Injection of botulinum toxin type A in the urethral sphincter to treat lower urinary tract dysfunction: a review of indications, techniques and results

Gilles Karsenty, MD, Abdulaziz Baazeem, MD, Ehab Elzayat, MD, Jacques Corcos, MD

Department of Urology, Jewish General Hospital, McGill University, Montreal, Quebec, Canada

KARSENTY G, BAAZEEM A, ELZAYAT E, CORCOS. Injection of botulinum toxin type A in the urethral sphincter to treat lower urinary tract dysfunction: a review of indications, techniques and results. The Canadian Journal of Urology. 2006;13(2):3027-3033.

The first application of botulinum toxin type A (BTA) in urology was its injection into the urinary sphincter to treat neurogenic detrusor-sphincter dyssynergia (DSD) in quadriplegic men. Since that first report in the eighties, the results of focal BTA injections into the sphincter, the bladder wall and lately into the prostate, have raised the interest of the urology community in this promising new therapeutic modality. An evidence-based review is presented of current indications, techniques and outcome of BTA injections into the urethral sphincter.

Key Words: neurogenic bladder, botulinum toxin, Botox, dyssynergia, sphincter, obstruction, multiple sclerosis

Introduction

The first application of botulinum toxin type A (BTA) in urology was its injection into the urinary sphincter to treat neurogenic detrusor-sphincter dyssynergia (DSD) in quadriplegic men.[1] Since that first report by Dykstra et al in 1988, the results of focal BTA injections into the sphincter, the bladder wall[2-5] and lately into the prostate,[6] have raised the interest of the urology community in this promising new therapeutic modality. An evidence-based review is presented of current indications, techniques and outcome of BTA injections into the urethral sphincter.

Accepted for publication March 2006

Address correspondence to Dr. Jacques Corcos, Department of Urology, Jewish General Hospital, 3755 Cote-Ste-Catherine, Montreal, Quebec, H3T 1E2

Method

The Medline database was searched for the years 1966 to September 2005, using the keywords "botulinum toxin" and" urethra" or "urinary sphincter". English-written articles that reported the results of BTA injection into the urethral sphincter to treat lower urinary tract dysfunction were selected. The references cited in these articles were also examined, and relevant papers were added to the selection. A level of evidence according to the Oxford Centre for Evidence-based Medicine[7] was assigned to each article.

Mode of action and indications

BTA blocks acetylcholine release from presynaptic cholinergic nerve endings. Neural influx transmission is, therefore, blocked at the level of the neuromuscular junction, leading to temporary, reversible chemo-denervation of the targeted muscle.[8] Figure 1a and 1b. The aim of BTA injection into the urethral striated sphincter (USS) is to induce muscle relaxation. In cases of DSD or USS hypertonia, such relaxation is thought to decrease urethral resistance and to improve bladder emptying. In urinary retention or incomplete micturition related to detrusor hypocontractility, a reduction of normal USS tonus has been proposed to help diminish the abdominal pressure needed to empty the bladder by Valsalva maneuver and, thus, to avoid catheterizations.

Urethral BTA injection has been used, first and mainly, to treat the consequences of neurogenic DSD.[1,9-14] DSD is related to various neurological conditions, primarily traumatic cervical spinal cord injury and multiple sclerosis (MS). The same approach has also been taken to treat non-neurogenic obstructive sphincter dysfunctions, such as detrusor-sphincter in-coordination, USS hypertony, or difficulty to void due to chronic prostatitis.[15] Lately, it has been proposed as an alternative to self-catheterization in urinary retention related to detrusor hypo contractility secondary to post-surgical bladder denervation or cauda equina injuries.[16]

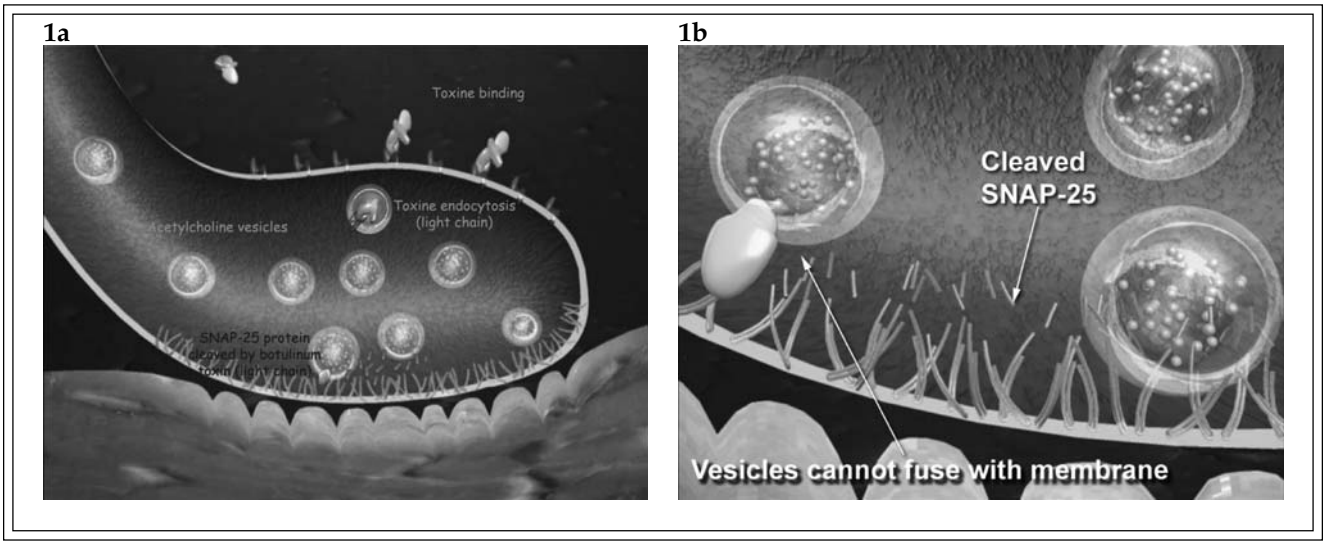

Figure 1. Mode of action of botulinum toxins (BTs)
BTs are macroproteins made of a heavy chain (100kD) and a light chains (50kD) linked by a disulfid thermo sensible bond (destroyed after 10 minutes at 80°C). BTs are endopeptidases that cleave SNARE proteins. SNARE proteins regulate exocytosis of vesicles carrying neurotransmitters (Nt). Cleavage of a SNARE protein results in a blockage of neural transmission due to absence of Nt release. Every serotype of BT cleaves a specific SNARE-protein. Type A cleaves a protein called SNAP-25 (synaptophysin-25).
Figure 1a. BT heavy chain recognizes a specific receptor at nerves terminal surface membrane and allows the internalization of the light chain by endocytosis. This receptor remains unknown for BT type A. BTs have an affinity for cholinergic motoneurons endings, it might be related to this receptor.
Figure 1b. After endocytosis, L chain is released into the cytosol of the nerve ending leading to cleavage of SNAP-25. Therefore release of the Nt is blocked resulting in a peripheral denervation. The mechanism by which an anatomically and functionally normal neuromuscular junction recovers is not fully understood. SNAP-25 turn-over or sprouting of temporary accessory nerve endings have been hypothesized.

Technique

BTA can be injected into the urinary sphincter under electromyographic (EMG) or cystoscopic guidance.

The EMG-based technique consists of locating the USS with an EMG needle doubling as an injection channel, Figure 2. In males, the needle is usually inserted into the perineal raphe at equal distances from the scrotum and anus. The needle is directed towards the prostatic apex which is palpated rectally.[14] In females, the technique derives from the urethral sphincter EMG technique.[17] The same type of needle is inserted, once medially or twice para-medially, into the anterior vaginal wall, underneath the mid-urethra, approximately 2 cm proximal to the meatus.

In both genders, recognition of the typical tonic activity of the USS or reflex activity elicited by glandular or clitoral squeezing (bulbo-cavernous reflex) ensures the correct location of the needle tip within the USS. Injection into the USS under EMG guidance has been shown by MRI studies to accurately and specifically target the USS.[18] No difference has been found between a single median injection and two para-median injections in each hemi-sphincter.

Cystoscopy-guided injection is delivered under visual control, with an endoscopic needle passed through a rigid or flexible endoscope. Two to four injection points are entered at 12, 3, 6, and/or 9 o'clock in the sphincter. The needle has to be inserted deeper than in bulking agent injection, to inject the muscle and not the sub-urothelial space.[19]

BTA doses injected into the USS range from 80 IU to 100 IU of Botox or from 150 IU to 250 IU of Dysport according to indications and authors. The total dose is usually diluted in 2 ml to 4 ml of saline 0.09%. Both techniques are usually performed under local anesthesia (10 ml of lidocaine gel, injected into the urethra, 10 minutes before injection) as an outpatient procedure. Patients with spinal cord injury levels higher than T6 need blood pressure monitoring during the procedure because of the risk of autonomic dysreflexia.

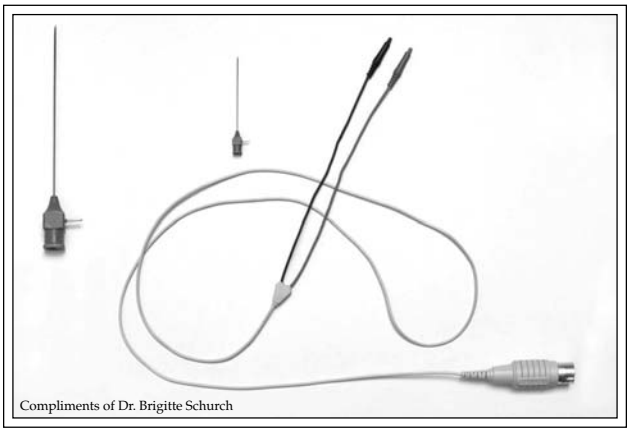

Figure 2. Example of electromyographic needle with injection channel used for sphincteric Botox injection.

The efficacy of both techniques, in terms of USS denervation and quality of bladder emptying, seems to be comparable.[1,14] The choice of one or the other depends on the physician's experience.

Results

After Dykstra's first report, urethral BTA injections were studied in 14 articles to treat 162, 80 and 35 patients with neurogenic DSD, non-neurogenic obstructive sphincter dysfunction and hypocontractile detrusor, respectively.

All authors affirmed BTA efficacy in treating neurogenic DSD, primarily in two populations, quadriplegic men unable to perform self-catheterization and MS patients of both genders. Efficacy was evaluated by various criteria: post-void residual (PVR), maximal urinary flow rate, maximum urethral pressure, maximal detrusor pressure, frequency of hyperreflexia episodes, objective USS denervation under EMG, Table 1.

Only two articles have specifically reported on non-neurogenic obstructive sphincter dysfunction. Zermann et al[15] observed that BTA injections improved bladder emptying and pain in patients with chronic prostatitis, whereas Fowler et al[20] found no effect of BTA injection when treating an infrequent form of urinary retention related to a myogenic disorder (Fowler's syndrome). In addition, other articles included non-neurogenic cases of sphincter dysfunction and recorded improvement of bladder emptying after BTA injection.[13,19,21]

Kuo et al studied the effect of BTA injection in 35 patients with detrusor hypocontractility.[16,21] They concluded that 81% had a perfect result or improvement in bladder emptying. Mean maximum urinary flow increased from 4.2 ml/s to 8.2 ml/s; mean voiding pressure and PVR decreased from 88 $cmH_20$to 64 cmH_2O and from 320 ml to 159 ml, respectively.

The duration of the BTA effect ranged from 1 to 4 months after a single injection. According to Schurch et al,[14] it can be increased up to 12 months with two consecutive monthly reinjections after the initial injection.

De novo stress incontinence after BTA injection into the sphincter was found to occur in 4% to 10% of

TABLE 1. **Efficacy of BTA injection in urethral striated sphincter**

Author, method	Patients	Dose, efficacy (criteria: results)[duration]	Level of evidence
Neurogenic detrusor-sphincter dyssynergia			
Dykstra et al 1988 Case series[1]	11 SCI m	Dose: nc; USS Denerv: 11/11; MUP↓ -27 cmH_2O; PVR↓-146ml; AD stop: ↓ 5 patients [50 days]	4
Dykstra and Sidé 1992 RCT vs. placebo[10]	5 SCI m	Dose: nc; USS Denerv: 3 vs 0; MUP ↓-25 cmH_2O vs. O; PVR: ↓ -125 ml vs. no change; [2 months]	1c
Schurch et al 1996 Case series[14]	24 SCI m	Dose: 100 Botox or 250 Dysport; ↓ MUP; ↓duration of DSD episodes; ↓AD; ↓PVR (ns), [3 months single inj; 9-12 months 1 inj at M1, 2, 3]	4
Petit et al 1998 Case series[12]	17 SCI m	Dose: 150 Dysport; MUP: ↓ -24 cmH_2O; PVR: ↓ -176 ml; MDP: ↓-19 cmH_2O [2-3 months]	4
Gallien et al 1998 Case series[11]	5 SCI m	Dose:100 Botox; ↓MUP; ↓PVR, ↓ AD [3 months]	4
Wheeler et al 1998 Case series[26]	3 SCI m	Dose: -; subjective improvement 2/3, ↓PVR, ↓HRA [3 months]	4
*Phelan et al 2001 Case series[13]	13/21 5 SCI m, 8 MS	Dose: 100 Botox; catheter removal: 11/13; PVR: ↓-174 ml; Subjective improvement: 67% [not usable]	4
de Seze et al 2002 RCT vs. lidocaïne[9]	13 9 SCI m, 3MS, 1P	Dose: 100 Botox; MUP ↓-32 cmH_2O vs. no change; PVR: ↓-159 ml vs ↓-60; MDP ↓ ns, [46%= 3 months, 23% > 3 months]	1c
*Kuo 2003 Case series[16]	29/103 nm	Dose: 50-100; MP: ↓-13 cmH_2O; Qmax:↑; RPM–161 ml [4 months]	4
*Smith et al 2005 Case series[19]	53/68, 32 MS, 9 SCI m 4 strokes, 8 np	Dose: 80-200 Botox; catheter removal 83%; MUP: -29 cmH_2O PVR:-152 ml [not usable]	4
Non-neurogenic obstructive sphincter dysfunction			
Fowler et al 1992 Case series[20]	6 Fowler's syndrome	6/6 failed	4
Zermann et al 2000 Case series[15]	11 Chronic prostatitis	Dose: 200 Botox; subjective improvement 9/11; pain ↓7.6 to 2.3; ↓ MUP; ↓ PVR; Qmax:↑[46% = 3 months, 23% > 3 months]	4
*Phelan et al 2001 Case series[13]	8/21 2 Post-op retention** 6 Perineal hypertonia	Dose: 100 Botox; catheter removal: 8/8; PVR: ↓-174 ml; Subjective improvement: 67% [not usable]	4
Smith et al 2002 Case report[27]	1 Post-op retention**	100 IU Botox, voiding resumed at 72h; Qmax 28 ml/s RPM:0	4
*Kuo 2003 Case series[21]	39/103 nm	Dose: 50-100; MP: ↓; Qmax: ↑; PVR ↓ [4 months]	4
*Smith 2005 Case series[19]	15/68 Perineal hypertonia	Dose: 80-200 Botox; catheter removal 83% MUP ↓-29 cmH_2O PVR: ↓-152ml [not usable]	4

*Studies including both neurogenic and non-neurogenic DSD

**Retention without anatomic obstruction after sub-urethral tape

RCT: randomized clinical trial; nc: non-comparable (Preparation of BTA that does not correspond to currently available product); ns: non-significant; nm: not mentioned; USS Denerv: Urethral striated sphincter denervation proved by EMG; Qmax: maximum flow rate; PVR: post-void residual; MUP: maximum urethral pressure; MDP: maximum detrusor pressure; MP: micturition pressure; AD: autonomic dysreflexia; SCIm: spinal cord-injured male; MS: multiple sclerosis; SP: spina bifida.

patients with initially normal/intact voluntary micturition.[19,21]

No severe side-effect was encountered after injection of BTA into the USS.[22] Transient upper limb muscle weakness, lasting from 2 weeks to 2 months, was seen in three quadriplegic patients after USS BTA injection. One case of unexplained fever, lasting 2 weeks that resolved spontaneously, also was reported.

Comments

Neurogenic DSD

All authors concluded that BTA injection was efficient in improving bladder emptying in the presence of neurogenic DSD. However, series with a small number of patients, different causes of neurogenic sphincter dysfunctions, variable patient expectations and treatment goals as well as differences in outcomes make comparison of these studies difficult.

Quadriplegic men were the most widely-studied population. BTA injection into the USS is proposed to these men as a chemical sphincterotomy, an alternative to surgical sphincterotomy or stent. Its goal is to obtain automatic bladder emptying, triggered by uninhibited bladder contractions. The potential advantages of BTA injections are its relatively limited invasiveness and reversibility. It gives the opportunity to patients who are reluctant to undergo sphincterotomy, to appreciate the results through a reversible intervention. It might be specifically valuable in the early phase of their disability after spinal shock has resolved, while they are still involved in heavy care programs and accept their handicap with difficulty. There are discrepancies in the impact of the treatment on PVR and bladder pressure. To evaluate BTA injection efficacy, none of the studies used detrusor leak point pressure (DLPP) as a primary outcome. This is surprising as we know the value of DLPP as a predictor of upper urinary tract damage.[23] Furthermore, the need for post sphincterotomy adjuvant treatment of bladder neck has to be evaluated.

MS patients represent the main other population that was studied. DSD in MS patients does not usually have the same features and consequences as in spinal cord- injured patients. Upper tract involvement as well as complete retention are infrequent.[24] The most common problems related to DSD are recurrent urinary tract infections,[24] which limit immuno modulator treatments of MS, worsen MS symptoms or aggravate overactive bladder symptoms which are frequently present in MS.[24] The goal of BTA injection into the USS in MS patients is to decrease urethral resistance enough to avoid chronic retention/urinary stasis/ PVR elevation but not to the point of inducing stress incontinence. The potential advantage of BTA injections over clean intermittent self-catheterization in MS patients is that patients' cognitive and visual impairment as well as manual dexterity do not affect their eligibility for treatment. MS patients have not been specifically investigated. Because they have different expectations about DSD treatment and their therapy involves different goals compared to quadriplegic men, dedicated studies are warranted.

Non-neurogenic obstructive sphincter dysfunction

Despite five publications on the efficacy of BTA injection into the USS to improve bladder emptying and obstructive symptoms of various non-neurogenic obstructive sphincter dysfunctions, it is difficult to make clear recommendations and indications. The same flaws, as previously noted in neurogenic DSD, have to be pointed out. The indications vary widely, from obstructive symptoms and pain associated with prostatitis to pelvic floor hypertonia or uncertain DSD secondary to the presence of a sub-urethral tape. Moreover, differences in outcome measurements and efficacy criteria preclude any comparative analysis. In addition to its pathophysiology, diagnostic criteria and the clinical relevance of non-neurogenic obstructive sphincter dysfunction remain questionable.

In case of Fowler's syndrome, the inefficacy of BTA, which acts on the neuromuscular junction, to treat retention is thought to be related to the myogenic nature of the sphincter dysfunction in this rare disorder.

Detrusor hypocontractility

Despite the report by Kuo et al on the efficacy of BTA to avoid self-catheterization in detrusor hypocontractility, this approach has raised concerns. Since the bladder neck in both genders and the prostate in men contribute to urethral resistance, one can wonder by how much an injection of BTA into a normal or hypotonic urethral sphincter can decrease total urethral resistance. And if it does so enough to dramatically reduce the pressure needed to void, why does it not induce stress incontinence?

The safety of micturition by abdominal straining, even with a supposed decrease in urethral resistance, is doubtful. Chronic abdominal straining is known to favor groin hernia and hemorrhoid formation or pelvic organ prolapse in women. Mean detrusor pressure at micturition in the study[16] was still 64 cmH_2O after BTA treatment, above the safe limit of 40

cmH_2O. Above this value, there is a heightened risk of vesico-ureteric reflux, which can be further aggravated by voiding in these patients, as it is not active physiological micturition involving the trigonal anti-reflux mechanism. The effect of chronic abdominal straining on the denervated perineum of women with cauda equina syndrome might be devastating, leading to early major pelvic organ prolapse. The risk of de novo stress incontinence related to induce sphincter insufficiency has to be evaluated specifically.

Recommendations for future studies

Because MS patients have different expectations about DSD treatment and their therapy involves different goals compared to quadriplegic men, these two populations must be studied separately in properly-powered randomized, placebo- controlled trials.

In quadriplegic men, the primary outcome to evaluate the efficacy of sphincter injection of BTA should be DLPP.

In MS patients, the primary outcome should include symptom evaluation, PVR measurement and number of urinary infections. De novo stress incontinence should be assessed and considered as a treatment adverse effect. Possible changes in detrusor hyperreflexia (DH) need to be examined since relief of obstruction might improve DH. Moreover, since intra-detrusor injection of BTA has been shown to be effective in treating incontinence related to DH in MS patients, a study evaluating combined therapy of DSD and DH with intra-detrusor and intra-sphincter BTA would be of interest.

All studies, in quadriplegic men as well as in MS patients, should include, as secondary outcomes, the Qualiveen[25] questionnaire as a yardstick of the impact of treatment on patient quality of life.

Another interesting and novel indication of sphincter injections of BTA in neurogenic patients is found in men with neurological impairment (MS, Parkinson's disease or stroke sequelae) associated with bladder outlet obstruction. Prostate surgery in such cases is known to lead to a high failure rate. Due to the reversible action on the USS and low invasiveness, intra-sphincteric BTA injections may help to distinguish benign prostatic hyperplasia-related from DSD-related bladder outlet obstruction. Therefore, BTA injections could be a valuable diagnostic and therapeutic test in such challenging cases.

In non-neurogenic obstructive sphincter dysfunction, further studies are required to confirm the early results. The presence of obstruction and urethral sphincter hypertonia or paradoxal contractions during micturition should be among the inclusion criteria and be confirmed by video-urodynamic tests. BTA injections should be compared to a placebo arm (saline injection). Outcomes should include video-urodynamic criteria as well as symptom score (IPSS, quality of life questionnaires and satisfaction scales.

The need for regular re-injections of BTA into the USS to maintain results suggests that cost-effectiveness analyses must be conducted with medium and long-term projections. These analyses will have to compare BTA treatments to alternative options (sphincterotomy or sphincteric stents in quadriplegic patients and intermittent self-catheterization in MS or non-neurological patients).

Conclusion

Intra-sphincteric injection of BTA was the first urological use of botulinum toxin. Although it achieves reversible denervation of the urethral sphincter and a subsequent decrease in urethral resistance (level 1c evidence), there is still a need for studies to determine its actual indications. At present, besides quadriplegic men with DSD unable to perform self-catheterization, those most likely to benefit from intra-sphincteric BTA injection are MS patients suffering the clinical consequences of DSD. □

References

1. Dykstra DD, Sidi AA, Scott AB, Pagel JM, Goldish GD. Effects of botulinum A toxin on detrusor-sphincter dyssynergia in spinal cord injury patients. *J Urol* 1988;139:919-922.
2. Hajebrahimi S, Altaweel W, Cadoret J, Cohen E, Corcos J. Efficacy of botulinum-A toxin in adults with neurogenic overactive bladder: initial results. *Can J Urol* 2005;12:2543-2546.
3. Rapp DE, Lucioni A, Katz EE, O'Connor RC, Gerber GS, Bales GT. Use of botulinum-A toxin for the treatment of refractory overactive bladder symptoms: an initial experience. *Urology* 2004;63:1071-1075.
4. Schurch B, de Seze M, Denys P, Chartier-Kastler E, Haab F, Everaert K, Plante P, Perrouin-Verbe B, Kumar C, Fraczek S et al. 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.

5. Schurch B, Stohrer M, Kramer G, Schmid DM, Gaul G, Hauri D: Botulinum-A toxin for treating detrusor hyperreflexia in spinal cord injured patients: a new alternative to anticholinergic drugs? Preliminary results. *J Urol* 2000;164:692-697.
6. Maria G, Brisinda G, Civello IM, Bentivoglio AR, Sganga G, Albanese A. Relief by botulinum toxin of voiding dysfunction due to benign prostatic hyperplasia: results of a randomized, placebo-controlled study. *Urology* 2003;62:259-64;discussion 264-265.
7. Phillips B, Ball C, Sackett D, Badenoch D, Straus S, Haynes B, Dawes M. Levels of evidence and grades of recommendation May 2001. http://www.cebm.net. level_of_evidence.asp
8. Hallen M. Effect of botulinum toxin at the neuromuscular junction, in Brin F, Hallet M, Jankovic J. *Scientific and Therapeutic Aspects of Botulinum Toxin*, Lippincott Williams and Wilkins, 1999, pp 167-170.
9. de Seze M, Petit H, Gallien P, de Seze MP, Joseph PA, Mazaux JM, Barat M. Botulinum a toxin and detrusor sphincter dyssynergia: a double-blind lidocaine-controlled study in 13 patients with spinal cord disease. *Eur Urol* 2002;42:56-62.
10. Dykstra DD, Sidi AA. Treatment of detrusor-sphincter dyssynergia with botulinum A toxin: a double-blind study. *Arch Phys Med Rehabil* 1990;71:24-26.
11. Gallien P, Robineau S, Verin M, Le Bot MP, Nicolas B, Brissot R. Treatment of detrusor sphincter dyssynergia by transperineal injection of botulinum toxin. *Arch Phys Med Rehabil* 1998;79:715-717.
12. Petit H, Wiart L, Gaujard E, Le Breton F, Ferriere JM, Lagueny A, Joseph PA, Barat M. Botulinum A toxin treatment for detrusor-sphincter dyssynergia in spinal cord disease. *Spinal Cord* 1998;36:91-94.
13. Phelan MW, Franks M, Somogyi GT, Yokoyama T, Fraser MO, Lavelle JP, Yoshimura N, Chancellor MB. Botulinum toxin urethral sphincter injection to restore bladder emptying in men and women with voiding dysfunction. *J Urol* 2001;165:1107-1110.
14. Schurch B, Hauri D, Rodic B, Curt A, Meyer M, Rossier AB. Botulinum-A toxin as a treatment of detrusor-sphincter dyssynergia: a prospective study in 24 spinal cord injury patients. *J Urol* 1996;155:1023-1029.
15. Zermann D, Ishigooka M, Schubert J, Schmidt RA. Perisphincteric injection of botulinum toxin type A. A treatment option for patients with chronic prostatic pain? *Eur Urol* 2000;38:393-399.
16. Kuo HC. Effect of botulinum a toxin in the treatment of voiding dysfunction due to detrusor underactivity. *Urology* 2003;61:550-554.
17. Olsen AL, Benson JT, McCellan E: Urethral sphincter needle electromyography in women: comparison of periurethral and transvaginal approaches. *Neurourol Urodyn* 1998;17:531-535.
18. Schurch B, Hodler J, Rodic B. Botulinum A toxin as a treatment of detrusor-sphincter dyssynergia in patients with spinal cord injury: MRI controlled transperineal injections. *J Neurol Neurosurg Psychiatry* 1997;63:474-476.
19. 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.
20. Fowler CJ, Betts CD, Christmas TJ, Swash M, Fowler CG. Botulinum toxin in the treatment of chronic urinary retention in women. *Br J Urol* 1992;70:387-389.
21. Kuo HC. Botulinum A toxin urethral injection for the treatment of lower urinary tract dysfunction. *J Urol* 2003;170:1908-1912.
22. De Laet K, Wyndaele JJ. Adverse events after botulinum A toxin injection for neurogenic voiding disorders. *Spinal Cord* 2005;43:397-399.
23. McGuire EJ, Woodside JR, Borden TA, Weiss RM. Prognostic value of urodynamic testing in myelodysplastic patients. *J Urol* 2002;167:1049-53;discussion 1054.
24. Litwiller SE, Frohman EM, Zimmern PE. Multiple sclerosis and the urologist. *J Urol* 1999;161:743-757.
25. Bonniaud V, Parratte B, Amarenco G, Jackowski D, Didier JP, Guyatt G. Measuring quality of life in multiple sclerosis patients with urinary disorders using the Qualiveen questionnaire. *Arch Phys Med Rehabil* 2004;85:1317-1323.
26. Wheeler JS Jr, Walter JS, Chintam RS, Rao S. Botulinum toxin injections for voiding dysfunction following SCI. *J Spinal Cord Med* 1998;21:227-229.
27. Smith CP, O'Leary M, Erickson J, Somogyi GT, Chancellor MB: Botulinum toxin urethral sphincter injection resolves urinary retention after pubovaginal sling operation. *Int Urogynecol J Pelvic Floor Dysfunct* 2002;13:185-186.