

Is there any Relationship Between Bladder Trabeculation and Efficacy and Safety of Intravesical Botulinum Toxin A Injection in Refractory Idiopathic Overactive Bladder Women?

Abstract

Background: Intradetrusor injection of botulinum toxin A (BTX-A) might serve as a minimally invasive substitute in patients with refractory idiopathic overactive bladder (RIOAB). The aim of this study was to evaluate the clinical outcomes related to two different doses of abo-BTX-A (AboBTX-A) in patients with RIOAB. **Materials and Methods:** This prospective clinical trial was performed on 55 women with RIOAB. After determination of trabeculation grade, 300 (no or mild) or 500 (moderate or severe) unit of AboBTX-A (Dysport) was intravesically injected. Before 1, 3, and 6 months after intervention, lower urinary tract symptoms during 24 h were recorded. **Results:** Of the study population, 62% had severe bladder trabeculation. The mean duration of overactive bladder (OAB) was 1.76 versus 5.85 years, for no or mild versus severe trabeculation, respectively. After injections of 300- and 500-unit dosage, there were 19% and 26% early complications such as urinary retention. There was a statistically significant difference between the two groups in OAB score after 1 month ($P < 0.001$) and duration of OAB symptoms, over three follow-up times ($P < 0.001$). The mean preinjection OAB scores between patients with and without recurrence were statistically significant (29.36 vs. 25.07; $P < 0.03$). Urinary tract infection as a late complication was distinguished in four patients. **Conclusion:** In RIOAB, by adjusted dosage of AboBTX-A related to the grade of bladder trabeculation, in addition to maintain efficacy, consequent complications might not be affected by dosage and the drug dosage could be increased to nearly 60% with less concern associated to complication

Keywords: Bladder, botulinum toxin A, idiopathic, trabeculation, women

Introduction

Voiding dysfunctions are common problems in urological practice. Overactive bladder (OAB) is defined as urgency with or without urge incontinence which is usually accompanied by frequency and nocturia.^[1,2] These symptoms are often due to involuntary detrusor contraction in filling phase of bladder. OAB has an considerable effect on social and personal lives of patients and negatively affects physical, psychological, and sexual lives of men and women.^[3] Nearly, 17% of adult population in Europe and United States of America experience OAB.^[4] Generally, the reasons of OAB are subdivided into three categories: neurogenic, peripheral, and myogenic.^[5-7] Primary idiopathic disease (idiopathic detrusor overactivity [IDO]) or secondary neurogenic diseases could cause an increase in detrusor activity. The most important sign of OAB is urinary urgency. Pathophysiology of urinary urgency has not recognized yet but its possible

mechanism could be mentioned as the increase of afferent nervous activity of detrusor. In other words, involuntary contractions of detrusor in filling phase are recognized as overactivity.^[5,6,8] Conservative treatment strategies of OAB are weight loss, smoking cessation, reducing caffeinated, pelvic floor muscle training, which all improve symptoms effectively. Anticholinergics drugs are the first-line of pharmacotherapy treatment for OAB. But complications related to autonomic nervous system make it as an unpleasant strategy, which the most patients would prefer to quit it.^[9,10] A recent publication suggested that percutaneous tibial nerve stimulation alone or in combination with anticholinergic could be a harmless, simple, and negligibly aggressive.^[11,12]

In the case of failure in all mentioned treatments, invasive surgery such as enterocystoplasty is suggested. A recently

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Zargham M, Abedi S, Alizadeh F, Khorami MH, Mohamadi M, Bahrami F, *et al.* Is there any Relationship Between Bladder Trabeculation and Efficacy and Safety of Intravesical Botulinum Toxin A Injection in Refractory Idiopathic Overactive Bladder Women? *Adv Biomed Res* 2017;6:113.

Received: August, 2014. **Accepted:** July, 2016.

Mahtab Zargham,
Shideh Abedi,
Farshid Alizadeh,
Mohamad Hatf
Khorami,
Mehrdad Mohamadi,
Faranak Bahrami¹,
Farzaneh
Sharifiaghdas,
Hamid Mazdak

From the Isfahan Kidney
Transplantation Research
Center, Isfahan University of
Medical Sciences, Isfahan,
¹Department of Urology, Shahid
Beheshti University of Medical
Sciences Tehran, Iran

Address for correspondence:
Dr. Farshid Alizadeh,
Isfahan Kidney Transplantation
Research Center, Isfahan
University of Medical
Sciences, Isfahan, Iran.
E-mail: f-alizadeh@med.mui.ac.ir

Access this article online

Website: www.advbiores.net

DOI: 10.4103/abr.abr_393_14

Quick Response Code:



recommended treatment for OAB is intravesical injections of botulinum toxin type A (BTX-A). This treatment is a useful intervention for refractory idiopathic OAB (RIOAB).^[13-15] BTX is produced by Gram-positive anaerobic bacterium called *Clostridium botulinum*. The mechanism of BTX is temporarily blocking the release of acetylcholine at the neuromuscular junction which paralyzes the target muscle; this toxin in bladder muscle decreases the symptoms of urgency and increase of bladder compliance.^[16-18] Despite the fact that most of OAB patients are idiopathic, there are few randomized clinical trials that have been performed on idiopathic OAB patients.^[19,20] In the study of Mahdavi *et al.*, statistically significant improvement has been observed in the urodynamic tests and lower urinary tract symptoms (LUTSs) after intradetrusor injection of neurotoxin BTX-A; 300 units of dysport in refractory IDO patients.^[21] Also in the study of Truzzi *et al.* (100 and 300 units)^[22] and Werner *et al.* (100 units),^[23] neurotoxin BTX-A improved the distressing complication such as acute urinary retention. Some studies have shown an increase in the quality of life by decreasing urinary urgency and frequency, after intervention.^[24] A 300 unit injection of ona-BTX-A (onaBTX-A), in 13 out of 15 women, showed the relief of urgency and frequency.^[25,26] The aim of our investigation was the comparisons of the effect of different doses of intravesical injections of aboBTX-A (AboBTX-A) on the improvement of LUTS among refractory idiopathic detrusor from mild to severe trabeculation.

Materials and Methods

The target population in this prospective clinical trial comprised 55 women with RIOAB, who were referred to the hospitals Noor and Al-Zahra between the 2012 and 2013. The study was conducted to Isfahan Kidney Transplantation Research Center and approved by the local Ethics Committee under the Grant No. of 392352. Inclusion criteria were as follows: (1) suffering from urgency-frequency (2) with OAB score (calculated according to OAB-questionnaire form) of more than eight and (3) those not responded to conservative treatment or oral medications between 6 and 12 weeks. Exclusion criteria were women with the following: (1) active urinary tract infection (UTI) (2) impaired renal function (3) neurologic disease (4) bladder disease, affecting bladder function (4) severe coagulopathy (5) bladder outlet obstructs (BOOs) (6) meatal stenosis (7) active hematuria (8) bladder stone and (9) inability to complete the questionnaire form. All included women were examined clinically and had sonography in order to rule out the following diseases: BOO, urethral diverticula, pelvic organ prolapsed, bladder tumor, and stone. Neurological examination was normal, and the result of urine analysis and culture was negative. Therefore, only women with IOAB entered to the study. Detrusor over activity was documented by urodynamic test before AboBTX-A injection.

All patients signed the consent form after being notified of all possible complications, especially urinary dysfunction. Anesthetist made decision about the local or general anesthesia. After the injection of prophylactic antibiotic, patient had cystoscopy in lithotomy position. After assuring about the lack of mucosal lesions and determination of trabeculation grade, degree of bladder trabeculation was detected by cystoscopy. Bladder trabeculation is known to be caused by morphological and histological changes due to hypertrophy and hyperplasia of the bladder muscle and the infiltration of the connective tissue. The mucosa of normal distended bladder seems smooth. When there is mild bladder trabeculation, detrusor muscle bundles become prominent. More than 30 cm H₂O detrusor contractions may be due to moderate bladder trabeculation and tends to push mucosa between detrusor bundles, causing the formation of cellules. If cellules force their way entirely through the musculature of vesicles, they become saccules and diverticules. This is cystoscopic appearance of sever bladder trabeculation. Figure 1 shows the flow chart assignment of patients to 300 or 500 units intravesical injection of aboBTX-A.

Three hundred (mild) or 500 (moderate or severe) units of AboBTX-A, was diluted in 3 cc (for 300 units) or 5 cc (for 500 units) normal saline. Dysport (AboBTX) is supplied as a vacuum dried powder of *C. botulinum* type A toxin – hemagglutination complex that excipients with human albumin solution and lactose, stored at or below 5°C. Each vial contains 300 or 500 international units (IU) that are diluted with preservative-free normal saline (marketing authorization number: PL34926/004). Then, it was divided into three (for 300 units) or five (for 500 units), insulin syringes (1 ml), and 0.1 cc was injected in each point, sparing the trigon. Bladder was divided into five linear strips, and each syringe was used for thirty (for 300 units) or fifty (for 500 units) sites of bladder [Figure 1]. Method of intratrabeculation injection was trigon-sparing and according to the American Cleveland Clinic protocol.^[27-29] Matching of patients according to age, weight, height, comorbidities, taking of anticholinergic drugs, and intensity of symptoms (according to OAB score) in two groups was checked. Before intervention, urodynamic findings (maximum pressure of detrusor, maximum cystometric and detrusor compliance) were determined. Before 1, 3, and 6 months, after intervention, LUTSs such as urinary frequency, urgency, nocturia, and urgency incontinency were recorded by questionnaire during 24 h. Also self-administered OAB-V8 questionnaire form was used to identify patients with bothersome OAB symptoms in four phases. The total score is forty and score of >8 could be defined as the sign of OAB. Other complications including urinary retention, UTI, fatigue, and apnea were reported. Finally, time of symptoms recurrence and time of reinjection were specified.

Statistical analysis

Independent *t*-test and Mann–Whitney *U*-test was used for comparing the two groups. Pearson Chi-square was performed for the evaluation of independency between categorical variables. Moreover, dataset were analyzed by Fisher’s exact test in the case of expected frequency <5. For longitudinal analysis of data, repeated measure analysis and similar nonparametric test (Friedman test) were performed. Receiver operating characteristic curve was used to determine a cut-off value for OAB score. The statistical analyses of data were performed using SPSS software for windows (SPSS Inc., Chicago, IL, USA). The statistically significant level was considered $P < 0.05$.

Results

Fifty-five patients with a mean age of 46.8 (standard deviation [SD] \pm 19.3) years old were studied. As shown

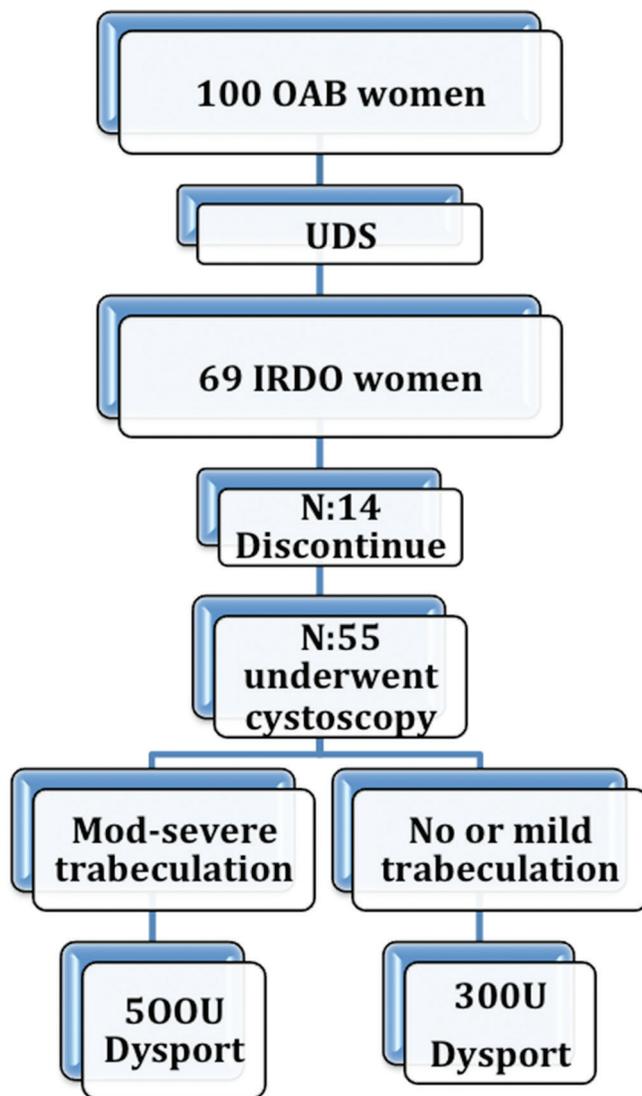


Figure 1: Assignment of patients to 300 or 500 units intravesical injection of abobotulinum toxin type A, UDS: Urodynamic study, IRDO: Idiopathic refractory detrusor over activity, N: Number, U: unit

in Table 1, out of the total population studied, there were 21 and 34 patients with mild (38%) and moderate to severe (62%) trabeculation, respectively. There was no statistically significant difference ($P = 0.2$) between mild and moderate to severe trabeculation in terms of age. Seventeen patients (30.9%) had previous injection of BTX. The mean \pm SD of OAB duration was 1.76 ± 1.45 and 5.85 ± 2.83 years in each group, respectively ($P = 0.05$).

Among early complications, the most frequent one was urinary retention in both groups of 300 (19%) and 500 (26%) unit dosage, respectively. In late complications, the most prevalent and the only one was UTI [Table 2].

In addition, 7 (33.3%) and 18 (52.9%) individuals experienced recurrence by 300 and 500 unit injections, respectively ($P = 0.05$). Result of comparison between mild and moderate to severe trabeculation showed that there was a statistically significant difference between two groups in OAB score after 1 month ($P < 0.001$) [Table 3]. The trends of changes in OAB score over three follow-up times are shown in Figure 2. There was no statistically significant difference between the two groups in frequency and nocturia in all follow-up times. However, there was a statistically significant difference between two groups in terms of duration of OAB symptoms ($P < 0.001$) [Table 3].

Table 1: Demographic characteristic of patients

Variables	Group	
	Mild trabeculation (n=21)	Moderate to severe trabeculation (n=34)
Age (years) (mean \pm SD)	43.24 \pm 18.50	50.20 \pm 20.19
Repeated injection, frequency (%)	5 (24)	12 (35)
Duration of OAB symptom, years (mean \pm SD)	1.76 \pm 1.45	5.85 \pm 2.83

OAB: Overactive bladder, SD: Standard deviation

Table 2: Frequency table of early and late complications

Complication	Group	
	300 units (n=21)	500 units (n=34)
Early complication, frequency (%)		
Urinary retention	4 (19)	9 (26)
Urinary tract infection	2 (9)	1 (3)
Systemic complication	3 (14)	0
Hematuria	2 (9)	2 (6)
Exacerbation	3 (14)	0
Late complication, frequency (%)		
Urinary retention	0	1 (3)
UTI	1 (5)	2 (6)
Systemic complication	0	0
Hematuria	0	0
Exacerbation	0	0

UTI: Urinary tract infection

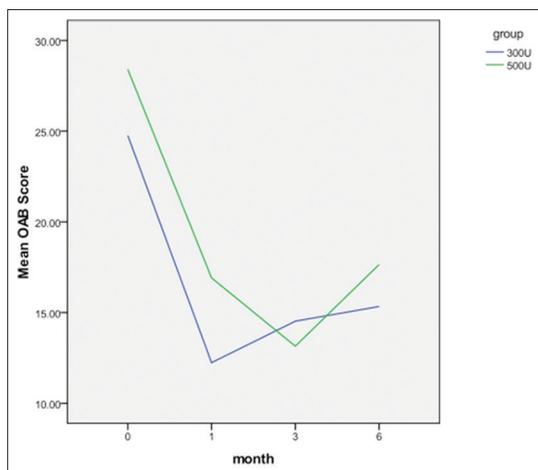


Figure 2: Overactive bladder score changes over four follow-up times

Previous injection of BTX did not influence trabeculation grade ($P = 0.7$). There was not any association between recurrence and BTX dosage ($P = 0.156$). Further analysis showed that there were no correlation between BTX dosage with; (1) retention ($P = 0.75$), (2) UTI ($P = 0.66$), (3) hematuria ($P = 0.63$), (4) exacerbation ($P = 0.51$), and (5) systemic complications ($P = 0.51$). Repeating of injection was not associated with the dosage of BTX ($P = 0.37$). Patients' satisfaction of injection was not relevant to BTX dosage ($P = 0.28$). In longitudinal analysis, there were no statistically significant differences between BTX dosage categories in the following: (1) frequency ($P = 0.32$), (2) nocturia ($P = 0.34$), and (3) OAB score ($P = 0.09$). There was a statistically significant difference in preinjection OAB score between patients with (mean OAB score of 29.36 ± 4.58) and without recurrence (mean OAB score of 25.07 ± 8.5) ($P = 0.03$).

Discussion

The results of this investigation showed that intravesical injection of AboBTX-A could be done, proportional to bladder trabeculation grade. Consequently, AboBTX-A dosage might not affect consequent complications. As a result, there might be opportunity for increase in drug dosage up to nearly 60% without concern for possible increase of complication rate such as urinary retention and patients' need for clean intermittent bladder catheterization (CIC).

Comparison of frequency, nocturia and OAB scores between moderate to severe and mild trabeculated groups, showed an equal efficacy of treatment in both groups (500 vs. 300 units of AboBTX-A), respectively. Besides not significant drug complications between two groups, this finding underscores the significance of considering trabeculation grade.

Although in a study by Dmochowski *et al.*, it was reported that an equal dosage increment among all patients (with or

Table 3: Results from overactive bladder, frequency-nocturia questionnaire in 1, 3 and 6 months of follow-up

LUT parameters	Group		P
	300 units (n=21)	500 units (n=34)	
OAB score (mean±SD)			
Preinjection	24.76±8.04	28.41±6.48	0.07
1 month	12.24±2.91	16.91±5.07	<0.001
3 months	14.52±4.15	13.15±6.19	0.372
6 months	15.33±3.89	17.65±8.88	0.191
Frequency (mean±SD)			
Preinjection	10.67±2.92	12±3.22	0.128
1 month	7.67±2.11	8.32±2.82	0.363
3 months	7.90±2.19	7.15±2.26	0.227
6 months	8.57±2.62	9.68±3.08	0.178
Nocturia (mean±SD)			
Preinjection	3.24±1.58	3.65±1.76	0.388
1 month	1.19±1.03	1.68±1.51	0.2
3 months	1.09±1.13	1.23±1.33	0.69
6 months	1.90±1.73	2.23±1.58	0.47

LUT: Lower urinary tract, OAB: Overactive bladder, SD: Standard deviation

without trabeculation), but with every 50 cc increase (from 10% to 30%), the incidence of urinary retention and severe systemic complications was increased.^[30] Although limited numbers of studies have been conducted on AboBTX-A in patients with IROAB, extensive double-blinded clinical trials have shown that 100 IU of onaBTX is sufficient for treating OAB. Considering that onaBTX has been reported to be 1.5–3 times powerful than AboBTX-A, a 300 IU dosage of AboBTX is equivalent to 100 IU of onaBTX-A.

In patients with severe bladder trabeculation, previous publications mentioned that increasing the dose up to 500 IU was not associated with more complications.^[30-32] Earlier investigation showed that repeated injections and formation of BTX antibody seem to be the reasons of drug resistance and efficacy reduction.^[33] However, in the current study, there was no efficacy reduction among patients with multiple injections, and it could be possible that repeated injections and formation of BTX antibody might not decrease the efficacy of BTX. Overall, 19% (in 300 units) and 26% (in 500 units) of patients had urinary retention and needed to CIC.

Although these figures are slightly different from other studies,^[31,34-36] but it could be attributed to different criteria for CIC initiation, as it was instructed for patients to perform it if; (1) they had feeling of incomplete evacuation (2) postvoid residual (PVR) urine was >200 cc (it was continued until PVR became <100 cc). The short-term need for CIC was not more than 7 days. The maximum effect of BTX in decreasing bladder contractility and precipitating retention lasts for 1–3 weeks after injection, while in this period, retention was very rare. Therefore, retention early

after injection could be due to concurrent use of epidural anesthesia and analgesics.

One of the limitations of this study is the exact definition of UTI. All patients received prophylactic antibiotics after intravesical injection. Those who developed the symptoms of cystitis with positive urine culture after drug cessation were recognized as UIT. This definition may be different with other studies, as there were not routinely recommended prophylactic antibiotics. Another limitation of this study was receiving higher dosage of drug among patients with severe trabeculation. Although it cannot be assured that they needed more AboBTX-A for the treatment of detrusor over activity. Finally, the presence of bladder trabeculation could be declared as a valuable clue in women with IROAB and it could be assumed that patients with more severe trabeculation might need higher doses of AboBTX-A. Further researches in these directions are recommended.

Conclusion

In patients with RIOAB, the intravesical injection of BTX-A could be considered an effective clinical approach. By adjusted dosage of AboBTX-A related to the grade of bladder trabeculation, in addition to maintain efficacy, consequent complications might not be affected by dosage. Finally, however, AboBTX-A dosage could be increased to nearly 60% with less concern associated to complications, but further studies of BTX-A in Iranian population with RIOAB seem to be valuable.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

- Osman N, Mangera A, Hillary C, Inman R, Chapple C. The underactive bladder: Detection and diagnosis. *F1000Res* 2016;5: pii: F1000 Faculty Rev-102.
- Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, *et al.* The standardisation of terminology in lower urinary tract function: Report from the standardisation sub-committee of the International Continence Society. *Urology* 2003;61:37-49.
- McKillop C. Interview with Chris Chapple overactive bladder: Tackling the problem. *Eur Urol* 2006;49:921-3.
- Wein AJ, Rackley RR. Overactive bladder: A better understanding of pathophysiology, diagnosis and management. *J Urol* 2006;175(3 Pt 2):S5-10.
- Vahdatpour B, Zargham M, Chatraei M, Bahrami F, Alizadeh F. Potential risk factors associated with stress urinary incontinence among Iranian women. *Adv Biomed Res* 2015;4:205.
- Zargham M, Alizadeh F, Moayednia A, Haghani S, Nouri-Mahdavi K. The role of pelvic organs prolapse in the etiology of urinary incontinence in women. *Adv Biomed Res* 2013;2:22.
- Drake MJ, Mills IW, Gillespie JI. Model of peripheral autonomous modules and a myovesical plexus in normal and overactive bladder function. *Lancet* 2001;358:401-3.
- Tyagi S, Thomas CA, Hayashi Y, Chancellor MB. The overactive bladder: Epidemiology and morbidity. *Urol Clin North Am* 2006;33:433-8.
- Cohen BL, Tunuguntla HS, Gousse A. Predictors of success for first stage neuromodulation: Motor versus sensory response. *J Urol* 2006;175:2178-80.
- Yeo EK, Hashim H, Abrams P. New therapies in the treatment of overactive bladder. *Expert Opin Emerg Drugs* 2013;18:319-37.
- Kizilyel S, Karakeçi A, Ozan T, Ünüs I, Barut O, Onur R. Role of percutaneous posterior tibial nerve stimulation either alone or combined with an anticholinergic agent in treating patients with overactive bladder. *Turk J Urol* 2015;41:208-14.
- National Collaborating Centre for Women's and Children's Health (UK). Urinary Incontinence in Women: The Management of Urinary Incontinence in Women. London: Royal College of Obstetricians and Gynaecologists (UK); 2013 September. National Institute for Health and Care Excellence: Clinical Guidelines; 2013.
- Orasanu B, Mahajan ST. The use of botulinum toxin for the treatment of overactive bladder syndrome. *Indian J Urol* 2013;29:2-11.
- Kim DK, Chancellor MB, Smith C, Thomas CA. The case for bladder botulinum toxin application. *Urol Clin North Am* 2006;33:503-10.
- 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;139:919-22.
- Chapple C, Patel A. Botulinum toxin – New mechanisms, new therapeutic directions? *Eur Urol* 2006;49:606-8.
- Curcio L, Costa F, Marinho MA, Cunha AC, Renteria J, Dibiasi Filho G. Use of botulinum toxin type A (Botox®) through transcystoscopicvesical insertion for overactive bladder syndrome non-responsive to oral medication or for parasympatholytic drugs use severe side effects. *Braz J Video Sur* 2008;1:97-103.
- Schurch B, Stöhrer 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(3 Pt 1):692-7.
- Léon P, Jolly C, Binet A, Fiquet C, Vilette C, Lefebvre F, *et al.* Botulinum toxin injections in the management of non-neurogenic overactive bladders in children. *J Pediatr Surg* 2014;49:1424-8.
- Morris AR, O'Sullivan R, Dunkley P, Moore KH. Extracorporeal magnetic stimulation is of limited clinical benefit to women with idiopathic detrusor overactivity: A randomized sham controlled trial. *Eur Urol* 2007;52:876-81.
- Mahdavi R, Sheikhi Z, Golshan A. Effect of botulinum neurotoxin type a injection in refractory idiopathic overactive bladder. *J North Khorasan Univ Med Sci* 2011;3:75-80.
- Truzzi J, Bruschini H, Simonetti R, Miguel S, editors. What is the Best Dose for Intravesical Botulinum-A Toxin Injection in Overactive Bladder Treatment? A Prospective Randomised Preliminary Study. Joint Meeting of the International Continence Society (ICS) and the International Uro-Gynaecological Association (IUGA), Paris, France; 2004.
- Werner M, Schmid DM, Schüssler B. Efficacy of botulinum-A toxin in the treatment of detrusor overactivity incontinence: A prospective nonrandomized study. *Am J Obstet Gynecol* 2005;192:1735-40.
- Kalsi V, Apostolidis A, Popat R, Gonzales G, Fowler CJ, Dasgupta P. Quality of life changes in patients with neurogenic versus idiopathic detrusor overactivity after intradetrusor

- injections of botulinum neurotoxin type a and correlations with lower urinary tract symptoms and urodynamic changes. *Eur Urol* 2006;49:528-35.
25. Rajkumar GN, Small DR, Mustafa AW, Conn G. A prospective study to evaluate the safety, tolerability, efficacy and durability of response of intravesical injection of botulinum toxin type A into detrusor muscle in patients with refractory idiopathic detrusor overactivity. *BJU Int* 2005;96:848-52.
 26. Asplund R, Marnetoft SU, Selander J, Akerström B. Nocturia in relation to somatic health, mental health and pain in adult men and women. *BJU Int* 2005;95:816-9.
 27. Roux JW, Shah SS, Khan MS, Sahai A. Intradetrusor botulinum toxin injections for overactive bladder. *Trends Urol Gynaecol Sex Health* 2008;13:27-8.
 28. Elbadawi A. Voiding dysfunction in benign prostatic hyperplasia: Trends, controversies and recent revelations. II. Pathology and pathophysiology. *Urology* 1998;51 5A Suppl:73-82.
 29. Brubaker L, Richter HE, Visco A, Mahajan S, Nygaard I, Braun TM, *et al.* Refractory idiopathic urge urinary incontinence and botulinum A injection. *J Urol* 2008;180:217-22.
 30. Dmochowski R, Chapple C, Nitti VW, Chancellor M, Everaert K, Thompson C, *et al.* Efficacy and safety of onabotulinumtoxinA for idiopathic overactive bladder: A double-blind, placebo controlled, randomized, dose ranging trial. *J Urol* 2010;184:2416-22.
 31. Kennelly M, Schaecher KL. New treatments in overactive bladder and implications for managed care. *J Manag Care Med* 2006;9:35.
 32. Tincello DG, Kenyon S, Abrams KR, Mayne C, Toozs-Hobson P, Taylor D, *et al.* Botulinum toxin a versus placebo for refractory detrusor overactivity in women: A randomised blinded placebo-controlled trial of 240 women (The RELAX study). *Eur Urol* 2012;62:507-14.
 33. McDougal WS, Wein AJ, Kavoussi LR, Novick AC, Partin AW, Peters CA, *et al.* *Campbell-Walsh Urology*. 10th Edition Review. Philadelphia, Pennsylvania: Elsevier Health Sciences; 2011.
 34. Kajbafzadeh AM, Nikfarjam L, Mahboubi AH, Dianat S. Antibody formation following botulinum toxin type A (Dysport) injection in children with intractable bladder hyper-reflexia. *Urology* 2010;76:233-7.
 35. Kessler TM, Khan S, Panicker J, Roosen A, Elneil S, Fowler CJ. Clean intermittent self-catheterization after botulinum neurotoxin type A injections: Short-term effect on quality of life. *Obstet Gynecol* 2009;113:1046-51.
 36. Jeffery S, Fynes M, Lee F, Wang K, Williams L, Morley R. Efficacy and complications of intradetrusor injection with botulinum toxin A in patients with refractory idiopathic detrusor overactivity. *BJU Int* 2007;100:1302-6.