Botulinum-A Toxin: Solo Treatment for Neuropathic Noncompliant Bladder

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Purpose: We investigated whether botulinum-A toxin is better used alone or in conjunction with oxybutynin chloride in the management of refractory neuropathic bladder.

Materials and Methods: Between March 2004 and February 2006 a total of 23 children (mean age 5.6 ± 2.5 years) with neuropathic bladder refractory to medical treatment underwent cystoscopic treatment with botulinum-A toxin. Patients were randomly assigned postoperatively using closed envelopes (blind randomization) into 2 equal groups. Group 1 (12 patients) continued to receive anticholinergics while in group 2 (11 patients) anticholinergics were discontinued. Clinical and urodynamic evaluations were performed before injection, and at 1 and 6-month intervals. Patients were then followed every 6 months with urodynamic study. The outcomes were compared between groups with a paired t test (2-tailed) and a significant p value <0.025.

Results: Maximum bladder capacity increased from 96 ± 67 (range 15 to 277) to 163 ± 96 ml (range 50 to 500, $p<0.001$) and 142 ± 65 ml (range 21 to 250, $p<0.006$) at 1 and 6 months, respectively. Maximal detrusor pressure decreased from 76 ± 36 (range 36 to 209) to 50 ± 22 cm H_2O (range 20 to 100, $p<0.001$) and 51 ± 21 cm H_2O (range 18 to 104, $p<0.001$) at 1 and 6 months, respectively. From a clinical point of view 9 of the 16 incontinent patients (56.2%) showed complete continence after treatment while 4 (25%) reported mild to moderate improvement and 3 (18.8%) showed no improvement. None of the patients had side effects related to the procedure or the material used.

Conclusions: We confirmed the beneficial use of botulinum-A toxin for the treatment of refractory neuropathic bladder and have not yet found any augmentative effect of oxybutynin chloride in this study group. Accordingly we can use such a modality as sole treatment for noncompliant neuropathic bladder.

Key Words: urinary bladder, neurogenic; botulinum toxin type A

Botulinum toxin is a presynaptic neuromuscular blocking agent inducing selective reversible muscle weakness for up to several months when minute quantities are injected intramuscularly.[1] BTX-A is a neurotoxin produced by the facultative anaerobe clostridium botulinum that blocks the release of acetylcholine into the synaptic gap of the neuromuscular junction. Injection of botulinum toxin near the nerves that supply the target organ selectively and temporarily paralyzes the organ. In the skeletal muscles it blocks acetylcholine release by modulating a membrane bound protein, SNAP25, and in smooth muscle it has been proven to trigger the release of nitric oxide that diffuses out of the endothelial cells into the muscle, causing relaxation.[2]

Since the success of purifying botulinum toxin type A in crystalline form in 1946, it has been extensively researched to identify clinical uses.[3] However, it was not until 1973 that Scott et al first published a study on the effect of botulinum toxin on the lateral rectus muscle of the monkey.[4] The first clinical study in humans was published in 1981 in patients with strabismus.[5] This modality of treatment was approved by the Food and Drug Administration in 1989 in the form of Botox®,[1] a year after the first published data on use in patients with urological dysfunction.[6] Today the clinical use of BTX-A has expanded to involve many medical specialties. In urology applications for BTX-A are increasing to include neuropathic detrusor overactivity, detrusor-sphincter dyssynergia, motor and sensory urge, chronic prostatic pain,[1] and recently benign prostatic hypertrophy.[7]

The use of BTX-A in children occurs worldwide and is becoming a standard in the treatment of spasticity secondary to cerebral palsy. No systemic side effects have been reported when the appropriate dose is used and the previous reported studies that used BTX-A on children did not report any side effects related the BTX-A.[8]

Children with neuropathic bladder are classically treated with anticholinergic drugs such as oxybutynin chloride and undergo intermittent catheterization 4 to 5 times daily.[9] Because this therapy fails in approximately 10% to 15% of patients, children are at risk from the high intravesical pressure that can cause significant renal damage. Others might have severe systemic side effects that necessitate discontinuation of the drug even if administered intravesically. This group of high risk patients is either treated with

Study received approval from the Ethical Committee of the College of Medicine Research Center, King Saud University, Riyadh, Kingdom of Saudi Arabia.

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incontinent urinary diversion or reconstructive bladder surgery with augmentation cystoplasty.

In 2002 the first study was published showing the effect of botulinum-A toxin on children with urological dysfunction. The study was designed for those who did not respond to CIC and oxybutynin or had significant side effects with oxybutynin.[10] The authors further analyzed the same group of patients in 2003.[4] They concluded that botulinum-A toxin is effective when injected into the hyperreflexive detrusor muscle in children where they found that mean reflex volume, maximal detrusor pressure and maximal bladder capacity were statistically significantly improved up to 6 months after injection with 12 U/kg (with a maximum dose of 300 U) Botox. No serious side effects such as weakness of the respiratory muscles or further paresis of the extremities were seen, nor were there complaints about dry mouth or dysphagia.[11] The same result was reproduced by Riccabona et al in a study of 15 patients, 3 of whom became completely dry with a mean maximum detrusor pressure significantly reduced to 42.76 ± 24.83 from 78.76 ± 23.14 cm H_2O, and bladder capacity significantly increased from 72 to 298 ml.[12] A similar encouraging result for BTX-A in children was reported by Kajbafzadeh et al.[13] They used BTX-A in 26 children of whom 73% became completely dry between clean intermittent catheterization and the end of treatment, with a mean detrusor maximal pressure improved to 83.2 ± 4.6 from 139.3 + 11.2 cm H_2O ($p < 0.01$), as well as a similar improvement in bladder capacity.

Previously published reports have not shown a synergistic effect between botulinum toxin and anticholinergic medication because using both or only 1 of them was not randomized. This study was designed to examine the effect of BTX-A and to see whether it is better used alone in the management of refractory neuropathic bladder or in conjunction with anticholinergic medications.

PATIENTS AND METHODS

Patient Population

In a prospective randomized study 23 children (2 to 11 years old, mean age 5.6 ± 2.5 years) with neuropathic bladder after repair of myelomeningocele were potential candidates for enrollment. The level of the lesion was lumbar in 15 patients, lumbosacral in 7 and sacral in 1. None had prior surgical intervention (open or endoscopic) to increase continence. Inclusion criteria were age range 1 to 14 years old with urodynamic evidence of high intravesical leak point pressure greater than 40 cm H_2O resistant to the maximal tolerable dose of anticholinergics (oxybutynin chloride 0.1 mg/kg) without significant side effects, and fully compliant to an every 4 to 6-hour program (CIC). We did not use intravesical oxybutynin in this group of patients, all of whom were tolerating it orally. All patients had already undergone baseline and followup assessment consisting of a serial history and clinical examination, urinalysis, renal and bladder ultrasound, voiding cystourethrogram and urodynamic studies.

Urodynamic Assessment

This was performed by the Duet® Logic G/2 after a negative urine culture and proper bowel preparation to ensure complete evacuation of the rectum at the time of the study. The intravesical pressure was measured using a 6Fr double lumen catheter. Abdominal pressure was measured with a 10Fr rectal catheter. Bladder filling with normal saline at room temperature was performed at a rate of 10% of predicted bladder capacity calculated with the Koff formula [(age +2) × 30]. Maximal bladder capacity and detrusor leak point pressure were measured. The continence scale was graded 0 to 3, with 0—completely dry, 1—wet once a day, usually at night, 2—wet for less than 50% of the time between catheterizations and 3—wet for more than 50% of the time between catheterizations.

BTX-A Injection

The procedure was done with the patient under general anesthesia, with a single shot prophylactic antibiotic. We used botulinum-A toxin in a dose of 12 IU/kg not exceeding a maximum of 300 IU diluted in normal saline, resulting in a concentration of 10 IU/ml. The injection needle (3.7Fr/35 cm, tip 23G) was introduced through a 10Fr cystoscope with an offset lens (Karl Storz, Tuttlingen, Germany). Injections (0.5 to 1 ml per injection) were spread along the midline and lateral walls of the bladder sparing the trigone and the bladder dome. A urethral catheter was left indwelling for 24 hours before resuming CIC regimen with the same preoperative frequency.

Randomization was performed using closed envelopes that were opened after injection. Accordingly patients were classified into 2 groups. Group 1 consisted of 12 patients, 3 males and 9 females, 2 to 11 years old (mean 6.1 ± 2.6). Oxybutynin chloride was continued with the same preinjection dose. Group 2 (11 patients) was 5 males and 6 females 2 to 9 years old (mean 5.1 + 2.5). Oxybutynin chloride was discontinued on the day of the BTX-A injection and remained so throughout the study. Repeat urodynamic study was performed at 1 and 6-month intervals. Patients were continued on conservative treatment (clean intermittent catheterization and oxybutynin chloride) for 1 to 8 years (mean 3.13 ± 1.8) with no difference between both groups (group 1—1 to 5 years, mean 2.5 ± 1.45 and group 2—1 to 8 years, mean 3.8 ± 2).

Parents were asked to sign an informed consent that detailed in full the aim and steps of the procedure, and nature of the material used. The study was approved by the Ethical Committee of the College of Medicine Research Center, King Saud University, Riyadh.

RESULTS

Initially we analyzed both groups (23 patients) as a whole and found that the maximum bladder capacity increased from 96 ± 67 ml (range 15 to 277) to 163 ± 96 ml (range 50 to 500, $p < 0.001$) and 142 ± 65 ml (range 21 to 250, $p < 0.006$) at 1 and 6 months, respectively. The maximal detrusor pressure decreased from 76 ± 36 cm H_2O (range 36 to 209) to 50 ± 22 cm H_2O (range 20 to 100, $p < 0.001$) and 51 ± 21 cm H_2O (range 18 to 104, $p < 0.001$) at 1 and 6 months, respectively. Of the 23 patients 13 (56%) had a decrease in maximal detrusor pressure below 40 cm H_2O at followup.

Looking at each group separately we found that in group 1 (12 patients with oxybutynin) maximum bladder capacity increased from 96 ± 66 (range 33 to 277) to 155 ± 73 ml (range 56 to 299, $p < 0.013$) and 141 ± 62 ml (range 21 to 230, $p < 0.024$) at 1 and 6 months, respectively. The maximum detrusor pressure in group 1 decreased from 66 ± 20

Analysis of study groups

	Mean ± SE Group 1	Mean ± SE Group 2	p Value
Base max bladder capacity	96.33 ± 19.063	96.36 ± 21.489	0.999
Base max detrusor pressure	66.42 ± 5.839	88.0 ± 14.313	0.164
Max bladder capacity at 1 mo	155.0 ± 21.33	172.18 ± 35.96	0.679
Max detrusor pressure at 1 mo	50.5 ± 6.609	50.82 ± 6.93	0.974
Max bladder capacity at 6 mos	141.75 ± 17.91	143.09 ± 21.97	0.962
Max detrusor pressure at 6 mos	47.92 ± 5.39	55.09 ± 7.57	0.443

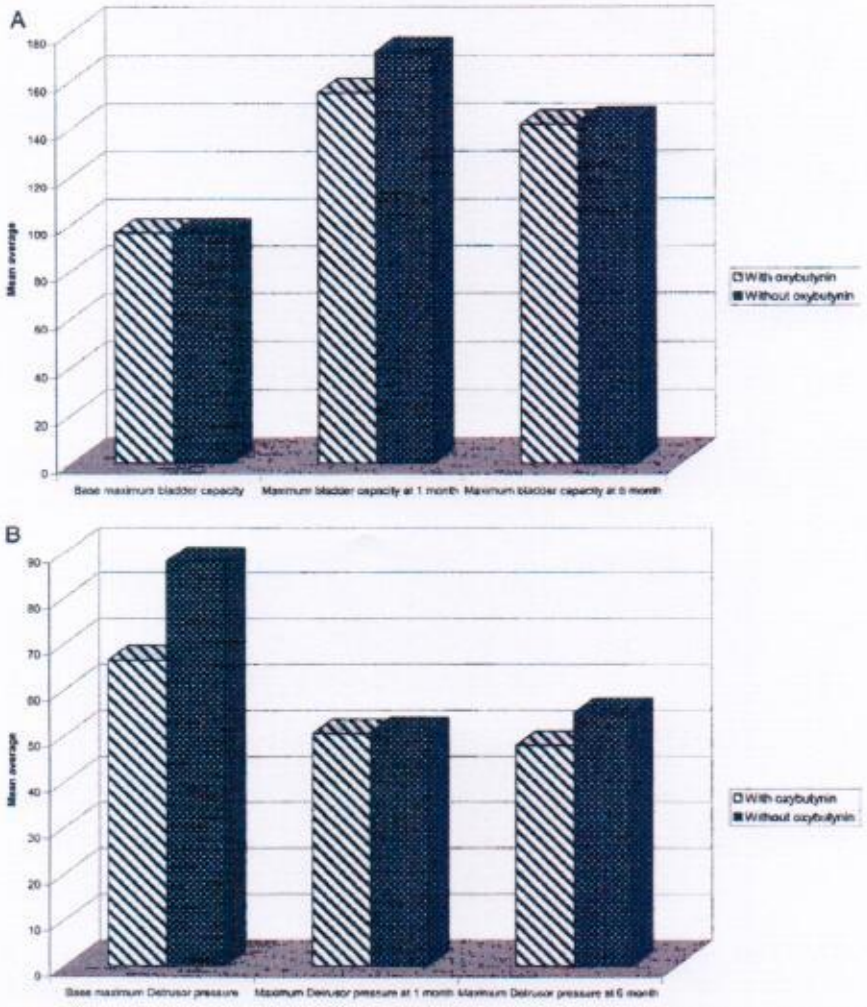
(range 36 to 99) to 50 ± 22 cm H_2O (range 20 to 100, $p < 0.001$) and 47 ± 18 cm H_2O (range 23 to 95, $p < 0.009$) at 1 and 6 months, respectively, while 7 (58%) patients maintained pressure below 40 cm H_2O.

For group 2 (11 patients without oxybutynin) maximum bladder capacity increased from 96 ± 71 ml (range 15 to 208) to 172 ± 119 ml (range 56 to 500, $p < 0.020$) and 143 ± 72 ml (range 40 to 250, $p < 0.007$) at 1 and 6 months, respectively. The maximum detrusor pressure in group 2 decreased from 88 ± 47 cm H_2O (range 50 to 208) to 50 ± 22 cm H_2O (range 20 to 95, $p < 0.017$) and 55 ± 25 cm H_2O (range 18 to 104, $p < 0.007$) at 1 and 6 months, respectively, while 6 patients (55%) maintained pressure below 40 cm H_2O.

Comparing groups 1 and 2 there were no statistical differences (with or without the use of oxybutynin chloride) in all the measured parameters at any point (see table and figure). The duration of followup was identical in both groups, repeating urodynamic study after 1 and 6 months, and planning followup every 6 months thereafter.

Of 4 patients with vesicoureteral reflux (7 refluxing ureters, 1 ureter GIII, 2 GIV and 4 ureters GV) only 1 patient had initial improvement. However, repeat voiding cystogram confirmed relapse of vesicoureteral reflux that was seen after hospitalization for acute pyelonephritis during followup.

Clinically of the 16 incontinent patients (8 in each group), 9 (56.2%, 5 in group 1 and 4 in group 2) showed complete



A, mean average of maximum bladder capacity. *B*, mean average of maximum detrusor pressure

continence after treatment, 4 (25%, 2 in each group) reported mild to moderate improvement and 3 (18.8%, 1 in group 1 and 2 in group 2) showed no improvement. We did not find any significant change in constipation status before vs after BTX-A, or comparing the groups with vs without oxybutynin chloride.

Of 46 renal units 25 had renal dilatation (3 GI, 12 GII and 10 GIII Society for Fetal Urology grading) from the 15 units dilated in group 1, 5 improved after treatment, none from the other 10 renal units had deterioration over the period of treatment. In group 2 of the 10 dilated renal units, 3 had improvement and none of the other 7 units had deterioration during the treatment period. None of those without dilatation became hydronephrotic during followup. None of our patients had side effects related to the procedure or the material used.

DISCUSSION

Management of neuropathic bladder in children with myelomeningocele is a continuing challenge to the pediatric urologist. In recent decades there have been significant advances made in this area based on progress in urodynamics and pharmacotherapy. The understanding of upper tract jeopardy when intravesical pressure exceeds 40 cm H_2O,[14] and the identification of a high risk subset of children with detrusor-sphincter dyssynergia[15] are 2 major cornerstones dictating a proactive treatment approach. The appropriate management is primarily aimed at protecting functional nephrons through reducing the intravesical pressure to safe levels. Providing the child with the social acceptability through acquisition of dryness and cleanliness in a diaper independent state comes next. The latter tends to become a major concern as the child advances to school age and beyond, and starts to reclaim rights to independence and autonomy.

To achieve these goals anticholinergics as oxybutynin chloride along with CIC are recruited to reduce intravesical pressure, improve capacity and ensure regularly timed proper emptying of the bladder. Nevertheless, there remains a group of children in whom these measures fail. This condition is either refractory to standard treatment or to the result of development of intolerable systemic side effects from anticholinergics even with intravesical administration. As a result augmentation cystoplasty is used to gain control of intravesical pressure. In addition to being a major surgery, incorporation of bowel segments into the urinary tract has well-known intermediate and long-term complications.[16] There is also increasing concern regarding the use of oxybutynin chloride even if used intravesically because up to 40% of patients had to discontinue this line of treatment because of significant side effects.[17]

Since the last decade there has been increasing evidence that BTX-A is a highly effective second line treatment for patients with neuropathic detrusor overactivity, which was pioneered by Schulte-Baukloh et al.[10] Patients with urodynamically proven neuropathic detrusor overactivity with spinal cord injury who emptied the bladder with clean intermittent self-catheterization were recruited into this preliminary study. Botox (200 to 300 U) was injected into the bladder at 30 sites under cystoscopic guidance, sparing the trigone. After BTX-A injection mean maximum bladder capacity increased by 62% ($p < 0.05$) and mean maximal detrusor pressure decreased by 46% ($p < 0.05$). In addition, 17 of 19 patients were completely continent at 6-week followup. The 2 patients who remained incontinent but still had moderate improvement in symptoms had received a lower dose of BTX-A. Ten patients reduced the anticholinergic medications required before injection and the 7 others no longer felt the need to take them at all. At 16 and 26 weeks after injection, 11 patients showed ongoing improvement in bladder function.

Furthermore, in a retrospective European multicenter experience involving 200 patients with neuropathic bladder dysfunction treated with detrusor BTX-A injection, Reitz et al reported that urodynamic testing revealed significant increases in maximum bladder capacity and decreases in voiding pressure at 3 months (200 of 200 patients) and 9 months (99 of 200 patients) of followup,[18] similar to earlier findings.

In 2002 the first data showing the effect of BTX-A on children with urological dysfunction were published.[10] The study was designed for those in whom intermittent catheterization and oxybutynin chloride failed, or those who had significant side effects from the latter treatment. The authors further analyzed the same group of patients in the data published in 2003.[11] They concluded that BTX-A is effective when injected into the hyperreflexive detrusor muscle, and they found that the mean reflex volume, maximal detrusor pressure and maximal bladder capacity were statistically improved up to 6 months after BTX-A injection (12 units per kg, maximum dose of 300 units). No serious side effects like weakness of the respiratory muscles or further paresis of the extremities were seen, nor were there complaints of dry mouth or dysphagia. Nevertheless, none of these pioneering reports clearly delineated the effect of BTX-A on the detrusor apart from anticholinergics in a planned comparative manner to define the exact role of this new modality without the interference of another extrinsic factor.

To the best of our knowledge the current study is the first to prove that oxybutynin has no augmentative effect in those treated with BTX-A, and that BTX-A can be used as a solo treatment for children with neuropathic overactive bladder. In both study groups intravesical injection of BTX-A significantly improved bladder capacity and compliance, and did not show any negative effect from stopping anticholinergic medications during the study. Furthermore, in our group BTX-A injection restored continence in 9 of 16 incontinent patients. The improvements in continence and urodynamic performance were maintained for up to 6 months. Despite the clear beneficial effect of BTX-A injection from a clinical and urodynamic point of view, it is still used with some limitation, particularly in children, primarily because it requires comprehensive followup with an average of 2 to 4 urodynamic studies per year. This might not be feasible at some centers and treatment has to be given to children while they are under general anesthesia. However, it is worth going through such difficulties and avoiding major reconstructive surgery with the sequela in children if such followup can be provided.

CONCLUSIONS

The current data independently confirmed the effectiveness and tolerability of BTX-A for detrusor overactivity as a solo treatment in children not responding to standard conserva-

tive treatment, a salvage procedure before reconstructive bladder surgery, although we recognize the need for larger, longer term studies with repeat injections. We investigated whether oxybutynin would have any augmentative effect on our protocol, which it did not. A similar protocol should be made for other anticholinergic medication to see if BTX-A alone would have a similar effect, or whether other anticholinergics would have an augmentative effect on intravesical BTX-A treatment.

Abbreviations and Acronyms

BTX-A = botulinum-A toxin
CIC = clean intermittent catheterization

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EDITORIAL COMMENTS

Although this is a well written article that investigates the effectiveness of BTX-A as a single agent to decrease leak point pressures in children with neurogenic bladder, it raises questions concerning its role in their treatment.

The authors state that Botox significantly reduced maximal detrusor pressure from 76 to 50 and 51 cm H_2O at 1 and 6 months after injection, respectively. Unfortunately these lower pressures are not at or below 40 cm H_2O, which is our goal in treating these children. It is encouraging to see that serial ultrasound examination is being performed with these children to ensure that hydronephrosis does not develop while leak point pressure remains increased.

It is also unclear what happens to the children in whom bladder pressure is not reduced after injection therapy. Although the authors state that patients were followed every 6 months with urodynamic study, they do not clarify how many of the children went on to require bladder augmentation.

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Since the first report on BTX-A in pediatric patients in 2002 there has been increasing enthusiasm for this agent in neuropathic bladder disease (references 10 and 12 in article). The relative value of BTX-A in the treatment of neuropathic bladder disorders is also confirmed by the underlying study. Despite the relatively small number of patients the authors convincingly show that solo BTX-A salvage treatment is effective in high risk patients with neuropathic bladder without any additional anticholinergic medication. The fact that anticholinergics may be omitted after BTX-A injections could help us avoid the significant side effects.[1] This is an important issue since there has been increasing evidence of serious side effects of oxybutynin and related substances, including impaired cognitive and psychomotor function.[1] Most importantly, constipation as an inherent feature of myelodysplasia may resolve or improve in some patients (reference 13 in article). Lastly, the relative burden of taking daily medication will be decreased using BTX-A in a solo fashion. The lack of synergistic effects between anticholinergics and BTX-A implies additional modes of action besides

traditional presynaptic blocking. Thus, other agents such as selective P2X3 receptor blockers may favorably add to BTX-A in the management of complex neuropathic bladder.

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REPLY BY AUTHORS

We agree that our goal always should be to keep the intravesical pressure below 40 cm H_2O. In the current study we were looking at a new group of refractory neuropathic bladders in which we were able to lower the intravesical pressure significantly in a minimally invasive manner, with resolution of the accompanying hydronephrosis. Persistent improvement was monitored during followup with ultrasound every 6 months. Close followup is highly recommended for patients with high intravesical pressure.