RESEARCH

EFFICACY AND SAFETY OF BOTULINUM NEUROTOXIN IN GERIATRIC PATIENTS WITH AN OVERACTIVE BLADDER: A MULTICENTRIC STUDY FROM TURKEY

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Abstract

Introduction: To evaluate the clinical efficacy and safety of botulinum neurotoxin A injection in geriatric patients with an overactive bladder.

Materials and Method: Data of 34 patients aged >65 years who received botulinum neurotoxin A injections (100 U) for overactive bladder at two different urology clinics from 2012 to 2018were retrospectively evaluated. Number of incontinence episodes, urinary frequency, nocturia occurrence, daily pad usage, maximum flow rate, post-void residual urine volume, treatment benefit scale and quality of life scores were evaluated for all patients at pre-treatment and then at 3 and 6 months post treatment.

Results: Comparison of the pre-treatment and the 3- and 6-month post-treatment data revealedno significant changes in maximum flow rate values (p=0.504 and 0.458, respectively); however, a statistically significant decrease was recorded in the urinary frequency, nocturia occurrence, daily pad usage and number of incontinence episodes (p=0.0001). The post-void residual urine volume significantly increased at 3 and 6 months post treatment (p=0.0001). Significant improvements were detected in the quality of life score at 3-months post treatment (p=0.0001).

Conclusion: Botulinum neurotoxin A injection is an efficacious and safe option for treating geriatric patients and improving their symptoms of overactive bladder and quality of life.

Keywords: Urinary Bladder, Overactive; Botulinum Toxin, Type A; Quality of life; Aged; Geriatrics

ARAŞTIRMA

AŞIRI AKTİF MESANESİ OLAN GERİATRİ YAŞ GRUBUNDAKİ HASTALARDA BOTULINUM NEUROTOXIN A ENJEKSİYONUNUN KLİNİK ETKİNLİĞİ VE GÜVENİLİRLİĞİ: TÜRKİYE'DEN ÇOK MERKEZLİ ÇALIŞMA

Öz

Giriş: Aşırı aktif mesanesi olan geriatrik hastalarda botulinum neurotoxin A enjeksiyonunun klinik etkinliğini ve güvenilirliğini değerlendirmek.

Gereç ve Yöntem: 2012-2018 yılları arasında iki farklı üroloji kliniğinde aşırı aktif mesane nedeni ile botulinum nörotoksin A enjeksiyonu (100 Ü) yapılan 65 yaş ve üstündeki 34 hastanın verileri geriye dönük olarak değerlendirildi. Tedavi öncesi ve tedavi sonrası 3. ve 6. Aydaki inkontinans ataklarının sayısı, idrar sıklığı, nokturia oluşumu, günlük ped kullanımı, maksimum akış hızı, sonrasındaki rezidüel idrar hacmi, tedavi yarar ölçeği ve yaşam kalitesi skorları değerlendirildi.

Bulgular: Tedavi öncesi ve tedavi sonrası 3 ve 6. aydaki verilerin karşılaştırılması, maksimum idrar akış hızı değerinde anlamlı bir değişiklik olmadığını ortaya koyarken (sırasıyla, p=0.504 ve 0.458); idrar sıklığı, nokturia oluşumu, günlük ped kullanımı ve idrar kaçırma ataklarının sayısında ise istatistiksel olarak anlamlı bir azalma kaydedildi (p=0.0001). Rezidüel idrar hacmi, tedaviden sonraki 3.ve 6 ayda önemli ölçüde artmıştır (p=0.0001). Tedavi sonrası 3. Aydaki yaşam kalitesi skorunda ise anlamlı iyileşmeler tespit edildi (p=0.0001).

Sonuç: Botulinum neurotoxin A enjeksiyonu, aşırı aktif mesaneli geriatrik hastaların tedavisinde, semptomların ve yaşam kalitesinin düzeltilmesinde etkili ve güvenli bir seçenektir.

Anahtar sözcükler: Mesane, Aşırı Aktif; Botulinum Toksin, Tip A; Yaşam kalitesi; Yaşlı; Geriatri

INTRODUCTION

The International Continence Society defines overactive bladder (OAB) as a complex of symptoms characterized by a sudden urge to urinate, with or without urge incontinence, usually with a high frequency and nocturiain the absence of an underlying pathology (1). Over 500 million individuals world wide experience OAB symptoms (2). The prevalence of OAB is approximately 16% in adults and increases with age, reaching up to 30% in geriatric patients aged >65 years (2). Overactive bladder symptoms lead to a feeling of embarrassment in social life and result in limitations in daily activities as well as cause sleep disorders, depression, anxiety and unfavorable sexual health-related effects (3,4). Moreover, frequent urination and urinary incontinence may be associated with fractures and may lead to mortality owing to falls on the way to the toilet (5).Considering the neural degeneration in the central nervous system, purinergic mechanisms and alterations in the response of muscarinic receptors are reportedly increasing the prevalence of OAB in geriatric patients (6).

Behavioral therapies, such as bladder re-training, changing the time and nature of liquid consumption, timed micturition and pelvic floor rehabilitation, are the first-line treatment options for OAB symptoms. However, first-line therapies are difficult to continue in geriatric patients; further, there are no supervised treatment centers for the proper guidance of patients (6). Thus, most patients discontinue treatment and show insufficient response to behavioral therapies. Second-line treatment options include oral medications with anti-muscarinic and/or beta-3 agonist agents. Although these agents exhibit a significantly better response than placebo, they induce insufficient efficacy and side-effects in geriatric patients, usually leading to the discontinuation of therapy in >50% of the patients by the 3rd month of treatment (6). Likewise, the use of medication in these patients is sometimes limited owing to the possibility of unfavorable side-effects on the cardiovascular and gastrointestinal systems as well as on cognitive functions (7).

In case the second-line treatment fails or cannot be tolerated due to side-effects, botulinum neurotoxin A (BoNTA) injection is considered the third-line treatment. Botulinum toxin reduces the expression of sensory receptors by targeting both the afferent and efferent neuronal pathways in the bladder and preventing the release of acetylcholine and other neurotransmitters. Because BoNTA does not interact with the muscarinic and/or beta 3 receptors, it does not induce any unfavourable effects on cognitive functions (6). Studies have reported satisfactory results regarding this treatment modality. The U.S. Food and Drug Administration approved BoNTA as a treatment modality for neurogenic bladder and OABin 2011 and 2013, respectively (8). Few previous studies have also confirmed the efficacy and safety of BoNTA in geriatric patients (6-9,10).

Currently, there are no suitable data on the use of BoNTA injection for OAB treatment in geriatric patients; moreover, to the best of our knowledge, no such experience has been reported in our country. Therefore, we aimed to retrospectively evaluate the clinical efficacy and safety of BoNTA injection in geriatric patients aged ≥65 years with OAB.

MATERIAL AND METHOD

Study group

Data of 40 patients aged >65 years who received botulinum neurotoxin A injections (100 U) for overactive bladder at two different urology clinics from 2012 to 2018were retrospectively evaluated Ethical Committee approval was obtained (06.09.2018/14/6), and the patients were informed about the injection method and the possible complications, such as urinary infection and retention. Written informed consent was obtained from all patients. All patients underwent detailed physical and urogynaecological examinations, and

laboratory tests, including urine analysis, culture and voiding diary for at least 3 days, uroflowmetry, post-micturition residual urine measurement, urodynamic and urinary system ultrasound, were performed. Patients with urinary infection were treated according to their urine culture results. Those with ≥1 urinary incontinence episodes per day, those who urinated >8 times per day and experienced ≥1 episode of nocturia per day according to the voiding diaries as well as those who were treated with two different anti-muscarinic and/or beta-3 agonists for a time period of ≥3 months and who did not respond to the treatment or had to quit the treatment due to side-effects were included in the study. Patients with urgency and/or urge incontinence due to neurological disorders, history of prior urinary BoNTA injection, previous pelvic surgery, stress-dominant urinary incontinence, bleeding tendency, bladder outlet obstruction (Benign prostatic hyperplasia, urethral stricture etc.) or a contractile bladder according to the urodynamic evaluation, muscular diseases (such as myasthenia gravis) and muscular dystrophies were excluded from the study.

Surgical technique

All patients received prophylactic antibiotic treatment one day before the operation, on the day of the operation and for 3 days postoperation. Under sedo analgesia and using a 20-F rigid cystoscope (Karl Storz; Tuttlingen, Germany), 100 U of BoNTA (BOTOX®, Allergan, Irvine, CA, USA) was diluted with10 mL saline and then injected into the detrusor muscles at 20 sites, excluding the trigone and bladder dome (0.5 mL for each injection). No urethral catheter was placed postoperation.

Outcome analysis

Post-void residual (PVR) volume >200 mL or the inability to void after the procedure was accepted as urinary retention, and a positive urine culture (>105colonies mL/U) with positive urine analysis (>5 leucocytes/HPF) was considered as urinary infection. At least one hour after termination of these do analgesia procedure and the patient was fully conscious, feeling uncomfortable due to the pain, burning, stinging sensation etc. in the pelvic area was also accepted pain at the injection site. Postoperative analgesia requirement of our patients was determined by examining medical records retrospectively. Complications, such as urinary infection, dysuria, urinary retention, haematuria, muscle weakness and pain at the injection site which may occur postoperation, were recorded.

To determine the success of the intervention, the patients were asked to fill the treatment benefit scale (TBS) form after 3and 6monthsof the injection treatment (11). The patients were asked to describe the treatment result as improved, quite improved, not changed or worsened. The answers quite improved and improved indicated surgical success. To evaluate the patients' quality of life (QoL) related to health affected due to OAB symptoms, the Turkish validated version of the incontinence QoL (I-QoL) scale comprising three groups, which is a measurement for the limitation of the mental and social life, was applied at pre-treatment and then at 3 and 6monthspost treatment (12,13). Incontinence episodes, frequency, nocturia status, daily pad usage, maximum flow rate (Qmax) and PVR volume were recorded pre-treatment and then at 3 and 6 months post treatment.

Statistical analysis

The 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 the continuous variables, and Chi-square or Fisher's exact test was used to compare the categorical variables. The results were analysed within a 95% confidence interval, and $p<0.05$ was regarded statistically significant.

RESULTS

Of the 40 patients that complied with the inclusion criteria, 6 were excluded due to various reasons (inability to follow up instructions or not answering

all questions). Thirty four patients patients, 17 (50%) were women and 17 (50%) were men. The mean patient age was 72.3±5.9 (range,65–85) years. The mean incontinence duration was 9.8±3.8 years. Additional comorbidities were observed in the majority of the patients. The demographic characteristics of the study population are shown in Table 1. On comparing the pre-treatment data with the3- and 6-month post-treatment duration, a statistically significant decrease was recorded in the frequency, nocturia, daily pad usage and incontinence episodes. An approximately 3-fold decrease was noted, particularly in terms of incontinence and the daily pad usage. The voiding diary after treatment is presented in Table 2.

There was no significant change in the Qmax valuesat3 and 6monthspost treatment when compared with that at pre-treatment (11.8±3.2, 11.2±3.5/s and 11.6±3.4 mL/s, respectively; p=0.504 and0.458, respectively). When compared with that at pre-treatment, the PVR values were significantly increased at 3 and 6 months after injection (102.0±55.4, 90.0±58.3and67.5±22.2mL, respectively; p=0.0001).

I-QoL scores of patients before the procedure were less compatible with the severity of symptoms; however, significant improvements detected at 3months post treatment (44.0±4.6 and 69.2±11.9, respectively; p=0.0001) (Figure 1). TBS score at 3months post treatment revealed a satisfaction rate of 70.6%.At 6monthsposttreatment, the I-QoL score showed a slight decrease, although it was still high as compared with that at pre-treatment, and treatment satisfaction according to TBS was 55.9% (Figure 1; Table 3).

Gross haematuria in 2 women and 1 man, urinary tract infection in 4 women and 1 man and high PVR (in 5 men and 1 woman)were detected after injection. While patients with urinary tract infection were treated with an appropriate antibiotic treatment, those with haematuria were conservatively treated thorough adequate hydration and parenteral fluid therapy without urinary catheterization and were

Table 1. The socio-demographic characteristics of the patients.

Variable	Mean
Age±sd (mean)	72.3±5.9 (65-85)
Duration of disease (±sd)	9.8±3.8 (2-15) year
Duration of using drug (±sd)	3.9±1.42 (1-5) years
Gender, n (%)	
Women	17 (50%)
Men	17 (50%)
Weight±sd (mean)	72±8.1 (57-100) kg
Height±sd (mean)	165.6±5.9 (150-180) cm
BMI±sd (mean)	26.4±3.2 (20-41.6) (kg/m^2)
Using tobacoo, n (%)	
Yes	9 (26.5%)
No	25 (73.5%)
Education level, n (%)	
Primary school	21 (61.7%)
Middle school	11 (32.3%)
High school	2 (6%)
University	0 (0%)
Comorbidity, n (%)	
No	10 (29.4%)
HT	7 (20.5%)
CAD	3 (8.9%)
DM	9 (26.5%)
Others	5 (14.7%)

BMI: Body Mass Index **HT:** Hypertension **CAD:** Coronary Artery Disease **DM:** Diabetes Mellitus

Table 2. Change from baseline in daily average episodes and total I-QOL scores.

	Min.-Max	Median	Mean±sd	p
I-QOL scores				
Preop	35.0- 50.0	45.0	44.0 ± 4.6	
Postop 3rd month	45.0 - 81.0	73.5	69.2 ± 11.9	**0.0001***
Postop 6th month	40.0 - 80.0	70.0	66.1 ± 10.5	**0.0001****
Daily pad usage± sd				
Preop	0.0 - 5.0	2.0	2.0 ± 1.8	
Postop 3rd month	0.0 - 3.0	0.0	0.5 ± 0.9	**0.0001***
Postop 6th month	0.0 - 3.0	0.0	0.6 ± 1.0	**0.0001****
Mean urinary frequency±sd				
Preop	8.0 - 18.0	14.5	14.1 ± 1.9	
Postop 3rd month	0.0 - 14.0	8.0	8.4 ± 2.3	**0.0001***
Postop 6th month	7.0 - 14.0	9.5	9.4 ± 1.5	**0.0001****
Mean nocturia episodes±sd				
Preop	2.0 - 5.0	4.0	3.6 ± 0.9	
Postop 3rd month	0.0 - 4.0	1.0	1.5 ± 0.9	**0.0001***
Postop 6th month	1.0 - 4.0	1.5	1.7 ± 0.9	**0.0001****
Mean UI episodes±sd				
Preop	0.0 - 10.0	3.0	3.5 ± 2.9	
Postop 3rd month	0.0 - 5.0	0.0	0.9 ± 1.5	**0.0001***
Postop 6th month	0.0 - 5.0	1.0	1.3 ± 1.6	**0.0001****
Q max±SD (mL/s)				
Preop	9.0 - 17.0	12.0	11.8 ± 3.2	
Postop 3rd month	5.0 - 16.0	11.0	11.2 ± 3.5	**0.4582***
Postop 6th month	6.0 - 17.0	12.0	11.6 ± 3.4	**0.5041****

Mean±SD: Mean±standard deviation, **Min:** Minimum, **Max:** Maximum, **Preop:** Preoperative, **Postop:** Postoperative **I-QOL:** Incontinence quality of life **UI:** Urinary incontinence **PVR:** Post-void residual **Q max:** Maximum flow rate **p*:** Comparison of Preop and post op. 3rd month **p**:** Comparison of Preop and post op. 6th month p **< 0.05:** Statistically significant value.

discharged after the haematuria are solved. Clean intermittent catheterization (CIC) was required in 6 patients for 4 weeks due to their high residual volume; no continuous retention was noted. Since none of the patients has described any pain in the injection area, no analgesics was required in any of our patients. Table 4presents the post-procedural outcomes and complications of the study.

Table 3. Postoperative treatment benefit scale results.

		n=34(%)
TBS at 3rd month (%)	Well improved	11 (32.4)
	improved	13 (38.2)
	No change	7 (20.6)
	worse	3 (8.8)
TBS at 6th month (%)		
	Well improved	9 (26.5)
	Improved	10 (29.4)
	No change	10 (29.4)
	worse	5 (14.7)

Table 4. Postoperative results and complications of patients.

	n=34(%)
Duration of operation (minute)	12.5
Urinary infection (%)	5 (14.7)
Urine retention (%)	6 (17.6)
Dysuria (%)	-(-)
Hematuria (%)	3 (8.8)
Muscle weakness (%)	-(-)
Pain at the injection site (%)	-(-)

TBS: Treatment benefit scale

DISCUSSION

This study is the first to evaluate the efficacy and safety of BoNTA injection in Turkish geriatric patients aged >65 years with OAB who did not respond to previous therapies. Our results reveal both statistically and clinically significant improvements in all OAB symptoms after the administration of 100 U of BoNTA injection. Likewise, TBS and QoL assessments revealed improved patient perception and procedural success.

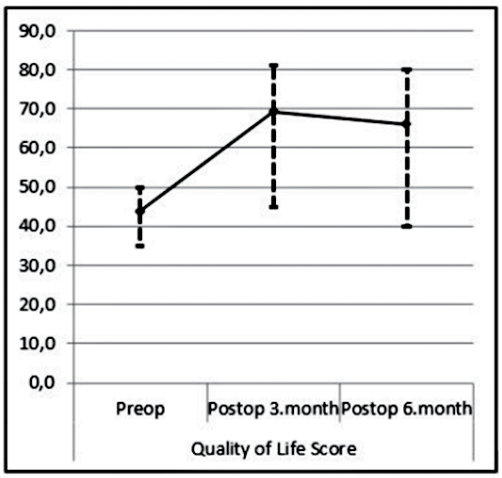
It has recently been reported that the efficacy of BoNTA injection is similar in young and geriatric patients. In comparison with that before injection, Liao et al. detected a significant decrease in the urgency episodes after the administration of 100 U BoNTA (16.3±18.2 vs. 11.7±31.4) (9). In his study evaluating geriatric patients aged >75 years, White et al. reported a decrease in the daily pad usage due to incontinence after 200 U of BoNTA injection at 1 and 6 months post treatment (4.0±0.89, 1.3±0.60, and 2.81±0.75 respectively). They also reported a significant decrease in the frequency as compared with that at pre-treatment (11.44±1.67, 5.19±0.83 and 7.44±1.67 respectively) (10). In our study, improvement in the mean frequency, nocturia, daily pad usage and incontinence episodes at 3 and 6 months after injection corroborated with that reported in the literature.

White et al. reported TBS of >50% in 76% of the patients within 1 month of treatment in their study on OAB in geriatric patients (10). Similarly, Liao et al. reported significant clinical improvement after the administration of 100U of BoNTA injection in the number of incontinence and QoL of three different patient groups with OAB who were aged <65 years, >65 years and in frail geriatrics (9).

In accordance with the literature, we noted improvement in QoL at 3 and 6 months post treatment. Although there were slight decreases in the scores at 6months, the results achieved were significant. TBS was corroborated with QoL. Moreover, 70.6% and 55.9%of the patients described their health status as quite improved and improved at 3 and 6 months post treatment, respectively.

Urinary retention and urinary tract infection are the most common complications of BoNTA injections; other adverse effects include haematuria, dysuria and pain at the injection site. In prior studies, such unfavourable complications were reported in approximately 20%–43%of all patients (14). In meta-analyses of side-effects after injection in patients aged >60 years, urinary infection was found to occur

Figure 1. Results of "Incontinence Quality of Life" scores.



in 10.3%–15.4% of the patients (10, 15). Jiang et al. reported that the incidence of urinary tract infection after injection is closely associated with female sex and baseline residual urine volume of >100 mL. However, they also reported no correlation between increased age and urinary tract infection occurrence. (15). In our study, urinary infection was detected in 5 patients (14.7%), all of whom were treated with antibiotics according to their urine culture results.

A residual urine volume of >200 mL after injection is described as urinary retention (16). A meta-analysis revealed a significant residual urine volume and CIC requirement after 100U of toxin injection as compared with placebo (17). Jiang et al. stated that higher rates of urinary retention in patients aged >60 years were associated with male sex, presence of comorbidities (e.g. frailty), initial maximum urinary flow rate <15and residual urine volume>100 mL. (15). Jiang et al. reported that the rates of patients with PVR >200 mL after the administration of 100 U of BoNTA injection were 35.6% in patients aged 60–75 and 29% in those aged >75 years (15). In another study, the rates of patients with PVR >250 mL after the administration of 100U of BoNTA injection were 60.7% in invalid geriatric patients and 39.7% in geriatric patients without any disability (9). In our study, we found lower PVR volumes, which may be attributed to the presence of female patients constituting 50% of the patient group, the absence of invalid and depending patients and to the fact that the mean pre-treatment PVR volume was <100 mL.

Our study has several limitations, including its retrospective design, short duration of follow-up, lack of placebo control and the small sample size. However, it also has several strengths; the main strength was that therapeutic success was based on patient satisfaction and that a standardized diagnostic and follow-up protocol could be implemented for all patients owing to the multicentre design of the study.

This study is the first Turkish multicentre study that evaluated geriatric patients aged >65 years. Our results indicate that 100 U of BoNTA injection is efficacious and safe for the treatment of geriatric patients and for improving their OAB symptoms and QoL. However, large series, placebo controlled and long follow-up studies are needed.

Conflict of interest

None.

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