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BOTULINUM TOXIN TYPE A IN THE TREATMENT OF BLADDER PAIN SYNDROME IN WOMEN: INITIAL RESULTS

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We present the results of botulinum toxin type A (BT-A) treatment in 49 women (aged 41–65 years) with bladder pain syndrome. Previously, all patients underwent oral and intravesical drug therapy in addition to hydrodistention of the bladder without significant clinical effect. BT-A at a dose of 100 U (20 points at 5 units) was injected into the bladder under general anesthesia. Treatment results were evaluated 3 months after the treatment using specialized questionnaires such as the Pelvic Pain and Urgency/Frequency (PUF) Scale, O'Leary-Sant Symptom Index and Interstitial Cystitis Scale, visual analogue pain scale (VAS), and urinary diaries. Remarkably, the treatment was effective in 46 (93.8%) patients. By the end of the third month after the BT-A injection, the PUF Scale score, the O'Leary-Sant Symptom and Interstitial Cystitis Scale, and VAS reduced by 41.3%, 32%, and 34%, respectively, and urination frequency decreased by 38.5%. Thus, BT-A is an effective method for treating bladder pain syndrome in patients who are refractory to other treatment methods.

Keywords: bladder pain syndrom; botulinum toxin type A.

БОТУЛИНИЧЕСКИЙ ТОКСИН ТИПА А В ЛЕЧЕНИИ СИНДРОМА БОЛЕЗНЕННОГО МОЧЕВОГО ПУЗЫРЯ У ЖЕНЩИН: ПЕРВЫЕ РЕЗУЛЬТАТЫ

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В статье представлены результаты применения ботулинического токсина типа А (БТ-А) у 49 женщин с синдромом болезненного мочевого пузыря в возрасте от 41 до 65 лет. Ранее всем пациентам проводили пероральную и внутрипузырную медикаментозную терапию, а также выполняли гидродистензию мочевого пузыря без значимого клинического эффекта. БТ-А вводили в стенку мочевого пузыря в дозе 100 Ед (20 точек по 5 Ед) под общей анестезией. Результаты лечения оценивали через 3 месяца после процедуры с помощью специализированных опросников PUF Scale, O'Leary Symptom Intersitial Cystitis Scale Index, визуальной аналоговой шкалы боли (ВАШ) и дневников мочеиспускания. Лечение оказалось эффективным у 46 (93,8 %) больных. К концу третьего месяца после инъекции БТ-А отмечено снижение суммы баллов опросника PUF Scale на 41,3 %, O'Leary Symptom Intersitial Cystitis Scale Index — на 32 %, ВАШ боли — на 34 %, частота мочеиспускания уменьшилась на 38,5 %. Таким образом, БТ-А является эффективным методом лечения больных с синдромом болезненного мочевого пузыря, рефрактерным к другим методам лечения.

Ключевые слова: синдром болезненного мочевого пузыря; ботулинический токсин типа А.

INTRODUCTION

Painful bladder syndrome (PBS), also known as interstitial cystitis, represents a significant problem in contemporary medicine. PBS is a condition that merges urology, gynecology, and neurology. The term "interstitial cystitis" was used for the first time by Samuel Gross (1876). Specifically, it was used to describe the state "when all layers of the bladder wall are involved in the pathological process". Subsequently, in 1887 the American gynecologist Alexander Skene characterized interstitial cystitis as an inflammatory process that "destroys the bladder mucous membrane partially or completely with possible spread to the muscle layers of the bladder wall", in the monograph "Diseases of the bladder and urethra" [1]. For over 100 years, urologists and gynecologists worldwide have extensively used the term "interstitial cystitis". This until the beginning of the XXI century, when it was recommended to replace the term "interstitial cystitis" with "painful bladder syndrome" or "painful bladder". The idea was to emphasize the difference between this condition and infectious inflammations of the bladder wall.

Currently, PBS represents one of the clinical manifestations of chronic pelvic pain. Specifically, it is characterized by the presence of persistent or recurrent pain in the bladder region. Additionally, pain is accompanied by at least one of the following symptoms: increased pain when filling the bladder; higher frequency of urination during the day and/or at night in absence of signs of infection or other obvious lesions [2]. Pain represents the most important clinical manifestation of PBS. Importantly, pain from PBS pain is debilitating and accompanied by negative psychoemotional disorders [3]. Such conditions cause a significant decrease in the quality of life of patients, along with pain in the bladder, urination and sexual disorders [4]. The significance of PBS is linked not only to the major deterioration of patients' quality of life, but also to its relatively high prevalence. Specifically, it has been reported that the incidence of PBS incidence is estimated to range between 52 and 500 cases per 100,000 women and between 8 and 41 cases per 100,000 men [5]. It has been shown that up to 30% of women in different times of their lives suffer from pelvic pain lasting more than 6 months [6]. Interestingly, PBS is predominantly observed in young and socially active women.

The etiology of PBS remains to date unclear. Possible causes at the basis of its development are urothelial dysfunction; mast cell activation; autoimmune, neurogenic and ischemic disorders. Furthermore, infectious lesions of the bladder wall are considered to be one among various other starting mechanisms of the disease [7-9].

The diagnostics of PBS is based on the: evaluation of the symptoms; results of cystoscopy; bladder wall biopsy in a subset of cases. In all cases it is mandatory to rule out other possible causes of pain and urination disorders [10–13]. To date, a significant number of studies have focused on the treatment of PBS. The clinical recommendations approach the treatment of the disease with various regimens. Initially, patients are prescribed behavioral and drug therapies. In the event these therapies were not effective, either an intravesical minimally invasive treatment or, in rare instances, surgical treatment are performed [2, 8, 11, 14].

Due to current poor understanding of the etiology and pathogenesis of PBS, the treatment of patients remains a very difficult task. Common guidelines for the treatment of this disease are unavailable. As a general rule, the treatment of PBS patients should: begin with less invasive methods; be tailored to each patient's needs, be based on the disease's clinical manifestations; limit the use of invasive techniques to cases in which oral pharmacotherapy and intravesical treatments were ineffective. Since PBS pathogenesis is associated, among other things, with urothelium damage, which leads to an inflammatory response, a possible treatment method is intravesical therapy. The use of medications directly in the bladder provides advantages such as higher drug concentration in the area of the bladder wall and reduced side effects. However, this therapeutic approach is frequently insufficient.

In recent years, botulinotherapy, specifically botulinum toxin type A (BT-A), has been widely used in the treatment of urological diseases. In its structure, botulinum toxin contains a neurotoxin and non-toxic proteins. The BT-A molecule consists of two chains,

heavy and light, connected by a disulfide bond. The heavy chain has a high affinity for specific receptors, localized on the surface of target neurons. The light chain is characterized by Zn^{2+}-dependent protease activity. Botulinotherapy is predominantly used in urology for the treatment of neurogenic and idiopathic detrusor overactivity and detrusor-sphincter dyssynergia, in both adults and children [15–17]. BT-A was first used for the treatment of PBS in 2004 [18]. While since then experiences have been accumulated on its use in PBS, to date some questions remain unanswered. Specifically, points that need to be clarified are the optimal dose of BT-A, the efficiency of treatment in different categories of patients with differing functional, and the anatomical state of the bladder.

The present *study aimed* to investigate the efficiency of BT-A in the treatment of female patients with PBS, refractory to other methods of treatment.

MATERIALS AND METHODS

We conducted this study in the Department of Urology of the I.P. Pavlov First St. Petersburg State Medical University between 2015 and 2017. A total of 49 PBS female patients aged 41 to 65 years (an average of 49.4 ± 10.2 years) were examined and treated. The average duration of the disease was 35.2 ± 27.1 months. All the enrolled patients were previously treated unsuccessfully, for at least 3 months, with both medical therapy (oral and intravesical) and hydrodistension of the bladder. The enrollment criteria were age over 18 years; duration of disease for over 6 months; absence of signs of urinary tract infection, including asymptomatic bacteriuria; in the previous three months, absence of diseases or conditions that could determine pelvic pain (tumors, radiation cystitis, endometriosis, neurological diseases, etc.). All the patients underwent a comprehensive examination which enabled the ruling out of other causes of pelvic pain, except for PBS.

All the 49 patients underwent, under intravenous anesthesia, intravesical administration of BT-A at a dose of 100 U into the bladder's wall. The submucosal membrane of the bladder was injected in 20 points using a standard procedure. Specifically, 5U of BT-A were injected in each point. The efficiency of botulinotherapy was evaluated 3 months after the procedure.

The severity of the clinical manifestations of PBS, both pre- and 3 months post-treatment, was assessed using specialized questionnaires: the Pelvic Pain and Urgency/Frequency Patient Symptom Scale (PUF Scale) [19]; the O'Leary-Sant Symptom Intersitial Cystitis Scale Index (O'Leary-Sant SI) [20]; a ten-point visual analog scale of pain (VAS); diaries of urination kept by the patients for three days before and 3 months post-treatment.

Statistical processing of the data obtained was performed by using the STATISTICA En software (StatSoft Inc.).

RESULTS AND DISCUSSION

Three months post-injection of BT-A into the bladder wall, 46 (93.8%) out of 49 patients observed a subjective improvement, with respect to the condition prior to the procedure. Moreover, all the patients who indicated an improvement of symptoms post-treatment, described the onset of the effects as early as 5–7 days post-injection. Subsequently none of these patients showed a deterioration in the condition by the third month post-treatment. Three patients were neutral to the treatment. A follow-up examination of the patients was performed 3 months after the BT-A administration. The high efficiency of treatment was indicated by the dynamics of the results of the questionnaire survey and the analysis of the diaries of urination (Table 1). Thus, the scores: on the O'Leary-Sant SI questionnaire decreased by an average of 5.6 points (–32%, $p = 0.0019$); on the PUF Scale questionnaire decreased by an average of 10.5 points (–41.3%, $p = 0.0001$); on VAS of pain decreased by an average of 1.8 points (–34%, $p = 0.0036$). The decrease in the frequency of urination, according to the diaries of urination, averaged 38.5%.

A detailed analysis of the case histories of three patients who did not achieve clinical improvement was performed.

Patient P., 54 years old, with an 87 months disease duration. Prior to BT-A administration, the score on

Table 1

Dynamics of the symptoms intensity of the painful bladder syndrome before and after the administration of BT-A (*n* = 49)

Questionnaires	Before treatment	3 months after treatment	*p*
PUF Scale, score	25.4 ± 10.2	14.9 ± 9.6	0.0001
O'Leary-Sant SI, score	17.5 ± 2.4	11.9 ± 2.1	0.0019
VAS of pain, score	5.3 ± 2.2	3.5 ± 1.6	0.0036
Number of urination for 3 days	44.9 ± 10.1	27.6 ± 8.7	0.0015

O'Leary-Sant SI was 19, that on PUF Scale was 31, while that on VAS of pain was 8. The average frequency of urination per day, according to the diary of urination, was 31.7. Cystoscopy revealed Hunner's lesion.

Patient A., 45 years old, with a 48 months disease duration. Prior to BT-A administration, the score on O'Leary-Sant SI was 20, that on PUF Scale was 32, and that on VAS of pain was 9. The average frequency of urination per day was 28. Cystoscopy revealed Hunner's lesion.

Patient K., 57 years old, with a 52 months disease duration. Prior to BT-A administration, the score on O'Leary-Sant SI was 20, that on the PUF Scale was 34, and that on the VAS of pain was 9. The average frequency of urination per day was 32. Cystoscopy revealed Hunner's lesion.

Along with the inefficient botulinotherapy, the three above mentioned patients described the following symptoms: highly severe symptoms of the disease (the score on O'Leary-Sant SI in all patients was higher than 19, that on PUF Scale was higher than 31, the frequency of urination was higher than 28 per day); disease duration longer than 48 months; presence of Hunner's lesions. Of note, none of the patients with effective administration of BT-A presented Hunner's lesions. All the three patients with Hunner's ulcers underwent laser ablation of these lesions followed by a second (in 1 month) intravesical administration of BT-A at a dose of 100 U with a positive effect.

The efficiency of botulinotherapy for the treatment of PBS is due to the motor and sensory mechanisms of BT-A action [21]. At the core of the motor mechanism there is the ability of BT-A to block the release of acetylcholine from the presynaptic terminals of peripheral cholinergic nerves. This causes a decrease in detrusor contractile activity. The sensory mechanism consists in a decreased release of afferent neurotransmitters. This determines pain in the bladder, under the influence of BT-A.

Consequently, intravesical injections of BT-A determine a significant clinical improvement in the majority of PBS patients, refractory to other types of therapy. Additionally, the results of the present study lead to the observation that the efficiency of botulinotherapy is significantly lower in case of: PBS of longer duration; greater pronouncement of symptoms; the presence of Hunner's lesion of the bladder.

CONCLUSIONS

Botulinotherapy is an effective method for the treatment of PBS patients. The results of the present study show that intravesical application of BT-A at a dose of 100 U was effective in 46 (93.8%) of 49 patients. Hunner's lesion of the bladder was observed in the three patients with inefficient BT-A.

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