Actas Urológicas Españolas. 2011;**35(2)**:89–92

Actas Urológicas Españolas

www.elsevier.es/actasuro

ORIGINAL ARTICLE

Injection of botulinum toxin (BTX-A) in children with bladder dysfunction due to detrusor overactivity

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Received April 22, 2010; accepted August 31, 2010

KEYWORDS
Neurogenic bladder dysfunction;
Non-neurogenic bladder dysfunction;
Urinary incontinence;
Bladder augmentation;
Botulinum toxin

Abstract
Introduction: Bladder dysfunction causes urinary incontinence and kidney damage in children. When treatment with anticholinergics and intermittent bladder catheterization fails, the alternative therapy is bladder augmentation.
Patients and methods: Between 2005 and 2009, a prospective study was carried out with Botox® injected into the detrusor of children suffering from high-pressure bladder despite anticholinergic treatment. We assessed their urodynamic, clinical and radiological evolution prior to and at 4 weeks, 6 months and 1 year after the injection (10 u/kg of weight up to 300 u). Reinjection was indicated in the event of clinical or urodynamic worsening. We employed the Wilcoxon test to statistically analyze the urodynamic parameters.
Results: 12 patients were treated, 11 with neurogenic bladder (91.7%) and 1 with posterior urethral valves (8.4%). The mean age was 12.6 (4.3-17.8) years and follow-up took place after 40.8 (16.9-45-7) months. Bladder capacity, detrusor compliance and pressure improved after 4 weeks in all the patients except in 2 (16.7%). This improvement decreased after 6 months, although successive injections produced similar changes. One patient (8.3%) received 1 dose, six (50%) two doses and five (41.7%) received three. Clinical and urodynamic improvement in 8 patients (66.7%) prevented bladder augmentation.
Conclusions: Repeated botulinum toxin injection in the detrusor is a therapeutic instrument for high pressure and hypocompliant bladders in children. It could replace bladder augmentation in some cases, however further studies with long-term follow-up care are required to appropriately evaluate its safety and effectiveness.

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PALABRAS CLAVE
Disfunción vesical neurógena;
Disfunción vesical no-neurógena;
Incontinencia urinaria;
Ampliación vesical;
Toxina botulínica

Es la inyección de toxina botulínica-A en el detrusor una alternativa a la ampliación vesical en niños

Resumen

Introducción: La disfunción vesical causa incontinencia urinaria y daño renal en niños. Cuando el tratamiento con anticolinérgicos y cateterismo vesical intermitente fracasa, la alternativa terapéutica es la ampliación vesical.
Pacientes y métodos: Entre 2005 y 2009 se ha realizado un estudio prospectivo con Botox® inyectado en el detrusor de niños por disfunción vesical con alta presión a pesar del tratamiento anticolinérgico. Se valora la evolución urodinámica, clínica y radiológica, antes y a las 4 semanas, 6 meses y 1 año tras la inyección (10 U/kg de peso hasta 300 U). La reinyección se indicó ante empeoramiento clínico o urodinámico. Se empleó test de Wilcoxon para el análisis estadístico de los parámetros urodinámicos.
Resultados: Se trataron 12 pacientes, 11 de causa neurógena (91,7%) y 1 por válvulas de uretra posterior (8,4%). La mediana de edad fue 12,6 (4,3-17,8) años y el seguimiento 40,8 (16,9-45,7) meses. A las 4 semanas se produjo mejoría en capacidad vesical, acomodación y presión del detrusor en todos los pacientes salvo en 2 (16,7%). Esta mejoría fue disminuyendo a partir de 6 meses, aunque inyecciones sucesivas produjeron cambios similares. Un paciente (8,3%) recibió 1 dosis, seis (50%) 2 y cinco (41,7%) 3. En 8 pacientes (66,7 %) la mejoría clínica y urodinámica permitió evitar ampliación vesical.
Conclusiones: La inyección de toxina botulínica repetida en detrusor es una herramienta terapéutica frente a disfunciones vesicales con alta presión y baja acomodación en niños. Puede sustituir a la ampliación vesical en algunos casos, pero se necesitan estudios con largo seguimiento para evaluar apropiadamente su seguridad y eficacia.

Introduction

Bladder dysfunction with overactivity of the detrusor is characterized by presenting high intravesical pressure, low bladder capacity, non-inhibited contractions of the detrusor, as well as hypocompliant bladder. It may condition kidney damage and urinary incontinence. The most frequent cause of this type of alterations of the detrusor in children is neurogenic bladder dysfunction secondary to myelomeningocele.

Classic treatment consists of administering oral anticholinergics and at the same time performing intermittent bladder catheterization (IC). When this treatment fails, it becomes necessary to augment the bladder, generally by means of apposition of a segment of intestine, thus improving bladder capacity, compliance and, in many cases, even reflux and continence. However, it entails high perioperative morbidity. The aim of our work is to assess the effect of the BTX-A injections in the detrusor and its therapeutic utility in the handling of children with high-pressure bladder dysfunction, hypocompliance and low capacity in which treatment with oral anticholinergics, avoiding bladder augmentation as far as possible.

Materials and methods

In January 2005, we introduced a protocol of BTX-A injection in the detrusor in children with high-pressure bladder dysfunction and hypocompliance, refractory to conventional treatment. This protocol includes a prospective record of clinical, radiological and urodynamic evolution. The data of these patients was included in a database comprising 12 children treated from January 2005 until February 2009.

The inclusion criteria in the treatment protocol and study was intolerance to anticholinergic treatment or its failure, defined by: i. The appearance of vesicoureteral reflux associated or not to reflux nephropathy; ii. Urodynamic worsening or lack of improvement following correction of the dosage of oral anticholinergics; iii. Worsening of continence or lack of improvement following correction of the dosage of oral anticholinergics; iv. Kidney damage characterized by new kidney scars in the gammagraphy.

The protocol includes the performance of a study prior to the injection, which consists of: a kidney ultrasound, kidney gammagraphy, serum biochemistry, sediment and urine culture, video urodynamics culture (table 1) and micturition record (episodes of leakage, volume obtained in the bladder capacity index, dry interval). In all the

Table 1 Data assessed in the video urodynamic study of the patients

Maximum bladder capacity
Compliance
Non-inhibited contractions of the detrusor and reflux volume
Maximum detrusor pressure
Vesicoureteral reflux and degree

cases, parents and children gave their informed consent for the Botox® injection in the detrusor. The children were subjected to reinjection in the event of clinical and/or urodynamic worsening.[1,2] The injection was administered with a Cook® needle, with injection of 10 IU per Kg of weight up to a maximum of 300 IU, with a dilution of 10 IU per ml of saline solution. 20 to 30 different points were injected into the detrusor with 1 ml of dilution per point, respecting the trigone. After the procedure, the patients were kept catheterized for 24 hours; treatment with oral anticholinergics was suspended and intermittent catheterization was maintained.

Follow-up was carried out by means of clinical check-up, kidney ultrasound, sediment and serial urinary culture, video urodynamics at 4 weeks and at 6 months. The subsequent video urodynamics at 6 months of the first injection and those subsequent to the consecutive injections were indicated in accordance with the clinical evolution of the children. We analyzed the evolution of three urodynamic parameters of the filling cystomanometry: bladder capacity, maximum detrusor pressure (MDP) and compliance (). The values of the quantitative variables are expressed as median and range. For the comparative statistical analysis, we used the Wilcoxon test and considered $p<0.05$ to be statistically significant.

Results

We treated a total of 12 patients with bladder dysfunction refractory to conventional treatment. Ten children presented hyper-reflexive bladder (83.3%) and two presented high-pressure bladder and low adaptation (16.7%). The boy/girl ratio was 2:1 and the mean age at the time of the first injection was 12.6 (4.3-17.8) years. The baseline diagnosis of the bladder dysfunction was myelomeningocele (n=9, 75%), in a case associated with anorectal atresia, spinal cord injury (n=1, 8.3%), neonatal spinal cord infarction (n=1, 8.3%) and posterior urethral valves (n=1, 8.3%). The patient with cloacal dysgenesis syndrome was included in the study as a result of not responding to the treatment with anticholinergics prior to the closure of the cutaneous ureterostomy, which drained his only kidney. The child with the posterior urethral valves had a long-term defunctionalized bladder, as he had a single ureterostomized kidney. In this case, the purpose of the BTX-A injection in the detrusor was to increase the capacity and compliance of the bladder prior to closure of the ureterostomy. This patient also required a bladder lavage programme with progressive volumes.

One patient (8.3%) required one injection, six patients (50%) required two injection and five patients (41.7%) required three injections. No patient presented complications or side effects of the treatment. Two children (16.7%) suffered febrile urinary tract infection in the days following the injection, which was treated satisfactorily with oral antibiotherapy. One developed giant bladder stone in the weeks following the injection, which required open lithotomy.

The mean follow-up was 40.8 (16.9-45.7) months. 83.3% experienced an improvement of all their urodynamic parameters, accompanied by an improvement in continence in the clinical control carried out four weeks after the first injection. We analyzed the evolution of bladder capacity, MDP and bladder compliance after the first BTX-A injection in the detrusor. The mean bladder capacity went from 110.5 (18-357) to 245 (90-408) ml at four weeks and to 271.5 (70-426) ml at six months after the first injection ($p<0.05$). The MDP went from 51 (20-130) to 34 cm H_2O (11-56) at four weeks ($p<0.05$), however at six months it returned to 63.5 cm H_2O (15-75). Compliance went from 3.3 (0-76,6) to 9.45 (1.7-94.7) ml/cm H_2O at four weeks ($p<0.05$), however at 6 months it was similar to the baseline, with a man of 5.9 (1.8-38) ml/cm H_2O. In short, the improvement in bladder capacity, MDP and compliance at four weeks was statistically significant, however at six months it disappeared and only the bladder capacity continued to be significantly greater than the baseline. The video urodynamics showed changes in the bladder morphology, which went from being smooth in 83.3% of the patients at four weeks after the injection. In three cases (25%) the urodynamic improvement remained the same a year after the first injection and one of them maintained the changes at 18 months after the first injection. 66.7% of the patients presented vesicoureteral reflux, which disappeared in 75% of them (4 weeks and 6 months). Ten patients (83.3%) presented non-inhibited contractions that disappeared in nine of them in the initial control and reappeared in 3 cases in the late controls.

We analyzed urodynamic evolution after the second and third injection. Bladder capacity after the second injection was a mean of 304 (100-425) ml and after the third injection, it was 293 (43-400) ml, ($p<0.05$ with respect to the first injection). The MDP was 33 (17-90) cm H_2O after the second injection and 30 (5-47) cm H_2O after the third. We only found statistical significance in the MDP changes after the second injection. Compliance after the second injection was 9.2 (3.8-90) ml/cm H_2O and 10.9 (0.6-25) ml/cm H_2O after the third injection, when the improvement was of statistical significance after the second injection with respect to the baseline.

In 58.3% of the cases, the result of the successive BTX-A injections was considered to be effective from a clinical and urodynamic viewpoint, remaining dry with IBC every 3 hours. These children have managed to avoid bladder augmentation. The child with the valves achieved good compliance and capacity after two injections in the detrusor, which allowed closing the ureterostomy. Subsequently, the patient maintained low bladder pressures without the need for new treatment. In three patients (25%), we considered the treatment with BTX-A in the detrusor had a bad or inadequate functional result, where it was necessary to perform bladder augmentation with sigma.

Discussion

The BTX-A injection in the detrusor produced a clinical and urodynamic improvement at 4 weeks in the majority of the patients with high-pressure bladder dysfunction and hypocompliance. In the filling cystomanometry, bladder capacity is the value that undergoes the greatest and

longest improvement. This fact may explain the fact that the majority of the patients continued to be dry with intermittent catheterization. In any case, the effect of the injection decreases with time, when it becomes necessary to administer more injections. The study of our series demonstrates that successive injections produce similar effects to those observed after the first injection. In the majority of the children treated for neurogenic bladder dysfunction, we managed to avoid performing a medium-term bladder augmentation.

We had two cases in which there was no urodynamic or clinical response after the first injection, nor improvement after repeated injections. These two patients presented urine infections in the days subsequent to the injection, which could have interfered with the results. More experience is needed to identify factors that determine the lack of response to treatment with BTX-A. The urodynamic behaviour of the child with urethral valves was superimposable on the rest of the patients of the series.[3]

Since 1990, different authors have communicated the use of BTX-A in urology, both for the treatment of overactivity of the detrusor, as well as for bladder sphincter dyssynergy and hyperactivity of the detrusor due to neurogenic bladder dysfunction in children.[4-7] The mechanism of action is based on blocking parasympathetic innervation. For this reason, achalasia or hyperhidrosis have also been successfully treated.[8] However, the effects of the BTX-A injection have been reduced with time, which has made it necessary to repeat the injections with time, so maintaining improvement,[9] although resistance following repeated injections has also been described.[10] The repeated injection of BTX-A in the detrusor allows to easily treat both clinical and urodynamic alterations in children with neurogenic and non-neurogenic bladder dysfunction with little morbidity. We were even able to avoid bladder augmentation in the majority of the patients in the short and medium term. However, studies with lengthy follow-ups are required to determine its long-term effect and safety. This treatment can also be considered in the case of oral anticholinergic intolerance due to its low incidence of complications and good tolerance. In short, the injection of BTX-A in the detrusor may be indicated both in patients with a hyper-reflexive bladder and in patients with hypocompliant and high-pressure bladder, given that the response is similar.

Conflict of interest

The authors declare not to have any conflict of interest.

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