

CLINICAL EFFECTIVENESS OF INTRADETRUSOR INJECTIONS OF BOTULINUM TOXIN TYPE A IN DOSE 100 UNITS IN MULTIPLE SCLEROSIS PATIENTS WITH NEUROGENIC DETRUSOR OVERACTIVITY

© E.S. Filippova^{1,2}, I.V. Bazhenov^{1,2}, A.V. Zyrjanov^{1,2}, V.N. Zhuravlev¹, I.V. Borzunov¹, G.S. Ustinov¹

¹Urals State Medical University of the Ministry of Healthcare of the Russian Federation, Ekaterinburg, Russia;

²Sverdlovsk Regional Clinical Hospital No. 1, Ekaterinburg, Russia

For citation: Filippova ES, Bazhenov IV, Zyrjanov AV, et al. Clinical effectiveness of intradetrusor injections of botulinum toxin type A in dose 100 Units in multiple sclerosis patients with neurogenic detrusor overactivity. *Urology reports (St. Petersburg)*. 2020;10(1):25-32. <https://doi.org/10.17816/uroved10125-32>

Received: 16.01.2020

Revised: 12.02.2020

Accepted: 19.03.2020

⊗ Intravesical injections of botulinum toxin type A (BTA) demonstrate good results in treatment of detrusor overactivity symptoms in patients with neurogenic low urinary tract dysfunction (NLUTD) when use in recommended doses of 200 and 300 Units. In clinical practice a government insurance dose not cover the price for the 200 BTA Units and only 100 Units may be injected in patients with neurogenic and nonneurogenic detrusor overactivity. **The aim** was to evaluate the efficiency of intradetrusor injections of BTA in patients with NLUTD. **Materials and methods.** The study included 28 MS patients with resistant to medical treatment neurogenic detrusor overactivity. All patients received intradetrusor injections of 100 BTA Units. The results were assessed after 1, 3 and 6 months after procedure. **Results.** Clinical improvement had been achieved in all 28 patients. According to the urodynamic studies three months after BTA injections maximal cystometric capacity increased by $119.9 \pm 37.6\%$ ($p < 0,05$), volume at first detrusor involuntary contraction increased by $74.8 \pm 21.4\%$ ($p < 0,05$), maximal detrusor pressure at involuntary contraction decreased by $53.5 \pm 29.7\%$ ($p < 0,05$). The NBSS total score decreased from 38.04 ± 14.27 to 29.06 ± 14.46 ($p = 0,000$), mainly because of questions about incontinence and urgency. SF-Qualiveen total score turned from 2.32 ± 0.70 to 1.61 ± 0.85 ($p = 0,000$). Before procedure 2 patients performed intermittent catheterization, 4 patients catheterized after BTA injections. **Conclusion.** Intradetrusor injection of 100 BTA Units in MS patients with NLUTD resulted in improvement of urodynamic parameters followed by reduction of clinical symptoms and life quality improvement for 6 months of observation. Using of BTA low dose didn't provide a total abortion of neurogenic detrusor overactivity symptoms but led to the starting of IC only in 2 patients.

⊗ **Keywords:** neurogenic bladder; detrusor overactivity; botulinum toxin.

ОЦЕНКА КЛИНИЧЕСКОЙ ЭФФЕКТИВНОСТИ ВНУТРИПУЗЫРНЫХ ИНЪЕКЦИЙ БОТУЛИНИЧЕСКОГО ТОКСИНА ТИПА А В ДОЗЕ 100 ЕД У ПАЦИЕНТОВ С РАССЕЯННЫМ СКЛЕРОЗОМ С НЕЙРОГЕННОЙ ДЕТРУЗОРНОЙ ГИПЕРАКТИВНОСТЬЮ

© E.C. Филиппова^{1,2}, И.В. Баженов^{1,2}, А.В. Зырянов^{1,2}, В.Н. Журавлев¹, И.В. Борзунов¹, Г.С. Устинов¹

¹Федеральное государственное бюджетное образовательное учреждение высшего образования «Уральский государственный медицинский университет» Министерства здравоохранения Российской Федерации, Екатеринбург, Россия;

²Государственное автономное учреждение здравоохранения Свердловской области «Свердловская областная клиническая больница № 1», Екатеринбург, Россия

Для цитирования: Филиппова Е.С., Баженов И.В., Зырянов А.В., и др. Оценка клинической эффективности внутривпузырных инъекций ботулинического токсина типа А в дозе 100 ЕД у пациентов с рассеянным склерозом с нейрогенной детрузорной гиперактивностью // Урологические ведомости. – 2020. – Т. 10. – № 1. – С. 25–32. <https://doi.org/10.17816/uroved10125-32>

Поступила: 16.01.2020

Одобрена: 12.02.2020

Принята к печати: 19.03.2020

⊗ **Актуальность.** Внутривпузырные инъекции ботулинического токсина типа А (БТА) демонстрируют хорошие результаты в лечении симптомов гиперактивности детрузора у больных нейрогенной дисфункцией нижних мочевыводящих путей (НДНМП) при использовании в рекомендованных дозах 200 и 300 ЕД. Существующие в системе обязательного медицинского страхования тарифы не покрывают стоимости внутривпузырных инъекций 200 ЕД препарата и часто вынуждают клиницистов использовать более низкую дозировку (100 ЕД) у пациентов с гиперактивностью детрузора как идиопатической, так и нейрогенной природы. **Цель исследования:** оценить эффективность внутривпузырных инъекций 100 ЕД БТА у больных НДНМП на фоне рассеянного склероза.

Материалы и методы. В исследование вошли 28 больных рассеянным склерозом с резистентной к консервативной терапии нейрогенной детрузорной гиперактивностью. Всем пациентам выполняли внутривезикулярные инъекции 100 ЕД БТА. Эффект от ботулинотерапии оценивали через 1, 3 и 6 мес. после процедуры. **Результаты.** Клиническое улучшение было достигнуто у всех 28 пациентов. По данным уродинамического исследования, через 3 мес. после инъекций ботулотоксина в детрузор максимальная цистометрическая емкость увеличилась на $119,9 \pm 37,6$ % ($p < 0,05$), объем мочевого пузыря, при котором возникало первое произвольное сокращение детрузора, — на $74,8 \pm 21,4$ % ($p < 0,05$), максимальное давление детрузора в момент гиперактивности уменьшилось на $53,5 \pm 29,7$ % ($p < 0,05$). Общий балл по шкале симптомов нейрогенного мочевого пузыря (NBSS) снизился с $38,04 \pm 14,27$ до $29,06 \pm 14,46$ ($p = 0,000$), преимущественно за счет вопросов, касающихся недержания мочи и urgency. Общий балл SF-Qualiveen уменьшился с $2,32 \pm 0,70$ до $1,61 \pm 0,85$ ($p = 0,000$). До ботулинотерапии самокатетеризацию выполняли 2 пациента, после процедуры — 4. **Выводы.** Внутривезикулярные инъекции 100 ЕД ботулотоксина типа А у больных НДНМП на фоне рассеянного склероза привели к улучшению уродинамических параметров, что сопровождалось значительным уменьшением клинической симптоматики и повышением качества жизни больных на протяжении 6 мес. наблюдения. Использование низкой дозы ботулотоксина не позволило добиться полного купирования симптомов нейрогенной детрузорной гиперактивности, однако привело к необходимости в самокатетеризации только у 7 % пациентов.

🔑 **Ключевые слова:** нейрогенный мочевой пузырь; гиперактивность детрузора; ботулотоксин.

INTRODUCTION

Intradetrusor injections of botulinum toxin A (BTX-A) decreases detrusor overactivity in patients with neurogenic lower urinary tract dysfunction (NLUTD). This procedure decreases urinary frequency, reduces urge urinary incontinence, improves urodynamic variables, and the quality of life of the patients [1]. The main mechanism of action of botulinum toxin is the inhibition of presynaptic acetylcholine release in neuro-muscular synapses [2, 3]. The direct specific effect of the agent on a bladder urothelium has also been described [4].

In 2004, A. Reitz et al. [5] reported data on the first treatment experience using onabotulinum toxin A in 200 patients with neurogenic detrusor overactivity (NDO) in Europe. The patients received intradetrusor injections of BTX-A at a dose of 300 U. The authors observed significant improvements in the urodynamic parameters at weeks 12 and 36 after treatment. Since 2011, results of studies have emerged, providing a high-level evidence for BTX-A in the treatment of NDO. Results of the multicenter, randomized, double-blind, placebo-controlled study known as DIGNITY (Double-Blind Investigation of Purified Neurotoxin Complex in Neurogenic Detrusor Overactivity) were published [6]. This study had 63 participating centers in Europe, North and South America, South Africa, and Asia. It involved 275 patients with urinary incontinence due to NDO: 154 with multiple sclerosis and 121 after spinal cord injury. Patients were randomly divided in three groups: 92 patients received intravesical injections of BTX-A at a dose of 200 U, 91 patients at a dose of 300 U, and 92 patients received a placebo [6]. The

program DIGNITY also conducted a second investigation, which included 85 centers worldwide. The results of these investigations which provided a high level of evidence for BTX-A efficacy in the treatment of NDO were published by D. Ginsberg et al. in 2012. [7]. This large study program involved 416 patients with NDO (227 with multiple sclerosis and 189 with spinal cord injury). In 2016, T. Cheng et al. [8] conducted a meta-analysis to assess the efficacy and safety of onabotulinumtoxin A in patients with NDO and their results confirmed the efficacy and safety of the botulinum toxin therapy for NDO.

According to A. Apostolidis [9], in patients with NDO after spinal cord injury, BTX-A at a dose of 200 U was associated with the highest effect and longest duration of action comparing with BTX-A at a dose of 50 and 100 U. However, several researchers have shown that there is no significant difference in terms of urologic efficacy and improvement of the quality of life between 200 U and 300 U of the drug [10]. According to A.S. Arkhireev et al. [11], a high dose of BTX-A did not guarantee a more longstanding improvement of the bladder function and 200 U had an equal efficiency compared with higher doses of the drug. Authors recommend 200 U injections for patients with NDO and 100 U for idiopathic detrusor overactivity.

In an effort to reduce the risk of urinary retention after botulinum toxin injection, U. Mehnert et al. [12] attempted to reduce its dose to 100 U diluted in 10 ml of 0.9% saline in patients with NDO associated with multiple sclerosis. The study showed that injecting the drug at such a dose improved the urodynamic parameters and reduced urgency for 12 weeks.

In Russian clinical recommendations for NLUTD in adults, BTX-A at a dose of not less than 200 U is recommended for the treatment of NDO. However, the tariffs existing in the system of obligatory health insurance do not cover the cost of intradetrusor injections of 200 U of the drug and often force clinicians to use a lower dosage (100 U) in patients with both idiopathic and neurogenic detrusor overactivity.

Therefore, *the aim* of this study was to investigate the efficacy of intradetrusor injections of 100 U of BTX-A in patients with NDO associated with multiple sclerosis.

MATERIALS AND METHODS

The study was performed at the Sverdlovsk regional urologic center of Sverdlovsk regional clinical hospital #1 in 2017–2019. The study included 28 patients with NDO associated with multiple sclerosis (64.3% were women and 35.7% were men) aged 18–70 years (mean age, 38.76 ± 12.43 years). Primary progressive multiple sclerosis was found in 7% of patients, secondary progressive in 37%, and relapsing-remitting in 56%. The average EDSS (Expanded Disability Status Scale) score was 3.94 ± 2.10 . In all the patients, a previous medical therapy with muscarinic antagonists had no clinical effect.

The patients underwent standard examination, including taking of the medical history and complaints, physical examination, general laboratory tests (urinalysis, urine culture and sensitivity analysis, biochemical blood test), ultrasonography of the bladder and upper urinary tract, keeping a micturition diary or self-catheterization for 3 days, filling the validated Russian versions of questionnaires (SF-Qualiveen, a short questionnaire that measures the urinary-specific quality of life; NBSS, a neurogenic bladder symptom score), uroflowmetry with measurement of the maximum flow rate (Q_{\max} , ml/sec), voided volume and postvoid residual urine volume, urodynamic study using the Triton measurement system (Laborie Medical Technologies, Canada) with 25 ml/sec rate of bladder filling to determine the maximal cystometric capacity (MCC, ml), maximum detrusor pressure during involuntary detrusor contraction ($P_{\det_{\max}} \text{IDC}$, cm H₂O), and the volume infused at the onset of the first involuntary detrusor contraction ($V_1 \text{IDC}$, ml).

The study design included several stages: comprehensive examination of the patients prior to BTX-A injection (visit 1); BTX-A therapy at the urology department (visit 2); filling of questionnaires 1, 3, and 6 months after BTX-A therapy (visits 3, 4, 5); repeated

uroflowmetry and urodynamic study 3 months after therapy (visit 4); and assessment of the final outcome of the BTX-A therapy (visit 6).

Regarding the BTX-A injection procedure, urethrocytoscopy was performed under intravenous anesthesia, after which an endoscopic needle was passed through the working channel of the urethrocytoscope, and 100 U of the onabotulinumtoxin A (Botox) was injected through the needle into 20 detrusor sites with the depth of 2–3–5 mm, depending on the thickness of its wall.

All the patients gave a voluntary informed consent with regards to the invasive manipulations, blood and urinary collection for investigation. The study design was approved by the local ethics committee of Sverdlovsk regional clinical hospital #1.

Statistical data analysis was performed using the SPSS v23.0 software package for Windows. Student's *t*-test was used to evaluate difference between means.

RESULTS

The enrolled patients complained of frequent urination (88%), micturition urgency (100%), urge urinary incontinence (85%), difficult urination (61%). According to the micturition diaries, the mean number of daytime voids varied from 5 ± 2.3 to 17 ± 3.6 (mean value, 9.5 ± 3.6) and nighttime voids from 0 to 7 ± 1.2 (mean value, 2.4 ± 1.8), while the mean volume of urine voided during a single micturition (mean voided volume of each micturition) was in the limits of 66.5 ± 51.4 to 339.3 ± 147.9 ml (mean value, 160.8 ± 73.4 ml). Total NBSS score was 38.08 ± 17.27 ; for domain "Incontinence" – 14.11 ± 8.18 , "Storage and Voiding" – 13.46 ± 4.05 , and "Consequences" – 7.24 ± 4.28 . All the patients reported a significant impact of urinary disorders on the quality of life. In the study group, the mean score in SF-Qualiveen was 2.20 ± 0.95 . More than 75% of patients reported that bladder problems graded as "quite a bit" or "extremely" complicate their life; 70% of those with "quite a bit" or "extremely" bladder problems, are worried that it will worsen, while 83% feel more or less embarrassed because of these problems.

During filling cystometry a detrusor overactivity was confirmed in all patients. The maximum cystometric capacity was reduced to 158.3 ± 72.2 ml. In some patients, a spontaneous involuntary bladder contraction was already observed when filled up to 20 ml (Fig. 1). A mean volume infused at the onset of the first involuntary detrusor contraction was 155.0 ± 47.6 ml and

the maximum detrusor pressure during involuntary detrusor contraction was 17.57 ± 11.3 cm H₂O. When urodynamic study was repeated 3 months after the intradetrusor botulinum toxin injections (Fig. 2), a significant difference in terms of positive dynamics in all the urodynamic parameters was registered. Maximum cystometric capacity, mean volume infused at the onset of the first involuntary detrusor contraction (Fig. 3) and maximum detrusor pressure during involuntary detrusor contraction (Fig. 4) were increased by $119.9 \pm 37.6\%$ ($p < 0.05$), $74.8 \pm 21.4\%$ ($p < 0.05$) and by $53.5 \pm 29.7\%$ ($p < 0.05$), respectively.

Figures 1 and 2 clearly illustrate a positive dynamic in urodynamic results. Despite the positive changes according to cystometry, statistical analysis of the micturition diary parameters showed no significant differences in the urination frequency before and after botulinum toxin therapy (Table 1). Nevertheless, all the patients reported an improvement, which was reflected in the results of the questionnaire survey.

The total NBSS score decreased from 38.04 ± 14.27 to 29.06 ± 14.46 ($p = 0.001$), predominantly due to questions about urinary incontinence and urgency (Fig. 5). The proportion of patients with urge urinary incontinence reduced from 84.6% to 62.5%, in addition, the number of patients who used 2 and more pads per day decreased from 50% to 18%, and the percentage of patients who noticed large loss of urine and needed 3 and more pads reduced from 19% to 6%.

According to SF-Qualiveen, the clinical effect of botulinum toxin therapy for NOD was associated with

significant ($p < 0.001$) improvement in the quality of life of the patients that had been lasting for the entire 6 months follow-up (Table 2). Only 21% of patients responded that bladder problems “quite a bit” complicated their life, in addition, none of the patients chose “extremely”.

Despite the fact that there was a statistically significant correlation between NBSS and SF-Qualiveen before and after botulinum toxin therapy (from 0.618 to 0.844 at $p \leq 0.001$), there was no significant relationship between the degree of change in symptoms according to the NBSS and quality of life, which may be explained by patients’ subjective perception of the dynamics of their condition.

Relapse of symptoms and the return of NBSS scores to baseline were considered as the end of effect of botulinum toxin therapy. The duration of the clinical effects of BTX-A at a dose of 100 U was 4–11 months (mean duration, 8.4 ± 2.1 months). There was no correlation between baseline urodynamic parameters and degree and duration of the clinical effect. There were also no association between changes in NBSS under botulinum toxin therapy and estimates of the patients according to EDSS.

Complications of botulinum toxin therapy were observed, including mild hematuria on day 1 (5.1%), increase in postvoid residual urine volume requiring the use of intermittent self-catheterisation (ISC) in 2 patients (7.14%). The quality of life in patients that were required to use ISC was similar compared to that of other patients.

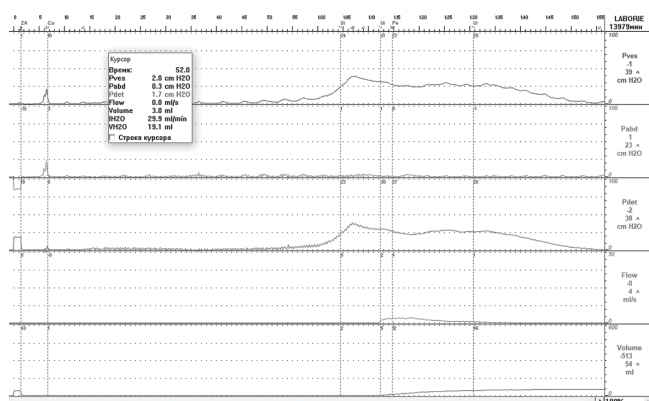


Fig. 1. Cystometry of patient F, 64 years old, suffering from multiple sclerosis with neurogenic detrusor overactivity. Urodynamic signs of detrusor hyperactivity. First involuntary detrusor contraction is accompanied by urge urinary incontinence. $V_1DC = 19.7$ ml, $Pdet_{max} IDC = 63.5$ cm H₂O

Рис. 1. Цистометрия пациентки Ф., 64 года, страдающей нейрогенной дисфункцией нижних мочевыводящих путей на фоне рассеянного склероза. Уродинамические признаки гиперактивности детрузора. Первое непроизвольное сокращение детрузора сопровождается ургентным недержанием мочи. $V_1DC = 19,7$ мл, $Pdet_{max} IDC = 63,5$ см H₂O

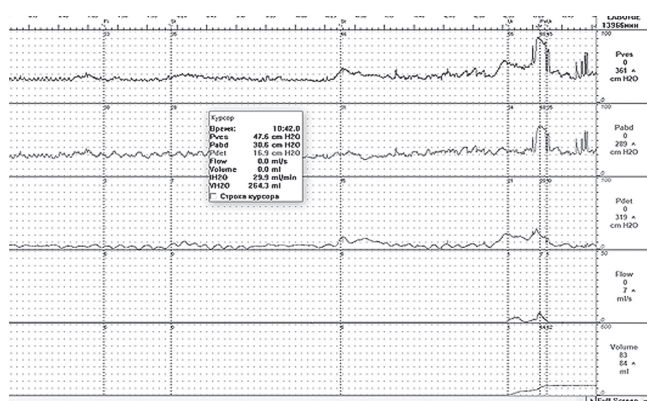


Fig. 2. Cystometry of patient F, 64 years old, suffering from multiple sclerosis with neurogenic detrusor overactivity in 3 months after botulinum toxin therapy. The volume of filling at the first involuntary detrusor contraction is 264 ml, urge urinary incontinence is absent

Рис. 2. Цистометрия пациентки Ф., 64 года, страдающей нейрогенной дисфункцией нижних мочевыводящих путей на фоне рассеянного склероза, через 3 мес. после ботулинотерапии. Объем наполнения при первом непроизвольном сокращении детрузора 264 мл, ургентное недержание мочи отсутствует

Table 1 / Таблица 1

Patient micturition diary analysis results before and after botulinum therapy ($n = 28$)Результаты анализа дневников мочеиспускания пациентов до и после ботулинотерапии ($n = 28$)

Parameter	Before BTX-A	1 month after BTX-A	3 months after BTX-A	6 months after BTX-A
Number of daytime voids, n	9.52 ± 3.59	8.22 ± 3.73 ($p = 0.290$)	7.95 ± 3.21 ($p = 0.755$)	8.45 ± 3.61 ($p = 0.344$)
Number of night-time voids, n	2.45 ± 2.17	2.18 ± 1.84 ($p = 0.722$)	2.27 ± 1.68 ($p = 0.560$)	2.36 ± 1.52 ($p = 0.540$)
Minimum voided volume, ml	69.44 ± 56.70	77.77 ± 38.00 ($p = 0.652$)	43.33 ± 15.55 ($p = 0.058$)	58.72 ± 22.15 ($p = 0.256$)
Maximum voided volume, ml	368.88 ± 178.28	315.55 ± 148.92 ($p = 0.477$)	368.33 ± 63.11 ($p = 0.145$)	345.21 ± 98.6 ($p = 0.350$)
Mean voided volume, ml	160.82 ± 73.41	170.27 ± 88.44 ($p = 0.058$)	162.1 ± 68.64 ($p = 0.355$)	170.27 ± 88.44 ($p = 0.098$)

DISCUSSION

The positive effect of botulinum toxin therapy at a dose of 200 U and 300 U on the quality of life of patients with NLUTD associated with multiple sclerosis was confirmed in randomized placebo-controlled trials [9, 13]. The assessment of the effect of botulinum toxin therapy on the quality of life of patients with neurogenic bladder was the aim of several studies. For example, V. Kalsi et al. [14, 15] evaluated the quality of life after intradetrusor injection of onabotulinumtoxin A in two studies. The first one involved 48 patients with NDO (including 24 patients with multiple sclerosis) and 16 patients with idiopathic detrusor overactivity [14]. Patients with neurogenic bladder received 300 U of botulinum toxin and the dose for idiopathic overactivity was 200 U. Despite the need for ISC in 29 patients with NDO and in 2 patients with idiopathic detrusor overactivity after therapy, the quality of life was improved significantly in both groups on weeks 4 and 16. Another study showed similar results in 43 patients with multiple sclerosis [15]. Authors proved that the need for ISC after botulinum toxin injection impaired the quality of life less than frequent urination and urge urinary incontinence.

As Table 2 shows, injection of 100 U of botulinum toxin into the detrusor also led to an improvement in the quality of life of the patients over the 6 months of follow-up, including those who were required to use ISC after the botulinum toxin therapy.

ISC was required in 7.4% of observed patients. According to different authors, the necessity for ISC after chemical denervation with botulinum toxin is variable. A. Kalsi et al. [14] noted that 88% of patients with NDO needed ISC after botulinum toxin injection. The study included only patients with multiple sclerosis and 65% of patients had been performing ISC before injection of botulinum toxin. After the procedure, all the 43 pa-

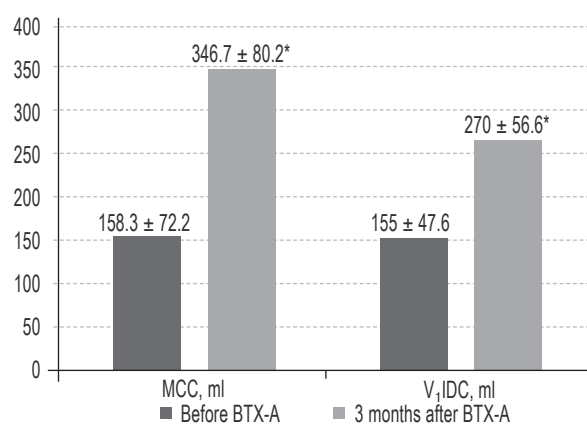


Fig. 3. Change in the urodynamic parameters of patients with neurogenic detrusor hyperactivity in 3 months after botulinum therapy at a dose of 100 Units, $n = 28$ (MCC — maximal cystometric capacity; V₁IDC — volume at first involuntary detrusor contraction; * $p < 0.05$ with a value before treatment)

Рис. 3. Изменение уродинамических параметров пациентов с нейрогенной детрузорной гиперактивностью через 3 мес. после внутридetrузорного введения ботулинотоксина типа А (БТА) в дозе 100 ЕД, $n = 28$ (MCC — максимальная цистометрическая емкость, V₁max IDC — объем мочевого пузыря при первом непроизвольном сокращении детрузора; * $p < 0,05$ достоверно со значением до лечения)

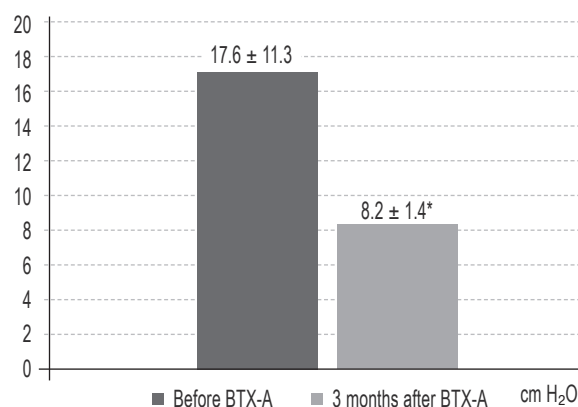


Fig. 4. Change in the maximum detrusor pressure at first involuntary contraction of patients with neurogenic detrusor hyperactivity 3 months after botulinum therapy at a dose of 100 Units, $n = 28$; * $p < 0.05$ with a value before treatment

Рис. 4. Изменение максимального детрузорного давления при первом непроизвольном сокращении детрузора у пациентов с нейрогенной детрузорной гиперактивностью через 3 мес. после внутридetrузорного введения ботулинотоксина типа А (БТА) в дозе 100 ЕД, $n = 28$; * $p < 0,05$ достоверно со значением до лечения

Table 2 / Таблица 2

Changes in the quality of life associated with micturition disorders in patients with neurogenic detrusor overactivity after botulinum therapy according to the SF-Qualiveen questionnaire ($n = 28$)

Изменения в качестве жизни, связанном с нарушениями микции, у пациентов с нейрогенной детрузорной гиперактивностью после ботулинотерапии по данным опросника SF-Qualiveen ($n = 28$)

SF-Qualiveen	Before BTX-A	1 month after BTX-A	3 months after BTX-A	6 months after BTX-A
Total score	2.32 ± 0.70	1.61 ± 0.85***	1.51 ± 0.91	1.59 ± 0.73
Domain "Bother with limitations"	2.43 ± 0.75	1.53 ± 0.94***	1.27 ± 0.95	1.38 ± 0.93
Domain "Fears"	1.93 ± 0.89	1.50 ± 1.12*	1.36 ± 1.07	1.42 ± 1.04
Domain "Feeling"	2.43 ± 1.17	1.68 ± 1.11*	1.45 ± 1.31	1.55 ± 1.28
Domain "Frequency of limitations"	2.50 ± 0.81	1.71 ± 0.97**	1.95 ± 1.08	1.65 ± 0.89

Note. * $p < 0.05$, ** $p < 0.01$, *** $p \leq 0.001$ – comparing with baseline before treatment.

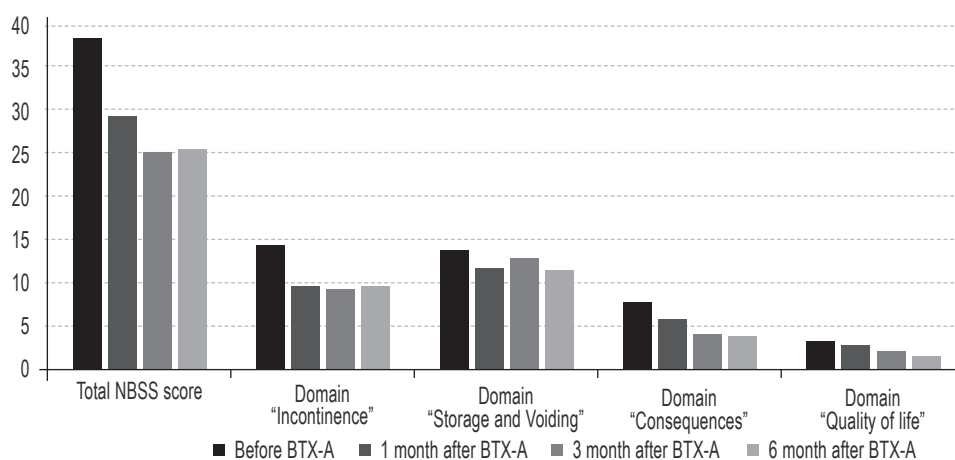


Fig. 5. The values of the indicators Neurogenic Bladder Symptom Score (NBSS) in patients with neurogenic detrusor overactivity before and after 1, 3 and 6 months after intradetrusor injection of BTA, points ($n = 28$)

Рис. 5. Значения показателей шкалы симптомов нейрогенного мочевого пузыря (NBSS) пациентов с нейрогенной детрузорной гиперактивностью до и через 1, 3 и 6 мес. после внутридetrузорных инъекций БТА, баллы ($n = 28$)

tients except one required ISC. Similar data published by S. Khan et al. [16] showed that 65% of patients with multiple sclerosis required ISC before botulinum toxin therapy and 95% after therapy. D. Ginsberg et al. [7] showed that of the 60% of patients who did not perform ISC before botulinum toxin injection, ISC after the procedure was required in 42% of patients who received a dose of 300 U, 35% of patients who received a dose of 200 U, and 10% of patients in the placebo group.

Low-dose botulinum toxin seems to result in a reduction of the probability of urinary retention in patients with multiple sclerosis, as was shown previously by U. Mehnert et al. [12].

Despite significant positive dynamics in symptoms according to the NBSS, a detrusor overactivity remained in all patients during filling cystometry. More than a half of patients still had an urge urinary incontinence, however, the severity of incontinence reduced. The subjective positive evaluation of BTX-A therapy outcomes by the patients corresponded with the changes in the urody-

namic parameters, although not in all the patients. Micturition diaries and repeated urodynamic study allowed for objective assessment of the efficacy of the botulinum toxin therapy, which is especially relevant in patients with high risk of upper urinary tract disorders. M. Koschorke et al. [17] analyzed records of 148 patients with NDO who had received botulinum toxin injections and concluded that urodynamic studies were essential both before and after the botulinum toxin therapy. High baseline detrusor pressure is a predictor for poorer urodynamic parameters after injection of botulinum toxin. High intravesicular pressure before treatment provides a more accurate evaluation of procedure's efficiency than clinical absence of urinary incontinence.

CONCLUSION

Intradetrusor injection of 100 U of BTX-A in patients with neurogenic bladder improves urodynamic parameters followed by significant reduction in clinical symptoms and quality of life improvement. Low-

dose BTX-A does not lead to a total reduction of NDO symptoms, but reduces the probability of urinary retention after botulinum toxin therapy in patients with multiple sclerosis.

REFERENCES

- Linsensmeyer TA. Use of botulinum toxin in individuals with neurogenic detrusor overactivity: state of the art review. *J Spinal Cord Med.* 2013;36(5):402-419. <https://doi.org/10.1179/2045772313Y.0000000116>.
- Montecucco C, Rossetto O, Caccin P, et al. Different mechanisms of inhibition of nerve terminals by botulinum and snake presynaptic neurotoxins. *Toxicon.* 2009;54(5):561-564. <https://doi.org/10.1016/j.toxicon.2008.12.012>.
- Schiavo G, Matteoli M, Montecucco C. Neurotoxins affecting neuroexocytosis. *Physiol Rev.* 2000;80(2):718-750. <https://doi.org/10.1152/physrev.2000.80.2.717>.
- Apostolidis A, Dasgupta P, Fowler CJ. Proposed mechanism for the efficacy of injected botulinum toxin in the treatment of human detrusor overactivity. *Eur Urol.* 2006;49(4):644-650. <https://doi.org/10.1016/j.eururo.2005.12.010>.
- Reitz A, Stohrer M, Kramer G, et al. European experience of 200 cases treated with botulinum-A toxin injections into the detrusor muscle for urinary incontinence due to neurogenic detrusor overactivity. *Eur Urol.* 2004;45(4):510-515. <https://doi.org/10.1016/j.eururo.2003.12.004>.
- Cruz F, Herschorn S, Aliotta P, et al. Efficacy and safety of onabotulinumtoxinA in patients with urinary incontinence due to neurogenic detrusor overactivity: a randomised, double-blind, placebo-controlled trial. *Eur Urol.* 2011;60(4):742-750. <https://doi.org/10.1016/j.eururo.2011.07.002>.
- Ginsberg D, Gousse A, Keppenne V, et al. Phase 3 efficacy and tolerability study of onabotulinumtoxinA for urinary incontinence from neurogenic detrusor overactivity. *J Urol.* 2012;187(6):2131-2139. <https://doi.org/10.1016/j.juro.2012.01.125>.
- Cheng T, Shuang WB, Jia DD, et al. Efficacy and Safety of Onabotulinumtoxin A in patients with neurogenic detrusor overactivity: a systematic review and meta-analysis of randomized controlled trials. *PLoS One.* 2016;11(7): e0159307. <https://doi.org/10.1371/journal.pone.0159307>.
- Apostolidis A, Thompson C, Yan X, Mourad S. An exploratory, placebo-controlled, dose-response study of the efficacy and safety of onabotulinumtoxinA in spinal cord injury patients with urinary incontinence due to neurogenic detrusor overactivity. *World J Urol.* 2013;31(6):1469-1474. <https://doi.org/10.1007/s00345-012-0984-0>.
- Schurch B, de Seze M, Denys P, et al. Botulinum toxin type A is a safe and effective treatment for neurogenic urinary incontinence: results of a single treatment, randomized, placebo-controlled 6-month study. *J Urol.* 2005;174(1):196-200. <https://doi.org/10.1097/01.ju.0000162035.73977.1c>.
- Архиреев А.С., Ромих В.В., Пантелеев В.В., и др. Эффективность лечения больных нейрогенной и идиопатической детрузорной гиперактивностью в зависимости от дозы ботулинического токсина типа А // Экспериментальная и клиническая урология. – 2017. – № 3. – С. 98–103. [Arhireev AS, Romih VV, Panteleev VV, et al. The efficacy of therapy in patients with neurogenic and idiopathic detrusor hyperactivity depending on the dose of botulinum toxin type A. *Experimental and clinical urology.* 2017;(3):98-113. (In Russ.)]
- Mehnert U, Birzele J, Reuter K, Schurch B. The effect of botulinum toxin type A on overactive bladder symptoms in patients with multiple sclerosis: a pilot study. *J Urol.* 2010;184(3):1011-1016. <https://doi.org/10.1016/j.juro.2010.05.035>.
- Schurch B, de Seze M, Denys P, et al. Botulinum toxin type A is a safe and effective treatment for neurogenic urinary incontinence: results of a single treatment, randomized, placebo-controlled 6-month study. *J Urol.* 2005;174(1):196-200. <https://doi.org/10.1097/01.ju.0000162035.73977.1c>.
- Kalsi V, Popat RB, Apostolidis A, et al. Cost-consequence analysis evaluating the use of botulinum neurotoxin-A in patients with detrusor overactivity based on clinical outcomes observed at a single UK centre. *Eur Urol.* 2006;49(3):519-527. <https://doi.org/10.1016/j.eururo.2005.11.006>.
- Kalsi V, Gonzales G, Popat R, et al. Botulinum injections for the treatment of bladder symptoms of multiple sclerosis. *Ann Neurol.* 2007;62(2):452-457. <https://doi.org/10.1002/ana.21209>.
- Khan S, Game X, Kalsi V, et al. Long-term effect on quality of life of repeat detrusor injections of botulinum neurotoxin-A for detrusor overactivity in patients with multiple sclerosis. *J Urol.* 2011;185(4):1344-1349. <https://doi.org/10.1016/j.juro.2010.12.002>.
- Koschorke M, Leitner L, Sadri H, et al. Intradetrusor onabotulinumtoxinA injections for refractory neurogenic detrusor overactivity incontinence: do we need urodynamic investigation for outcome assessment? *BJU Int.* 2017;120(6):848-854. <https://doi.org/10.1111/bju.13976>.

Information about the authors:

Ekaterina S. Filippova — Candidate of Medical Sciences, Associate Professor of the Department of Urology, Urals State Medical University of the Ministry of Healthcare of the Russian Federation, Ekaterinburg; Urologist, Sverdlovsk Regional Clinical Hospital No. 1, Ekaterinburg, Russia. E-mail: filippova.cat@yandex.ru.

Сведения об авторах:

Екатерина Сергеевна Филиппова — канд. мед. наук, доцент кафедры урологии, ФГБОУ ВО УГМУ Минздрава России, Екатеринбург; врач-уролог, ГБУЗ СО «СОКБ № 1», Екатеринбург. E-mail: filippova.cat@yandex.ru.

Information about the authors:

Igor V. Bazhenov — Doctor of Medical Sciences, Professor of the Department of Urology, Ural State Medical University of the Ministry of Healthcare of the Russian Federation, Ekaterinburg, Russia; Head of the Urological Unit, Sverdlovsk Regional Clinical Hospital No. 1, Ekaterinburg, Russia. E-mail: biv@okb1.ru.

Aleksandr V. Zyrjanov — Doctor of Medical Sciences, Professor. Chairman of the Department of Urology, Ural State Medical University of the Ministry of Healthcare of the Russian Federation, Ekaterinburg, Russia; Head of the Regional Urological Center of the Sverdlovsk Regional Clinical Hospital No. 1, Ekaterinburg, Russia. E-mail: zav1965@mail.ru.

Vladimir N. Zhuravlev — Doctor of Medical Sciences, Professor. Urals State Medical University of the Ministry of Healthcare of the Russian Federation, Ekaterinburg, Russia. E-mail: zhuravlev@okb1.ru.

Igor V. Borzunov — Doctor of Medical Sciences, Professor of the Department of Urology, Ural State Medical University of the Ministry of Healthcare of the Russian Federation, Ekaterinburg, Russia. E-mail: ivborzunov@e1.ru.

Gennadiy S. Ustinov — Student. Ural State Medical University of the Ministry of Healthcare of the Russian Federation, Ekaterinburg, Russia. E-mail: GennadiyUstinov@mail.ru.

Сведения об авторах:

Игорь Владимирович Баженов — д-р мед. наук, профессор кафедры урологии, ФГБОУ ВО УГМУ Минздрава России, Екатеринбург; заведующий урологическим отделением, ГАУЗ СО «СОКБ № 1», Екатеринбург. E-mail: biv@okb1.ru.

Александр Владимирович Зырянов — д-р мед. наук, профессор, заведующий кафедрой урологии, ФГБОУ ВО УГМУ Минздрава России, Екатеринбург; руководитель Областного урологического центра ГБУЗ СО «СОКБ № 1», Екатеринбург. E-mail: zav1965@mail.ru.

Владимир Николаевич Журавлев — д-р мед. наук, профессор кафедры урологии. ФГБОУ ВО УГМУ Минздрава России, Екатеринбург. E-mail: zhuravlev@okb1.ru.

Игорь Викторович Борзунов — д-р мед. наук, профессор кафедры урологии. ФГБОУ ВО УГМУ Минздрава России, Екатеринбург. E-mail: ivborzunov@e1.ru.

Геннадий Сергеевич Устинов — студент. ФГБОУ ВО УГМУ Минздрава России, Екатеринбург. E-mail: GennadiyUstinov@mail.ru.