Endoscopic Botulinum Toxin Injection for Refractory Enuresis Based on Urodynamic Assessment

Running title: Botulinum Toxin Injection for Refractory Enuresis

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ABSTRACT

**Purpose:** This study aimed to determine the urodynamic characteristics of refractory enuresis and explore whether they can be managed through differential endoscopic injection with botulinum toxin.

**Methods:** A total of 27 patients with nonmonosymptomatic enuresis who showed no response after conservative treatment for more than 12 months were included herein. Patients then underwent videourodynamic study and received a differential endoscopic injection of botulinum toxin within the same day. Reduced capacity, detrusor overactivity, and bladder neck widening were the three major abnormal findings assessed during the filling phase, while sphincter hyperactivity was the only abnormality assessed during the emptying phase. Intravesical or intrasphincteric injection of botulinum toxin was attempted according to videourodynamic study findings. Follow-up was conducted 1, 3, 6, and 12 months after treatment.

**Results:** The median age was 10 (7–31) years. Although 19 and 8 patients had preoperative diagnosis of overactive bladder or dysfunctional voiding, respectively, urodynamic diagnosis was different in more than half of them. Those showing detrusor overactivity benefited from intravesical botulinum toxin injection, whereas those with only sphincter hyperactivity benefited from both intravesical and intrasphincteric injections. Treatment resistance to botulinum toxin seemed to have been attributed to bladder neck widening. Time had no apparent effect on efficacy, which remained 6 months after the injection. More than 80% of the patients retained the benefits of injection after 1 year.

**Conclusions:** Videourodynamic study was useful in identifying reasons of refractory nonmonosymptomatic enuresis and helpful in determining appropriate sites of botulinum toxin
injection.

**Keywords:** Enuresis; Refractory; Nonmonosymptomatic; Urodynamics; Botulinum toxin
INTRODUCTION

Enuresis can be a frequent and bothersome problem. Although most cases resolve spontaneously with age, some experience a protracted course and even persist into adulthood. [1] Cases that persist into adulthood may cause significant distress to and potential social withdrawal among affected individuals. [2] Given the significant individual variation in the natural resolution of such a problem, it is inappropriate to withhold treatment on the premise that children would eventually experience spontaneous resolution, especially in severe cases wherein spontaneous resolution is unlikely. [1,3]

Once enuresis treatment is decided, the first step involves determining whether patients experience daytime symptoms caused by lower urinary tract dysfunction (LUTD). [3,4] Accordingly, the nature of enuresis can be categorized into monosymptomatic enuresis (ME) or nonmonosymptomatic (NME) based on the presence of LUTD. Treatment for NME is complicated given the presence of multiple relevant etiologies that need to be addressed individually in accordance with the pathophysiology. One study on patients with nonneurogenic voiding dysfunction revealed that most LUTD found in NME cases can be classified into either an overactive bladder (OAB) or dysfunctional voiding (DV). [5] Since both are urodynamic abnormalities, differential diagnosis between the two should require invasive urodynamic study (UDS). In practice, however the diagnosis is made with noninvasive diagnostics including symptomatology, voiding diary and uroflowmetry with or without simultaneous electromyography (EMG). Fortunately, management based on noninvasive diagnostics works well in most cases. After successfully converting NME into ME through appropriate treatment, the latter could then be managed using the established treatment. Occasionally, however, cases
refractory to treatment emerge and often need invasive diagnostics to determine new and relevant pathologic findings that could guide treatment. Cystometry in these patients may reveal a novel pathophysiology previously undetectable with noninvasive diagnostics.\textsuperscript{[6]} The addition of fluoroscopy [videourodynamiic study (VUDS)] or needle electromyography may facilitate the correct identification of sphincter movement.\textsuperscript{[7]} A potential list of urodynamic pathologies include detrusor overactivity (DO), sphincter hyperactivity (SH) during voiding (dysfunctional voiding), bladder outlet obstruction (or bladder neck dysfunction), and intrinsic deficiency of sphincter function as previously reported.\textsuperscript{[5,6,8]} Although VUDS can reveal the potential contribution of the aforementioned etiologies, the odds of identifying relevant findings had been reported to be low.\textsuperscript{[9]}

Given the 60\%–80\% efficacy of drugs and biofeedback for the management of OAB and DV,\textsuperscript{[10]} approximately 20\%–40\% of cases do not respond to treatment. Such odds in controlling enuresis still remains unacceptable and constitutes another reason why managing NME is difficult.

Botulinum toxin (BTX) has been applied to treat refractory overactive bladder and DV in both children and adults. Given that most cases of refractory enuresis were found have either OAB or DV, BTX injection may be effective in treating enuresis and could facilitate the control of LUTD.\textsuperscript{[11,12]} Thus, we hypothesized that VUDS would reveal the underlying LUTD in patients with refractory enuresis, which would be effectively addressed by selective BTX injection. Our treatment had been designed such that it could be completed within a day, because most parents expressed reluctance when the diagnostic procedure and injection treatment were separated, leading to frequent absence from school. They preferred to completing the diagnostic VUDS and therapeutic BTX injection in a single day.
The current study details our experiences with endoscopic treatment among children with refractory enuresis. To correctly determine the site of injection, VUDS was performed beforehand. This study aimed to determine the underlying urodynamic problems among patients with refractory enuresis and investigate the treatment course following endoscopic injection.

MATERIALS AND METHODS

This is retrospective evaluation of cases series reviewing our enuretic patients’ database. This study was approved by institutional review board.

Management Protocol and Determination of Treatment Refractoriness

Patients with enuresis were initially evaluated with dysfunctional voiding symptoms scores (DVSS) and selective physical examination of back and genitalia and 2-days voiding diary. Those without LUTD in DVSS were offered to receive either desmopressin or enuretic alarm, but those with LUTD were requested for uroflowmetry with simultaneous EMG, and postvoid residual (PVR) urine measurement. Those who were diagnosed with NME were further classified into the OAB and DV group based on clinical features and noninvasive assessment. Those with OAB featured frequency and urgency in their history and small voided volume in their voiding diary. Uroflowmetry showed tower- or bell-shaped curve patterns and minimal PVR urine. Those with DV were mainly characterized by staccato or intermittent uroflowmetry. They often showed features of emptying symptoms or increased PVR or significant fecal impaction.

To address LUTD, they initially received urotherapy with regular water intake and timed voiding and active bowel control regimen for 2 months. Then, those without improvement received
antimuscarinic agents (solifenacin 5 mg/day) or biofeedback with pelvic floor muscle training for 3 or 4 months. Those without improvement in DVSS should require further treatment. For the next 6 months, those with OAB received double antimuscarinics (solifenacin 5-10mg/day and oxybutynin 10mg/day) and biofeedback for the first and the last 3 months, respectively. Meanwhile, those with DV received biofeedback and antimuscarinics for the first 3 months and alpha antagonist and antimuscarinics for the last. Refractory enuresis was confirmed when no improvement was observed after 1 year of various treatment in the presence of good treatment compliance. Such patients were considered potential candidates for salvage treatment using BTX. Given that most parents were eager to obtain control of enuresis as early as possible, they agreed to the treatment and provided informed consent.

**VUDS and Endoscopic Injection of BTX**

On the day of treatment, patients were admitted to the outpatient surgery center and transferred to the operating room where VUDS and subsequent injection were performed. VUDS was conducted according to the International Children's Continence Society (ICCS) standards. [13,14] Accordingly, one or two study cycles were performed depending on the detection of clinically relevant findings. After placing patients in the supine position, a double-lumen 6Fr cystometry catheter and an 8Fr ballooned rectal catheter were inserted. The bladder was filled with sterile normal saline mixed with a contrast medium at 10% of expected bladder capacity. Patients were allowed to void upon feeling the urge before capacity was reached. When age-adjusted expected capacity was reached, patients were asked to void in either the supine or sitting position and were
observed for 20 min for spontaneous voiding. Sense of bladder filling, cystometric capacity, detrusor overactivity (DO), bladder compliance, and widening of the bladder neck (WBN) were assessed during the filling phase of VUDS. SH during the voiding phase was defined as electromyographic hyperactivity or shuttering sphincter movement that resembled a spinning top on fluoroscopy during spontaneous voiding. Patients who failed to void in the presence of catheter for more than 20 min were assumed to have SH. Following VUDS and determination of enuresis etiology, patients were placed in the lithotomy position and general anesthesia was established. During this preparation, treatment was planned based on VUDS findings. Further injection procedures were attempted to correct abnormalities revealed during the VUDS. Intravesical BTX was attempted when findings suggested reduced cystometric capacity (RC) or DO. BTX was diluted in normal saline at 10 units/kg to a maximum of 300 units. Multiple injections were distributed throughout the detrusor up to 20 sites. Those suspected to have SH received intrasphincteric BTX diluted in normal saline to 25–33 units/mL and injected into the external urethral sphincter across three to four quadrants to a maximum of 100 units. [15,16] Following injection, patients were observed for 4 h to detect potential complications, after which they were discharged home.

**Follow-up and Assessment of Treatment Responses**

Patients were advised to continue with the standard urotherapy and were followed up 1 month after the injection. When improved responses were not observed at the 1 month follow-up, desmopressin or prior anticholinergics were added to enhance responses. Changes in enuresis and LUTS were assessed every 3 months for 1 year. Responses were evaluated according to the
RESULTS
Since 2016, among the 282 patients with enuresis who were treated with same treatment protocol at our hospital, 27 (10.4%; 14 boys and 13 girls) ultimately received endoscopic treatment (Table 1). All patients were considered to have NME and exhibited at least one kind of storage (urgency and frequency) or emptying (straining and intermittency) symptom. More than three quarter (21 patients) of them still showed concomitant daytime incontinence. A history of constipation was noted in 13 (48%) patients who received polyethylene glycol treatment for a median of 7 (4–31) months. Based on their clinical findings, 19 and 8 patients were diagnosed with OAB and DV, respectively. Prior to endoscopic treatment, patients received a median of 16 (6–31) months of treatments for enuresis and LUTD as described previously. Overall, 7 (36.8%) and 3 (37.5%) patients with OAB and DV exhibited improvement in their daytime incontinence or daytime symptoms, though no patient indicated any improvement of their enuresis. With regard to voiding diary, none of the patients with OAB and only two patients with DV showed normalized maximal and average voided volumes. Thus, both were found to be treatment resistant.

Figure 1 presents the VUDS results for the included patients. The two major abnormalities observed during the filling phase were DO and RC found in 14 (52%) and 22 (82%) patients, respectively. During the voiding phase, 15 (56%) patients had SH. Additionally, 9 (33%) patients showed gradual WBN during the filling phase. Among the 19 patients clinically presumed to have OAB, 11 (58%) and 16 (84%) had DO and RC, respectively. Four (21%) patients showed
WBN during the filling phase. During the voiding phase, 9 (47%) patients showed synergic voiding. Among the 8 patients presumed to have DV, 3 (38%) and 6 (75%) had DO and RC, respectively. During the filling phase, 5 (63%) showed WBN, while during the voiding phase, same number of patients showed SH. Four patients presumed to have OAB failed to void despite being catheterized. They were subsequently diagnosed with SH and grouped with the six patients who showed RC but not DO. Nondilating vesicoureteral reflux was observed in two patients.

Consistency between clinical and urodynamic diagnoses was unsatisfactory with an overall concordance rate of 52%. The sensitivity and specificity of clinical versus urodynamic diagnosis were 75% and 33%, respectively.

Given our determination to treat patients according to their VUDS findings, intravesical and intrasphincteric BTX injections were attempted for urodynamic DO/RC and SH, respectively. Initially, only sphincteric BTX was attempted for the first four patients with SH, two of whom exhibited mild DO. Assuming that SH was the main pathophysiology, we believed that addressing only SH would sufficiently relieve enuresis. However, after recognizing unsatisfactory results among patients who received only sphincteric BTX injection, the remaining nine patients with DV who had SH also received intravesical BTX. Figure 2 summarizes the treatments provided to patients and enuresis outcomes at the 1-year follow-up.

Figure 3 reveals that time courses for responses can differ according to the type of urethral movement during voiding. Accordingly, patients showing synergic urethral movement showed a better treatment course than those showing SH. All but one synergic patient showed at least improvement of enuresis, while 75% experienced CR. Patients showed a transition from PR or NR to CR after 6 months of treatment. On the other hand, initial responses worsened in the SH
group, with 6 (40%) patients eventually showing NR. Although 11 (73%) patients showed CR or PR after 1 month of treatment, two patients with PR experienced a loss in efficacy, leading to NR. On the other hand, only one patient with PR transitioned to CR at 1 year. Responses became stabilized after 6 months of injection.

Apart from patients with CR who no longer required any treatment, four patients showing PR were able to control their enuresis with desmopressin or imipramine treatment.

Seven patients with NR, one with synergic voiding and six with SH, failed to show any meaningful improvement. Most of them did not receive intravesical BTX injection. Moreover, four patients, two of whom were girls, exhibited WBN in the filling phase and suffered persistent daytime incontinence and enuresis. One was found to have DO and synergic voiding, while the others showed SH.

Neither significant anesthesia nor acute treatment related complication was noted around the procedure. No postoperative complication was noted during follow-up.

**DISCUSSION**

The current study presented several urodynamic findings and combinations thereof that could explain treatment refractoriness. Our results showed that determining the injection site based on urodynamic findings promoted a response rate of more than 70%. Furthermore, improved responses were maintained for up to 12 months. As such, performing endoscopic treatment with BTX based on urodynamic findings within a single a day can be considered an effective salvage treatment strategy.

All patients included herein had been diagnosed with NME, which has been considered hard to
treat and requires prolonged treatment durations. [18] This is understandable given that the treatment of NME requires the treatment of both LUTD and enuresis. One caveat is that LUTD consists of heterogeneous urodynamic abnormalities. Thus, individual LUTD should be clarified and treated accordingly. However, current management schemes are mainly nonspecific and noninvasive. As revealed by the European Bladder Dysfunction Study the clinical diagnosis of OAB or DV was inconsistent with urodynamic results, while treatment aimed at either condition showed cross-efficacy to the other. [19,20] This redundancy in diagnosis and treatment supports current management systems, which we acknowledge as helpful in most cases. However, establishing the correct diagnosis and tailored treatment may be needed especially among refractory cases, such as those included herein.

Our data confirmed that noninvasive test results could not predict features observed during VUDS. Accordingly, only about half of the patients showed consistency between preoperative assumption and urodynamic diagnosis. We believe that the diagnostic discrepancy between clinical features and VUDS could partly explain treatment failures among patients. Moreover, five patients showed urodynamic features comprising both DO and SH, which shared features of OAB and DV. Such results cannot be determined from noninvasive diagnostic methods.

Unlike previous negative assertions for urodynamic study in refractory enuresis, [9,21] all patients included herein showed at least one abnormal finding, highlighting the usefulness of VUDS. The most notable finding was that approximately half of those with clinically OAB turned out to have SH. This finding is consistent with previous reports of increased numbers of DV among refractory cases. [22,23] Although the application of fluoroscopy facilitated better identification of SH, the lack of DO during UDS did not seem to justify withholding treatment.
for DO as reflected by the higher prevalence of NR among those receiving only intrasphincteric BTX for urodynamic DV compared to those receiving both intravesical and intrasphincteric BTX. Glassberg et al. [24] indicated, that the patients with DV should receive anticholinergics to alleviate storage symptoms despite the absence of DO during VUDS.

Gradual WBN during the filling phase had been observed in 9 (35%) patients and was associated with daytime incontinence. Although WBN has not been identified as an independent predictor of incontinence, our result suggested that this may play a role in the development of treatment resistance. Accordingly, one patient showed synergic voiding, while the three showed SH. Considering that the other three patients exhibiting WBN reported CR after treatment, WBN may not be the sole risk factor for treatment resistance. However, the presence of WBN as the only risk factor for nonresponsiveness in four patients may provide insight into its inhibitory role against continence. We have no knowledge whether WBN is related to pelvic floor laxity[25] or intrinsic sphincter problem.[26] However, one previous study reported that colposuspension successfully treated girls with congenital bladder neck insufficiency.[26]

Unlike adults, most of the children who responded to treatment required just a single BTX shot. This is interesting considering that the effects of intravesical BTX are unlikely to last for more than a year. We speculated that the endoscopic injection was helpful in correcting DO and DV, which may be evidence of immaturity in bladder control, and facilitated the achievement of normal bladder or urethral control to such a degree that further correction by injection was not necessary.

Like other small case series, this study also suffers the problems of retrospective study. However given the nature of enuresis of which most conventional treatments show good response, our data
are valuable guide in managing refractory cases. Although we did not revealed the association between UDS and noninvasive studies, we have not checked the relationship between invasive UDS and noninvasive uroflowmetry with concomitant electromyography (EMG-UFM) which is useful for describing childhood voiding dysfunction. As the role of SH is highlighted in the development of refractory enuresis, correlation cystometric findings with EMG-UFM during uroflowmetry may spare the invasive study in the future.

In conclusion, the present study suggested that utilizing VUDS for those with refractory enuresis with LUTD can help reveal the underlying pathophysiology and determine how to address the problem. VUDS was especially helpful in revealing sphincter pathology. Moreover, BTX injection was quite effective in controlling enuresis when administered in accordance with VUDS results. The beneficial effects of BTX were maintained once symptoms stabilized after 6 months of treatment.
REFERENCES


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Legends for Table and Figures

**Table 1.** Clinical features of the 27 patients who underwent endoscopic injection following videourodynamic study.

**Figure 1.** Videourodynamic study results for the included patients.
OAB, overactive bladder; DO, detrusor overactivity; RC, reduced capacity; WBN, widening of the bladder neck; SH, sphincter hyperactivity; DV, dysfunctional voiding

**Figure 2.** The treatments provided to patients and enuresis outcomes at the 1-year follow-up.
UDS, urodynamic study; DO, detrusor overactivity; RC, reduced capacity; WBN, widening of bladder neck; SH, sphincter hyperactivity; IV, intravesical; Sph, sphincter; BTX, botulinum toxin; CR, complete remission; PR, partial remission; NR, no response

**Figure 3.** Time courses for responses can differ according to the type of urethral movement during voiding.
TABLE 1. Clinical features of the 27 patients who underwent endoscopic injection following videourodynamic study.

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Number of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ages (median, years)</td>
<td>10 (7–22)</td>
</tr>
<tr>
<td>Boys</td>
<td>14 (52)</td>
</tr>
<tr>
<td>Severity of enuresis (% times per week)</td>
<td></td>
</tr>
<tr>
<td>More than 5</td>
<td>24 (89)</td>
</tr>
<tr>
<td>2–4</td>
<td>3 (11)</td>
</tr>
<tr>
<td>Main daytime symptoms</td>
<td></td>
</tr>
<tr>
<td>Urgency</td>
<td>11 (41)</td>
</tr>
<tr>
<td>Incontinence</td>
<td>8 (30)</td>
</tr>
<tr>
<td>Holding and infrequent voiding</td>
<td>6 (22)</td>
</tr>
<tr>
<td>Straining</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Daytime incontinence</td>
<td>21 (78)</td>
</tr>
<tr>
<td>Constipation (Rome IV compatible)</td>
<td>13 (48)</td>
</tr>
<tr>
<td>Maximal voided volume (% of age adjusted volume)</td>
<td></td>
</tr>
<tr>
<td>More than 80%</td>
<td>7 (26)</td>
</tr>
<tr>
<td>60%–80%</td>
<td>12 (44)</td>
</tr>
<tr>
<td>Less than 60%</td>
<td>8 (30)</td>
</tr>
<tr>
<td>Clinical diagnosis</td>
<td></td>
</tr>
<tr>
<td>OAB</td>
<td>19 (70)</td>
</tr>
<tr>
<td>DV</td>
<td>8 (30)</td>
</tr>
<tr>
<td>Treatments that have been attempted</td>
<td></td>
</tr>
<tr>
<td>Desmopressin</td>
<td>27 (100)</td>
</tr>
<tr>
<td>Imipramine</td>
<td>18 (67)</td>
</tr>
<tr>
<td>Anticholinergics</td>
<td>23 (85)</td>
</tr>
<tr>
<td>Pelvic floor muscle biofeedback</td>
<td>9 (33)</td>
</tr>
</tbody>
</table>

OAB, overactive bladder; DV, dysfunctional voiding.
Fig. 1.
Fig. 2.
**Fig. 3.**

Response rate for patients with sphincter synergy (N=12)

Response rate for patients with sphincter hyperactivity (N=15)