ABSTRACT
Objectives. To evaluate the efficacy of botulinum toxin A in the treatment of children with detrusor hyperreflexia caused by myelomeningocele and the effects of this treatment on neuropathic bladder and bowel dysfunction.

Methods. In a prospective study, 26 children with myelomeningocele (20 boys and 6 girls, mean age 6.9 years) were included. All patients had been nonresponders to medical treatment and required clean intermittent catheterization. Under cystoscopic guidance, 10 IU/kg of botulinum toxin A was injected into the detrusor muscle, sparing the trigone and ureteral orifices. In each patient, urinary incontinence grade and improvement in parameters of interest in the evaluation of bowel dysfunction were assessed before and 4 months after injection. Conventional urodynamic studies to determine maximal bladder capacity and maximal detrusor pressure and voiding cystoureterography were also performed.

Results. Four months after procedure, 19 patients (73%) had become completely dry between clean intermittent catheterizations, and the total improvement in urine incontinence was 88%. The mean maximal detrusor pressure was decreased to 83.2 ± 4.6 cm H₂O from the baseline of 139.3 ± 11.2 (P <0.01). The average maximal bladder capacity increased from 102.8 ± 6.3 mL to 270.2 ± 9.5 mL (P <0.01). Of the 15 patients who had varying degrees of vesicoureteral reflux before the procedure, 11 (73%) had decrease in the vesicoureteral reflux grade. Also, bowel dysfunction improved in 10 (66%) of the 15 patients.

Conclusions. Botulinum toxin A appears to be a safe, minimally invasive procedure for the management of neuropathic bladder and bowel dysfunction in children with myelomeningocele.

Myelomeningocele is associated with neuropathic abnormalities of the bladder and bowel function. In these patients, bowel and bladder dysfunction have the greatest impact on social integration. Detrusor hyperreflexia in children with myelomeningocele leads to high intravesical pressure, low compliance of the bladder, reduced capacity, incontinence, and ultimately, deterioration of the upper tract. The manifestations of bowel dysfunction in these children range from chronic constipation to fecal incontinence due to the increase in the frequency of bowel movements, decreased sensation of rectal fullness, and an inability to hold stool.¹

Currently, the prophylactic and therapeutic use of clean intermittent catheterization (CIC) and anticholinergic medication in patients with neuropathic bladder is the standard initial treatment for urinary incontinence.² However, a significant proportion of patients are unable to tolerate such medications or have severe incontinence or side effects from the anticholinergic medications. Many other therapeutic modalities, such as intravesical resiniferatoxin,³ biofeedback,⁴ and neurostimulation,⁵ have been developed, but the results have not been completely satisfactory. Bowel continence can typ-
ically be achieved with dietary modification, oral medication, or routine enema use. A minority of myelomeningocele patients will not respond to medical therapy and require surgical intervention to achieve renal preservation, as well as bladder and bowel continence. The frequent systemic side effects of medical treatments and complications of surgical interventions have prompted urologists to seek new treatment modalities.

Recently published reports have discussed the successful outcome of intravesical injections of botulinum toxin A (BTX-A) in patients with neuropathic or nonneuropathic detrusor hyperreflexia. This procedure, in general, has not been offered as an option to patients with neuropathic bladder and bowel dysfunction. However, our preliminary experience has shown encouraging results with this less-invasive technique in the treatment of neuropathic bladder and bowel dysfunction in children with myelomeningocele. We conducted a prospective study to evaluate the safety, tolerability, and efficacy of intravesical injection of BTX-A into the detrusor muscle. We assessed urinary and fecal efficacy of intravesical injection of BTX-A into the detrusor muscle. We assessed urinary and fecal incontinence, urodynamic variables, and vesicoureteral reflux (VUR) in patients before and 4 months after the procedure.

MATERIAL AND METHODS

This single-center, prospective, unrandomized study included 26 children (20 boys and 6 girls) with a mean age of 6.9 ± 2.6 years (range 3.5 to 13). All children had urodynamically proven detrusor hyperreflexia caused by myelomeningocele. All patients had been taking anticholinergic medications since birth and underwent CIC every 3 to 4 hours, with unacceptable adverse effects or little or no success from treatment. All subjects had a stable neurologic status and had not undergone surgery during the previous 2 years. The exclusion criteria consisted of coagulopathy, inflammation of the injection site, and urinary tract infection. The local ethics committee approved the study. The patients’ parents agreed to the treatment and were informed that the treatment was an unlicensed use of BTX-A, with the long-term effects unknown. Anticholinergic medication was discontinued at least 10 days before urodynamic assessment. In children with bowel dysfunction, suppositories or enema protocols were discontinued, but the usual diet was maintained. The initial evaluation of each patient included a full history and physical examination, the current degree of urinary incontinence and bowel dysfunction, and serum chemistry analysis, urinalysis, urine culture, and voiding cystoureterography (VCUG) findings before hospitalization. Daytime incontinence was documented in a voiding diary in which any episodes of wetness during the 4 hours between two consecutive catheterizations were recorded. Improvement in urine incontinence was defined as a decrease of two or more degrees in the daily incontinence score. The daily incontinence score was recorded on a scale of 0 to 3, as described by Schurch et al.8: score 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. Bowel dysfunction was assessed according to previously described parameters.6 Complete success was defined as improvement in all parameters of interest, and moderate success included improvement in any, but not all, parameters. Treatment failure was defined as a lack of improvement in any parameter. Four parameters were evaluated: a decrease in the number of stooling episodes, increased sensation for having a bowel movement, an increased ability to consciously hold a bowel movement, and the subjective report of significant changes in bowel habits.

For each patient, a conventional urodynamic study was performed using the Merkur 4000b urodynamic system (F.M. Wiest Medizintechnik GmbH, Unterhaching, Germany). We paid special attention to the maximal detrusor pressure and the maximal bladder capacity. Factors considered important on VCUG were the presence and grade of VUR, the severity of bladder trabeculation, and dilation of the posterior urethra.

Patients were admitted for treatment and received preoperative antibiotic treatment. Cystoscopy was performed under light general anesthesia and BTX-A (Botox, Allergan Ltd, France) was injected intravesically into at least 40 sites, sparing the trigone and ureteral orifices (Fig. 1). The toxin was diluted in 20 mL of normal saline and the dosage of BTX-A depended on the patient’s weight (10 IU/kg).8 A Foley catheter of appropriate size was inserted for 12 hours. Parents were told to start CIC afterward but the treatment with anticholinergic drugs was terminated. All patients were discharged from the hospital on the next day.

Children returned for follow-up every month. At all visits, subjects were assessed using a verbal questionnaire for evidence of adverse effects, including systemic muscle weakness, focal weakness in muscles proximal to the bladder, new onset urinary leakage, urinary tract infection, parameters of interest in bowel dysfunction, and other side effects. Four months after procedure, a thorough evaluation was performed, including urinalysis, serum blood chemistry analyses, urodynamic study, and VCUG.

Statistical analysis was performed with Statistical Package of Social Sciences software (SPSS, Chicago, Ill). The paired t test was used to compare the parametric data, and the Wilcoxon signed rank test was used in the comparison of the nonparametric data. Data are expressed as mean ± SEM, and P < 0.01 was considered statistically significant.

RESULTS

All 26 children were available for follow-up (Table I). All tolerated the procedure well, and none experienced major treatment-related adverse effects. Four months after the procedure, the mean incontinence score had improved from 2.5 to 0.3 (P < 0.001). Of the 26 patients, 19 (73%) became completely dry between two consecutive CICs and 4 of the remaining 7 patients had improved from score 3 to 1. The total improvement rate was 88% in our study.

The results of the urodynamic study showed that the average maximal detrusor pressure decreased to 83.2 ± 4.6 cm H2O from a baseline value of 139.3 ± 11.2 cm H2O (P < 0.01). The mean maximal bladder capacity had increased from 102.8 ± 6.3 mL before injection to 270.2 ± 9.5 mL at 4 months after the procedure (P < 0.01; Table I).

Of the 26 children, 15 exhibited different grades of VUR on VCUG before injection of BTX-A. A statistically significant decrease was seen in the mean VUR grades from 1.7 before the procedure to 0.7, 4 months after injection (P < 0.01). The VUR grade decreased in 11 patients (73%) (Fig. 2 and
Dilation of the posterior urethra from long-standing detrusor sphincter dyssynergia had disappeared in 7 (64%) of 11 affected children. The bladder trabeculation grade was reduced in 15 (68%) of 22 patients on the postinjection VCUG. All 15 patients with preoperative VUR had been using prophylactic antibiotic regimens since the diagnosis. The prophylactic antibiotic treatment was continued postoperatively in all children in whom VUR persisted. All these patients had experienced episodes of urinary tract infection or had renal scarring on nuclear renal scans before the procedure. However, no episode of urinary tract infection was recorded in any of the children during the follow-up study. No children required additional surgical intervention for correction of VUR postoperatively.

Considerable improvement occurred in the fecal continence of patients and the need to wear diapers or other types of protection to prevent fecal soiling decreased. Because the bowel management of each patient during and after the procedure was not changed, the improvements can be attributed to the procedure itself. Of the 15 patients with neuropathic bowel dysfunction, BTX-A injection led to complete success in 8 patients (53%) and moderate success in 2 (13%) for alleviation of symptoms.

### TABLE I. Summary of patient characteristics, urodynamic results, VUR grade, and urine incontinence score before and 4 months after treatment

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<thead>
<tr>
<th>Variable</th>
<th>Before Procedure</th>
<th>4 mo After Procedure</th>
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<tr>
<td>Urine incontinence grade</td>
<td>0</td>
<td>19</td>
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<tr>
<td></td>
<td>1</td>
<td>6</td>
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<tr>
<td></td>
<td>2</td>
<td>1</td>
</tr>
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<td></td>
<td>3</td>
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<tr>
<td>Pdet max (cm H2O)</td>
<td>139.3 ± 11.2</td>
<td>83.2 ± 4.6</td>
</tr>
<tr>
<td>MBC (mL)</td>
<td>102.8 ± 6.3</td>
<td>270.2 ± 9.5</td>
</tr>
<tr>
<td>VUR grade</td>
<td>0</td>
<td>11</td>
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*KEY:* VUR = vesicoureteral reflux; Pdet max = maximal detrusor pressure; MBC = maximal bladder capacity.

Data presented as mean ± SEM or numbers of patients.

Table 1). Dilation of the posterior urethra from long-standing detrusor sphincter dyssynergia had disappeared in 7 (64%) of 11 affected children. The bladder trabeculation grade was reduced in 15 (68%) of 22 patients on the postinjection VCUG. All 15 patients with preoperative VUR had been using prophylactic antibiotic regimens since the diagnosis. The prophylactic antibiotic treatment was continued postoperatively in all children in whom VUR persisted. All these patients had experienced episodes of urinary tract infection or had renal scarring on nuclear renal scans before the procedure. However, no episode of urinary tract

**COMMENT**

Neuropathic bladder and bowel abnormalities in patients with myelomeningocele require treatment for preservation of the upper urinary tract, bladder and bowel continence, autonomy, and social integration. The mainstay of treatment includes CIC and anticholinergic medication for urinary incontinence. Traditional management of defecation problems is based on dietary modification, stool softeners, frequent enemas, and supplements of olive oil. A minority of children will not respond to conservative therapy and will ultimately require surgical intervention. We have previously reported our surgical experience in the management of neuropathic bladder and bowel dysfunction. However, the complications of surgical procedures have limited their application. Recently, the promising effects of BTX-A for the treatment of neuropathic and idiopathic detrusor hyperreflexia have been shown by other investigators. Our re-
Results have confirmed those of earlier reports of improvement in urodynamic parameters in patients with myelomeningocele. To our knowledge, this is the first report showing the beneficial effects of intravesical BTX-A injection on bowel dysfunction and VUR in these patients.

Botulinum toxin is the strongest natural lethal toxin that inhibits the release of acetylcholine at the neuromuscular junction and causes muscular flaccid paralysis. BTX-A products were first used in urology to treat patients with spinal cord injury who complained of detrusor-sphincter dyssynergia. In 2000, Schurch et al. were the first to demonstrate the effectiveness of the toxin in the treatment of detrusor hyperreflexia that was resistant to anticholinergic drugs in adult patients with spinal cord disease. In 2002, intravesical treatment was extended to children with myelomeningocele by Schulte-Baukloh et al. They reported the use of BTX-A (12 U/kg with the maximal dose of 300 U) intradetrusral injection for the treatment of 20 patients. Riccabona et al., in 2004, also reported the use of BTX-A (10 U/kg with maximal dose of 360 U) injection for treatment of 15 children with myelomeningocele. Both groups reported a significant improvement in bladder capacity, compliance, and reflex volume and a decrease in maximal detrusor pressure.

We found comparable results to those of other studies performed of children with myelomeningocele. In our study, the daily incontinence score and maximal detrusor pressure decreased significantly, with an increment in maximal bladder capacity. The best reflection of having achieved the...

FIGURE 2. Dramatic improvement in patients with high-grade VUR. (A,C) Preoperative VCUG scan of 2 patients. (B,D) VCUG of same patients 4 months after BTX-A injection.
desired goals was the maintenance of no need for diapers or pads.

Of the 15 patients with VUR, 11 showed improvement, which was more prominent in children with worse grades of VUR. The VUR grade in all patients with a high VUR grade (1 child with grade 5 and 5 children with grade 4) decreased, indicating that this minimally invasive procedure could be a therapeutic option for VUR in these patients.

The mechanism of action of BTX-A was assumed to be the paralysis of the detrusor; however, how BTX works in the bladder is unclear. Haferkamp et al. found no ultrastructural differences in biopsies obtained from the detrusor before and 6 weeks to 4 months after BTX-A treatment. In contrast, preliminary reports have demonstrated that intravesical BTX-A injection affects the bladder’s afferent pathways, inducing prominent decreases in the expression of sensory receptors in suburothelial nerves. Moreover, the reduction in the sensation of urge has been reported in the patients treated with BTX-A for idiopathic detrusor overactivity, which may provide further support for the latter hypothesis.

In many children with neuropathic bowel dysfunction, conservative measures such as cathartics, bulking agents, enemas, and digital stimulation are successful. However, in those who did not respond, other modalities such as biofeedback techniques or more invasive approaches, including antegrade enema continence catheters and/or anal sphincter. Generalized weakness in patients who have received intravesical injections of BTX-A for idiopathic detrusor overactivity, which may provide further support for the latter hypothesis.

The same spinal cord segments are involved in coordination of bowel movements in terminal alimentary tract, as well as bladder voiding. With regard to the possible effects of BTX-A on the bladder’s afferent pathways, the presence of the common neural pathways for bowel and bladder function may explain the effects of BTX-A on bowel dysfunction. Moreover, these effects would be attributable to the absorption of toxin by adjacent structures such as the pelvic diaphragm and/or anal sphincter. Generalized weakness in patients who have received intravesical injections of BTX-A has been reported and was probably due to the diffusion of the toxin into the circulation secondary to the injection technique and a thin-walled bladder. These reports support the idea that high toxin concentrations in the local pelvic blood and lymphatic circulation have contributed to the effects of BTX-A on bowel movements. However, additional studies are needed to clarify the underlying mechanisms of this improvement.

CONCLUSIONS

The results of the present study have confirmed the safety of BTX-A treatment of detrusor hyperreflexia in children affected by myelomeningocele. We consider intravesical injection of BTX-A to be an alternative treatment to surgical procedures for those patients in whom conventional therapies have failed to produce symptomatic improvement. We have also noted efficacy of BTX-A application in the treatment of high-grade VUR in patients with myelomeningocele. Moreover, this minimally invasive procedure provided satisfactory improvement in neuropathic bowel dysfunction in these patients to the point of eliminating the need for diapers or pads. Although understandable excitement exists about the application of intravesical BTX-A in the treatment of high-grade VUR and neuropathic bowel dysfunction in children with myelomeningocele, more clinical and experimental data are required before widespread use can be recommended.

REFERENCES

is the optimal time to reinject to avoid damage to the upper tract. Clearly, additional studies are necessary before BTX-A injection can be recommended as a new modality in VUR management. The authors also found improvement in fecal incontinence in 10 of 15 affected patients. The preoperative and postoperative bowel management was not altered and the improvement was, therefore, attributed to the procedure itself. The authors suggest that the effect resulted from local absorption of the neural toxins by adjacent muscle structures such as the anal sphincter. Eight patients became completely continent of stool without further need for diapers or pads. It is certainly possible that the positive effects of BTX-A on neurogenic bladders can also relieve bowel dysfunction. Additional investigations should include standardization of the preoperative and postoperative bowel management and the addition of a control group to validate this important observation. Additionally, histologic and molecular studies are needed to better understand the mechanisms of BTX-A to develop a longer-lasting effect without the need for repeated injections.

REFERENCES

EDITORIAL COMMENT
The successful use of intravesical injections of botulinum toxin for neurogenic bladder disorders has been well reported. The mechanisms are not clearly understood, but BTX-A decreases acetylcholine release at the presynaptic level, leading to a decrease in detrusor contractility. Recently, Giannantoni et al. reported that intravesical BTX-A treatment induces a state of nerve growth factor deprivation in bladder tissue that persists for up to 3 months.

BTX-A can be used for patients who do not respond to anticholinergic therapy in combination with CIC as an alternative to delay or avoid surgical intervention. Reitz et al. reported on 231 patients from 10 European centers. Smith et al. reported their experience with 110 patients, and Giannantoni et al. demonstrated the clinical and urodynamic benefits of BTX-A toxin in a prospective randomized study. Several other investigators have verified the promising results in a variety of patients with bladder dysfunction.

The authors have confirmed these results in their group of 26 children with detrusor hyperreflexia using 10 IU/kg BTX-A. In addition to the successful bladder treatment, they report accompanying improvement in VUR and bowel dysfunction. Four months after treatment, 3 of 15 children with initial VUR had complete resolution and 8 more a decrease in their initial VUR grade. Antibiotic prophylaxis was continued in cases of persistent VUR, and no additional surgical intervention was performed. Although the VUR grades decreased, it should be remembered that BTX-A injections into the detrusor have a temporally limited effect. Most investigators have reported a range of 3 to 9 months until repeated injection is necessary in affected patients. Additionally, some patients become BTX-A resistant after repeated injections. Therefore, the question arises of whether VUR returns before bladder symptoms worsen and whether it is safe to not use prophylactic antibiotics in such patients. Thus, the question remains of whether VUR resolution is a temporary effect and, if not, when is the optimal time to re injected to avoid damage to the upper tracts? Clearly, additional studies are necessary before BTX-A injection can be recommended as a new modality in VUR management. The authors also found improvement in fecal incontinence in 10 of 15 affected patients. The preoperative and postoperative bowel management was not altered and the improvement was, therefore, attributed to the procedure itself. The authors suggest that the effect resulted from local absorption of the neural toxins by adjacent muscle structures such as the anal sphincter. Eight patients became completely continent of stool without further need for diapers or pads. It is certainly possible that the positive effects of BTX-A on neurogenic bladders can also relieve bowel dysfunction. Additional investigations should include standardization of the preoperative and postoperative bowel management and the addition of a control group to validate this important observation. Additionally, histologic and molecular studies are needed to better understand the mechanisms of BTX-A to develop a longer-lasting effect without the need for repeated injections.

REFERENCES

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REPLY BY THE AUTHORS
Local injection of BTX-A is now used for a wide range of neuropathic voiding dysfunctions, including neurogenic detrusor overactivity, detrusor-sphincter dyssynergia, and urge incontinence. Because most patients require annual injection of BTX-A, the treatment may appear to postpone, but not replace, permanent forms of treatment such as augmentation cystoplasty. However, Schulte-Baukloh et al. have proven the safety of up to seven repeated intravesical injections of BTX-A for treatment of children with neurogenic detrusor overactivity. They found no evidence of tachyphylaxis or drug tolerance. Thus, the treatment can be considered a valuable alternative to invasive reconstructive surgery. The chemodenervation of bladder smooth muscles lasts for 9 to 12 months after BTX-A injection. The long-term results of BTX-A injection in our patients have been quite similar to those reported by Riccabona et al., with a mean durability of 10.5 months after the first injection. We had no patient who required repeated injection earlier than 6 months. We have repeated the injection as soon as the effects of BTX-A have