Brazilian Journal of Videoendoscopic Surgery

Original Article

Use of Botulinum Toxin Type A (Botox®) Through Transcystoscopic Vesical Insertion for Overactive Bladder Syndrome Non-Responsive to Oral Medication or for Parasympatholytic Drugs use Severe Side Effects

LESSANDRO CURCIO*; FABICIO COSTA; MARCOS AUGUSTO MARINHO; ANTONIO CLAUDIO CUNHA; JUAN RENTERIA; GERALDO DIBIASE FILHO

** Department of micturition dysfunction - Urology Service at Hospital Geral de Ipanema.*

ABSTRACT

The botulinum toxin type A (Botox®) has been used in several specialties, and has showed to be efficient in the improvement of urodynamics parameters and the quality of life of patients with overactive bladder symptoms. We present in this study our initial case series of intradetrusor injection. The patient was placed in lithotomy position and through a rigid cystoscope an endoscopic needle was inserted and injected in 20 sites. We injected 100 U of BTX-A for idiopathic patients and 200 U of BTX-A for neurogenic patients. Ambulatory follow-up was performed at 2, 4, 6, 12 and 24 weeks after BTX-A injection. Eleven applications were done in 9 patients. The voiding diary parameters emphasized the good results in terms of nocturia and frequency (nocturia decreased 64,2% and daily frequency decreased 50,8%). Urodynamics parameters showed an improvement in maximum cystometric capacity and a reduction in the detrusor pressure of uninhibited contraction (76%). The quality of life parameter improved 74,8%. No serious complication had occurred. We had an initial experience of eleven cases of BTX-A injection, where no significant side effects were observed, with good results concerning quality of life and urodynamics parameters. The botulinum toxin type A has been emerging in urology as a great ally to fight against voiding dysfunction; however, its substantial costs and the necessity of reapplication are still factors that hinder the widespread use of this approach.

Key words: Botulinum toxin; overactive bladder, neurogenic bladder.

Braz. J. Video-Sur, 2008, v. 1, n. 3: 097-103

Accepted after revision: June, 10, 2008.

INTRODUCTION

Overactive bladder syndrome (OAB) is a public health issue with severe physical and financial consequences to the population with greater incidence in the elderly. It is the fourth chronic disease in prevalence behind cardiopathies and sinusites[1] and with annual incidence of 16% in Brazil and 19% in the USA[2]. The estimated annual economic cost of OAB is of $ 26 billions in the USA including diagnosis and treatment[3].

The method of choice to treat OAB syndrome is the use parasympatholytic drugs (in association to behavioral treatment); however, they have failed (20%) or even they have been discontinued (achieving up to 58% in 6 months) due to side effects, mainly xerostomia (40 % with the use of oxybutinin)[4].

As neurostimulators, with an overall success of 56%, are very expensive (U$18mil), it is necessary an efficient treatment with reasonable costs to help these patients. Botulinum toxin type-A initially described in urology for detrusor-sphincter dyssynergia[5], depicted satisfactory results to control OAB symptoms. We showed our initial prospective casuistic as well as a literature review of the use of BTX-A off label in patients with neurogenic and idiopathic OAB that have not improved with habitual anticholinergic or who had intense side effects with these drugs.

MATERIALS AND METHODS

The inclusion criteria for this study are: patients that with the use of anticholinergic drugs in high doses did not improve OAB symptoms within three months or patients in whom the use of these drugs cause severe side effects (xerostomia, blurred vision, digestive tract manifestations or dizziness)

leading to treatment discontinuity and symptomatic recrudescence. Contraindications are: blood dyscrasia, the use of botulinum toxin A for other therapeutic purpose in the last three months, polyneuropathies (such as Guilliam-Barré Syndrome), pregnancy or suspicion of bladder cancer.

Patients sign an informed consent acknowledging their participation in a study of a drug approved by the FDA (Food and Drug Administration), in which the purpose of its use is off label. Before BTX-A injections the patients fill out a 3-day urinary diary, a questionnaire of quality of life and perform an urodynamic study. Hospitalization is on the same or the day before the procedure, where quinolone prophylaxis has been initiated at home during three days.

Lithotomy position is used and medullar block (raquianesthesia) or propofol sedation and a laryngeal mask airway are performed. Local anesthesia is performed in one case using 2% xylocaine gel in the urethra and instillation of 40ml 2% lidocaine, where 20 minutes later the device is inserted.

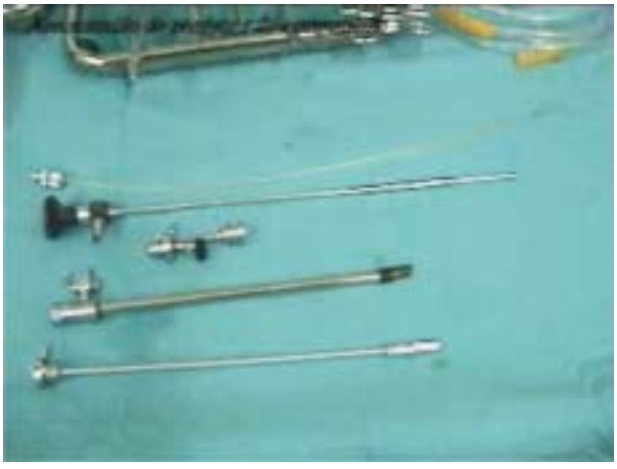


Figure 1 - *Instruments for injection: 24 Fr rigid cystoscope, mandrel and needle.*

Toxin (Botox®) is diluted in 20 ml normal saline solution, and 100 U was used for idiopathic overactive bladder and 200 U for neurogenic overactive bladder. Dilution should be carefully managed because if the bottle is heavily shaken to homogenize the content the disulfide bridge that links the light and heavy toxin chain might be broken, inactivating the toxin as a consequence. A 24 Fr cystoscope sterilized needle used in the past to inject Teflon was used to treat stress urinary incontinence (Figure 1). Injections were performed without sparing the trigone in 20 different sites with careful attention not to deepen it too close to the cupula avoiding inadvertently intraabdominal viscera injection and observing the development of an increased local consistency (bulking) (Figure 3), which lead us to believe that there were no lost and that the injection was performed in the right place(detrusor). When there are trabeculations (Figure 2), they should not be spared from the injections as they derived from a focal detrusor hypertrophy. A catheter is left in case of spinal anesthesia and patients are discharged home on the same day of the treatment or the day after due to social issues.

Ambulatory follow-up is performed at 2, 4, 6, 12 and 24 weeks after BTX-A injection, symptoms subjective improvement were verified by means of a questionnaire of quality of life, and objective improvement were confirmed through urodynamics

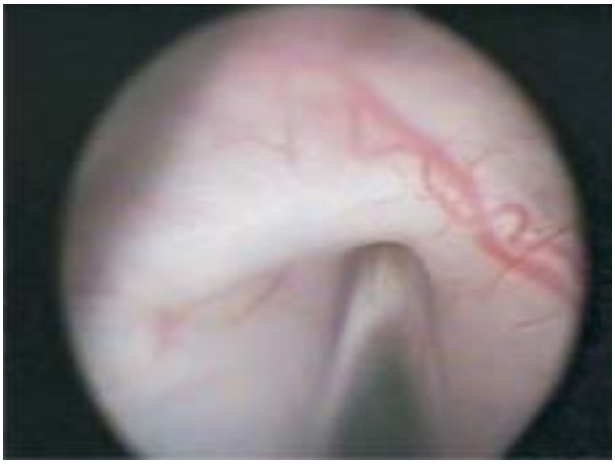


Figure 2 - *Intradetrusor endoscopic needle. Trabeculations should be prioritized.*

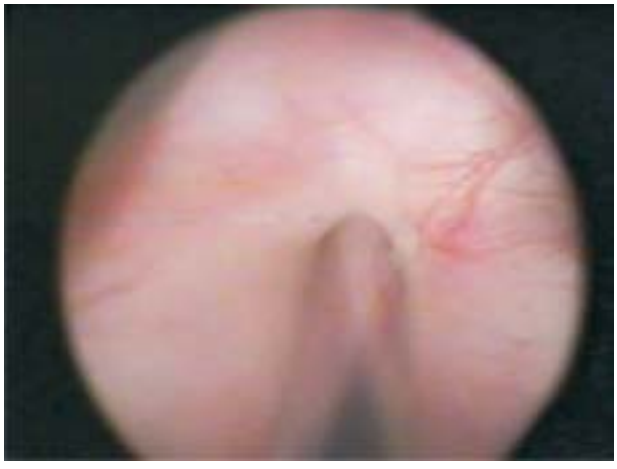


Figure 3 - *Bulking depicting the toxin being correctly injected into the detrusor.*

(on the sixth week and if symptoms got worse on the following week). Every 6 months reinjection is available to alleviate patients' complaints due to symptomatic recrudescence.

The topics evaluated through micturition diary were total micturition frequency and nocturia as well as incontinence episodes. However, the International Consultation on Incontinence Questionnaire-Short Form (ICIQ-SF) was evaluated through the numerical sum of three easily understandable questions. Urodynamics emphasized the maximum cystometric capacity and the permanence or not of uninhibited contraction, and if contraction was present its intensity and quantity of normal saline solution infusion was measured.

RESULTS

A total of 11 patients (2 patients were retreated), 7 women and 2 men, were treated with injections of BTX-A. The mean age was 55.8 years, the cause of overactive bladder syndrome in 6 patients were idiopathic and in 3 patients neurogenic. Indications to treatment were 8 patients with overactive bladder refractory to anticholinergic therapy and one patient with intolerable side effects to the oral drugs. Regarding the chronic conditions associated with overactive bladder, systemic arterial hypertension was observed in 5 patients and diabetes in none of them. The mean disease duration was 5.4 years. Of the patients with neurogenic overactive bladder two have suffered a medullar lesion for raquimedular trauma (one with C5 ASIA B lesion and the other with lesion between T9 and T12 ASIA A) and one patient depicted sequela of tropical spastic paraparesis by HTLV-1.

The mean operative time was 19.5 minutes, in the majority of the patients the surgery was under propofol sedation and a laryngeal mask airway, raquianesthesia was performed in two patients and local anesthesia in one patient. Patients received 200 U of BTX-A in 10 injections and 100 U in one injection. The mean hospitalization time was 24 hours and 2 small complications were reported, one patient with a light hematuria without hemodynamic repercussion which improved after 3 days of conservative treatment and a non-neurogenic patient with urinary retention of 29ml detected by echography ultrasound in whom an intermittent catheterization was necessary, so patient's condition improved within 2 weeks.

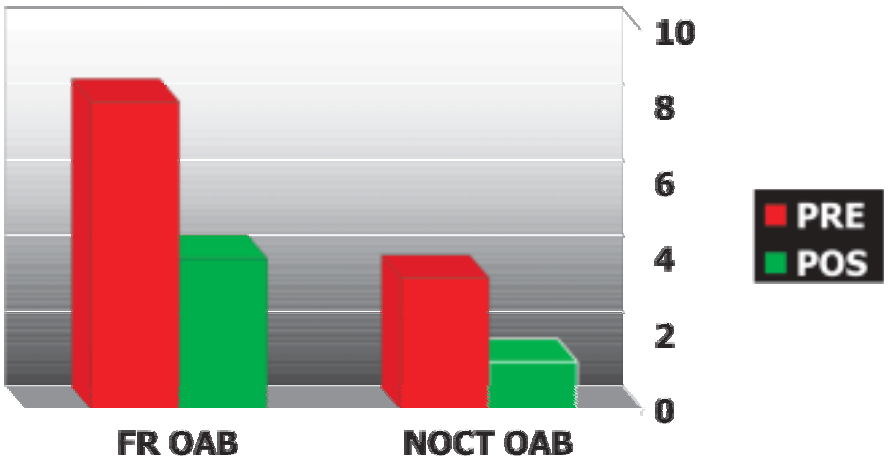
Nocturia and micturition frequency which were evaluated through the micturition diary decreased in 64.2% and 50.8%, respectively (Graphic 1). Among neurogenic patients there was substantial improvement of incontinence episodes between the catheterizations, thus a patient continued to have incontinence episodes at night; however, at re-treatment these episodes improved considerably. Bladder capacity improved significantly from 317 ml to 430 ml and uninhibited contraction pressure decreased 76% (Graphic 2). In average the quality of life questionnaire decreased from 14.5 to 2.2 (Graphic 3). A paraplegic patient with neurogenic overactive bladder and sensibility partially preserved was retreated after 6 1/2months with local anesthesia, on a 10 points pain scale the patient reported pain intensity of 4 points, revealing similar parameters of the first re-treatment.

Of the 6 patients that received BTX-A more than 6 months ago, 2 patients have already been re-treated; one patient is waiting to be called for re-treatment, another patient lost contact. Although one patient admits a significant symptomatic improvement, she is apprehensive and afraid of a new urinary retention even after it was explained about its eventuality. One patient is under the suspicion of a vesical blastoma, in spite of being asymptomatic at the time of the injection.

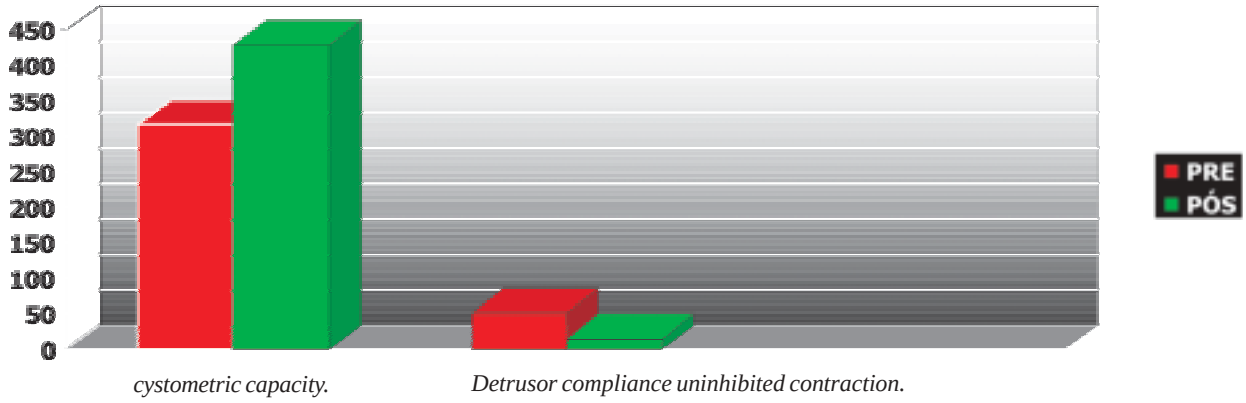
DISCUSSION

Several studies have been analyzing the use of botulinum toxin type A (BTX-A) in urology in which the first approach was for sphincter dyssynergia[5]; however, other diseases have been treated with reasonable success with this medication such as benign prostatic hyperplasia (BPH) [6] and interstitial cystitis (IC). Nevertheless, overactive bladder syndrome of either idiopathic or neurogenic origin is the pathological condition mostly treated with BTX-A. The effect of BTX-A in the bladder are inhibition of acetylcholine release blocking the motor activity, inhibition of ATP, the calcitonin gene-related peptide (CGRP) and substance P release[7,8,9]. BTX-A reduces the fibrosis on the vesical wall[10] and leads to decrease the nerve growth factor (NGF) [11] content.

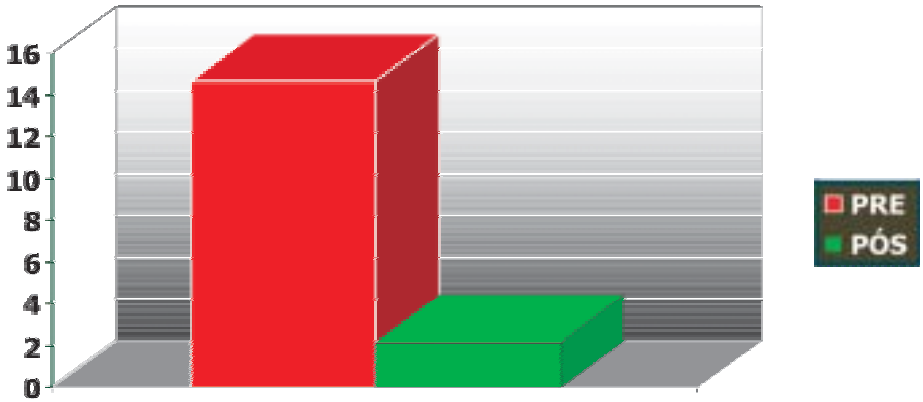
Urodynamic (detrusor lost of pressure, maximum cystometric capacity) and quality of life as well as urinary frequency and leakage have been the most analyzed factors in studies. In one of the first manuscripts about BTX-A in patients with spinal cord



Graphic 1 - *Improvement of micturition frequency as well as nocturia after BTX-A injection.*



Graphic 2 - *Maximum cystometric capacity by urodynamic one month after BTX-A injection, as well as reduction of the voiding pressure of uninhibited contraction.*



Graphic 3 - *Important improvement in the quality of life measured by the ICIQ-SF.*

injury and neurogenic bladder, Shurch e cols [12] depicted an increased volume reflex and vesicle capacity from 215.8 +/- 90.4 ml. to 415.7 +/- 211.1 (p <0.016) and 296.3 +/- 145.2 to 480.5 +/- 134.1 (p <0.016), respectively. Detrusor compliance also decreased significantly from 65.6 +/- 29.2 cm. de H2O to 35 +/- 32. 1 (p <0.016). Post-void residual volume reduced from 261.8 +/- 241.3 ml. to 490.5 +/- 204.8 (p <0.016). Currently, there have been studies[13] with 200 cases of neurogenic bladder with encouraging outcome. Regarding the idiopathic overactive bladder the greatest study performed in only one institution[14] was published and it demonstrated that there was a significant subjective and objective improvement of 88% among the several parameters analyzed after 4 and 12 weeks. Urgency disappeared in 82% of the patients and incontinence was successfully treated in 86% of the cases within 1 to 2 weeks, frequency improved in 50% and nocturia episodes decreased from 4 to 1.5 with maximal bladder capacity improving in 56%.

In our casuistic, we obtained parameters of decreased micturition frequency and nocturia similar to the literature and what most surprised us was the reduction of 76% of the detrusor pressure of the uninhibited contraction, depicting the anticholinergic feature of the botulinum toxin. The quality of life was another parameter that depicted significant improvement from 14.7 to 2.2, patients with idiopathic detrusor overactivity(IDO) reported a great satisfaction regarding urgency. Though among patients with neurogenic detrusor overactivity (NDO) incontinence episodes between the catheterizations was the factor that most pleased them, as there is a reduction of the use of diapers and absorbent pads which directly affects the patients' daily routine.

One of our questions was if the patient with IDO despite the lower dose of toxin used would have the same outcome of the patient with neurogenic bladder. This was studied by POPAT and cols [15], where 31 patients with NDO and 44 patients with IDO received 200 U and 300 U of BTX-A, it was also observed that urodynamic improvement of micturition diary and quality of life parameters were similar between both groups of patients. This question could not be confirmed in our casuistic, first because of a small number of patients with NDO (3 patients) when compared to the 6 patients with IDO, and second because we reduced the number of BTX-A units injected in the IDO group (from 200 to 100 U) and in the NDO group (from 300 to 200 U).

According to the majority of the studies the mean BTX-A re-injection is performed every 6 months; however, would the re-injected patients have the same results? Grosse and cols. demonstrated that 66 patients retreated up to 6 times with either Botox® or Dysport® had similar outcomes after repeated injections. Nevertheless, another author[18] depicted that 27 patients had undergone additional injections, though he concluded repeated injections lasted longer and delayed the symptomatic recrudescence maintaining its efficacy for one year. In a cohort study of 20 children with myelomeningocele, it was not observed any case of hypersensitivity to reinjection[19]. There were only two cases of repeated injections in patients with NDO who depicted the same improvement outcome of the first injection.

In our study the trigone was spared and we did not observe any case of symptom of reflux, in spite of some author have already proved that there is no difference in injecting BTX-A in the trigone or not. In a study[20] with 10 patients with IDO, 200 U of intradetrusor BTX-A was injected and after 6 weeks a voiding uretrocystography did not show reflux in any of the cases and in another case series[21] of BTX-A injection there were two groups: the trigone group and trigone-sparing group and in 6 months of follow-up no difference was observed between both groups.

The cost of treatment with BTX-A(only the toxin is a great part of the costs) as well as the necessity to perform it at the ambulatory lead us to use local anesthesia with 2% lidocaine initially for patients with spinal cord injury and later for patients with IDO. Rackley [22] have already described an approach with local anesthesia with 100ml 2% lidocaine for 15-20 minutes; however, the patient still experienced some pain as the anesthetic does not fully penetrate the bladder wall. Drug administration by iontophoresis has demonstrated satisfactory results with reduction of pain from 4 to 1.6 on a 10-point pain scale. This demonstrate that iontophoresis may be associated with local anesthesia leading to a deeper penetration of the anesthetic drug [24], which makes the procedure more feasible and less costly.

CONCLUSION

BTX-A is becoming a viable alternative with good objective and subjective results, when the parasympatholytics drugs are not effective or when their side effects lead the patient to abandon the treatment. However, high costs and necessity of re-treatment are factors that prevent the widespread use of botulinum toxin type A.

REFERENCES

1. Debruyne FM, Heesakkers JP: Clinical and socioeconomic relevance of overactive bladder. Urology 2004 Mar, 63(3 Suppl 1):42-4.
2. Stewar WF, Van Rooyen JB, Cundiff GW, Abrams P, Herzog AR: Prevalence and burden of overactive bladder in USA. World J Urol. 2003 May; 20(6):327-36. Epub 2002 Nov 15 .
3. Hu TW, Wagner TH, Bentkover JD, Leblanc KÇ :Estimated economic costs of overactive bladder in the USA; Urology. 2003 Jun; 61(6): 1123-8
4. Kelleher CJ, Reese PR, Pleil AM, Okano GJ: Health-related quality of life of patients receiving extended-release tolterodine for overactive bladder. Am Manag Care, 2002, Dec; 8(19 suppl):S608-15
5. Dykstra DD, Sidi AA, Scott AB, Pagel JM, Goldish GD,: Effects of botulinum A toxin on detrusor-sphincter dyssynergia in spinal cord injury. J Urol. 198 139:919.
6. Maria G, Brisinda G, Civello IM, Bentivoglio AR Albanese A: Relief by botulinum toxin of voiding dysfunction due to benign prostatic hyperplasia: results of a randomized, placebo-controlled study. Urology, 2003 Aug 62(2):259-64
7. Rapp DE, Turk KW, Bales GT, Cook SP: Botulinum toxin type A inhibits calcitonin gene-related peptide release from isolated rat bladder. J Urol. 2006 Mar;175(3 Pt 1):1138-42.
8. Cui M, Khanijou S, Rubino J, Aoki KR: Subcutaneos administration of botulinum toxin A reduces formalin-induced pain. Pain. 2004 Jan; 107(1-2):125-33.
9. Apostolidis A, Popat R, Yiangou Y, Cockayne D, Ford AP, Davis JB, Dasgupta P, Fowler CJ, Anand P: Decreased sensory receptors P2X3 and TRPV1 in suburothelial nerve fibers following intradetrusor injections of botulinum toxin for human detrusor overactivity. J Urol.2005 Sep;174(3):977-82;discussion 982-3.
10. Compérat E, Reitz A, Delcourt A, Capron F, Denys P, Chartier-Kastler E: Histologic features in the urinary bladder wall affected from neurogenic overactivity-a comparison of inflammation, oedema and fibrosis with and without injection of botulinum toxin type A. Eur Urol. 2006 Nov;50(5):1058-64. Epub 2006 Feb 6
11. Giannantoni A, Di Stasi SM, Nardicchi V, Zucchi A, Macchioni L, Bini V, Goracci G, Porena M : Botulinum-A toxin injections into the detrusor muscle decrease nerve growth factor bladder tissue levels in patients with neurogenic detrusor overactivity. J Urol. 2006 Jun;175(6):2341-4.
12. Schurch B, Schmid DM, StöhrerM: Treatment of neurogenic incontinence with Botulinum Toxin A. New Engl J Med 2000, 342 (9): 665.
13. Reitz A, Stöhrer M, Kramer G, Del Popolo G, Chartier-Kastler E, Pannek J,: European experience of 200 cases treated with botulinum-A toxin injections into the detrusor muscle for urinary incontinence due to neurogenic detrusor overactivity. Eur Urol. 2004 Apr;45(4):510-5.
14. Schmid DM, Sauermann P, Werner M, Schuessler B, Blick N, Muentener M,: Experience with 100 cases treated with botulinum-A toxin injections in the detrusor muscle for idiopathic overactive bladder syndrome refractory to anticholinergics. : J Urol. 2006 Jul;176(1):177-85.
15. Popat R, Apostolidis A, Kalsi V, Gonzales G, Fowler CJ, Dasgupta P: A comparison between the response of patients with idiopathic detrusor overactivity and neurogenic detrusor overactivity to the first intradetrusor injection of botulinum-A toxin. J Urol. 2005 Sep;174(3):984-9.
16. Schurch B, de Seze M, Denys P, Chartier- Kastler E, Haab F: Botulinum toxin type A is a safe and effective treatment for neurogenic urinary incontinence: results of a single treatments, randomized, placebo controlled 6- month study. J Urol .2005; 174:196-200
17. Grosse J, Kramer G, Stoher M: Success of repeat detrusor injections of botulinum A toxin in patients with severe neurogenic detrusor overactivity and incontinence. Eur Urol. 2005; 47: 653-9
18. 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
19. Altaweel W, Jednack R, Bilodeau C, Corcos J: Repeated intradetrusor botulinum toxin type A in children with neurogenic bladder due to myelomeningocele. J Urol. 2006 Mar;175(3 Pt 1):1102-5 ..
20. Karsenty G, Elzayat E, Delapparent T, St Dennis B: Botulinum toxin type A injections into the trigone to treat idiopathic overactive bladder do not induce vesicoureteral reflux. J Urol. 2007; Mar 177(3): 1011-4.
21. Lucioni A, Rappi DE, Gong EM, Fedunok P, Bales GT: Intravesical botulinum type A injection in patients with overactive bladder. Trigone versus trigone sparing injection. Can J Urol. 2006 Oct; 13(5):3291-5
22. Rackley RR, Frenk TL, Abdelmalak JB: Botulinum toxin: the promise of therapy for complex voiding dysfunctions. Cont Urol. 2005; 38-52.
23. Shurch B, Reitz A, Tenti G: Electromotive drug administration of lidocaine to anesthetize the bladder before botulinum-A toxin injections into the detrusor: Spinal Cord . 2004; 42, 338-341.

24. Gurpinar T, Wong HY,, Griffith DP.: Eletromotive drug admnistration of intravesical lidocaine in patient with interstitial cystitis; J endourology 1996, 10: 443-447).

Correspondence address:
LESSANDRO CURSIO
Av. das Américas, 13.554 / bl 02 / ap 805
Barra da Tijuca, Rio de Janeiro, RJ
CEP: 22790-700
lessandrocg@ig.com.br
Phones: (21) 7896-3739 / 9991-9485 / 2430-3257