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Botulinum toxin injections in the management of non-neurogenic overactive bladders in children

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ABSTRACT

Introduction: Non-neurogenic detrusor overactivity in children leads to varying degrees of functional impairments (urinary urgency, pollakiuria, urge incontinence, nocturia). Botulinum toxin has shown its effectiveness in the management of detrusor overactivity in neurological patients.
Objectives: To evaluate the relevance of intravesical Botulinum toxin injections for the treatment of non-neurogenic overactive bladders in children. These pediatric patients were resistant to all the usual therapeutics (e.g. bladder/bowel rehabilitation, anticholinergic drugs, management of diet/hygiene habits and constipation, percutaneous posterior tibial nerve stimulation).
Materials and methods: 8 children (mean age: 12.5 years), 5 girls, 3 boys with daytime and/or nighttime incontinence and non-neurogenic detrusor overactivity validated by urodynamic testing. Urodynamic testing was conducted before the injections as well as 6 weeks and 1 year post injections. We used Dysport® 8 Speywood Units/kg injected via cystoscopy into 25 different sites.
Results: We noted improvements without any complaints during bladder voiding for all patients, in 6 patients the overactivity disappeared after 1 injection. Compliance was improved early-on in half the cases and at 1 year for all cases (from 12% to 61%, $p = 0.01$). Noninhibited contractions decreased constantly in both frequency and intensity. Clinical symptoms improved: mean of 7.75 daytime urinary incontinence episodes (IE) per week before the injection vs. 3 after the procedure ($p = 0.04$). For nighttime IE the improvement was even more noticeable with 7.38 nighttime IE episodes per week before the injection vs. 2.06 after the procedure ($p = 0,02$).
Conclusion: Intradetrusor Botulinum toxin injections are a potential therapeutic option for the management of non-neurogenic detrusor overactivity in children resistant to the usual treatments.

Detrusor overactivity (DOA), in non-neurogenic patients, leads to functional disorders, urinary urgency, incontinence, pollakiuria and/or nocturia, having an impact on the quality of life. Idiopathic detrusor overactivity is defined, according to the International Continence Society (ICS), as involuntary detrusor contractions (spontaneous or provoked) observed during urodynamic testing when the bladder is filling-up.

In urology, the use of Botulinum toxin A (BTA) was first reported by Dyskra et al. in 1998 [1] for the management of bladder sphincter dyssynergia (BSD); application to the detrusor was described for the first time in 2000 by Schuch et al. [2] in patients with paraplegia using intermittent self-catheterization. Since then, BTA has shown its effectiveness in DOA in patients with neurological disorders. Mechanisms of Botulinum toxin are becoming well known. It creates a specific and localized temporary presynaptic neuromuscular block which is long-lasting but reversible [3].

Guidelines from the ICS published in 2004, recommended treating DOA initially with bladder rehabilitation and anticholinergic therapy. In that context, anticholinergic drugs can lead to an improvement in 50% of cases, often in association with rehabilitation or behavioral treatments [4]. However for many patients, anticholinergic therapy leads to temporary or only partial improvement of the symptoms and is not exempt of adverse events [3]. In fact, it was estimated that one year after the first prescription of anticholinergic drugs 85% of patients had stopped their treatment [5].

It is well known now, thanks to the experience of BTA use in neurogenic bladders, that detrusor overactivity is the most sensible component of BTA injections in lower urinary tract disorders. In light of this, the use of BTA is indicated in non-neurogenic patients, adults and children alike.

The objective of our study was to evaluate the results of our intravesical BTA experience in the management of non-neurogenic detrusor overactivity in children.

1. Materials and methods

The use of BTA was proposed to 8 children (mean age 12.7 years old [6–11]) presenting with lingering and distressing incontinence in spite of a well-conducted treatment over a long period of time.

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After approval by our institutional review board, we collected a signed informed consent from the parents and children, before the study inclusion; they were informed that BTA had not yet gotten Marketing Authorization Application (MAA) in our country for this indication.

We prospectively included 5 girls and 3 boys from January 2009 to January 2011. All patients were previously treated with anticholinergic drugs associated with detrusor rehabilitation by perineal electrostimulation and biofeedback, diet advice, bladder voiding hygiene and constipation treatment when needed. Two of these children were also treated by percutaneous posterior tibial nerve stimulation (PTNS).

The mean duration of the previously described treatment was 20 months [R: 2–48] prior to the surgical decision. The patient treated for only two months had already been followed in another center and had a long history of incontinence. Six patients had nighttime and daytime incontinence as part of an overactive bladder syndrome. The 2 remaining patients no longer had daytime incontinence at the time of inclusion but a nighttime lingering and bothersome incontinence remained. Urodynamics validated detrusor overactivity which, despite a long history of proper therapeutic management seemed to play a role in this nighttime incontinence.

No patient had dysfunctional voiding at the time of the procedure, as ruled out by urodynamic testing.

Before the procedure all children had an MRI of the spinal cord and a complete clinical examination to eliminate any neurological causes for their DOA. When in doubt, as in associated urinary tract infections (UTI) or abnormal uroflowmeter measurements, a cystography was able to discard vesicoureteral reflux or morphological bladder alterations or urethral defects.

For each patient, each incontinence episode (IE) was noted in a diary during the 7 days preceding the injection to be compared to the post-injection diary filled-out 3 months after the BTA injection.

1.1. Urodynamic

Each patient underwent preoperative urodynamic testing to validate detrusor overactivity followed by postoperative urodynamics at 6 weeks and one year after the procedure. Urodynamic testing was performed by one sole technician on the same machine (Duet Machine, Peters Compass catheter) using a 3-way catheter adapted to pediatrics (diameter: 6 or 7 Fr) and a fill-up flow of 10 ml/min. When children were anxious they were given MEOPA (inhalation sedation with nitrous oxide and oxygen) for the procedure.

All patients were seen again 3 months after the procedure for complete clinical evaluation and analysis of the 7-day micturition diary implemented by the patient post-injection in order to compare it to the preoperative diary. Anticholinergic drugs were stopped at least three weeks before preoperative urodynamic testing.

1.2. Surgical technique

Intravesical Botulinum toxin injections were conducted as outpatient procedures when possible. Antibiotic prophylaxis was implemented during the injection. We chose the deep intradetrusor injection technique (fan-like mapping), excluding the trigone, into 25 points in accordance with the most commonly reported practices [12]. We used Dysport® for all our patients at the dose of 8 US/kg per injection; the same surgeon performed all procedures according to the same modalities (Fig. 1).

BTA was injected via cystoscopy. After filling the bladder with 100 ml of saline solution, the injection was performed using a flexible 23 Gauge needle measuring 35 cm inserted into the superficial part of the detrusor in 25 sites (sparing the trigone), each measuring 1 cm^3. The product was diluted in 25 cm^3 of injectable saline solution following guidelines established in our department according to each patient's weight. Each syringe was reconnected to the following one making sure that the needle stayed in the muscle to avoid reflux of the intravesical saline solution into the flexible tube.

Discharge was only authorized once the team had made sure the patient's bladder voiding was easy and complete. The next day, a phone call to the parents enquired about the patients' status and if they had experienced urinating difficulties, hematuria, pain and/or muscle weakness. Wilcoxon signed rank test was used for statistical analysis.

2. Results

On a clinical level (Table 1): All patients reported major improvements. By observing the micturition diaries, we noticed a decrease in the number of IE: 7.75, (median 7) IE per week in average before the surgery vs. 3 (median 1.5) post-surgery ($p = 0.04$). Regarding nighttime incontinence we also observed a clear improvement with 7. 38 IE per week (median 7) before the surgery vs. 2.06 IE (median 1) post-surgery, ($p = 0.02$). No adverse side events were reported besides postoperative macroscopic hematuria that spontaneously resolved; no toxin diffusion or allergic reactions were evidenced in our series. In our study population, there were no difficulties with bladder voiding.

Urodynamics (Table 2). In 6 patients the detrusor overactivity disappeared after 1 injection, with total resolution of inhibited contractions. For the remaining two patients, we noted some involuntary detrusor contractions during bladder filling but slight ones and with diminished maximal pressure. In half the cases, compliance had improved early on and in all cases compliance was achieved after one year. Preoperative compliance varied from 6.19 cc/H_2O to 57 cc/H_2O (mean 20.65 cc/H_2O, median 17.61 cc/H_2O). Postoperative compliance varied from 6.90 cc/H_2O to 88.25 cc/H_2O

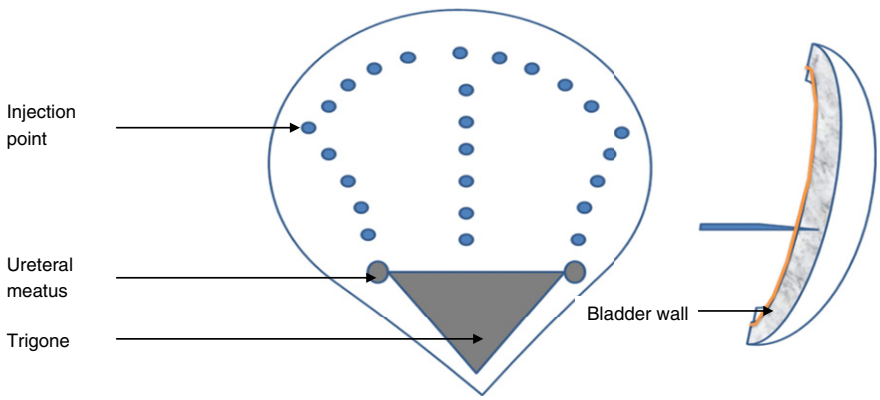

Fig. 1. Injection of toxin into the bladder wall.