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# The Efficacy and Safety of Intradetrusor Botulinum Toxin Injection in Urinary Incontinence in Geriatric Patients

**Burak Elmaağaç[1*], Aydin Yenilmez[2]**

[1]*Department of Urology, Yunus Emre State Hospital, Eskisehir, Turkey*
[2]*Department of Urology, School of Medicine, Eskisehir Osmangazi University, Eskisehir, Turkey*

**ABSTRACT**

Antimuscarinic agents play an important function in the treatment of urinary incontinence. Intradetrussor onabotulinum toxin (Btx-A) injection is recommended if antimuscarinic drugs fail. This study examined Btx-A injection efficacy and adverse effects by age. The study has 54 patients who did not respond or tolerate two antimuscarinic drugs were injected with Btx-A. Before operation, urodynamics, voiding diary, International Consultation Incontinence Questionnaire Short-Form (ICIQ-SF) and Incontinence Quality of Life (I-QoL) were assessed. Six weeks after operation, these values were repeated. In light of these findings, the treatment efficacy of the Btx-A injection was assessed. A two-way ANOVA test was performed for repeated measurements.

The study included 54 patients, 37 female and 17 male. Twenty patients were 65 or older, 34 were under 65. Most patient groups benefited from Btx-A injections.

Age doesn't affect Btx-A injection effectiveness. In 54 patients, maximal bladder capacity increased 50%, maximum detrusor pressure decreased 42%, incontinence quality of life score increased 71%, and average daily incontinence decreased 69%. Nine patients (16%) had urinary tract infections and one had urine retention (1.8%).

IntradetrussorBtx-A injections should be favored due to their adequate efficacy and low incidence of side effects. Injection of intradetrussorBtx-A is a reliable, tolerable, reproducible, and effective invasive treatment for resistant urinary incontinence or overactive bladder.

Considering the adverse effects of antimuscarinic agents in OAB patients 65 and older who are resistant, Btx-A injection should be recommended due to its low rate of complications and efficacy.

**Keywords:** Botulinum toxin, incontinence, overactive bladder

## Introduction

The regulation and neural control of the urinary bladder, and consequently the process of micturition, are mediated by both the central nervous system and the peripheral nervous system. The regulation mechanisms involve the participation of adrenergic and cholinergic systems, as well as several neurotransmitters. Acetylcholine is the primary transmitter implicated in the formation of this nerve-muscle junction. Currently, numerous therapy modalities have demonstrated efficacy in targeting acetylcholine.

The diagnosis of urine incontinence involves the utilization of many clinical tools and assessments, including clinical history, evaluation of incontinence quality of life, international urinary incontinence questionnaires, maintenance of a voiding diary, and conducting bladder pressure flow investigations. Bladder training, pelvic floor exercises, management of caffeine and water intake are indicated in primary care. Pharmacotherapy is indicated for patients who have inadequate response to the aforementioned suggestions. Antimuscarinic and Beta-3 agonist medications are employed in the pharmacological treatment of patients with overactive bladder (OAB) who exhibit symptoms of urge type incontinence. Refractory urinary incontinence is a term used to describe cases of urine incontinence that do not exhibit satisfactory response to primary care therapies. In the management of refractory urine incontinence, therapeutic approaches such as intradetrussor botulinum toxin injection and sacral neuromodulation are employed.

The European Urology Guidelines advocate the use of intradetrusor botulinum toxin injection treatment for both neurogenic and non-neurogenic urine incontinence (1).

**Botulinum Toxin Injection**: The phenomenon of botulinum poisoning was initially characterized and documented in Germany during the latter part

***Corresponding Author:** Burak Elmaagac, Department of Urology, Eskisehir Yunus Emre State Hospital, 26190 Eskisehir, Turkey
E-mail: burakelmaagac@gmail.com, Phone: +90 505 628 72 59
**ORCID ID: Burak Elmaağaç:** 0000-0001-5853-0256, **Aydin Yenilmez:** 0000-0002-7623-2145
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of the 18th century, afterwards becoming recognized as "Kerner's Disease" (2). The bacterium Clostridium botulinum, which is an obligate anaerobe capable of producing spores, was first isolated in 1985 by Van Ermengen (3).

Botulinum toxins are produced in the form of single-chain polypeptides with an approximate molecular weight of 150 kilodaltons (kDa) (4). The process of paralysis resulting from toxin exposure can be delineated into four distinct stages.

1. The initial step involves the attachment of the toxin's heavy chain to a specific receptor located at the terminal end of a neuron.
2. The process of internalizing the poison into the nerve terminal
3. The translocation of light chain to the cytoplasm is a process that involves the movement of the light chain from one cellular compartment to another, namely from the extracellular space to the cytosol.
4. The suppression of neurotransmitterrelease.

Therefore, it inhibits the fusion process between the vesicle and the plasma membrane (5).Btx-A therapy exhibits both long-lasting and reversible effects, since individuals undergoing this treatment have the potential to gradually restore their normal functions through neuron regeneration. The normal period of action of Btx-A in skeletal muscular spasticity is 3-4 months; however, it has been shown that Btx-A injections administered to bladder smooth muscle have a prolonged effect lasting 6-9 months. Tissues that possess autonomic innervation have more enduring clinical reactions in comparison to tissues that possess somatic innervation (6-8).

**Effect Mechanism:** The Btx-A exhibits two distinct mechanisms of action, namely efferent and afferent effects. The efferent effect was observed in mouse bladders that were injected with Btx-A, resulting in a significant reduction in the release of labeled acetylcholine (9). While Btx-A is recognized for its specificity towards the cholinergic system, it has also been observed to inhibit the release of several neurotransmitters. In addition to acetylcholine, decreases in ATP release were also observed in bladder tissue (10). Nearly half of the contractility in bladder tissues in patients with idiopathic detrusor overactivity is caused by purinoceptors. ATP is an excitatory neuromuscular transmitter in the urinary bladder, possibly acting as a cotransmitter with acetylcholine from postganglionic parasympathetic nerves to activate P2X purinoceptors. As a result, Btx-A, along with acetylcholine, reduces the release of neurotransmitters such as ATP by reducing contractility (11).

**Dose Adjustment:** Dose adjustment is a process that involves modifying the dosage of a medication in order to achieve optimal therapeutic outcomes while minimizing adverse effects. The recommended dose for efficacy and side effect profile in cases of neurogenic detrusor overactivity is an injection of 200 IU Btx-A. The study demonstrated that the use of Btx-A with a dosage of 200 IU yielded significant effectiveness. However, no discernible difference in efficiency was observed between the 200 IU and 300 IU dosages. In contrast, there was an observed escalation in the occurrence of adverse effects associated with 300 IU Btx-A injections. The study findings indicated a decline in the efficacy of Btx-A when administered at doses below 200 IU, as reported in previous research (12,13). The study determined that a dosage of 100 IU was shown to be appropriate in patients without neurogenic conditions. The study found that the maximum effectiveness was observed at a dosage of 100 IU. However, it was also observed that as the dosage increased, there was an increase in the volume of residual urine (14).

**Injection Areas:** The regions of the body where injections are administered. Following the combination of 100 (IU) of Btx-A with 10 ml of saline solution, it was observed that 1 ml resulted in a range of 10 to 10 distinct sites of application. Similarly, while administering 0.5 ml, the number of distinct points varied between 5 and 20. Furthermore, the application of 0.25 ml yielded a range of 2.5 to 40 distinct points across three separate instances. The study revealed that there was no statistically significant difference in effectiveness ($p = 0.55$).

**Adverse Reactions:** The fatal dose of Btx-A ranges from around 2000 to 3000 IU. There is an absence of systemic adverse effects within the range of 100-300 IU. Systemic side effects of fetal heart block include muscle weakness, upper extremity weakness, weakness above the lesion, and autonomic side effects. Additional local side effects, such as bladder infection, detrusor areflexia, and urine retention, may also be noticed.

This study aims to evaluate the efficacy of intradetrussor administration of Btx-A. The present study aimed to explore the efficacy of an injectable treatment in elderly patients aged 65 years and above who shown resistance to medicinal therapy for urine incontinence. To achieve the objective, a voiding diary, urodynamic investigation, and urine incontinence

questionnaires were administered. The investigation focused on the variations in these parameters prior to and following the administration of Btx-A.

## Materials and Methods

The decision of the ESOGU Faculty of Medicine Non-Pharmaceutical Clinical Research Ethics Committee (Dated October 3, 2017, number 257) deemed this retrospective thesis study appropriate.

When patients were clinically diagnosed, urodynamics were performed, and voiding diaries, ICIQ-SF, and I-QoL forms were filled out. Following six weeks of Btx-A injection was administered, urodynamics were repeated, and voiding diaries and incontinence forms were compared.

**Selection of Patients:** Patients with incontinence who did not respond to medical treatment and who received botulinum toxin injections at the Urology Department of the Eskisehir Osmangazi University Faculty of Medicine were screened retrospectively.

Btx-A injections were administered to 54 patients in our clinic, and all of their records were located. Prior to injection, patients' medical histories, medications, urodynamic investigations, voiding diaries, and incontinence quality of life forms were evaluated.

The medical history of incontinent patients is crucial. In the patients' medical history, it was ascertained if they had received previous treatment. All of the patients had previously received numerous treatments, none of which were effective. For these patients, resistant urinary incontinence was defined, and botulinum toxin injections were administered.

**Urinary Diary:** Three-day urinary diaries were prepared. Patients kept voiding diaries for three days prior to and following Btx-A injection.

From the voiding diaries, the average number of daily urinations and the average number of incontinence were determined. These values were compared to the voiding diaries following treatment.

**Forms of Life Quality:** In our study, standard and Turkish versions of the ICIQ-SF and I-QoL were utilized. Before and after injection, these forms were applied to patients and compared.

**Urodynamic Parameters:** Before and six weeks after botulinum toxin injection, the following urodynamic parameters were compared: first sensation of bladder filling, first involuntary contraction volume, maximum detrusor pressure, and maximum bladder capacity.

**Operative Methods and Clinical Procedures:** As the botulinum toxin serotype, type A onabotulinum toxin was utilized. In the operating room, 100 IU of botulinum toxin preserved in cold chain vials was diluted with 10 ml of saline. To prevent foaming during reconstitution, the vials were not agitated.

Injections of Btx-A were administered to patients in the operating room while they were sedated and anesthetized. Cystoscopy was performed on lithotomy-positioned patients. The needle point is set to a 5 mm depth. 0.5 ml of 100 IU of diluted Btx-A was injected into 20 distinct bladder locations. Patients received quinolone or cephalosporin group antibiotic prophylaxis.

At the conclusion of the procedure, 16fr foley catheters were inserted into the patients. The catheter was withdrawn on the first day following surgery. Patients were discharged from the hospital after urinating with warnings about inability to urinate and elevated fever.

One week after the injection of Btx-A into the patient, a urinalysis and ultrasonographic examination of residual volumes were performed. Patients with urinary tract infections or residual urine underwent weekly monitoring. Patients with elevated residual urine (>150 ml) had a foley catheter inserted. Urine culture and, if necessary, antibiotic therapy was administered to patients with urinary tract infections.

The urodynamics, voiding diary, and quality of life forms were repeated six weeks after the operation.

**Statistical Analysis**: Continuous data are represented by the Mean ± Standard Deviation. The percentage value for categorical data is provided. The Shapiro Wilk test was used to examine the data's normal distribution compatibility. Dependent sample t test analysis was used to evaluate the difference between measurement times. The analysis was conducted utilizing the IBM SPSS Statistics 21.0 and Sigma Stat 3.5 programs. In all statistical analyses, p values 0.05 were considered statistically significant.

## Results

The investigation included 54 patients, 37 of whom were female and 17 of whom were male. Twenty patients were aged 65 and older, while there were 34 patients under the age of 65. The

**Table 1:** General Findings

| | Mean ± Standard Deviation (Min - Max) | | p* |
|---|---|---|---|
| | Before Btx-A | After Btx-A | |
| First Sensation of Bladder Filling (ml) | 82.7 ± 55.9 (10 - 274) | 133.6 ± 72.9 (20 - 356) | <0.001 |
| First Involuntary Contraction Volume (ml) | 91.5 ± 87.5 (0 - 470) | 130.4 ± 120.3 (0 - 510) | <0.001 |
| Maximum Detrusor Pressure (cm H2O) | 61.3 ± 50.2 (6 - 233) | 35.9 ± 21.2 (3 - 107) | <0.001 |
| Maximum Bladder Capacity (ml) | 157.3 ± 114.0 (36 - 651) | 236.0 ± 132.4 (60 - 680) | <0.001 |
| Average Number of Voiding Per Day | 11.6 ± 3.4 (6 - 24) | 9.1 ± 1.9 (6 - 15) | <0.001 |
| Average Number of Incontinence Per Day | ± 3.0 (1 - 13) | ± 2.1 (0 - 9) | <0.001 |
| ICIQ Score | 16.4 ± 3.5 (8 - 21) | 8.5 ± 5.3 (0 - 21) | <0.001 |
| I-QoL Score | 42.2 ± 11.2 (22 - 80) | 72.5 ± 19.3 (30 - 102) | <0.001 |

Comparison of all patients' overall results six weeks after doing a botulinum toxin injection
Btx-A: Botulinum Toxin A

following table summarizes the results for 54 patients.

We compared the findings below;

- Urodynamicfindings;
  - First Sensation of BladderFilling
  - First Involuntary Contraction Volume
  - Maximum Detrusor Pressure
  - Maximum Bladder Capacity
- Voiding diary findings;
  - Average Number of Voiding Per Day
  - Average Number of Incontinence Per Day
- ICIQ-SF and I-QoL

All urodynamic findings improved following onabotulinum toxin injection for six weeks (Table 1). Patients' average daily urination frequency and incontinence decreased. At the sixth week after botulinum toxin A injection, complete dryness was observed in 31 (57.4%) of 54 incontinent patients.

Six weeks after the injection of botulinum toxin, all parameters improved, regardless of age. These advances in the patients' daily lives correspond with the urodynamic parameters.

As delineated in our research, a distinction was made and a comparison was conducted between patients aged below 65 years and those aged above 65 years. Based on the data shown in Graph1, it can be concluded that age did not demonstrate any significant impact on urodynamic parameters. Similarly, it was noted that the administration of botox injections yields positive effects on urodynamic measures. The observed alterations in all of these indicators exhibited statistical significance ($p<0.001$).

Similar improvements in urodynamic parameters were observed in I-QoL, ICIQ-SF, and Voiding Diary. With a decrease in the number of daily urination, the real improvement has been in urination withdrawal. Total dryness was observed at week 6 after injection in 31 (57.4%) of 54 patients (Table: 2).

Nine patients were diagnosed with urinary tract infection, and one patient had an increased residual volume of 300 mL. After receiving the required treatment, it was determined that these complications did not persist at the 6-week control period. The patient whose residual volume was detected continued to undergo weekly monitoring. After 3 weeks, this residual volume was determined to be below 150 mL.

**Table 2:** Voiding Diary and Urinary Incontinence Questionnaires Findings

| | | Mean ± Standard Deviation (Min - Max) | | p |
|---|---|---|---|---|
| | | Before Btx-A | After Btx-A | |
| | | I-QoL Score | | |
| Age | <65 | 43.88 ± 12.04 (22 - 80) | 72.91 ± 20.62 (30 - 102) | <0.001 |
| | >=65 | 39.55 ± 9.43 (26 - 55) | 71.8 ± 17.36 (30 - 98) | <0.001 |
| | | ICIQ-SF Score | | |
| | <65 | 16.59 ± 3.6 (8 - 21) | 8.82 ± 5.55 (0 - 21) | <0.001 |
| | >=65 | 16.3 ± 3.66 (10 - 21) | 8.2 ± 5.13 (3 - 21) | <0.001 |
| | | Average Number of Voiding Per Day | | |
| | <65 | 11.65 ± 3.64 (6 - 24) | 9.06 ± 2.06 (6 - 15) | <0.001 |
| | >=65 | 11.7 ± 3.31 (6 - 21) | 9.25 ± 1.74 (6 - 14) | <0.001 |
| | | Average Number of Incontinence Per Day | | |
| | <65 | ± 2.9 (1 - 10) | 1.38 ± 2.23 (0 - 8) | <0.001 |
| | >=65 | 4.6 ± 3.22 (1 - 13) | 1.05 ± 2.11 (0 - 9) | <0.001 |

Comparison of incontinence questionnaires and voiding diaries of people over 65 and under 65 before and six weeks after botulinum toxin injection
I-QoL: Incontinence Quality of Life
ICIQ-SF: Incontinence Questionnaire Short-Form

## Dıscussıon

The relationship between Btx-A administration and age was investigated in this study. It has been determined that the toxin's efficacy in patients 65 and older is equivalent to that in patients younger than 65. The effectiveness of anticholinergic therapy is diminished in elderly patients with urge urinary incontinence. Btx-A injection is a leading treatment for incontinence resistant to anticholinergic therapy that can be administered safely to geriatric patients. The patient's age was also found to be unrelated to the effect of Btx-A administration. Given that elderly patients may be more sensitive to the adverse effects of anticholinergic drugs, the efficacy of Btx-A injection in elderly patients is crucial. Btx-A injection has been shown to be efficacious, tolerable, and safe in elderly patients in two separate studies (15,16).

Male patients with bladder outlet obstruction exhibit altered protein synthesis in the bladder epithelium and smooth muscle cells. These processes result in numerous structural alterations. They compared light and electron microscopy using normal, aged, and obstructed human bladders. They reported that the smooth muscle cells of the obstructed bladder had lost their contractile function (17). These functional deficits observed in obstructive bladder have not been observed in the bladders of elderly humans. It has been observed that the aging bladder is morphologically similar to the normal bladder. Given the histological changes associated with bladder outlet obstruction, it is not anticipated that the obstructive bladder will respond to Btx-A in the same manner as a normal bladder. In a study evaluating the efficacy of Btx-A in male patients with non-obstructive over active bladder, it was found that patients with bladder outlet obstruction requiring transurethral resection of the prostate responded less favorably to Btx-A than non-obstructive patients (18). In conclusion, in these two investigations, the aging of the


**Graph1:** Urodynamic Findings
Comparison of incontinence urodynamic parameters of people over 65 and under 65 before and six weeks after botulinum toxin injection

bladder does not diminish the effectiveness of Btx-A. Since male patients with obstructive symptoms were not included in our study, our results indicate that the efficacy of Btx-A for male and female patients is comparable.

A study was conducted on post-urinary residual urine in geriatric patients. The effect of Btx-A injection on residual urine did not differ significantly between elderly and younger patients. There are reports of elevated post-voiding residue levels in elderly patients who are frail. This is because the detrusor muscle is the most fragile muscle group in the body, according to research (19). A 62-year-old patient was diagnosed with PVR in our study. There was no correlation between age and residual urine volume.

Low-dose intradetrusorBtx-A injections should be favored due to their sufficient efficacy and low complication rates. Before injection, patients should be informed about urinary tract infection and urinary retention. Age and gender of the patient have no effect on the effectiveness of Btx-A. Intradetrusor injection of Btx-A is a safe, tolerable, repeatable, and efficacious minimally invasive treatment for urinary incontinence or OAB that is resistant. Considering the adverse effects of antimuscarinic agents in patients with refractory OAB aged 65 years and older, Btx-A injection should be recommended due to its low complication rate and high effectiveness.

## References

1. Professionals S-O. Urinary Incontinence. Uroweb. http://uroweb.org/guideline/urinary-incontinence/?type=pocket-guidelines. Accessed April 3, 2018.
2. Dickson EC, Shevky R. Botulism. Studies on the manner in which the toxin of clostridium botulinum acts upon the body :i. the effect upon the autonomic nervous system. J Exp Med.
3. Van Ermengem E. Classics in infectious diseases. A new anaerobic bacillus and its relation to botulism. E. Van Ermengem. Originally published as "Uebereinenneuenanaëroben Bacillus und seine BeziehungenzumBotulismus" in Zeitschriftfür Hygiene und Infektionskrankheiten 26: 1-56, 1897. Rev Infect Dis. 1979; 1(4):701-719.
4. Das Gupta BR. Structure and biological activity of botulinum neurotoxin. J Physiol (Paris). 1990; 84(3):220-228.

5. Schiavo G, Santucci A, Dasgupta BR, Mehta P, Jontes J, Benfenati F, Winson MC, Montecucco C. Botulinum neurotoxins serotypes A and E cleave SNAP-25 at distinct COOH-terminal peptide bonds. FEBS Lett. 1993; 335(1):99-103.
6. Heckmann M, Ceballos-Baumann AO, Plewig G, Hyperhidrosis Study Group. Botulinum toxin A for axillary hyperhidrosis (excessive sweating). N Engl J Med. 2001;344(7):488-493.
7. Porta M, Gamba M, Bertacchi G, Vaj P. Treatment of sialorrhoea with ultra-sound guided botulinum toxin type A injection in patients with neurological disorders. J NeurolNeurosurg Psychiatry. 2001; 70(4):538-540.
8. Von Lindern JJ, Niederhagen B, Bergé S, Hägler G, Reich RH. Frey syndrome: treatment with type A botulinum toxin. Cancer. 2000; 89(8):1659-1663.
9. Smith CP, Franks ME, McNeil BK, Ghosh R, Groat WCD, Chancellor MB, Somogyi GT. Effect of botulinum toxin A on the autonomic nervous system of the rat lower urinary tract. J Urol. 2003;169(5):1896-1900.
10. Smith CP, Boone TB, Groat WCD, Chancellor MB, Somogyi GT. Effect of stimulation intensity and botulinum toxin isoform on rat bladder strip contractions. Brain Res Bull. 2003;61(2): 165-171.
11. O'Reilly BA, Kosaka AH, Knight GF. P2X receptors and their role in female idiopathic detrusor instability. J Urol. 2002; 167(1):157-164.
12. Ginsberg D, Gousse A, Keppenne V. Phase 3 efficacy and tolerability study of onabotulinumtoxinA for urinary incontinence from neurogenic detrusor overactivity. J Urol. 2012; 187(6):2131-2139.
13. Apostolidis A, Thompson C, Yan X, Mourad S. An exploratory, placebo-controlled, dose-response study of the efficacy and safety of onabotulinumtoxinA in spinal cord injury patients with urinary incontinence due to neurogenic detrusor overactivity. World J Urol. 2013;31(6):1469-1474.
14. Denys P, Le Normand L, Ghout I. Efficacy and safety of low doses of onabotulinumtoxin. A for the treatment of refractory idiopathic overactive bladder: a multicentre, double-blind, randomised, placebo-controlled dose-ranging study. Eur Urol. 2012; 61(3):520-529.
15. White WM, Pickens RB, Doggweiler R, Klein FA. Short-term efficacy of botulinum toxin a for refractory overactive bladder in the elderly population. J Urol. 2008; 180(6):2522-2526.
16. Kim SH, Habashy D, Pathan S, Tse V, Collins R, Chan L. Eight-Year Experience With Botulinum Toxin Type-A Injections for the Treatment of Nonneurogenic Overactive Bladder: Are Repeated Injections Worthwhile? IntNeurourol J. 2016; 20(1):40-46
17. Mirone V, Imbimbo C, Longo N, Fusco F. The detrusor muscle: an innocent victim of bladder outlet obstruction. Eur Urol. 2007;51(1):57-66.
18. Habashy D, Losco G, Tse V, Collins R, Chan L. Botulinum toxin (Onabotulinum toxin A) in the male non-neurogenic overactive bladder: clinical and quality of life outcomes. BJU Int. 2015;116 Sup.3:61-65.
19. Liao, C. H., Kuo, H. C. Increased risk of large post-void residual urine and decreased long-term success rate after intravesical onabotulinumtoxinA injection for refractory idiopathic detrusor overactivity. The Journal of urology, 189(5), 1804-1810.