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ORIGINAL ARTICLE

Urinary incontinence in children: botulinum toxin is a safe and effective treatment option

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Abstract
Purpose This study's aim was to assess the use of intravesical injection of botulinum neurotoxin type A (BoNT-A) as a treatment of overactive bladder (OAB) in children.
Methods A 6-year retrospective study of children who received BoNT-A for OAB was performed. Treatment outcome was classified as complete success (CS), partial success (PS) or treatment failure (TF).
Results Of the 57 patients who received BoNT-A treatment for OAB, 35 were males. CS occurred in 74.2% of males and 54.5% of females. PS was achieved in 20% of males and 18.2% of females. TF occurred in 2.9% of males and 22.7% of females. Anticholinergics had previously been used and had been effective in 58.6% and 83.3% of males and females. Significant side effects to medications were experienced in 12 (41.4%) males and 4 (22.2%) females. Of these, BoNT-A achieved CS in seven (53.3%) males and two (50%) females and PS in three (25%) males and one (25%) female. BoNT-A was successful in seven (58.3%) males and two (66.7%) females where anticholinergics were ineffective.
Conclusions BoNT-A has a role in a carefully selected subgroup of children with overactive bladder symptoms including those with medication side effects and treatment compliance issues. It may have a role in patients who do not respond to conventional therapy.

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Introduction

Kerner, a German physician, described 'sausage poisoning' in 1820 and suggested that a biological poison caused it. He postulated that "the capacity of nerve conduction is interrupted by the toxin in the same way as in an electrical conductor by rust''. He suggested that, in small doses, this toxin might be beneficial in conditions with hyperexcitation of the sympathetic nervous system. By the end of the 19th century, the Belgian, van Ermengem, discovered the neurotoxin-producing pathogen, *Clostridium botulinum*. In the 1970s, Alan Scott first used BoNT for the treatment of strabismus [1]. Currently, there are numerous applications for botulinum toxin in humans [2].

Bladder overactivity is usually managed with a combination of bladder training and anticholinergic medications. A more recently explored therapeutic option has been the intravesical injection of BoNT-A. This is an off-label use of BoNT-A at present. Injections can be either suburothelial or directly into the detrusor muscle, and are given at multiple sites but generally sparing the trigone. Schurch et al. [3] originally described this option in adults. Following injection into the bladder, effects generally last between 6 and 12 months [4, 5].

Botulinum neurotoxins block presynaptic acetylcholine (ACh) release from intramuscular neurons. Type A toxin (BoNT-A) cleaves the synaptosomal associated protein SNAP-25. This protein is one of the soluble *N*-ethylmaleimide-sensitive fusion attachment protein receptor (SNARE) proteins involved in the exocytosis of acetylcholine from the presynaptic motor endplate [6].

It is now becoming clear that BoNT-A has a more complex mechanism of action on the urinary bladder. BoNT-A also inhibits other excitatory neurotransmitters including substance P and glutamate. It causes a reduction in axonal receptor expression, in particular the suburothelial vanilloid receptor 'TRPV1', a capsaicin receptor and the purinergic receptor 'P2X3'. The end result is inhibition of both afferent and efferent nerve pathways thought to form the pathological basis of detrusor overactivity [7].

There have been two recent, detailed systematic reviews on BoNT use for detrusor overactivity in adults. Duthie et al. in 2007 compared botulinum toxin injections with other treatments for neurogenic and idiopathic overactive bladder in adults. Eight studies were included in the final analysis. He concluded that there is consistent evidence that BoNT intravesical injection reduces incontinence episodes, increases urodynamically assessed bladder capacity and reduces maximum detrusor pressure, as well as improving quality of life. Heterogeneity of outcome measures meant it was not possible to combine the results for further statistical analysis. They advise that lack of long-term safety data warrants ongoing caution [8].

Anger et al. limited their remit to adult patients with idiopathic OAB. There were three randomized placebo-controlled trials with 99 patients included in the analysis. The conclusions stated that botulinum toxin does result in improvement in medication-refractory OAB symptoms. The risk of elevated post-void residual and symptomatic urinary retention was significant [9].

But as De Ridder points out in his recent review in *British Journal of Urology*, there are still many areas of uncertainty regarding botulinum toxin use in urology, including optimal dose and injection technique, the question of repeat dosing, as well as consideration of who not to inject [10].

The majority of studies in children have mainly focused on those with neuropathic bladders. To date, only two studies have looked at the use of botulinum toxin in children with OAB. Both studies have shown an excellent response to treatment in medication-resistant OAB. Some patients did require repeated injections; however, the long-term outcome resulted in high success rates with minimal side effects [11, 12].

The aim of this study was to retrospectively look at the outcomes in these children, ascertain those who benefit most from therapy, and identify predictive factors of either success or failure.

Methods

A retrospective chart review of all patients with OAB who received BoNT-A by intravesical injection between 2006 and 2011 was undertaken. Information regarding history (including frequency/volume charts), uroflowmetry parameters and outcome data was collated. At our institution, BoNT-A (Dysport®) is administered via cystoscope into the suburothelium of the bladder. A dose of 12 IU/kg is divided into 0.1 ml aliquots (10 IU/0.1 ml) and injected at multiple sites up to a maximum dose of 480 IU.

Children with bladder dysfunction, daytime wetting and lower urinary tract symptoms of frequency and urgency were considered eligible. These patients may have had a poor or no response to conventional treatment with bladder training and anticholinergics. The anticholinergic medication used in the study were oxybutynin as first-line with tolterodine as second-line treatment. Children who had a good response to anticholinergic medication but experienced significant side effects or were non-compliant were included. Children had a urinalysis and mid-stream urine (MSU) for culture performed pre-treatment and were excluded if they had signs of a urinary tract infection (UTI). They were also excluded if constipation had not been completely addressed.

All patients had baseline uroflowmetry performed pre-BoNT-A. Functional bladder capacity (FBC) was calculated from the patient's observed bladder capacity by expressing it as a percentage of that expected for age (expected bladder capacity for age (ml) = (age + 2) × 30) [13].

Complete success was defined a priori as having no lower urinary tract (LUT) symptoms and having achieved daytime and nighttime dryness. Partial success was deemed to have occurred if there was subjective improvement in symptoms according to either patients or parents, but not complete resolution of symptoms. If there was no improvement at all in symptoms, this was defined as treatment failure.

The Hospital Medicines Advisory Committee for OLCHC granted permission for the use of BoNT-A and informed consent was obtained from the children's parents before each procedure. This study is a retrospective audit of a treatment already employed, so no formal ethics committee approval was required.

Results

Patients and response to treatment

Of the 57 patients who received BoNT-A treatment, 38 (66.7%) and 11 (19.3%) achieved a complete response (CS) and partial response (PS) to treatment, respectively. Treatment failure accounted for six (10.5%) patients and two (3.5%) patients were lost to follow-up. Thirty-five (61%) of the cohort of 57 were male. CS was observed in

26 (74%) males and 12 (55%) females. PS was seen in seven (20%) males and four (18%) of females (Table 1).

Multiple doses of BoNT-A

A group of patients ($n = 23$) went on to have a second dose of BoNT-A, with ten (43.5%), eight (34.8%) and three (13%) cases achieving a CS, PS and TF, respectively. Of the 11 male patients who achieved CS from the first dose of BoNT-A, 6 (54.5%) achieved CS after the second dose, compared to 3 (42.8%) of the female patients ($n = 7$). PS from the second dose of BoNT-A accounted for two (18.2%) male and two (28.6%) female cases who had achieved a CS from the first dose of BoNT-A. There were three treatment failures in patients who initially had CS, two (18%) male and one (14%) female. Patients who had PS to the first dose of BoNT-A comprised three male patients and one female. CS from this group was seen in a male patient only. All other cases resulted in PS. There was no TF in this subgroup of patients. A single patient with TF on the first dose of BoNT-A obtained PS after the second dose with duration of effects lasting 5 months (Table 2).

Patient characteristics and symptoms

FBC was calculated with observed bladder capacity expressed as a percentage of that expected for age. All patients had an FBC measured pre-BoNT-A therapy using uroflowmetry. The mean pre-BoNT-A FBC was 42.4% (range 23.9–90.6%) for males and 56.9% (9.9–153.4%) for females. Post-BoNT-A FBC was 62.7% (range 26.7–124.6%) for males and 81.5% (range 29–127%) for females. Frequency, urgency and nocturnal enuresis affected a higher proportion of males than females. Fewer males had a background history of UTIs (Table 3).

Table 1 Effect of first dose of BoNT-A in the patient cohort

	CS	PS	TF	Insufficient follow up/ no data
Response to first dose of BoNT-A				
Male ($n = 35$)	26 (74.2%)	7 (20%)	1 (2.9%)	1 (2.9%)
Female ($n = 22$)	12 (54.5%)	4 (18.2%)	5 (22.7%)	1 (4.5%)
Total ($n = 57$)	38 (66.7%)	11 (19.3%)	6 (10.5%)	2 (3.5%)
Mean duration of effects in months (range)				
Male	6.0 (2–12)	6.9 (1–18)		
Female	6.7 (3–18)	9.3 (3–14)		
Total	6.1 (2–18)	7.7 (1–18)		

CS complete response, *PS* partial response, *TF* treatment failure

Table 2 Effect of second dose of BoNT-A in the patient cohort

	CS	PS	TF	Insufficient follow-up/ no data
CS with first dose of BoNT-A				
Male ($n = 11$)	6 (54.5%)	2 (18.2%)	2 (18.2%)	1 (9.1%)
Female ($n = 7$)	3 (42.8%)	2 (28.6%)	1 (14.3%)	1 (14.3%)
Total ($n = 18$)	9 (50%)	4 (22.2%)	3 (16.7%)	2 (11.1%)
Mean duration of effects in months (range)				
Male	9.3 (3–24)	4.5 (3–6)		
Female	5.3 (3–7)	4.5 (3–6)		
Total	8 (3–24)	4.5 (3–6)		
PS with first dose of BoNT-A				
Male ($n = 3$)	1 (33.3%)	2 (66.7%)	0 (0%)	0 (0%)
Female ($n = 1$)	0 (0%)	1 (100%)	0 (0%)	0 (0%)
Total ($n = 4$)	1 (25%)	3 (75%)	0 (0%)	0 (0%)
Mean duration of effects in months (range)				
Male	8 (8)	9.5 (3–16)		
Female	n/a	11 (11)		
Total	8 (8)	10 (3–16)		
TF with first dose of BoNT-A				
Male ($n = 0$)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Female ($n = 1$)	0 (0%)	1	0 (0%)	0 (0%)
Total ($n = 1$)	0 (0%)	1	0 (0%)	0 (0%)
Mean duration of effects in months (range)				
Male	n/a	n/a		
Female	n/a	5 (5)		
Total	n/a	5 (5)		

CS complete response, *PS* partial response, *TF* treatment failure

Duration of response

For the overall cohort, the mean duration of the effects of BoNT-A is 6.1 months for CS and 7.7 months for PS. The mean duration of effect of treatment for CS was 6 (range 2–12) and 6.7 (range 3–18) months for males and females, respectively. For male patients with PS, the mean duration of BoNT-A effects was 6.9 months (range 1–18), while for females it was 9.3 months (range 3–14) (Table 1).

Anticholinergic medication and response

Prior to treatment with BoNT-A, 29 (85.3%) males and 18 (81.8%) females had been treated with anticholinergic medication. This was effective in 17 (58.6%) males and 15 (83.3%) females. Significant side effects were experienced in 12 (41.4%) males and 4 (22.2%) females with altered mood, aggressive behaviour, blurring of vision and dry mucous membranes reported most commonly. Of this group of patients, seven (53.3%) males and two (50%)

Table 3 Patient characteristics and symptoms

Demographic details	Male ($n = 35$)	Female ($n = 22$)
Mean age in years (range)	9.1 (4.3–14.9)	9.4 (5.8–15.1)
Urinary symptoms		
Duration of symptoms <3 years	14 (40%)	10 (45.5%)
Duration of symptoms >3 years	18 (51.4%)	9 (40.9%)
Duration of symptoms, no data	3 (8.6%)	3 (13.6%)
Frequency	33 (94.3%)	19 (86.4%)
Mean frequency (range)	10 (8–20)	16.3 (8–72)
Urgency	34 (97.1%)	20 (90.9%)
Eneuresis	31 (88.6%)	22 (100%)
Nocturnal eneuresis	34 (97.3%)	20 (90.9%)
Nocturnal eneuresis every night	24 (60.6%)	8 (36.4%)
Previous UTI	9 (25.7%)	15 (68.2%)
Previous constipation	6 (17.1%)	5 (22.7%)
Medications used prior to BoNT-A		
Anticholinergics	29 (85.3%)	18 (81.8%)
Anticholinergics effective	17 (58.6%)	15 (83.3%)
Desmopressin	18 (51.4%)	6 (27.2%)
Demospressin effective	7 (38.9%)	4 (66.7%)
Significant side effects	12 (41.4%)	4 (22.2%)
Personality changes (aggressiveness)[a]	2	1
Low mood	1	1
Dry skin/mucous membranes[a]	6	3
Diarrhoea, flushing, dizzy spells	3	0
Functional bladder capacity		
Mean FBC Pre-BoNT-A (Range)	42.4% (23.9–90.6%)	56.9% (9.9–153.8%)
Mean FBC post-BoNT-A (Range)	62.7% (26.7–124.6%)	81.5% (29–127%)

FBC functional bladder capacity

[a] One female patient experienced personality changes and dry mucous membranes

females achieved CS. PS was obtained in three (25%) males and one (25%) female. There was no TF in this small cohort of patients. Where anticholinergic medication was ineffective, CS was observed in seven (58.3%) males and two (66.7%) females. PS was seen in five (41.7%) males. Treatment failure occurred in one (33.3%) female. Where anticholinergic medication was effective, BoNT-A achieved CS in 14 (82.3%) males and 8 (53.3%) females. Treatment failed in two (13.3%) females. PS was seen in two (11.8%) males and four (26.7%) females (Table 4).

Side effects of BoNT-A

Regarding side effects to BoNT-A, all patients had demonstrable microscopic haematuria, but there was no macroscopic haematuria. Significant pain was not reported by any patient. There was no known case of urinary retention, cystitis or UTI post the procedure, but routine urine culture was not performed. There was no case of an anaphylactic reaction.

Treatment failure group

There were six treatment failures after the first dose of BoNT-A, one male and five female. The male patient had a background history of hypospadias repair and recently had a diagnosis of attention deficit hyperactivity disorder (ADHD). Of the five female patients, one had a history of dyslexia, one with features of ADHD (but no confirmed diagnosis), two patients with poor compliance with bladder training and one patient with no known cause for failure. One patient with a history of constant dribbling during the day but dry at night has, after extensive investigations, been diagnosed with female epispadias and will require reconstructive bladder neck surgery.

There were three treatment failures after the second dose of BoNT-A, two males and one female. All patients had an initial complete response to the first dose of BoNT-A. All patients underwent a third injection of BoNT-A (Table 2). One female had a further complete response, while the remaining two patients have insufficient follow-up to date to comment on their outcome.

Discussion

The primary objective of treatment of patients with OAB is improvement in daytime LUT symptoms and daytime wetting. Bladder training is essential and anticholinergic medication may be beneficial. Side effects from these medications can be significant, thus inhibiting their use. Compliance with medication is always an issue in any patient group, and with children it is no different. In our experience, the parents of children are not always satisfied with having their children taking regular medication, especially when the child is medication dependent. Commonly, both the parents and the children are frustrated when despite being compliant with medication and bladder training they fail to remain free of the symptoms of an OAB. These patients have very limited options open to them. BoNT-A may have a dramatic and vital role to play.

In our cohort of patients, 86% achieved improvement in symptoms with 67% achieving CS. This is consistent with previous studies in children with OAB [11, 12]. From our

Table 4 BoNT-A outcomes relating to medication efficacy, inefficacy and side effects (medication treatment occurred prior to BoNT-A treatment)

	CS	PS	TF	Insufficient follow-up/no data
Anticholinergic medication side effects ($n = 16$)	9 (56.3%)	4 (25%)	0 (0%)	3 (18.7%)
Anticholinergic medication side effects, males ($n = 12$)	7 (53.3%)	3 (25%)	0 (0%)	2 (16.7%)
Anticholinergic medication side effects, females ($n = 4$)	2 (50%)	1 (25%)	0 (0%)	1 (25%)
Anticholinergic failure group ($n = 15$)	9 (60%)	5 (33.3%)	1 (6.7%)	0 (0%)
Anticholinergic failure group, male ($n = 12$)	7 (58.3%)	5 (41.7%)	0 (0%)	0 (0%)
Anticholinergic failure group, female ($n = 3$)	2 (66.7%)	0 (0%)	1 (33.3%)	0 (0%)
Anticholinergic medication effective group ($n = 32$)	22 (68.8%)	6 (18.8%)	2 (6.2%)	2 (6.2%)
Anticholinergic medication effective group, male ($n = 17$)	14 (82.3%)	2 (11.8%)	0 (0%)	1 (5.9%)
Anticholinergic medication effective group, female ($n = 15$)	8 (53.3%)	4 (26.7%)	2 (13.3%)	1 (6.7%)

CS complete response, *PS* partial response, *TF* treatment failure

data, male patients had higher rates of both complete and partial success. There was a higher number of treatment failures in the female patients compared to males, although the overall number was small. A difference between the sexes has not been demonstrated before. There was a much higher rate of previous UTIs in the female group. The detrusor overactivity may reflect a secondary problem in girls where it follows a UTI and/or the development of holding behaviour. These girls typically have a prior history of normal toileting behaviour. Because the absolute numbers for treatment failure is small, it is difficult to draw any conclusions from this data except that females are more likely to have treatment failure. There were no consistent underlying factors in these patients.

There was an increase in the FBC following BoNT injection. This has been observed previously [11, 12, 14, 15]. It is interesting that there was a significant improvement in nocturnal symptoms where they existed. The increased FBC post-BoNT injection may be responsible for this improvement.

Our results had similar outcomes in the medication-resistant, medication side effects and medication-sensitive groups. Treatment failure within these subgroups revealed that all patients were female. Previous studies in children have included only patients with medication resistance or intolerant to the side effects [11, 12]. Our study included patients in whom compliance and medication dependency were major problems. Makovey et al. in 2011 found that botulinum toxin injections were more effective in the medication intolerability group than the medication resistance group [16]. This study was performed in an adult population and may well reflect the difference between the pathophysiology of adult and paediatric OAB.

Apart from transient microscopic haematuria, detectable in all our patients post-injection, there was no other significant side effect encountered. This is in keeping with the literature to date, which has shown botulinum toxin to be well tolerated and quite safe, with no tachyphylaxis or neutralizing antibody problems as yet reported in the paediatric population [14, 15, 17, 18]. In fact, Kajbafzadeh et al. in 2010 demonstrated transient increases in antibody formation following administration. Repeated injections do not boost the immune system to produce higher levels of antibodies. They postulate that treatment failure may not be attributed to increased levels of antibody [19]. In our own data, 23 patients underwent repeat injections with 78% achieving improvement in symptoms and 44% achieving a CS.

It should be noted that there are a number of limitations to this study. It is a retrospective study and thus has associated inherent flaws. Secondly, formal urodynamic studies were not performed on these patients. This was due to the sheer number of patients seen in our department and the invasive nature of the test. All patients were assessed on uroflowmetry parameters and frequency/volume charts. Thirdly, treatment outcome data were obtained from the clinical notes rather than from a more objective source, such as the use of a questionnaire. In a prospective study to assess the role of BoNT-A in non-neurogenic OAB, urodynamics and objective measurement of treatment outcomes would be essential.

Conclusion

Bladder training and anticholinergic medication remain the gold standard of treatment for OAB. BoNT-A should not be used as a first-line treatment, However, it is an extremely useful and safe therapy for a carefully selected subgroup of children who have been through a standard assessment and treatment regimen. Male patients appear to achieve better results than female patients; however, female patients should not be precluded from treatment. Response to anticholinergic medication should not be used

as a discriminating factor to treatment with BoNT-A. Further studies are warranted and careful audit of its use should continue.

Conflict of interest The authors declare that they have no conflict of interest and no funding was received for this project.

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