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Review Article

Satisfaction and quality of life issues in patients receiving urethral botulinum toxin A injections for detrusor sphincter dyssynergia and detrusor botulinum toxin A injections for neurogenic detrusor overactivity

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ABSTRACT

Detrusor sphincter dyssynergia (DSD) and neurogenic detrusor overactivity (NDO) are common conditions in patients with spinal cord injury, multiple sclerosis, and transverse myelitis. With advancements in the clinical application of botulinum toxin A (onabotulinumtoxinA, BoNT-A) injections in the treatment of chronic lower urinary tract dysfunction, there has been much improvement in the management of DSD and NDO. Therefore, we reviewed the current literature with focus on subjective outcomes and patient satisfaction scores after BoNT-A treatment. We searched PubMed for articles on the management of neurogenic bladder using the following keywords: DSD, NDO, BoNT-A, satisfaction, dissatisfaction, quality of life, urodynamics, and lower urinary tract dysfunction. Patients receiving BoNT-A urethral injections for DSD have improvements in voiding volume, decreased postvoid residual (PVR) urine, and maximal urethral pressure. Most patients are satisfied and benefit from less difficult urination. However, some patients are dissatisfied with increased urinary incontinence. The BoNT-A detrusor injections for NDO can significantly increase reflex volume and maximal bladder capacity as well as decrease uninhibited bladder contractions. Most patients are satisfied with reduced urinary incontinence. However, some patients are dissatisfied with increased volumes of PVR urine and more difficult urination. Although published clinical studies usually include only a small number of patients and lack randomization and placebo-controlled groups, they provide important evidence of subjective improvement in the management of patients with DSD and NDO using BoNT-A injections. Urologists should inform patients about the main therapeutic effects and possible disadvantages of BoNT-A injections.

1. Introduction

> "Chung" means bent neither one way or another, and "Yung" represents unchanging.
>
> Doctrine of the Mean, Confucius 551–479 BC

The micturition cycle involves two relatively separate processes, namely, (1) bladder filling and urine storage and (2) bladder emptying. Bladder filling requires accommodation of increasing volumes of urine at a low intravesical pressure, a closed bladder outlet, and absence of involuntary bladder contractions. Bladder emptying requires an adequate magnitude of bladder contraction and a concomitant lower outlet resistance [1]. The balance and coordination between bladder and bladder outlet contribute to the normal function of the lower urinary tract. However, in cases of detrusor sphincter dyssynergia (DSD) and neurogenic detrusor overactivity (NDO), which are commonly found in patients with spinal cord injury (SCI), multiple sclerosis, and transverse myelitis, the balance cannot be maintained and lower urinary tract dysfunction occurs [2].

Patients with DSD often have voiding difficulty, elevated intravesical pressure, and a greater volume of postvoid residual urine

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(PVR) that requires intermittent or long-term urethral catheterization. Long-term complications are repeated urinary tract infections (UTIs), upper urinary tract damage, and vesical stone formation [3]. In addition, patients with NDO usually have urgency, nocturia, and urge incontinence. These adverse events cause poor quality of life (QOL), high health-service costs, and depression in these patients.

Recently, botulinum toxin A (BoNT-A) has emerged as a novel treatment for DSD and NDO in patients who are refractory to conventional treatment methods [4–8]. Results of several studies have shown that urethral injections of BoNT-A can reduce urethral resistance and possibly restore bladder emptying [4]. Detrusor injections of BoNT-A can reduce episodes of urge urinary incontinence, decrease neurogenic NDO, and improve bladder compliance [8]. However, detrusor injections of BoNT-A usually induce detrusor underactivity, increase the PVR, and even cause urinary retention [9]. Patients may need periodic clean intermittent catheterization (CIC) and repeated UTI can become a *de novo* problem. By contrast, urethral injections may cause undesired exacerbation of urinary incontinence, although the PVR volume can be reduced [10]. For a patient with both storage and voiding dysfunction, choosing between being "continent with CIC" and "incontinent with spontaneous voiding" is difficult.

The priorities in managing neurogenic bladder dysfunction should not only be based on improvement of urodynamic parameters, freedom from indwelling catheters, and preservation of renal function, but should also consider the patient's needs and preferences, hand function, ability to perform CIC, and family support [11]. Patient-reported outcomes, including health-related QOL, goal attainment, and treatment expectations, are important considerations and it is necessary to inform patients about the possible advantages and disadvantages of BoNT-A treatment [12]. Here, we review recent evidence on satisfaction and QOL issues in patients with DSD receiving urethral BoNT-A injections and in patients with NDO receiving detrusor BoNT-A injections.

2. Satisfaction and QOL after urethral BoNT-A injections for DSD

In 1988, Dykstra and colleagues first reported on a treatment method involving administration of 100 U onabotulinumtoxinA (Allergan, Irvine, CA, USA) injections into the external sphincter of 11 patients with SCI and DSD [13]. Eight (72%) of these patients benefited from the therapeutic effects of the injection for an average of 50 days. In these patients, the maximal urethral pressure decreased by 27 cmH_2O and the PVR volume decreased by 146 mL. Subsequent studies also showed significant improvements in the voided volume, PVR volume, and maximum urethral pressure [4,7,14]. Similar effects were noted with transrectal ultrasound-guided botulinum toxin injection [15]. Recovery of spontaneous micturition was noted in approximately 50–70% of patients. However, there were rare reports of worsening urinary incontinence and QOL (Table 1) [7,10,16].

In 2002, de Sèze et al first compared satisfaction and urodynamic changes between five SCI patients receiving onabotulinumtoxinA urethral injections and eight receiving lidocaine injections [7]. The BoNT-A group had significantly higher scores for satisfaction (6.8 ± 0.9 vs. 3.4 ± 1.0, $p = 0.02$) and fewer cases of PVR (105 ± 100 vs. 263 ± 116, $p = 0.01$) than the lidocaine group. Reinjection was necessary in all eight patients (100%) in the lidocaine group, but in only one (20%) patient in the BoNT-A group.

In 2005, Schulte-Baukloh et al injected onabotulinumtoxinA into dual positions, the urethra and bladder, for overactive bladder syndrome [16]. There were significant reductions (16–43%) in the scores of the three questionnaires used for evaluation [Urogenital Distress Inventory 6-item Short Form (UDI-6), The Symptom Severity Index, and The Symptom Impact Index] from 1 to 6 months. The overall satisfaction rate was as high as 86%. Noticeable, the volume of PVR of the patients after dual injections was distinctly less than that of the patients receiving detrusor injections alone.

In 2008, Kuo comprehensively demonstrated an increased maximum flow rate and decreased PVR and maximal voiding pressure 3 months after treatment with urethral sphincter injections of 100 U onabotulinumtoxinA [10]. Compared with baseline, the Incontinence Impact Questionnaire 7-item (IIQ-7) score (baseline vs. 3 months, 19.0 ± 2.4 vs. 17.1 ± 2.9, $p = 0.001$) significantly improved but the UDI-6 (baseline vs. 3 months, 8.6 ± 2.7 vs. 7.9 ± 3.7, $p = 0.25$) score remained about the same. Less difficult urination and a decreased PVR volume were noted in 78.8% and 69.7% of the patients, respectively. However, increased urinary incontinence and persistent difficulty in urination were found in 48.5% and 21.2% of the patients, respectively (Table 2). The overall satisfaction rate was 61%.

3. Satisfaction and QOL after detrusor BoNT-A injections for NDO

In 2000, Schurch et al studied 21 SCI patients with NDO receiving detrusor 200 U–300 U onabotulinumtoxinA injections [17]. After 6 weeks of follow-up, 19 patients were found to be fully continent. Of these, six patients were able to stop anticholinergic drug therapy, and the remaining 13 were able to reduce the dose by half. Urodynamic studies found a significant increase in the reflex volume and maximal bladder capacity and a significant decrease in the maximal detrusor pressure during uninhibited bladder contractions. No side effects were observed.

In recent years, data from several randomized, double-blind, placebo-controlled trials have demonstrated similar findings compared with placebo. A single detrusor injection of either 200 or 300 U onabotulinumtoxinA improved overactive bladder symptoms, urodynamic parameters, and QOL [18–20]. Despite heterogeneous study designs, almost all of these studies showed significant improvement in incontinence episodes, maximum cystometric capacity, and bladder compliance. The mean duration of efficacy in single-injection trials was 8 months (range: 12–36

Table 1
Subjective outcome and satisfaction in patients receiving botulinum toxin A urethral injection for detrusor sphincter dyssynergia.

Study	No. of patients	BoNT-A type, dose	Follow-up duration (mo)	Subjective measures	Subjective outcomes	Satisfaction rate
de Sèze et al [7] (2002)	13	100 U onabotulinumtoxinA	1	Satisfaction score (1–10)	Mean satisfaction score: 6.3	NA
Schulte-Baukloh et al [16] (2005)	22	50–100 U onabotulinumtoxinA	3	UDI-6, SSI, SII, satisfaction scale (0–10)	↓UDI-6 (25–70%), satisfaction scale: 6.6	86%
Kuo [10] (2008)	33	100 U onabotulinumtoxinA	3	UDI-6, IIQ-7	No difference in UDI-6, ↓IIQ-7 (10%)	61%

BoNT-A = botulinum toxin A; IIQ-7 = Incontinence Impact Questionnaire 7-item; SII = Symptom Impact Index; SSI = Symptom Severity Index; UDI-6 = Urogenital Distress Inventory 6-item Short Form.

Table 2
Main therapeutic effect and causes of dissatisfaction after botulinum toxin A urethral sphincter injection for patients with detrusor sphincter dyssynergia.

Less difficult urination	26 (78.8)	Increased urinary incontinence	
Decreased PVR	23 (69.7)	Persistent difficulty in urination	
Less CIC	7 (21.2)	Increased urgency	
Less autonomic dysreflexia	2 (50)	*De novo* frequency	
Less UTI	10 (67)	—	

BoNT-A = botulinum toxin A; CIC = clean intermittent catheterization; PVR = postvoid residual; UTI = urinary tract infection.

Table 4
Main therapeutic effect and causes of dissatisfaction after BoNT-A urethral detrusor injection for patients with neurogenic detrusor overactivity.

Main therapeutic effect	Patients (%)	Causes of dissatisfaction	Patients (%)
Decreased incontinence	45 (90)	Increased PVR	25 (50)
Increased bladder capacity	36 (72)	Difficult urination	16 (32)
Fewer urgency episodes	31 (62)	Nocturnal incontinence	10 (20)
Complete dryness	29 (58)	Severe incontinence	6 (12)
Less autonomic dysreflexia	5 (71)	Needing CIC	5 (10)

BoNT-A = botulinum toxin A; CIC = clean intermittent catheterization; PVR = postvoid residual.

weeks). Repeated injections showed sustained clinical benefits in open-label studies [21,22].

The primary and secondary end points of previous studies mainly focused their attention on changes in parameters in voiding diaries and urodynamic studies. A limited number of studies evaluated the therapeutic satisfaction and QOL in patients with NDO who received detrusor BoNT-A injections. Table 3 [20,23–25] summarizes the subjective measures and satisfaction rate in recent NDO clinical trials. Most studies used the UDI-6, IIQ-7, and Incontinence Quality of Life and Satisfaction scales as subjective variables. The overall satisfaction rate was approximately 69–83% [20,23–25].

In 2007, Ghalayini and Al-Ghazo from Jordan assessed NDO patient satisfaction with 500 U DYSPORT (Ipsen Biopharm Ltd, Slough, Berkshire, UK) intradetrusor injections using a 5-point scale (1 = very dissatisfied; 2 = dissatisfied; 3 = undecided; 4 = satisfied; and 5 = very satisfied) [24]. The satisfaction score significantly increased at 6 weeks compared with baseline (1.6 ± 0.5 vs. 3.8 ± 1.0, $p = 0.002$). However, the underlying reasons for satisfaction or dissatisfaction were not revealed. In 2008, Kuo reported a significantly increased maximal bladder capacity and PVR and decreased detrusor pressure 3 months after 200 U onabotulinumtoxinA detrusor injections in patients with NDO [23]. Significant improvements in the UDI-6 and IIQ-7 scores were also reported at 3 months. Forty-five (90%) patients had decreased incontinence and 36 (72%) patients had increased bladder capacity. However, 25 (50%) were dissatisfied with increased PVR and 16 (32%) had more difficult urination or urinary retention. The overall satisfaction rate was 78% (Table 4).

In 2009, Hori et al evaluated patients' perspective ($n = 72$) on whether they would consider BoNT-A injections as a long-term treatment option for managing their NDO secondary to SCI [25]. Of them, 67% agreed to repeated injections and 69% were either satisfied or very satisfied with their treatment. The mean patient satisfaction score was 6.2 (1 = not satisfied; 10 = very satisfied). Of interest, younger patients were likely to choose this option at a later interval than those who were older. Recently, a level A evidence study showed that BoNT-A significantly reduced urinary incontinence and improved urodynamics and QOL in patients with NDO [20]. During week 6, 7.6%, 38.0%, and 39.6% of patients in the placebo, 200 U, and 300 U onabotulinumtoxinA groups, respectively, were fully dry. The mean changes from baseline in the Incontinence Quality of Life total scores were significantly higher in the 200 U (24.4) and 300 U (24.3) onabotulinumtoxinA groups than the placebo group (11.7).

4. Urethral injections for DSD, detrusor injections for NDO, or dual injections?

Both DSD and NDO commonly occur in patients with SCI and multiple sclerosis. The DSD causes voiding problems such as micturition difficulty, abdominal straining, and an increased PVR volume. Thus, some patients need to perform CIC to empty their bladders periodically. Recent evidence has suggested that urethral sphincter BoNT-A injections can decrease urethral resistance and possibly restore physiological voiding. However, increased incontinence is an important concern, and up to 48% patients have urinary incontinence, even though their voiding function has improved. By contrast, NDO induces storage problems such as frequency, urgency, and urinary incontinence. Although detrusor BoNT-A injections can provide clinical and urodynamic improvement, an increased PVR and/or urinary retention usually occurs and some patients might be disappointed by the development of *de novo* problems that they did not expect.

Is it possible to consider both continence and appropriate voiding to achieve the maximum satisfaction rate for SCI patients with DSD and NDO? In 2005, Schulte-Baukloh et al showed that dual BoNT-A urethra and detrusor injections in patients with refractory overactive bladder could improve the micturition volume, daytime frequency, and pad use [16]. Changes in the PVR volume were not statistically significant during follow-ups at 4th week and 3rd month. No patient had to use a catheter to empty the bladder.

Table 3
Subjective outcome and satisfaction in patients receiving botulinum toxin A detrusor injection for neurogenic detrusor overactivity.

Study	No. of patients	BoNT type and dose	Follow-up duration	Subjective measures	Subjective outcomes	Satisfaction rate
Ghalayini and Al-Ghazo [24] (2007)	14	500 U DYSPORT	6 wk	Satisfaction scale (1–5)	Mean satisfaction scale: 3.8	83%
Kuo [23] (2008)	50	200 U onabotulinumtoxinA	3, 6 mo	UDI-6, IIQ-7, incontinence grade, voiding difficulty grade and satisfaction score (0, 1, 2, 3)	↓ UDI-6, ↓IIQ-7, 90%↓incontinence, 32%↑voiding difficulty	78%
Hori et al [25] (2009)	72	750 U and 1000 U DYSPORT	7 mo	Satisfaction score (1–10)	Mean satisfaction score: 6.2	69%
Sussman et al [20] (2013)	275	Placebo and 200 U, 300 U onabotulinumtoxinA	6 and 12 wk	I-QOL, OAB-PSTQ, PGA	↑I-QOL (25%), ↓OAB-PSTQ (approximately 30–40%), PGA (approximately 50–80%) improvement	Approximately 70–80%

I-QOL = Incontinence-Related Quality of Life; IIQ-7 = Incontinence Impact Questionnaire 7-item; OAB-PSTQ = Overactive Bladder-Patient Satisfaction with Treatment Questionnaire; PGA = Patient Global Assessment; UDI-6 = Urogenital Distress Inventory 6-item Short Form.

Table 5
Differences in opinions between the sexes in the management of neurogenic bladder.

	Female	Male
Most bothersome	Severe incontinence	Greater PVR urine volume, voiding difficulty
Continence device	Diaper	External appliance or diaper
Treatment goal	Stay dry and avoid diaper use	Voiding by abdominal tapping
Treatment suggestion	Approximately 200 U–300 U onabotulinumtoxinA detrusor injection	200 U onabotulinumtoxinA detrusor injection with/without 100 U onabotulinumtoxinA urethral injection

BoNT-A = botulinum toxin A; PVR = postvoid residual urine.

The only drawback was a slightly higher incidence of stress urinary incontinence after injection. On an average, the score for urine control (1 = better, 2 = same, and 3 = worse) improved by 1.30 compared with that before injection therapy, and 86% of the patients were satisfied and would choose the procedure for their bladder condition.

Multiple considerations and tailor-made therapeutic plans are necessary before administering BoNT-A injections. For example, patients with high cervical SCI or poor hand function might not be able to perform CIC. Support from a readily available caregiver is very helpful for patients after they receive intradetrusor BoNT-A injections for NDO. Otherwise, urethral injections may be a better solution for DSD. The CIC can be avoided and an external device can be used to prevent incontinence [10,23]. In addition, in cases of severe urge incontinence and refractory diaper dermatitis, complete dryness with CIC may be preferable, and higher doses of intradetrusor BoNT-A injections are suggested. Physicians should evaluate patients' hand dexterity, abdominal muscle power, bladder sensation, the degree of DSD and NDO, and family and economic support and communicate well with patients to design an appropriate treatment protocol. Patient satisfaction is determined by many factors, such as improvement in incontinence, the burden of CIC, improvement in difficult urination, *de novo* problems, and meeting initial expectations. Improvement in objective parameters is not completely correlated with subjective therapeutic satisfaction. Management of voiding dysfunction and incontinence in patients with DSD and NDO is a great challenge for urologists.

Gender is another important consideration for management of neurogenic lower urinary tract dysfunction (Table 5). Female SCI patients usually have more severe urinary incontinence and use diaper protection. Therefore, the desire to become dry to avoid use of diapers is a great therapeutic goal for women. Higher doses of onabotulinumtoxinA detrusor injections (200 or 300 U) are suggested and "continence with CIC" is a more accepted therapeutic choice for female patients. By contrast, male SCI patients have greater PVR volume and can use external appliances more easily to prevent wetting underwear. "Incontinence without CIC" is a more acceptable compromise than "performing CIC" for male patients with SCI. Thus, 200 U or lower doses of onabotulinumtoxinA detrusor injections are suggested. In addition, addition urethral or bladder neck injections to improve emptying function are also recommended for male patients [26].

5. Conclusion

In the era of BoNT-A, urethral injections to reduce bladder outlet resistance, detrusor BoNT-A injections to decrease bladder uninhibited contractions, and combined injections are effective treatments for patients with DSD and NDO. Physicians should discuss the main therapeutic effects and possible disadvantages with patients before commencing treatment. A complete understanding of the patient's preferences for management, their hand function, and capacity for self-care, and social, economic and family support can bring about better QOL. Achieving the "balance" in Chinese ancient wisdom between storage and emptying functions can benefit most patients with DSD and NDO.

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