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Assessment of the perioperative status in children with SMA receiving nusinersen and undergoing reconstructive orthopedic interventions

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Abstract

Surgical methods for treatment of spinal muscular atrophy (SMA) in children are aimed at improving their positioning and maintaining the ability of verticalization. Assessment of neurological, somatic and motor status of patients, individual selection of drugs for anesthesia and sedation at the stage of planning surgical interventions allow the anesthesiologist/resuscitator to avoid perioperative adverse events. **Purpose** To compare the course of the perioperative period in children with SMA who received pathogenetic therapy with nusinersen with the control group during orthopedic correction of acquired skeletal deformities. **Materials and methods** The retrospective analysis for the period from 2019 to 2021 included 23 children. Depending on the ongoing pathogenetic therapy, children with SMA were divided into 2 groups. The main group (SMA+N) included 9 children who received nusinersen; the control group (CG) included 14 children without antisense oligonucleotide therapy. Co-morbidities, hemodynamic parameters, blood loss, need for analgesics and complications were studied. **Results** Insignificant differences between the groups were recorded based on the Hammersmith Extended Scale (HFMSE). At the same time, similar comorbid pathology, the severity of respiratory failure, and the absence of differences in the frequency of the NIV application indicated that the groups were comparable. This is probably due to the late start of SMA treatment, degenerative changes in motor neurons, and fatty degeneration of muscle tissue. **Conclusion** Intake of nusinersen in patients with SMA type II-III and a long period of illness, severe neurological and respiratory disorders do not lead to a significant regression of symptoms in the perioperative period. The therapy with antisense oligonucleotides in severe muscle hypotonia does not exclude the risk of adverse events in the perioperative period in children with SMA type II-III during orthopedic correction of skeletal deformities.

Keywords: spinal muscular atrophy, neurological status, pathogenetic therapy, orthopaedic interventions

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INTRODUCTION

Spinal muscular atrophy (SMA) is a neuromuscular disease associated with a deletion or mutation in the SMN1 gene, decreased synthesis of the SMN protein (survival motor neuron protein), and degeneration of alpha motor neurons in the spinal cord. Clinically, SMA is manifested by varying severity of the bulbar syndrome and progressive symmetrical muscle weakness [1, 2]. Against this background, neurogenic kyphoscoliosis, deformity of the chest, subluxations or dislocations of the hips, contractures of large joints of the lower extremities, spontaneous fractures due to osteopenia impair the activity of patients, reduce their functionality, are a source of chronic pain, lead to severe disability and loss of function of daily activities [3-7].

To date, the pathogenetic therapy of SMA in Russia is carried out with nusinersen. This drug is an antisense oligonucleotide that modifies the splicing of the pre-messenger RNA of the SMN2 gene and increases the production of the full-length SMN protein. Surgical treatment strategies are aimed at eliminating spinal curvatures using posterior dynamic instrumental systems, at performing multilevel interventions on tendons and muscles and corrective osteotomies of limb bones to improve patient's positioning and maintaining the possibility of their verticalization [8-11].

Cardiomyopathy, dysfunction of the upper respiratory tract, reduced ability to cough up and evacuate tracheobronchial secretions, respiratory failure are the main and frequently diagnosed disorders in children with SMA [12, 13]. In combination with comorbid diseases, issues related to ensuring adequate venous access, patency of initially difficult airways, prevention of prolonged action of non-depolarizing muscle relaxants, and the development of rhabdomyolysis induced by the use of succinylcholine or halogen-containing inhalation anesthetics need to be addressed at the stage of preparation for surgery [14].

Thus, assessment of the neurological, somatic, motor status, risk analysis of possible complications, individual selection of drugs for anesthesia and sedation, as well as the development of a strategy for

managing patients at the stage of early rehabilitation allow the anesthesiologist/resuscitator to avoid perioperative undesirable phenomena by planning surgical interventions in patients with SMA [15, 16].

Purpose To compare the course of the perioperative period in children with SMA who received pathogenetic therapy with nusinersen with the control group during orthopedic correction of acquired skeletal deformities.

MATERIALS AND METHODS

The null hypothesis was based on the assumption that treatment with nusinersen of children with spinal muscular atrophy improves their neurological status and reduces the risk of perioperative complications compared with patients without pathogenetic therapy.

A retrospective analysis of the data was carried out on the basis of medical records of 23 children who underwent orthopedic interventions on the spine or bones of the lower extremities.

The selection of archival documentation was carried out for the period from 2019 to 2021.

The work was carried out at the Ilizarov National Medical Research Center for Traumatology and Orthopedics of the Ministry of Health of the Russian Federation.

Criteria for data extraction:

1) age from 2 to 16 years;

2) spinal muscular atrophy of types II-III [16];

3) neuromuscular kyphoscoliosis, contractures of the joints of the lower extremities or dislocations and subluxations of the hips;

4) correction of spinal deformity with posterior dynamic instrumental systems, operations on the bones of the lower extremities;

5) anesthesia: general intravenous anesthesia with mechanical (non-invasive) lung ventilation (NIV).

All children with spinal muscular atrophy were divided into 2 groups depending on the pathogenetic therapy. Among 23 children selected for analysis, 9 (39 %) received nusinersen for at least a year and were included into the main group (SMA+N) [18, 19]. Moreover, 7 out of 9 (77 %) were with type II spinal muscular atrophy, and 2 (23 %) with type III.

The second group, the control group (CG), included 14 out of 23 (61 %) patients with SMA who did not receive antisense oligonucleotides. Type II SMA was diagnosed in 6 out of 14 (43 %) patients and 8 were with type III (57 %).

The groups were comparable to each other in terms of the main indicators that determine the results of the study. The SMA+N group included 3 girls and 6 boys, while the CG included 7 girls and 7 boys ($p = 0.43$). The mean age (standard deviation - SD) in the groups was 9.8 (3.4) and 9.1 (2.5) years and did not differ significantly ($p = 0.57$). The mean values (SD) of weight were 30.3 (11.5) and 34.1 (11.4) kilograms, respectively ($p = 0.48$).

Based on the operational and anesthetic risks according to MNOAR, four children in the SMA+N group had grade III and 5 people had grade IV, while in the CG group 3 children had grade III, 11 had grade IV ($p = 0.24$).

All children had operations under total intravenous anesthesia with mechanical ventilation. During induction into anesthesia, propofol was used at a dose of 3 mg/kg, fentanyl 100 μg, rocuronium bromide 0.3 mg/kg. In order to maintain sedation and analgesia throughout the operation, propofol at the rate of 10 mg/kg/h and fentanyl 3 μg/kg/h were administered intravenously microfluidically using syringe dispensers.

As an antifibrinolytic agent, tranexamic acid was used intraoperatively and then 6 hours after the first injection at a dose of 15 mg/kg. At the end of the surgical intervention, all patients were extubated on the operating table and sent to the anesthesiology and intensive care unit (A&R) for observation.

Postoperative analgetic sedation in A&R was carried out by intravenous microfluidic administration of fentanyl using a syringe dispenser at the rate of 1.5 μg/kg/h. Additionally, paracetamol was prescribed in the study groups at the decision of the resuscitator based on the results of pain assessment on the visual analogue scale (VAS).

The control of the general blood test was carried out before the operation and upon admission to the department of anesthesiology and resuscitation.

Indications for blood transfusion were blood loss of more than 25 % of the circulating blood volume (BCV), a decrease in hemoglobin level lower than 80 g/l, and the development of generalized tissue hypoperfusion.

Criteria for evaluation:

1) co-morbid diseases;

2) neurological status upon admission to the hospital;

3) indicators of spirometry in the preoperative period;

4) perioperative hemodynamic parameters: mean arterial pressure (MAP), heart rate (HR);

5) volume of intraoperative external blood loss;

6) volume of infusion therapy in the perioperative period;

7) level of hemoglobin in capillary blood in the perioperative period;

8) blood transfusion in the operating room and A&R;

9) need for additional administration of analgesics in A&R;

10) number of complications in the perioperative period.

Statistical processing of the material was carried out using the StatPlus 7 software When numerical values were submitted to the criteria of the Gaussian distribution

(Kolmogorov-Smirnov/Lillifors), quantitative characteristics were described using the mean and standard deviation. In cases where the estimated indicators did not correspond to the normal distribution parameters, the median and interquartile interval (Q1; Q3) were calculated. To determine statistical significance when comparing two independent samples, Student's t-test or non-parametric Mann-Whitney test were used. When comparing qualitative characteristics, Pearson's $\chi 2$ test was used. In all cases, the significance level p was taken equal to 0.05. The study was approved by the institution's ethics committee and was conducted in accordance with the ethical standards set out in the Declaration of Helsinki.

RESULTS

There were no statistically significant differences in the number of co-morbid diseases observed in the patients of the studied groups in the preoperative period ($p > 0.05$), the data are presented in Table 1.

Minor differences in motor abilities between the subgroups were recorded based on the Hammersmith Hospital HFMSE Expanded Scale ($p = 0.01$), while other parameters that determined the neurological status of children before surgery did not differ ($p > 0.05$). The data are presented in Table 2.

Restrictive lung lesions were diagnosed by the analysis of spirometry in children with SMA, and the assessed indicators of respiratory function were comparable in both groups ($p > 0.05$). The data are presented in Table 3.

At the initial and main stages of the operation, differences in hemodynamic parameters (MAP) were recorded; however, they had no clinical significance, since they were within the acceptable range for this category of patients (data are presented in Table 4). Arterial hypotension requiring correction with vasopressors occurred in one case in the patients of the SMA+N group, but not in the CG group ($p > 0.05$).

The volume of external blood loss in the intra-operative period was determined at the level of 60 (50; 70) ml in the SMA+N group and 40 (30; 50) ml in the CG group ($p = 0.29$), which, as a percentage of the volume of circulating blood, was 2.1 (1.6; 7.1) % and 1.5 (1.3; 2.4) % ($p = 0.22$).

Infusion therapy was carried out with crystalloids and amounted to 13 (9) ml/kg/h in the SMA+N group during surgery, 14 (5) ml/kg/h in the CG group ($p = 0.83$), while in the anesthesiology and resuscitation department it was 2.0 (0.5) ml/kg/h and 1.8 (0.4) ml/kg/h, respectively ($p = 0.65$).

Table 1

Concomitant pathology in children with SMA (n; %)

		Group (n = 23)		
		SMA+N (n = 9)	CG (n = 14)	P
Body mass	overweight	1 (11)	6 (42)	0.11
	underweight	3 (33)	2 (14)	0.28
Retardation in psychic development		0 (0)	1 (7)	0,44
Pathology	Heart	9 (100)	11 (78)	0.14
	Lungs (НИВЛ)	8 (89)	12 (85)	0.83
	Digestion tract	3 (33)	3 (21)	0.53
	ENT organs	3 (33)	2 (14)	0.28
	Eyes	4 (44)	3 (21)	0.17

Notes: n – number of patients; criterion χ^2; $p > 0.05$

Table 2

Preoperative neurological status of children in the studied groups (n; %)

		Total group (n = 23)		
		SMA+V (n = 9)	CG (n = 14)	p
Disease manifestation (months after birth)		11 (6; 24)**	9 (4)*	0.26
Muscle strength in points (MRC)	arm	2 (2; 3)**	2 (2; 2.5)**	0.69
	leg	2 (1; 2)**	1 (1; 1.5)**	0.69
HFMSE (points)		5 (2)	3 (1)	0.01
EDACS (level)	I	6 (67)	12 (86)	0.36
	II	2 (22)	2 (14)	
	III	1 (11)	0 (0)	
GMFCS (level)	I	3 (33)	3 (22)	0.38
	II	4 (44)	10 (71)	
	III	2 (23)	1 (7)	

n – number of patients; * – mean and standard deviation (SD); ** – median (Q1; Q3)

Table 3

Preoperative spirometry indicators in patients of the studied groups (mean value and standard deviation – SD)

	Group (n = 23)		
	SMA+N (n = 9)	CG (n = 14)	p
VC (l)	1.2 (0.5)	1.3 (0.5)	0.99
% from norm	61 (17)	58 (15)	0.85
FVC (l)	0.9 (0.3)	1.3 (0.5)	0.22
% from norm	43 (11)	60 (20)	0.13
FEV1 (l)	0.8 (0.3)	1.1 (0.5)	0.5
% from norm	41 (10)	55 (19)	0.16
R. Tiffeneau	70 (14)	85 (23)	0.35
% from N	69 (14)	91 (25)	0.18
FEF 75 (l/sec)	0.9 (0.1)	0.8 (0.4)	0.33
% от N	64 (9)	59 (24)	0.88
FEF 50 ((l/sec)	1.6 (0.4)	1.6 (0.4)	0.43
% from norm	57 (10)	61 (16)	0.57
FEF 25 ((l/sec)	2.2 (0.7)	2.0 (0.6)	0.39
% from norm	54 (13)	50 (14)	0.92
MVV ((l/sec)	2.0 (0.7)	2.2 (0.6)	0.95
% from norm	45 (16)	50 (12)	0.25

Note: unifactorial dispersion analysis; $p > 0.05$; Vital capacity (VC), Forced vital capacity (FVC), Forced expiratory volume (FEV) at timed intervals of 0.5, 1.0 (FEV1), 2.0, and 3.0 seconds, forced expiratory flow 25-75 % (FEF 25–75) and maximal voluntary ventilation (MVV)

Table 4

Perioperative hemodynamic parameters of children in the groups (mean value and standard deviation – SD)

	Group (n = 23)			
	SMA+N		CG	
	ABP (mm Hg)	Heart rate/min	ABP (mm Hg)	Heart rate/min
At admission to operation room	76 (15)	99 (10)	81 (9)	108 (20)
At the beginning of surgery	64 (9)*	95 (13)	76 (8)	98 (20)
Main phase of surgery	65 (12)*	94 (17)	75 (7)	95 (22)
At the end of surgery	73 (9)	99 (14)	80 (12)	94 (16)
At A&R transfer	76 (12)	110 (17)	74 (12)	98 (20)
In the specialized department	71 (7)	114 (15)	76 (11)	107 (15)

Note: unifactorial dispersion analysis*; $p > 0.05$

The analysis of hematological parameters did not reveal significant differences in the level of hemoglobin in capillary blood, which was determined before surgery in children of the SMA+N group at the level of 129 (10) g/l, in children of the CG group 130 (5) g/l (p = 0, 72), in the early postoperative period 117 (14) g/l in the SMA+N group and 122 (116; 127) g/l in the CG group (p = 0.89). Hemotransfusion in the intra-operative period was not performed in patients of the studied groups. In the A&R department, two children from the subgroup with pathogenetic therapy of SMA required transfusion of erythrocyte-containing blood components, and one child in the control group (p = 0.24).

Additional prescription of paracetamol in A&R was required in 4 (44 %) patients of the SMA+N group, 7 (50 %) patients in the CG group, and did not differ significantly (p = 0.79).

There were no complications in the perioperative period (0 %, 95 % CI 0 % to 12.2 %).

DISCUSSION

Based on the marginally better Hammersmith Hospital Scale (HFMSE) locomotor ability in the patients with specific SMA therapy, it can be said that antisense oligonucleotides (nusinersen) are beneficial. At the same time, similar comorbid pathology, the severity of respiratory failure and the absence of statistically significant differences in the frequency of NIV application indicate the comparability in the subgroups. This circumstance is probably associated with the late start of SMA treatment with nusinersen, degenerative changes in motor neurons, limited regeneration, and fatty degeneration of muscle tissue [18, 20-22]. However, the statistical power of our study is insufficient to confirm this assumption.

The lack of the desired effect from the treatment of spinal muscular atrophy may also be due

to the variability of the response to the drug. Currently, the control of sensitivity to treatment is carried out on the basis of scales for assessing motor abilities and has certain subjectivity [23, 24]. Biomarkers (neurofilaments (NF), CSF proteomic profile, etc.) will help predict the effect of therapy and avoid long-term use of expensive drugs, but they are under development [23, 25, 26].

The significant differences in hemodynamic parameters (MAP) in the subgroups at the stages of surgery are most likely due to different severity of cardiomyopathy in children with SMA, a decrease in cardiac output on induction into anesthesia, dilatation of the vessels of the extremities and deposition of blood in them, and initial hypovolemia. Intra-operative infusion therapy with vasopressor support enables to correct hemodynamics and level out differences in mean arterial pressure [27, 28].

According to Kannan S et al (2002) and Wijngaarde CA et al (2020), there is an increase in prothrombin time in patients with spinal muscular atrophy, activated partial thromboplastin time, a decrease in the activity of factor VII, von Willebrand factor, and impaired platelet adhesion [29, 30]. Intra-operative depletion of a functionally defective hemocoagulation system in the studied groups, dysfunction of the external and internal blood coagulation pathways could contribute to ongoing wound blood loss, and, as a result, postoperative hemotransfusion in three children of this series.

Our retrospective analysis did not reveal any discrepancies in the prescription of additional pain medications in the compared samples. This fact indicates the effectiveness of analgetic sedation with fentanyl in A&R in this category of patients, and the absence of adverse events associated with the use of narcotic analgesics indicates the safety of the method [15, 31].

Thus, the better neurological status as well as the absence of adverse events in the perioperative period (0 %, 95 % CI 0 % to 28.3 %) in the patients treated with nusinersen allow us to accept the null hypothesis. But, on the other hand, a similar clinical picture, an equal complication rate with the control group (0 %, 95 % CI from 0 % to 19.3 %) makes us analyze the results, requires a deep study of this topic, a rationale for the low effectiveness of antisense oligonucleotide therapy .

CONCLUSIONS

The intake of nusinersen by patients with SMA type II-III characterized by a long period of illness, severe neurological and respiratory disorders does not lead to a significant regression of symptoms in the perioperative period.

The therapy with antisense oligonucleotides in severe muscle hypotonia does not exclude the risk of adverse events in the perioperative period in children with SMA type II-III during orthopedic correction of skeletal deformities.

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