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Intradetrusor injection of botulinum toxin A in children: a 10-year single centre experience

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Abstract

Purpose We evaluated the efficacy and safety outcomes of endoscopic intradetrusor botulinum toxin A (BTA) injections for the treatment of children with neuropathic bladder (NB) and non-neuropathic bladder (NNB) with or without detrusor overactivity in a single centre with a retrospective analysis.

Methods For the period 2006–2015, children who received BTA in our hospital were analysed. They were divided into group 1, those with underlying NB and group 2, those without a clear neuropathic cause of symptoms (NNB). Data are given as percentages or medians (interquartile range).

Results Over the study period, 52 children (28 boys, 54%) received BTA, 28 in group 1 (54%; 17 (61%) boys) and 24 in group 2 (46%; 11 (46%) boys). Age at first injection was 11.8 (9.5–14.4) years. After initial injection, 40 (77%) reported symptomatic improvement, 17 (43%) becoming dry. There was no significant difference in response to initial injection between groups ($p=0.11$). Duration of improvement after first injection was 7 (5.8–14) months. Twenty-five (48%) had further injections, of whom 3 (12%) were initial non-responders. Ongoing improvement was reported in 20 (80%), 11 (44%) of whom were dry. There was no significant difference in overall response to injections between groups ($p=0.11$). Of the 11 non-responders, none (0/3) improved after subsequent injection and 3 (27%) subsequently underwent major urological surgery. Of the 40 who responded, 2 (5%) underwent major surgery.

Conclusion BTA injection produced symptomatic improvement in 77% of our study population, with no significant differences in response between NB and NNB groups. In 95% of those who improved, major urinary tract procedures were avoided during the period studied. None of the initial non-responders improved after subsequent BTA injection. BTA injection is effective and reliable in the management of children with NB and NNB refractory to medical therapy.

Keywords Children · Urology · Botulinum toxin A · Overactive bladder · Neurogenic bladder

Introduction

The key aim of therapies targeting the poorly compliant or overactive bladder, whatever the aetiology, is to protect the upper urinary tract from damage. In addition, the continence of patients should be improved to increase their quality of life [1]. Botulinum toxin A (BTA) is a purified neurotoxin produced from *Clostridium botulinum.* It inhibits the release of presynaptic vesicular acetylcholine at the neuromuscular junction which has the effect of suppressing bladder muscle contractility when administered by intradetrusor injection [2]. If conservative measures, including clean intermittent catheterisation (CIC) and oral anticholinergic medication, are unable to improve bladder dysfunction and continence, intradetrusor injection of BTA may be considered in lieu of major surgical procedures [3].

Paediatric urology has seen a growing use of BTA in the treatment of refractory detrusor overactivity (DO) and dysfunctional voiding [4, 5]. However, the evidence for this use is predominantly from adult urology, with a paucity of literature in which long-term outcomes in children have been described [2].

In this study we retrospectively analysed the management and outcomes of children who underwent intradetrusor

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botulinum toxin A (BTA) injection in a single centre over a 10-year period.

Patients and methods

For the period 2006–2015, a consecutive series of children with wetting who underwent intradetrusor injection of BTA (abobotulinumtoxinA, Dysport™; Ipsen Ltd, UK) in our hospital were retrospectively reviewed. Clinical and demographic details were obtained from contemporaneous records.

All patients had symptoms of involuntary voiding or urinary incontinence between CICs and all had either neuropathic bladder (NB, group 1), or idiopathic aetiology [non-neuropathic bladder (NNB, group 2)]. All had received maximal bladder management (including optimising hydration, improving toileting posture and normalising voiding frequency) and treatment with oral anticholinergics, including changes in type and preparation (short- and long-acting) and escalation in dose. Bowel management was optimised in all with dietary advice and titration of laxatives to achieve easy bowel motions daily. Preoperatively, most children had renal tract ultrasound scan (RUS).

All had urodynamically proven impaired bladder compliance, DO or reduced bladder capacity. Videourodynamic studies (VUD) were performed via a 6 Fr or 8 Fr dual channel cystometry catheter (Digitimer, UK), rectal pressure transducer, and, in most of cases, perineal surface electromyography (EMG). In 48 (92%), the cystometry catheter was placed urethrally, and in 4 (8%) via suprapubic route under GA the previous day. From 2008 onwards, a 50:50 mixture of nitrous oxide (N_2O) and oxygen (O_2) (ENTONOX®; BOC Healthcare, UK) was administered by inhalation to help reduce the child's discomfort during insertion of the urethral and rectal catheters. VUD equipment (Life-Tech, USA) was used with a Urovision (Medi-Globe, Germany) software package for data acquisition.

Slow or medium fill cystometry took place using warmed Urografin 150 (Bayer Healthcare, UK). Measurement of fill rate, filling pressures, detrusor pressures during episodes of DO, detrusor leak point pressure (LPP) and cystometric capacity were taken. Radiographs were taken during early, mid and end-fill as well as when possible during voiding, and post-void. Voided volumes were measured, as were post-void bladder residuals when present. EMG was analysed and findings of detrusor sphincter dyssynergia (DSD) were noted. Bladder compliance was characterised as 'normal' or 'reduced' based on the shape of the VUD pressure/volume curve, with an end-fill pressure of > 10 cm H_2O indicating reduced compliance [6].

All injections of BTA were performed under general anaesthesia using a rigid 9.5 Fr cystoscope (Karl Storz, UK) with a straight working channel to enable easy passage of a 5 Fr Williams cystoscopic injection needle (Cook Medical, Ireland). Either 375 units or 500 units (not in those < 12 years) of Dysport™ diluted with normal saline to a total volume of 20 ml (concentration either 18.75 units/ml or 25 units/ml) were loaded onto the Williams needle. Aliquots of 1 ml were injected at twenty equally distributed sites in the detrusor muscle, sparing the trigone. If the patient had previously undergone augmentation cystoplasty, injections were placed in the native bladder and the bowel augment was avoided. All patients received prophylactic antibiotic cover. Patients were allowed home on the day of the procedure and instructed to resume their preoperative anticholinergic and CIC regimen.

Initial clinical review was at 3 months and regularly thereafter. Response effect was categorised as none, moderate (less frequent and/or reduced volume wetting episodes) or dry. Repeat injection was offered if there was no effect after an initial injection or a waning response following initial or multiple injections. The use of a symptom score (dysfunctional voiding symptom score [7] or wetting and functional voiding disorder score [8]) to objectively measure symptom severity and response to treatment was evaluated as they potentially enable a more structured analysis. However, due to the retrospective nature of this study, neither scoring system could be applied to archived patient records and so were not employed in the final analysis.

Statistical method

Data were collated and analysed with Excel® (Microsoft, US) and are given as percentages, medians (interquartile range, IQR) or mean (standard deviation, SD). Statistical tests were performed with online software (VassarStats.net). Categorical variables were described by frequency and percentage, and numerical variables were described by mean and standard deviation (SD) or median and interquartile range (IQR). Relationship between categorical variables was analysed by Chi-square. Two independent means were compared by Student's t test and two independent medians were compared by Mann–Whitney U test. $p < 0.05$ was regarded as statistically significantly different.

Results

Over the 10-year study period, 102 intradetrusor injections of BTA were performed in 52 children (28 boys, 54%). Group 1 (NB) comprised 28 children (54%), of which 17 (61%) were boys. Group 2 (NNB) comprised 24 children (46%) with 11 (46%) boys.

In group 1, 23 (82%) had normal upper renal tracts on RUS, with one showing right pelvicalyceal dilation and scarring of poles, one showing a small left kidney and one being a transplanted kidney. There was no RUS for two patients. Spinal dysraphism was present in 18 (64%), with 17 (94%) open myelomeningoceles and 1 (6%) closed defect (tethered cord within lipomatous mass with associated sacral agenesis). Of the open defects, 1 was thoracic (6%), 4 lumbar (24%) and 12 sacral (71%). The causes of NB in the other 10 (36%) included cerebral palsy and idiopathic congenital dystonia.

CIC was being performed by 21 (75%) (including all 18 with spinal dysraphism). Recurrent urinary tract infections (UTI) were present in 7 (25%). Eleven (39%) had undergone bladder procedures prior to injection of BTA. Four had suprapubic catheter (SPC) insertion alone. Four had augmentation colocystoplasty, three of whom had appendicular Mitrofanoff formation, including one who also had two cadaveric renal transplant procedures. One had an appendicular Mitrofanoff and injection of Deflux® (hyaluronic acid/dextranomer, Salix Pharmaceuticals, USA) to the bladder neck, one had ureteric reimplantation, ureterocele excision and Deflux® and one had Deflux® alone.

In group 2, 18 (75%) had normal upper renal tracts on RUS, with no RUS for the other 6. All had clinically normal spinal examination, and 7 (29%) underwent spinal MRI which ruled out a spinal cord anomaly. Two (8%) had refractory daytime only symptoms, 20 (83%) had day and night time wetting, 1 (4%) nocturnal enuresis and 5 (21) recurrent UTI. Four (17%) had undergone bladder procedures prior to injection of BTA. Two had SPC insertion, one had a vesicostomy and subsequent closure and one had Deflux® alone.

Forty-five (87%) had reduced bladder compliance with or without DO (Fig. 1), 28 in group 1 (100%) and 17 in group 2 (71%). Mean end-fill detrusor pressure was 63 cm H_2O (SD 26 cm H_2O) in group 1 and 74 cm H_2O (SD 47 cm H_2O) in group 2 ($p = 0.45$, Student's t test). The median bladder capacity was 40.4% below expected for age (IQR 12.1–61.6%) (32.6% (5.1–70.5%) for group 1 and 45.2% (23.7–59.2%) for group 2, $p = 0.62$, Mann–Whitney U test). There was no leak demonstrated during urodynamics for 28 (54%), so no LPP was recordable for these. A leak was significantly more likely to be demonstrated during urodynamics in group 1 than group 2 [18 of 28 (64%) versus 6 of 24 (25%), respectively ($p = 0.01$, Chi-square test)]. For those who leaked, there was no significant difference in the mean LPP between groups 1 and 2 [35.9 cm water (SD 11.6 cm) and 41.2 cm water (SD 17.0 cm), respectively ($p = 0.4$, Student's t test)].

The median age at first injection was 11.8 years (9.5–14.4 years) and there was no significant difference between group 1 and group 2 [11.1 (9.2–14.0) and 12.3 (10.0–14.6) years, respectively ($p = 0.24$, Mann–Whitney U test]. After initial injection, 40 (77%) reported symptomatic improvement and 17 of these 40 (43%) became dry (Fig. 2 and Table 1). There was no significant difference in response to the initial injection between groups ($p = 0.11$, Chi-square test). The median duration of improvement after first injection was 7 months (6–14 months) [10.5 (5.5–14.25) months in group 1 and 6.5 (5.75–9.25) months in group 2 ($p = 0.36$, Mann–Whitney U test].

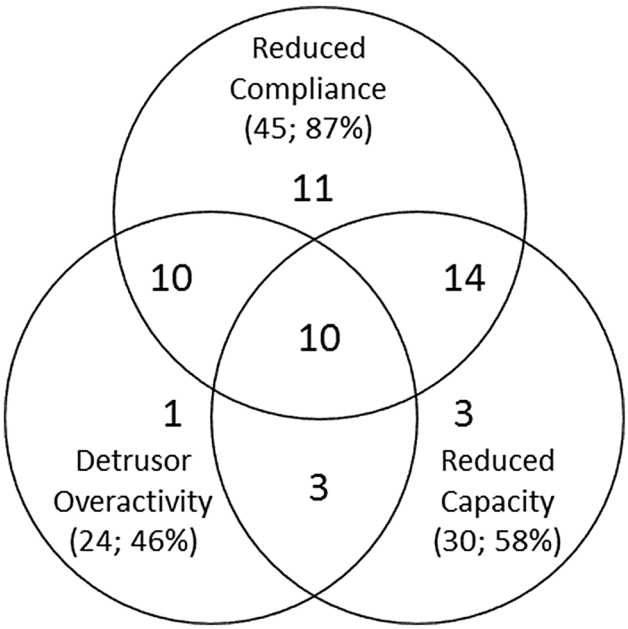

Fig. 1 Prevalence within study population ($n = 52$) of detrusor overactivity, reduced bladder compliance and reduced bladder capacity (40% or more below expected volume for age of patient)

Twenty-five (48%) had further injections (Fig. 2), of whom three (12%) were initial non-responders (two in group 1 and one in group 2). Nineteen had an initial dose of 375 units of BTA, of whom six (32%) had subsequent injections at the higher dose of 500 units. The higher dose was usually indicated if there was only a moderate response to the initial dose, or the child was < 12 years of age at initial injection and > 12 years of age at subsequent injection. Of those undergoing multiple injections, 11 (44%) had 2 injections, 10 (40%) had three injections and 4 (16%) had four or more injections. Twenty (80%) reported ongoing improvement, 11 (44%) of whom were dry (Table 1). There was no significant difference in overall response to injections between groups ($p = 0.11$, Chi-square test). The median interval between injections was 14 months (10–20 months). Those with repeat injections had a median duration of improvement of 11.5 (6–20) months after each repeat injection [9 (5.5–12) months in group 1 and 9.5 (6–21) months in group 2 ($p = 0.90$, Mann–Whitney U test)]. Comparison of median duration of improvement with initial injection versus repeat injections was not significantly different in group 1 (10.5

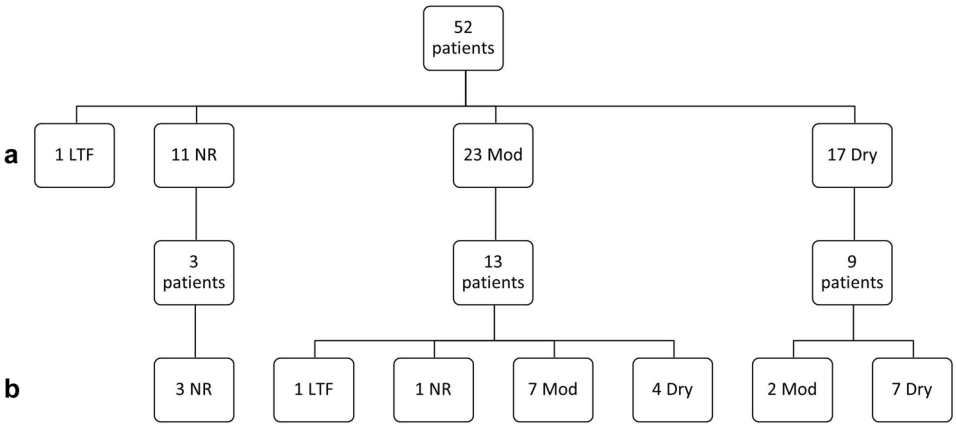

Fig. 2 Responses to botulinum toxin A after initial (**a**) and further intradetrusor injections (**b**). *LTF* lost to follow-up, *NR* no response, *Mod* moderate response

Table 1 Responses to botulinum toxin A after initial and multiple intradetrusor injections

Group	LTF	NR	Mod	Dry	Total
After one injection					
All	1 (2%)	11 (21%)	23 (44%)	17 (33%)	52
NB	0	8 (29%)	14 (50%)	6 (21%)	28
NNB	1 (4%)	3 (13%)	9 (38%)	11 (46%)	24
After 2+ injections					
All	1 (4%)	4 (16%)	9 (36%)	11 (44%)	25
NB	1 (6%)	3 (18%)	7 (41%)	6 (35%)	17
NNB	0	1 (13%)	2 (25%)	5 (63%)	8
Overall					
All	2 (4%)	12 (23%)	19 (37%)	19 (37%)	52
NB	1 (4%)	9 (32%)	11 (39%)	7 (25%)	28
NNB	1 (4%)	3 (13%)	8 (33%)	12 (50%)	24

NB neuropathic bladder (group 1), *NNB* non-neuropathic bladder (group 2), *LTF* lost to follow-up, *NR* no response, *Mod* moderate response

Table 2 Response of patients by aetiology following initial botulinum toxin A injection

	NR	Mod	Dry	Total
NB (SD)	3	12	3	18
NB (non-SD)	5	2	3	10
NNB	3	9	11	23
Overall	11	23	17	51[a]

NB neuropathic bladder (group 1), *SD* spinal dysraphism, *NNB* non-neuropathic bladder (group 2), *NR* no response, *Mod* moderate response

[a]One lost to follow-up

Table 3 Response of patients with or without detrusor overactivity following course of botulinum toxin A injections (one or more injections)

	NR	Mod	Dry	Total
DO present	7	12	4	23
DO absent	5	7	15	27
Overall	12	19	19	50[a]

DO detrusor overactivity, *NR* no response, *Mod* moderate response

[a]Two lost to follow-up

vs 9 months; $p=0.28$, Mann–Whitney U test) or in group 2 (6.5 vs 9.5 months; $p=0.13$, Mann–Whitney U test) when analysed separately, but was significantly different overall (7 vs 11.5 months; $p=0.04$, Mann–Whitney U test). Four children (8%) went on to have further injections of BTA following transition of their care to adult urology.

Eleven patients (21%) did not improve, 8 (73%) in group 1 and 3 (27%) in group 2 (Table 2). There was no difference in mean LPP between those who responded to BTA injection and those who did not [37.5 cm water (SD 14.8) and 36.6 cm water (SD 7.9), respectively ($p=0.88$, Student's t test)].

On comparing specific responses (none, moderate and dry) after initial injection, those in group 1 with spinal dysraphism were significantly less likely to achieve dryness ($p=0.034$, Chi-square test; Table 2). However, there was no significant difference after initial injection in the rate of overall positive response (moderate and dry combined) between aetiological groups ($p=0.06$, Chi-square test). Additionally, there were no significant differences in overall ($p=0.11$, Chi-square test) or specific ($p=0.13$, Chi-square test) responses between aetiological groups when multiple injections were considered. Although there was no significant difference in specific response between those with and those without DO after initial injection ($p=0.49$, Chi-square test), those with DO were significantly less likely to achieve dryness when multiple injections were considered ($p=0.021$, Chi-square test; Table 3).

Four children had undergone prior bladder augmentation (all in group 1) and all had received two injections at the time of data collection. One reported no effect, two reported moderate improvement and one achieved dryness. Of the

other 11 children to have undergone prior bladder procedures (SPC, Mitrofanoff formation, Deflux® injection), 8 (73%) responded to BTA injection.

Of the 11 (21%) non-responders to initial injection, 8 (73%) were in group 1 and 3 (27%) in group 2. None (0/3) improved after subsequent injection. Three of the 11 (27%) (all in group 1) subsequently underwent major urological surgery (bladder augmentation in one, urinary diversion in another and urethral closure in the third).

Three (8%) of the 40 who responded to BTA injection eventually required surgery (all in group 1), with two of these (5%) undergoing major urinary tract procedures. The first reported moderate improvement for 18 months following BTA injection and underwent bladder neck surgery and Mitrofanoff formation 4 years after injection. The second reported moderate improvement with two BTA injections and underwent bladder augmentation, with a further BTA injection resulting in a moderate response. The third reported moderate to complete improvement with two BTA injections and underwent Deflux® injection to the bladder neck.

Seventeen (33%) required further urodynamics (12 in group 1, 5 in group 2), with repeat studies offered based on clinical indications (deterioration in appearance of renal tracts or worsening symptoms) or prior to surgery. There was no significant difference in bladder capacity ($p = 0.41$, paired t test) or bladder filling pressure ($p = 0.25$, paired t test) following BTA injection. Of the six who underwent surgery post-BTA injection (all group 1), none of the three non-responders, but all three of the responders had a repeat study pre-operatively.

The median duration of follow-up was 25 months (11–53 months). One (2%) was lost to follow-up after their first injection and one (2%) after their second injection. Three (6%) had short-lived adverse effects after BTA injection including difficulty initiating voiding, painful penile sensation and mild lower abdominal pain. One (2%) had a UTI post-procedure and one (2%) had haematuria (child was on aspirin for cerebrovascular disease).

Discussion

Spina bifida is the most common congenital cause of neurogenic bladder [2]. Children with neurogenic bladder may initially be treated with anticholinergic drugs and undergo CIC [9]. However, in some patients, surveillance upper tract RUS may demonstrate new hydronephrosis or renal scarring. In addition, the child may suffer from significant UTIs despite medical management or become frustrated by ongoing urinary incontinence or wetting in between their catheterisations. Other treatment options then need to be explored, including newer modalities such as biofeedback and neuromodulation, but these have not been consistently reported to provide satisfactory results [10].

Surgical treatment such as bladder augmentation may then come under consideration, but such major procedures may result in long-term complications including recurrent UTIs, excessive mucus production, stone formation, metabolic problems and, in the longer-term, neoplasm. Bladder rupture, although rare, can occur in augmented bladders, and this carries a serious risk of mortality [5].

BTA contains 50-kDa light chain protease enzyme which blocks the fusion protein SNAP-23 at the neuromuscular junction. This blocks the release of acetylcholine at the neuromuscular junction interfering with nerve impulses and thus causing temporary paralysis of the target organ. In urological conditions, these injections reduce activity on the external sphincter and detrusor, leading to bladder paresis and a low-pressure reservoir. BTA injection has also been shown to lead to a reduction in muscular M2 and M3 receptors and sensory P2X2 and P2X3 receptors [5, 11, 12].

A range of studies have shown that BTA injection is beneficial in adult populations with DO [3, 13]. Schurch was the first to report on its effectiveness in treatment of teenagers and adults with anticholinergic-resistant DO from spinal-cord injury in 2000 [14], with the first report of its use in children published by Schulte-Baukloh in 2002 [15]. There have since been several studies indicating that BTA injections improve both the urodynamic measurements (reflex volume, maximal detrusor pressure, bladder capacity, and compliance) and symptoms of DO in neurogenic [12, 15–17] and non-neurogenic bladder [18] in children.

One factor that can affect the long-term efficacy of BTA is the formation of neutralizing antibodies. This has only been noted in one study, but levels of antibodies did not increase on repeated injection [19]. Although BTA injection has been reported to lead to axonal sprouting and the generation of new synaptic contacts on paralysed muscle fibres, this has only been observed in striated muscle. No structural effects have been shown to occur within smooth muscle when the effects of BTA injection on human detrusor were analysed [20]. The recurrent trauma to the detrusor of repeated injections of BTA may also result in scarring and subsequent reduction of bladder compliance [20]. However, despite these concerns regarding the sustainability of response to BTA, in studies with repeated injections where BTA was injected again after urodynamic parameters returned to baseline values, each new injection produced similar, if not better urodynamic measurements as well as prolonged effective duration lasting from 8 to 15 months [1, 21–24].

The aim of the present study was to evaluate the decade-long experience of our centre in providing intradetrusor BTA injection as a management option in children with bladder dysfunction of neurogenic or idiopathic aetiology that was refractory to maximal conservative management

with anticholinergics and CIC. Our data shows that overall, over three quarters of the children treated experienced a prolonged positive response to initial BTA injection, with almost one-third achieving dryness. Of those who underwent further injections, 80% continued to respond with nearly half becoming dry. Although we did not perform assays to determine the presence of neutralising antibodies to BTA, our results would suggest that over the long term, tolerance to the effects of BTA injection is not a major issue in those who benefit from it, with our duration of response to injection comparable to previous reports [1, 21–24]. Indeed, our results demonstrated a significantly increased duration of response to repeat injections in comparison to initial injection of BTA. Use of the onabotulinumtoxinA form (BotoxTM, Allergan, US) of BTA in children has been documented previously [1, 3, 16, 21], but only the abobotulinumtoxinA form of BTA (DysportTM) was used for injection in our unit, as has been reported in other studies [19, 23].

As none of the initial non-responders improved after subsequent BTA injection, we would advocate against multiple attempts at eliciting a response to BTA if there is no evidence of a beneficial response after one injection. Those with spinal dysraphism were significantly less likely to achieve dryness after a single injection, but this effect did not persist once multiple injections were considered. The mechanism for this is uncertain, but our findings provide optimism for ongoing improvement in response to repeated BTA injections in those with spinal dysraphism. In contrast, those with DO were significantly less likely to achieve dryness when multiple injections are taken into account and may indicate that while BTA may ameliorate symptoms in this group of children, careful follow-up is necessary, and consideration of operative intervention may be appropriate if they remain refractory to treatment.

An encouraging finding was the positive response to BTA injection of 3 of the 4 children who had previously undergone bladder augmentation. This indicates that even when major urinary tract surgery has been resorted to, but where symptoms remain persistent, BTA injection may yet contribute to the management of these children. Over the period of follow-up, only 5% of those who improved with BTA injection eventually underwent major surgery, in comparison with 27% of the non-responders. Although we did not demonstrate any improvement in urodynamic parameters as reported elsewhere [16, 18, 24], our findings provide further evidence of the role of BTA injection in reducing the need for more invasive approaches over the medium to long term.

We recognise this study has limitations due to its retrospective nature and that a prospective randomised trial may provide more robust data in future. A further limitation was that subjective assessment, rather than a validated voiding symptom score, was used for determining response to injection and decision-making regarding further BTA injections. Our decisions on BTA dosage were based on available data at the start of the study period in 2006 from adult and paediatric reports of BTA use, with adult doses of up to 600 units being used in our unit. The dose was not adjusted based on weight or response as has been reported elsewhere [16].

Conclusion

Intradetrusor injection of BTA produced symptomatic improvement in 77% of our study population, with no significant differences in response between NB and NNB groups and minimal adverse effects. In 95% of those who improved, major urinary tract procedures were avoided during the period studied. None of the initial non-responders improved after subsequent BTA injection. Our results provide further evidence that intradetrusor BTA injection is a safe and effective therapy option in the management of children with neuropathic and non-neuropathic bladder who fail to respond to conservative medical therapy.

Compliance with ethical standards

Conflict of interest The authors have no conflict of interest to declare. No funding source was involved in this study.

Ethical approval All procedures performed on human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from the parents of each child prior to all the procedures. All parents were informed about the procedure and off-label status of the BTA therapy.

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