Use of the Botulinum Toxin A in the Treatment of the Neurogenic Detrusor Overactivity

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Abstract

Introduction and Objectives. Neurogenic detrusor overactivity (NDO) is the condition where the detrusor overactivity is caused by a disturbance of nervous control mechanism with evidence of a relevant neurological disorder. For patients who abort the anticholinergic drugs, the recommended first line therapy, other type of treatments should be considered. The use of botulinum toxin A administered as intradetrusor injections has emerged as an effective alternative.
Materials and methods. The goalwas to assess the efficacy of botulinum toxin A for the treatment of NDO from the published literature in the last five years, starting 2010. The search was performed in the PubMed database, using the following terms: botulinum toxin A, onabotulinumtoxin A, abobotulinumtoxin A, incobotulinumtoxinA, neurogenic detrusor overactivity, overactive bladder, NDO. The search was limited to articles presenting clinical trials with adult human subjects and written in the English language.Published reviews on the topic were excluded.
Results. Eight studies were reviewed. All of them reported a major improvement in the urodynamic parameters – MCC, MDP. There was also a significantly decrease in the urinary incontinence episodes, frequency and urgency episodes. All authors reported an increase on patients' quality of life, regardless of the underlying neurological condition. There were no major registered adverse events. Furthermore, BoNT/A injections proved to have a good long term efficacy and tolerability.
Conclusions. Botulinum toxin A appears to be a feasible second line treatment for patients with neurogenic detrusor overactivity non responsive or who fail to tolerate anticholinergic medication.

Keywords: botulinum toxin type A, neurogenic detrusor overactivity, urinary incontinence, urodynamic parameters.

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Introduction

The International Continence Society defined the overactive bladder (OAB) as a symptom syndrome, which implies the presence of urinary urgency that can be usually accompanied by frequency and nocturia, with or without urge urinary incontinence (UUI), in the absence of urinary tract infection (UTI) or other pathological condition. Detrusor overactivity (DO) is an urodynamic diagnosis and it is characterized by the presence of involuntary detrusor contractions during the filling phase that can be spontaneous or provoked [1]. Neurogenic detrusor overactivity (NDO) is the condition where the detrusor overactivity is caused by a disturbance of nervous control mechanism and there is evidence of a relevant neurological disorder, temporary related to symptoms' debut [2].

Several neurological conditions, such as Parkinson's disease (PD), multiple sclerosis (MS) or spinal cord injury (SCI) can determine the presence of NDO. The overall burden of NDO is quite high: MS has a median global incidence of 2.5 per 100.000 and a median prevalence of 30 per 100.000 (80/100.000 in Europe and 135/100.000 in the USA), out of which a mean of 65% patients have signs of NDO, and 51 to 80% patients experience bladder dysfunction about 50% of subjects with MS confront with urge urinary incontinence; traumatic SCI has an estimated incidence of 16/1.000.000 on the European Continent with about 80% of these patients developing Neurogenic Lower Urinary Tract Dysfunction, with a prevalence of urge urinary incontinence of approximately 50%. [3].

Antimuscarinic agents are agreed to be the first-line treatment for neurogenic detrusor overactivity [4]. Even though this category of drugs has been used for many years to treat patients with NDO, the evidence is still limited, while the response to treatment is variable [5, 6].

EAU Guidelines 2015 recommend higher doses or combination of antimuscarinic agents as an option to maximizethe outcome of therapy in patients with neurological impairment [4]. The main issue concerning this pharmacological treatment is the high incidence of adverse events (AE) experienced by patients, which appears to be the main cause for therapy discontinuation [7, 8, 9]. Most cited AE in the literature are dry mouth, constipation, drowsiness, blurred vision and cognitive impairment, especially in elderly patients [10]. Another matter of concern regarding the use of anticholinergic agents is their risk of cardiac adverse effects: prolonged QT interval and ventricular tachycardia, making them difficult to administer to patients at risk [11].

For patients who abort anticholinergic drugs due to the adverse events or for those who are unresponsive to antimuscarinic agents, other types of treatments should be considered. The use of botulinum toxin A administered as intradetrusor injections has emerged as an effective alternative, which can be considered for this group of patients. Botulinum toxin (BoNT) is a neurotoxin produced by a gram-positive anaerobic bacteria capable to block the release of acetylcholine at the neuromuscular junction. Although several types of BoNT have been identified (A-G), serotype A proved to be especially clinically relevant mainly due to its long duration of action [11]. There are three forms of BoNT/A available on the pharmaceutical market with proprietary names of Botox®, Dysport® and Xeomin® (Table 1).

Table 1: DCI and proprietary names of the botulinum toxin type A

Non-proprietary name	Proprietary name
abobotulninumtoxinA	Dysport®
incobotulinumtoxinA	Xeomin®
onabotulinumtoxinA	Botox®

Due to differences in molecular structure, the forms of BoNT/A may have different characteristics in terms of potency, efficacy and safety, therefore it is necessary to emphasize that the doses, expressed in units (U) for all formulations of BoNT/A, are not interchangeable[11]. Although it has been used "off-label" for about twenty years in the urological field [12], only in 2011, onabotulinum toxin A received approval from the Food and Drug Administration (FDA) for treatment of NDO patients who presented an inadequate response or were intolerant to anticholinergic medication [13]. In 2015, the European Association of Urology, through its' Guidelines, recommend Botulinum toxin injection in the detrusor as the most effective minimally invasive treatment to reduce neurogenic detrusor overactivity, causing long-lasting, reversible chemical denervation [4].

Material and method

The aim of this article is to assess the efficacy of botulinum toxin A for the treatment of neurogenic detrusor overactivity. Therefore, articles published between 2010 and September 2015 were reviewed, excluding the published reviews on the topic. The search was performed in the PubMed database, using the following terms: botulinum toxin A, onabotulinumtoxin A, abobotulinumtoxin A, incobotulinumtoxin A, neurogenic detrusor overac-

tivity overactive bladder, NDO. Our search was limited to clinical trials involving adult human subjects and all the articles had to be written in the English language.

Results

Eight studies were found and reviewed. They were evaluated in terms of urodynamic results, clinical efficacy, adverse events and patients' quality of life, where available. The articles are presented in the following lines and summarized in table no. 2.

In 2011, Deffontaines-Rufin et al. [14] presented their results from a prospective, open-label clinical trial on the use of botulinum toxin type A (BoNT/A) 300 U in 71 patients with NDO due to multiple sclerosis (MS). Following administration of BoNT/A,77% of patients achieved clinical improvement of their incontinence episodes, if not full control, also with a significant improvement of the urodynamic parameters. The mean maximum cystometric capacity (MCC) increased from 240 ml to 328 ml, while the mean maximum detrusor pressure (MDP) was decreased from 61 cm/$H_2$0 to 36 cm/$H_2$0at the 3 month evaluation. The post voiding residual volume (PVR) was not evaluated. Although 46% of the study population gained full control on incontinence episodes and another 31% of patients achieved partial improvement, with reduction of urgency and incontinence, BoNT/A still failed to treat 23% of the patients (16 subjects) from this clinical trial. The authors concluded the reason was the advanced neurological damage caused by the MS.

In 2011, Kuo HC and Liu SH investigated the therapeutic effect of repeated detrusor onabotulinumtoxin A injections on urinary incontinence in 33 patients with suprasacral SCI. The Onabotulinumtoxin A 200 U detrusor injections were repeated every 6 months for two years. Patients were instructed to perform clean intermittent catheterization (CIC) during treatment and follow-up periods. Videourodynamic study and 99mTc-DTPA renal scanning for glomerular filtration rate (GFR) were performed at screening and every 3 months to assess the therapeutic effects on bladder and renal function. The Quality of life was also measured. At study completion, 18 patients presented with improved continence and 12 subjects became completely dry. Mean MCC increased from an average of 207 ml (± 111 ml) to 412 ml (± 33 ml), whereas mean MDP decreased from 39.8 cm/H_2O (± 21.7) to 20.6 cm/H_2O (± 19.1) (results statistically significant, with a P value< 0.05). The mean GFR decreased from a median value of 93.4ml/min to 83.5 ml/min (P value of 0.028). The quality of life was improved for the 30 patients with increased continence control. [15]

A prospective, double blind, multicenter, placebo-controlled trial came from Herschorn et al. and was published in "The Journal of Urology" in 2011. The 57 patients with NDO secondary to MS or SCI were randomized to 300 U BoNT/A (28) or placebo (29). MDP decreased from baseline (60 cm/H_2O) at 6 weeks (32.5 cm/H_2O), increasing slowly at 36 weeks (41 cm/H_2O) compared to placebo where the values were 72; 85 and 72.5 cm/$H_2$0, respectively. The mean MCC increased from 297.5 ml at baseline to 521.5 ml at 6 weeks and decreased to 361.5 ml at 36 weeks, compared to placebo (270->241->211 ml). The reflex volume also improved from baseline (132.5 ml) to 357 ml and 173 ml at 6 and 36 weeks, respectively. The rate of UI was lower in the active treatment group - mean daily UI episodes at 6 weeks of 1.3 (±1.3) versus placebo -4.8 (±2.9). The most frequent adverse eventwas UTI, occurring at a similar rate in the two study groups. The QoL score was higher in the BoNT/A treatment group compared to the placebo group. [16]

Khan et al. reported in 2011 their results from a prospective, open-label study. They injected 300 U BoNT/A to 137 patients with NDO due to MS. The urodynamic parameters were not assessed, but the continence rate and the quality of life were primary endpoints of the study. The continence rate improved significantly. There were 83% incontinent patients at baseline and 76% full continent patients at 4 weeks. The QoL was also improved as shown by the IIQ-7 and MUDI scores. The study is important as it also shows the efficacy and safety of reinjection. The mean follow-up was 29 months, 72% of the study population received a second injection, 34,3% a third one, 18,25% a fourth one, 10,2% a fifth one and 3,6% a sixth injection, with a mean period between injections of 12 months.Due to the increased PVR, 95% of patients were performing CIC after the first injection, compared to baseline where 65% needed CIC [17].

One of the largest clinical trials aiming to assess the effects of onabotulinumtoxin A injections and quality of life in patients with NDO was conducted by Francisco Cruz et al. and was published in the European Urology in 2011 [18]. Also known as the "DIGNITY" study, it was a phase III, randomized, double blind, placebo-controlled trial comprising 275 NDO patients (121 SCI and 154 MS patients). The patients were randomized to onabotulinumtoxin A 200 U, onabotulinumtoxin A 300 U or placebo, delivered through 30 intradetrusor injections. At the primary endpoint (6 weeks after injection procedure),

BoNT/A 200 U and 300 U significantly reduced weekly incontinence episodes: -21,8 and -19,4 versus placebo (13,2). There was no clinically relevant difference between the two groups receiving BoNT/A. There were 39,6%, 38% and 7,6% fully continent patients from the three study groups (300U, 200U and placebo, respectively). MCC increased from an average value of 247 ml to 404 ml in both active treatment arms (200U and 300U), compared to placebo (249 ml to 256 ml). MDP values showed: an increase in the placebo group from 41 to 48 cm/H_2O, a decrease from 52 to 23 cm/H_2O in the 200 U arm and a decrease from 42 to 15 cm/H_2O in the 300 U arm. PVR increased from 79 to 167 ml for 200U injected patients, from 64 to 248 ml for 300U injected patients, compared to placebo – 57 to 60 ml. Patients' quality of life was significantly increased compared to placebo: 24,4; 25,1 points for the 200U arm and 24,3; 25,9 points for the 300 U arm at 6 and 12 weeks, respectively, versus placebo 11,7 and 8,6 points (p value < 0,001). In terms of adverse events, they were slightly higher for the 300U arm: 57 patients with UTI (64%) with 300U BoNT/A versus 51 patients (56%) with 200U BoNT/A, 28 patients with urinary retention (31,5%) with 300U BoNT/A versus 18 patients (19,8%) with 200U BoNT/A, 9 patients with hematuria (10,1%) with 300U BoNT/A versus 5 patients (5,5%) in the 200U BoNT/A. Another important aspect evaluated in the trial was the median time before the patients asked for retreatment, which revealed to be 42 weeks. Finally, there were no noted differences in terms of efficacy or duration of action between the 200U and 300U dose, but the lower dose showed a slightly improved safety profile.

One year later, in 2012, there came another double-blind, randomized, placebo control trial on 416 patients with NDO due to MS or SCI. Ginsberg et al.'s results showed that 200 U, 300 U BoTN/A decreased the incontinence episodes at 2,6 and 12 weeks after treatment compared to placebo. There was a -67%, -74%, -30% change from baseline for the 200U,300U and placebo arms, respectively, with 36% (200 U arm) and 41% (300 U arm) dry status in the active treatment groups. No clinically significant differences between the two active doses were found. At 6 weeks, mean MCC increased by 151 ml from 252 for the 200U group and by 168 ml from 256 for the 300U, compared to placebo. Mean MDP decreased with 35,1 cm/H_2O (baseline of 51,3) in the 200U group and with 33,3 cmH_2O (baseline of 47,1) in 300U group compared to the placebo group, where it decreased with 2,4 cm H_20 from a baseline of 50,9. The I-QOL total score was also improved in the two active treatment groups, compared to placebo. The mean time until patient retreatment request was 92, 254 and 256 days for the placebo, 300U and the 200U group, respectively. The most common adverse events were UTI and urinary retention. It is noticeable that 50% of the patients not undergoing CIC at baseline, distributed in the active treatment group, began catheterization (35% in 200-U group and 42% in 300-U group due to urinary retention), whereas in the placebo group only 22% started CIC. The two treatment doses were absolutely comparable in terms of efficacy and effect duration, but the adverse events tended to be lower for the 200U dose [19].

Later that year, Carlos Arturo Levi D'Ancona et al. reported the results of a prospective, open-labeled clinical trial showing that botulinum toxin type A injections improved the urodynamic parameters and quality of life (QoL) of the study group [20]. This study consisted of 34 enrolled adult patients with SCI and DO, who were regularly undergoing CIC, out of whom only 28 completed the study successfully; the used dose was 300 U BoNT/A and the end points were defined at 4 and 24 weeks. At study completion, mean MCC improved from 172 ml to 461 ml, mean MDP decreased from 79 to 30 cm/H_2O, while average daily number of incontinence episodes decreased from 7 (±1) to 1 (±3). In terms of adverse events, eight patients presented in the first 24 hours with gross hematuria, systemic adverse events were not encountered. A very important aspect of this trial was evaluating the QoL. Assessed on its specific impact of urinary problems (SIUP), the score was decreased from 3,38 at baseline to 1,90 at 6 months [20].

Closer to the present times, Waleed Al Taweel et al. performed a retrospective study upon the efficacy of onabotulinumtoxin A injection in NDO following SCI, published in the "Urology Annals", in July 2015. The trial included 103 patients, the treatment consisted of 30 intradetrusor injections with 300 U BoNT/A. The urodynamic tests showed a decrease of the MDP mean value from 31,2 cm/H_2O to 20,8cm/H_2O and an increase in MCC from 223,3 to 331,5 ml. The average reflex volume modified from 178,2 ml to 285 ml. The rate of incontinence was declared improved, but not quantified, the adverse events accounted for hematuria in 20 patients and UTI in 15 patients. The authors also tried to stratify the results regarding the localization of the SCI injury, concluding that thoracic and lumbar injuries had better results in lower urinary tract dysfunction control compared to cervical spine injuries. [21]

Table 2: Characteristics of evaluated studies.

Author/Year	Study design	No. pts.	Neurogenic disorder type	Evaluation	BoNT/A* Dose	MCC (ml)	MDP (cm/H_2O)	Incontinence Reduction (%)	PVR (ml)	Most freq. AE
Deffontaines-Rufin et al. 2011[14]	Prospective	71 pts.	MS - 71 pts.	3 mo.	300 U	240 → 328	61→36	46%- FC	NA	NA
	Open Label							31%- PI		
Kuo et al. 2011 [15]	Prospective	33 pts.	SCI - 33 pts.	3 mo.	200 U (a)	207 → 412	39,8 → 20,6	36%- FC	NA	NA
	Open Label							54%- PI		
Herschorn et al. 2011 [16]	Prospective	57 pts.	MS and SCI - 57 pts.	Baseline	300 U	297,5	60			
	Double- blind			6 wks		521,5	32,5	1,3 ± 1,3 UIE	NA	UTI - most freq.
	Placebo- controlled			36 wks		361,5	41			
Khan et al. 2011 [17]	Prospective	137 pts.	MS -137 pts.	4 wks	300 U (b)	NA	NA	76% FC	NA / 65% CIC	NA
	Open Label									
Cruz et al. 2011 [18]	Randomized	275 pts.	MS - 154 pts;	6 wks	200 U	247→404	52→23	-21,8 UIE weekly, 39,6%-FC	79→167	UTI, AUR, hematuria
	Double- blind		SCI - 121 pts		300 U	247→404	42→15	-19,4 UIE weekly, 38%-FC	64→248	higher for 300 U
	Placebo- controlled									
Ginsberg et al. 2012 [19]	Randomized	416 pts	MS and SCI - 416 pts.	6 wks	200 U	252→403	51,3→15,8	- 67%; 36%- FC	NA (35% CIC)	UTI, AUR, hematuria
	Double- blind				300 U	256→424	47,1→13,8	- 74%; 41%- FC	NA (42% CIC)	higher for 300 U
	Placebo- controlled									
Levi D'Ancona et al. 2012 [20]	Prospective	34 pts	SCI - 34 pts.	4 wks	300 U	172→461	79→30	daily UIE: 7→1	NA	Gross hematuria
	Open Label									
Waleed Al Taweel et al. 2015 [21]	Prospective	103 pts	SCI - 103 pts.	NA	300 U	223,3→331,5	31,2→20,8	NA	NA	Hematuria, UTI
	Open Label									

* onabotulinumtoxinA(Botox®); (a) Reinjection at every 6 months for 2 years; (b) Reinjection at 12 months until 7 years; MS – multiple sclerosis; SCI – spinal cord injury; MCC – maximum cystometric capacity; MDP – maximum detrusor pressure; UIE – urgency incontinence episodes; PVR – post void residue; CIC – clean intermittent catheterization; UTI – urinary tract infection; AUR – acute urinary retention; mo – months; wks – weeks; FC – full control; PI – partial improvement; NA – not available

Discussion

The use of BoNT/A in the treatment of NDO has shown an increased interest in the recent years, according to the large number of clinical trials and studies published in the literature. It is the data from these clinical trials that led to the approval of the onabotulinumtoxin A for treatment of NDO in several countries, including the United States of America.

The form of botulinum toxin that was used in all our analyzed studies was onabotulinumtoxin A; in five of them the 300 U dose was used, in one the 200 U dose and there were two studies that actually compared between the two doses (200U/300U). There were no major differences in terms of clinical effect and effect duration, somehow the adverse events were lower in the 200 U dose [19, 20]. Furthermore, the literature of the past five years seems to agree that the 200 U dose carries the most acceptable risk-benefit ratio in the treatment of NDO [22, 23].

Urodynamic parameters (MCC and MDP) were significantly improved in all the reviewed articles. In terms of clinical outcomes, all of the authors reported a decrease in the urinary incontinence episodes, frequency and urgency episodes. The percent of patients with full control on incontinence ranged from 36% to 76% in the analyzed studies.

Although it was not assessed in all studies, the injection of BoNT/A for the treatment of NDO revealed to improve the patients' quality of life, regardless of the underlying neurological disorder.

The adverse events were evaluated only in five of the reviewed articles and the most frequently observed were urinary tract infection, followed by acute urinary retention and hematuria. No major adverse events were reported.

Regarding the long term efficacy and tolerability, the majority of studies evaluated the effects after a single injection. There were several investigators reporting reinjection with good results.[15, 17, 24]. The median time upon patient reinjection request resulted from the studies we reviewed was between 36 and 42 weeks.

Another matter of concern regarding reinjection was the histological change that can occur in the bladder wall after intradetrusor administration of botulinum toxin. This was not assessed in our analyzed studies, except one, where the data was not well defined [17]. Still, it is an issue assessed by the literature, where several authors reported no major histological changes in the bladder wall after repeated injections. [25, 26]

Conclusion

Botulinum toxin A appears to be a feasible second line treatment for patients with neurogenic detrusor overactivity non responsive or who fail to tolerate anticholinergic medication. The intradetrusor injections of botulinum toxin type A seem to be well tolerated, improving patients' quality of life, clinical status, as well as urodynamic parameters.

Although it has been approved by several important healthcare authorities for the use in NDO treatment, further high level of evidence studies will need to be conducted to assess and establish a guideline recommendation in terms of dosage, injection and reinjection protocol.

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