume of 200 cc or higher; 1 person required catheterization; UTI occurred in 2 patients in the BTX-A group and in 2 patients of placebo group
8	Sahai A. et al.[15]	2009	Randomized Double-blind Placebo controlled	34	200 U BTX-A (16) Placebo (18)	10	Quality of life was significantly improved in all patients treated with BTX-A compared to placebo;
9	Dmochowski R. et al.[16]	2010	Randomized Double-blind Placebo controlled	313	50 U BTX-A (57) 100 U BTX-A(54) 150 U BTX-A (49) 200 U BTX-A (53) 300 U BTX-A (56) Placebo (44)	20	BTX-A at doses of 100 IU or more were demonstrated durable efficacy in the management of idiopathic overactive bladder and urge urinary incontinence. 100 U BTX-A may be the dose that appropriately balances the symptom benefits and the side effects.
10	Rovner E. et al.[17]	2011	Randomized Double-blind Placebo controlled	313	50 U BTX-A (57) 100 U BTX-A (54) 150 U BTX-A (49) 200 U BTX-A (53) 300 U BTX-A(56) Placebo (44)	20	29.8-57.1% of subjects treated with BTX-A have not shown urge urinary incontinence (compared to 15.9% in the placebo group); Improvements in urodynamic parameters were shown. Higher doses of 150 U were more frequently associated with a post-void residual volume > 200 ml.
11	Fowler C.J. et al.[18]	2012	Randomized Double-blind Placebo controlled	313	50 U BTX-A (57) 100 U BTX-A (54) 150 U BTX-A (49) 200 U BTX-A (53) 300 U BTX-A(56) Placebo (44)	20	BTX-A in doses greater than 100 U showed higher improvements than the placebo study in all related quality of life scores at the follow-up from week 2 - week 24.
12	Denys P. et al.[19]	2012	Randomized Double-blind Placebo controlled	99	50 U BTX-A (21) 100 U BTX-A (22) 150 U BTX-A (27) Placebo (29)	15	More than a half of patients had significant improvements in clinical outcome and also improvements in quality of life. High post-void residual volume was observed in the 150 U BTX-A group.
13	Tincello D.G. et al.[20]	2012	Randomized Double-blind Placebo controlled	240	200 U BTX-A (122) Placebo (118)	20	Significant clinical improvements: Continence achieved in 31% of treated patients versus 12% on placebo; 31% developed UTI (versus 11% on placebo) 16% required catheterization (compared to 4% of placebo)
14	Nitti V.W. et al.[21]	2013	Randomized Placebo controlled	557	100 U BTX-A or Placebo (1:1)	20	BTX-A showed significant clinical improvement in OAB symptoms. Quality of life is improved; Uncomplicated UTI was the most common adverse event.

parameters where significant improvement was noted: mean volume at first desire to void increased (from 126 to 212ml), and so did the mean urge volume (from 214 to 309ml). Urgency disappeared in 82% patients, incontinence resolved in 86%. Also, they observed that the frequency decreased to 50%, and nocturia decreased. The adverse effects in the two studies mentioned were temporarily self-catheterisation, infections of the urinary tract and temporary urine retention.

In 2008, a prospective study[11] was conducted on 39 patients using 200U of BTX-A injected intravesical, on 20 different sites. It observed that urgency disappeared in 80% cases, incontinence in 85% and frequency decreased by 60%. Regarding the urodynamic parameters, the maximum cystometric capacity of bladder increased by 60% (from 205 to 331ml), the volume at first desire to void increased from 104ml to 204ml, and the detrusor pressure decreased by 49%. It didn't find any adverse effects.

In 4 randomised double-blinded placebo-controlled studies,[8,10,12,18] 200U BTX-A was injected in the intra-detrusor muscle. All studies reported a significant improvement in incontinence episodes, decreased frequency and nocturia, but there was also a significant increase in the post-void residual urine. There was a higher incidence of UTIs among patients treated with BTX-A vs placebo, and more than half required catheterisation.

In recent literature, Dmochowski et al and Rovner et al[14,15] in a randomised double-blinded placebo-controlled study evaluated 313 patients, of whom 269 were injected in the intra-detrusor muscle in 20 sites with 1 of 5 doses of BTX-A (50U to 300U) and 44 with placebo. The first study[14] evaluated the effectiveness of different doses of BTX-A, and it was observed that 50U dose was less effective than 100U or more; 150U or more consistently were not differentiated from each other and did not appear to provide additional significant efficacy; and a dose of 200U showed the greatest increase in the PVR volume leading to a higher incidence of catheterisation associated with UTI and urinary retention. In the second study[15] it was identified that at 3 months after the treatment, between 29.8% and 57.1% patients injected with BTX-A and 15.9% with placebo became continent. Changes from baseline in the maximum cystometric capacity (MCC) of the bladder at week 12 were higher in patients treated with doses of BTX-A of more than 100U compared to placebo. The MCC was dose-dependent. Increase in the MCC was observed at week 12 for all doses of BTX-A, and at 36 weeks for higher doses of 150U.

Other studies found have shown an improvement in the overactive bladder symptoms, after the treatment with BTX-A. One study[13] used the King's Health Questionnaire (KHQ) and it identified an improvement of the urinary symptoms among patients injected with 200U of BTX-A compared to the placebo group, at 3 months after the treatment. Another study[16] also evaluated the quality of life of patients after treatment. It used the Incontinence-Specific Quality of Life Instrument, the KHQ symptom component and the Medical Outcomes Study 36 Item Short Form Health Survey. It concluded that the use of BTX-A in doses greater than 100U showed higher improvements than the placebo in all related quality of life scores at the follow-up from week 2 to week 24.

A randomised, placebo-controlled study[17] identified complete continence in 55% patients treated with a dose of 100U BTX-A and in 50% with 150U BTX-A. It also observed improvement in the urgency and urge urinary incontinence in 65%, with 56% patients being those who were treated with different doses of BTX-A. After 6 months of treatment, the quality of life and frequency symptoms significantly improved. As side effects, it found 3 patients with PVR volume >200ml in the group treated with 150 U BTX-A.

The most recent study conducted in 2013[19] is the largest study found reviewing the literature. It compared the effects of intra-detrusor injection of 100U of BTX-A and placebo in 557 women. Complete continence was achieved in 22.9% vs 6.5% for placebo. It demonstrated also that the frequency of incontinence significantly decreased in treated patients compared to placebo. The most common side effect encountered was the uncomplicated urinary infection, and it also found 5.4% urinary retention. Overall, 60.8% patients reported a good response on scale benefit of the treatment.

All clinical trials have demonstrated the efficacy of botulinum toxin type A in idiopathic OAB. The studies showed an improvement in the quality of life by relieving symptoms (decreased urinary frequency, urgency episodes, incontinence and nocturia).

Studies also show improvements in urodynamic parameters (MCC, volume at first desire to void, the detrusor pressure). The positive effects were variable from 24 weeks to 12 months.

Following treatment, most studies showed a significant increase in PVR volume, a fact that leads to urinary tract infections and urinary retention that required catheterisation.

BTX-A doses used were from 50U to 500U. Doses of 100-200U seem to be the most safe and effective doses, with

higher doses being associated with PVR volume >200 ml, leading to a higher incidence of urinary catheter associated with urinary tract infections.

Further studies are needed to help establish injection protocols and optimal dosage to achieve a lasting effect. The effects of long-term repeated intravesical injections of BTX-A are not known.

Conclusions

BTX-A is an effective treatment for idiopathic OAB. BTX-A results in a significant improvement in the quality of life of patients with OAB. The most common adverse effects are urinary retention requiring catheterisation. And urinary retention may result in urinary tract infections.

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