BOTULINUM TOXIN-A THERAPY IN PEDIATRIC POPULATION – SINGLE-CENTER EXPERIENCE

TERAPIJA BOTULIN TOKSINOM A U PEDIJATRIJSKOJ POPULACIJI – ISKUSTVO JEDNE KLINIKE

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Abstract

Introduction. This study aims to evaluate the efficacy and safety of Botulinum toxin-A therapy in pediatric population with lower urinary tract symptoms. **Material and Methods**. A retrospective review was conducted on our initial clinical experience in treating lower urinary tract symptoms with Botulinum toxin-A at the Institute for Child and Youth Health Care of Vojvodina. Given the diversity of symptoms and the heterogeneity of underlying pathological conditions, each patient and their treatment outcomes were individually analyzed. **Results**. Our clinical experience revealed that 80% of the patients demonstrated significant improvement in symptoms following Botulinum toxin-A injections. Specifically, of the 17 patients treated, 15 reported symptom relief, with 7 achieving complete regression of lower urinary tract symptoms. Only two patients with developmental delays exhibited partial improvement, with persistent lower urinary tract symptoms. **Conclusion**. Botulinum toxin-A injections have shown promising efficacy in managing refractory bladder dysfunction in the pediatric population. The majority of patients experienced symptom regression, with many achieving complete remission. The treatment protocol was well-tolerated, with no adverse effects observed. However, the variability in treatment responses, particularly in patients with developmental delays, underscores the need for individualized treatment planning. Larger cohort studies with extended follow-up periods are needed to validate the long-term efficacy and safety of Botulinum toxin-A therapy in pediatric population. Among available therapeutic options, Botulinum toxin-A plays a significant role in improving the quality of life for children with lower urinary tract symptoms.

Keywords: Botulinum Toxins, Type A; Pediatrics; Child; Lower Urinary Tract Symptoms; Urinary Bladder, Overactive; Urinary Bladder Diseases; Treatment Outcome

Sažetak

Uvod. Cilj rada je procena efikasnosti i sigurnosti terapije botulin toksinom A kod pedijatrijske populacije, a u sklopu lečenja simptoma donjeg urinarnog trakta. **Materijal i metode.** Sprovedena je retrospektivna studija koja predstavlja pregled inicijalnog kliničkog iskustva u lečenju tegoba donjeg urinarnog trakta botulin toksinom A u pedijatrijskoj populaciji na Institutu za zdravstvenu zaštitu dece i omladine Vojvodine. Zbog velike raznovrsnosti tegoba i heterogenosti patoloških stanja, pacijenti i rezultati njihovih lečenja razmatrani su pojedinačno. **Rezultati.** Naše kliničko iskustvo pokazalo je da je 80 procenata pacijenata imalo značajno poboljšanje simptoma nakon injekcija botulin toksina A. Konkretno, 15 od 17 pacijenata prijavilo je smanjenje tegoba, a kod sedam dolazi do potpune regresije tegoba. Kod samo dva pacijenta, koji su praćeni zbog kašnjenja u razvoju, postignuto je delimično poboljšanje, uz perzistiranje simptoma donjeg urinarnog trakta. **Zaključak.** Upotreba injekcija botulin toksina A u pedijatrijskoj populaciji sa refraktornom disfunkcijom bešike, pokazala je obećavajuće rezultate. Kod većine pacijenata verifikovano je regrediranje tegoba, dok je značajan broj pacijenata bez ikakvih simptoma nakon tretmana. Pacijenti su dobro tolerisali terapijski protokol i nisu registrovani neželjeni efekti. Varijabilnost u samom odgovoru na terapiju, posebno kod pacijenata sa kašnjenjem u razvoju, ističe potrebu za individualizovanim planom lečenja. Kako bi se potvrdila dugoročna efikasnost i sigurnost primene botulin toksina A u pedijatrijskoj populaciji, potrebne su studije koje bi obuhvatile veći broj pacijenata i duži period praćenja. Opravdano, terapija botulin toksinom A ima značajno mesto u lečenju i unapređivanju kvaliteta života pacijenata sa simptomima u donjem urinarnom traktu.

Ključne reči: botulin toksin-A; pedijatrija; dete; simptomi donjeg urinarnog trakta; hiperaktivna bešika; bolesti mokraćne bešike; ishod lečenja

Introduction

Lower urinary tract symptoms (LUTS) encompass a wide range of issues stemming from various disorders involving the central or peripheral nervous systems. General classification of causes refers to any anatomic, neurogenic, or non-neurogenic conditions [1, 2]. Regardless of etiology, treatment aims to address two primary goals: optimizing bladder storage and ensuring effective bladder emptying. These measures are essential for preventing permanent damage to both the upper and lower urinary tract. In older children, the primary therapeutic challenge is achieving social continence and fostering independence in bladder man-

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Abbreviations

LUTS – lower urinary tract symptoms
ICCS – International Children's Continence Society
OAB – overactive bladder
IU – international unit

agement, which should persist into adulthood. Diagnosing bladder disorders in children typically involves physical examination, urinalysis and urine culture, biochemical tests, abdominal ultrasound, and urodynamic investigations. Additional tests such as cystography, renal scans, intravenous pyelography, and computed tomography may also be employed to assess the extent and severity of the condition. Early evaluation and appropriate treatment are crucial for minimizing or preventing damage to the upper urinary tract and the bladder, and maximizing safe, socially acceptable continence. Management strategies focus on reducing bladder pressures, increasing capacity and compliance. The International Children's Continence Society (ICCS) recommends urotherapy as the initial treatment for all types of LUTS. This non-invasive, non-pharmacological approach emphasizes bladder re-education or rehabilitation to optimize filling and voiding functions. Success rates for urotherapy range from 40 to 90 percent [3, 4]. This treatment protocol combines education and demystification, behavioral modification guidance, lifestyle adjustments regarding fluid intake, and tracking of voiding frequencies, volumes, and incontinence episodes, along with constant support and encouragement for both children and their guardians [2, 5]. Standard urotherapy is a valuable cost-free option as it is a purely behavioral intervention with no side effects that can sometimes lead to spontaneous resolution of the symptoms [2, 6]. When conservative measurements fail to provide sufficient results, pharmacological treatments are indicated. Antimuscarinic agents, particularly oxybutynin, are the first-line pharmacologic options for pediatric patients. Oxybutynin, accepted and validated for use in children for over 20 years, is the only antimuscarinic medication approved by the U.S. Food and Drug Administration for managing overactive bladder symptoms in children aged five and older. Unlike other anticholinergics, oxybutynin is a non-selective and, short-acting drug, and its dosage can be tailored to periods of peak symptoms [3]. Newer generation of antimuscarinics, including propiverine, tolterodine, and solifenacin, have recently gained approval for use in pediatric patients, although they are still less commonly prescribed than oxybutynin. While all antimuscarinics are considered safe and well-tolerated, certain side effects such as dry mouth, dizziness, headache, and constipation, occur in 3% to 23% percent of cases, sometimes prompting discontinuation [2, 3]. Additional pharmacological options include mirabegron and imipramine. Mirabegron is an innovative drug, recognized as the first ß3-adrenergic receptor agonist available for treating overactive bladder (OAB). While proven effective and safe in adults, its efficacy in pediatric patients remains under investigation. In severe OAB cases, combination therapy involving anticholinergic and β2-adrenergic receptor agonists offers a potent alternative for pediatric patients unresponsive to single-agent anticholinergic therapy [3]. Recent pediatric literature highlights Botulinum toxin-A as a treatment option for bladder disorders and lower urinary tract symptoms. The substance is effective in managing high bladder pressures and incontinence caused by both uninhibited bladder contractions and sphincter dysfunction. As evidence supporting its safety and efficacy grows, pediatric urologists increasingly adopt Botulinum toxin-A as a preferred long-term treatment of children with both non-neurogenic and neurogenic bladder disorders.

Material and Methods

We reviewed our initial clinical experience with pediatric patients treated with Botulinum toxin-A at the Institute for Child and Youth Health Care of Vojvodina. The patients included were those with neurogenic bladder, overactive bladder with daytime incontinence, and patients with non-monosymptomatic nocturnal enuresis. The inclusion criteria for the procedure were the absence of a clinical response to any of the treatment protocols such as standard urotherapy, biofeedback, medicaments (such as antimuscarinics and/or B3 agonists), clean intermittent catheterization, etc. For patients with neurogenic bladder, the indication for Botox instillation besides the positive findings on urodynamic testing was incontinence between catheterizations. For patients with therapy-resistant enuresis, inclusion required that the patient had been on a combined treatment regimen for at least 3 months, in addition to the diagnostic workup. The exclusion criteria were any contraindications to Botulinum toxin-A. All patients underwent a comprehensive diagnostic evaluation before the intervention, including mandatory urodynamic testing. Both pre and post-intervention data were collected through medical history. The data included symptoms of the lower urinary tract, such

as urgency, frequency, and urinary incontinence, as well as drug therapy, uroflowmetry, and urodynamic studies. Due to a great diversity of underlying conditions, all patients and their outcomes were presented individually.

Results

In this retrospective clinical study, we reviewed the medical records of 17 pediatric patients treated with Botulinum toxin-A (Botox) at the Institute for Child and Youth Health Care of Vojvodina, Department of Surgery. The cohort included 3 patients with overactive bladder (OAB), 7 with neurogenic bladder, 5 with non-monosymptomatic nocturnal enuresis, and 2 with other underlying conditions. All procedures were performed under general anesthesia, with intravenous antibiotic prophylaxis administered preoperatively. The intervention involved rigid cystoscopy and the intradetrusor injection of Botox, diluted in 10 ml of 0.9% saline. Twenty injections, each approximately 0.5 ml, were distributed evenly through the detrusor muscle, avoiding the trigone area, using a Deflux needle. The dosing was determined based on clinical experience rather than specific symptomatology or urodynamic parameters. A total of 14 patients received 100 international units (IU) of Botox, while 3 older patients (aged over 15 years) received 200 IU. Post-intervention catheterization was maintained for 48 hours for all patients. To maximize the bladder volume and facilitate continence, all patients received urotherapist-guided bladder training following the procedure.

Among the 7 patients with neurogenic bladder, 4 had myelomeningocele, 1 had a spinal cord injury, 1 had undergone pelvic neuroblastoma surgery, and 1 had for a history of sacral teratoma surgery. Of the 3 patients with OAB, 2 achieved complete symptom resolution after a single treatment. The remaining patient, a female now over 18 years old, continues to experience symptoms. Among the 5 patients with therapy-resistant enuresis, 3 became symptom-free after one treatment, while 2 with developmental delays continued to experience symptoms; one received a single treatment, and the other received two treatments. Additionally, two patients were not classified within any category due to their underlying conditions.

The first, diagnosed with urinary incontinence, exhibited bladder dysfunction confirmed through urodynamic studies. Extensive evaluations by neurosurgeons, neurologists, and gastroenterologists revealed no significant dysfunctions. After radiography and MRI of the lumbosacral region, the treatment regimen started involving Macrogolaxan and other supportive therapies. The patient underwent an initial Botulinum toxin-A treatment (100 IU) coupled with biofeedback therapy, followed by a second Botox intervention, which reinforced the positive outcomes of the first intervention, resulting in a marked reduction in incontinence.

The second patient initially presented with urinary retention and hematuria. An abdominal ultrasound identified a bladder wall lesion protruding into the lumen. Cystoscopy with biopsy revealed a lesion at the entrance of the bladder, with histopathological analysis confirming the diagnosis of Rhabdomyosarcoma. Surgical treatment was performed at a specialized center abroad, with administration of neoadjuvant therapy followed by partial resection of the bladder, and brachytherapy targeting the bladder and prostate. The completion of postoperative chemotherapy finalized the primary treatment course. After completing the tumor treatment, the patient continued to experience discomfort such as recurrent episodes of itching and increased urinary frequency, sometimes associated with incontinence. To manage these persistent symptoms, the patient underwent cystoscopy with instillation of Botulinum toxin-A into the bladder wall (100 IU), and was prescribed Solifenacin 5 mg once a day.

Both of these two additional cases highlight the potential efficacy and safety of Botulinum toxin-A in managing refractory LUTS, emphasizing the need for individualized treatment plans in addressing challenging bladder dysfunctions in pediatric patients.

Discussion

Lower urinary tract symptoms affect individuals across all age groups, with two notable incidence peaks, one in childhood and another in adulthood (ages over 40). The overall prevalence of LUTS is estimated to range between 25% and 45%, with 20% to 30% of children experiencing dysfunctional voiding and related symptoms, such as incontinence and enuresis [5, 7, 8]. The causes are typically classified into three main groups: 1) anatomic, 2) neurogenic, and 3) non-neurogenic. Anatomic and neurogenic causes, including posterior urethral valves and spinal dysraphisms, require immediate recognition and management, which extends beyond the scope of this paper. Conversely, non-neurogenic causes, including OAB, voiding postponement, and dysfunctional voiding, stem from a complex interaction of behavioral, genetic, and functional factors [5]. Dysfunctional voiding, also re-

ferred to as "non-neurogenic bladder" or "Hinman-Allen Syndrome", was initially described by Hinman and Baumann in 1973. They observed a group of children who, despite having no signs of neurologic disease, exhibited abnormal non-relaxation of the external sphincter during voiding. Although various patterns of dysfunctional voiding have been identified, they all share the common feature of sphincter non-relaxation during the voiding process [6]. LUTS can manifest as isolated symptoms or may be associated with and/or worsened by any accompanying disorder that affects the nervous system, such as myelomeningoceles, Parkinson's disease, or stroke [2]. In children, LUTS can also be a symptom of various non-neurological voiding disorders. The most common of these include dysfunctional voiding, detrusor overactivity disorder, and giggle incontinence [2–4]. Daytime urinary incontinence, affecting 7% to 10% of children aged 5 to 13, and nocturnal enuresis, defined as sleep-associated incontinence, are particularly prevalent. Monosymptomatic nocturnal enuresis refers to bedwetting without other LUTS, whereas non-monosymptomatic nocturnal enuresis involves bedwetting accompanied by daytime symptoms of the lower urinary tract. Three primary causes of nocturnal enuresis include nocturnal polyuria, detrusor overactivity, and an increased arousal threshold during sleep [3]. As the child matures, voiding gradually comes under voluntary control. The first awareness of bladder function typically occurs around the age of 1 to 2 years, when toilet training is often initiated. Given that each child develops at own pace, it is expected that the adult-like voiding pattern will be established by ages 3 to 5. Consequently, any form of lower urinary tract dysfunction is considered physiological in children up to 5 years old. Beyond this age, any symptoms such as recurrent urinary tract infections (UTIs), incontinence, frequency, hesitancy, and holding maneuvers, should be carefully evaluated [2]. Child bladder capacity is estimated by two formulas: for children younger than 2, the formula is 7 x weight in kg, and for older ones (ages in years + 1) x 7. As bladder capacity increases and the cortical pathways regulating detrusor and sphincter function continue to develop, there is a corresponding decrease in voiding frequency. This frequency typically reduces from around 24 times per day at birth to about 4 to 6 times daily by the age of 4 [2, 5].

Diagnostic tools include thorough medical history, physical examinations, bladder diaries, questionnaires, urinalysis, post-void residual volume measurement, flowmetry, and ultrasound [3, 9]. The primary objective of these initial assessments is to identify the specific subtype of LUTS, evaluate the frequency and severity of the symptoms, assess their impact on the patient's quality of life, and determine the appropriate level of treatment required [7]. A detailed voiding and medical history explores voiding frequency, sensation of urgency, hesitancy, feelings of complete or incomplete emptying, daytime and/or night-time incontinence, and the quality of the urinary stream. This helps physicians determine patterns and triggers associated with a particular subtype of disorder. After the detailed anamnesis, a physical examination focuses on anatomic abnormalities and other possible contributing causes [1]. While, the majority of physical examinations of the abdomen, lower back, and genitalia are regular, the examination can also identify a distended bladder, full rectal ampulla, signs of an occult spinal dysraphism, or other malformations of the external genitalia (phimosis, meatal stenosis, or labial fusion). Bladder diaries are typically recorded on paper charts or through various smart device applications, tracking both voided volumes and liquid intake. Most physicians who specialize in voiding disorders emphasize the importance of using incontinence questionnaires. Over the past few decades, several voiding and elimination questionnaires have been developed specifically for children with voiding disorders, with the Dysfunctional Voiding Symptom Score being the most widely used [3]. Once a comprehensive voiding history is gathered, further diagnosis steps are taken. Initially, urine studies, including urinalysis and urine culture, are conducted to rule out urinary tract infections as a potential cause of the symptoms. The post-void residual calculation is also useful if the child is suspected for overflow incontinence. It can be measured using either ultrasound or intermittent bladder catheterization after the patient has emptied their bladder fully to determine the amount of urine left in the bladder. Volumes greater than 200 ml are indicative of overflow incontinence, while a residual volume of less than 50 ml effectively rules out overflow incontinence as a contributing factor to a patient's symptoms [1]. Transabdominal ultrasound is a valuable tool for visualizing the bladder, assessing bladder wall thickness, determining whether the bladder neck is open or closed, and measuring the diameter of the rectum [2, 3]. Uroflowmetry, as a next step in the diagnostic protocol, provides a graphical recording of the urinary stream, offering insights into voided volume, flow time, initial stream velocity, maximal flow rate, and the flow pattern.

Cystometry and urodynamics are also beneficial diagnostic tools [3]. According to the ICCS, a conservative approach should be prioritized in treatment strategies. If necessary, pharmacological treatment may be added but always combined with other treatment modalities [3, 7]. As mentioned above, Botulinum toxin injections are one of the options for children with idiopathic detrusor overactivity, refractory to non-invasive procedures [10]. Botulinum toxin is a potent neurotoxin produced by the facultative anaerobic bacteria Clostridium botulinum, discovered and used for medicinal purposes in 1897 by Van Ermegam [11]. For over 30 years, Botulinum toxin-A has been utilized in treating lower urinary tract dysfunction, and it is widely used to restore urinary continence and enhance quality of life. Its effectiveness stems from its ability to inhibit the calcium-mediated release of acetylcholine vesicles at the presynaptic neuromuscular junction in peripheral nerve endings, leading to temporary flaccid muscle paralysis [12]. The mechanism involves inhibiting the abnormal release of neurotransmitters like acetylcholine, adenosine triphosphate, and substance P, as well as the abnormal expression of transient receptor potential cation channel subfamily V member 1 (TRPV1) and the purinergic receptor (P2X3). These neurotransmitters play a role in bladder sensation and inflammation, influencing detrusor muscle contraction [13]. Subureteral toxin injection causes relaxation of striated/smooth muscles and helps control local inflammation. This action increases bladder capacity, reduces intravesical pressure, and leads to an overall improvement in continence. Currently, there are seven serotypes of Botulinum toxin-A (A, B, C1, D, E, F, G), all of which are derivatives of the toxin produced by Clostridium botulinum. Among these, Botulinum toxin-A is the most commonly used for medicinal purposes in humans. The three commercially available formulations of the toxin are Botox, Dysport, and Myobloc [11]. Botulinum toxin is applied intravesically under general anesthesia, with rigid cystoscopy and injections equally distributed into the detrusor muscle. When comparing treatment outcomes across various doses of Botox, it was observed that 100 international units (IU) achieved a 73.3 percent success rate, with fewer adverse events occurring at this dose compared to higher ones. Based on these findings, along with results from other clinical studies, 100 IU of Botulinum toxin-A has become a standard dose that delivers satisfactory outcomes. A double-blind, placebo-controlled, randomized, dose-ranging trial that tested doses of 50, 100, 150, and 200 IU of Botulinum toxin-A found that the 100 IU dose was particularly effective [13]. The higher dose of BTX-A showed a favorable response in the short term but outcomes in the long term were similar between the two groups [12]. The lethal dose of Botulinum toxin for humans is approximately 3000 IU (39 IU per kilogram of body weight), and must be administered intravascularly to achieve lethality [11]. The effects of Botulinum toxin injections typically last 6 to 9 months, which is significantly longer than if the toxin is injected into skeletal muscle. On the other hand, therapeutic effects were found to last longer with repeated Botox injections compared to a single injection. Administering Botox injections every 6 months extended the duration of therapeutic benefits. It is recommended that the interval between retreatments should not be shorter than 3 months, with a preferred interval of 6 to 9 months. This period is recommended to prevent the development of residual circulating antibodies that could diminish the efficacy of subsequent Botox injections [13]. One of the primary drawbacks of this procedure in pediatric patients is the necessity for general anesthesia [14]. Aside this, there are relatively few reported side effects [15]. The most common reasons for discontinuing Botox treatment include inadequate efficacy and issues related to the need for clean intermittent catheterization. Importantly, there have been no reports of serious systemic adverse events, like respiratory depression or generalized muscle weakness, following Botox injection. The most frequently observed local adverse events include gross hematuria, a significant post-void residual volume exceeding 150 mL, difficulty urinating, and urinary tract infections [13, 12]. The primary disadvantage of Botox treatment is its transient effect, typically lasting no more than 6 months, necessitating repeated injections. This requirement for ongoing re-injections can be particularly challenging for patients transitioning to adult care centers [16].

Conclusion

Intravesical Botulinum toxin type A injections have emerged as a promising therapeutic option for pediatric patients. Accordingly, our results demonstrate that intravesical Botulinum toxin-A therapy is a safe and effective treatment option for pediatric patients with neurogenic, non-neurogenic, and refractory overactive bladder. The majority of the patients included in our study showed significant symptom improvement, including reduced urinary incontinence and enhanced

bladder compliance. While generally well-tolerated, individual responses may vary, particularly in patients with other underlying conditions. Further studies with larger cohorts and long-term follow-ups are essential to optimize the dosing strategies and understand the long-term benefits and potential risks associated with repeated injections. Nevertheless, Botulinum toxin-A represents a valuable addition to the therapeutic options available in pediatric urology, improving the quality of life for children with challenging bladder dysfunctions and lower urinary tract symptoms.

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