

External Sphincter Injection of Onabotulinum-A Toxin in Treatment of Children with Bladder- Sphincteric Dyssynergia

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Abstract

Background: The first application of Onabotulinum-A Toxin in urology was its injection into the urinary sphincter to treat neurogenic detrusor-sphincter dyssynergia in quadriplegic men. Since that first report by Dyskatra et al., in 1988, the results of focal Onabotulinum-A Toxin injections into the sphincter, the bladder wall and lately into the prostate have raised the interest of the urology community in this promising new therapeutic modality. This is an evidence-based review of the current indications, techniques and outcomes of Onabotulinum-A Toxin injections into the urethral sphincter.

Aim of Study: We evaluated the effect of detrusor injection of onabotulinum-A toxin into the urethral urinary sphincter in children with bladder-external sphincter dyssynergia to decrease urethral resistance and improve voiding.

Material and Methods: Prospective treatment was performed in 25 children 4 to 15 years old (mean age 7) with bladder-neck dyssynergia using onabotulinum-A toxin. Preoperatively all children were evaluated by ultrasound, voiding cystourethrography, excretory urography, magnetic resonance imaging and urodynamic studies, including pressure flow, electromyography and uroflowmetry. Using a rigid pediatric endoscope and a 4Fr injection needle 50 to 100 IU onabotulinum-A toxin was injected into the external sphincter at the 5 and 7 o'clock positions. Follow-up was 6 to 15 months. Repeat injections every 6 months were given according to the response with a maximum of 3 injections.

Results: Immediately after onabotulinum-A toxin injection all except 1 patient were able to void without catheterization. No acute complications occurred. Postoperatively post-void residual urine decreased by 30%, detrusor leak point pressure decreased significantly by a mean \pm SD of 66 ± 18 vs 37 ± 4 cm H₂O and uroflowmetry showed a marked increase in maximum urine flow of 7 ± 2 vs 17.3 ± 8 ml per second.

Conclusions: Urethral sphincter onabotulinum-A toxin injection could be considered a reliable treatment modality in children with nonneurogenic neurogenic bladder after the failure of conservative therapy.

Key Words: Onabotulinum-A toxin – Nonneurogenic neurogenic bladder – Bladder-neck dyssynergia – Bladder-external sphincter dyssynergia.

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Introduction

DYSSYNERGIA is the kinesiologic disassociation of two groups of muscles that, in general, work in harmony. Sphincter dyssynergia is an involuntary-contraction, or lack of relaxation, of the striated sphincter. The storage phase of the bladder can be switched to the voiding phase either involuntarily (reflexively) or voluntarily. The former is readily demonstrated in the human infant or in patients with neuropathic bladder when the bladder wall tension due to increased volume of urine exceeds the micturition threshold. At this point, increased afferent firing from tension receptors in the bladder reverses the pattern of efferent outflow, producing firing in the sacral parasympathetic pathways and inhibition of sympathetic and somatic pathways. The expulsion phase consists of an initial relaxation of the external urethral sphincter followed in a few seconds by a contraction of the bladder, an increase in bladder pressure, and the flow of urine. During the storage phase, the lumbosacral efferent pathways in the pudendal nerves provide cholinergic excitatory inputs to the striated muscle of the urethral sphincter [1].

During voiding, three changes are occurred and coordinated by three sets of nerves (parasympathetic, sympathetic, and somatic) that emerge from the sacral and thoracolumbar spinal cord [1].

Sacral parasympathetic (pelvic) nerves provide excitatory inputs (cholinergic and purinergic) to the bladder and have an inhibitory (nitrgic) effect on the smooth urethral sphincter [2,3]. Secondary reflexes elicited by flow of urine through the urethra facilitate bladder emptying. These reflexes require the integrative action of neuronal populations at various levels of the neuraxis [4].

Stoffel et al., [5] published a consensus paper on the management of nonneurogenic urinary re-

tion, defined as a postvoid residual above 300mL that has persisted for at least 6 months and documents on at least two occasions and is classified as high or low risk. The high-risk variable is hydronephrosis, hydroureter, chronic kidney disease, recurrent UTI, or urinary incontinence with skin sequalae.

The scientific background for the application of BonT-A in the external urethral sphincter in patients with DESD is based on its known effect of blocking the presynaptic vesicular release of acetylcholine (ACh) at the neuromuscular junction. This leads to temporary reversible chemodenervation of the targeted muscle [6].

BOTOX is the brand name for the formulary that uses onabotulinum-A, serotype A Onabotulinum-A neurotoxin, as a therapeutic agent.

Material and Methods

A prospective single-armed cohort study was designed. From January 2016 to May 2019, children complaining of LUTS and diagnosed with Detrusor External sphincteric dyssynergia (DESD) on EMG and video-urodynamic, with a Qmax < 15ml/sec. Patients with prior urethral or bladder surgery, posterior urethral valve, anorectal congenital anomalies and detrusor-internal sphincter dyssynergia are excluded. Also Non complicated type I excluded from the study. The study was conducted according to Declaration of Helsinki [7] and was approved by our Institute Ethical Committee.

Diagnosis requires pressure flow electromyographic evidence of bladder emptying occurring simultaneously with involuntary striated sphincter contraction in the absence of any element of abdominal straining, either in an attempt to augment bladder contraction or as a response to discomfort during urination.

Preoperatively all children were evaluated by clinical history including details of any neurological disease or injury, familial history. Then, details of delivery and perinatal life and the milestones of development were included in the history. The history also included age of bladder and bowel control, voiding pattern, potty training, character of the stream, outflow pattern, urinary leakage and sensation pattern. Periods of dryness and incontinence were recorded accurately.

Physical examination included abdominal, genital, perineal, anal and careful inspection of the child's back. Careful neurological examination was an essential component which included perianal and perineal sensation to pin prick and light touch.

Sacral arc reflexes were examined and eliciting carefully. These included anal sphincter tone, bulbocavernous and cutaneous anal (wink) reflex, suprapubic tap reflex and catheter tug reflex (patients with indwelling catheters). Motor and sensory lower extremities evaluation was taken.

Laboratory studies included urine analysis, urine culture, serum creatinine and/or cystatin C. Imaging included ultrasound, voiding cystourethrography, excretory urography, magnetic resonance imaging and urodynamic studies including pressure flow, electromyography and uroflowmetry. Video-urodynamic was done to confirm the diagnosis and exclude detrusor internal sphincter dyssynergia. Classification of DESD According to Blaivas and coworkers⁸ have described three main types of DESD. Type 3 not mentioned in last national in the International Continence Society (ICS) report but still valid as subgroup [8].

Type 1 DSD, there is a progressive increase in external urinary sphincter (EUS) contraction activity that peaks at maximal detrusor contraction followed by sudden relaxation of the EUS as the detrusor pressure declines allowing urination. Type 2 occurs with continuous EUS contraction throughout the entire detrusor contraction resulting in urinary obstruction or inability to urinate [9].

In type 3, there is a crescendo-decrescendo pattern of sphincter contraction that results in outlet obstruction throughout the entire detrusor contraction. Non complicated type I excluded from the study.

Ultrasound examination evaluated renal size and structure, cortex thickness, presence and degree of hydronephrosis, ureteral dilation (ureterectasies), bladder volume, bladder wall thickness and postvoiding residual (PVR) urine volume. Nuclear medicine clearance study may be indicated if renal function impairment is suspected.

Capacity (mL) = (2 + age [years]) x 30 (Koff formula) was calculated before urodynamic study and cystography to avoid complications. Consenting patients received 50UI of BTA (BOTOX, Allergan pharmaceuticals, Clonhaugh coolock, D17 E400, Duplin, Irland) diluted in 4ml of saline solution 12.5U/ml) injected transurethrally into the external sphincter (4 sites, 1ml/site) using a 10F-17F rigid cystoscope in general anesthesia according to child age, sex and urethral diameter. A Foley catheter was inserted transurethrally only in patients with postoperative urinary retention. All patients were discharged the next day after voiding without problems. Patients were assessed

at baseline and at 2, 6 and 12 months postoperatively by means of uroflowmetry with post-void residual urine volume scan (PVR urine), IPSS-QoL questionnaire and a self-administered Patient Reported Outcomes (PROs) questionnaire including questions on the Patient Global Impression of Improvement (PGI-I; range 1-7), of Satisfaction (PGI-S; range 0-5) and of Efficacy of the procedure (PGI-E; range 0-5) with higher score indicating better outcome. One month after treatment, all patients underwent video-urodynamic examination with EMG [10].

Results

Of 28 consecutive patients fulfilling the inclusion criteria, 3 patients were excluded (two with sign of posterior urethral valve at cystoscopy, and one none consenting to the study).

Symptoms were slow stream (22/25), splitting/spraying (18/25), intermittency (21/25), hesitancy (22/25), straining (15/25), and terminal dribbling (9/25). The primary outcome measure was a reduction of IPSS > from baseline. The secondary outcome measures were maximum urinary flow (Qmax), PVR, IPSS-QoL item score and PROs.

Table (1): Slow stream distribution along treatment course.

Slow stream (22/25)	No.	%
6 months post intervention	6	27
1 year post intervention	11	50
2 year post intervention	15	68

**Highly significant at $p \leq 0.01$.

Table (2): Splitting/spraying distribution along treatment course.

Splitting/spraying (18/25)	No.	%
6 months post intervention	9	50
1 year post intervention	14	77
2 year post intervention	15	83

**Highly significant at $p \leq 0.01$.

Table (3): Intermittency distribution along treatment course.

Intermittency (21/25)	No.	%
6 months post intervention	5	23
1 year post intervention	4	19
2 year post intervention	7	33

**Highly significant at $p \leq 0.01$.

Table (4): IPSS, Q-Max and Mean PVR (25 patients) along treatment course.

	Mean IPSS	Mean Q-Max	Mean PVR
Pre-operative	19.6±7.6	7.2	34.2
6 months post intervention	12.9±5.3	11.3	16.3
1 year post intervention	11.5±6.2	11.5	11.6
2 year post intervention	11.3±1.2	17.3	10.3

Postoperatively post-void residual urine decreased by 30%, detrusor leak point pressure decreased significantly by a mean ± SD of 66±18 vs 37±4cm H₂O and uroflowmetry showed a marked increase in maximum urine flow of 7±2 vs 17.3±8ml per second.

A statistically significant reduction in mean IPSS from 19.6±7.6 to 12.9±5.3 was observed at 6 months follow-up, to 11.5±6.2 at 12 months follow-up and to 11.3±1.2 at 24 months ($p=0.145$). Q max mean value increased from 7.2 to 11.3ml/s at 6 months, rising to 11.5ml/s at 12 months and to 12.3ml/s at 24 months ($p=0.4101$). Mean PVR urine decreased from 34.2% to 16.3 at 6 months, by 11.6% at 12 months and by 10.3% at 24 months ($p=0.4201$).

Table (5): Relation of dyssynergia type and IPSS, Q-Max and Mean PVR (25 patients) 2 years after treatment.

Dyssynergia	No.	Mean IPSS	Mean Q-Max	Mean PVR urine
Type 1	4	12.3	11.5	11
Type 2	18	7.9	10.1	8
Type 3	3	12.3	13.4	10.8
All types	25	11.3±1.2	17.3	10.3

A statistically significant reduction in mean IPSS to 12.3 was observed at 2 year post intervention in type I, to 7.9 in type II and to 12.3 in type III. Q max mean value increased to 11.5 in type I, to 10.1 in type II and to 13.4 in type III. Mean PVR decreased to 11% in type I, to 8% in type II and to 10.8% in type III.

No systemic adverse effects occurred and 12 patients (63%) reported self-limiting local side effects related to the procedure: 15 (60%) hematuria, 16 (64%) stranguria, 9 (36%) postoperative urinary retention requiring transitory catheterization.

After onabotulinum-A toxin injection all except 1 patient were able to void without catheterization.

Vesicoureteral reflux was found in 5 male patients at baseline. They underwent follow-up cystourethrogram that showed complete disappearance of the reflux in two of them and improvement degree of reflux in one.

Transurethral injections of Botox showed statistical improvement of patient's sphincter dysfunction.

Three injections at eight month intervals provided long term (nine to 12 months) efficiency.

Discussion

Without proper treatment, more than 50% of men with DSD will develop significant complications, such as VUR, upper tract deterioration, urolithiasis, urosepsis, and ureterovesical obstruction. Transurethral injections of Botox showed statistical improvement of patient's sphincter dysfunction [3]. Three injections at eight month intervals provided long term (nine to 12 months) efficiency [11].

Gallien et al., published a trial evaluating the effectiveness and safety of Botox in 86 patients, 58 of whom were women, with detrusor sphincter dyssynergia secondary to multiple sclerosis. 54 Subjects were randomized to intrasphincteric injection of Botox vs placebo. Compared to placebo, Botox significantly increased voiding volume ($p=0.02$) and reduced pre-micturition ($p=0.02$) and maximal detrusor pressures ($p=0.02$) in his study. In our study there was significantly increased voiding volume ($p=0.02$) and reduced pre-micturition ($p=0.02$) and maximal detrusor pressures ($p=0.02$) in his study [12].

Desrosiers et al., concluded that there are evidence suggesting decreased postvoid residual, maximum urethral closure pressure, and maximum voiding detrusor pressure after treatment with Botox-while still protecting the upper urinary tract-indicates that patients with detrusor sphincter dyssynergia may benefit from treatment with botulinum toxin A [13]. Soler et al., published a trial evaluating the PVR urine was significantly reduced following urethral injection of botulinum toxin (from 227 to 98ml, $p<0.01$ and from 63 to 27%, $p<0.01$). Their study focused on ninety-nine consecutive adult men with SCI (72 tetraplegic and 27 paraplegic) [14].

Our study revealed decrease of post voiding residual urine from 34.2% to 10.3% at 24 months. Kroll concluded that botox injection has shown effectiveness in the treatment of detrusor sphincter dyssynergia when injected into sphincter either

transurethral or trans perineally [15]. Felony and Leslie and concluded that the botulinum toxin injections to the urethral sphincter is reasonable primary treatment strategy when conservative treatments fail [16].

Conclusion:

Urethral sphincter onabotulinum-A toxin injection could be considered a reliable treatment modality in children with non-neurogenic neurogenic bladder after the failure of conservative therapy. External sphincter injection of BTA could be considered as a minimally invasive treatment option in patients with detrusor-external sphincter dyssynergia if the promising results of the present study will be confirmed in prospective randomized trials.

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حقن عضلة الصمام الخارجى للبول بمادة البوتكس فى الاطفال المصابين بعدم التجانس بين عضلة الصمام الخارجى وعضلة المثانة

الهدف من البحث: تقييم التأثير الناتج عن حقن الصمام الخارجى للبول بمادة البوتكس فى الاطفال المصابين بعدم التجانس بين عضلة الصمام الخارجى للبول وعضلة المثانة لتقليل مقاومة مجرى البول وتحسين تدفق البول.

المرضى وطرق البحث: تمت الدراسة على ٢٥ طفل من عمر ٤ حتى ١٥ عام (متوسط ٧ سنوات) المصابون بعدم تجانس بين عضلة المثانة والعضلة الصمام الخارجى للبول عن طريق حقن عضلة الصمام الخارجى للبول بمادة البوتكس. تم تقييم جميع الاطفال عن طريق الاشعة التليفزيونية وتصوير المثانة والإحليل بالإفراغ وتصوير المسالك البولية عن طريق افراز الكلى وأشعة الرنين المغناطيسى ودراسات ديناميكا البول متضمنة تدفق الضغط وتخطيط كهربية العضل وقياس تدفق البول. باستخدام منظار الاطفال الصلب واستخدام ابرة حقن ٤ فريش لحقن ٥٠ إلى ١٠٠ وحدة دولية من مادة البوتكس فى الصمام الخارجى فى موقع الساعة ٥ و٧. والمتابعة ٦ إلى ١٥ شهر. إعادة الحقن كل ٦ شهور حسب الاستجابة بعد أقصى ٣ مرات للحقن.

النتائج: مباشراً بعد الحقن تمكن كل الحالات من التبول بدون استخدام القسطرة عدا طفل واحد. لم تحدث أى مضاعفات حادة. كمية البول المختزنة بعد التبول انخفضت بنسبة ٣٠٪ وانخفض ضغط نقطة تسرب النافصة بشكل ملحوظ وأظهر مقياس تدفق البول زيادة ملحوظة فى الحد الأقصى لتدفق البول.

الاستنتاج: يمكن اعتبار حقن البوتكس فى الصمام الخلفى فى الاطفال الذين يعانون من المثانة العصبية غير العصبية علاج موثوق بعد الفشل فى محاولات العلاج التحفظى.