ORİJİNAL ARAŞTIRMA ORIGINAL RESEARCH

DOI: 10.5336/urology.2021-81573

Results of 100 Units of Botulinum Toxin Administration in Overactive Bladder Treatment

Aşırı Aktif Mesane Tedavisinde 100 Ünite Botulinum Toksini Uygulamasının Sonuçları

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This study was presented as an oral presentation in the 6th Baltic Meeting in conjuction with the EAU, 24-25 May 2109,Talinn, Estonia.

ABSTRACT Objective: This study aimed to analyze the efficiency and safety of botulinum toxin in patients who presented to urology clinic with overactive bladder (OAB). **Material and Methods:** Between 2015 and 2019, forty patients who were administered intravesical 100 units of botulinum toxin for OAB treatment were evaluated retrospectively in terms of efficacy and safety. Efficacy was evaluated by using the treatment benefit scale (TBS) at 3 months after injection The quality of life for OAB symptoms was evaluated via the incontinence quality of life scale before treatment and at the 3rd month after treatment. Likewise, parameters such as incontinence, nocturia, urinary frequency, post-void residual urine values, maximum urine flow rate, number of pads used were evaluated before and at the 3rd month after the procedure. **Results:** Significant increases were detected in post-procedure incontinence quality of life scores compared to pre-procedure, and in parallel with these results, significant increases were recorded in the post-treatment questionnaire (38.5±15.0 and 69.9±6.3, respectively); p<0.001). In addition, according to the TBS results at the 3rd month, 80% of the patients who underwent the procedure did benefit from the treatment. **Conclusion:** Botulinum toxin injection still remains to be an effective option in refractory OAB treatment.

Keywords: Urinary incontinence; botulinum toxin; treatment outcome

ÖZET Amaç: Bu çalışma, aşırı aktif mesane (AAM) ile üroloji kliniğine başvuran hastalarda botulinum toksininin etkinliğini ve güvenliğini incelemeyi amaçlanmıştır. **Gereç ve Yöntemler:** 2015-2019 yılları arasında AAM tedavisi için intravezikal 100 ünite botulinum toksini uygulanan 40 hasta, etkinlik ve güvenlik açısından retrospektif olarak değerlendirildi. Etkinlik, enjeksiyondan 3 ay sonra tedavi fayda ölçeği kullanılarak değerlendirildi. AAM semptomlarının yaşam kalitesine etkisi, tedavi öncesinde ve tedavi sonrası 3. ayda inkontinans yaşam kalitesi ölçeğiyle değerlendirildi. Aynı şekilde işlem öncesinde ve işlem sonrası 3. ayda inkontinans, noktüri, idrar sıklığı, post-miksiyonel rezidü değerleri, maksimum idrar akım hızı, kullanılan ped sayısı gibi parametreler değerlendirildi. **Bulgular:** İşlem sonrası inkontinans yaşam kalitesi skorlarında işlem öncesine göre anlamlı bir artış gözlendi ve bu sonuçlarla uyumlu olarak tedavi sonrası ankette anlamlı artış saptandı (sırasıyla 38,5±15,0 ve 69,9±6,3); p<0,001). Ayrıca 3. aydaki sonuçlarına göre işlem uygulanan hastaların %80'i tedaviden fayda gördü. **Sonuç:** Botulinum toksin enjeksiyonu, dirençli AAM tedavisinde etkili bir seçenek olmaya devam etmektedir.

Anahtar Kelimeler: Üriner inkontinans; botulinum toksini; tedavi sonucu

Overactive bladder (OAB) is frequently observed as a chronic pathological condition characterised by lower urinary tract symptoms accompanied by complaints of urgency, frequency and nocturia with or without incontinence in the absence of urinary infection and other organic pathologies.[1] Approximately 16% of those living in Europe and the United States are thought to have OAB syndrome, with females more likely to be affected than males. Although the aetiology remains unclear; pathologies in the inhibitory pathways of the central nervous system, increased excitability of detrusor muscle cells are considered as the causing factors.[2]

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Peer review under responsibility of Journal of Reconstructive Urology.

Received: 23 Jan 2021 ***Received in revised form:*** 04 Mar 2021 ***Accepted:*** 08 Mar 2021 ***Available online:*** 11 Mar 2021

The International Continence Society recommends conservative methods, such as adjustment of fluid and food habits, review of drug therapy, scheduled voiding, bladder training or pelvic floor muscle training and pharmacological treatment options with anticholinergic agents or beta-3 agonists for at least three months as first-line treatment. However, many patients fail to respond to oral therapies or suffer from adverse effects that cause them to discontinue their medication.[3] Botulinum toxin-A injection emerges as an effective second-line treatment in patients refractory to conservative approaches and anticholinergic treatment.[4] It may be administered locally or as intravesical injections performed via cystoscopy under general anaesthesia. However, due to the gradual reduction in activity, repeated injections are needed at 6 to 9 month intervals.[5]

Since data on the use and results of botulinum toxin in our country is limited, we aimed to analyse the efficiency and safety of botulinum toxin in patients who presented to urology clinic with OAB.

MATERIAL AND METHODS

Between 2015 and 2019, forty patients who were administered intravesical 100 units of botulinum toxin for OAB treatment were evaluated from outpatient clinic data records retrospectively in terms of efficacy and safety. Our study was approved by Fırat University Ethics Committee (2019/05/02). Written informed consent forms were obtained from all patients. Each phase of the study was carried out in accordance with the 1964 Helsinki Principles. Detailed physical and urological examination with complete urine analysis, urine culture, a 3-days minimum voiding diary, uroflowmetry (MMS solar, ADS Ltd, Enschede, Netherlands), post-voiding residual urine (PVR) measurement and urinary ultrasound prior to the procedure were performed in all patients. Additional urodynamic assessments (MMS solar, ADS Ltd, Enschede, Netherlands) were performed in patients who did not respond to pharmacological treatment with anticholinergic/antimuscarinic agents or beta-3 receptor agonists for at least three months or had to discontinue their medication due to adverse effects. Patients with urinary tract infection were treated with appropriate antibiotics. Based on data from the 3-day voiding diary, patients with urinary incontinence or a frequency of more than eight urine passages daily, having PVR of less than 100 ml, greater than 15 ml/s maximum urinary flow rate (Q_{max}), at least one episode of nocturia and patients who had to discontinue medication due to adverse effects or lack of benefit despite using two different anticholinergic drugs and/or beta-3 receptor agonists for at least three months were included in the study. Patients with neurogenic OAB symptoms, neurological disorder, previous botulinum toxin injections for urinary system problems, stress-dominant urinary incontinence, prior history of bladder or pelvic surgery, susceptibility to bleeding, urodynamically documented bladder outlet obstruction and planning pregnancy were excluded from the study. Written informed consent forms were obtained from all patients after they were informed about the method of injection and any possible complications, such as urinary infection and urinary retention.

SURGICAL TECHNIQUE

All patients received prophylactic antibiotics beginning one day prior to the surgery until the third postoperative day. After appropriate surgical sterilisation and draping, the bladder was visualised by performing 20 Fr rigid cystoscopy (Karl Storz, Tuttlingen, Germany) under sedo-analgesia. Onabotulinumtoxin A 100 U (BOTULINUM TOXIN®, Allergan, Irvine, CA, USA) was diluted with 10 mL isotonic fluid and administered as twenty 0.5 mL intra-detrusor injections via adjustable botulinum toxin needle (injeTAK® Adjustable Type Needle 70 cm, Laborie, Chicago, USA) into the detrusor at regular spaces avoiding the trigone and vascular structures by a surgical team with at least 5 years of experience. No postoperative catheter was inserted in any patient. Residual volume measuring more than 200 mL after the procedure was considered as urinary retention. A positive urine culture ($>10^5$ colonies mL/U) and a positive urinalysis (>5 leucocytes/high power field) was considered as urinary infection. After the procedure, complications such as urinary tract infection, urinary retention, dysuria, haematuria, muscle weakness and pain at the injection site were recorded. Patients who did not develop complications after the procedure were discharged on the same day.

MEASURE OF SUCCESS

Efficacy was evaluated using the treatment benefit scale (TBS) at 3 months after injection.[6] The scale asked patients to rate their condition after injection as "well improved", "improved", "unchanged" or "worse". Responses of "well improved" and "improved" were considered as surgical success and patients indicating these responses were scheduled for a repeat dose after 6 to 9 months. The quality of life for OAB symptoms was evaluated via the incontinence quality of life (I-QoL) scale before treatment and 3 months after treatment based on a Turkish validated version of I-QoL scale, which consisted of three groups measuring restriction in behaviors and in psychological and social life.[7,8] Likewise, parameters such as incontinence, nocturia, urinary frequency, PVR, maximum urinary flow rate (Q_{max}), number of pads used were evaluated before the procedure and at the 3rd month after the procedure.

STATISTICAL ANALYSIS

Statistical Package for Social Sciences (SPSS Inc. V20.0, Chicago, IL, USA) for Windows was used for statistical analyses. Mann-Whitney U test was used to compare continuous variables, and chi-square or Fisher's exact tests were used to compare categorical variables. The results were analyzed within 95% confidence interval and $p<0.05$ was regarded as statistically significant.

RESULTS

The study population consisted of 21 women (52.5%) and 19 men (47.5%). The mean age was 57.6±17.1 years (range: 18-65 years). The mean duration of incontinence in our patients was 10.7±3.8 years. Demographic characteristics of the study population are shown in Table 1. After botulinum toxin injection, significant improvements were reported in OAB symptoms (voiding frequency, and number of nocturia and incontinence episodes) and a significant reduction was observed in the number of pads used (Table 2). The most common adverse events related to botulinum toxin injection (such as voiding difficulty and urinary retention) were not detected in any of our patients. There was no significant change in Q_{max} and PVR values before and after the procedure (Table 2).

TABLE 1: The socio-demographic characteristics of the patients.

Age (year)		57.6±17.1 (18-85)
Disease duration (year)		10.7±3.8 (5-20)
Gender	Woman	21 (52.5%)
	Man	19 (47.5%)
Weight (kg)		71.5±9.1 (56-95)
Height (cm)		166.4±6.0 (155-178)
BMI (kg/m²)		26±4.1 (19.5-39.5)
Using tobacoo	Yes	17 (42.5%)
	No	23 (57.5%)
Education level	Primary school	23 (57.5%)
	Middle school	10 (25.0%)
	High school	7 (17.5%)
	University	0 (0%)

BMI: Body mass index.

I-QoL scores of the patients before the procedure were found to be lower, consistent with the severity of the symptoms. However, significant increases were found in all three categories on the post-treatment questionnaire (38.5±15.0 vs 69.9±6.3, respectively; $p<0.001$; Table 2). The three month post-injection TBS results showed that 80% of our patients benefited from the procedure. There was no significant difference in TBS scores in OAB patients with wetting and OAB patients with urgency only (78% and 81%, respectively). Most common complications after three months of the injection were observed as the urological complications, including transient macroscopic haematuria in two female and one male patient and urinary tract infection in three female patients. While patients with urinary tract infection were managed by appropriate antibiotic treatment, patients with haematuria were managed conservatively by adequate hydration and parenteral fluid therapy without urinary catheterisation, and were discharged after the resolution of haematuria. Table 3 demonstrates post-procedural outcomes and complications in the study.

TABLE 2: Change from baseline in daily average episodes and total incontinence quality of life scores.

	Minimum-Maximum	Median	Mean±SD	p value
IQoL				
Pre-op	46.0-80.0	70.0	69.9±6.3	<0.001
Post-op	22.0-70.0	33.0	38.5±15.0	
Pad number (n)				
Pre-op	0.0-5.0	3.0	2.3±1.9	<0.001
Post-op	0.0-5.0	1.0	1.0±1.4	
Frequency (episodes/day)				
Pre-op	3.0-20.0	12.0	12.3±4.1	<0.001
Post-op	2.0-15.0	5.0	6.7±3.8	
Nocturia (episodes/day)				
Pre-op	2.0-5.0	3.0	3.6±1.0	<0.001
Post-op	0.0-5.0	1.0	1.6±1.1	
Incontinence (episodes/day)				
Pre-op	0.0-10.0	3.0	3.5±3.0	<0.001
Post-op	0.0-7.0	0.0	1.1±1.6	
PVR (mL)				
Pre-op	0.0-40.0	20.0	20.5±11.7	0.718
Post-op	0.0-35.0	15.0	17.3±10.5	
Q_{max}				
Pre-op	13.0-38.0	20,0	22.1±6.7	0.649
Post-op	10.0-40.0	18.0	20.6±6.9	

SD: Standard deviation; IQoL: Incontinence quality of life; Qmax: Maximum urinary flow rate; PVR: Post-micturition residual urine.

TABLE 3: Postoperative results and complication rates of patients.

		n=40
TBS (%)		
	well improved	20 (50)
	improved	12 (30)
	unchanged	8 (20)
	worse	0 (0)
Duration of operation (minute)		9.5
Urinary infection (%)		3 (7.5)
Urine retention (%)		0 (0)
Dysuria (%)		0 (0)
Hematuria (%)		3 (7.5)
Muscle weakness (%)		0 (0)
Pain at the injection site (%)		0 (0)

TBS: Treatment benefit scale.

DISCUSSION

After introduction of botulinum toxin-A in the treatment of neurogenic detrusor overactivity, a large number of randomised controlled trials and case series have reported improvements in urodynamic parameters and clinical outcomes in patients with idiopathic OAB.[9] We performed a single-centre study to assess the therapeutic success of botulinum toxin-A in patients with idiopathic OAB and urge urinary incontinence who did not respond to anticholinergic therapy. The results of this study revealed both statistically and clinically significant improvements in all OAB symptoms after 100 U botulinum toxin injection in idiopathic OAB patients. These results were consistent with TBS and I-QoL questionnaires which confirmed the decrease in patient complaints.

Botulinum toxin reduces the expression of sensory receptors by targeting both afferent and efferent neuronal pathways in the bladder and preventing the release of acetylcholine and other neurotransmitters. Meta-analyses of the clinical efficacy of botulinum toxin reported 5.13 times less daily voiding frequency and 3.85 times less incontinence episodes in the injection group compared to placebo.[9-11] Similarly, Nitti et al. reported significant reductions in mean voiding frequency, urgency, and nocturia three months after 100 U botulinum toxin injections.[12] Furthermore, Deny et al. reported 75% improvement in voiding fre-

quency and incontinence at the end of the third month of botulinum toxin injection in patients with idiopathic OAB.[13] Consistent with these meta-analyses and other studies in the literature, our findings revealed a significant reduction (2 fold reduction in urinary frequency, three fold reduction in incontinence and 2.5 fold reduction in nocturia) in OAB symptoms at the end of the third month.

We applied 100 U botulinum toxin injections in all our patients, while sparing the trigone. A dose of 100 to 150 U of botulinum toxin injection is preferred in the treatment of idiopathic OAB. Dmochowski et al. reported that they detected clinically significant results after 100 U botulinum toxin injections that only improved minimally after injection of 150 U.[14] However, the post-cure residual urine volume and the use of clean intermittent catheterisation increased in a dose-dependent manner. In contrast, Nitti et al. demonstrated that 100 and 150 U of botulinum toxin injections did not reveal clinically different results in patients with resistant OAB.[12] The U.S. Food and Drug Administration and European Urology Guidelines have approved 100 U botulinum toxin treatments in patients with urinary incontinence due to OAB resistant to standard pharmacological treatment.[15] Initial studies have claimed that trigone injections might cause reflux to the upper urinary tract, whereas recent studies show that this theory is not accurate and there is no clinical difference.[16,17]

OAB is associated with restricted social life especially due to urinary incontinence and caused reduced quality of life particularly in patients with an active life.[18] Chapple et al. showed that there were significant improvements ($p<0.001$) in I-QoL scale and benefit from treatment in the third period after 100 U botulinum injections.[19] Similarly, the study by Onem et al. reported statistically significant improvements in I-QoL at three months after 100 U botulinum toxin injection compared to the pre-treatment level (49.02±14.9 vs 77.13±18.18, $p<0.001$).[20] In the same study, 68% of patients reported "well improvement" or "improvement" in TBS scores, compared to their pre-injection status. Our study is consistent with these reports wherein we found significant increases in I-QoL at three months post-injection compared to before injection. Seventeen patients (51.5%) reported their status as "benefited well" from the treatment, while ten patients (30.3%) reported "improvement" and six patients (18.2%) stated "no change". Thus, significant improvements in TBS score were found in comparison to pre-injection. We believe that one possible reason for our TBS scores are higher compared to those reported in the literature is because our patients had very low I-QoL prior to injection.

Urinary retention and urinary tract infection are the most common complications of botulinum toxin injection, while other adverse effects include haematuria, dysuria, and pain at injection site.[9] A meta-analysis of side effects found urinary infection to be significantly higher after injection than in the placebo group (22.1% vs 6.4%, respectively).[21] Jiang et al. reported that the incidence of urinary tract infection after injection is closely related to the female sex and a baseline residual urine volume of >100 mL.[22] In our study, urinary infection and haematuria were detected in three patients (7.5%). Lower infection rates in our study could be attributed to the fact that most of our patients had initial PVR of <100 mL and only 52.5% of our patients were women.

A PVR of >200 mL after injection is described as urinary retention.[19] Meta-analysis revealed a significant amount of residual urine and clean intermittent catheterisation requirement after 100 U toxin injection compared to placebo (6.9% vs 0.7%, respectively).[19,23] In our study, no statistically significant difference was found in both PVR and Q_{max} compared to pre-injection. Jiang et al. reported higher rate of urinary retention in patients older than 60 years, with initial Q_{max} of <15 mL/s and PVR >100 mL after botulinum toxin injection.[22] Based on this finding, we think that less residual urine as well as voiding difficulty and urinary retention in our study could be explained by the lower age of our study population, higher initial Q_{max} and lower clean intermittent catheterisation PVR urinary volume.

Although our study has some limitations, including small sample size, single-centre and retrospective design, short duration of follow-up, lack of placebo control, and lack of other questionnaires such as the OAB symptom score, it also has several strengths, because therapeutic success was based on

patient satisfaction and a standardised diagnostic and follow-up protocol could be implemented for all patients owing to the single-centre design.

CONCLUSION

Our study showed that botulinum toxin injection remains as an effective option for OAB patients refractory to conservative approaches and anticholinergic treatment.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Ahmet Karakeçi, Rahmi Onur;* ***Design:*** *Ahmet Keleş, Ahmet Karakeçi;* ***Control/Supervision:*** *Rahmi Onur, İrfan Orhan;* ***Data Collection and/or Processing: Ahmet Karakeçi,*** *Tunç Ozan, İrfan Orhan;* ***Analysis and/or Interpretation:*** *Ahmet Keleş, Rahmi Onur;* ***Literature Review:*** *İrfan Orhan, Ahmet Keleş, Tunç Ozan;* ***Writing the Article:*** *Tunç Ozan, Ahmet Keleş;* ***Critical Review:*** *Rahmi Onur, İrfan Orhan;* ***References and Fundings:*** *Tunç Ozan, Ahmet Keleş, Ahmet Karakeçi;* ***Materials:*** *Ahmet Karakeçi, Tunç Ozan.*

REFERENCES

1. Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, et al; Standardisation Sub-Committee of the International Continence Society. The standardisation of terminology in lower urinary tract function: report from the standardisation sub-committee of the International Continence Society. Urology. 2003;61(1):37-49. [Crossref] [PubMed]
2. Milsom I, Abrams P, Cardozo L, Roberts RG, Thüroff J, Wein AJ. How widespread are the symptoms of an overactive bladder and how are they managed? A population-based prevalence study. BJU Int. 2001;87(9):760-6. Erratum in: BJU Int. 2001;88(7):807. [Crossref] [PubMed]
3. Asimakopoulos AD, Cerruto MA, Del Popolo G, La Martina M, Artibani W, Carone R, et al. An overview on mixed action drugs for the treatment of overactive bladder and detrusor overactivity. Urol Int. 2012;89(3):259-69. [Crossref] [PubMed]
4. Cerruto MA, Asimakopoulos AD, Artibani W, Del Popolo G, La Martina M, Carone R, et al. Insight into new potential targets for the treatment of overactive bladder and detrusor overactivity. Urol Int. 2012;89(1):1-8. [Crossref] [PubMed]
5. Mohee A, Khan A, Harris N, Eardley I. Long-term outcome of the use of intravesical botulinum toxin for the treatment of overactive bladder (OAB). BJU Int. 2013;111(1):106-13. [Crossref] [PubMed]
6. Colman S, Chapple C, Nitti V, Haag-Molkenteller C, Hastedt C, Massow U. Validation of treatment benefit scale for assessing subjective outcomes in treatment of overactive bladder. Urology. 2008;72(4):803-7. [Crossref] [PubMed]
7. Patrick DL, Martin ML, Bushnell DM, Yalcin I, Wagner TH, Buesching DP. Quality of life of women with urinary incontinence: further development of the incontinence quality of life instrument (I-QOL). Urology. 1999;53(1):71-6. Erratum in: Urology 1999;53(5):1072. [Crossref] [PubMed]
8. Eyigor S, Karapolat H, Akkoc Y, Yesil H, Ekmekci O. Quality of life in patients with multiple sclerosis and urinary disorders: reliability and validity of Turkish-language version of Incontinence Quality of Life Scale. J Rehabil Res Dev. 2010;47(1):67-71. [Crossref] [PubMed]
9. Cui Y, Wang L, Liu L, Zeng F, Niu J, Qi L, et al. Botulinum toxin-A injections for idiopathic overactive bladder: a systematic review and meta-analysis. Urol Int. 2013;91(4):429-38. [Crossref] [PubMed]
10. Flynn MK, Amundsen CL, Perevich M, Liu F, Webster GD. Outcome of a randomized, double-blind, placebo controlled trial of botulinum A toxin for refractory overactive bladder. J Urol. 2009;181(6):2608-15. [Crossref] [PubMed] [PMC]
11. Sahai A, Dowson C, Khan MS, Dasgupta P. Improvement in quality of life after botulinum toxin-A injections for idiopathic detrusor overactivity: results from a randomized double-blind placebo-controlled trial. BJU Int. 2009;103(11):1509-15. [Crossref] [PubMed]
12. Nitti VW, Dmochowski R, Herschorn S, Sand P, Thompson C, Nardo C, et al; EMBARK Study Group. OnabotulinumtoxinA for the treatment of patients with overactive bladder and urinary incontinence: results of a phase 3, randomized, placebo controlled trial. J Urol. 2013;189(6):2186-93. [Crossref] [PubMed]
13. Denys P, Le Normand L, Ghout I, Costa P, Chartier-Kastler E, Grise P, et al; VESITOX study group in France. Efficacy and safety of low doses of onabotulinumtoxinA for the treatment of refractory idiopathic overactive bladder: a multicentre, double-blind, randomised, placebo-controlled dose-ranging study. Eur Urol. 2012;61(3):520-9. [Crossref] [PubMed]
14. 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(6):2416-22. [Crossref] [PubMed]

15. Lucas MG, Bosch RJ, Burkhard FC, Cruz F, Madden TB, Nambiar AK, et al; European Association of Urology. EAU guidelines on assessment and nonsurgical management of urinary incontinence. Eur Urol. 2012;62(6): 1130-42. Erratum in: Eur Urol. 2013;64(1):e20. [Crossref] [PubMed]
16. Karsenty G, Elzayat E, Delapparent T, St-Denis B, Lemieux MC, Corcos J. Botulinum toxin type a injections into the trigone to treat idiopathic overactive bladder do not induce vesicoureteral reflux. J Urol. 2007;177(3): 1011-4. [Crossref] [PubMed]
17. 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(4):311-4. [Crossref] [PubMed]
18. Sexton CC, Coyne KS, Vats V, Kopp ZS, Irwin DE, Wagner TH. Impact of overactive bladder on work productivity in the United States: results from EpiLUTS. Am J Manag Care. 2009;15(4 Suppl):S98-S107. [PubMed]
19. Chapple C, Sievert KD, MacDiarmid S, Khullar V, Radziszewski P, Nardo C, et al. OnabotulinumtoxinA 100 U significantly improves all idiopathic overactive bladder symptoms and quality of life in patients with overactive bladder and urinary incontinence: a randomised, double-blind, placebo-controlled trial. Eur Urol. 2013;64(2):249-56. [Crossref] [PubMed]
20. Onem K, Bayrak O, Demirtas A, Coskun B, Dincer M, Kocak I, et al; Turkish Urology Academy, Incontinence/Neurourology Study Group. Efficacy and safety of onabotulinumtoxinA injection in patients with refractory overactive bladder: First multicentric study in Turkish population. Neurourol Urodyn. 2018;37(1):263-8. [Crossref] [PubMed]
21. Sun Y, Luo D, Tang C, Yang L, Shen H. The safety and efficiency of onabotulinumtoxinA for the treatment of overactive bladder: a systematic review and meta-analysis. Int Urol Nephrol. 2015;47(11):1779-88. [Crossref] [PubMed]
22. Jiang YH, Ong HL, Kuo HC. Predictive factors of adverse events after intravesical suburothelial onabotulinumtoxina injections for overactive bladder syndrome-A real-life practice of 290 cases in a single center. Neurourol Urodyn. 2017;36(1):142-7. [Crossref] [PubMed]
23. López Ramos H, Torres Castellanos L, Ponce Esparza I, Jaramillo A, Rodríguez A, Moreno Bencardino C. Management of overactive bladder with onabotulinumtoxinA: systematic review and meta-analysis. Urology. 2017;100: 53-8. [Crossref] [PubMed]