Benefits of Intradetrusor Botulinum Toxin Type A Injections in Children with Neurogenic Detrusor Overactivity

Benefícios da aplicação intravesical de Toxina Botulínica do Tipo A em crianças com Hiperatividade Neurogénica do Detrusor

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Abstract

Objectives: *Neurogenic Detrusor Overactivity (NDO) consequences include urinary incontinence, vesicoureteral reflux and impairment of kidney function, with important implications for life expectancy and quality of life. Botulinum toxin type A (BoNT-A) may be a reliable alternative in patients who fail to respond or do not tolerate first line treatment (timed bladder catheterization plus oral anticholinergic medication) for NDO. The aim of this study was to assess the effectiveness and safety of intradetrusor injections of BoNT-A used to treat NDO in children followed in the Pediatric Rehabilitation Service of the Centro de Medicina de Reabilitação - Alcoitão.*

Material and Methods: *We retrospectively reviewed the records of seven children with NDO managed with intradetrusor BoNT-A injections between 2007 and 2011. Descriptive data analysis was performed using SPSS for Windows version 17.0 (SPSS Inc, Chicago, IL, USA). Wilcoxon Test was used to compare urodynamic parameters before and after intradetrusor BoNT-A injections. Significance was set at p-value ≤ 0.05.*

Results: *After the first intradetrusor BoNT-A treatment, there was a statistically significant improvement in the mean Maximum Cystometric Capacity (MCC) without leakage (p=0.018), mean Maximum Detrusor Pressure (MDP) (p=0.043) and mean Bladder Compliance (BC) (p=0.043). There also was a statistically significant improvement of the mean MCC without leakage (p=0.028) after the second intradetrusor BoNT-A injection sessions, when compared with the urodynamic studies performed before the second series. According to subjective information, there was an overall clinical improvement: urinary continence, number of lower urinary tract infection (LUTI) episodes and pyelonephritis. Patients and their caregivers referred to decreased urinary leakage after intradetrusor BoNT-A injection sessions.*

Conclusions: *Intradetrusor BoNT-A injections in patients with NDO was safe and effective. They achieved a significant improvement in urodynamic parameters which could be related to clinical benefits (improved continence and reduction in the number of LUTIs), and certainly in the safeguarding of the urinary tract. All these can lead to a better quality of life for the patients. Thus, although BoNT-A is an expensive treatment, we consider that the cost of incontinence equipment, UTI treatments (some with hospitalization), urologic surgeries or even the treatment for deteriorating function of the upper urinary tract, are much more expensive and time-consuming.*

Keywords: *Botulinum toxin type A, urinary bladder, neurogenic detrusor overactivity*

Resumo

Objetivo: A Hiperatividade Neurogénica do Detrusor (HND) pode ter como consequências importantes a incontinência urinária, o refluxo vesicoureteral e o comprometimento da função renal, com implicações importantes na sobrevida e na qualidade de vida. A toxina botulínica do tipo A (BoNT-A) pode ser uma alternativa em pacientes que não respondem ou não toleram tratamento de primeira linha (cateterismo vesical intermitente associado a medicação anticolinérgica) para o tratamento da HND. O objetivo deste estudo foi o de avaliar a eficácia e a segurança das injeções intradetrusor de BoNT-A, usado para tratar HND, em crianças seguidas no Serviço de Reabilitação Pediátrica do Centro de Medicina de Reabilitação - Alcoitão.

Material e Métodos: Foram analisados retrospetivamente os processos de sete crianças com HND tratadas com BoNT-A intradetrusor, entre 2007 e 2011. A análise descritiva dos dados foi realizada usando o programa SPSS para Windows versão 17.0 (SPSS Inc, Chicago, IL, EUA). O Teste de Wilcoxon foi utilizado para comparar os parâmetros urodinâmicos antes e depois da aplicação intradetrusor de BoNT-A. A significância estatística foi estabelecida para valores de p≤0,05.

Resultados: Após a primeira aplicação de BoNT-A intradetrusor, verificou-se uma melhoria estatisticamente significativa da média da Capacidade Vesical Máxima (CVM) sem perdas (p=0,018), média da Pressão Máxima do Detrusor (PMD) (p=0,043) e média da *Compliance* Vesical (CV) (p=0,043). Também se observou uma melhoria estatisticamente significativa da CVM média sem perdas (p=0,028) após a segunda aplicação de BoNT-A intradetrusor, quando comparados com os estudos urodinâmicos realizados antes da segunda série de injeções. De acordo com informação subjetiva, houve uma melhoria clínica geral: continência urinária, número de episódios de infeções do trato urinário inferior (ITUIs) e de pielonefrites. De igual forma, doentes e cuidadores referiram diminuição de perda urinária após as aplicações de BoNT-A intradetrusor.

Conclusões: A aplicação de BoNT-A intradetrusor em crianças com HND foi segura e eficaz. Verificou-se uma melhoria significativa nos parâmetros urodinâmicos, o que poderá estar relacionado com os benefícios clínicos (melhoria da continência e redução do número de ITUIs) e, certamente, com preservação do trato urinário. Tudo isto poderá conduzir a uma melhoria da qualidade de vida destas crianças. Assim, embora a BoNT-A seja um tratamento dispendioso, consideramos que o custo do equipamento para tratamento da incontinência, o tratamento das ITUIs (por vezes, com necessidade de internamento), as cirurgias urológicas ou mesmo o tratamento das complicações resultantes da deterioração da função do aparelho urinário superior, são bastante mais caros e demorados.

Palavras-chave: Toxina botulínica tipo A, bexiga, hiperatividade neurogénica do detrusor

Introduction

Disturbances in the normal control of bladder reflexes may lead to an overactive detrusor[1], which is characterized by the urodynamic observation of involuntary detrusor contractions during the filling phase, involving a detrusor pressure increase of greater than 15 cm H_2O above baseline[2].
In children, neurogenic detrusor overactivity (NDO) is usually due to spinal cord lesions, which may be congenital or acquired. Myelomeningocele is the most frequently associated pathology; traumatic and neoplastic spinal cord lesions are less frequent causes[3,4].
NDO can be associated with diminished bladder capacity and compliance, and high intravesical pressure. Its consequences include urinary incontinence, vesicoureteral reflux and impairment of kidney function, with important implications for life expectancy and quality of life[3,5,6].
The main treatment goals are to prevent upper urinary tract lesion, by achieving low bladder pressures and to achieve social continence by establishing a program that will allow children autonomy in the future[5,7]. The first line treatment for NDO combines intermittent bladder catheterization with anticholinergic medication (such as oxybutynin)[3,5,7]. This treatment is used to decrease bladder pressure, improve vesical capacity and ensure a regular and complete bladder voiding. In patients who fail to respond or do not tolerate this treatment, surgery is typically considered[3,5], even though it is associated with adverse events[3]. For these patients, botulinum toxin may be a reliable alternative, preventing early surgeries and their complications[8].
Botulin toxin is a potent neurotoxin produced by the bacterium Clostridium botulinum. *The use of botulinum neurotoxin type A (BoNT-A) therapy has been based on its reversible inhibition of acetylcholine neurotransmitter release, at the neuromuscular junction, resulting in striated muscle*

relaxation. Recent evidence suggests that BoNT-A has a primary peripheral effect which consists of the inhibition of the release of neurotransmitters (acetylcholine, adenosine triphosphate, and neuropeptides like substance P) and reduction in the expression of purinergic and capsaicin receptors on afferent neurons within the bladder. There is a secondary key effect - central desensitization through a decrease in central uptake of substance P and neurotrophic factors. Today, it is generally accepted that BoNT-A treatment of NDO is based on the summation of these effects, which include both motor and sensory pathways[5,9,10].

The use of BoNT-A in the lower urinary tract was first investigated in 1990, in adult patients with spinal cord injury, for the treatment of detrusor external sphincter dyssynergia. The effect of injecting BoNT-A into the detrusor muscle of adults with NDO was presented for the first time at the International Continence Society Meeting in 1999[3,5,11,15].

In 2002, Schulte-Baukloh et al. reported for the first time the effect of BoNT-A on children with NDO[5]. *Several pediatric studies were subsequently reported, each supporting the initial results*[5,7,8,16].

The consensus dosage of Botox® was of 5-12 U/kg of body weight up to 300U. Dysport® was used in dosages of 20 U/kg of body weight up to 400 U. Usually around 10-30 injection sites were selected per session[5,17]. *BoNT-A demonstrated its effectiveness in the pediatric population showing improvements in urinary continence, maximum cystometric capacity, maximum detrusor pressure, bladder compliance, incidence of urinary tract infections and vesicoureteral reflux*[5,17]. *Side-effects were rare. In addition, the beneficial effects of BoNT-A detrusor injections (at intervals of 6-9 months) seemed to persist after repeated procedures*[7,8].

The aim of this study was to assess the effectiveness and safety of intradetrusor injections of BoNT-A used to treat NDO, in children followed in the Pediatric Rehabilitation Service of the Centro de Medicina de Reabilitação - Alcoitão.

Material and Methods

We retrospectively reviewed the records of seven children aged between 6 and 17 years old, managed with intradetrusor BoNT-A injections between 2007 and 2011 (7/7: one injection series; 5/7: two injection series; 3/7: three injection series; 2/7: four injection series). All children were incontinent, despite intermittent bladder catheterizations and anticholinergic agents. Oxybutynin dose was prescribed according to the weight and symptoms (therapeutic dosage of 0.3-0.5 mg/Kg/day).

The following clinical information was collected: gender, age, age at the time of the diagnosis, NDO etiology, time between disease diagnosis and NDO diagnosis, time between NDO diagnosis and the first intradetrusor BoNT-A treatment, urinary bladder training characterization, concomitant treatments - baclofen, BoNT-A in other areas of the body, for other medical indications, intradetrusor injection complications, number of lower urinary tract infection (LUTI) episodes and of acute pyelonephritis, urinary continence, prophylactic antibiotic for LUTI, imaging results of renal and vesical ultrasound and retrograde cystography. Since this was a retrospective study, clinical data such as urinary continence, the number of LUTI episodes and pyelonephritis were accessed by the medical records and/or based on subjective information given by caregivers/patients.

The following urodynamic data were assessed: 1) maximum cystometric capacity (MCC) without leakage, 2) reflex volume (RV), which is the filling volume at which the first uninhibited detrusor contraction occurred, 3) maximum detrusor pressure (MDP) or highest detrusor pressure recorded during cystometry, and 4) bladder compliance (BC).

These clinical and urodynamic parameters were assessed before and three months after each intradetrusor BoNT-A injection series.

Urodynamic tests were performed and interpreted as recommended by the International Children's Continence Society[2]. *Urodynamic studies were conducted with the patient in the supine position using an 8Fr triple lumen catheter. Room temperature saline solution was infused at physiological filling rate (body weight in kg divided by 4 and expressed in ml per minute). Intra-abdominal pressure was monitored with a 12Fr intra-rectal catheter.*

BoNT-A injections into the detrusor, sparing the trigone and ureteral orifices (figure 1), were performed under vesical anesthesia (with lidocaine instillation), light sedation and endoscopic guidance, at the dose of 20 U/kg of Dysport®. BoNT-A was diluted in saline solution at a ratio of 100 U/10 ml and the number of injection sites was determined by the total BoNT-A volume injected to give 10 U per site. All the patients received LUTI prophylaxis. In the 24 hours post injection, they used an indwelling urinary catheter and then timed intermittent catheterization was restarted.

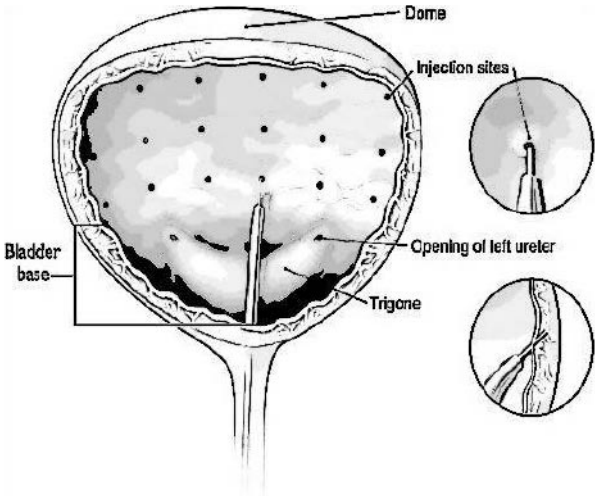

Figure 1) Intradetrusor BoNT-A injections, sparing the trigone and ureteral orifices.

Descriptive data analysis was performed using SPSS for Windows version 17.0 (SPSS Inc, Chicago, IL, USA). Wilcoxon Test was used to compare urodynamic parameters before and after intradetrusor BoNT-A injections. Significance was set at p≤0.05.

Results

Table I presents the main features of our seven patients with NDO. Table II shows the urodynamic data before and after the BoNT-A injection sessions.

The decision was made to repeat the intradetrusor treatment with BoNT-A when worsening of the urodynamic study results or of the clinical symptoms was verified.

The second BoNT-A injections were carried out after 9.6 months (min 5, max 12). The third BoNT-A injections were administered 15 months (min 14, max 16) after the second injection series and the fourth injection sessions 11.5 months (min 10, max 13) after the third injection sessions.

All children were placed on an oral oxybutynin therapeutic regimen. The dose was reduced in two patients after one intradetrusor BoNT-A injection session. However, in these two patients, due to a deterioration of clinical symptoms, it was decided to increase oxybutynin again, in order to reduce incontinence episodes. The remaining patients stayed on an oral oxybutynin regimen after each BoNT-A injection session.

No complications after intradetrusor BoNT-A injections were encountered. None of the patients experienced injection site pain or hematuria, or adverse events, such as dysphagia, respiratory difficulties or muscle weakness.

Variables	No of patients
Gender (F/M)	4/3
Age (years)	11.57 ±4.16
Age at the time of the diagnosis (years)	5.88 ±3.76
Spinal-Cord Injury Acquired • Traumatic • Infection - Pott's disease • Tumoral - Nephroblastoma metastasis Congenital • *Spina bifida*	7 4 1 1 1
Time between disease diagnosis and neurogenic detrusor overactivity diagnosis (months)	7.14 ±5.14
Time between neurogenic detrusor overactivity diagnosis and the initiation of intradetrusor BoNT-A treatment (years)	4.05 ±2.98
Urinary bladder training	
Daytime (3-3h) • Intermittent catheterization - self • Intermittent catheterization - caregiver	 2 5
Nocturnal • Urinary leakage • Continuous catheterization	 3 4
Existence of family and social conditions to do the intermittent catheterization	7
Medication	
Prophylactic antibiotic for LUTI	3
Oral baclofen	3
BoNT-A in other regions	1
Diagnostic imaging exams	
Vesicoureteral reflux • grade 1 • grade 3 • grade 4	5 2 1 2
Abnormal reno-vesical echography • renal ectasia • renal microlithiasis • hydronephrosis	4 1 2 1

LUTI – Low Urinary Tract Infection

Table I) Main clinical features of our seven patients with neurogenic detrusor overactivity.

	Before treatment	After 1st injection session	After 2nd injection session	After 3rd injection session	After 4th injection session
No of patients	(7/7)	(7/7)	(5/7)	(3/7)	(2/7)
Mean MCC without leakage (ml)	132.14 ±72.96	288.00 ±125.765	316.00 ±83.25	220*	150**
Mean RV (ml)	79.71 ±49.23	83.00 ±74.95 only 2 patients have UDC	136.67 ±78.01 only 3 patients have UDC	139*	117**
Mean MDP (cmH_2O)	58.00 ±32.22	35.60 ±22.12	31.00 ±8.94	45*	40**
Mean BC (ml/cmH_2O)	2.99 ±2.25	21.51 ±16.58	8.73 ±5.70	2,5*	2,5**

MCC - Maximum Cystometric Capacity; RV – Reflex Volume; MDP – Maximum Detrusor Pressure; BC - Bladder Compliance; UDC - uninhibited detrusor contractions.
*Results of two patients; **Results of one patient.
NOTE: After the third and fourth BoNT-A injection sessions, one of the patients missed the urodynamic study.

Table II) Urodynamic and clinical data before and after BoNT-A intradetrusor injections.

According to the Wilcoxon test used to compare the results of the urodynamic studies before and after the first intradetrusor BoNT-A treatment, there was a statistically significant improvement of the mean MCC without leakage (p=0.018), mean MDP (p=0.043) and mean BC (p=0.043). There also was a statistically significant improvement in the mean MCC without leakage (p=0.028) after the second intradetrusor BoNT-A injection session, when compared with the urodynamic studies performed before the second series.

According to subjective information, there was an overall clinical improvement in urinary continence, number of LUTI episodes and pyelonephritis. Although LUTIs are described in all patients after BoNT-A injections, their recurrence decreased. In the same way, patients and their caregivers referred to decreased urinary leakage after intradetrusor BoNT-A injection sessions. Before treatment, 2 patients had pyelonephritis, and after the third intradetrusor BoNT-A injection one of those patients had another pyelonephritis episode.

One patient registered positive results in her urodynamic and clinical parameters after the first two BoNT-A injection sessions, and two more sessions of injections were performed without any improvement. There was a progressive deterioration of her urodynamic studies and continence, and an increased number of LUTIs. An episode of acute pyelonephritis was recorded after the third BoNT-A injection session. She was then referred for a urology consultation in order to consider the possibility of enterocystoplasty.

One child required no further BoNT-A applications after the second application of BoNT-A (2 years ago), because he remains clinically well with urodynamic parameters within the normal range.

Discussion

In the last decade, BoNT-A use in children with NDO has gained worldwide acceptance due to its low risk-to-benefit ratio and its associated urodynamic and clinical benefits, resulting in substantial improvement in the quality of life[5,16,18].

Our population was small but homogeneous, with all seven patients having NDO due to spinal cord lesions.

We would like to emphasize the fact that all patients had good social and familiar support which allowed proper timed intermittent bladder catheterization, an essential element in their treatment.

In this study, BoNT-A treatment was not conceived as a replacement for anticholinergics, but rather as complementary treatment, as all patients were kept on an oral oxybutynin therapeutic regimen. In some studies, the dose of antimuscarinics could be reduced or even discontinued[14]. Neel et al. reported that oxybutynin had no augmentative effect on Botox[5]. In our study, despite the fact that oxybutynin dosage was reduced in two patients, the decision was made to subsequently increase the dose due to the deterioration in the patient's clinical symptoms. Therefore, future studies should better describe the most adequate antimuscarinic regimen for each case and whether or not adjuvant antimuscarinic drugs have an impact on the efficacy or duration of the BoNT-A effect.

We found that BoNT-A was consistently effective in reducing detrusor overactivity refractory to anticholinergic medication. This finding is consistent with previous reports[5]. According to the Wilcoxon Test, after the first intradetrusor BoNT-A treatment almost all urodynamic parameters improved compared with baseline values. There was a statistically significant increase in mean MCC without leakage after the first and the second session of injections. In most patients, mean MDP was reduced to at least 40 cm H_20. After the first intradetrusor BoNT-A injection session, mean RV increase was not statistically significant due to the fact that non-inhibited detrusor contractions were only verified in two patients. In our study, we observed increased mean BC in urodynamic parameters after the first and the second injection sessions.

We believe the results found in the patient that was considered for enterocystoplasty could be explained by the natural course of the underlying disease (spinal cord injury at birth), although tachyphylaxis cannot be excluded. Since our sample is small, we believe that the results after the third and fourth BoNT-A injection sessions were negatively influenced by this patient's results.

On the other hand, it must be noted that one child, after the second application of BoNT-A (2 years ago) did not require any additional BoNT-A applications since he remains clinically well and has urodynamic parameters within the normal range.

Improved continence and decreased total number of LUTIs were observed in most patients. However, it was not possible to quantify the improvement in these areas since this is a retrospective study and the information was collected based on clinical data and on testimonials given by children and parents/caregivers (subjective information). Future studies should more adequately document and report continence status and LUTI statistics, such as use of continence

scales. For this purpose, the authors developed an evaluation and follow-up protocol for NDO patients treated with intradetrusor BoNT-A.
Long-term changes in the detrusor after multiple injections need to be assessed as they could be related to added risk of developing drug resistance, with diminished efficacy of subsequent treatments[13]. However, there is no study in children that assesses the impact of repeated injections on the bladder wall and on the increased risk of fibrosis. Although Pascali et al. suggested intradetrusor BoNT-A injections do not increase fibrosis in the pediatric population[16], these impacts need to be further clarified in specifically designed studies[5].
In our patients, the time between injections was longer than in earlier reports, ranging from 9.6 to 15 months. Recurrent incontinence and deterioration on urodynamic studies led to subsequent intradetrusor injections. The optimal policy for reinjections and when patients should return for additional injection are questions of great importance[5]. Three main options may be evaluated and compared: 1) reinjection after a predefined time interval of 7-8 months based on literature data on duration of effect; 2) reinjection at the tail-end of the previous active injection, which takes into account interindividual variation; and 3) reinjection only based on symptoms or urodynamic worsening[5]. Patients suffering from NDO should not receive repeated injections in case of: 1) remaining compliance problems; 2) limited or no urodynamic or symptomatic improvement after two injection sessions; or 3) severe adverse events whatever the number of injections.

Conclusions

In our retrospective study, intradetrusor BoNT-A injection sessions in patients with NDO was safe and effective, except in one patient. They achieved a significant improvement in urodynamic parameters which could be associated with clinical benefits (improved continence and reduction in the number of LUTIs) and certainly with safeguarding of the urinary tract. All these can lead to a better quality of life for the patients. Thus, although BoNT-A is an expensive treatment, we consider that the cost of incontinence equipment, UTI treatments, some with hospitalization, urologic surgeries or even the treatment of deteriorating function of the upper urinary tract, are much more expensive and time-consuming.
The small number of patients and retrospective design are the main limitations of our study. In the future, more accurate clinical data should be recorded (continence status, LUTI and pyelonephritis). To further improve the future application of intradetrusor BoNT-A, research should focus on assessing the optimal dose (including dilution volume, number and location of injections) and time between injections of BoNT-A. All of these questions should be aid in the preparation of adequately powered, well-designed and controlled trials in the future.

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