

## Additional Action of Alpha-blockers in the Correction of Neurogenic Bladder in Children with Spina Bifida

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### Abstract

**Objective:** The morbid condition of children with spina bifida is caused mainly by severe kidney disease as a result of impairment of urinary tract emptying. One of the complications of spinal cord and urinary tract denervation is detrusor-sphincter incoordination. The purpose of the study is to identify additional pathogenetic factors, besides the denervation, that underlies the contracture of the urinary sphincter.

**Materials and methods:** The blood flow in the vessels of the anterior pelvic region was estimated by the method of rheopelviography in 37 children of 12-15 years with detrusor neurogenic overactivity, detrusor-sphincter incoordination, 2-3-degree vesicoureteral reflux in 25 patients out of 37. All patients had angiospasm in the basin of the anterior pelvic region. Patients were divided into two groups. In the 1<sup>st</sup> group (17 people) oxybutynin was administered, whereas the 2<sup>nd</sup> group (20 people) got a combination of oxybutynin and doxazosin. After 1, 3 and 12 months, urodynamic and rheographic monitoring was performed.

**Results:** After one month of treatment, a decrease in intravesical pressure from 27-35 cm H<sub>2</sub>O to 23-25 cm H<sub>2</sub>O was noted in patients of the group 1. The effective volume of the bladder increased from 30 ml to 50-60 ml, which indicated a partial cessation of detrusor spasm. Angiospasm persisted. Two months after the end of treatment the reservoir function of the bladder worsened, returning to almost initial values. In children of the 2<sup>nd</sup> group, treatment with oxybutynin and doxazosin did not cause adverse reactions. At the end of the first month there was a significant improvement in rheographic indices, the volume of the bladder increased to 70-80 ml, the intravesical pressure decreased. These changes were maintained during control follow-up examination in a month. Subsequently, both groups were administered oxybutynin and doxazosin for one year in courses of 30 days every two months. After one year in all children the reservoir function of the bladder was restored and its emptying improved. In 9 cases, reflux has

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completely stopped, in 6 cases it became less pronounced, in 10 cases no change was observed.

**Conclusion:** Spina bifida with detrusor-sphincter incoordination in children is characterized by a persistent vasospasm in the basin of the lower arteries. For such patients it is advisable to provide complex therapy aimed at stabilizing the detrusor and eliminating angiospasm.

**Key words:** Spina bifida, Children, Neurogenic detrusor overactivity, Blood circulation, Alpha-blockers

## Introduction

Malformations of the spinal cord – spina bifida occur in 1-2 in 100 000 newborns [1]. The severity of the condition of such children is determined mainly by neurogenic bladder, which leads to disruption of urodynamics of the upper urinary tract, chronic inflammatory process, renal insufficiency. One of the types of denervation disorders in spina bifida is detrusor-sphincter incoordination (DSI), which manifests itself as a syndrome of chronic urinary retention [2]. The treatment of such patients is based on the principles of selective action on spinal and supraspinal micturition centers, taking into account the level of disturbances of segmental innervation of the bladder. That is why, in the presence of partially preserved segmental innervation, experimental and clinical studies focused on neurotropic drugs and physiotherapy [3]. It is also known that the use of alpha-1 adrenoreceptor blockers is justified in patients with DSI due to their direct relaxing effect on the smooth muscle fibers of the neck of the bladder and urethra [4]. But it should be taken into account that the contractile activity of the muscular structures directly depends on the blood supply of the myocytes [5]. Perhaps the effect of relaxing the sphincter with the use of alpha-blockers in children with spina bifida is due to their vasodilation effect. To test this hypothesis, the present study has been carried out.

## Materials and methods

In a randomized, open clinical trial we observed 37 children aged 12–15 years who had undergone operative treatment for hernia during the neonatal period. Patients retained the capacity for independent urination, but its effectiveness was dramatically reduced, and the amount of residual urine reached 85% with a general decrease in the voiding volume (main inclusion criteria. Ortostatic episodes in the anamnesis and current urinary infections were exclusion criteria. At the beginning of the study 26 children had to be catheterized from 1 to 3 times per day. Urodynamic study demonstrated neurogenic detrusor overactivity and DSI. Twenty-five patients (68%) had vesicoureteral reflux (VUR) of grade 2-3 revealed during micturition cystography.

The condition of the blood supply of the bladder was assessed using the method of rheopelviography (RPeG). The main parameters were the amplitude of the systolic wave ( $N - 0.033 \pm 0.002$  Om), the maximum speed of the fast filling period ( $N - 0.450 \pm 0.01$  Om/s), the average velocity of the slow blood-filling period ( $N - 0.215 \pm 0.028$  Om/s).

Drug therapy of the patients included alpha-1

blocker doxazosin and antimuscarinic drug oxybutynin hydrochloride.

Patients were randomly divided into two groups using a random table by the simple randomization method. In the first (17 children), oxybutynin was administered as the main medication: 5 mg  $\times$  2 times a day after meals for 30 days with one-month intervals between courses. During the year the average of 6 courses was administered. In the second, a combination of oxybutynin (in a similar dose) and doxazosin was used at 1 mg (half the daily average dose for adults) in the morning once a day under the control of blood pressure.

The duration of the course was 30 days. In the course of the study, the dynamics of the state of accumulation and emptying of the bladder, rheographic characteristics of the anterior parts of the small pelvis, the degree of VUR were evaluated. The study conformed to the Declaration of Helsinki and the protocol was approved by the Institutional Ethics Committee of Moscow children's Speransky hospital and written informed consent was obtained from all the subjects.

## Results and Discussion

Initially, in patients of both groups, filling cystometry showed a decrease in urinary bladder capacity by more than 50 percent relative of the average age norm. The pressure bladder in the accumulation phase accounted for  $38.4 \pm 8,8$  cm H<sub>2</sub>O which is more than three times higher than the normal value, the match was reduced to 13 percent.

Micturition cystography in 15 children showed unilateral vesicoureteral reflux of 2-3 degree, and in 10 children it was bilateral. RPeG revealed significant violations of the spastic type blood flow in the basin of the bladder arteries. The amplitude of the systolic wave (as a measure of the total blood supply) was  $0.021 \pm 0.004$  Om, the maximum speed of the fast filling period (as an indicator of the tone of large arteries of distribution) was  $0.567 \pm 0.03$  Om/s, the average velocity of the slow blood filling period (as an indicator of the tone of small arteries of resistance) –  $0.309 \pm 0.07$  Om/s. When the bladder was filled, the amplitude of the systolic wave decreased. There were no significant changes in the maximum speed of the fast filling period ( $0.57- 0.67$  Om/s).

Thus, all patients initially experienced a chronic urinary retention caused by neurogenic detrusor overactivity in combination with the pathological activity of the sphincter mechanism of the bladder and urethra. In most cases this was accompanied by an anomaly of the upper urinary tract urodynamics in the form of VUR, and angiologic changes were characterized by a pronounced shortage of blood ply to the anterior parts of the pelvis.

In patients of group 1, a decrease in bladder pressure to  $23.6 \pm 5.4$  cm of H<sub>2</sub>O was observed in one month after the initiation of treatment. The effective volume of the bladder increased from  $30.5 \pm 17.5$  ml to  $67 \pm 18.4$  ml, which indicated partial decrease of neurogenic detrusor overactivity. In 11 cases a significant amount of residual urine was retained. The control RPeG demonstrated

evidence of a persistent blood flow deficit in the basin of the lower arteries due to angiospasm. In one month after the end of treatment, a decrease in the capacity of the bladder almost to the initial values was observed.

Thus, the effect of oxybutynin on the detrusor was relatively short and did not improve its blood supply. In patients of group 2 after one course of treatment, we noted an improvement in the function of the lower urinary tract in the form of an increase in the volume of the urinary bladder by 22–30 percent, detrusor compliance reached 33–35 percent. The RPeG revealed an increase in the amplitude of the systolic wave in the emptied bladder up to 0.21 om, and when filled up to 0.28 om. The rate of blood filling increased to 0.15–0.17 Om/s. Control studies performed 1 month after the end of the treatment course showed no significant deterioration in the state of the bladder function compared with the results obtained immediately after the withdrawal of the drugs.

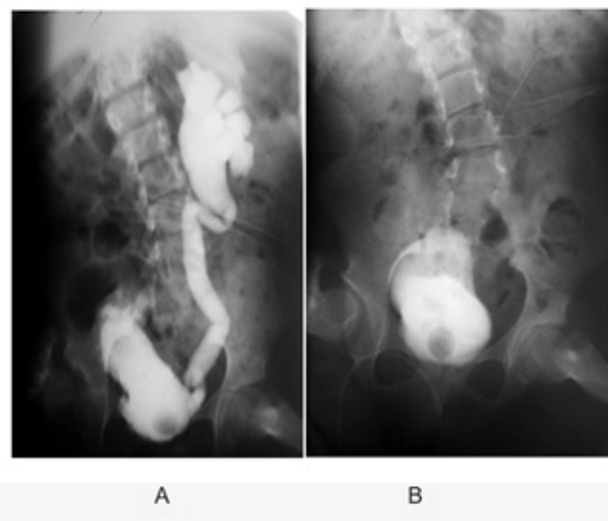
Later combined treatment with oxybutynin and doxazosin was continued in both groups with courses of the same duration and frequency for 1 year. As a result of a decrease in bladder pressure and an improvement in the circulation of the bladder neck and urethra, the vesicoureteral reflux was partially cured.

All patients who had been diagnosed with VUR prior to initiation of treatment, had a follow-up micturition cystography in a year. In 6 cases, reflux was stopped, in 9 cases it decreased, and in 10 patients the degree of VUR remained the same. A positive example of cystography changes is shown in Figure 1.

The achieved decrease in intravesical pressure in 11 children with persistent VUR permitted to perform an endoscopic correction of VUR, 8 patients required the administration of a botulinum toxin type A to the external urethral sphincter, and then endoscopic correction of reflux was also performed. Thus, improving the blood flow in the basin of the anterior pelvic region contributes to more persistent positive changes in bladder function.

## Conclusion

In patients with spina bifida, the character of angiologic changes in the basin of the lower arteries correlates with the tone of the sphincter apparatus. In our study, at a sufficiently high sphincter pressure characteristic of the DSI, we recorded all the typical rheographic indices of angiospasm. The effectiveness of the single use of oxybutynin in this case was lower than in combination with doxazosin. This led to the



**Figure 1:** A is the patient's cystography initially. B is after 1 year of repeated courses of treatment.

conclusion that for the spinal patients the inclusion of alpha blockers in complex pharmacotherapy is a pathogenetically substantiated step and improves the results of treatment.

## Conflict of interest

Authors would hereby like to declare that there is no conflict of interests that could possibly arise.

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