 doi:10.20944/preprints201807.0424.v1

Endoscopic Botulinum toxin-A injections are equally efficient in the treatment of neurogenic bladder dysfunctions in children in different age groups.
A single centre experience after more than 550 procedures.

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Summary: To evaluate the usefulness of cystoscopic injections of Botulinum-A toxin (BTX) in the detrusor wall in the treatment of children with decreased bladder capacity due to the neurogenic bladder.

A prospective, randomized non placebo controlled trial has been conducted in our institution since 2006 with the approval of the local Ethics Committee.

556 cystoscopic injections of BTX were performed in 141 children aged 1 to 18 with a neurogenic bladder.

In all cases decreased bladder capacity and bladder overactivity with urine incontinence were estimated.

The pre-and post-treatment evaluations included determination of the urinary continence status, the bladder function in a frequency/volume chart of catheterized urine and in urodynamic studies. Parameters measured in urodynamic investigations included the maximum cystometric capacity, the detrusor reflex volume, the maximum detrusor pressure.

Parameters were analyzed before the cystoscopy and during follow-up examinations.

 doi:10.20944/preprints201807.0424.v1

Values of all measured parameters improved significantly and equally after the therapy in every of the 5 age groups.

The results obtained from the study confirmed that endoscopic administration of BTX improves the function of the urinary bladder in children with a neurogenic bladder, and the method represents an alternative approach to the conservative treatment and surgical augmentation.

Key words: neurogenic bladder, botulinum toxin, bladder overactivity, urodynamics, child

1. Introduction

The proper function of the lower urinary tract consists of two phases: the storage and voiding phase. It means periodic and planned urination by a patient in volumes appropriate for the patient's age while preserving continence between urinations.

Overactive bladder (OAB) is defined by the International Continence Society as a syndrome characterized by urinary urgency and frequency with or without urinary incontinence in the absence of a urinary tract infection. OAB symptoms are often associated with detrusor overactivity (DO). [1]

OAB could be caused by neurogenic problems, or have an idiopathic origin.

Both in neurogenic and idiopathic patients OAB leads to two principal problems: decreased functional bladder capacity and increased intravesical pressure.

OAB may be associated with additional symptoms such as urgency, frequency, nocturia, day time urine incontinence (UI) or nocturnal enuresis.

If OAB is associated with high intravesical pressure during the storage or voiding phase, additional urological complications may develop, such as recurrent urinary tract infections or secondary anatomic malformations in the urinary tract (diverticula of the bladder wall, megaureter, hydronephrosis, vesico-ureteric reflux or stone formation). [1-4]

Abnormal function of the lower urinary tract may be caused by congenital malformations of spine or acquired diseases of the nervous system, in such cases the term of neurogenic detrusor overactivity (NDO) is used.

Idiopathic or non-neurogenic detrusor overactivity (IDO) is recognized if no neurological cause or the defect in the nervous system was detected. [5-7]

In children NDO develops most frequently due to dysraphic malformations of the spinal cord and results in significant decrease or lack in the sensation of the bladder and sensation of the

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urethra.

Therefore, a patient loses control over the function of his/her lower urinary tract which manifests itself on the one hand by his/her inability to void urine effectively in a single large portion and on the other hand by urinary incontinence.

In patients with a severe neurogenic bladder and sphincters dysfunctions the treatment is based on clean intermittent catheterization (CIC) and pharmacological correction of high intravesical pressure caused by DO. The golden standard of pharmacotherapy of the NDO is the oral therapy with anti-cholinergic drugs. Unfortunately the anticholinergic therapy is introduced as off-label in younger children. [6, 7-12].

Nevertheless in some children, such an approach fails to increase bladder volume and decrease detrusor pressure, some patients complain about troublesome side effects. In such children low bladder capacity and urinary incontinence persists.

In cases when the conservative approach gives no improvement, or complications develop in spite of the proper conservative treatment, complicated surgical procedures are suggested to the patients and their parents aimed at the surgical reconstruction of the urinary system.

At present, bladder augmentation represents the most effective way of surgical correction of the urinary bladder's functional parameters, leading to its increased capacity and decreased intravesical pressure. [12-15]

In younger children the operative cystostomy provides an effective way to decrease intravesical pressures. [16, 17]

In the last years some reports have been published on the favourable results of Botulinum-A toxin (BTX) administration in patients with a low capacity, high pressure neurogenic bladder.

Most of the reports pertained to the treatment of adult patients, some of them reported good results also in children. [18-21]

We describe our own experience with endoscopic administration of BTX in children with bladder dysfunctions.

The aim of the study

To evaluate the usefulness of the cystoscopic injection of BTX in the detrusor wall in the treatment of children with decreased bladder capacity due to NDO.

2. Material and methods

The prospective, randomized, non-placebo controlled study was initiated with the approval of

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the Local Ethics Committee in 2006 (protocol number: 1222/06).

This trial was conducted in the Paediatric Surgery and Urology Department of the University of Medical Sciences and St. Joseph Hospital in Poznań.

The inclusion criteria were: decreased bladder capacity and urine incontinece, lack of improvement on conservative treatment or side effects of the oral anticholinergic therapy, no previous surgery affecting the function of the bladder.

Children after surgical bladder augmentation, bladder neck surgery or malignancy of the bladder were not included in the study.

Study population

Cystoscopic procedures were performed in 153 children with NDO, in 141 children post-operative course was documented and they were included in this study.

In all but 1 child the procedure was performed successfully. In a 5 year old boy we found stricture in the posterior urethra, after the incision of the stricture we decided not to inject BTX in the bladder wall and he was not included in the study.

The group consisted of 80 girls, and 61 boys.

556 cystoscopic procedures were performed.

In 114 children open myelomeningocele, in 12 occult spinal dysraphism, in 7 sacral agenesis, in 5 cerebral palsy, in 2 transverse myelitis, in 1 child spine injury was the cause of NBO.

Children under the study were aged 1 to 18 years; the median age of the patients was 6 years (Q25-Q75= 3-10).

Due to the large age range, children were divided as follows: 1-3 years, n=37; 4-6 years, n=35; 7-9 years, n=32; 10-12 years, n=18, 13-18 years, n=19.

The median body weight was 24 kg (5-82 kg, Q25-Q75= 15-37). The data according to age groups is given in Table 1.

Table 1 provides the number of children, who were administered doses of the toxin depending on their body weight. The next column provides the due bladder capacity calculated according the the formula in relation to age.

Table1. Characteristics of the study group

Age	Body mass	Age in years	Expected age-related bladder

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groups	median (Q25-Q75)		capacity
1-3, n=37	12 (10-15)	1 2 3	60 90 120
4-6, n=35	19 (15-28)	4 5 6	150 180 210
7-9, n=32	30 (22-36)	7 8 9	240 270 300
10-12, n=18	39 (32-45)	10 11 12	330 350 350
13-18, n=19	52 (44-60)	13 14 15 16 17 18	350 350 400 450 450 500

In all children participating in the study: decreased functional bladder capacity was estimated in Bladder Diaries (BD) and in urodynamic investigations (UD).

Data for BD were collected for at least 3 consecutive days.

UD were performed in a routine manner according to recommendations of ICCS using a double lumen catheter for measuring intravesical pressure and infusion, a rectal tube for intraabdominal pressure, 0,9% NaCl saline in room temperature and infusion with the filling rate of 5-10% of the expected age-related bladder capacity (EBC).

Infusion during cystometry was conducted until one of the three situations occurred: urine leakage from the urethra (leak point), exceeding pressure of 40cm H2O or complains about urgency or bladder pain.

Detrusor reflex volume (DRV), volume at which the first detrusor contraction occurred and maximal bladder capacity (MCC) were noted.

EBC was calculated according to the Hjälmås formula: Bladder volume (ml) = 30 x age

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(years) + 30.

Decreased bladder capacity (< 65% of EBC) was the most important including criterion.

In all children with decreased bladder capacity due to NDO the initial conservative treatment was started with oral anticholinergics: oxybutynin at a maximum dosage of 0,4 mg/kg or solifenacin at a maximum dosage of 0,2 mg/kg.

Children with no improvement following the conservative management were qualified for the procedure of endoscopic injections of BTX.

Cystoscopy:

In the majority of cases cystoscopic procedures (CS) were performed without any anaesthesia, as the majority of children with neurogenic bladder dysfunction have no sensation of the lower urinary tract.

If during the endoscopic procedure a child was unsettled or stated any pain, anaesthetics or sedatives (methamizol or pethidine with midazolam) were administrated intravenously.

In children with the preserved bladder and urethra sensation CS were performed in general anaesthesia.

Rigid cystoscopes with an operative channel were used.

The diameter of the instrument was adjusted to the age of a patient and size of the urethra.

The size and shape of the urethra, the pattern of the bladder wall and morphology of ureteric orifices were evaluated during CS.

The bladder was partially filled with 0.9% NaCl solution.

A rigid needle was introduced through the operative channel.

The dose of BTX was calculated for every patient, and diluted in 10 ml 0.9% NaCl.

According to the protocol we used a dose of, respectively 10-30 units/kg body weight of abobotulinum (Dysport) or 2,5-10 units/kg body weight of onabotulinum (Botox), not exceeding the maximum dosage of 500 units of abobotulinum and 100 units of onabotulinum for a patient.

Twenty consecutive sites of the bladder dome were injected each with 0.5 ml of the solution, taking care not to inject the preparation into regions of ureteric orifices.

Following the procedure urine was evacuated from the bladder by catheterization.

After the procedure, the catheter was removed from the bladder.

It was recommended to discontinue administration of oral anticholinergic drugs after the procedure and to continue antimicrobial prophylaxis and CIC if needed.

Subsequently, patients were followed-up. They were monitored by telephone interviews and follow-up visits at the office.

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Follow-up included urinalysis, clinical and ultrasonographic examination, UD performed: first 1- 6 weeks after the injection. UD tests were also performed 4-9 and 10-14 months after the endoscopic procedure.

Changes in the bladder volume, detrusor overactivity and pressure were estimated in cystometric evaluations.

Parameters measured in UD included MCC, DRV and maximum detrusor pressure.

Changes in the volume of catheterized urine were estimated in BD.

The following parameters from BD were analysed: maximum catheterized volume (CICmax), average volume of catheterized urine (CICav).

In the group of catheterized children with lack of bladder and urethra sensation observed preoperatively (in UD evaluation and during CIC), 12 patients required analgesia and sedation at the time of the procedure because children were unquiet or stated the pain sensation during injection.

No serious adverse events were observed after the procedure.

Statistical methods

The qualitative and quantitative analyses were carried out using the Statistica 10.0 package of statistical programs (StatSoft, Inc. 2007 Statistica for Windows). The descriptive statistics were shown as medians and quartiles. Statistical analyses were performed using nonparametric tests: the chi2 test to estimate the number of children in the compared groups, U Mann-Whitney test or Kruskal-Wallis ANOVA to investigate the differences between two or many groups. The p-value of less than 0.05 was considered statistically significant.

3. Results

The post-procedure course was documented in 141 patients by the data of daily BD and by UD tests.

In 112/141 children increase in the bladder volume was observed with the improvement in the continence.

The effect of improvement was observed for 3 to 14 months, the mean time of improvement was 8,3 months.

In a single girl her continence deteriorated following the procedure. Volumes of catheterized urine decreased, UD one month after BTX injection disclosed a weakened function of sphincters, expressed by the decreased leak point volume and decreased leak point pressure.

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In 12 children with no signs of bladder sensation before BTX injection, this sensation occured in the post-treatment period.

The descriptive statistics (median, quartiles, minimum and maximum) of the analysed urodynamic parameters at baseline and after Botulinum-A toxin treatment were presented in Table 2.

The differences of the investigated parameters were analysed.

When children were divided according to sex, no significant differences were observed in the number of children who did or did not show improvement, as calculated with the chi2 test(CICmax- females improvement/no improvement 65/15, males 47/14, no significant difference; CICav- females 62/18, males 47/14, no significant difference; DRV - females 57/23, males 37/24, no significant difference; MCC- females 62/18, males 40/21, no significant difference).

Next, children were divided according to age groups and the exact data are given in Table 2.

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Table 2.

Parameter/age group	CICmax; improvement YES/NO	CICav; improvement YES/NO	DRV; improvement YES/NO	MCC; improvement YES/NO
1-3, n=37	33/4	30/7	28/9	28/9
4-6, n=35	31/4	30/5	27/8	28/7
7-9, n=32	26/6	26/6	19/13	20/12
10-12, n=18	11/7	11/7	12/6	13/5
13-18, n=19	11/8	12/7	8/11	13/6
Chi2 test	13.10; p=0.011	6.85; p=0.014	9.00; p=0.06	2.93; p=0.57

The next step in the data analysis was to calculate the percentage of the analyzed volume growth after treatment in proportion to volumes at baseline (Table 3).

The analysis compared the difference between due and real volume before and after the procedure. The difference between real and due volume was calculated before and after the procedure, and the two values were next substracted. The way of calculation is shown on Figure 1. The decrease of the difference was regarded as improvement. Exact data is given in the Table 3.

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Figure 1. The way of expressing the results of volumetric investigation before and after treatment with toxin

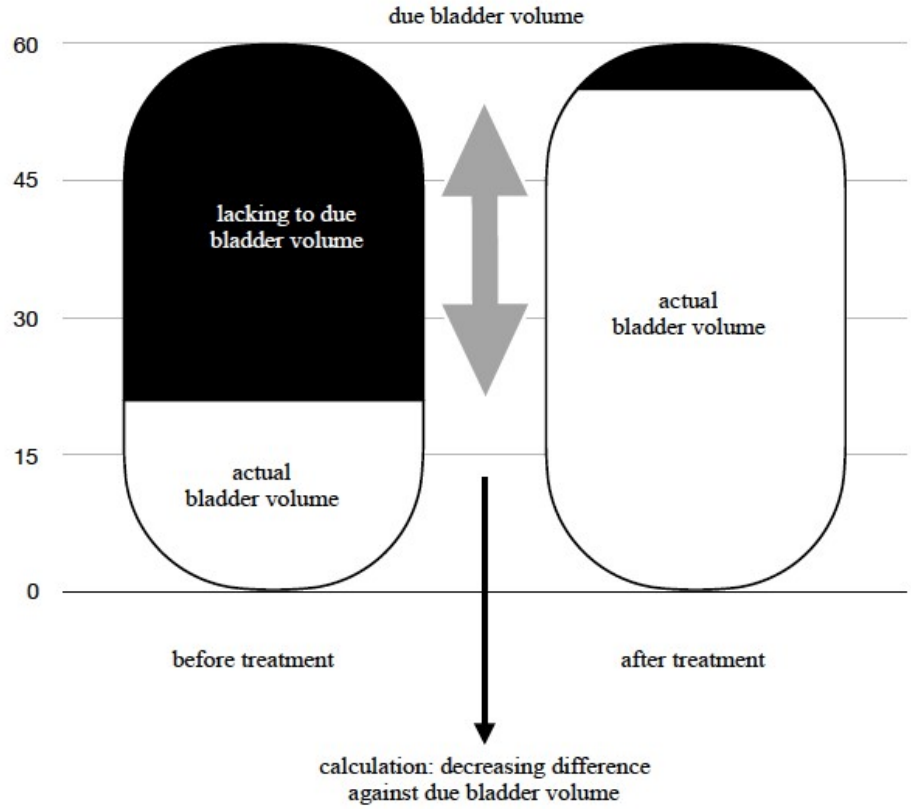

Table 3. The difference of differences between due and real volume, before and after the procedure

Parameter/ age group	CIC max; Me (Q25-Q75)	CIC av; Me (Q25-Q75)	DRV; Me (Q25-Q75)	MCC; Me (Q25-Q75)
Whole group, n=141	70 (10-120)	50 (10-90)	25 (0-69)	46 (0-92)
1-3, n=37	70 (30-90)	30 (20-50)	29 (1-59)	56 (3-71)
4-6, n=35	100 (50-130)	70 (30-100)	31 (7-71)	55 (2-113)
7-9, n=32	85 (15-160)	60 (10-65)	24 (0-70)	30 (0-77)
10-12, n=18	85 (0-150)	65 (0-100)	38 (0-80)	42 (0-108)
13-18, n=19	30 (0-70)	20 (0-90)	0 (-9 – 21)	10 (0-83)
Kruskal-Wallis ANOVA	10.68; p=0.030 between 4-6 and	NS	NS	NS

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	13-18, p=0.023			

Differences between the due bladder volume and the investigated parameters, broken down by the type of toxin adjusted for the body weight, are given in Table 4. There was no difference in the improvement achieved due to the toxin (botox - dysport), neither for the whole group nor by age subgroups.

Table 4. Differences between the due bladder volume and the investigated parameters; broken down by the type of toxin adjusted for the body weight

Variable	onabotulinum (Botox) Median (Q25-Q75)	abobotulinum (Dysport) Median (Q25-Q75)	U Mann- Whitney test
The difference between due bladder volume and CIC max	70 (20-120)	70 (10-130)	NS
The difference between due bladder volume and CIC av	50 (10-80)	50 (10-90)	NS
The difference between due bladder volume and UD max	61 (0-80)	34 (0-104)	NS
The difference between due bladder volume and IDC	39 (0-72)	21 (0-66)	NS

4. Discussion

Conservative management with clean intermittent bladder catheterization (CIC) and oral anticholinergic pharmacotherapy represents the golden standard in the treatment of children with overactive neurogenic bladder. [6,7, 12, 13]

CIC is a treatment of choice in children with neurogenic bladder and lack of urethra sensation if voiding is ineffective. [22, 23]

Decreased bladder capacity related to DO and decreased bladder walls compliance are caused by overexpresion of the cholinergic part of the autonomic nervous system.

Cholinergic M_3 receptors are located in high numbers in walls of the dome of the urinary bladder – the detrusor muscle. This part of the bladder controls storage of urine and at the voiding phase it contracts participating in urine evacuation. [24]

Decreased bladder capacity related to DO and low bladder walls compliance are managed

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conservatively with oral anticholinergics. Conservative treatment prevents complications in the majority of patients. Anticholinergic drugs decrease detrusor muscle contractility leading to decrease of intravesical pressures and increase of functional bladder capacity expressed by elevated volumes of catheterized urine and extended period of dryness between catheterizations. [7, 9, 10, 12, 13]

Oxybutinin (Ditropan, Driptane), solifenacin (Vesicare), tolterodin (Detrusitol, Uroflow), triospiumchloride (Spasmex, Regurin), propiweryn (Detrunorm, Mictonorm), darifenacin (Emselex) or the latest on the market betmigron (Betmiga) were described to be effective both in increasing bladder volume with subsequent decreasing intravesical pressure and improvement in urine continence. Unfortunately, only oxybutynin is the only anticholinergic drug approved for use in children, despite its frequent and troublesome side effects.

According to data from many studies, in significant percentage of patients treated with anticholinergics some side effects occur, even when administrated intravesicaly. [7-10, 19,25]

It is of special importance in children who are treated off-label.

The problem involves also children in whom conservative treatment with oral anticholinergics brings no expected results.

In cases of no improvement of the oral therapy or when complications develop operative treatment of surgical bladder augmentation or diversion can be considered. [13-17]

Intradetrusor, endoscopic administration of BTX represents an alternative to operative treatment.

The toxin penetrates the cell membrane and temporarily blocks the pre-synaptic release of acetylcholine from the parasympathetic efferent innervations producing a paralysis of the detrusor smooth muscle, but also through the inhibition of excitatory neurotransmitter release from bladder afferents and urothelial cells.

The suggested mechanism is multidirectional and involves acting on the fusion protein SNAP-25, synaptic protein VAMP, Substance P, muscular receptors M2 and M3 and other factors.

Action of BTX is reversible. [18-21, 24-27]

Children who have been qualified for BTX treatment demonstrated lack of improvement despite conservative treatment, having decreased bladder capacity (< 65% of EBC). The expected age-related bladder capacity can be calculated from many formulas, for our study we used Hjälmås formula which is also recommended by ICCS. Some rules were proposed for calculation of age-related bladder capacity in children. The ICCS proposed the one by Hjälmås. According to ICCS significantly decreased bladder capacity is recognized in a child

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voiding in volumes < 65 % of EBC. [28,29]

The lack of improvement was concluded also when DO, high detrusor pressures (>40 cm H_2O) and decreased bladder capacity were documented in urodynamic studies. The pressures above 40 cm H_2O were considered as elevated although some authors postulate maintenance of pressures below 20 cm H_2O in a neurogenic bladder. [2, 3, 6, 30]

In our study, the bladder capacity was estimated both in UD evaluations and BD. The frequency/volume chart or BD is the systematic registration of time and volume of voided or catheterized urine carried out by the patient or his/her caregivers in their own environment for a specified period of time, usually 2-3 consecutive days. [31, 32]

A decreased bladder capacity leads to urinary incontinence, understood as leakage of urine from the neurogenic bladder after less than two hours following catheterization in a patient drinking normal amounts of fluids, so BD can be supplemented with registration of fluid intake and incontinence episodes. Measurements obtained from BD include the total voided volume/24 hours, frequency of micturition, mean voided volume, largest single voided volume and the range of voided volumes. BD provides a reliable and, importantly, non-invasive estimate of the functional bladder capacity both in children with IBO and in children with NBO. However, it gives no information about the volume-specific pressure and DO, so it should be used supplementarily to UD testing. [31,32]

In cases of significant sensory defects in urethra and bladder documented by urodynamic tests children in our study were not given a general anaesthesia for the cystoscopy.

Nevertheless, in some catheterized patients we were forced to administer neuroleptoanalgetics during the procedure as the patients were unsettled or complained about pain in the lower abdomen during cystoscopic administration of the BTX.

During cystoscopy, 10ml of BTX solution were injected in 20 consecutive sites of the bladder dome as is reported for many authors, but some other reported also successful injections in the bladder trigone. [33]

Surprisingly for us, in 12 children with no signs of bladder sensation before BTX injection, this sensation occurs in the post-treatment period.

We suppose that the possible reason is cessation of oral anticholinergics, as both oxybutynin as solifenacin also have the anaesthetic effect on the bladder.

The potentially anaesthetic action of BTX could be discussed, but from our observations the BTX effect is predominantly paralytic.

Bladder capacity assessed in urination diaries and in urodynamic studies increased in all age groups.

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The pre-and post-treatment evaluations included determination of the urinary continence status, bladder function in the frequency/volume chart of catheterized urine and in UD studies. Like in other trials, parameters measured in urodynamics included DRV, MCC and MDP. [34]

Maintaining or increase in bladder capacity following administration of BTX and discontinuation of oral drugs was regarded as demonstrating the favourable effect.

In our study, repeated injections were also effective as reported by others. [35, 36]

Out of the numerous side effects of BTX injections described in literature in our group of patients we noted no serious adverse events. [37-42]

For several years, Botulinum toxin has been successfully used in neuromuscular diseases with excessive muscular tension. It used to be administrated to muscles of extremities in children with spastic forms of infantile cerebral palsy. It is used also in the treatment of torticollis, blepharospasm and in aesthetic surgery. In the literature, efficacy of BTX has been well documented in adults with either neurogenic or non-neurogenic dysfunctions of the urinary tract. [18, 21, 27, 33-41]

Reports on the efficacy of BTX in treatment of neurogenic urinary bladder in children have been far less frequent. [19, 43-45]

In urology, the Botulinum toxin has been used mainly to inject detrusor muscles in order to decrease intravesical pressure in the storage phase, but it has also been applied to sphincters to abolish detrusor-sphincters dyscoordination in the voiding phase. Efficacy of injections to the detrusor has been noted in 60-80% of patients. BTX injection is effective to treat detrusor-sphincter dyssynergia when injected either transurethral or transperineally. After treatment, external urethral sphincter pressure, voiding pressure and post-void residual volume decreased. The effect lasts between 2 to 12 months. [46]

BTX is available on the Polish market as two preparations, abobotulinum: Dysport and onabotulinum: Botox. They are not equivalent both in duration of action and effective dosage and, taken together, the findings retrieved from this literature research suggest a conversion ratio of 1:3 or 1:4 (Botox:Dysport). In BO in adults a dosage of BTX has been reported at 500 to 1500 units of abobotulinum or 100 to 300 units of onabotulinum.

So in our study, in children, respectively 10-30 units/kg body weight abobotulinum or 2,5-10 units /kg body weight of onabotulinum were used. [33-37, 40-50]

Estimating the optimal dosage both in children and adolescents is still discussed. Some authors show, both for abobotulinum or onabotulinum, no clear dose-related effect with the observation indicating that a dose greater than 50 U is significantly more effective for certain

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symptoms of OAB compared with placebo. [50]

In our study, like in others, a dose of the toxin was administered in divided doses into 20 sites of the bladder dome. The activity of BTX in the urinary bladder was described to persist for 6 to 9 months and even for above 12 months. This was confirmed by our observations with the longest period of improvement of 14 months. Afterwards, the procedure can be repeated. In our observations, repeated intradetrusor BTX injections were found to be also effective at their first application. [35,36,44, 50]

In our opinion endoscopic administration of the Botulinum toxin should be considered as an alternative method first in the following cases: lack of efficacy of conservative treatment, hypersensitivity to oral anticholinergic drugs or side effects resulting from their administration, lack of parental consent to surgical treatment (cystostomy, augmentation).

If it is considered to be an alternative to surgery, then the obvious limitation of this therapy is the transient effect of the endoscopic procedure, in our opinion it could also be an alternative to the oral anticholinergic therapy.

Recently, intradetrusor Botox injection was found to be a cost-effective therapy for the overactive bladder. [50]

Although many questions remain regarding the optimal use of this minimally invasive option for urologic applications, the opportunity for expanding indications will provide urologists with more options for addressing difficult challenges of the voiding dysfunction.

5. Conclusions

The results obtained from the study confirmed that:

1. Endoscopic administration of Botulinum-A toxin improves functional parameters of urinary bladder equally in different age groups of children with NDO.
2. The method may represent an alternative approach both to oral anticholinergic and to operative reduction of intravesical pressures.

Compliance with Ethical Standards:

The authors declare that there are no conflicts of interest.

Declaration of funding interests: nothing to declare.

Ethical approval: All procedures performed in studies involving human participants were performed in accordance with the ethical standards of the institutional and national research

 doi:10.20944/preprints201807.0424.v1

committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The agreement of Local Ethics Committee was obtained for this trial.

Informed consent was obtained from parents/caregivers of all individual participants included in the study.

This article does not contain any studies with animals performed by any of the authors.

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