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Botulinum toxin therapy for non-neurogenic overactive bladder: first experience

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The paper presents early experience in the treatment of 20 patients with botulinum toxin injections into the detrusor muscle for the treatment of non-neurogenic overactive bladder (OAB) resistant to anticholinergic drugs.

Background. Botulinum toxin, a presynaptic neuromuscular blocking agent, reduces the involuntary bladder contractions that cause urgency, frequency and urge incontinence. We present our early experience with Dysport® injections into the detrusor for the treatment of non–neurogenic overactive bladder (OAB) resistant to anticholinergic drugs.

Materials and methods. Using intravenous anaesthesia, 20 patients (18 female and 2 male) with non-neurogenic OAB were injected with botulinum toxin A (Dysport®250 IU diluted in 4 ml normal saline) under cystoscopic visualization in 20 sites in the detrusor muscle, sparing the trigone. The urethral catheter was removed 24 hours after the procedure. Follow-up at 3 and 6 months after the injection included the Urogenital Distress Inventory UDI-6, the Incontinence Impact Questionnaire IIQ-7, clinical parameters and ultrasound measurement of bladder capacity and post-void residual urine volume.

Results. All 20 patients completed questionnaires and were examined after 3 and 6 months.

At the 3-month follow-up, the median daytime micturation frequency decreased from 10.4 to 4.6 times ($p < 0.0001$) and at the 6 months follow-up 5 times ($p < 0.0001$), while nocturia decreased from 4.2 to 1.3 times after 3 months ($p < 0.0001$) and after 6 months to 2 times ($p < 0.0001$). Urgency decreased from 6 to 1.5 times after 3 months ($p < 0.0001$) and to 2 times after 6 months ($p < 0.0001$), and incontinence decreased from 4.2 times to 1.5 times after 3 months ($p < 0.0001$) and to 2.1 times after 6 months ($p < 0.0001$). The median maximum bladder capacity increased from 250 to 420 ml after 3 months ($p < 0.0001$) and decreased to 350 ml after 6 months ($p < 0.0001$). The post-void median residual urine volume was 10 ml. Only one patient mentioned a post-operative obstructive voiding difficulty.

Eighteen (90%) patients were satisfied with the treatment. In two patients (10%), the amelioration of symptoms lasted for one month only, and later OAB symptoms reappeared.

Analysis of the UDI-6 and IIQ-7 questionnaires revealed that botulinum toxin A intradetrusor injection had decreased discomfort for patients and ameliorated their quality of life.

Conclusions. Botulinum toxin A injections in the detrusor are effective for the treatment of non-neurogenic OAB. Botulinum toxin A injections are a minimally invasive therapy and offer an alternative treatment for non–neurogenic OAB dysfunction resistant to conservative treatment. The durability of the treatment effect is the objective of the further investigation.

Key words: botulinum toxin, overactive bladder, urinary incontinence

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INTRODUCTION

According to the International Continence Society, overactive bladder is a clinical syndrome characterised by the urgency of urination with or without incontinence during urgent urination, related to pollakiuria and nycturia.

It is estimated that 19 % of the population have an overactive bladder. This disease is more common among females than among males; elderly people have the disease more frequently. Five EU Member States spend around EUR 4.2 billion per year on treating this disease (1–4).

The pathology affects the quality of life: it restricts physical and social activities, disrupts work and rest, affects sexual activity. The reasons for overactive bladder can be neurogenic and non-neurogenic. It is very important to exclude infectious cystitis in the determination of this pathology.

The neurogenic overactive bladder is found in post-traumatic paratetraplegia or multiple sclerosis. A damage to the brain stem and the spine in cases of neurologic diseases causes a defective absence of relaxation of the sphincter of the bladder or increased contractions of the sphincter with the contraction of the detrusor. The disorder of the vesicosphincter coordination results in a functional obstruction to the flow of urine, preventing a full voiding of the bladder (dysuria, residual urine, vesicorenal refluxes) and causing urinary infections and damage to the kidney (2, 5–11). The neurogenic overactive bladder is treated with anticholinergic drugs or, in the case of ineffectiveness of the latter, with botulin toxin injections (12). In case of urinary retention, autocatheterisation, neuromodulation, or bladder augmentation surgery are applied (2, 13).

The causes of non-neurogenic overactive bladder can be urological (obstruction – hyperplasia of the prostate, narrowing of the urethra, post-operative condition, urinary infections (cystitis, urethritis, TBC), tumours, foreign bodies, gynaecological (climacteric cystopathy, prolapse, cystocele, tumours), iatrogenic (taking of alpha- or beta-blockers), ideopathic (where the cause cannot be established) or psychogenic. The causes can also be surgical (chronic appendicitis, sigmoiditis, diverticula) or therapeutic (diabetes mellitus, gastric or intestinal disorders).

According to the International Continence Society and the European Association of Urology (EAU) 2011 guidelines anticholinergic medications, intravesical injections, physiotherapy and surgery are applied in the treatment of non-neurogenic overactive bladder. Neuromodulation or, where there are indications, enterocystoplasty can be also applied (1–4, 6, 7, 11, 12).

However, these are invasive methods of treatment; therefore, they are not used frequently. Anticholinergic drugs improve the continence of urine but often have side effects (12, 13). Thus, in cases the treatment with drugs is not effective or there is intolerance to the drugs, a minimally invasive method – injections of botulinum toxin into the detrusor – is applied as an intermediate option between conservative and operative treatment (14–22).

Botulinum toxin is a neurotoxin released by the anaerobic bacteria *Clostridium botulinum*.

The first works on botulinum toxin date back to 1820. The bacterium was discovered by Van Emergen in 1895 (1, 2).

In 1988, Dyskra applied botulin toxin in urology by injecting it into the striated muscle of external urethral sphincter to treat the vesicosphincteral disorders. In 2000, Schurch injected botulinum toxin into the detrusor to treat the neurogenic overactive blader, while Rapp in 2003 did it to treat the non-neurogenic overactive blader (2, 23–31).

Botulinum toxin selectively blocks the relaxation of acetylcholine from the nerve terminations at the point where the nerves and muscles are linked, blocks the transmission of the nerve impulse to the fibres of the muscle and causes a paralysis of the muscle, lasting for 6 to 12 months. After that, new synapses with the fibres of the adjacent muscles appear, and new nerve–muscle links are formed. This procedure results in an increased storing capacity of the bladder, decreased urgency of urination, urination becomes less frequent, and urinary continence is improved (in case of injection into the detrusor). In case of injection into the sphincter, its becomes easier for the patient to urinate himself /herself or by the Valsalva method. The quality of life of the patients improves after the injections (2, 23, 24, 31, 32).

Botulinum toxin is administered upon diagnosing the overactive neurogenic or non-neurogenic bladder, which is characterised by pollakiuria and imperative urination where anticholinergic drugs, electrostimulation or other methods of treatment have proven to be ineffective (2, 23, 32).

According to the literature, botulinum toxin (DYSPORT®) doses for intravesical injections are as follows:

– for neurogenic OAB 500–1000 IU,

– for non-neurogenic OAB – 200–300 IU up to 500 IU (2, 3, 23, 31).

Botulinum toxin is administered by the following methods: intradetrusor injection (with botulinum toxin injected during cystoscopy, using a special needle to treat the overactive neurogenic or non-neurogenic bladder, or injection into the sphincter area (through a cystoscope with a special needle into the sphincter or through the perineum into the sphincter). If there are indications, the procedure may be repeated (2, 14, 17, 23, 28, 31).

MATERIALS AND METHODS

This work is based on the latest literature on the application of botulinum toxin in the treatment of urological diseases, including publications in PubMede®, urology magazines, multiple scientific studies, the 1st European Conference on the application of botulinum toxin (Thessaloniki, Greece,

2008), and observations on the practical application of botulinum toxin at the Rouen Urology Department in France in 2004 and 2008.

We have been applying this method of the overactive bladder treatment since 27 July 2005 when we performed the first endovesical injection of botulinum toxin.

Botulinum toxin A (DYSPORT®) was injected into patients diagnosed with the overactive non-neurogenic bladder. The patients complained of very frequent and urgent urination with or without urgent incontinence.

All these patients had been treated previously for 3 months with anticholinergic drugs, and the treatment was discontinued due to lack of effect or the presence of side effects of the drugs (such as mouth dryness, constipation, vision disorders).

Prior to the botulinum toxin treatment, the patients must undergo a full examination: visual examination, urine test, biochemical blood test, prostate examination *per rectum*, echoscopy (kidneys, bladder, residual urine). In case of indications, we also performed intravenous urograms, cystoscopy, neurologic examination, surgical or gynaecological examination.

Upon completing the examination, 20 patients (18 female and 2 male) received botulinum toxin A (DYSPORT®) injections. The average patient age was 40.3 and the disease history 5 years. Upon injecting sol. Cefuroximi 1.5 g for preventive purposes, using intravenous anaesthesia, through the working channel of the rigid cystoscope, under cystoscopic visualization, upon filling the bladder with 100 ml sol. Natrii chloridi 0.9%, 250 IU DYSPORT® diluted with 4 ml of normal saline was injected with a Williams Cook 23G 35 cm 5 Fr needle into 20 sites of the detrusor (Fig. 1). No complications were observed during the injections.

The catheter was removed 24 hours following the procedure.

The patients filled in the questionnaires (Urogenital Distress Inventory UDI-6 and Incontinence Impact Questionnaire IIQ-7) which have a validated translation into the Lithuanian language (33).

The clinical parameters were assessed, the capacity of the bladder and the residual urine were determined by ultrasound examination.

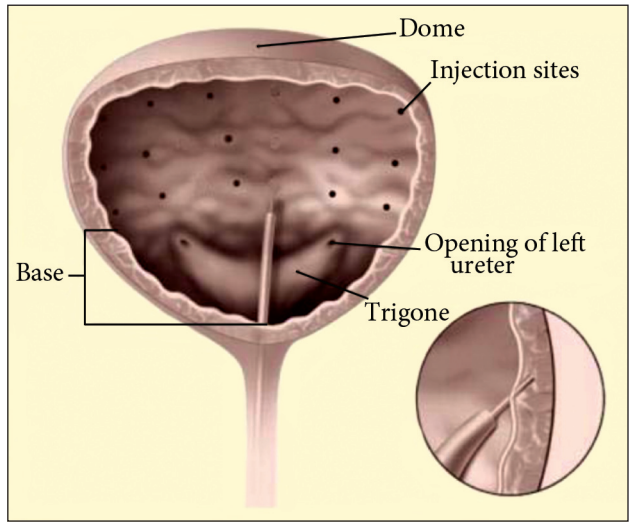

Fig. 1. Distribution of injection sites 12.5 UI BTX-A / site in the face of the bladder: posterior, superior, lateral

RESULTS

A follow-up of the patients was performed 3 and 6 months following botulinum toxin A (DYSPORT®) injections.

Twenty patients filled up the questionnaires (UDI-6 and IIQ-7) and were examined after 3 and 6 months.

In the patients examined, the urination frequency decreased from 10.4 to 4.6 times in the daytime after 3 months ($p < 0.0001$) and to 5 times after 6 months ($p < 0.0001$). Nocturia decreased from 4.2 to 1.3 times after 3 months ($p < 0.0001$) and to 2 times after 6 months ($p < 0.0001$) (Table 1).

The urination urgency decreased (Table 2): from 6 to 1.5 times after 3 months ($p < 0.0001$) and to 2 times after 6 months ($p < 0.0001$). There was also a decrease in the urinary incontinence episodes (Table 2): from 4.2 to 1.5 times after 3 months ($p < 0.00001$) and to 2.1 times after 6 months ($p < 0.0001$).

The median maximum bladder capacity increased from 250 to 420 ml (Fig. 2) after 3 months ($p < 0.0001$) and decreased to 350 ml after 3 months ($p < 0.0001$). The median residual urine was 10 ml; one patient noted that the urination had become more difficult after the injections.

Table 1. **Changes in clinical parameters before and after BTX-A injections**

Clinical parameters	Preoperative	3 months postoperative	P value	6 months postoperative	P value
Daytime frequency, n	10.4 ± 1.2	4.6 ± 0.6	<0.0001	5 ± 0.4	<0.0001
Nocturia, n	4.2 ± 0.7	1.3 ± 0.1	<0.0001	2 ± 0.2	<0.0001

Table 2. **Changes of urgency and incontinence before and after BTX-A injections**

Clinical parameters	Preoperative	3 months postoperative	P value	6 months postoperative	P value
Urgency, n	6 ± 0.5	1.5 ± 0.1	<0.0001	2 ± 0.3	<0.0001
Urinary incontinence, n	4.2 ± 0.7	1.5 ± 0.1	<0.0001	2.1 ± 0.6	<0.0001

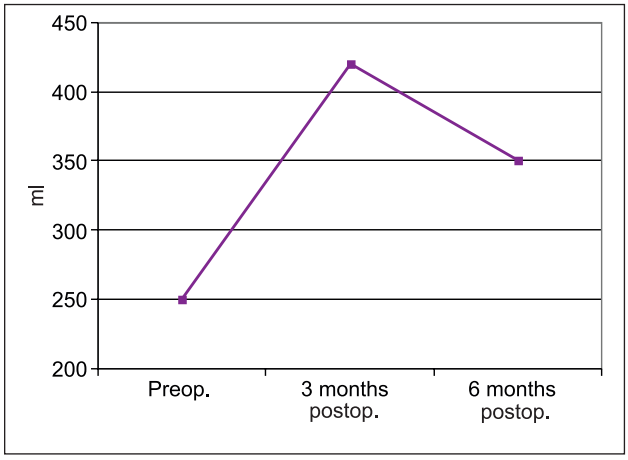

Fig. 2. Changes of bladder capacity after DYSPORT® injections

Eighteen patients (90%) were satisfied with the botulinum toxin treatment. In two patients (10%), the improvement lasted only one month, after which the symptoms of overactive bladder reappeared.

To evaluate the quality of life (Table 3), the patients filled in the IIQ-7 and UDI-6 questionnaires. After 3 and 6 months, the symptom scores of the questionnaires decreased: IIQ-7 – from 14.8 before injections to 10.2 after 3 months ($p < 0.0001$) and to 12 after 6 months ($p < 0.0001$); UDI-6 – from 10.0 before injections to 8.1 after 3 months ($p < 0.0001$) and to 8.5 after 6 months ($p < 0.0001$). This shows that the improvement in the indicators such as urination frequency, urgency, nycturia and urinary incontinence resulted in the improvement of the quality of life.

DISCUSSION

Overactive bladder presents a significant problem. The diagnostics of this disease is characterised by the fact that, upon diagnosing the non-neurologic overactive bladder, the urodynamic tests do not show hyperactivity of the detrusor in 30 to 60% of cases (2, 23, 32).

Treatment with anticholinergic drugs is administered in order to reduce bladder contractions of and to improve urine continence. According to the literature, however, this treatment results in only a 50% improvement of the continence. Furthermore, anticholinergic drugs have side effects such as mouth dryness, constipation, vision and sleep disorders, and the patients experiencing such side effects discontinue the treatment (2, 12, 15). The other methods of treatment, such as neuromodulation and surgery, are invasive and more traumatic. This encourages a search for new and minimally invasive treatment methods. Botulinum toxin is an alternative to the treatment with drugs and surgery. This has been confirmed by many authors (2, 23, 32).

According to the literature, the lethal intramuscular dose of Dysport is 6700–9000 units, the maximum dose per injection being 1000 units. Tissue fibrosis, contractions, denervation are described as the outcomes of multiple injections. No cases of anaphylaxis or shock are described in the literature. Muscular weakness and fatigue are sometimes mentioned. In individual cases, haematoma, infections, high blood pressure are noted (2, 5, 15). According to the literature, intradetrusor injections of botulinum toxin sometimes result in urination difficulty, residual urine or containment of urine; however, these are recurrent complications (11, 26, 28, 32). Botulinum toxin may not be administered in case of coagulation disorders, myasthenia, breast-feeding, pregnancy and lateral amyotrophic sclerosis. It is not recommended to be administered together with aminosides, curare, aminoquinolones and cyclosporines (2, 23, 30).

The efficiency of the overactive bladder treatment with botulinum toxin injections is assessed according to the following criteria (2, 23, 32–39):

♦ whether the residual urine quantity has been reduced, pollakiuria has weakened, hyperreflection has decreased and the parameters of urodynamic tests have improved;

♦ whether the patient's quality of life has improved.

The literature presents data on different studies of treatment with botulinum toxin (2, 7, 10, 23, 32, 40–48). Good treatment results are reported in:

• 11 papers – from 60 to 100% goods results in patients who have been treated with botulinum toxin for overactive non-neurogenic bladder;

• 12 papers – from 66 to 80% goods results in patients who have been treated with botulinum toxin for overactive neurogenic bladder.

Our results of treatment with botulinum toxin are similar to those presented in the literature: after injecting botulinum toxin A, the frequency of urination and nocturia have decreased, the urgency of urination has been reduced, urine continence has improved, the bladder capacity has increased, and the patients' quality of life has improved. In our opinion, despite the good effect of botulinum toxin, there are limitations of this treatment modality: the effect is limited to 6–12 months, and the high costs are not reimbursed by health insurance.

Table 3. **Responses to the IIQ-7 and UDI-6 questions before and after BTX-A injections**

Questionnaire	Preoperative	3 months postoperative	P value	6 months postoperative	P value
IIQ-7	14.8	10.2 (–4.6)	<0.0001	12.0 (–2.8)	<0.0001
UDI-6	10.0	8.1 (–1.9)	<0.0001	8.5 (–1.5)	<0.0001

In case of reappearance of the overactive bladder symptoms after botulinum toxin injections, the treatment can be repeated. The literature recommends maximum seven injections into the bladder (2, 23, 31).

Discussions are still going on concerning the optimal doses of intradetrusor injections and the bladder areas that are best for injections.

However, all authors agree that in the overactive bladder diagnosis, botulinum toxin injections into the detrusor result in an increased capacity of the bladder, reduction of urination frequency, improved results of urodynamic tests and a better quality of life of the patients. The conclusions were confirmed also by the questionnaires filled up by the patients. Our first results of treatment are also in line with these conclusions.

Endovesical injections of botulinum toxin are a minimally invasive method of treatment and an alternative to conventional surgery.

Therefore, one may conclude that in the future both investigators and practitioners should expand the studies and practical application of botulinum toxin (23, 49–54).

CONCLUSIONS

1. Injections of botulinum toxin A (Dysport®) into the detrusor is an effective method of treatment of overactive non-neurogenic bladder when the treatment with anticholinergic drugs is ineffective.

2. Botulinum toxin-A injections are a minimally invasive, easy to perform method of treatment.

3. After injecting botulinum toxin A, the frequency of urination and nocturia decrease, the urgency of urination reduces, the urine continence improves, the bladder capacity increases, and the patients' quality of life also improves.

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PIRMIEJI HIPERAKTYVIOS NE NEUROGENINĖS ŠLAPIMO PŪSLĖS GYDYMO BOTULINO TOKSINO INJEKCIJOMIS REZULTATAI

Santrauka

Tikslas. Botulino toksinas – presinaptinis nervų ir raumenų jungtį blokuojantis preparatas, mažinantis nevalingus šlapimo pūslės susitraukimus, kurie sukelia skubų norą šlapintis, dažną šlapinimąsi ir šlapimo nelaikymą skubaus šlapinimosi metu. Straipsnyje pateikiami pirmieji Dysport® injekcijų į šlapimo pūslės raumenį rezultatai gydant ne neurogeninę hiperaktyvią šlapimo pūslę, kai gydymo efektas nepasiekiamas anticholinerginiais vaistais.

Medžiagos ir metodai. Taikant intraveninę nejautrą**,** 20 % (18 moterų ir 2 vyrams), kuriems diagnozuota ne neurogeninė hiperaktyvi šlapimo pūslė, atliktos botulino toksino A injekcijos (Dysport® 250 TV, praskiesta 4 ml fiziologinio tirpalo) į 20 detrusoriaus vietų, išskyrus trigonumo sritį; vaizdo kontrolė atlikta pro kieto cistoskopo darbinį kanalą. Kateteris ištrauktas praėjus 24 val. po procedūros. Pacientai patikrinti praėjus 3 ir 6 mėn. po injekcijų: užpildė klausimynus „Urogenital Distress Inventory" (UDI-6) ir „Incontinence Impact Questionnaire" (IIQ-7), taip pat buvo įvertinti klinikiniai jų parametrai, echoskopu nustatyta šlapimo pūslės talpa ir likutinis šlapimas.

Rezultatai. Šlapinimosi dažnis dienos metu sumažėjo nuo 10,4 iki 4,6 kartų po 3 mėn. ($p < 0,0001$) ir iki 5 kartų po 6 mėn. ($p < 0,0001$), nikturija sumažėjo nuo 4,2 iki 1,3 karto po 3 mėn. ($p < 0,0001$) ir iki 2 kartų po 6 mėn. ($p < 0,0001$). Šlapinimosi skubumas sumažėjo nuo 6 iki 1,5 karto po 3 mėn. ($p < 0,0001$) ir 2 kartų po 6 mėn. ($p < 0,0001$). Šlapimo nelaikymas sumažėjo nuo 4,2 iki 1,5 karto po 3 mėn. ($p < 0,0001$) ir 2,1 karto po 6 mėn. ($p < 0,0001$). Vidutinė maksimali šlapimo pūslės talpa padidėjo nuo 250 iki 420 ml po 3 mėn. ($p < 0,0001$) ir sumažėjo iki 350 ml po 6 mėn. ($p < 0,0001$). Likutinis šlapimo vidurkis – 10 ml. Tik vienas pacientas nurodė, kad po injekcijų šlapinimasis pasunkėjo.

18 pacientų (90 %) buvo patenkinti gydymu, dviem (10 %) pacientams pagerėjimas truko tik mėnesį, vėliau vėl atsirado hiperaktyvios šlapimo pūslės simptomai.

Užpildytų UDI-6 ir IIQ-7 klausimynų analizė rodo, kad botulino toksino A injekcijos į šlapimo pūslės raumenį sumažino diskomfortą ir pagerino pacientų gyvenimo kokybę.

Išvados. Botulino toksino A injekcijos į šlapimo pūslės raumenį yra efektyvus hiperaktyvios ne neurogeninės šlapimo pūslės gydymo būdas. Ši minimalios invazijos procedūra gali būti alternatyva ne neurogeninės hiperaktyvios šlapimo pūslės disfunkcijos gydymui, kai konservatyvus gydymas neveiksmingas. Gydymo rezultatų ilgalaikiškumas lieka tolesnių tyrimų objektu.

Raktažodžiai: botulino toksinas, hiperaktyvi šlapimo pūslė, šlapimo nelaikymas