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Current State of Using Botulinum Toxin in Pediatric Urology. Literature Review

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Abstract

Botulinum Toxin Type A (BTTA) was first used in medicine in the late 1960s.During its relatively short history, botulinum toxin has found application in various fields of medicine such as urology, neurology, ophthalmology, gastroenterology, pediatrics, endocrinology, otorhinolaryngology, proctology, and others. However, the use of this toxin in pediatric urology began only in 2003. BTTA is mainly used to treat neurogenic urinary disorders (urinary incontinence), most of which are caused by myelodysplasia. It is difficult to overestimate the importance of chemodenervation with botulinum toxin in children with gallbladder-dependent hydroureteronephrosis, since if conservative treatment is unsuccessful, such children undergo traumatic augmentation surgeries with adverse long-term consequences, and chemodenervation is the last line of therapy in these patients. It should also be noted that although the data on detrusor denervation efficacy by botulinum toxin are very promising, there are no clear indications for intervention. This study was conducted with the aim of reviewing and interpreting the currently existing information on the use of BTTA in pediatric urology.

Key words: *botulinum toxin type A, children, urinary incontinence, myelodysplasia.*

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"All things are poison, and nothing is without poison; the dosage alone makes it so a thing is not a poison." These words belong to the great physician and naturalist Paracelsus, and probably no one doubts them today. This dictum is fully applicable to botulinum toxin. The history of its use in medicine is relatively short. The use of botulinum toxin was first reported in the late 1960s by Alan Scott of the Smith Kettlewell Institute for Visual Sciences, now known as the Smith Kettlewell Eye Research Institute, San Francisco. He used intramuscular injections of botulinum toxin type A (BTTA) to weaken the eye muscles of monkeys and proposed his method as an alternative to surgical correction of non-accommodating strabismus [I].

Dr. Scott's research led to FDA approval for human studies with the toxin used to treat strabismus (1979). Ultimately, the FDA approved the use

of Schantz's toxin for the treatment of strabismus, blepharospasm, and hemifacial spasm (HFS) in 1989. The research did not end there, and botulinum toxin
is now approved for use in a variety of diseases, including urinary disorders [II].

Botulinum toxin is produced by the anaerobic Gram-positive bacterium Clostridium botulinum of the Clostridium genus. Botulinum toxin is a neurotoxin, the main pathogenic factor of C. botulinum, belongs to zinc
metalloproteases and differs in antigenic properties. Currently, it has 8 known main serotypes, designated as A, B, C, D, E, F, G and H. Botulinum toxin is produced in the form of protein complexes consisting of a neurotoxin and a stabilizer protein that protects the toxin from proteolytic enzymes.
As a result of mild proteolysis due, in most types of the toxin, to their own endoproteases, protoxin is split into two polypeptide chains:
light L-chain (fragment A) and heavy H-chain (fragment B). Fragment A has a toxic effect on target cells, while fragment B transports and attaches fragment A [III].

The action of BTTA is realized by suppressing the exocytosis of acetylcholine from the presynaptic membrane of motor neurons into the synaptic cleft, due to proteolytic cleavage of the synaptosomal-associated protein SNAP-25, which results in muscle contraction impairment. In the case described above, the efferent transmission of excitation to the muscle fiber is disrupted, but botulinum toxin also reduces afferent impulses, thereby suppressing nervous activity leading to spasticity and hypertonicity of the muscles. It should also be noted that the BTTA molecule does not pass through the blood-brain barrier, and therefore has no effect on the central nervous system [IV].

Currently, three type A toxins and one type B toxin have been approved by the FDA for clinical use in the United States. Type A toxins include Botox by Allergan Inc., Xeomin by Merz Pharma, and Dysport by Ipsen. Type B toxin Myobloc is manufactured by Solstice/US World Meds [I].

Botulinum toxin has found application in completely different fields of medicine, such as neurology, ophthalmology, urology, gastroenterology, pediatrics, endocrinology, otorhinolaryngology, proctology, etc. It is used for a huge number of diseases (more than 200), and the main goal, of course, is to reduce muscle hypertonicity. The use of botulinum toxin in pediatric urology is relatively new. The first report on the use of BTTA in children appeared in 2003. H. Schulte-Baukloh et al. (Germany) in 2002 used intradetrusor BTTA administration in 17 children with detrusor hyperreflexia associated with myelodysplasia due to unsatisfactory results of anticholinergic drugs (oxybutynin and tolterodine). The results of this study turned out to be very promising, which caused research in this direction to continue throughout the world [V].

In pediatric urology, BTTA has found application for chemodenervation of the bladder detrusor and urethral sphincter. Botulinum toxin is of great importance in the treatment of neurogenic detrusor overactivity, especially in children with myelodysplasia. Neurogenic detrusor overactivity is manifested by symptoms such as urinary incontinence, frequent urination, residual urine, and enuresis. In this regard, it is difficult for this category of patients to socialize and lead a normal life, i.e. the quality of life is greatly deteriorating. The classification of one of the founders of Russian neurologic urology E.L. Vishnevsky (1982) is used to assess neurogenic dysfunction in patients with myelodysplasia, taking the severity of bladder denervation into account:

1. Nonreflex hypotonic bladder.
2. Nonreflex hypertonic bladder (adapted and unadapted, non-inhibited).
3. Nonreflex hypertonic ("contracture"? or spastic bladder) is the most severe disorder, characterized by extremely high intravesical pressure and small effective
volume of the bladder [VI, VII].

Botulinum toxin injections into the urethral sphincter are performed for hypertonicity and detrusor-sphincter dyssynergia manifested by severe dysuria and the absence/difficulty of independent urination. The majority of such patients are children after severe spinal injuries. Detrusor-sphincter dyssynergia in myelodysplasia, as well as hypertonicity of the urethral sphincter, are relatively rare. The likelihood of success of intrasphincteric injection varies greatly; moreover, many patients remain unhappy with such treatment due to developing or worsening urinary incontinence after surgery. Thus, Y. Jiang et al. showed that the efficacy of BTTA injections into the urethral sphincter does not exceed that of injected saline. Other studies show excellent results with this method: discontinuation of intermittent catheterization, appearance

of spontaneous urination and decrease in residual urine. As a result, this method has very contradictory results according to different authors, and therefore requires further development and clear indications for its use [VIII].

Due to severe damage to the spinal cord, children with myelodysplasia have disorders other than those of the pelvic organs, in particular of the lower extremities in the form of various types of paralysis and paresis. With spastic paresis, such children are injected with botulinum toxin into the muscles to reduce spasticity (and pain in some cases). Reducing muscle overactivity usually results in an increase in the range of motion and an overall improvement in motor performance. For example, an injection into the calf muscle of a paraplegic child increases the passive range of dorsiflexion of the ankle. The intended population for these procedures is patients with infantile cerebral palsy, and the study of combined use (for limb muscles and detrusor) of botulinum toxin in children with myelodysplasia remains an important area of research [IX].

Currently, indications for detrusor chemodenervation by BTTA injection in pediatric urology are not clearly defined. However, the most significant ones are: severe urinary incontinence (worsening the child's quality of life), decreased bladder compliance, increased intravesical pressure and detrusor tone, pollakiuria. In such cases, the first line of therapy is intermittent catheterization and the use of M-anticholinergics; epidural, presacral neurectomy and electrotherapy are also used, but when they are not sufficiently effective, and the effective volume of the bladder cannot be restored, BTTA administration is indicated [X].

The positive changes in the course of hydroureteronephrosis after the use of BTTA are very important. In children with myelodysplasia, neurogenic detrusor overactivity is often complicated by hydroureteronephrosis. In this case, it is bladder-dependent: a sharp increase in intravesical pressure and detrusor tone leads to the appearance of substrate for the reflux. In such cases, progressive renal dysfunction (with the failure of conservative therapy) calls for the next stage of treatment: augmenting surgeries on the bladder, which are very traumatic and serious. The effects of intradetrusor BTTA administration actually eliminate the reflux substrate itself, reducing intravesical pressure, detrusor tone and increasing compliance and effective bladder volume. Thus, traumatic surgery can be avoided in many children. Perhaps, further research in this field will lead to an expansion of the range of indications for BTTA in such children [V, XI].

Chemodenervation of the BTTA detrusor has the following peculiarities. The intervention is carried out endoscopically. The bladder is filled to its physiological volume with sterile saline. Then the operator assesses the presence of suspension (sediment), the state of the mucous membrane, the presence or absence of inflammation, its location and nature (if any). It is also necessary to determine the orifices of the ureters and assess their closure, configuration, and presence of active emissions. The next step is BTTA administration. The method of administration is very variable according to different authors; nevertheless, the data do not differ greatly. The calculation is carried out by body weight (5–12 units of botulinum toxin per 1 kg of body weight), the drug is diluted with saline, injections are carried out along the posterolateral wall in the amount of 20–30 units, 5 units of the drug per injection on average, the depth of injection does not exceed 2–3 mm [XII].

Complications after surgery are few and rare. These include: urinary tract infection, increased residual urine volume, acute urinary retention, injection site hematoma, bleeding. Urinary tract infection is the most common complication. However, this complication is easily avoided with proper perioperative antibiotic support. The increase in residual urine in some patients is a direct consequence of the action of botulinum toxin and, in fact, has nothing to do with complications in the classical sense. It is rather due to the incorrect selection of patients for the surgery, i.e. there is an incorrect interpretation of urodynamic, clinical and other factors when examining a patient. It should also be noted that in a certain cohort of patients with pre-existing residual urine, BTTA administration is still the indicated and correct solution; this applies to children undergoing intermittent catheterization in certain clinical cases. In addition, surgery should be avoided when a concomitant disease can aggravate its effect and lead to adverse consequences. Such diseases include myasthenia gravis and Lambert-Eaton syndrome [XIII, XIV].

Another noteworthy application of BTTA is its use in patients after bladder augmentation surgery. Augmentation surgery is used to treat refractory overactive bladder and neurogenic detrusor overactivity in cases where other treatments have proven ineffective. In a small number of such patients, symptoms persist or recur postoperatively, and there are few guidelines for the management of these patients. Houston

Methodist Hospital conducted a study of the effectiveness of intradetrusor BTTA injections into the augmented bladder. The surgery was performed in 13 patients (9 women, 4 men) with previous augmentation cystoplasty. The indications for injections were persistent symptoms in the postoperative period (urinary incontinence). All patients underwent urodynamic examination prior to treatment. As a result, 10 patients (77%) reported an improvement in all subjective parameters (frequency and urgency of urination, urinary incontinence). Thus, the authors suggest that intra-augmentation BTTA injection may improve symptoms and urinary retention after augmentation cystoplasty in a specific cohort of patients [XV].

There are methods for the so-called non-injection chemodenervation of the detrusor using BTTA. Intraluminal instillation of BTTA without injection failed due to decomposition of the toxin by urine proteases, dilution of the toxin in the urine during instillation, and poor absorption by the urothelium due to the large size of the toxin molecule. Nevertheless, attempts have been made to mix it with various agents that increase the absorption of BTTA by the bladder urothelium. These include: dimethyl sulfoxide, protamine and protein transduction domains, thermosensitive hydrogel, liposomes. Liposomes were shown to be the most effective. Thus, a multicenter, placebo-controlled study was conducted to evaluate the safety and efficacy of BTTA in combination with liposomes in men and women with an overactive bladder. This treatment successfully reduced the frequency and urgency of urination, but did not reduce the number of urge incontinence episodes. Instillation of BTTA in combination with liposomes successfully disrupts afferent neurotransmission, but does not in any way affect the efferent part, in contrast to intradetrusor injections. New approaches to the non-injection administration of BTTA have not yet demonstrated an efficacy comparable to intradetrusor injection, although they may find application in certain clinical situations [XII, XVI, XVII].

In summary, it can be said that chemodenervation of the detrusor by BTTA injections is a safe and effective surgery for the treatment of patients with neurogenic detrusor overactivity. BTTA injections significantly reduce the severity of symptoms, restoring effective bladder volume and improving the quality of life of patients. Also, an important effect is the reduction (or complete disappearance) of vesicoureteral reflux, which in many cases allows to avoid the more traumatic augmenting bladder surgeries. But since this method is very novel, it warrants further study and final conclusions are still ahead.

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