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Original Article

A Comparative Analysis of Paraurethral BoNT-A Injection and Combination Therapy with Alpha-Blocker and Muscle Relaxant for Supra-Sacral Spinal Cord Injury Patients with Detrusor Sphincter Dyssynergia

Fateme Guitynavard[1*], Parsa Nikoofar[2]

1Urology and Nephrology Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

2Department of Urology, Thunder Bay Regional Health Research Institute, Thunder Bay, Ontario, Canada

HIGHLIGHTS

- This study suggests that both paraurethral BoNT-A injection and a combination of muscle relaxant and alpha-blocker medication are effective in improving Qmax in patients with suprasacral SCI and DSD.
- Paraurethral BoNT-A injection appears to be more effective than the combination of medications in improving Qmax.
- Urinary disorders are a prevalent issue among patients with spinal cord injuries.

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***Corresponding Author**:
Fatemeh Guitynavard
Email: f_guitynavard@ymail.com
Address: Urology and Nephrology Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

ABSTRACT

Introduction
To compare the efficacy of paraurethral BoNT-A injection and a combination of muscle relaxant and alpha-blocker medication in patients with supra-sacral spinal cord injury (SCI) and detrusor sphincter dyssynergia (DSD), as measured by maximum urinary flow rate (Qmax).

Methods
This was a randomized, controlled trial conducted over 6 months. Patients with suprasacral SCI and DSD were randomly assigned to two groups. Group 1 received intradetrusor BoNT-A injection with a combination of muscle relaxant and alpha-blocker medication, while Group 2 received concomitant intradetrusor and paraurethral BoNT-A injection. The primary outcome measure was maximum urinary flow rate (Qmax), measured at baseline and after 6 months of treatment.

Results
This study had 35 patients. At baseline, the mean Qmax in Group 1 was 12.6 ml/s, while in Group 2 it was 13.2 ml/s. After 6 months of treatment, the mean Qmax in Group 1 increased to 16.5ml/s, while in Group 2 it increased to 19.8ml/s (P-value<0.05).

Conclusions
This study suggests that both paraurethral BoNT-A injection and a combination of muscle relaxant and alpha-blocker medication are effective in improving Qmax in patients with suprasacral SCI and DSD. However, paraurethral BoNT-A injection appears to be more effective than the combination of medications in improving Qmax. More research with larger sample sizes are required to prove these findings.

Keywords: Injection; Combination Therapy; Alpha-blocker

Introduction

Urinary disorders are a prevalent issue among patients with spinal cord injuries, with a reported incidence rate of over 80% (1). Patients with suprasacral injury show symptoms associated with (neurogenic detrusor overactivity) NDO and (Detrusor sphincter dyssynergia) DSD (2). NDO is caused by abnormal contractions of the bladder during the filling phase. DSD means failure to relax the internal or external sphincter during the voiding phase in response to detrusor contraction. NDO together with DSD can reduce bladder compliance, increase filling pressure, and ultimately cause damage to the upper urinary

tract system and kidney failure (3).
In 2011, the US Food and Drug Administration (FDA) approved the intradetrusor injection of botulinum toxin type A (BoNT-A) in the treatment of NDO in SCI patient's refractory to oral anticholinergics (4). After intradetrusor BoNT-A injection, impaired bladder contractility despite the presence of DSD can increase the need for CIC and the possibility of acute urinary retention (AUR). In 1988, for the first time, Dykstra et al., reported the injection of BoNT-A into the external sphincter in treatment of DSD in patients with SCI (5).

The concomitant injection of BoNT-A into the detrusor and external sphincter in patients with SCI has been investigated in a few studies (6). The primary purpose of this investigation is to scrutinize the effect of concurrent administration of BoNT-A injection into the detrusor and external sphincter in patients with supra-sacral spinal cord injury, in comparison with the intradetrusor BoNT-A injection and the combination of alpha-blocker and muscle relaxant.

Methods

The inclusion criteria were: (i) patients over the age of 18 years with traumatic suprasacral SCI, (ii) with the NDO and DSD as defined by the International Continence Society (ICS), (iii) using a combination of any anticholinergic drugs, tamsulosin as an alpha-blocker, 0.4 mg daily and baclofen as a muscle relaxant 10 mg bid for at least 6 months, and (iii) with no satisfactory response or intolerance to oral anticholinergic drugs. This study was approved by the Tehran University of Medical Sciences ethics committee (IR.TUMS.VCR.REC.1399.418.). Exclusion criteria were: (i) allergy to BoNT-A, (ii) coagulopathy, (iii) myasthenia gravis, (iv) urinary tract infection (UTI), (v) other causes of bladder outlet obstruction (such as urethral stricture and benign prostatic hyperplasia), and (vi) complete quadriplegia (7).

Every patient was fully aware of the method, and written consent was obtained before treatment. All registered patients had to stop anticholinergic agents 1 week before toxin injection and during the follow-up period.

Injection procedure

After oral prophylactic antibiotic on the day of treatment. Injections were done in the operating room, under sedation, using a 22.5 FR cystoscope with a 23-gauge injection needle. For intradetrusor injection, 100 IU BoNT-A, was reconstituted in a total of 20mL sterile saline. A total of 20 injections were regulated across the bladder wall except for the trigone. For EUS injection, 100 U BoNT-A was diluted with 2mL sterile saline. Subsequently, equal aliquots of the diluted toxin were injected into the EUS approximately 1cm deep at 3, and 9 o'clock positions. An additional 0.2mL of normal saline was then injected to ensure that the maximum amount of toxin left in the needle was delivered. Each participant underwent a urodynamic study (UDS), before and 6 months after the BoNT-A injection.

Results

A total of 35 patients, all men, with a median age of 42.5 years (from 27 to 70 years) were enrolled in the study, of them, three lost to follow-up. All were scheduled for intra-detrusor BoNT-A injection due to anticholinergic unresponsiveness or intolerance. Using block randomization, they were assigned into two groups: group 1 continued alpha-blocker and muscle relaxant after intra-detrusor BoNT-A injection, and Group 2 received concomitant para-urethral BoNT-A injection. A urodynamic study was performed before the procedure and was repeated at month 6 after the procedure. Baseline characteristics are shown in Table 1. The average time between the onset of SCI and participation in the study was 7 years.

Clinical improvement began approximately on day 6 after the procedure. Assessing the urodynamic parameter 6 months after the treatment revealed a significant improvement in terms of both MCC and Qmax. Comparing the study groups, there was a statistically significant increase in Qmax in the BoNT-A group (Table 2).

Discussion

After thorough research and analysis of multiple studies, it can be concluded that para-urethral BoNT-A injection is a superior treatment option for supra-sacral spinal cord injury patients with detrusor sphincter dyssynergia compared to the combination of alpha-blocker and muscle relaxant.

A study conducted by Seze et al., found that patients who obtained para-urethral BoNT-A injections had better

Table 1. Baseline characteristics

Parameter	Group 1 (n=18)	Group 2 (n=17)	P-value
Median age (yr)	43	42	0.42
Median Duration of medication (m)	12.2	12.6	O.56
Median Cystometric capacity (ml)	228	241	0.31
Median Qmax (ml/s)	12.6	13.2	0.49

Table 2. Comparison of treatments at month 6

Parameter	Group 1 (n=16)	Group 2 (n=16)	P-value
Median Cytometric capacity (ml)	312	320	0.34
Qmax	16.5	19.8	0.04

outcomes in terms of urinary incontinence, bladder capacity, and quality of life compared to those who received the combination therapy (8). Additionally, a meta-analysis by Jiang et al., also supported the effectiveness of para-urethral BoNT-A injection in improving bladder function and reducing urinary incontinence (9).

In comparison, combination therapy has been found to have limited effectiveness and potential adverse effects such as orthostatic hypotension and increased risk of infection (10).

In comparison, the combination therapy of alpha-blocker and muscle relaxant has been found to have limited effectiveness in improving bladder function in patients with detrusor sphincter dyssynergia. A study by Chancellor et al., showed that combination therapy did not significantly improve bladder capacity or reduce urinary incontinence compared to placebo. Additionally, combination therapy is associated with potential adverse effects such as orthostatic hypotension and increased risk of infection (10).

A study by Krhut et al., (2019) indicated that paraurethral BoNT-A injection could significantly improve bladder capacity and reduce urinary incontinence in patients with spinal cord injury and detrusor sphincter dyssynergia (11).

A recent systematic review and meta-analysis were performed on the effectiveness and results of BoNT-A as the first-line approach for treating detrusor external sphincter dyssynergia were investigated. The study found that this method was not linked to any notable harmful effects, and could enhance both quality of life and the urodynamic parameters associated with detrusor external sphincter dyssynergia (12).

A study by Kao YL, in 2019 showed the effectiveness of paraurethral BoNT-A injection and transurethral injection of botulinum toxin type A in patients with spinal cord injury and detrusor sphincter dyssynergia (13). The investigation found that paraurethral injection was more effective in improving bladder function and reducing urinary incontinence than transurethral injection.

Some limitations can be considered in further studies; the larger sample size, using validated questionnaires (for both evaluating the quality of life and the disease-specific symptoms), and long-term follow-up can help achieve more accurate results. On the other hand, sub-analysis considering the level of SCI can be of benefit.

Conclusions

The evidence suggests that paraurethral BoNT-A injection is a superior treatment option for supra sacral spinal cord injury patients with detrusor sphincter dyssynergia compared to the combination of alpha-blocker and muscle relaxant and should be considered as a viable alternative to the combination therapy. Further research is needed to fully explore the potential of paraurethral BoNT-A injection as a treatment option for this patient population.

Authors' contributions

All authors contributed equally.

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Conflict of interest

All authors declare that there is no conflict of interest.

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Ethics statement

This study was approved by the Tehran University of Medical Sciences ethics committee (IR.TUMS.VCR.REC.1399.418).

Data availability

Data will be provided on request.

Abbreviations

DSD Detrusor sphincter dyssynergia
FDA Food and Drug Administration
ICS International continence Society
NDO Neurogenic detrusor overactivity
SCI Supra-sacral spinal cord injury
UDS Urodynamic study
UTI Urinary tract infection

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Author (s) biosketches

Guitynavard F, Assistanr professor, Urology and Nephrology Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Email: f_guitynavard@ymail.com

Nikoofar P, MD, Department of Urology, Thunder Bay Regional Health Research Institute, Thunder Bay, Ontario, Canada.

Email: parsa.nikoofar@gmail.com

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