
The Use of Botulinum Toxin A Injection for the Management of External Sphincter Dyssynergia in Neurologically Normal Children

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Purpose: Botulinum toxin A has previously been used for neurogenic and nonneurogenic urgency and urge incontinence. We evaluated the effects of sphincteric botulinum toxin A injection in a series of neurologically normal children with evidence of external sphincter dyssynergia with various voiding problems documented by abnormal voiding electromyography as well as voiding cystourethrography to assess its effectiveness for eliminating post-void residual urine.

Materials and Methods: We retrospectively reviewed the charts of 16 dysfunctional voiders who underwent botulinum toxin A injection to the external sphincter between 2002 and 2006, including 1 to 3 injections in 14, 1 and 1, respectively. Of 19 injections 17 were performed with 300 U to the sphincter, while 2 of 19 were done with 200 U. Two patients also received 100 U injected into the detrusor. Mean patient age at surgery was 9.0 years (range 6 to 16). Preoperative clinical data were recorded, including medications, electromyography, uroflowmetry with post-void residual urine, ultrasound and voiding cystourethrography. Before botulinum toxin A injection medical therapies had failed in all patients, including α -blockers in 100%, biofeedback in 100%, oxybutynin in 33% and tricyclics in 3 (20%). One patient was on intermittent catheterization. All patients were refractory to bowel regimens and timed voiding. Postoperative parameters consisted of medications, symptoms and post-void residual urine. In the 3 males the resolution of epididymitis symptoms and prevention of recurrence were evidence of success.

Results: Before treatment patients experienced symptoms of urge incontinence (14 of 16), recurrent urinary tract infections (66%), voiding postponement (45%) and epididymitis (3 of 16). All patients had external sphincter dyssynergia, as documented by preoperative electromyography or voiding cystourethrography. Average preoperative post-void residual urine was 107 cc (range 49 to 218). Two patients who underwent preoperative voiding cystourethrography had unilateral grade 1 reflux. Of the 16 children 12 (75%) were dry at the first postoperative visit. The remaining 2 patients had decreased enuresis and 13 of 16 were dry at the second postoperative visit. The last patient became dry after treatment for attention deficit disorder was initiated. Average initial postoperative post-void residual urine volume was 43 cc (range 0 to 141) and the average best postoperative visit post-void residual urine was 8 cc (range 0 to 26). Uroflow data revealed no difference in uroflow before or after injections. Neuropsychiatric problems were present in 9 of the 16 patients, including depression in 4, anxiety in 3 and attention deficit disorder in 2.

Conclusions: Before our study in the pediatric literature doses between 50 and 100 U were used. We used a significantly higher dose with increased efficacy and no increased morbidity. Endoscopic botulinum toxin A injection of the external sphincter appears to be a safe and efficacious way to treat refractory nonneurogenic voiding dysfunction in children with external sphincter dyssynergia. Long-term followup is necessary and repeat endoscopic injections may be required in select patients.

Key Words: bladder; botulinum toxin type A; urinary incontinence; endoscopy; urinary bladder, overactive

Botulinum toxin A was first discovered in 1897 by van Ermegam.¹ It has been used in neurology for severe muscle spasticity for many years and by ophthalmologists for strabismus. Its use was first introduced into urology by Dykstra et al in 1988 for DSD in spinal cord injured patients.² Subsequent studies of sphincter spasticity in adult patients had significant positive results, in particular decreased PVR.³⁻⁸

The use of botulinum toxin A was first described as treatment for ESD in 1997 by Steinhardt et al in a neurologically

normal child.⁹ They injected a total of 20 U in 4 quadrants at the external sphincter in a 7-year-old girl with recurrent UTIs and wetting as well as dramatic urethral dilatation due to severe ESD. After 18 months the child was infection-free and dry. At the American Academy of Pediatrics, Section of Urology meeting in 2001 Maizels et al presented a series of 20 females with lazy bladder and external sphincter spasticity who were treated with botulinum toxin A on a prospective basis.¹⁰ At 2 years of followup the patients had had no recurrent UTIs compared with a pre-procedural average of 3 infections per year. However, voiding diaries revealed no statistical differences in voided volumes or voiding intervals. Maizels et al favored botulinum toxin A injection with 50 U and concomitant urethral dilation. Their results showed subjective improvements in daytime/night-

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time urine flow and they postulated that intravesical pressure after botulinum toxin A was likely decreased. Although the number of UTIs was reduced, Maizels et al did not achieve total continence in the patients in their study. Although this study appears to have been flawed by the fact that the children underwent urethral dilation along with botulinum toxin A injections, making it impossible to determine which procedure caused the improvements, it further strengthens the foundation for the use of botulinum toxin A injections in neurologically normal children.

More recently a larger series of 20 patients presented by Radojicic et al indicated that DSD treatment is clearly helped by the use of botulinum toxin A injections in neurologically normal children.¹¹ A recent report by Mokhless et al indicated successful treatment in 10 children with what the authors classified as nonneurogenic neurogenic bladder dysfunction.¹² Nine of the 10 children were on intermittent catheterization, of whom 8 resumed normal urination after treatment.

We evaluated whether treatment in children in whom who all medical therapy as well as biofeedback had failed would be helped by botulinum toxin A injections to the external sphincter. In many of these children this was the only viable treatment option left.

MATERIALS AND METHODS

From 2002 through 2006 there were 4,201 visits for urinary incontinence (International Classification of Diseases, revision 9, 788.30) and 1,121 for urinary retention (International Classification of Diseases, revision 9, 788.20 and 788.21) to our offices. Of these patient visits we retrospectively identified the charts of 16 dysfunctional voiders who underwent botulinum toxin A injection to the external sphincter between 2002 and 2006, including 1 to 3 injections in 14, 1 and 1, respectively. A total of 19 injection procedures were performed, including 17 with 300 U to the sphincter and 2 with 200 U. Two patients also received 100 U injected into the detrusor. Mean patient age at surgery was 9.0 years (range 6 to 16). Average followup was 21 months (range 1.5 to 39). Only 1 patient had a followup of less than 6 months. Preoperative clinical data recorded in all patients including medications, uroflowmetry with EMG, bladder ultrasound with PVR calculations and VCUG.

The reasons to be considered a candidate for botulinum toxin A injection were recurrent bouts of epididymo-orchitis in males with evidence of ESD confirmed on uroflowmetry/EMG and validated on VCUG. In female patients the primary reason for inclusion was recurrent UTIs with increased PVR, and evidence of ESD confirmed on uroflowmetry/EMG and validated on VCUG. External sphincter detrusor-sphincter dyssynergia was defined as inappropriate contraction of the external sphincter along with concomitant detrusor contraction, as confirmed on uroflowmetry/EMG and/or micturition cystography.

Before any patient received botulinum toxin A injection all medical and behavioral therapies were exhausted. Medical therapy included α -blockers in all 16 patients (100%) for internal sphincter dyssynergia and/or urgency, biofeedback in all 16 (100%), anticholinergics in 5 (33%) and tricyclics in 3 (20%). One patient was on intermittent catheterization due to recurrent UTIs caused by persistently high PVR. All patients were treated with a bowel program that included

GlycoLax™ or mineral oil with or without sensors. All patients had been on a timed voiding regimen with or without a vibratory watch.

The injection technique in males consisted of a 3.7Fr Deflux® needle passed through a 10Fr Storz® offset endoscope. The external sphincter was visualized and the area from the sphincter to the verumontanum was injected at the 3, 6, 9 and 12 o'clock positions in equal amounts with diluted botulinum toxin A. In females the cystoscope was placed in the urethra. Using a 22 or 23 gauge needle we placed the needle beside the urethra with the endoscope in position with care taken to ensure that the needle was adjacent to the urethra. We injected again in 4 quadrants as we pulled the needle out.

Post-injection parameters that were evaluated included medications, symptoms and PVR. PVR was measured using a SDU-350xl ultrasound machine (Shimadzu, Kyoto, Japan) with the built-in protocol to measure bladder volume. In the 3 males resolution of epididymitis symptoms and prevention of recurrence were the parameters that indicated success. The maximum botulinum toxin A dose was a total of 300 U in almost all patients. The average dose injected was 8.85 U/kg (range 11 to 7.58).

RESULTS

Before treatment 14 of 16 patients experienced urge incontinence symptoms, 66% had recurrent UTIs, 45% had voiding postponement and 3 had epididymitis. All 16 patients (100%) had ESD, as documented by preoperative EMG or VCUG. Average preoperative PVR was 107 cc (range 49 to 218). Of the 16 children (75%) 12 were dry at the first postoperative visit at week 2. Of the remaining 4 children all except 1 had decreased enuresis, documented as a reduction in the number of wetting accidents and/or the volume of wetting. Of the 16 children 13 were dry at the second postoperative visit. Two of these 3 patients became dry after imipramine was added to the treatment regimen to control urge incontinence and the remaining patient became dry after treatment for ADD was initiated.

All 3 males with recurrent epididymo-orchitis and testicular pain responded immediately with the resolution of pain and no further episodes of epididymo-orchitis. One patient experienced 2 additional episodes of epididymo-orchitis, which occurred at least 6 months after botulinum toxin A treatment. This was the same patient who was treated for ADD. After the initiation of ADD treatment he remained free of epididymo-orchitis for 1 year but it recently recurred due to poor compliance with ADD medications. Average initial postoperative PVR was 43 cc (range 0 to 141) and the average best postoperative visit PVR was 8 cc (range 0 to 26) (see table).

Uroflowmetry data after injection were not available on a consistent basis for all patients, making statistical analysis inconclusive. Neuropsychiatric problems were present in 9 of the 16 patients, including depression in 4, anxiety in 3 and ADD in 2. The 2 patients who required multiple injections have neuropsychiatric problems, that is significant problems with depression in 1 and ADD in the other.

Initially after injections some patients experienced increased incontinence, which was transitory. Incontinence was seen in children who had a tendency toward voiding postponement. After injection they were unable to retain

<i>PVR in all patients except males with epididymitis</i>			
Pt	PVR (ml)		Δ
	Before Botulinum A	After Botulinum A	
UV	126.00	9.00	117.00
AP	62.00	7.00	55.00
AE	50.00	5.00	45.00
SW	117.00	6.00	111.00
SS	49.00	8.00	41.00
DB	73.00	16.00	57.00
CF	217.00	5.00	212.00
EM	218.00	0.00	218.00
NM	35.00	7.00	28.00
MB	184.00	26.00	158.00
KM	55.00	0.00	55.00
MJ	0	0	0
LB	Not available		
Av	107.8	8.0	99.7
Student's t test		0.00037	
p value			

urine and experienced wetting at an increased rate due to the lack of external sphincter contraction. This resolved after the children were made aware that they could no longer volitionally contract the external sphincter. We found this to be a powerful tool to train voiding postponers, who in general tend to show oppositional behavioral traits. No patient experienced any complaints of weakness that may have been related to botulinum toxin A injections.

DISCUSSION

Botulinum toxin A is produced by the facultative anaerobe *Clostridium botulinum*. Botulinum toxin A acts by inhibiting acetylcholine at the presynaptic cholinergic junction. Inhibited acetylcholine release results in regionally decreased muscle contractility and muscle atrophy at the injection site. The chemical denervation that ensues is a reversible process since axons resprout in approximately 3 to 6 months. The toxin acts at the neuromuscular junction at the external sphincter to block vesicle transport of acetylcholine in essence producing chemical denervation. Clinical effects begin within 5 to 7 days and are reversible because of terminal resprouting occurs within six months.¹³ The clinical success of botulinum toxin A is supported by laboratory research showing marked decreases in the release of labeled norepinephrine and acetylcholine in botulinum toxin A injected rat bladders and urethras.¹⁴ While therapeutic effects of inhibiting acetylcholine release is obvious, blocking norepinephrine release may provide clinical benefit by inhibiting sympathetic transmission in smooth muscle dyssynergia. This is why some of the patients whom we treated who had combined internal and external dyssynergia responded well to botulinum toxin A injections.

Botox® A is the most widely used version for human medicinal purposes in the United States. Investigational use in animals is generally done with botulinum D toxin. First approved for use in patients with strabismus, Botox remains Food and Drug Administration approved only for strabismus and cosmetic wrinkle therapy. Despite its limited Food and Drug Administration approval practitioners of many specialties have embraced the toxin to counter various maladies. Most recently off-label use was popularized for migraine headaches and myofascial pain.

Botulinum toxin A has also been used to inject the bladder to decrease detrusor hyperactivity. Studies in adult spinal cord injured patients¹⁵ and children with spina bifida¹⁶ indicated success with multiple injections throughout the bladder floor. A recent study by Hoebeke et al indicated that it is useful and safe in children with nonneurogenic OAB.¹⁷ Botulinum toxin A injections to the detrusor have been performed for nonneurogenic OAB in symptomatic adults with some success.

A drawback of this treatment is the need for re-treatment since the probable underlying cause is not in the bladder but elsewhere. On the other hand, botulinum toxin A injections for internal sphincter dyssynergia could possibly be beneficial in the regimen that is necessary to treat OAB. Elimination of the dyssynergic voiding pattern could possibly help eliminate the detrusor hypertrophy that is commonly associated with OAB. Botulinum toxin A injection produces reversible chemical sphincterotomy, which avoids a major surgical procedure with its attendant risks. These benefits of botulinum toxin A injection were seen in several of our patients who had no other treatment options. One girl was on intermittent catheterization and unable to empty the bladder, leaving a PVR of 250 cc at a time. This child is completely dry, and she has had no accidents and voids to completion a year and a half after injection. A boy was offered augmentation cystoplasty to manage intractable wetting and severe DSD, leading to chronic epididymitis. He was treated with multiple injections, thereby avoiding a urinary diversion procedure with its associated morbidity.

The use of botulinum toxin A in human pathology has focused on end organ therapies. It was postulated that this type of toxin isolation would decrease morbid side effects. Doses of 50 to 300 U per dose have been documented in the literature by different specialists. Riccabona et al used a dose of 10 U/kg to a maximum of 300 U,¹⁸ while Schulte-Baukloh et al used a dose of 12.5 U/kg to a maximum of 300 U.¹⁹ In the study by Radojicic et al the dose was set at 50 U for weights less than 40 kg, making the maximum dose injected 1.25 U/kg.¹¹ In the study by Mokhless et al the dose of 50 U was used in children younger than 6 years, while all others received a dose of 100 U.¹² In 1 child in this study a total of 300 U were injected in a 3-month period without side effects. The rationale for this pattern of injection was not described but it is obvious that this patient benefited from the higher dose. The fact that the injections were performed during 3 months before the effect of botulinum toxin A would dissipate indicates that the higher treatment dose was necessary to achieve success. In the study by Radojicic et al PVR was greater than 10 ml in 11 of 20 patients,¹¹ while in our cohort we found a PVR of greater than 10 ml in only 2 of 12. The highest PVR noted was 26 cc, while in the study by Radojicic et al PVR was as high as 100 cc. When we compared PVR data in the study by Mokhless et al we found that average PVR at 6 months was 75 cc,¹² while the average was 8 cc in our study. Superficially it appears that the higher doses used in our study may be more efficacious when considering PVR data.

The lethal dose of botulinum toxin A is 39 to 49 U/kg.²⁰ If this dose is extrapolated to a 70 kg human, it would be 2,800 U. To achieve lethality the dose must be injected intravascularly. Therapeutic botulinum toxin A is never injected intravascularly and it is used at much lower doses than 3,000 U (range 50 to 300). Most urological applications

do not exceed 300 U. In many situations the botulinum toxin A dose in children has been based on the recommendation in the neurological literature of a dose of 10 to 12 U/kg, which in fact is not based on evidence.²¹

Obvious fears of toxicity due to higher doses are something that worries many investigators, leading them to use the lower doses. The only side effects documented in the urological literature are isolated muscle weakness, which uniformly resolves within 1 to 3 months. None of these side effects have been documented in children and the patients had neurogenic voiding dysfunction, unlike our cohort. The use by Chancellor and Smith of 200 U botulinum toxin A in patients with multiple sclerosis without any neurological complications²² is closer to our experience since many of our patients were older and almost adult size.

The dose and injection volume used in this study were much higher than in the previously reported studies by Mokhless¹² and Radojicic¹¹ et al. We used an average dose of 8.85 U/kg or a maximum of 300 U per patient. The 300 U per patient maximum that has been imposed in the urological literature is an arbitrary value and in some of our patients this would have been below the 10 to 12 U/kg dose in the neurological literature as well as the doses used by Riccabona¹⁸ and Schulte-Baukloh¹⁹ et al in the pediatric urological literature.

We chose an endoscopic approach to botulinum toxin A injection to maximize its placement at the external sphincter in males, while in the females we injected periurethrally with the endoscope in the urethra to visualize the injection and ensure ideal periurethral placement. The volume of injection (10 cc) was higher than in other studies to maximize the dispersion of botulinum toxin A to a greater area but was less than that used by Hoebeke et al in their patients.¹⁷ Again, this larger dispersion volume poses a theoretically higher risk of potential neurological side effects, which were not identified in this series. This greater dispersion area could have beneficial effects on the bladder neck as well as on the pelvic floor musculature. We found that there were no issues with persistent incontinence that would be associated with bladder neck dysfunction combined with external sphincter relaxation. All leakage that occurred was limited to voiding postponement activity and after this was suppressed no patient continued to experience leakage. Also, there were no episodes of stool incontinence, which would indicate any overall laxity of the pelvic floor mechanism. It is unfortunate that post-injection VCUG was unavailable on these children (due to parental opposition) to test the hypothesis that botulinum toxin A can have an effect on nor-epinephrine based contractility of the bladder neck. It is clear that some of these children had mixed internal and external sphincter dyssynergia since many were on α -blockers, in addition to anticholinergics.

It is possible that external sphincter denervation by botulinum toxin A can have an effect on the sensory feedback loop of the micturition reflex. With this feedback inhibition in effect the overactive guarding reflex is taken out of the loop and the child can easily be retrained using biofeedback to void appropriately. Whether this overactive guarding reflex is a result of detrusor instability due to recurrent UTIs or learned behavior, or possibly to a link with dysfunction in the frontal lobes, is irrelevant when considering the efficacy of botulinum toxin A, allowing for proper sphincter relaxation. Possible blockage of sensory pathways could explain

the relief of pain that patients experienced in the study by Zermann et al, in which they injected botulinum toxin A in 11 men with chronic prostatitis.²³ They found a marked decrease in PVR as well as improved flow rates but also a reduction of pain.

Two of our patients who required multiple injections have significant neuropsychiatric disorders, requiring medication. Many other patients in this group had neuropsychiatric problems, requiring medications to treat the disorders. Urgency and urge incontinence were the overwhelming symptoms seen in this group with neuropsychiatric problems. When the neuropsychiatric problems were controlled, urgency disappeared and the need to reflexively contract the external sphincter would be abated, allowing easy retraining of voiding using biofeedback techniques. The 2 more refractory cases responded to botulinum toxin A injection with decreased PVR and improved flow rates after injection. Incontinence and PVR returned after the botulinum toxin A wore off or when they were off their medications, indicating that the control of neuropsychiatric problems is an integral part of their care.

CONCLUSIONS

Before our study in the pediatric literature doses between 50 and 100 U were used. We used a significantly higher dose and volume than reported in other series when injecting botulinum toxin A into the sphincter with what appears to be increased efficacy and no increased morbidity. Endoscopic botulinum toxin A injection of the external sphincter appears to be a safe and efficacious way to treat refractory nonneurogenic voiding dysfunction in children with ESD. Long-term followup is necessary and repeat endoscopic injections may be required in select patients.

On the horizon it would be interesting to evaluate these children in a randomized, prospective clinical trial. Our assumptions are drawn from subjective results and post-therapy PVR measurements. Ideally it would be useful to perform videourodynamics in all of these patients at uniform intervals after injection. This would give us the opportunity to standardize our results. Unfortunately there are few parents who will agree to invasive testing like videourodynamics after their child has shown improvement.

Abbreviations and Acronyms

ADD	=	attention deficit disorder
DSD	=	detrusor-sphincter dyssynergia
EMG	=	electromyography
ESD	=	external sphincter dyssynergia
OAB	=	overactive bladder
UTI	=	urinary tract infection
VCUG	=	voiding cystourethrography

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EDITORIAL COMMENTS

These authors report excellent symptom improvement after botulinum toxin A injection into the external sphincter of neurologically normal children with ESD. This adds to the growing literature that demonstrates the safe and effective role of botulinum toxin for the treatment of various types of voiding dysfunction. Whereas many earlier reports were restricted to patients with neurological impairment, this study confirms the applicability of this form of treatment to those with more functional nonneurological disorders.

One may question though whether the dose of 300 U botulinum toxin A used in this study is overkill. The authors note that prior reports of sphincteric injection showed the use of 50 to 100 U and results were inferior to those reported in the current study. While it may be true that doses higher than 50 U are necessary, the authors present no data to suggest that 300 U are optimal. Perhaps 150 or 200 U may achieve the same result. Given the high cost per unit of Botox and the potential morbidity, especially in children, intermediate doses should be compared and studied to delineate the true optimal dose. Furthermore, many references that the authors cite to support the use of 300 U involve multiple injections into the detrusor spread over a wide area and they may not be comparable to sphincteric injections.

Almost all patients had followup greater than 6 months with the majority not requiring repeat injection. This is contrary to what has been noted for sphincteric injections in patients with neurogenic DSD, in whom the effect appears to last 4 to 7 months. The authors hypothesize that botulinum toxin A injection into the sphincter of these neurologically normal patients may actually break the loop and allow the restoration of normal voiding reflexes even after the botulinum toxin A wears off. While this is provocative, other recent studies described a similar pattern in patients with idiopathic voiding dysfunction with a number of patients achieving long-term benefit and not requiring repeat injection.¹

Now that a positive response to this type of therapy has been established, further study to delineate some of the unanswered questions (optimal dose, optimal patient, etc) should be performed to allow expansion of this therapy to even more patients in a cost-effective, efficient manner.

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These authors report the successful treatment of 1 group of patients who were previously treated unsuccessfully. They compare their results with those in similar studies. Again, it is necessary to use uniform terminology and standardized procedures in this field.

1) I would like to emphasize the importance of using International Children's Continence Society terminology. The authors use (or cite other authors who use) various terms, including DSD, nonneurogenic neurogenic bladder dysfunction, dysfunctional voiding, etc. I think that the appropriate term according to the International Children's Continence Society proposal is dysfunctional voiding¹ and the use of other terms can lead to unnecessary confusion.

2) The authors emphasize the use of larger doses of Botox than in previous series, making a direct connection to better PVR results. PVR is a parameter that is highly dependent on measurement conditions and the comparison may be significant if the measurement is performed in the same way and under similar conditions.

3) There are 2 commercially available preparations of botulinum A toxin on the world market, that is Dysport® and Botox. One U Botox is not bioequivalent to 1 U Dysport, so it is not adequate to simply exchange 1 dose for the other. In everyday practice we use 4 U Dysport as equivalent to 1 U Botox.² When comparing results, it is necessary to emphasize which preparations are compared as well as the dilution and application method.

Successful treatment of these long-term patients must be recognized and all of us who believe in this method of treatment must be happy. However, we must be careful when unreservedly accepting findings (ours or those of others) that do not result from prospective, randomized, double-blind studies. One is eager to easily accept opinions and facts confirming one's ideas, whether true or false, no matter how hard and honest one's endeavors are to find the scientific truth.

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REPLY BY AUTHORS

The post-void residuals obtained in this study were garnered in the same fashion in all patients. Patients drank fluids

as desired to the point that they had a maximal urge to void and then a post-void residual measurement was done immediately after voiding using the same ultrasound machine and technician each time. In no case did a child wait more than 2 minutes to have the post-void residual measured. By being scrupulous with this we believe that we eliminated the possibility of excessive upper tract drainage into the bladder and possibly kept the post-void residuals low. Our decreased post-void residuals were confirmed by the elimination of urinary tract infections in this group of patients. If these patients had increased post-void residuals they would have continued having UTIs as did those in other studies.

We agree that the ideal dose has not been defined to treat this condition. We may have used a dose that may have been overkill as evidenced by the fact that 2 patients responded to treatment with 200 U botulinum toxin A but more studies need to be done in a prospective fashion to determine the ideal dose. What is obvious from the literature is that 50 U is not the appropriate dose either. We chose 300 U based on prior reports of dosage regimens based on weight, and we chose the higher end of the scale without adverse effects. Reports of muscle weakness have only been seen in neurologically impaired patients, indicating that the populations may be different. Whether the dose is spread over a large area or is concentrated in a more localized area as we did in the sphincter makes a difference. When multiple injections (10 to 20) are made in the detrusor botulinum toxin A is more likely injected intravascularly since each injection risks injury to a blood vessel. Sphincteric injection in 4 sites reduces the risk of intravascular injection, thereby reducing the risk of dissemination of the toxin intravascularly and the risk of systemic absorption.

Another reason that our results are superior to those of other studies is most likely due to the intensive nature of the adjuvant therapy used in our patients. It was obvious that if the underlying neuropsychopathology was not adequately addressed patients required repeat injection. Treating the sphincteric dysfunction solely will only lead to limited success in some patients and abject failure in others as seen in this and other studies. The sphincteric dyssynergia will persist (and we believe that in these patients it is a neurogenic bladder disturbance according to the ICCS nomenclature recommendations) and will not be cured. Correction of OAB in this group of patients was an essential part of the overall treatment, without which there could not be any form of sphincteric reeducation. In the most recalcitrant patients with anticholinergic resistant OAB treatment with centrally active drugs targeted to the behavioral problems was successful, and we have become even more aggressive in treating the neuropsychiatric problems. Taking this approach in the 2 years since the data were gathered for this study we have seen a decrease in the need to use botulinum toxin A.