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Review Article

The effect of botulinum toxin A in children with non-neurogenic therapy-refractory dysfunctional voiding – A systematic review

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Summary

Introduction
Dysfunctional voiding (DV) is a habitual voiding disorder caused by involuntary contraction or non-relaxation of the external urethral sphincter (EUS) during voiding. This contraction causes high post-void residuals (PVR), urinary incontinence and urinary tract infections (UTIs). Various treatments for DV are available, but some children do not respond. Intersphincteric botulinum toxin-A (BTX-A) may be a possible treatment for therapy-refractory children with DV.

Objective
The aim of this systematic review is to summarize the effects and safety of intersphincteric BTX-A as a treatment for therapy-refractory DV in children.

Methods
A systematic search in Embase, MEDLINE, Cochrane, and Web of Science databases was performed. Studies reporting on the usage of intersphincteric BTX-A as a treatment for DV in children were included. Data on PVR, maximum flow rate (Qmax), repeat injections and complications were extracted.

Results
From a total of 277 articles, five cohort studies were identified, reporting on 78 children with DV of whom 53 were female (68 %) and 25 were male (32 %). Sample sizes ranged from ten to twenty patients. Mean or median age at the time of intervention ranged from 8 to 10.5 years. Meta-analysis could not be performed due to lack of data. The narrative synthesis approach was therefore used to summarize the results. All studies showed significant decrease in PVR after BTX-A injection. Three studies showed a 33–69 % improvement on incontinence after BTX-A injection. Less UTIs were reported after treatment. A temporary increase in incontinence, UTIs and transitory numbness to the gluteus muscle were reported as side-effects.

Conclusions
BTX-A could be a safe and effective treatment option for therapy-refractory DV in children by reducing PVR, UTIs and incontinence. Hereby, the synergistic effect of BTX-A and urotherapy should be emphasized in future management. Furthermore, this study identified gaps in current knowledge that are of interest for future research.

Introduction

Dysfunctional voiding (DV) is a voiding disorder due to involuntary intermittent contraction or non-relaxation of the external urethral sphincter (EUS) during voiding [1]. The disorder can occur at any age. In young children it often presents as urinary incontinence, nocturnal enuresis, or recurrent urinary tract infections (UTIs) [2]. The micturition cycle process consists of the storage of urine and emptying the bladder. This process is controlled by the central nervous system, coordinating the sympathetic, parasympathetic and the somatic nervous system. The involuntary contraction of the EUS during voiding due to a brain, spinal cord or nerve issue is called detrusor sphincter dyssynergia [3]. However, this urodynamic term is only used for children with neurogenic bladder. Contrary to detrusor-sphincter-dyssynergia, dysfunctional voiding in children is characterized by the inability to relax the EUS during voiding without a demonstrable neurological disorder. The etiology of DV is not completely understood, but is likely to be multifactorial. Inappropriate toilet training might play a role in the development of DV, as well as pelvic pain, constipation or a sense of urgency. It is also believed that a midbrain

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maturation delay, and therefore a delay in the development of the pontine micturition center, might play a roll. This suggests that infantile voiding patterns persist [4]. Both theories are supported by the fact that DV is common in children with attention deficit disorder (ADHD), which is also associated with brain maturation delay and behavioral issues.

Biofeedback, a form of urotherapy, is a conservative treatment for DV to train patients to relax the urethral sphincter during voiding. Although this treatment has shown good results, some children do not respond [5]. Several new treatment options have been researched in treating DV, including hypnosis and anticholinergic medication to relax the bladder [6]. Intersphincteric botulinum toxin-A (BTX-A) may also be a possible treatment for DV. Clinical trials have shown that intravesical BTX-A injections are useful in adults and children with detrusor overactivity refractory to anticholinergics by improving compliance and maximum cystometric capacity [7]. However, in DV intersphincteric BTX-A injections may be more appropriate as management should focus on the issue of involuntary contraction of the urethral sphincter and not detrusor overactivity. Intersphincteric injections have also shown positive effects on the reduction in post-void residual urine volume (PVR) [7]. In recent years, more research has been done on the effects of intersphincteric BTX-A as treatment for DV in children. The aim of this systematic review is to summarize the effects and safety of BTX-A as management for DV in children.

Methods

This systematic review was reported based on the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement and was registered in PROSPERO (www.crd.york.ac.uk/prospero, CRD42023392250) [8].

Study design

Randomized controlled trials (RCTs) and prospective or retrospective cohort studies including more than ten cases were included if they met the following inclusion criteria: reporting on the usage of BTX-A as a treatment for DV in the EUS for children $<$18 years of age. If adults were also included, at least 90 % of the population had to be younger than 18. Exclusion criteria were (1) studies which included patients with underlying neurogenic disorder, (2) if the mean or median follow-up time was less than 6 months, and (3) if $>$10 % of the study population received concomitant intravesical BTX-A injections. Case reports, experimental studies, review articles, meta-analyses, letters, abstracts, or comments were excluded.

Systematic literature search

A biomedical information specialist (WB) performed a systematic search. The Medline, Embase and Web of Science databases were searched on May 9, 2023, without time and language limitations. Search syntaxes and results per database are provided in the Appendix. An additional search through reference lists was performed. All titles and abstracts and, subsequently, full texts identified by the literature search were independently reviewed for eligibility by two reviewers (IdA and ZB) using a standardized form and EndNote X9. If eligibility was unclear based on the abstract, a full text of the study was collected in order to allow a more detailed assessment. Any disagreements were resolved by discussion between the reviewers or by consulting a third review author (LH).

Data extraction

The variables extracted included study design, countries and institutions where the data was collected, inclusion period, length of follow-up, number of participants included, description of the definition of dysfunctional voiding, description of the intervention used and the type of BTX-A neurotoxin product used, including dosages. Extracted baseline patient characteristics were gender, age, previous treatments, PVR, Qmax, urinary incontinenceand UTIs. Moreover, the following outcomes were collected: PVR, Qmax, incontinence, UTIs, repeat injections and complications. Also, information on upper tract dilatation and flow patterns were included in this review.

Risk of bias assessment

The risk of bias (RoB) of each included study was assessed independently by two reviewers (IdA and SH). Any disagreements were resolved by discussion or by consulting a third review author (LH). RoB was assessed by using the recommended tools in the Cochrane Handbook for Systematic Reviews of Interventions [9]. This includes the assessment of: random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; selective reporting; and other sources of bias. RoB in non-randomized comparative studies (NRS) was assessed using all domains above, and an extra item to assess the risk of findings being explained by confounding.

Data synthesis

Meta-analysis could only be performed if more than one randomized controlled trial reporting on the same outcome was included in this study.

Results

Search results

Details of the study selection are provided in a PRISMA flow diagram (Fig. 1). After duplicate removal, 277 of 430 articles were further assessed. Eventually, five articles were included after title and abstract screening and full-text reading. One article by Gasimov et al. met the inclusion criteria, but did not report on the same outcome data and was therefore excluded [10]. Meta-analysis could not be performed due to the lack and heterogeneity of data. Therefore, the narrative synthesis approach was used to summarize the results.

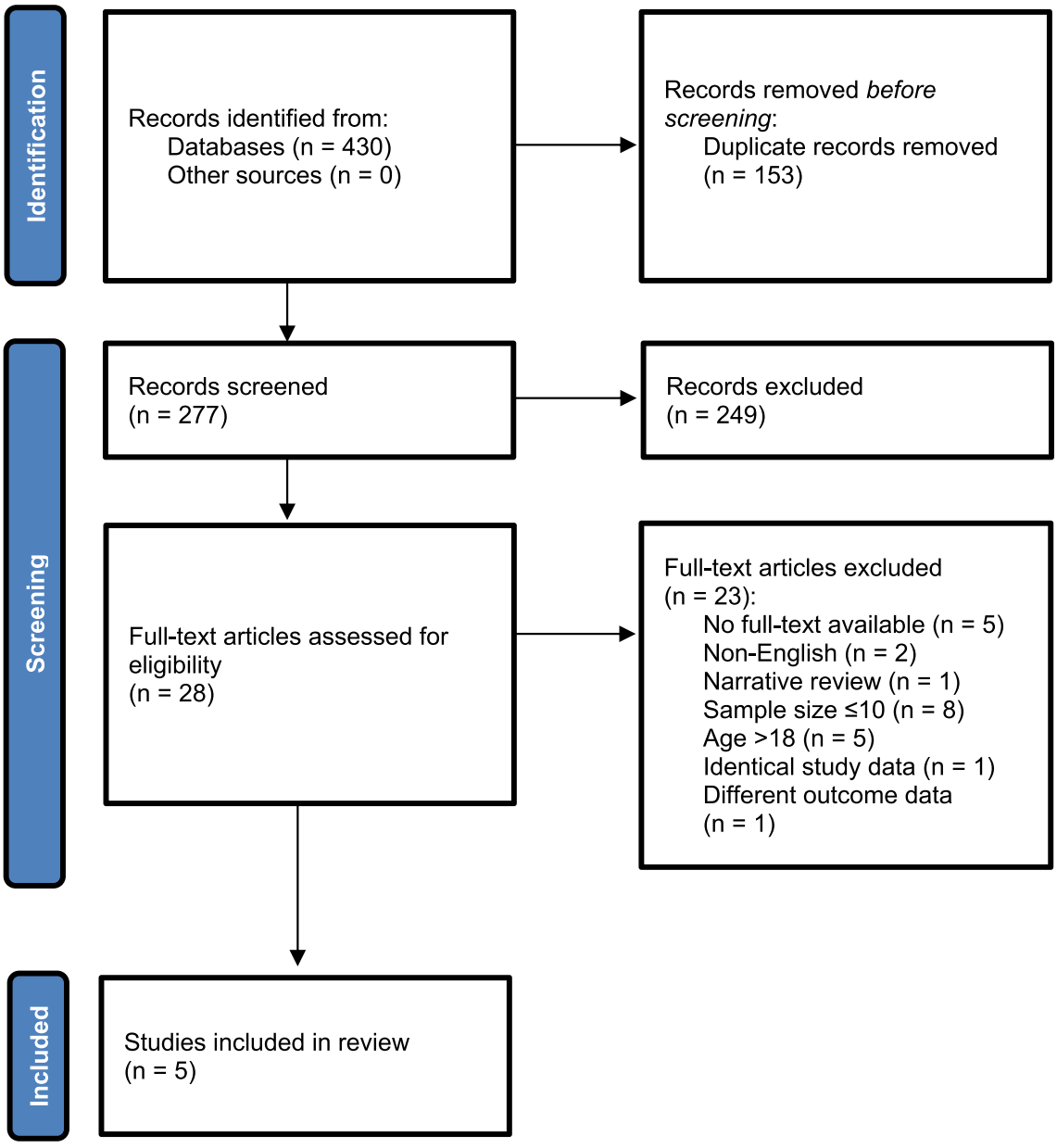

Fig. 1 PRISMA flowchart.

Study and patients characteristics

All five studies were single arm case studies, of whom three had a retrospective design [11—13] and two a prospective design [14,15]. The included studies were published between 2006 and 2015. All studies included patients with DV. The definition of each study included contraction of the EUS and/or pelvic floor muscles during voiding, in four studies confirmed by uroflowmetry combined with electromyography (EMG) [11,12,14,15]. Vricella et al. was the only study that did not use EMG during uroflowmetry to evaluate DV, but they did state that all children showed repeated staccato (83,3 %) or interrupted (16,7 %) flow during flow measurements [13]. 't Hoen et al. also showed that all children displayed either staccato (85 %) or interrupted (15 %) curves [12].

In total, 78 patients with DV were included of whom 53 females (68 %) and 25 males (32 %). Sample size ranged from ten to twenty patients. Mean or median age at the time of intervention ranged from 8 to 10.5 years. At baseline, most patients suffered from incontinence and recurrent UTIs as a result from the DV. All studies reported mean or median PVR at baseline which varied between 47.5 and 335 mL. Three studies reported mean Qmax ranging from 2.17 to 11.8 mL/s [12—14]. Two studies reported on upper tract dilatation. Vricella et al. showed that two patients had grade 2 hydronephrosis, one unilateral and one bilateral [13]. Mokhless et al. reported on four patients with bilateral grade 1—3 hydronephrosis [14].

All five studies used onabotulinumtoxin-A (BOTOX®) with dosages ranging from 50 to 300 units. Also different procedures were described between studies, the main

Table 1 Study and patient characteristics.

Reference	Year of publication	Country	Study design	Recruitment	Patients (female/male)	Mean age [years] (range)	Description of disorder	Previous treatment	Neuropsychiatric disorders	Description of intervention	Additional intervention (n)	Follow-up [months] (range)
Franco et al. [11]	2007	United States of America	Cohort study, R	2002—2006	14 (11/3)	9 (6—16)	Inappropriate contraction of the external sphincter along with concomitant detrusor contraction confirmed with uroflowmetry/EMC and/or MCU	Alpha-blockers (n = 3), anticholinergics (n = 5), tricyclics (n = 3), urotherapy including biofeedback (n = 16), CIC (n = 1)	Depression (n = 4), anxiety (n = 3), ADD (n = 2)	200-300 IE BOTOX® injected at 3, 6, 9 and 12 o'clock. In females with a 22 or 23 gauge needle and in males with a 3,7Fr Deflux needle, both using cystoscopy	Imipramine (n = 3) Intravesical BTX-A (n = 2)	Mean = 21 (1.5—39)
't Hoen et al. [12]	2015	The Netherlands	Cohort study, R	2010—2013	20 (16/4)	9 (5—14)	An abnormal flow pattern and increased pelvic floor tone during uroflowmetry/EMG	Urotherapy including biofeedback (n = 20)	N = 0	100 IE BOTOX® injected para-urethral at 3, 9 and 12 o'clock. In females using a 23-gauge needle without cystoscopy, in males with a 4Fr injection needle using a 9Fr cystoscope	Urotherapy including biofeedback (n = 14)	Median = 13 (5—34)
Mokhless et al. [14]	2006	Egypt	Cohort study, P	NA	10 (4/6)	8 (6—17)	Inappropriate contraction of the external urethral sphincter with concomitant detrusor contraction	Alpha blockers (n = 10), CIC (n = 9)	NA	50-100 IE BOTOX® injected at 3, 6, and 9 o'clock. In all patients a 4Fr injection needle and a cystoscope were used	None	NA (6—15)
Vricella et al. [13]	2013	United States of America	Cohort study, R	2006—july 2012	12 (8/4)	10.5 (4—19)	Habitual contraction of the EUS during voiding	Medication (n = 12), of whom anticholinergics (n = 6), conservative urotherapy (n = 12)	N = 4 (learning disorder, autism, ADHD)	100 IE BOTOX® injected mid-urethrally at 3, 6, 9 and 12 o'clock. In females with a 23-gauge needle and in males with a 23 gauge needle, both using cystoscopy	Behavioral modification and physical therapy initiated at 1 month (n = 12)	Median = 45 (20—71)
Radojicic et al. [15]	2006	Serbia and Montenegro	Cohort study, P	august 2002—january 2004	20 (12/8)	9 (1—12)	Dysfunction during bladder storage or emptying characterized by a different degree of incomplete relaxation or even by overactivity of the pelvic floor muscles and EUS	Urotherapy including biofeedback, alpha blockers (N = NA)	N = 0	50-100IE BOTOX® injected 1.5—2.0 cm deep at the 3, 6 and 9 o'clock positions using a 21 or 23-gauge needle using cystoscopy in males. In females the 12 o'clock position was also injected and no cystoscopy was used	Chemoprophylaxis (n = 20), urotherapy including biofeedback (n = 20)	NA (9—14)

Abbreviations: R = retrospective, P = prospective, NA = not available, CIC = clean intermittent catheterization, ADD = attention-deficit disorder, IE = international Enheder/international units, ADHD = attention-deficit/hyperactivity disorder.

Table 2 Study results.

Reference	PVR [mL] (range/sd)			Qmax [mL/sec] (sd)			Incontinence			Urinary tract infections			Repeat injections (n)	Time until repeat injection	Complications
	Pre-operative	Post-operative	P-value	Pre-operative	Post-operative	P-value	Pre-operative	Post-operative	P-value	Pre-operative	Post-operative	P-value			
Franco et al. [11]	Mean = 107 (NA)	Mean = 43 (NA)	$P < 0.001$	NA	NA	NA	n = 14	n = 3[£]	NA	n = 11	NA	NA	n = 2	NA	Transitory incontinence (N = NA)
't Hoen het al. [12]	Median = 47,5 (16.3–88.5)	Median = 0 (0–28)[β]	P = 0.001	Median = 18 (12.4–25.6)	Median = 18.5 (14.3–27.3)	P = 0.600	n = 20	n = 11[¥]	$p < 0.001$	n = 11	n = 6	p = 0.003	n = 4	Median = 12 months	UTI (n = 1), other (n = 10)
Mokhless et al. [14]	Mean = 335 (166)	Mean = 75 (70.87)	P = 0.003	Mean = 2.17 (2.48)	Mean = 14 (10.96)	NA	NA	NA	NA	NA	NA	NA	n = 1	Monthly based on response	n = 0
Vricella et al. [13]	Mean = 115 (83)	Mean = 57 (61)	P = 0.016	Mean = 11.8 (8.1)	Mean = 20.4 (7.9)	P = 0.012	n = 7	n = 3	NA	n = 7	n = 3[Ω]	NA	n = 6	Median = 15 months	UTI (n = 2)
Radojicic et al. [15]	Mean = 70 (31.83)	Mean = 24.39 (25.21)	$P < 0.001$	NA	NA	NA	NA	NA	NA	n = 20	n = 5[±]	NA	n = 0	NA	Transitory incontinence (n = 1)

Abbreviations: PVR = postvoid residual, NA = not available, β = at best postoperative visit (t = NA), £ = one child was dry after initiation of ADD treatment, ¥ = daily incontinence (N = 4), Ω = patients were still on chemoprophylaxis, UTI (n) not reported, ± = at first post-operative visit at 6–12 weeks.

difference being the use of cystoscopy in girls. Length of follow-up ranged between 1.5 and 45 months.

Effects of botulinum toxin-A

The included studies described various techniques for injecting the BTX-A as shown in Table 1. In all males, BTX-A was injected by using cystoscopy. For females, either cystoscopy was used [11,13,14] or the BTX-A was injected paraurethrally [12,15]. Most studies included additional interventions, such as urotherapy and chemoprophylaxis.

The efficacy of BTX-A was first measured by PVR volume. Postoperative PVR was measured at different times across all five studies, ranging from two weeks to six months. As shown in Table 2, all studies showed a significant decrease in PVR after BTX-A injection. Mokhless et al. measured PVR volumes multiple times during follow-up, showing an increase in PVR over time [14]. At six months, PVR volumes were still significantly lower compared to baseline PVR. Secondly, uroflowmetry was used in three studies to measure the maximum speed of urinating and thereby the severity of obstruction by the urethral sphincter combined with the pelvic floor muscles, expressed in mL/s [12—14]. Vricella et al. showed significant improvement in Qmax, improving from 11.8 to 20.4 mL/s, p-value = 0.012 [13]. Mokhless et al. did not report p-values, but showed clinical improvement, comparing 2.17 mL/s pre-operatively to 14 mL/s post-operatively [14]. Also, flow patterns improved post-injection. Vricella et al. and 't Hoen et al. both showed that flow patterns improved to bell-shaped in eight children (66.7 %) and eighteen children (90 %), respectively [12,13]. After BTX-A injection, hydronephrosis resolved in some patients, and downgraded in others. In one case, the hydronephrosis sustained and did not downgrade [13].

In some cases, repeat injections were necessary. Vricella et al. documented that 50 % received repeat injection after a median period of 15 months [13]. In 't Hoen et al. repeat injections were necessary in 20 %, received after a median of 12 months [12]. Mokhless et al. intended to repeat injections every month according to the response with a maximum of 3 injections, which was only necessary in one patient (10 %) [14].

Also, incontinence and UTIs were reported as primary or secondary outcome measures across studies. Three studies showed improvement on incontinence after BTX-A injection with a 33—69 % decrease [11—13]. Also, less UTIs were reported after treatment. Vricella et al. reported three patients with a UTI after treatment, who continued with chemoprophylaxis and Radojicic et al. reported five patients with signs of a UTI in combination with positive urine cultures, but without fever [13,15].

Safety of BTX-A

Three studies reported transitory incontinence after intersphincteric BTX-A injections which disappeared after 48—72 hours. Vricella et al. and 't Hoen et al. showed that four patients suffered from a UTI after treatment without further complications [12,13]. Finally, 't Hoen et al. reported that one patient complained of one-sided numbness of the gluteus muscle, which was also transitory [12].

Risk of bias assessment

The risk of bias assessment is shown in Fig. 2. The following factors were considered as potential confounding factors: previous treatment, gender and the dosage of BTX-A used. The risk of the findings being explained by confounding factors was high because, due to small sample sizes, correction was not possible in the included studies, or confounding factors were not discussed at all. Only single-armed cohort studies were included in this study, therefore sequence generation and allocation concealment were retained as domains but assessed by default as 'high risk of bias' given the non-randomized nature of these studies.

Discussion

In this systematic review the effects and possible complications of intersphincteric BTX-A injections as treatment for children with therapy-refractory DV are summarized. Several arguments can be identified to support the choice of BTX-A as treatment for these children. Firstly, intersphincteric BTX-A injections result in a decrease of PVR. It also results in less incontinence and UTI. In addition, the only possible complications described were all of transitory nature which suggests that injecting BTX-A into the urethral sphincter is a safe treatment.

Recurrent febrile UTIs is one of the most frequent symptoms of DV, which can have devastating effect on children's kidney function. Preventing children from such scars is therefore one of the main goals of treating children with DV. The study of 't Hoen et al. showed a significant reduction in UTIs pre- and post BTX-A injections [12]. A study by Petronijevic et al., not included in this review,

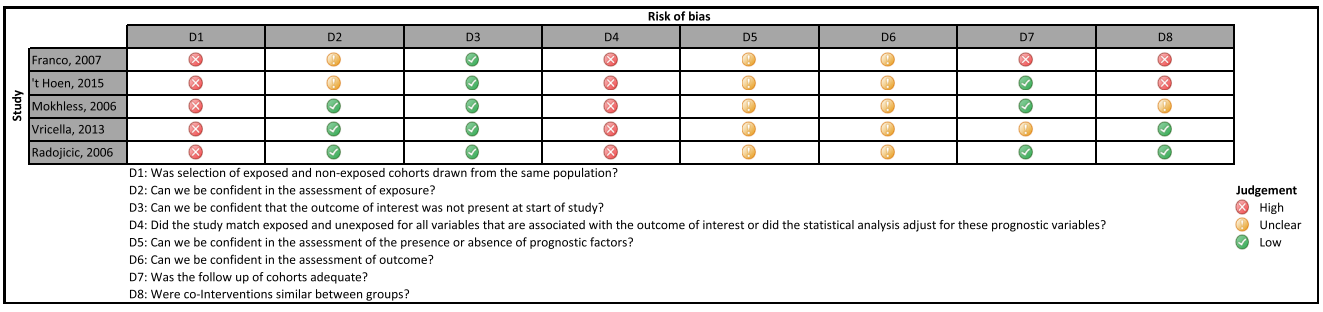

Fig. 2 Risk of bias assessment.

may confirm these findings as they found a 75 % decrease in recurrent UTI incidence in their study population, consisting of nine female children [16]. One could hypothesize that this positive finding is probably achieved by reduction of PVR. Reduction of UTIs should be considered as an important outcome of BTX-A in daily clinical practice [15,16].

More than half of the studies used additional interventions besides BTX-A injection, such as a form of urotherapy and chemoprophylaxis. Due to these additional interventions the conclusions may not be entirely attributed to the BTX-A injections. The reason for the combined strategy is often due to the relatively short effect of the BTX-A when used in a striated muscle (8—12 weeks, peaking at day 10) [17]. By combining BTX-A and urotherapy, the effect can be maintained even after cessation of the toxin effects. As such, children are reeducated by making them aware of the elements of normal voiding and teaching them to relax the pelvic floor muscles during voiding. This could be bothersome for children suffering from a neuropsychiatric disorder, as urotherapy can be frustrating and requires permanent cooperation [15]. For example, Vricella et al. showed that three of the four patients who failed to show improvement after BTX-A injection, in combination with behavioral modification and physical therapy initiated at one month, had underlying neuropsychiatric problems [13]. This suggests that not all children with DV are suitable for this treatment combination.

The use of intersphincteric BTX-A injections is a safe treatment for DV as no acute complications were reported. Increase in incontinence was reported as a side effect and can be explained by the mechanism and hence the therapeutic effect sought after. BTX-A decreases urethral resistance via paralysis of the striated sphincter muscle by inhibiting acetylcholine release in the neuromuscular junction [18]. In order to be continent, the sphincter muscle should be contracted when not urinating. So when BTX-A is injected, an increase in incontinence can subsequently occur. However, the increase in incontinence was transitory in all children. Franco et al. stated that the increase in incontinence resolved after making the children aware that they could no longer volitionally contract the external sphincter [11]. This was shown to be helpful, because voiding postponers tend to show oppositional behavioral traits in voiding [11].

Finally, there are uncertainties about the duration of the BTX-A effect, especially in the urethral sphincter. For intravesical use, it was shown that the effect of BTX-A lasted for six months on average. The duration of efficacy of intersphincterical BTX-A is two to three months. The results found in this systematic review show that the effectiveness is in fact longer than three months. Some patients needed repeat injections because of an increase of symptoms. However, 't Hoen et al. showed that this was only necessary in four patients after a median of 15 months, implying that mechanisms other than the BTX-A itself are accountable for this sustainable effect [12]. By eliminating one factor with the BTX-A injection, the vicious circle can be disrupted. The period during which the effect of the BTX-A sustains should be used to continue or start non-invasive therapy to retrain patients in normal voiding.

There are some limitations to the present study that are important to acknowledge. No RCTs on this topic have been published to this date and therefore only single-arm cohort studies were included in this review. The results were based on small sample sizes, with the largest population consisting of 20 children [12,15]. Performing a meta-analysis was not possible and the magnitude of the effect remains unknown. Also the short-term of follow-up, the lack of information on voided volume and PVR outcomes, limits the interpretation of the study's findings.

Furthermore, the effect of BTX-A injections may not be generalizable to the general population. For example, the number of children with neuropsychiatric problems included in the studies may not correspond with the number of dysfunctional voiders with neuropsychiatric problems in the general population. Recent studies have shown that there is a relation between children with neuropsychiatric problems and urination disorders [19]. Vricella et al. showed that three out of the four patients who failed to show improvement after BTX-A injection had neuropsychiatric problems, consisting of ADHD, autism, anxiety and a learning delay [13]. They concluded that neuropsychiatric problems appear to negatively influence the impact of BTX-A. Because the number of children with DV and neuropsychiatric problems could be higher in the general population, the effect of BTX-A could be overestimated.

Moreover, the included studies used different dosages of the BTX-A neurotoxin. All five included studies used onabotulinumtoxin-A with dosages ranging from 50 to 300IE with two studies basing their dosage on the patient's weight [14,15]. These two studies reported less transitory incontinence than the studies using 100IE in all patients. This can be explained by the fact that higher dosages of BTX-A can cause more paralysis to the sphincter and therefore cause more transitory incontinence. As such basing dosage on patient's weight can be more desirable. Franco et al. used significantly higher dosages than the other studies, using 200-300IE [11]. All studies showed significant improvements, implying that lower dosages are preferable. Further studies will be necessary to determine the optimal dosage of BTX-A for intersphincteric use.

None of the included studies reported on patients reported outcome measures (PROMs). Since DV can cause urinary incontinence and affect children's quality of life (QoL), PROMs should be considered when investigating different types of treatment. Gasimov et al. used the Dysfunctional Voiding and Incontinence Symptoms Score (DVISS) and general QoL to assess the efficacy of intersphincteric BTX-A [10,20]. They showed clinical improvement in 75 % of the children with a significant decrease in mean DVISS and significant increase in QoL ($p < 0.001$). Nadeem et al. assessed QoL using the International Prostate Symptom Score QoL, as this questionnaire is also validated for use in female lower urinary tract symptoms (LUTS) [21]. They showed an improvement in QoL in 60 % of the included patients. Since there has been a global shift towards value-based healthcare, PROMs should also be incorporated in pediatric studies.

To overcome some of the mentioned methodological limitations and to find evidence to fill in the identified gaps in current knowledge, future research might benefit from gathering data in the context of multi-center or (inter)national audit studies. Long term multi-center and

prospective data collection in a large sample of patients has the ability to provide insight into current clinical practice, analyze outcomes with adjustment for known confounders, as well as assess outcomes in subgroups such as patients with neuropsychiatric disorders.

Conclusion

In conclusion, this systematic review shows that intersphincteric BTX-A could be a safe and effective treatment option for therapy-refractory DV in children by reducing PVR, number of UTIs and incontinence. Hereby, the synergistic effect of BTX-A and urotherapy should be highlighted. In addition, this study identified gaps in current knowledge, most importantly the reporting of PROMs, that are of interest for future research.

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Conflict of interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpurol.2023.10.034.