

Experience with Different Botulinum Toxins for the Treatment of Refractory Neurogenic Detrusor Overactivity

Cristiano M. Gomes, Jose E. de Castro Filho, Ronald F. Rejowski, Flavio E. Trigo-Rocha, Homero Bruschini, Tarcisio E. P. de Barros Filho, Miguel Srougi

Division of Urology, University of Sao Paulo School of Medicine, Sao Paulo, Brazil

ABSTRACT

Purpose: To report our experience with the use of the botulinum toxin-A (BoNT/A) formulations Botox® and Prosigne® in the treatment of neurogenic detrusor overactivity (NDO).

Materials and Methods: At a single institution, 45 consecutive patients with refractory urinary incontinence due to NDO received a single intradetrusor (excluding the trigone) treatment with botulinum toxin type A 200 or 300 units. Botox was used for the first 22 patients, and Prosigne for the subsequent 23 patients. Evaluations at baseline and week 12 included assessment of continence and urodynamics. Safety evaluations included monitoring of vital signs, hematuria during the procedure, hospital stay, and spontaneous adverse event reports.

Results: A total of 42 patients were evaluated (74% male; mean age, 34.8 years). Significant improvements from baseline in maximum cystometric capacity (MCC), maximum detrusor pressure during bladder contraction, and compliance were observed in both groups ($P < 0.05$). Improvement in MCC was significantly greater with Botox versus Prosigne (+103.3% vs. +42.2%; $P = 0.019$). Continence was achieved by week 12 in 16 Botox recipients (76.2%) and 10 Prosigne recipients (47.6%; $P = 0.057$). No severe adverse events were observed. Mild adverse events included 2 cases of transient hematuria on the first postoperative day (no specific treatment required), and 3 cases of afebrile urinary tract infection.

Conclusions: Botox and Prosigne produce distinct effects in patients with NDO, with a greater increase in MCC with Botox. Further evaluation will be required to assess differences between these formulations.

Key words: *botulinum toxins; urinary bladder; overactive; neurogenic bladder; urinary incontinence; urodynamics*
Int Braz J Urol. 2010; 36: 66-74

INTRODUCTION

Urinary incontinence due to detrusor overactivity is a common problem in patients with neurological diseases such as spinal cord injury, with significant impact on quality of life. Moreover, in this population, detrusor overactivity is frequently accompanied by high bladder pressure, and may pose a risk to the upper urinary tract (1,2). First-line treatment for detrusor overactivity is usually pharmacological, with oral anticholinergic agents used to decrease detrusor contractility, resulting in lower bladder pressures and

improved continence. However, distressing adverse effects, such as dry mouth, constipation, and blurred vision, may limit doses or lead to discontinuation of therapy, decreasing the effectiveness of treatment (3-5). When pharmacological therapy fails, invasive therapies are usually considered. Surgery, such as bladder augmentation, may be an option with good long-term results, but it is a permanent treatment with significant potential complications such as calculi, malignancy, and bowel complications (6,7).

The efficacy and safety of local administration of botulinum toxin A (BoNT/A) into the bladder

has been investigated in previously reported studies (8-10). BoNT/A blocks neuromuscular activity in skeletal muscle by preventing neurotransmitter release at presynaptic cholinergic nerve terminals (11). BoNT/A inhibits acetylcholine-mediated detrusor contraction and may inhibit release of other vesicle-bound neurotransmitters in the afferent and efferent pathways of the bladder wall, urothelium, or lamina propria (12,13).

While the overwhelming majority of investigators have used the BoNT/A formulation Botox® (Allergan, Inc., Irvine, CA), other BoNT/A formulations are being marketed. There is a lack of evidence as regards the clinical efficacy and safety of the recently released Chinese BoNT/A (Prosigne®, Lanzhou Biological Products Institute, Lanzhou, China) for the treatment of detrusor overactivity. This product has recently become available in Brazil, but there is scarce data on this pharmaceutical formulation. It is known that they differ in the external excipients that are added to BoNT/A. Botox vials contain sodium chloride 0.9 mg and human albumin 0.5 mg, and the protein load is 5 ng/100 units, while in Prosigne vials, the external excipients are porcine gelatin (Haemacell) 5 mg, dextran 25 mg, and sucrose 25 mg, and the protein load is 4.0-5.0 ng/100 units of BoNT/A (14). In terms of potency, little is known since only two studies have compared both formulations, with conflicting results. In a major Chinese study the two formulations were used in patients with various types of focal dystonias, Botox was found to be 1.5 times more potent than Prosigne (14). In another study in patients with blepharospasm, comparable efficacy was observed (15). There may also be differences in the toxicity profile due to differences in the preparation procedure for both formulations (14,16).

Botox is currently the only BoNT/A formulation approved in Brazil for the treatment of overactive bladder. The aim of our study was to report our experience with the use of the two formulations in the treatment of detrusor overactivity.

MATERIALS AND METHODS

This study was carried-out in accordance with the Ethics Committee regulations and written informed consent was obtained from all patients.

A prospective study was conducted at a single institution in which 45 consecutive patients received a single intradetrusor treatment with BoNT/A between April 2003 and April 2007. Inclusion criteria were urinary incontinence due to neurogenic detrusor overactivity (as demonstrated by urodynamics), failure of oral anticholinergic therapy, and use of clean intermittent catheterization or willingness to do so, if necessary. Exclusion criteria included previous bladder surgery, previous treatment with an endovesical pharmacological agent, symptomatic urinary tract infection, and a history of neurological disease of less than 6 months. Among the 45 patients enrolled in the study, neurogenic detrusor overactivity resulted from spinal cord injury in 36 patients (80.0%), viral myelitis in 4 (8.9%), multiple sclerosis in 3 (6.7%) and schistosomal myeloradiculopathy in 2 patients (4.4%).

The BoNT/A formulation Botox was used for the first 22 patients, whereas the subsequent 23 patients received Prosigne. The different BoNT/A formulations were used because the hospital changed the supplier due to cost restrictions.

The injection procedure was performed as described previously by Schurch et al. (9). Briefly, the BoNT/A dose (200 or 300 units) was reconstituted with saline 0.9% at a total volume of 30 mL. The bladder was distended with 100 mL of saline, and 30 injections of 1.0 mL each were performed intramuscularly throughout the bladder wall, excluding the trigone. A rigid cystoscope and 23-gauge flexible needle (Handle Cook®) were used, yielding an injection depth of 3-5 mm. A Foley catheter was left indwelling overnight, and patients were discharged the following morning, after catheter removal, resuming clean intermittent catheterization. Antibiotics were administered during anesthesia and for 2 days after the procedure. Patients receiving anticholinergic drugs were instructed to stop the medication 2 weeks after BoNT/A injection.

Evaluations

Evaluations at baseline and 12 weeks post-treatment included a clinical assessment of continence and a standard urodynamic study. Twelve weeks was selected as the follow-up duration because it is a mid-

term evaluation, and also because previous studies with Botox have shown that peak efficacy is established after 4 weeks and maintained up to 12 weeks (and longer) (9). Patients were considered continent when they were not using any pads or diapers and had no episodes of incontinence during the 7 days before evaluation.

The primary efficacy variable was improvement of urodynamic parameters compared to baseline at the 12-week timepoint. The measurements included maximum cystometric capacity (MCC), volume of first detrusor overactivity (reflex volume), maximum detrusor pressure during bladder contraction, and bladder compliance, based on the terminology of the International Continence Society (17). The secondary outcome measure was continence status.

Safety evaluations included monitoring of vital signs and hematuria during the procedure and hospital stay, and spontaneous reports of adverse events.

Statistical Analysis

Numerical data were reported as mean ± standard deviation and range. Categorical variables were reported as numbers and percentages. Results of treatment with the different BoNT/A formulations and doses were analyzed for the whole population as well as for between-group comparisons. Within-group changes from baseline in the urodynamic parameters were analyzed using the paired t-test. Between-group

comparisons were performed using analysis of variance for repeated measurements. The chi-squared (x²) test or the Fisher’s exact test was used for categorical variables. Data were processed using SPSS 12.0 for Windows statistical software (SPSS Inc., Chicago, Ill). P-values < 0.05 were considered statistically significant.

RESULTS

Of the 45 recruited patients, 3 were excluded for not returning for the postoperative follow-up evaluation (1 from the Botox group and 2 from the Prosigne group); thus, 42 patients (21 in each group) were evaluable. Of the 42 evaluable patients, the majority were male (31/42; 73.8%), and the mean age was 34.8 ± 12.7 years (range, 18 to 73 years). No statistically significant differences were found between the two groups for any demographic or baseline characteristics (Table-1).

In the Botox group, 9 patients (42.9%) received a BoNT/A dose of 200 units and 12 (57.1%) received 300 units. In the Prosigne group, 5 patients (23.8%) received a BoNT/A dose of 200 units and 16 (76.2%) received 300 units.

Urodynamic Findings

MCC significantly improved from baseline in both groups, increasing from 184 ± 62 to 375 ± 109

Table 1 – Baseline characteristics of evaluable patients treated with Botox or Prosigne.

Parameter	Botox (N = 21)	Prosigne (N = 21)	p Value
Age (years), mean ± SD	37.2 ± 14.4	32.5 ± 10.6	0.234
Gender (female), n (%)	6 (28.6%)	5 (23.8%)	0.500
MCC (mL), mean ± SD	184 ± 62	204 ± 83	0.388
Reflex volume (mL), mean ± SD	180 ± 78	199 ± 102	0.743
MDP (cm H ₂ O), mean ± SD	68 ± 33	82 ± 27	0.158
Compliance (mL/cm H ₂ O), mean ± SD	19.4 ± 12.8	23.5 ± 10.6	0.267

MCC = maximum cystometric capacity; MDP = maximum detrusor pressure; SD = standard deviation.

mL (+103.3%; $P < 0.001$) in the Botox group and from 204 ± 83 to 290 ± 134 mL (+42.2%; $P = 0.002$) in the Prosigine group. The increase from baseline in MCC was significantly greater in the Botox group than in the Prosigine group when considered as a whole ($P = 0.019$; Figure-1). When the different BoNT/A doses were considered, no statistically significant differences were found between the subgroups (Figure-2).

The changes from baseline in reflex volume were from 180 ± 78 to 226 ± 79 mL ($P = 0.150$) in the Botox group and from 173 ± 71 to 199 ± 102 mL ($P = 0.255$) in the Prosigine group. The evaluation of this parameter was greatly influenced by the fact that

a substantial number of patients in both groups became areflexic at the week 12 evaluation (11 patients [52.4%] in the Botox group and 6 [28.6%] in the Prosigine group; $P = 0.116$). These patients, who had the most favorable results of BoNT/A injection, were not included in the calculation of mean reflex volume.

MDP decreased significantly from baseline in both groups, from 68 ± 33 to 28 ± 18 cm H₂O (-58.8%; $P < 0.001$) in the Botox group and from 82 ± 27 to 47 ± 30 cm H₂O (-42.7%; $P < 0.001$) in the Prosigine group. Compliance increased significantly from baseline in both groups, from 19 ± 13 to 42 ± 29 mL/cmH₂O (+121.0%; $P = 0.006$) in the Botox group

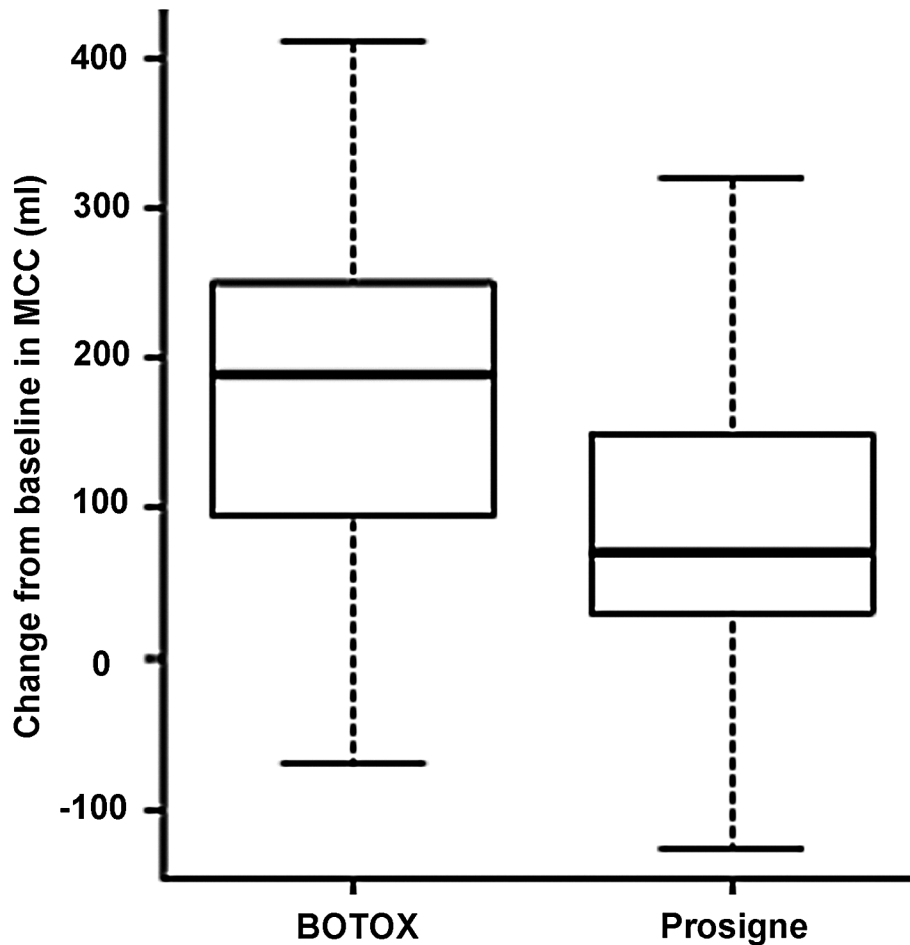


Figure 1 – Box-plot analysis of change from baseline in maximum cystometric capacity (MCC) at week 12, according to treatment group.

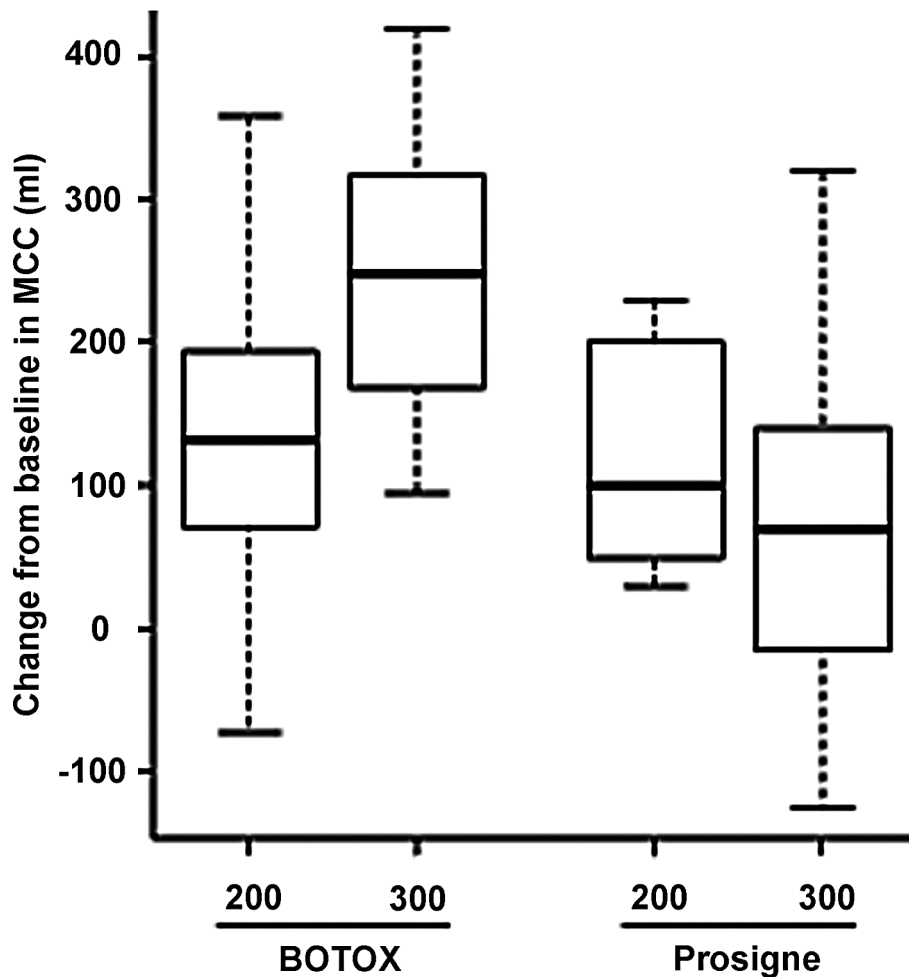


Figure 2 – Box-plot analysis of change from baseline in maximum cystometric capacity (MCC) at week 12, according to treatment group and dose level (200 or 300 units).

and from 23 ± 11 to 42 ± 42 mL/cmH₂O (82.6%; $P = 0.024$) in the Prosigne group.

In the two groups, significant ($P < 0.001$) improvements from baseline in the continence status were observed at week 12. Continence was achieved by week 12 in 16 patients (76.2%) in the Botox group and 10 (47.6%) in the Prosigne group ($P = 0.057$).

The administration of BoNT/A was uneventful and the entire procedure required no more than 30 minutes in all patients. Anesthesia was general in 28 patients (66.7%), spinal in 10 (23.8%), and local in 4 patients (9.5%).

There were no severe adverse events observed in any patient. Mild adverse events included 2 cases of transient hematuria on the first postoperative day that did not require specific treatment, and 3 cases of afebrile urinary tract infection. All patients were discharged home on the first postoperative day.

COMMENTS

Determining a more precise role of the different formulations of BoNT/A in the treatment of detru-

sor overactivity is of paramount importance, because BoNT/A treatments may have a significant economic impact on health services. To our knowledge, this is the first reported study on the use of Prosigne for the treatment of detrusor overactivity. Our study was originally designed to compare the use of two doses of Botox (200 vs. 300 units) in patients with neurogenic detrusor overactivity. However, an unpredicted change of the hospital supplier of BoNT/A prevented us from completing the designed study and gave us the opportunity to evaluate the new formulation (Prosigne). Because our original plan was to compare two doses of BoNT/A (200 vs. 300 units), patients from the Botox group were randomized to one of the two doses, and 12 received 300 units while 10 received 200 units. One of these patients was excluded from the study for not returning for the follow-up evaluation. When we started patients from the Prosigne group, we initially maintained the randomization for the two doses, since the manufacturers of Prosigne claim that the two formulations are comparable in potency, with each preparation expressed in units, 1 unit representing the LD50 for mice (14). However, after unsuccessfully treating a few patients using 200 units, we chose to inject 300 units of BoNT/A in the subsequent patients. For this reason, more patients in the Prosigne group received the higher BoNT/A dose.

It should be noted that prescribing information for Botox states that units of biological activity of this formulation cannot be compared or converted into units of any other botulinum toxin, due to specific details of the assay method used (18). In fact, there are limited published data on Prosigne in the literature, and only two studies have compared it with Botox. In a study conducted in China, Tang and Wan evaluated a large group of patients with hemifacial spasm and various types of focal dystonias (including blepharospasm) in which Botox was found to be 1.5 times more potent than Prosigne (14). The second study was conducted by Rieder et al. in patients with blepharospasm and hemifacial spasm which found that the two BoNT/A formulations had comparable short-term efficacy and safety in these indications (15). The authors of this study acknowledge that different BoNT/A formulations are not considered bioequivalent and recommend further studies to establish the clinical comparability of these formulations. The

differences observed in these studies may result from differences in patient population, clinical indication and/or application technique. Our results appear to be in accordance with the Chinese study, indicating that Prosigne is not as potent as Botox. It is important to acknowledge that we used it for a different clinical indication, injecting the toxin in the smooth muscle rather than an striated muscle, which may be another possible reason for distinct effects of the formulations.

Patients in the two groups did not differ significantly in any of the baseline parameters. Despite the fact that a larger proportion of patients in the Prosigne group received the higher BoNT/A dose, treatment with Botox resulted in a significantly greater increase from baseline in MCC, and, although not statistically significant, improvements in the Botox group were numerically superior on all the other evaluated urodynamic parameters.

An interesting finding was that 52% of the patients in the Botox group and 29% of those in the Prosigne group did not experience a hyperreflexive detrusor contraction at the follow-up evaluation. This is a strong indication of the efficacy of therapy with BoNT/A, and this finding appeared to favor Botox. However, it was a confounding factor for the evaluation of the reflex detrusor volume, since it was necessary to exclude patients who became areflexic, who represent the best responders to treatment, from analyses of this endpoint.

A tendency for better results was also observed for patients treated with Botox in terms of improvement in continence rates. Their complete continence rate at week 12 was 76%, as opposed to 48% for the patients treated with Prosigne.

As mentioned previously, our initial objective was to compare two different Botox doses (200 vs. 300 units), but we ultimately had four subgroups based on different doses and BoNT/A formulations. We attempted to compare the two BoNT/A formulations based on the doses of 200 or 300 units, but the subgroups were too small for significant comparisons.

Both drugs were well tolerated by patients and no significant adverse event occurred in any group.

We acknowledge that our study was not designed to compare the two BoNT/A formulations.

Therefore, patients were not randomized to the two groups. However, the two groups were composed of consecutive patients and the comparison of baseline parameters did not reveal differences between the groups, indicating that the populations were quite comparable.

CONCLUSIONS

Our study provides the first experience with the use of the formulation Prosigne for the treatment of refractory detrusor overactivity, indicating that Botox and Prosigne may have distinct effects in the detrusor of patients with neurogenic detrusor overactivity, with Botox promoting superior results in terms of increase in bladder capacity. Due to the limitations of this study in terms of patient selection (not randomized) and small sample size to compare the effect of different doses, as well as the short follow-up period, additional studies should be conducted to determine the differences in the safety profile and specific benefits between these two BoNT/A formulations for the treatment of patients with neurogenic detrusor overactivity.

ACKNOWLEDGEMENTS

Editorial support was provided by Sushma Soni, funded by Allergan, Inc.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Weld KJ, Graney MJ, Dmochowski RR: Clinical significance of detrusor sphincter dyssynergia type in patients with post-traumatic spinal cord injury. *Urology*. 2000; 56: 565-8.
2. Weld KJ, Graney MJ, Dmochowski RR: Differences in bladder compliance with time and associations of bladder management with compliance in spinal cord injured patients. *J Urol*. 2000; 163: 1228-33.
3. Andersson KE: Antimuscarinics for treatment of overactive bladder. *Lancet Neurol*. 2004; 3: 46-53.
4. Rovner ES, Gomes CM, Trigo-Rocha FE, Arap S, Wein AJ: Evaluation and treatment of the overactive bladder. *Rev Hosp Clin Fac Med Sao Paulo*. 2002; 57: 39-48.
5. Rovner ES, Wein AJ: Update on overactive bladder: pharmacologic approaches on the horizon. *Curr Urol Rep*. 2003; 4: 385-90.
6. Hohenfellner M, Dahms S, Pfitzenmaier J, Thüroff JW: Orthotopic bladder augmentation and substitution. *Curr Opin Urol*. 1999; 9: 309-14.
7. Quek ML, Ginsberg DA: Long-term urodynamics followup of bladder augmentation for neurogenic bladder. *J Urol*. 2003; 169: 195-8.
8. Mascarenhas F, Cocuzza M, Gomes CM, Leão N: Trigonal injection of botulinum toxin-A does not cause vesicoureteral reflux in neurogenic patients. *Neurourol Urodyn*. 2008; 27: 311-4.
9. Schurch B, de Sèze M, Denys P, Chartier-Kastler E, Haab F, Everaert K: Botulinum toxin type a is a safe and effective treatment for neurogenic urinary incontinence: results of a single treatment, randomized, placebo controlled 6-month study. *J Urol*. 2005; 174: 196-200.
10. Smith CP, Nishiguchi J, O'Leary M, Yoshimura N, Chancellor MB: Single-institution experience in 110 patients with botulinum toxin A injection into bladder or urethra. *Urology*. 2005; 65: 37-41.
11. Dolly O: Synaptic transmission: inhibition of neurotransmitter release by botulinum toxins. *Headache*. 2003; 43 (Suppl 1): S16-24.
12. Apostolidis A, Papat R, Yiangou Y, Cockayne D, Ford AP, Davis JB, et al.: Decreased sensory receptors P2X3 and TRPV1 in suburothelial nerve fibers following intradetrusor injections of botulinum toxin for human detrusor overactivity. *J Urol*. 2005; 174: 977-82; discussion 982-3.
13. Chuang YC, Yoshimura N, Huang CC, Chiang PH, Chancellor MB: Intravesical botulinum toxin a administration produces analgesia against acetic acid induced bladder pain responses in rats. *J Urol*. 2004; 172: 1529-32.
14. Tang X, Wan X: Comparison of Botox with a Chinese type A botulinum toxin. *Chin Med J (Engl)*. 2000; 113: 794-8.
15. Rieder CR, Schestatsky P, Socal MP, Monte TL, Fricke D, Costa J, et al.: A double-blind, randomized, crossover study of prosigne versus botox in patients with blepharospasm and hemifacial spasm. *Clin Neuropharmacol*. 2007; 30: 39-42.

16. Tamura BM, Cucé LC, Rodrigues CJ: Allergic reaction to botulinum toxin: positive intradermal test. *Dermatol Surg.* 2008; 34: 1117-9.
17. Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, et al.: The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. *Neurourol Urodyn.* 2002; 21: 167-78.
18. Allergan I: BOTOX (Botulinum toxin type A) US prescribing information [Revised October 2006]. Ref. type: Generic. pp. 1-16.

*Accepted after revision:
July 29, 2009*

Correspondence Address:

Dr. Cristiano Mendes Gomes
Divisão de Clínica Urológica
Av. Dr. Enea de C. Aguiar, 255 / 710F
São Paulo, SP, 05403-000, Brazil
Fax: + 55 11 3064-7013
E-mail: crismgomes@uol.com.br

EDITORIAL COMMENT

Patients with various neurological conditions (e.g. spinal cord injury) may present detrusor overactivity (DO), formally classified as neurogenic DO (NDO), that knowingly causes great social embarrassment and inconvenience for the patient.

The current treatment for NDO consists of a combination of clean intermittent self-catheterization and the pharmacological management. However, many patients discontinue treatment due to side-effects (1). In such cases where the inability to tolerate the antimuscarinic drug therapy incurs in the failure of the treatment, intradetrusor botulinum neurotoxin type A (BoNT/A) may be an excellent alternative (2). Since it is a minimally invasive treatment, as opposed to a clam ileocystoplasty, a conventional surgical procedure, it has currently been increasing in popularity. However, its results are temporary and can ultimately increase the costs of the treatment.

In Brazil, Botox® may cost up to 20% more than Prosigne®*, which could be an obstacle in the way of those seeking to purchase it, considered that this is a developing country. Therefore, it is important

to emphasize the development of comparative studies analyzing the different formulations of BoNT/A and questions such as its potency and final sale price. Nevertheless, aside from this proposed study, there are no comparative studies using different types of BoNT/A to treat NDO. (Botox® versus Prosigne®).

In spite of the possible methodological failures prompted by a non-randomized study and small patient samples, the authors proposed an interesting paper, where they analyzed the action of two different formulations of BoNT/A in the treatment of NDO.

The urodynamic findings showed that the improvement of maximum cystometric capacity was significantly higher in Botox® group than in the Prosigne® one. Apart from a better continence on week 12 in the Botox® group (76.2% vs. 47.6% respectively, $p = 0.057$), all the other parameters did not show significant differences in the two groups. Moreover, perhaps if the quantity of data was increased this would be even more evident.

There are several questions to be addressed regarding the intradetrusor injection of BoNT/A to

treat NDO. Similar randomized trials should be done to clearly determine which formulation of BoNT/A has the best cost-efficiency with greater safety and lower morbidity.

REFERENCES

1. Colli E, Digesu GA, Olivieri L: Overactive bladder treatments in early phase clinical trials. *Expert Opin Investig Drugs*. 2007; 16: 999-1007.
2. Karsenty G, Denys P, Amarenco G, De Seze M, Gamé X, Haab F, et al.: Botulinum toxin A (Botox) intradetrusor injections in adults with neurogenic detrusor overactivity/neurogenic overactive bladder: a systematic literature review. *Eur Urol*. 2008; 53: 275-87.

Dr. João Luiz Amaro
Department of Urology
UNESP, School of Medicine
Botucatu, São Paulo, Brazil
E-mail: jamaro@fmb.unesp.br