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REVIEW

The use of botulinum toxin in the treatment of neurogenic bladder following spinal cord injury

Sivetidou S[1], Evangelopoulos ME[2]

[1]*MD: Consultant, Department of Physical Therapy & Rehabilitation, KAT Hospital, Athens, Greece*

[2] *MD, PhD: Ass. Professor, Department of Neurology, Eginition University Hospital, Athens, Greece*

ABSTRACT

Spinal cord injury patients suffer from neurogenic lower urinary tract dysfunction, associated with symptoms of urinary incontinence (UI), urgency and frequency, which may affect upper urinary tract function and has a negative impact on health-related quality of life.

Botulinum toxin is a neurotoxin derived from the bacterium Clostridium botulinum. Dykstra et al, in 1988, first injected 100 BoNT-A units into the external urethral sphincter to treat patients with spinal cord injury.

The aim of this study is to search in the literature about the effectiveness, safety and side effects of botulinum toxinin treatment of neurogenic bladder (NB) due tospinal cord injuries (SCI)

Botulinum toxin is an effective and safe option for the management of neurogenic bladder in patients who have an inadequate response to, or are intolerant of, oral medication. In SCI patients with neurogenic detrusor overactivity (NDO), botulinum toxin injection significantly decreased UI and detrusor pressure, thus increasing bladder capacity and quality of life.

KEY WORDS: botulinum toxin, neurogenic bladder, overactive detrusor, spinal cord injury

Introduction

Spinal cord injury (SCI) is a major cause of morbidity and mortality in young people, in developing countries, with 25 new cases per million. Normal bladder emptying is a voluntary action, although it is predominantly under parasympathetic control, with somatic nerves playing a lesser part. During bladder' filling phase, the urothelium release acetyl choline (Ach), nitric acid, adenosine triphosphate (ATP) and nerve growth factor (NGF) modifying the excitability of bladder afferent fibres. These afferents including small myelinated Ad and unmyelinated C nerve fibers, respond to increases in tension of the bladder wall and trigger the spinobulbospinal micturition reflex, leading to the release of Ach in efferent nerves in the detrusor muscle. This produce muscle contraction and micturition (1). In patients with traumatic subcervical spinal cord injury (SCI),

CORRESPONDING AUTHOR, GUARANTOR

Sivetidou Sofia, MD:
Consultant, Department of Physical Therapy & Rehabilitation, KAT Hospital, Athens, Greece. Email: atz.sivet@yahoo.gr

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interference with spinal pathways above lumbosacral levels releases sacral reflex activity from higher level inhibitory inputs, resulting in a variety of lower urinary tract symptoms (LUTS), generally referred to as overactive bladder. LUTS occur in most patients with SCI (1).

In traumatic SCI, during the spinal shock, there is loss of bladder control and the bladder becomes atonic. After a period of 6–8week, neuronal reorganization occurs, with the onset of spinal mediated reflex voiding and neurogenic detrusor overactivity (NDO), with or without detrusor-sphincter dyssynergia (DSD) (loss of coordination between bladder contraction and relaxation of the internal urethral sphincter during emptying phase). These changes lead to involuntary contractions of the detrusor during filling phase, interfering with the urine outflow. The symptoms of overactive bladder that are attributable to neurogenic detrusor overactivity, include urinary urgency, occurring with or without urge incontinence (UI), increase in the frequency of urination, low urine volume and nocturia (2).

This can lead to incomplete emptying of the bladder, high intravesical pressure, thus increasing the risk of infection and damage to the upper urinary tract (3). Available urodynamic tests (cysteometry, uroflowmetry, etc.) lead to diagnosis and monitor the progression of the disease over time.

Effective control of neurogenic detrusor overactivity (ND0) during SCI is a major challenge. Active treatment of these urinary conditions is essential to reduce morbidity and mortality, and to maintain health-related quality of life (HRQoL).

The primary goal of bladder management is to maintain renal function by achieving safe pressures in bladder, low rates of urinary tract infection and socially acceptable restraint (4). The loss of voluntary urination control is one of the most serious side effects of NDO and is a major cause of social isolation, as patients prefer to quit the rehabilitation process. Therefore, the management of neurogenic bladder is a priority in the rehabilitation process (5). Treatment strategies for NDO are to prevent urinary reflux and kidney damage resulting from high intravesical pressures and incontinence. The first choice treatment is anticholinergics and / or α-adrenergic antagonists, in combination with intermittent catheterization or supraventricular catheter. Anticholinergics reduce detrusor's pressure; improve bladder's capacity, improving quality of life. This therapy causes side effects in 61% of patients and effectiveness decreases over time, while increasing the dose often increases the side effects.

Botulinum toxin (BoNT) is a second choice treatment of NDO when anticholinergic drugs reduce their effectiveness (5) In 2011, BoNT-A was approved for patients with NDO after SCI by the US Food and Drug Administration (FDA) and by the European Medicines Agency (EMA) as botulinum toxin-A (BoNT-A).

Botulinum toxin is a neurotoxin derived from the bacterium Clostridium botulinum. Dykstra et al. in 1988, were the first to inject 100 BoNT-A units into the external urethral sphincter to treat patients with spinal cord injury.They concluded that urethral and bladder pressure decreased simultaneously.

There are seven immunologically distinct serotypes from type A to type G which have been isolated but only the A and B serotypes are commercially available. The most commonly used serotype within the lower urinary tract is BoNT-A (6).

Mechanism of action

BoNT-A appears to have a dual mechanism of action on both the motor and sensory pathways responsible for NDO, blocking the release of acetylcholine in neuromuscular junction. This inhibits parasympathetic signaling to the bladder, reducing involuntary detrusor contractions, reducing the ability of the detrusor muscle to contract. This reduction in contractions reduces NDO symptoms (6). The inhibition is temporary, but generally it lasts for 6 to 9 months. Muscle contraction will return after the effect of medication, as neurons regain the ability to release neurotransmitters. After the injection with the BoNT-A, the average number of daily incontinence episodes decreased steadily, the urinary urine volume almost doubled after each treatment and total I-QOL scores were increased following botulinum toxin-A 200U injection, as demonstrated in two randomized, multicenter, multinational Phase III studies (7). Both motor and sensory effects

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are reversible, but regeneration of sensory receptors appears to take longer and it is the sensory effects which determine the duration of action of BoNT-A (6). The suggested doses are 200U to 300U, since no improvement was observed with higher doses.

The effectiveness of BoNT-A is monitored by results of the urodynamic parameters (compliance of the detrusor, bladder capacity, maximum detrusor pressure) and from the opinion of the patients for their well-being. The effectiveness of a BoNT-A injection lasts, on average, 9 months, although patients experience beneficial effects for up to 12 months or more during the first 4 years of cyclic therapy. Overtime, the effectiveness of BoNT-A decreases until complete loss of its therapeutic effects. On average, 12-14 years after the first injection, 60% of patients still experience beneficial effects, while 40% of them have stopped treatment (5).

Side effects and contraindications

The most commonly observed side effects after toxin injections are urinary tract infections (UTI), the increased urinary retention andrarely - general muscle strength that can last 1-2 months.Side effects are temporaryand can be treated with antibiotics and clean intermittent catheterization (CIC). BoNT A injection into the detrusor is contraindicated for use in patients with UTI or bladder plaster. It is also contraindicated for patients who do not use CIC, if they have urinary retention at the time of injection and for those who are unable or unwilling to start CIC if required after treatment.

The *safety and efficacy* of BoNT A have not been established inpatients with NDO and incontinence who are aged 18 years and the drug is not recommended for use in this age group.

Antibody Formation NAbs

Botulinum neurotoxins have the potential to elicit immune responses in humans, including the development of neutralizing antibodies (NAbs).The risk of developing NAbs is low. If and when it occurs, it can reduce the effectiveness of treatment. Because Nab formation may be more likely with frequent injections and at higher doses, the use of BoNT-A at the lowest effective dose and for the longest clinically indicated period is recommended (1).

This treatment is minimally invasive and causes a significant reduction in morbidity as well as the costs associated with essential drugs (7).

In SCI patients, a serious and threatening condition is autonomic dysreflexia. In a SCI animal model, BoNT-A intravesical injection significantly decreases NGF levels in the bladder and in the dorsal root ganglion of the T4 root. Several studies report that BoNT-A block autonomic dysreflexia, suggesting that NGF interferes with the etiology of autonomic dysreflexia and that BoNT-A therapy, might control this condition (1).

The aim of this study was to assess effectiveness, safety and side effects of botulinum toxinin treatment of neurogenic bladder (NB) due to spinal cord injuries (SCI). A literature search was performed on published articles mainly in PubMed database, using the following key words: botulinum toxin, neurogenic bladder, overactive detrusor, spinal cord injury. A total of 264 articles were initially identified for use in this study, 258 in PubMed and 6 from other sources. Of these, 35 were excluded as duplicates. Of the remaining 229 articles, 81 were excluded by reading titles and abstracts. Of the 148 remaining full- text articles 124 articles were excluded due to antiquity (<2005). Eventually, 24 full -text articles were included in this study.

Discussion

The first-line pharmacotherapeutic treatment for neurogenic bladder, are muscarinic receptor antagonists. However, patients may have a suboptimal response or find that antimuscarinic therapy is limited by associated AEs, therefore, there is a need for a new treatment that is effective, well-tolerated, with a distinct mechanism of action. The BoNT-A injection into the detrusor muscle has been demonstrated in neurogenic bladder. Also BoNT-A may be a useful treatment to augment existing NDO treatments or other invasive surgical options.

The last two decades, treatment of lower urinary tract conditions using BoNT-A has rapidly expanded. In the literature, there has been a large number of studies investigating the effective and safe use of the BoNT as well as the most effective dose with the

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fewest side effects. So far, BoNT-A is a well-established therapy in the management of neurogenic detrusor overactivity (NDO) and is recommended by the majority of international bodies and guidelines as a second-line treatment for NDO in patients who have symptoms refractory to antimuscarinics or β3 adrenoceptor agonists (6). Cruz et al (8) compared BoNT-A with placebo in terms of efficacy and safety in patients with NDO secondary to SCI, in two double-blind, placebo-controlled, randomized DIGNITY trials. Patients with NDO who experienced UI episodes and were not sufficiently managed with anticholinergic agent were randomized to receive either BoNT-A 200U, 300U or placebo. Patients had to be using clean intermittent catheterization (CIC) or be able and willing to do so. At week 6, in both studies, BoNT-A 200U significantly reduced UI episodes / week and improved MCC and Pdetmax IDC compared with placebo (P<0.001). Also patients without an involuntary detrusor contraction were notably more in the BoNT-A group compared with placebo, indicating that BoNT-A decreases a major risk factor (duration of the involuntary detrusorcontraction) for upper urinary tract impairment. Duration of positive effect for BoNT-A group was 38.4 weeks, with meaningful changes in I-QOL scores. In this study the most common reported adverse events were urinary tract infection (UTI) and urinary retention, while in one third of BoNT-A patients, CIC was initiated due to urinary retention compared with almost none in placebo. Authors mention that the use of BoNT-A in patients with high cervical lesions above T1 should be careful, due to the risk of developing muscular weakness in the respiratory muscles. The positive effects after BoNT-A treatment were independent of anticholinergic use. However, more studies are required to investigate additional benefit from combination therapy. After repeated injections of BoNT-A 200U the UI episodes per week were consistently reduced over five cycles of treatment and also there were statistically significant improvements from baseline in all I-QOL.

X.-T. G et al. (4) evaluated the effects of Botulinum Toxin A injection into the detrusor muscle, measuring voiding parameters in SCI patients with detrusor overactivity and urinary incontinence who were refractory to oral medications. They concluded that the use of botulinum toxin in the treatment of neurogenic detrusor overactivity in patients with SCI is safe, valuable and promising option especially to those who resisted to anticholinergic medications. They noted that BoNT-A 300 IU into the detrusor, showed significant effects on the episodes of incontinence per day, maximal voiding volume, and urodynamic parameters (cystometric capacity and maximal detrusor pressure). They noted remarkable reduction in incontinence episodes of approximately 50% from base line at 6 and 24 weeks after treatment. There was no increase in AE rates over repeated treatments, suggesting that BoNT-treated patients were completely dry after 24 weeks post-injection. The urodynamic study showed signifying decrease of maximum detrusor pressure, increase of the mean cystometric bladder capacity after injection at 2 and 24 weeks (P<0.05). Quality of life and patient' satisfaction were remarkably improved due to decrease of leakage, and number of incontinence.

Kennelly et al. (7), in a long-term extension study investigating the efficacy and safety of BoNT-A, demonstrated that treatment with BoNT-A 200U is effective and well tolerated through 4 years. They also confirmed that there are non-clinically relevant differences in the treatment response between BoNT-A 200 and 300U dose groups. Repeated treatment with BoNT-A led to excessive reduction in the number of daily UI episodes. After 4 years of observation, they noted >50% decrease in UI episodes, while 43–56% of patients achieved complete continence, markedly higher than in other treatments for NDO. Following each treatment with BoNT-A, it was noted consistent increase of volume/void. In addition, the remarkable improvements in urinary symptoms, after BoNT-A treatment, kept up with meaningful improvements in QOL, suggesting that BoNT-A could maximize treatment success. The therapeutic effect of BoNT-A across all patients was 9 months. In this study the reported AEs were UTIs, while the rate of treated UTIs was rather reduced. Observation of long-term treatment with BoNT-A noted that there was no increase in AEs rates, suggesting that BoNT-A did not have a cumulative action or toxic duration. After the first BoNT-A treat-

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ment, the incidence of CIC was greatly reduced during following treatments. These results suggested that if patients did not initiate CIC during their first BoNT-A treatment, they would rather not need to initiate CIC at all. In this extension study the rate of antibody formation was low in patients, and half of the antibody positive patients continued to experience clinical benefit. The authors concluded that there was clinically serious improvement in urinary symptoms and QOL following BoNT-A treatment in patients with UI, due to NDO, who are inadequately managed by >1 anticholinergic medication ,during the 4-year study, with no new safety signals.

Zhang et.al (9), in a review study with eight selected studies (n=1879 participants), noted that the use of BoNT-A was related to urinary tract infection (UTI) in both BoNT-A 200U and 300U groups, significantly higher than the placebo. There was significant reduction of the frequency of urinary incontinence episodes in BoNT-A group compared to placebo. Authors noticed that the maximum cystometric capacity (MCC) was incised and maximum detrusor pressure (MDP) was decreased than the placebo, with no statistical differences between BoNT-A 200U and 300U doses in UTI, MCC and MDP. Evaluation of the impact of BoNT-A 200U and 300U on QOL showed significant improvement in the mean change from baseline, which was superior to the effect of placebo ($p<0.001$), at weeks 6 and 12. They concluded that BoNT-A provided clinical and urodynamic benefit for populations with NDO but did not find clear dose differences (200 VS 300 U).

Sheng-Mou Hsiao et al (39) concluded that the therapeutic effects of BoNT-A can last till 6 months after treatment, while female gender, low overactive bladder symptoms score (OABSS) and the presence of OAB-wet were associated with better therapeutic efficacy.

Sheng-Fu Chen et al (11), in a small study, attempted to investigate the therapeutic effects on urothelial dysfunction after repeated detrusor injections of BoNT-A in SCI patients with neurogenic detrusor overactivity (NDO). The patients received 300 U BoNT-A injection into the detrusor every six months. The urothelium was assessed by cystoscopic biopsy. The authors determined the adhesive and tight junction protein levels, at baseline and six months after each BoNT-A treatment. After repeated BoNT-A injections a significant increase in cystometric bladder capacity (CBC) and post-void residual (PVR) volume, and a significant decrease in detrusor pressure at Qmax (Pdet.Qmax) were shown. They noticed that the urothelial barrier function recovered by improving adhesive and tight junction protein levels, providing evidence that repeated BoNT-A injections can have a sustained therapeutic effect on NDO in SCI patients.

Jean-Jacques Wyndaele (2) mentioned that treatment with BoNT-A seems to be safe and effective, with positive effects on many urodynamic and clinical parameters, lasting for 6 to 16 months. However, no additional benefit results from the combination of BoNT-A with antimuscarinics was noted, while the repeated injections of BoNT-A seemed to produce similar effects to those of the previous injection. The most important adverse events mentioned were the increased PVR in patients who could void a higher incidence of UTI and rarely a loss of general muscular power that could last for 1–2 months.

Soler et.al (12) conducted a study to determine outcome predictors for urethral injection of 100 U BoNT-A to treat detrusor sphincter dyssynergia (DSD) in patients with spinal cord injury. They concluded that strong predictors of excellent outcome were the detrusor contractions and normal bladder neck activity.

Moore et al. (13) evaluated the change in UI episodes per week, and secondary outcomes included urodynamics (UDS) findings and Incontinence Quality of Life (I-QOL) score in patients with NDO who received BoNT-A 200 U, 300 U, or placebo. It was recorded statistically significant decrease in UI episodes per week in the 200 U and 300 U groups, when compared to placebo. In all patients, they noted significant increases in their I-QOL scores compared to placebo. Six weeks after injection, repeat UDS studies were performed. Patients treated with 200 U and 300 U showed increased maximum cystometric capacity (MCC) and maximum detrusor pressure during first IDC, compared to placebo. Authors reported that the most frequent AEs were UTI across all patients, which was defined by

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positive urine culture. In SCI patients, the reported incidence of UTI was similar between BoNT-A and placebo (44.8% and 49.5%, respectively). Evaluation of long-term efficacy of BoNT-A injections for NDO patients demonstrated sustained improvements in UI episodes per week and I-QOL score. The number of new patients initiating CIC decreased dramatically with each treatment; those who did not require CIC after three treatments ever went on CIC. Reported AEs and AE rates were similar. With 200 U dosing, the median duration of treatment effect was nine months.

Detrusor Sphincter Dyssynergia (DSD) can lead to incomplete emptying, thus increasing the risks of UTI and upper urinary tract damage. Authors referred to small studies in which demonstrated the efficacy of 100 U BoNT-A injection into the external sphincter for treatment of DSD. Meta-analysis of these studies in patients with SCI noted a reduction of PVR after treatment with BoNT-A lasting up to six months, as well as a reduction in UTIs and CIC in some series. AEs described in these studies have been minimal.

Cheng et al (14) evaluated the efficacy of different doses of BoNT-A in patients with NDO, performing a meta-analysis with six randomized controlled trials (RCTs) to assess the AEs associated with BoNT-A use. The study compared three groups (BoNT-A 300U, BoNT-A 200U group and the placebo group) with the reported data for the mean changing from baseline of UI episodes per week (at 6 weeks). There were significant decreases in UI episodes in the BoNT-A 200U group (P<0.00001) and the BoNT-A 300U group (P<0.00001). Compared to the placebo group, there was no significant heterogeneity in either BoNT-A group. Interestingly, there were no significant differences between the BoNT-A -treated groups in the number of weekly UI episodes (P=0.95). This result suggested that BoNT-A has significant beneficial effects in UI episodes compared to a placebo. This meta-analysis showed improvements in the urodynamic parameters. Treatment with BoNT-A (200U and 300U) compared to the placebo was significantly superior for increasing the maximum cystometric capacity (MCC) and reducing the maximum detrusor pressure (MDP). However there was no significant difference between the two BoNT-A-treated groups (P=0.56). In this study, all reported Adverse Events **(**AEs) including rate of UTIs, urinary retention, hematuria, and muscle weakness were either transient or easily manageable and dose-related, in patients not using CIC. The results reported the main AEs as UTIs (P<0.00001), urinary retention (P<0.00001), hematuria (P=0.05), and muscle weakness (P=0.004). In conclusion, this meta-analysis demonstrated that a statistically significant improvement in the frequency of incontinence and urodynamic parameters was reported in the BoNT-A 200U and 300U groups versus the placebo. Also in almost all patient QoLs was significantly improved in the BoNT-A -treated groups following treatment, and changes in the urodynamic parameters were accompanied by improvements in patient symptoms.

Duthie JB et al (15) support the efficacy of botulinum toxin in the treatment of OAB. There are limited data about the long-term safety, optimal dose and best injection technique, despite some studies trying to explore these issues with higher doses of botulinum toxin. There were various thresholds for commencing CIC. There is some suggestion from the data that lower doses may offer comparable efficacy with fewer adverse events, albeit for a shorter duration than higher doses. The effect of BoNT-A treatment may last from three to twelve months, while the botulinum toxin type B treatment seems to be limited less than ten weeks.

Yuan et al (16) performed a systematic review with 6 randomized double-blind, placebo-controlled trials, involving 871 patients, to assess the efficacy and safety of BoNT-A treatment in neurogenic detrusor overactivity. The results suggested that BoNT-A significantly reduced the daily frequency of UI and MDP during first involuntary detrusor contraction, and improved MCC in patients with UI due to NDO. Also, the BoNT-A was regularly associated with complications localized primarily to the urinary tract. Higher rates of increased PVR may be found.

Hui-Yun Gu et al (17), in their systematic review and meta-analysis including 11 studies comparing doses of 200U and 300U vs placebo at 2 ,6 12 and

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36 weeks after treatment, concluded that BTX-A 300U and 200U significantly improved symptoms of NDO (UI episodes per week, MCC, and I-QOL), compared with placebo. Jianshu Ni et al (18), in a systematic review and meta-analysis, demonstrated that sustained improvements were noted in patients with NDO after repeat BoNT-A injections. They analyzed eighteen studies, involving 1533 patients with SCI and MS after the first and last injections. Only minor non-significant changes in MCC, MDP, RV, and BC (bladder compliance) were noted. After the first and last injection, in the group that received ≤4 injections, stable improvements in QOL was noted, whereas in the group that received ≥5 injections, a moderate decreased of QOL ($0.5 < SMD < 0.8$) was reported after the last injection. In this study, for patients who received repeat injections of BoNT-A300 U, the improvement in QOL was stable until the fifth injection, while significant decrease in QOL was noted after the last two injections. In the same study, dose of BoNT-A 200 U improves QOL until the ninth injection. These results may be caused by the difference in the treatment dose. No significant change in the intervals between repeat BoNT-A injections was observed. In all studies, sustain improvement in UI was noted by the repeat BoNT-A injections and results were consistent with the outcomes of urodynamic variable. The most frequently reported AEs were urinary tract infection, urinary retention and hematuria. The rate of AEs was stable and low. This analysis confirms the efficacy and safety of three to four injections, suggesting that BTX-A does not have cumulative dose or duration toxicity.

The study of Aaron Kaviani et al (19), through 2 double-blind, placebo-controlled, phase III studies, compared the response to BoNT-A with response to placebo in patients with NDO due to SCI or MS. The results showed that BoNT-A injections effectively decreased UI, improved UDS parameters and increased QOL. So, there is strong evidence that intradetrusor BoNT-A injection, in treatment of refractory NDO in SCI patients, is associated with significantly improved UDS performance and achievement of patients' goal.The mostcommon adverse events reported are urinary tractinfections (UTI), increased postvoid residual and the need for de novo CIC, especially in patients who do not already perform CIC. They also referred that the potential effect on autonomic dysreflexia is a clinically important consideration of the use of BTX-A in SCI patients. Animal and human studies have shown that intradetrusor injections of BTX-A decrease the severity and frequency of bladder-related incidents of autonomicdysreflexia (AD).

Young Sam Cho et al (20), reported a significant improvement of urodynamic parameters including increase of the maximum cystometric capacity (MCC), decrease of the maximum detrusor pressure (MDP) and incontinence episodes after BoNT-A treatment, in SCI patients with NOB. The improvement was noted after the first injection and then remained constant after 4-5 repeated injections at 2 weeks and continued throughout the 6-month period. Moreover, at 6 months, a significant improvement in QoL was observed. In order to minimize the need for clean intermittent catheterization (CIC), due to urinary retention caused by BoNT-A, a 200U dose rather than 300U, was used.This study documented a reduced need for anticholinergic medications after the injection, while a beneficial effect on AD was noted after BoNT-A injection into the bladder wall. After BoNT-A, the most common reported adverse effects (AE) were the UTIs (pyelonephritis, orchitis, prostatitis) and the increase of postvoid residual urine (PVR).

In order to evaluate the efficacy and safety of BTX-A, according to injection site in NOB, Jung Ki Jo et al (21) conducted this meta-analysis.The use of different BoNT/A injection sites to treat OAB leads to different outcomes. Between intradetrusor and suburothelial injection sites, there were no differences in efficacy or safety regarding the incidence of vesicoureteral reflux, hematuria, general weakness, bladder discomfort, large post-void residual and urinary tract infection.Improvement in patient symptoms(higher complete dryness rate and lower frequency of incontinence episodes) was noted in Trigone-including injection. Trigone-including injection also provides patients with higher volume at the first void following treatment, with lower detrusor pressure and without an increase in adverse ef-

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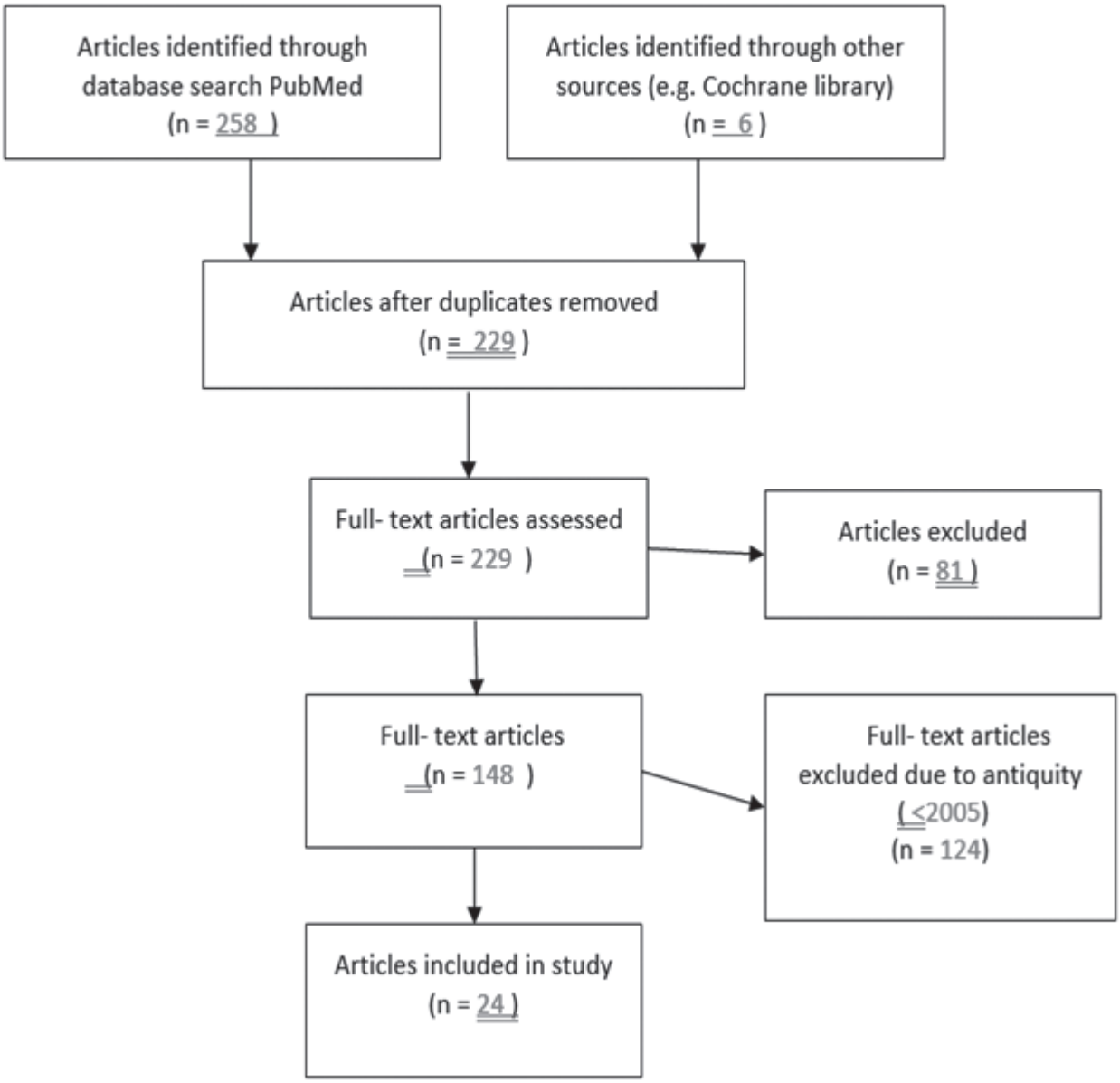
Flowchart of the study selection process



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fects. In contrast, according to depth of injection, no difference in efficacy or safety findings were shown.

David Eldred-Evans et al (6), in their review for the use BTX-A in voiding dysfunction due to detrusor sphincter dyssynergia (DSD), noticed improvements in QMax, maximum urethral closure pressure, frequency of voiding and QoL. Also, the meta-analysis of SCI patients found a mean postvoid residual (PVR) decrease for up to 6 months. Nevertheless, they noted that the current evidence for BoNT-A in DSD is of limited quality due to the small number of participants in level 1 trials and the risk of bias from observational studies. The authors also mentioned that a surgical sphincterotomy may provide greater efficacy and longer duration effect.

Jeremy B. Myers et al (22) in a multicenter, prospective, observational study in SCI patients performing CIC, found that patients who underwent cystoplasty had better scores on quality of life scales and NBSS (Neurogenic Bladder Symptom Score), than those who underwent catheterization with or without the use of toxin. They also observed that there no significant improvements in urodynamic parameters and quality of life as a result of the use of toxin, as observed in other studies.

Guang-Ping Li et al (23,) in a systematic review and meta-analysis of 17 studies involving 1,455 patients, compared with placebo and baseline and noted that BoNT-A was effective in increasing maximum cystometric capacity (MCC), volume at first involuntary detrusor contraction (Pdet), compliance, the number of patients with complete dryness (CD) and decreasing detrusor pressure, the number of patients with no involuntary detrusor contractions, the maximum flow rate, the incidence of detrusor overactivity and the number of urinary incontinence (UI) episodes. There were no statistically significant differences between doses of 200 U and 300 U or between injections into the detrusor and submucosa. In addition, comparing the injection locations (sparing the trigone and excluding the trigone) both methods increased the number of patients with CD, improved IQoLdecreased UI episodes, and Pdet. However, sparing the trigone was considered preferable. The most common referred AEs were symptomatic urinary tract infection. They concluded that BoNT-A is effective and safe in treating NDO after SCI.

Guoqing Chen et al (24), conducting a small study in patients with neurogenic detrusor overactivity, underwent BTX-A injection into the urethral sphincter. After treatment, they report that the maximum urinary flow rate was increased, while residual urine, maximum urethral pressure and detrusor leak point pressure were decreased. Patients still did not completely detach from CIC, but they can partially urinate autonomously, and the frequency of CIC was reduced improving the quality of life. The effect of BTX-A lasts for only three to 4 months and repeated injections were required.

In conclusion, BTX-A injection is a safe and valuable therapy, in the treatment of neurogenic bladder due to SCI. Significant improvement in incontinence severity, urodynamic parameters and QoL measures was observed, in most patients who received repeated BTX-A, without any significant difference between the 200-Uand 300-U dose.

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