FEMALE UROLOGY
Invited Review

Botulinum toxin injections for treating neurogenic detrusor overactivity

Nörojenik detrüsör aşırı aktivitesinin tedavisinde botulinum toksin enjeksiyonları

Ömer Bayrak[1], Erkan Sadioğlu[1], Rahmi Onur[2]

ABSTRACT

Neurogenic detrusor overactivity (NDO) is a disorder that can cause high intravesical pressure, decreased capacity, decreased bladder compliance, and upper urinary system damage. The current treatment options for NDO are established on the basis of agents that block parasympathetic innervation of the detrusor and inhibit involuntary bladder contractions. Several side effects, such as dryness of mouth, constipation, dyspepsia, changes in visual accommodation, somnolence, and being unable to obtain consistently favorable results, caused by anticholinergic agents, which are frequently used for this purpose, decrease the patient's compliance to treatment. Procedures such as neuromodulation, auto-augmentation, and enterocystoplasty are surgical options, and they could be used as the last alternative. Thus, botulinum toxin (BTX) injections to the detrusor have been commonly performed in recent years and lead to satisfactory results. The mechanism of action of BTX in NDO is based on the principal of smooth muscle relaxation in the bladder by the transient inhibition of neuromuscular nerve signals. The aim is to decrease acetylcholine secretion by blocking presynaptic vesicles in the neuromuscular junction. When studies were evaluated, it was observed that BTX injections to the detrusor muscle are a necessary and effective option in patients with incontinence caused by NDO. This treatment option could be indicated in situations where anticholinergic agents are not effective or could not be tolerated, and it could be a valuable alternative to major surgical treatments. In this review, we evaluated the effectiveness and reliability of BTX in patients with NDO.

Keywords: Botulinum toxin; detrusor overactivity; injection; neurogenic.

ÖZ

Nörojenik detrusör aşırı aktivitesi (NDAA); yüksek intravezikal basınca, azalmış mesane kapasitesine, mesanenin kompliyansının düşmesine ve üst üriner sistem hasarına sebep olabilecek bir bozukluktur. Güncel tedavi seçenekleri ağırlıklı olarak detrusörun parasempatik innervasyonunda blokaj yapan ve istemsiz mesane kasılmalarını inhibe eden ajanlar üzerine kurulmuştur. Bu amaçla en sık kullanılan antikolinerjiklerle; ağız kuruluğu, konstipasyon, dispepsi, görsel akomodasyonda değişiklikler, somnolans gibi yan etkilerin meydana gelmesi, ayrıca etkinlik konusunda her zaman istenilen sonuçların elde edilememesi hastanın tedaviye uyumunu azaltmaktadır. Bu hastalara uygulanan otoaugmentasyon ve enterosistoplasti gibi girişimler oldukça invaziv cerrahi seçeneklerdir ve son alternatif olarak tercih edilmektedir. Bu nedenle son yıllarda detrusöre botulinum toksin (BTX) enjeksiyonları tedavi seçenekleri arasında sıklıkla yer bulmakta ve tatmin edici sonuçlar elde edilmektedir. BTX'un detrusör aşırı aktivitesinde etki mekanizması; nöromusküler sinir sinyallerini geçici olarak inhibe ederek mesanedeki düz kasların gevşemesi esasına dayanmaktadır. Nöromusküler bileşkede, presinaptik veziküller bloke edilerek asetilkolin salınımının azaltılması hedeflenmektedir. Bu konuda yapılmış çalışmalar irdelendiğinde, NDAA'ne bağlı inkontinansı olan hastalarda detrusör kasına BTX Tip A enjeksiyonunun etkin ve güvenilir bir seçenek olduğu görülmektedir. Bu tedavi alternatifinin, antikolinerjik ajanların etkili olmadığı veya tolere edilemediği durumlarda endike olabileceği ve diğer cerrahi yaklaşımlara göre değerli bir opsiyon olduğu söylenebilir. Bu derlemede mevcut literatür verileri ışığında; NDAA olan hastalarda BTX'nin etkinliğini ve güvenilirliğini ortaya koymayı amaçladık.

Anahtar kelimeler: Botulinum toksin; detrusör aşırı aktivitesi; enjeksiyon; nörojenik.

[1]Department of Urology, Gaziantep University, Gaziantep, Turkey

[2]Department of Urology, Marmara University, Istanbul, Turkey

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Correspondence: Ömer Bayrak
E-mail: dromerbayrak@yahoo.com

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Introduction

Neurogenic detrusor overactivity (NDO) is a disorder that can cause high intravesical pressure, decreased capacity, decreased bladder compliance, and upper urinary system damage. Current treatment options are established on the basis of agents that block parasympathetic innervation of the detrusor and inhibit involuntary bladder contractions.[1,2] Several side effects, such as dryness of mouth, constipation, dyspepsia, changes in visual accommodation,

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somnolence, and being unable to obtain consistently favorable results, caused by anticholinergic agents, which are frequently used for this purpose, decrease the patient's compliance to treatment.[3-6] Procedures such as neuromodulation, auto-augmentation, and enterocystoplasty are surgical options, and they could be used as the last alternative. Thus, botulinum toxin (BTX) injections to the detrusor have been commonly performed in recent years and lead to satisfactory results.

History of botulinum toxin use in the therapeutic era

Although it has been estimated for ages that BTX affects human life, it was first reported in the 18th century that some cases of intoxication developed due to BTX and that they were mainly due to sausage consumption. Toward the end of the 1800s, the clinical symptoms of the disease were defined, and case series were published. During this period, serial intoxication and death occurred in Belgium, and *Clostridium botulinum* bacteria were detected for the first time in autopsies.[7] It was reported that the pure form of BTX type A was first isolated as a stable acidic solution by Dr. Sommer at the University of California in 1920.[8] In 1946, Schantz et al.[9,10] isolated the crystallized form of pure BTX type A. Toward the mid-1900s, Dr. Brooks found that when BTX type A was injected in the hyperactive muscle, it blocks acetylcholine secretion from the presynaptic end of the motor nerve, and thus, it could induce paralysis.[8,11] Following these developments, it was thought that BTX could also be used in the treatment of some diseases, and studies on this topic have gained importance. In 1973, Dr. Scott published a study related to the effects of BTX on the lateral rectus muscle in monkeys, and in 1981, he reported the first use of BTX in humans by treating patients with strabismus.[12,13]

Following the approval of BTX type A (Botox®) use in the treatment of eye diseases by the Food and Drug Administration of the United States in 1989, the first clinical administration of BTX was used in patients with strabismus, benign essential blepharospasms, and hemifacial spasms. Over the following years, this toxin came to be used for a wide range of indications, including urological pathologies.[14] The injection of the toxin to the detrusor sphincter in patients with spinal cord trauma and detrusor sphincter dyssynergia (DSD) was first defined in 1988 by Dykstra.[15] The use of BTX type A in the same patient population by Schurch et al.[16] accelerated studies on this topic and led to further development.

Therapeutic types of botulinum toxin

Botulinum toxin is a neurotoxin that is secreted by a gram positive, anaerobic, Azotobacter *C. botulinum*. Seven immunological subtypes, including A, B, C, D, E, F, and G, have been defined.[17,18] The most common subtypes widely used at the present time are BTX types A and B.[19,20] In many previous comparative studies, it has been demonstrated that type A is less potent than type B and that it has a longer duration of action potential.[21,22]

The commercial forms that are used in clinical practice are BTX type A containing Botox® (Allergan, USA-onabotulinumtoxin A), Dysport® (High Value Biotech, France-abobotulinumtoxinA), and Xeomin® (Merz Pharmaceuticals, Frankfurt, Germany-IncobotulinumtoxinA) and BTX type B containing Myobloc® and Neurobloc®. The dose equivalence of Botox® and Dysport®, which are the available preparates in Turkey, is approximately 1 to 3.

Mechanism of action and indications

The mechanism of action of BTX in detrusor overactivity is based on the principal of smooth muscle relaxation in the bladder by the transient inhibition of the neuromuscular nerve signals. The aim is to decrease acetylcholine secretion by blocking presynaptic vesicles in neuromuscular junction. Recent studies have demonstrated that in this way, neurotransmitters, such as neuropeptide and substance p, decrease and downregulation develops in capsaicin TPRV1 receptors, which plays a role in afferent desensitization in purinergic P2X3 receptors and in urothelial and suburothelial nerve endings.[23]

The inhibition, which develops in motor neurons following the injection of the toxin to the bladder, decreases acetylcholine secretion and inhibits involuntary contractions. The decrease in phasic contractions, increase in cystometric capacity, and improvement in continence depends on this motor neuron inhibition. A significant decrease in the feeling and degree of urinary urgency and a decrease in nerve growth factor levels develop thorough its effect on sensorial neurons.[24] It is stated that the frequency of urge incontinence, nocturia, and pollakiuria decreases following injection.[25,26] It was determined that in this way, the number of daily used pads decreases or complete dryness is ensured, and thus, the quality of life also increases.[27]

The area of BTX type A use in urology could be summarized as detrusor overactivity, DSD, spastic conditions of the urethral rhabdosphincter, chronic prostatic pain, interstitial cystitis, non-fibrotic bladder outlet obstruction, and motor and sensorial urgency (Table 1). Injections are contraindicated in cases of sensitivity to any of the substances in the toxin preparate and in the presence of infection. Pregnancy, motor neuropathies, disorders affecting neuromuscular junction, and the use of drugs such as aminoglycosides or drugs affecting neuromuscular conduction constitute relative contraindications.[28,29]

Surgical technique

The procedure can be performed under local, spinal, or general anesthesia. Prior to injection, local anesthesia is performed with 30 mg of intravesical 2% lidocaine, and 15–20 min later, a rigid

Table 1. The indications of botulinum toxin usage in urology
Detrusor overactivity
Detrusor external sphincter dyssynergia
Spastic conditions of urethral rhabdosphincter
Chronic prostatic pain
Pelvic floor spasticity
Interstitial cystitis
Non-fibrotic bladder outlet obstructions
Motor and sensorial urge, urinary retention

or flexible cystoscope is introduced into the urinary bladder. The toxin diluted in 10–30 mL of serum physiologic solution or 5% human albumin is injected to the base or walls of the bladder in 10–40 different regions (Figure 1).[27,30] Injection to the dome of the bladder is not recommended to avoid perforation and intestinal infections. The data indicating that BTX type A affects the sensorial nerves has generated the idea of toxin injection to the trigone and suburethral region; no vesico-urethral reflux was observed after trigonal injections.[30-35]

There is no consensus on a standard protocol related to BTX treatment. The maximum dose used in humans is accepted as 400 U for Botox® and 2000 U for Dysport®. There are several studies in which 100–300 U of Botox® and 500 U of Dysport® were injected to 10–40 different regions of the bladder wall. Although the injections of more toxins to more regions produces better and prolonged results, this situation increases the risk of voiding dysfunction, increased post voiding residue (PVR), and urinary retention, requiring clean intermittent catheterization following treatment.[31-35] Another important point is that there is the possibility of developing tolerance to BTX due to neutralizing agents. As the development of tolerance is rapid in patients who have high initial and repeating doses, the initial doses of BTX should be at the lowest possible dose. The efficacy continues for a certain period, and new injections are frequently required approximately 6 to 9 months after the first injection.[31-35]

Urinary tract infection (3.6–44%) is a common side effect, which is encountered as a result of the procedure. In some cases, PVR levels may reach up to 100–150 cc (0–75%) and the requirement of urine excretion by clean intermittent catheterization (0–43%).[36]

Clinical results of botulinum toxin use in NDO

The effects of BTX type A injections to the detrusor muscle in patients with spinal cord damage was first demonstrated by Schurch et al.[37] in a non-randomized retrospective study. In this study, patients with NDO who had incontinence resistant to anticholinergic agents were evaluated in 2000. The patients whose bladder compliance was low due to organic changes or fibrosis in the detrusor muscle were excluded. Two hundred to four hundred units of BTX type A were injected to the detrusor muscle by preserving the trigone. All 19 patients were followed-up with clinical evaluations and urodynamic procedures for 9 months. It was observed that the reflex volume increased by 54% from 207 mL to 320 mL and that the maximum cystometric capacity of the bladder increased by 60% from 286 mL to 458 mL at the 36th week following injection, which was statistically significantly (p=0.007 and p=0.003, respectively). Furthermore, a mean decrease from 62 cmH_2O to 36 cmH_2O was detected in the maximum detrusor pressure (41.9%).

Giannantoni et al.[38] compared BTX type A injection with intravesical vanilloid administration in the treatment of NDO in patients with spinal cord damage. They administered intravesical resiniferatoxin (RTX) to 35 patients and BTX type A to 40 patients. The patients were evaluated with clinical and urodynamic examinations at the beginning and at the 6th, 12th, and 24th months following treatment. A significant improvement in continence and a decrease in intermittent catheterization requirements were observed at the 6th month, and this improvement continued till the 24th month. Additionally, it was noted that although at lower doses, the anticholinergic requirements continued in 20 patients. The current study revealed that BTX type A decreased the detrusor contraction pressure to a greater extent than RTX.

Ginsberg et al.[39] published a study including a total of 416 patients, 227 with multiple sclerosis (MS) and 189 with spinal cord injuries. BTX type A injection at a dose of 200 U and 300 U were administered to 135 and 132 patients, respectively, and 149 patients were included in the placebo group. They reported that improvement in the bladder capacity and maximum detrusor pressure during the first involuntary detrusor contractions following injections were better in the placebo group (p=0.001). Retreatment was required after 256 days, 254 days, and 92 days in patients receiving BTX injections of 200 U and 300 U and the placebo, respectively. Furthermore, 10% of the placebo group, 35% of the 200 U injection group, and 42% of the 300 U injection group required clean intermittent catheterization due to urinary retention. In another study conducted by Cruz et al.[40], intravesical BTX injections of 200 U and 300 U were administered to 92 and 91 patients, respectively, and 92 patients were included in the placebo group. One hundred fifty-four patients had MS and 121 had spinal cord injuries. The mean number of incontinence episodes in a week was calculated as 33.5 at the beginning. A decrease in the mean number of incontinence episodes to 21.8 and 19.4 were detected at the 6th week in the 200 U and 300 U BTX injection groups, respectively. This value was

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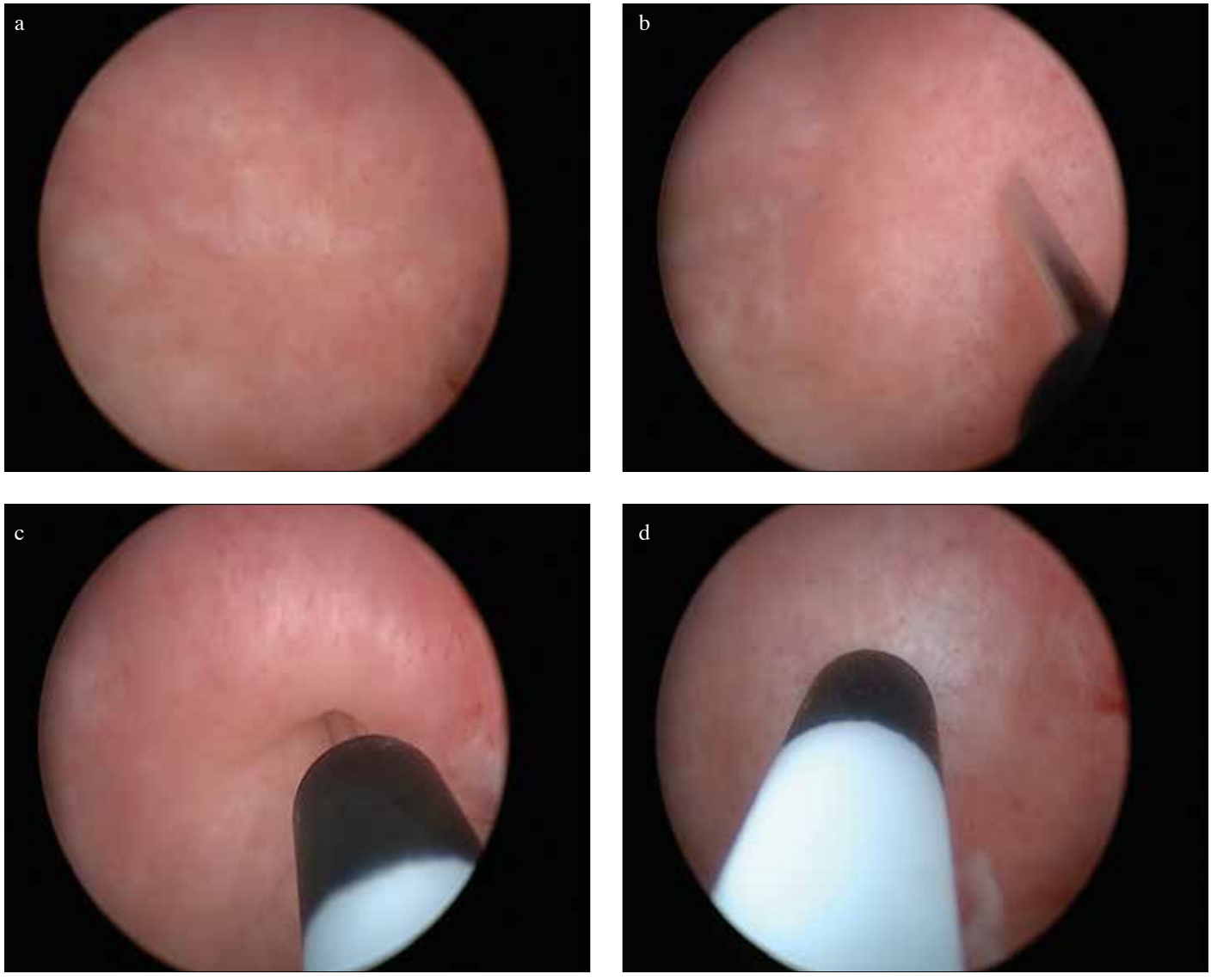

Figure 1. a-d. The endoscopic images of the patient who underwent botulinum toxin injection for the treatment of neurogenic detrusor overactivity

reported to be 13.2 in the placebo group. Moreover, while there was an increase of 157 cc in cystometric capacity in the BTX injection groups, this increase was calculated to be 6.5 cc in the placebo group. There was also a significant improvement in the maximum detrusor pressure. While decreases of 28.5 and 26.9 cmH_2O were observed in the detrusor pressures of patients in whom 200 and 300 U BTX injections were administered, respectively, there was a decrease of 6.4 cmH_2O in the placebo group. The mean treatment requirement was calculated to be 42 weeks in the treatment groups and 16 weeks in the placebo group.

Another study was performed by Schulte-Baukloh et al.[41], and the effectiveness of BTX type A was tested in children with NDO due to myelomeningocele. Pediatric patients aged between 1 and 16 years had intravesical pressures above 40 cmH_2O. Patients resistant to anticholinergic treatment and in whom intermittent clean catheterization was performed were included in the study. Eighty-five to three hundred units of BTX type A were injected into the detrusor, and urodynamic examinations were performed 2 to 4 weeks after the injection. It was found that the mean reflex volume increased from 95 cc to 201 cc (an increase of 121%), the mean maximum bladder capacity increased from 137 cc to 215 cc (an increase of 56%), and the mean detrusor compliance increased from 20.4 mL/cmH_2O to 45.4 mL/cmH_2O. All results were significant, and it was observed that after a follow-up period of at least 4 weeks, compliance was achieved. In a multicenter study that was conducted by Reitz et al.[42], a total of 200 patients (11 patients with MS, 22

Table 2. Studies about botulinum toxin injection in neurogenic detrusor overactivity

	Dosage of BTX	Number of patients	Evaluation criterias	Results
Schurch[37]	200-400 U	19	*Reflex volume *MCC *MDP	At the 36th week; *Increase in reflex volume from 207 mL to 320 mL (54%), *Increase of MCC from 286 mL to 458 mL (60%), *Decrease in mean MDP from 62 cmH_2O to 36 cmH_2O (42%), were demonstrated.
Schulte-Baukloh[41]	85-300 U	17	*Mean reflex volume *Mean detrusor compliance *Mean MCC	*Increase in mean reflex volume from 95 cc to 201 cc (121%), *Increase of mean MCC from 137 cc to 215 cc (56%), *Increase of mean detrusor compliance from 20.4 mL/cmH_2O to 45.4 mL/cmH_2O, were stated.
Reitz[42]	300 U	200	*Mean MCC *Mean reflex volume *Continence situation	*Increase in mean MCC from 272 to 420 ($p<0.0001$) and in mean reflex volume from 236 cc to 387 cc ($p<0.0001$), *Complete continence in 73% of the patients, were reported.
Giannantoni[38]	300 U	75	*Continence situation *Requirement for catheterization *Mean MDP	*A significant improvement in continence and decrease in the requirement of intermittent catheterization within 6 months, *A more effective decrease in detrusor contraction pressure by BTX when compared with RTX was demonstrated.
Klaphajone[45]	300 U	10	*Mean bladder compliance *Mean MCC *Situation of continence	*Increase in mean bladder compliance from 6.5 mL/cmH_2O to 13.2 mL/cmH_2O, *Complete continence in 7 patients, *Increase in mean MCC ($p=0.08$), was observed.
Kalsi[44]	300 U	43	*Continence situation *Mean MCC *MDP	*Decrease in the frequency of incontinence in 80% of the patients ($p<0.0001$), *Increase in MCC and decrease in maximum detrusor pressure, were found.
Deffontaines				
Rufin[43]	300 U	71	*Mean MCC *Mean MDP *Continence situation	*Complete continence was reported in 46% of the patients. *Mean MCC increased from 240 cc to 328 cc ($p<0.001$). *Mean MDP decreased from 61 cmH_2O to 36 cmH_2O.
Cruz[40]	200-300 U	275	*Mean number of UI in a week *MDP *MCC	*While the mean number of UI in a week was 33.5 at the beginning, it decreased to 21.8 and 19.4 in the 200 U and 300 U Botox injection groups, respectively, and it decreased to 13.2 in the placebo groups at the sixth week. *An increase was observed in MCC of approximately 157 cc in Botox injection groups and 6.5 cc in the placebo group. *A decrease in MDP from 28.5 cmH_2O to 26.9 cmH_2O in 200 U and 300 U Botox groups and a decrease of 6.4 cmH_2O in the placebo group.
Ginsberg[39]	200/300 U	416	*MCC *MDP at the time of first involuntary bladder contraction *Requirement for retreatment	*The improvement in MCC and MDP during the first involuntary detrusor contraction following treatment was better than that in the placebo group ($p=0.001$). *Retreatment was required at 256, 254 and 90 days following treatment in the 200 U and 300 U BTX injection groups and placebo group, respectively.

U: unit; BTX: botulinum toxin; UI: urinary incontinence; MDP: maximum detrusor pressure; MCC: maximum cystometric capacity; RTX: resiniferatoxin

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with meningomyelocele, and 167 with spinal cord trauma) had symptoms of incontinence and received clean intermittent catheterization and were included in the study. The patients received an injection of BTX type A at a dose of 300 U, and it was demonstrated that complete continence was achieved between catheterization periods in 73% of the patients. Furthermore, it was observed that the mean maximum bladder capacity increased from 272 cc to 420 cc ($p<0.0001$) and that the mean reflex volume increased from 236 cc to 387 cc ($p<0.0001$).

In a series of 71 patients with MS, Deffontaines et al.[43] administered 300 U of BTX type A injection, and they reported that urinary incontinence disappeared and that no NDO was observed in urodynamic examinations in 46% of the patients; 50% improvement was obtained in 31% of the patients, and no significant change was observed in 23% of the patients. In this series, it was mentioned that the mean maximum bladder capacity increased from 240 cc to 328 cc ($p<0.001$) and that the mean maximum detrusor pressure decreased from 61 cmH_2O to 36 cmH_2O. Furthermore, they found that the duration of MS was an important factor affecting the success of treatment ($p=0.015$).

In another study that was conducted by Kalsi et al.[44], they included 43 patients with MS in which 300 U of BTX type A injection was administered, and they detected a significant decrease in the frequency of incontinence in 80% of the patients ($p<0.0001$). Furthermore, the increase in the maximum cystometric capacity and the decrease in the maximum detrusor pressure were also significant. Klaphajone et al.[45] administered a 300 U BTX type A injection to 10 patients with spinal cord injuries and reported a low compliance. They reported that the mean bladder compliance increased from 6.5±5.0 mL/cmH_2O to 13.2±5.2 mL/cmH_2O following the injection. There was complete continence and an increase in the mean bladder capacity in 7 patients ($p=0.08$). The details and results of all these studies are summarized in Table 2.

When the aforementioned studies were evaluated, it was observed that BTX type A injections to the detrusor muscle are a necessary and effective option in patients with incontinence caused by NDO. This treatment option could be indicated in situations where anticholinergic agents are not effective or could not be tolerated, and it could be a valuable alternative to major surgical treatments.[46,47] Its systemic side effects are minimal. However, prior to injection, it should be noted that urinary retention could develop, and it should be emphasized that clean intermittent catheterization and recurrent injections might be necessary.

In the 2014 EAU guideline, it was stated that the best alternative among the minimally invasive treatment options in NDO is BTX type A (recommendation level A). The effectiveness of BTX type A was supported by several randomized, placebo-controlled studies, and there was no loss in effectiveness with repeated injections.[47]

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