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ISSN 2411-7110 (online)

GENERAL REANIMATOLOGY

SCIENTIFIC-AND-PRACTICAL JOURNAL

ОБЩАЯ РЕАНИМАТОЛОГИЯ

научно-практический журнал

Volume 20 Том 20

№ 5

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ISSN 1813-9779 (print) ISSN 2411-7110 (online)

GENERAL REANIMATOLOGY

OBSHCHAYA REANIMATOLOGIYA

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Registration certificate of the Journal «Obshchaya reanimatologiya» (General Reanimatology): ПИ № ФС77-18690, November 2, 2004, Federal Service for Supervision of Compliance with Legislation in the Sphere of Mass Communications and Protection of Cultural Heritage
Publication Frequency: 6 numbers per year.
Founder:

ОБЩАЯ РЕАНИМАТОЛОГИЯ

OBŜAÂ REANIMATOLOGIÂ

научно-практический рецензируемый журнал
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Свидетельство о регистрации: ПИ № ФС77-18690 от 02 ноября 2004 г. Печатное издание журнал «Общая реаниматология» зарегистрирован Федеральной службой по надзору за соблюдением законодательства в сфере массовых коммуникаций и охране культурного наследия.
Периодичность: 6 раз в год
Учредитель: © Фонд «Медицина критических состояний», Москва, Россия

Издатель:
Федеральный научно-клинический центр реаниматологии и реабилитологии (ФНКЦ РР), Москва, Россия
Publisher:
Federal Research and Clinical Center of Intensive Care Medicine and Rehabilitology, Moscow, Russia

При поддержке Общероссийской общественной организации «Федерация анестезиологов и реаниматологов»
Supported by Russian Federation of Anesthesiologists and Reanimatologists

Artwork: Natalia V. Golubeva
Page-proof: Sergey V. Shishkov
Printing House:
Printed at LLC «Advanced Solutions». 19, Leninsky prospekt, build. 1, Moscow, 119071. www.aov.ru
Contacts:
25 Petrovka Str., Bldg. 2, 107031 Moscow, Russia.
Tel. +7-495-694-17-73.
E-mail: **journal_or@mail.ru;**
Web: **www.reanimatology.com**

Subscription:
Index 46338, refer to catalog of «Книга-Сервис»
Signed for printing: 08.11.2024

Оригинал-макет: Н. В. Голубева
Верстка: С. В. Шишков
Типография: отпечатано в ООО «Адвансед солюшнз». 119071, г. Москва, Ленинский пр-т, д. 19, стр. 1. www.aov.ru
Контакты с редакцией:
Россия, 107031, г. Москва, ул. Петровка, д. 25, стр. 2.
Тел.: +7-495-694-17-73.
E-mail: **journal_or@mail.ru;**
сайт: **www.reanimatology.com**

Подписка и распространение: индекс издания по каталогу «Книга-Сервис» — 46338.
Цена свободная
Подписано в печать: 08.11.2024

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https://doi.org/10.15360/1813-9779-2024-5-4-14

The Effect of Lactic Acidosis on Neonatal Outcomes in Premature Infants

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For citation: *Svetlana A. Perepelitsa.* The Effect of Lactic Acidosis on Neonatal Outcomes in Premature Infants. Obshchaya Reanimatologiya = General Reanimatology. 2024; 20 (5): 4–14. https://doi.org/10.15360/1813-9779-2024-5-4-14 [In Russ. and Engl.]

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Summary

The aim of the study was to evaluate neonatal outcomes in preterm infants.

Materials and methods. The study included 58 premature neonates divided into 2 groups: «A» (*N*=34) with an adverse neonatal period ending in death and «B» (*N*=24) who survived. Clinical assessment of the infant, measurement of blood gases, acid-base balance (ABB) and lactate, recording of lung ventilation parameters, calculation of mean airway pressure, oxygenation index (OI) and ventilation efficiency index (VEI), neurosonography and, in case of death, pathological and histological examination of the brain were performed.

Results. Elevated lactate was found in 24 patients (70.5%) in group A and in 12 patients (50%) in group B. The mean lactate levels in groups A and B were 8.1±3.3 and 6.3±2.8 mmol/L, respectively. In group A, 19 (55.9%) infants had severe acidosis, corresponding to a pH of 7.19 to 6.80. In group B, only 8 (33.3%) infants had a pH between 7.0 and 7.19. At birth, neonates in both groups were found to have a base deficit (BD), which was significantly lower in group A than in group B (*P*=0.004). There were no trends toward reduction of acidosis or normalization of ABB in infants in group A. Plasma BE levels in group B had returned to normal by 96 hours postpartum. The frequency of grade II, III peri/intraventricular hemorrhage (PIVH) and hemorrhage of other localization in group A were 8 (23.5%), 9 (26.5%), and 3 (8.8%), respectively. In group B, grade I PIVH and hemorrhage of other localization occurred in 5 (20.8%) and 1 (4.2%) cases, respectively. In neonates with grade II PIVH, severe lactic acidosis was diagnosed at birth: venous blood pH was 6.97 [6.8; 7.22], BE was (–21.6) [–30; –7.2] mmol/L, lactate level was 8.5 [6.3; 12.9] mmol/L, and pO_2 was 50.5 [20.5; 64] mm Hg. In infants with grade III PIVH, pH was 7.26 [7.12; 7.28], BE was (–8.1) [–8.9; –7] mmol/L, lactate was 7.6 [4.8; 8.9] mmol/L, and pO_2 was 33 [30; 50] mm Hg. Cell damage of varying severity affected all brain structures, as evidenced by absence or deformation of nuclei and nucleoli, and peripheral chromatin condensation. Morphological immaturity of brain structures was another negative factor.

Conclusion. Lactic acidosis diagnosed at birth in premature infants is one of the indicators of perinatal hypoxia severity. Critical pH, BE, and lactate levels, as well as lack of response to treatment, contribute to structural brain damage and worsen prognosis. Severe changes in oxygen and lactate levels that persist for two days after birth lead to severe PIVH and irreversible brain changes.

Keywords: preterm infants, hypoxia, neonatal lactate acidosis, oxygenation index, germinative matrix, hemorrhage, neurons, cerebral cortex

Conflict of interest. The authors declare no conflict of interest.

Some of the study findings were published in «Metabolic lactic acidosis and variants of perinatal damage of central nervous system in neonates» by S. A. Perepelitsa and A. M. Golubev, Proceedings of the 3rd Russian Congress of Pediatric Anesthesiologists and Intensivists, April 21–22, Moscow, pp. 236–238.

Introduction

Neonatal brain injury remains a pressing issue in perinatal medicine. Main factors include antenatal hypoxia, intrapartum hypoxia and early postnatal hypoxia, which result in alteration of cerebral hemodynamics and microcirculation in various brain structures. The spectrum of possible changes is quite wide, depending on the duration of hypoxia and the severity of the hemodynamic disturbances. Short-term exposure to hypoxia in children causes transient ischemic changes, while prolonged severe hypoxia results in extensive damage localized in various brain structures, leading to death or permanent disability of the child [1–5].

Vutskits L., Camfferman F. A., et al. showed that premature infants have a higher incidence of brain damage compared to term infants, which is due to unfavorable factors such as morphological immaturity, the presence of the germinal matrix — especially in newborns with a gestational age of 22–28 weeks — insufficient vascularization of the white matter, and immaturity of autoregulation of cerebral blood flow. The presence of these factors leads to isolated and systemic fluctuations in cerebral blood flow, especially in combination with changes in central hemodynamics [6, 7].

Under hypoxic conditions, neurons switch to anaerobic metabolism, resulting in lower glucose and adenosine triphosphate (ATP) production and higher intracellular lactate. Low levels of ATP contribute to impaired function of energy-dependent ion channels in the cell membrane, intracellular Ca^{2+} and Na^{+} influx, abnormal membrane depolarization, and extracellular glutamate accumulation, while

high levels of intracellular lactate increase reactive oxygen species levels and cell damage [8–10].

The severity of hypoxia can be determined using blood lactate levels and the oxygenation index. Lactate levels gradually increase as ischemia and hypoxia worsen, while the oxygenation index decreases. In addition, the severity of lactic acidosis, pH, and time to normalization are associated with the severity of hypoxic and ischemic encephalopathy [5, 11] and neonatal mortality [3, 12].

Damage-associated molecular patterns (DAMPs) such as IL-33, high-mobility group protein B1 (HMGB1), and ATP activate microglia, astrocytes, cerebral vascular endothelial cells, and perivascular macrophages, resulting in a cascade of abnormal responses [13]. TNF (tumor necrosis factor)-R1, expressed on neurons and glial cells, activates apoptosis and necrosis, and upregulates MHC II and cell adhesion molecules in astrocytes. TNF-α production increases within hours of cerebral hypoxia, causing damage to the blood-brain barrier [2, 10, 14, 15].

A further cascade of reactions leads to an increase in interleukin-6 (IL-6) and IL-16, which are early biomarkers of the severity of brain ischemia in neonates and can be used to predict long-term outcome [16]. The level of IL-1β in residual cord blood and neonatal cerebrospinal fluid correlates with the severity of brain ischemia. IL-1β induces neuronal apoptosis and chemokine expression in microglia, astrocytes, and immature brain cells, and inhibits neuronal and oligodendrocyte proliferation [17,18].

The priority diagnostic task in the early neonatal period is to detect hypoxia and lactic acidosis, which trigger a cascade of abnormal responses leading to damage to organs and systems, including the brain. Changes in these biological markers can be used to predict how the child will respond to treatment.

The aim of the study was to evaluate the neonatal outcomes in premature infants.

Materials and methods

This retrospective study was approved by the Independent Ethics Committee of the Clinical Research Center of I. Kant Baltic Federal University (Protocol No. 14, dated October 27, 2020). All newborns included in the study were treated at the Maternity Hospital of Kaliningrad Region No. 1 and the Perinatal Center of Kaliningrad Region from October 2010 to October 2020. Scientific analysis of the results was conducted from January 2022 to May 2023.

Initially, a retrospective analysis of the medical records of 250 newborns was performed; as a result, 192 children were excluded from the study due to non-compliance with the inclusion criteria. Fifty-eight premature infants diagnosed at birth with varying degrees of hypoxia were included in the study (Fig. 1).

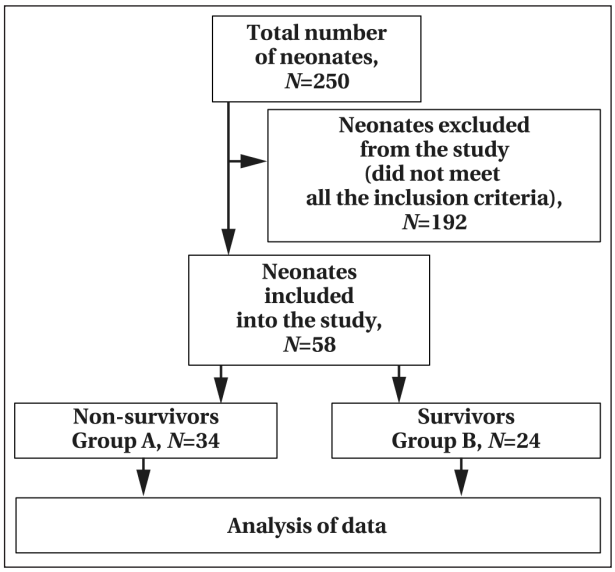

Fig. 1. Study flowchart.

Study inclusion criteria:

1. Moderate to severe birth asphyxia: Apgar score at 1 minute after birth less than 7 points;
2. Hyperlactatemia (blood lactate > 2 mmol/L);
3. Blood acidosis (pH < 7.35);
4. Blood base deficiency (BE < –2.5 mmol/L);
5. Ultrasonographic evidence of brain immaturity not consistent with gestational age [19];
6. Ultrasound evidence of peri-/intraventricular hemorrhage of varying degrees [20];
7. Mechanical or noninvasive ventilation.

Exclusion criteria were congenital malformations associated with severe hypoxia.

No preliminary sample size calculation was performed.

Patients were divided into two groups according to the disease outcome in the early neonatal period:

- Group A included 34 infants with a mean gestational age of 27.4±4 weeks, a birth weight of 992.9±560 g, and a mean Apgar score of 3 [2.0; 5.0] at 1 minute after birth and 5 [4.0; 6.0] points at 5 minutes after birth. Despite treatment, the neonates continued to deteriorate until death.
- Group B included 24 neonates with a gestational age of 28.9±2.3 weeks, a birth weight of 1138.1±320.9 g, and mean Apgar scores of 5 [3.5; 6.0] at 1 minute after birth and 6 [5.5; 7.0] at 5 minutes after birth. Neonates stabilized and improved as a result of treatment, with no deaths in the group.

There were no significant differences in birth weight or gestational age between the groups (P=0.258 and P=0.113, respectively). Median Apgar scores at 1 minute after birth were significantly lower in group A than in group B (P=0.009).

At birth, all neonates received primary or intensive care according to neonatal protocols [21].

Maternal factors such as age, course of pregnancy, causes of preterm labor, and labor activity were assessed.

Clinical evaluation of the newborn at birth included the following criteria: Apgar score (AS) at 1 and 5 minutes after birth, presence of regular spontaneous breathing, signs of acute respiratory failure of varying severity, and need for respiratory therapy.

Laboratory evaluation of blood gas and acid-base balance (ABB). Gas exchange, acid-base balance, and lactate concentration in the residual umbilical cord and arterialized blood were assessed using a Gem Premier 3000 analyzer (USA). The study was conducted at birth and at 6, 12, 24, 48, 72, 96, 120, 144, and 168 hours postnatally.

Lung ventilation changes were recorded, including mode, ventilator respiratory rate (RR), fraction of oxygen in the gas mixture (FiO_2), peak inspiratory pressure (PIP), positive end-expiratory pressure (PEEP), and inspiratory time (T_{in}).

The calculation of the oxygenation index, mean airway pressure, and ventilation efficiency index. Calculation of the oxygenation index (OI): $OI = MAP \times ((FiO_2 \times 100) / pO_2)$, where MAP is the mean airway pressure, FiO_2 is the fraction of oxygen in the inspired gas mixture, and pO_2 is the partial pressure of oxygen in the blood.

The calculation of the mean airway pressure (MAP):

$$\mathbf{MAP=K\times(PIP–PEEP)\times(T_{in}/(T_{in}+T_{ex}))+PEEP,}$$

where **K** is a constant; **PIP** is the peak inspiratory pressure; **PEEP** is the positive end-expiratory pressure; $\mathbf{T_{in}}$ is the inspiration time; and $\mathbf{T_{ex}}$ is the expiration time.

The calculation of the ventilation efficiency index (VEI), which is an empirical analog of dynamic lung compliance:

$$\mathbf{VEI=3800/(\triangle P\times F\times PaCO_2)\ (mL/mmHg/kg),}$$

where $\triangle$**P** is the difference between inspiratory and expiratory pressures (PIP–PEEP) and **F** is the respiratory rate.

These parameters were recorded and evaluated at birth, 6, 12, 24, 48, 72, 96, 120, 144, and 168 hours postnatally.

Multiplanar neurosonography (NS). The study was performed on days 1–2 after birth through natural acoustic windows (large and small fontanels).

Histological examination of the brain. The following structures were examined: cortex, subcortical substance of the parietal region, hippocampus, striatum, cerebellum, and areas of hemorrhage. After labeling the material in plastic cassettes, standard histologic processing was performed, followed by embedding in Histomix and making paraffin blocks. Histological sections were stained with Nissl hematoxylin and eosin and examined using a Nikon Eclipse 55i microscope. In documenting the changes in the specimens, the correspondence of the morphological structure of the brain with gestational age, the degree of severity of cerebral edema, the condition of the vessels, the germinal matrix, and the presence and localization of hemorrhages were considered. The results of morphological examination were compared with gestational age, status of the child at birth and duration of the disease.

Statistical analysis of the data. Statistical analysis was performed using the Statistica 10.0 software package (StatSoft Inc., USA). The aim of the statistical analysis of the data was to identify the link between studied parameters and early neonatal period and disease outcomes in preterm infants. The Shapiro-Wilk test was used to evaluate the distribution of quantitative parameters. For variables with normal distribution, the arithmetic mean *(M)* and standard deviation *(SD)* were calculated. For quantitative parameters with non-normal distribution, the median *(Me)* and interquartile range *(Q1; Q3)* were determined, where *Q1* is the 1st quartile (25th percentile) and *Q3* is the 3rd quartile (75th percentile). Comparison of the results for dependent and independent samples with normal distribution was performed using the ANOVA test. Differences between two non-normally distributed samples were determined using the Mann–Whitney *U*-test. Pearson's parametric correlation method was used to analyze quantitative parameters with a normal distribution. In the study sample, qualitative data were analyzed by calculating the proportion of cases (percentage). The Wilcoxon test was used to compare two related groups, the Mann–Whitney test was used to compare unrelated groups by quantitative variables, and the Kruskal–Wallis test and post-hoc pairwise comparisons were used to compare three groups. Comparison of unrelated groups by qualitative variables was performed using Pearson's χ^2 test or Fisher's exact test. The two-tailed *P*-value was used. The non-parametric Spearman correlation method was used to analyze quantitative parameters with non-normal distribution. Differences were considered significant at $P \leqslant 0.05$.

Results

Maternal factors affecting the fetus and neonate. Table 1 shows the demographic characteristics and the most common conditions leading to perinatal hypoxia and lactic acidosis in the newborn. No significant differences were found between the groups in terms of age, parity, and mode of delivery.

Premature release of amniotic fluid was the cause of preterm labor in 9 (28.1%) pregnant women in group A and 3 (13%) in group B. Natural delivery was more common in group A and operative delivery was more common in group B (P=0.0087). The causes of operative preterm delivery in both groups were pre-eclampsia and eclampsia, critical disorders of uteroplacental blood flow, and placental abruption.

Table 1. Demographic characteristics of mothers and risk factors for neonatal hypoxia, *M*±σ; *Me [Q1; Q3]*; *N* (%).

Parameter	Values in groups		*P*-value
	Group A, *N*=32	Group B, *N*=23	
Age of mothers, years	31.2±6.5	30.5±6.7	0.715
Number of pregnancies	3 [1; 4]	3 [1; 4]	0.958
Parity	2 [1; 3]	2 [1; 3]	0.747
Premature rupture of membranes	9(28.1)	3 (13.0)	0.183
Natural delivery	11 (34.4) *	1 (4.3)	0.0087
Operative delivery	21 (65.6) *	22 (95.7)	0.0087
Causes of operative delivery			
Placental abruption	9(28.1)	4 (17.4)	0.349
Disorders of uteroplacental circulation	5 (15.6)	8 (37.8)	0.067
Preeclampsia, eclampsia	3(9.4)	6 (26.1)	0.094
Uterine scar	2 (6.3)	4 (17.4)	0.195
Abnormal fetal positioning	2 (6.3)	0 (0)	0.242

Note. Here and in the Table 2: * — significant differences between groups, $P \leqslant 0.05$.

Another cause of operative preterm delivery was the onset of spontaneous labor in patients with uterine scarring or abnormal fetal position.

Blood lactate measurement. The results of plasma lactate measurements are shown in Fig. 2, *a*. At birth, mean lactate levels were significantly higher (*P*=0.04) in children of group A vs. group B. Hyperlactatemia was found in 24 (70.5%) children in group A, mean blood lactate was 8.1±3.3 mmol/L. In group B hyperlactatemia was found in 12 (50%) children, the mean value was 6.3±2.8 mmol/L.

At 6 hours, the lactate level decreased significantly (*P*=0.015) in neonates in group A. The rate of decrease was 0.48 mmol/hour. A further significant decrease occurred at 48 hours (*P*=0.039); this trend continued for 120 hours of treatment (*P*=0.023). In the following hours, the lactate level began to increase.

In group B, the decrease in blood lactate occurred gradually. By 6 hours of postnatal life, its value significantly decreased (*P*=0.02), but by 12 hours, it had increased again. Normalization of lactate oc-

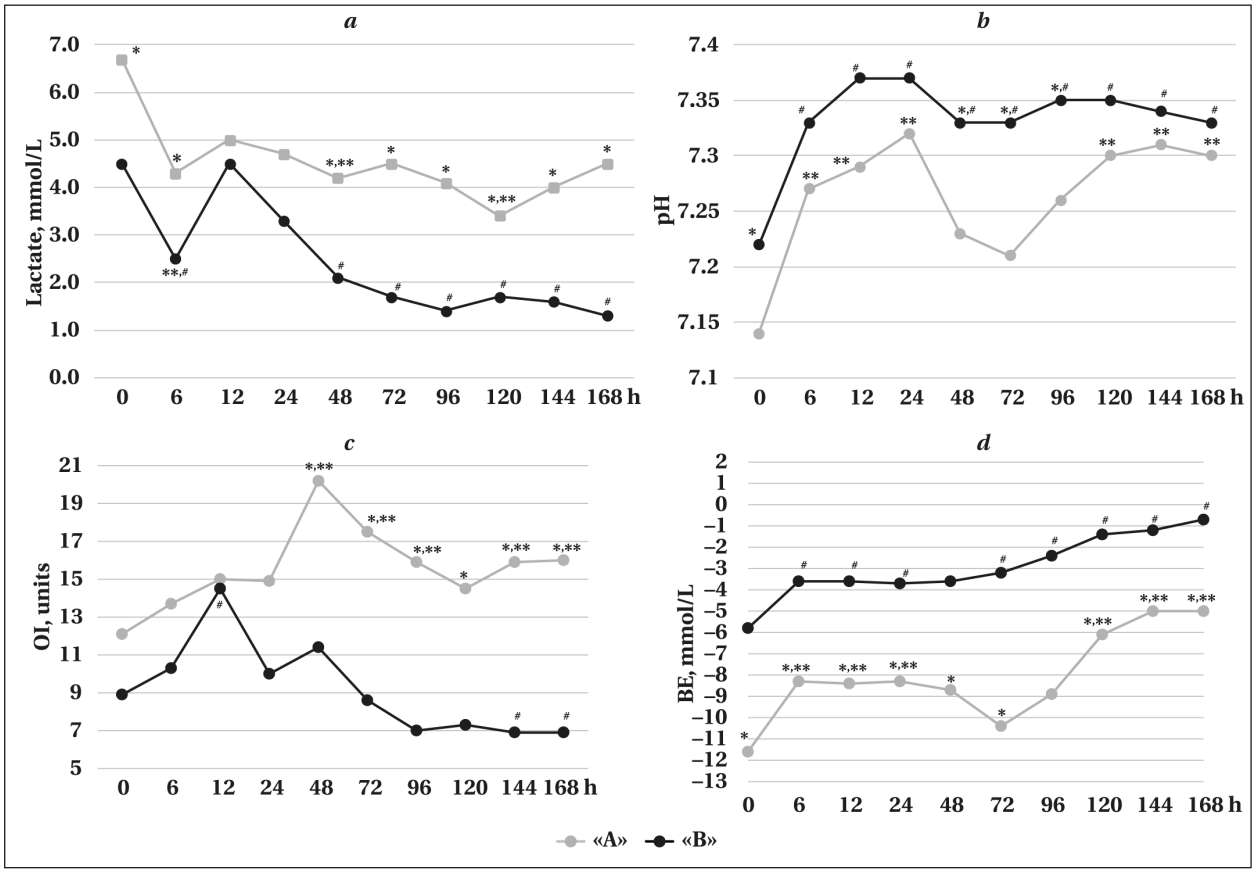

Fig 2. Change of the studied parameters during the treatment.
Note. Significant differences during the treatment, $P \leqslant 0.05$: * — between groups; ** — group A and # — group B,compared to the value at birth in both groups A and B.

curred by 48 hours of postnatal life, and the rate of reduction was also 0.48 mmol/hour (P=0.003). The lactate concentration was higher in group A than in group B throughout the observation period.

Study of blood ABB parameters. The integral parameter determining blood ABB disorders is pH (Fig. 2, *b*).

At birth, the pH of neonates in both groups indicated acidosis, but in group A the value was significantly lower than in group B (P=0.05). In group A, 19 (55.9%) neonates had severe acidosis, corresponding to a pH between 7.19 and 6.8, whereas in group B, only 8 (33.3%) neonates had a pH between 7.0 and 7.19.

In the first 6 hours after birth, the mean pH of the newborns in group A increased from 7.14±0.2 to 7.27±0.16; after 24 hours, it increased to 7.31±0.18, indicating a significant increase in this parameter (P=0.004, P=0.0006, respectively), reflecting a decrease in acidosis and representing the child's response to treatment. However, over the next 48 hours, the mean pH decreased to 7.2±0.2. Only after 96 hours of treatment was there a trend toward improvement in this parameter, but complete normalization did not occur.

In group B, normalization of ABB occurred after 12 hours of treatment, pH increased from 7.22±0.1 to 7.37±0.12 (P=0.00007), but after 48 hours the average pH value slightly decreased and was 7.33±0.07, the final normalization of pH occurred after 96 hours of treatment.

At birth, the neonates of both groups were found to have a base deficit (BD), which was significantly lower in group A compared to group B (P=0.004) (Fig. 2, *c*). Throughout the early neonatal period, a significant BD was detected in neonates of group A. Within 6 hours, plasma BE increased 1.5-fold, but remained unchanged in the following hours of treatment, i. e., signs of base deficit persisted. No tendency to decrease acidosis and normalization of ABB was observed in children of this group.

In group B, blood plasma BE increased 1.6 times within 6 hours (P=0.02) and gradually normalized by 96 hours after birth, i. e. the children responded to the treatment.

Oxygenation index (OI). The analysis showed that the OI was elevated at birth in both groups (Fig. 2, *d*). Its further change was multidirectional. In group A, OI increased significantly within 48 hours compared to the period at birth (P=0.00001), i. e., hypoxia resistant to therapy persisted during this period.

In the following hours of treatment, a slight decrease in OI persisted until 120 hours, after which its value began to increase, indicating that hypoxia persisted. In group B, the studied parameter increased up to 12 hours after birth (P=0.001), further confirming the presence of hypoxia and the lack of response to treatment during this period. In the following hours, OI gradually decreased and reached its minimum values at 144 hours after birth (P=0.009), indicating that the period of documented hypoxia was short and transient. In group A, OI values were significantly higher than in group B between 48 and 168 hours (Fig. 2, *c*).

Neurosonographic results. In the first hours after birth, the majority of neonates in group B showed only signs of morphological immaturity compared to group A (P=0.01). The incidence of grade II and III peri-intraventricular hemorrhage (PIVH) was significantly higher in group A than in group B (P=0.009 and P=0.006, respectively) (Table 2).

Subgroups of neonates were identified in each group based on NS changes. In group A, the following subgroups were identified: subgroup 1 with brain immaturity, subgroup 2 with PIVH grade II, and subgroup 3 with PIVH grade III and bleeding in other locations. In group B, subgroup 1 had brain immaturity, while subgroup 2 had PIVH grade I and bleeding in other locations. We examined the main parameters of hypoxia severity and oxygen status in each subgroup at birth, as well as blood ABB, ventilation parameters, and OI.

Table 3 summarizes the analysis of laboratory parameters and NS data for group A. Lactic acidosis was found in children from subgroup 1 who showed only signs of brain immaturity. Children in subgroup 2 also had lactic acidosis, but their pH and BE were in the critical range and significantly different from those in subgroups 1 and 3 (P=0.059 and P=0.023, respectively). OI was also higher in subgroup 2 than in subgroup 1 (P=0.007). The pH, BE, and OI values in subgroup 3 were different from those in subgroup 1 (P=0.047, P=0.04, P=0.036, respectively). Only in subgroup 3 was ventilation performed with a higher FiO_2 than in subgroups 1 and 2; no differences were found in this parameter, whereas MAP and VEI varied between subgroups.

Correlation analysis of the parameters in group B revealed several relationships of different strength and direction:

Table 2. Brain ultrasound findings, *N* (%).

Parameter	Frequency in groups		*P*-value
	Group A, *N*=34	Group B, *N*=24	
Brain immaturity	14 (41.2)*	18 (75)	0.01
PIVH, I grade	0 (0)*	5 (20.8)	0.005
PIVH, II grade	8 (23.5)*	0 (0)	0.009
PIVH, III grade	9 (26.5)*	0 (0)	0.006
Other hemorrhage	3 (8.8)	1 (4.2)	0.24

Table 3. Parameters in the subgroups of group A *(Me; Q1; Q3)*.

Parameters	Values in the subgroups of group A			P_{1-2}	P_{1-3}	P_{2-3}
	Subgroup 1, *N*=14	Subgroup 2, *N*=8	Subgroup 3, *N*=12			
pH	7.19 [7.09; 7.24]	6.97 [6.8; 7.22]*	7.26 [7.12; 7.28]**	0.059	0.474	0.047
BE, mmol/L	–8.7 [–10; –7]	–21.6 [–30; –7.2]*	–8.1 [–8.9; –7]**	0.023	0.923	0.04
Lactate, mmol/L	5.3 [1.6; 8.2]	8.5 [6.3; 12.9]	7.6 [4.8; 8.9]	0.138	0.43	0.29
pO_2, mm Hg	65 [47; 88]	50.5 [20.5; 64]	33 [30; 50]**,#	0.07	0.03	0.02
FiO_2, %	40 [35; 50]	40 [37.5; 71]	50 [40; 80]	0.0532	0.488	0.693
OI, units	8.2 [3.5; 12.9]	11.6 [8.3; 18.4]*	18.2 [8.2; 19.8]#	0.007	0.036	0.817
MAP, cm H_2O	9.6 [9.1; 10.4]	8.6 [8.4; 9.1]	9.3 [8.8; 10.6]	0.317	0.876	0.067
VEI, mL/mm Hg	0.09 [0.06; 0.09]	0.09 [0.05; 0.11]	0.11 [0.07; 0.13]	0.863	0.198	0.269

Note. Significant differences, $P \leqslant 0.05$: * — between subgroups 1–2; ** — between subgroups 2–3; # — between subgroups 1–3.

Table 4. Parameters in the subgroups of group B *(Me; Q1; Q3)*.

Value	Values in the subgroups of group B		*P*-value
	Subgroup 1, *N*=18	Subgroup 2, *N*=6	
pH	7.21 [7.16; 7.23]	7.18 [7.08; 7.32]	0.574
BE, mmol/L	–5.5 [–7.5; –3.9]	–7.1 [–10.2; –5.3]	0.413
Lactate, mmol/L	3.6 [2.2; 5.2]	4.8 [3.2; 7.6]	0.168
pO_2, mm Hg	47 [42; 52]	44.5 [40.5; 46]	0.345
FiO_2, %	40 [30; 45]	45 [40; 85]	0.183
OI, units	8.4 [5.9; 11.8]	9.5 [8.4; 18.3]	0.364
MAP, cm H_2O	8.8 [8.5; 9.6]	8.8 [8.85; 9.5]	0.748
VEI, mL/mm Hg	0.11 [0.09; 0.12]	0.09 [0.06; 0.2]	0.241

- Strong negative correlation between BE and plasma lactate at birth: *R*=–0.8053; *P*=0.0009;
- Strong positive correlation between plasma lactate and FiO_2 at birth: *R*=0.7897; *P*=0.0013;
- Strong negative correlation between plasma lactate and VEI at birth: *R*=–0.855; *P*=0.014;
- Moderate negative correlation between plasma BE and FiO_2 at birth: *R*=–0.573; *P*=0.04;
- Strong negative correlation between plasma pO_2 and OI at birth: *R*=–0.7585; *P*=0.0042.

Table 4 shows the results of the analysis of the laboratory parameters along with the NS data of the neonates in group B. In the second subgroup, the values of pH, BE, lactate, and OI were worse than those in the first subgroup, but no statistically significant differences were found. The values of FiO_2, MAP, and VEI were not significantly different in both subgroups.

Correlation analysis in group B revealed correlations of different strength and direction:

- Moderate negative correlation between BE and plasma lactate at birth: *R*=–0.708; *P*=0.0005;
- Strong negative correlation between HCO3 and plasma lactate at birth: *R*=–0.79; *P*=0.0003;
- Moderate positive correlation between OI and MAP at birth: *R*=0.6359; *P*=0.0355;
- Moderate negative correlation between lactate level and Apgar score at 1 minute after birth: *R*=–0.481; *P*=0.032.

Histologic examination of neonatal brains in group A. All neonates had immature brain structures for their gestational age, but only 10 (29%) did not have PIVH. The remaining cases were characterized by morphological immaturity and grade III–IV PIVH with hemorrhagic tamponade and blood leakage into the cerebello-medullary cistern, which was the primary cause of death.

Morphological analysis of brain structures revealed the presence of small hyperchromic (intensely stained) neurons in the molecular, outer, and inner granular layers of the cerebral cortex of the large hemispheres, with chromatin localized to the periphery and no nucleoli detected in a number of nuclei. The pyramidal cell layer consisted mainly of hyperchromatic pyramidal and rounded neurons. The inner pyramidal layer also contained pyramidal, predominantly intensely stained neurons, some of which were deformed, and rounded neurons with hyperchromic nuclei, whereas rounded and pyramidal neurons with hyperchromic nuclei were more common in the polymorphic cell layer. All cortical layers showed tortuosity and irregular blood filling of capillaries or their congestion and pericellular edema.

Neuronal polymorphism was seen in the white matter, including groups of dark neurons with shrunken or displaced nuclei and nucleoli, and cells with hypochromatic or unstained nuclei. Satellitosis and neuronophagia were prominent. Extensive hemorrhages were found in the white matter of the brain, including under the ventricular ependymas. Thrombi were observed in the ventricular cavity. Siderophages were seen at the margins of the hemorrhages. Capillary and venous congestion and focal gliosis were also observed.

Some vascular plexus epithelial cells had vacuolated cytoplasm, while others had unstained nuclei. There were areas without epithelial lining, with congested vessels and swollen stroma.

Some Purkinje cells in the cerebellum were absent, while other cells had shrunken or absent nuclei. Tigrolysis was common, and neither nuclei nor nucleoli were stained with Nissl stain. Pericellular edema was noted.

The cytoplasm of neurons in the striatum was homogeneous; cells with chromatin at the nuclear periphery were detected, but nucleoli were not detectable in some nuclei. Scattered glial cells were observed near some neurons. Nissl staining of the cells showed uniform cytoplasmic staining but no tigroid substance. There was also perivascular edema.

Discussion

Lactate, pH, and BE levels at birth indicate the severity of neonatal asphyxia. Lactate has been shown to be more diagnostically significant than pH [22–24]. Our study found multiple correlations between blood lactate at birth and pH, BE, and FiO_2, demonstrating lactate's diagnostic value in the context of hypoxia. Gjerris A. C. et al. investigated this issue and discovered correlations between lactate and pH (R=–0.73), standard base excess (R=–0.76), and actual base excess (R=–0.83). ROC analysis revealed that the lactate concentration threshold for detecting intrauterine asphyxia is 8 mmol/L [25].

The Apgar score is relatively important in the diagnosis of asphyxia in preterm infants because low scores at birth can be caused by immaturity of the surfactant system and respiratory center, as well as inadequate development of the respiratory muscles [19]. For a more accurate diagnosis of asphyxia, the study discovered that neonates in group A had a lower median Apgar score at 1 minute of life than neonates in group B, while lactate levels were higher. Correlation analysis revealed a negative correlation between Apgar score and lactate level at birth.

Lactate acidosis diagnosed at birth is associated with the development of acute respiratory failure. All infants with such signs were placed on a ventilator. Critical parameters of pH, BE and lactate measured in the early neonatal period were associated with grade II PIVH in group A (non-survivors).

The study by Tuuli et al. also showed that an elevated blood lactate concentration at birth (>3.9 mmol/L) increased the risk of adverse outcomes with a sensitivity of 83.9% (95% CI, 71.9–92.4%) and specificity of 74.1% (95% CI, 72.9–75.4%) [26].

In addition, Allanson E. R. et al. found an association between blood lactate at birth and short-term neurological outcomes [23] due to hypoxic brain injury. The effectiveness of lactate measurement in predicting neurological outcome in hypoxic and ischemic encephalopathy has been demonstrated. To improve diagnostic accuracy, measurement of pH and severity of base deficit is recommended [23].

In premature infants, PIVH is a leading cause of death [27, 28]. Most hemorrhages occur in the germinal matrix of the lateral ventricles [19, 20, 29]. However, prolonged and treatment-resistant perinatal hypoxia causes the hemorrhage to expand. With prolonged lactic acidosis, cerebral ventricular dilatation occurs, and the initial ventricular hemorrhages increase in volume or new hemorrhages form and spread to the brain parenchyma surrounding the ventricles.The etiology of PIVH is multifactorial. First, prolonged blood desaturation has been associated with the development of hemorrhages of any severity in brain structures [30]. Second, hemorrhages that occur during pregnancy or within the first 12 hours after birth are most likely caused by the production of free radicals and activation of pro-inflammatory cytokines, as well as persistent disturbances in oxygen status and metabolism [31, 32].

Hemorrhage in the first 72 hours after birth is caused not only by the immaturity of the vessels in the germinal matrix [33], but also by increased cerebral perfusion and fluctuations in systemic and cerebral blood flow [34–37]. Persistent disturbances in gas exchange and blood acid-base balance contribute to the development of grade III and IV PIVH [9, 31, 38]. It has been demonstrated that the severity of the lactic acidosis at birth correlates with the severity of PIVH, which can occur as early as 1–2 days after birth. The early neonatal period was extremely unfavorable in children with severe lactic acidosis that was not reversed in the first hours and days after birth, because the hypoxia that occurred intrapartum caused irreversible damage to the immature brain structures [33, 38].

The profound disturbance of oxygen balance and the depletion of compensatory responses cause a metabolic shift to anaerobic glycolysis, which is accompanied by lactate production. The high initial level of lactate in the infant's body at birth and its subsequent production lead to the accumulation of lactate in extracellular structures, exacerbating the existing acidosis [39, 40]. Zheng Y. and Wang X. demonstrated in an experiment that after an episode of cerebral hypoxia, the blood lactate level reaches its peak in 2–6 hours, but damage to astrocytes and neurons does not occur concurrently [41, 42]. The entire cascade of abnormal responses causes brain structure damage within 48–96 hours of birth [43].

The period of 24–48 hours after birth was used to determine the reversibility of the identified oxygen status and acid-base disturbances. If hypoxia and metabolic lactic acidosis were diagnosed in the newborn during this period, the likelihood of damage to immature brain structures increased in proportion to their severity. Failure of the body to respond to treatment aimed at eliminating hypoxia and normalizing ABB is most likely a negative prognostic factor, because persistent hypoxia and

lactic acidosis contribute to disease progression and the emergence of new foci of damage to brain structures, up to massive ischemic and hemorrhagic lesions.

Prematurity and brain morphological immaturity are unfavorable factors that contribute to the development of lactic acidosis in the presence of severe perinatal hypoxia.

Conclusion

Lactic acidosis is one of the criteria for determining the severity of birth asphyxia. Decompensated lactic acidosis diagnosed at birth in preterm infants and resistant to therapy, with laboratory values such as pH < 7.15, lactate > 7.5 mmol/L, and BE < (–12) mmol/L, is associated with the development of peri-intraventricular hemorrhage of varying severity. Death is caused by blood tamponade and blood leakage into the cerebello-medullary cistern. Failure to respond to treatment aimed at reversing hypoxia and restoring acid-base balance is a poor prognostic factor.

References

1. *Ristovska S., Stomnaroska O., Danilovski D.* Hypoxic ischemic encephalopathy (HIE) in term and preterm infants. *Pril (Makedon Akad Nauk Umet Odd Med Nauki)*. 2022; 43 (1): 77–84. DOI: 10.2478/prilozi-2022-0013.PMID: 35451288.
2. *Ophelders D. R. M. G., Gussenhoven R., Klein L., Jellema R. K., Westerlaken R. J. J., Hütten M. C., Vermeulen J., et al.* Preterm brain injury, antenatal triggers, and therapeutics: timing is key. *Cells*. 2020; 9 (8): 1871. DOI: 10.3390/cells9081871. PMID: 32785181.
3. *Salah M. M., Abdelmawla M. A., Eid S. R., Hasanin R. M., Mostafa E. A., Abdelhameed M. W.* Role of matrix metalloproteinase-9 in neonatal hypoxic-ischemic encephalopathy. *Open Access Maced J Med Sci*. 2019; 7 (13): 2114–2118. DOI: 10.3889/oamjms.2019.618. PMID: 31456835.
4. *Vik S. D., Torp H., Follestad T., Støen R., Nyrnes S. A.* NeoDoppler: new ultrasound technology for continuous cerebral circulation monitoring in neonates. *Pediatr Res*. 2020; 87 (1): 95–103. DOI: 10.1038/s41390-019-0535-0. PMID: 31404920.
5. *O'Sullivan M. P., Looney A. M., Moloney G. M., Finder M., Hallberg B., Clarke G., Boylan G. B., et al.* Validation of altered umbilical cord blood microRNA expression in neonatal hypoxic-ischemic encephalopathy *JAMA Neurol*. 2019; 76 (3): 333–341. DOI: 10.1001/jamaneurol.2018.4182. PMID: 30592487.
6. *Vutskits L.* Cerebral blood flow in the neonate. *Paediatr. Anaesth*. 2014; 24: 22–29. DOI: 10.1111/pan.12307. PMID: 24238074
7. *Camfferman F. A., de Goederen R., Govaert P., Dudink J., van Bel F., Pellicer A., Cools F.* Diagnostic and predictive value of Doppler ultrasound for evaluation of the brain circulation in preterm infants: a systematic review. *Pediatr Res*. 2020; 87 (Suppl 1): 50–58. DOI: 10.1038/s41390-020-0777-x. PMID: 32218536.
8. *Lai M.-C., Yang S.-N.* Perinatal hypoxic-ischemic encephalopathy. *J Biomed Biotechnol*. 2011; 609813. DOI: 10.1155/2011/609813. PMID: 21197402.
9. *Millar L. J., Shi L, Hoerder-Suabedissen A., Molnár Z.* Neonatal hypoxia ischaemia: mechanisms, models, and therapeutic challenges. *Front Cell Neurosci*. 2017; 11: 78. DOI: 10.3389/fncel.2017.00078. eCollection 2017. PMID: 28533743.
10. *Chaparro-Huerta V., Flores-Soto M. E., Sigala M. E. M., de León J. C. B., Lemus-Varela M. de Lourdes, Torres-Mendoza B. M. de Guadalupe, Beas-Zárate C.* Proinflammatory cytokines, enolase and S-100 as early biochemical indicators of hypoxic-ischemic encephalopathy following perinatal asphyxia in newborns. *Pediatr Neonatol*. 2017; 58 (1): 70–76. DOI: 10.1016/j.pedneo.2016.05.001. PMID: 27522459.
11. *Mooney C., O'Boyle D., Finder M., Hallberg B., Walsh B. H., Henshall D. C., Boylan G. B., et al.* Predictive modelling of hypoxic ischaemic encephalopathy risk following perinatal asphyxia. *Heliyon*. 2021; 7 (7): e07411. DOI: 10.1016/j.heliyon.2021.e07411. PMID: 34278022.
12. *Eriksen V. R., Trautner S., Hahn G. H., Greisen G.* Lactate acidosis and cardiac output during initial therapeutic cooling in asphyxiated newborn infants *PLoS One*. 2019; 14 (3): e0213537. DOI: 10.1371/journal.pone.0213537. eCollection 2019. PMID: 30870445.
13. *Gadani S. P., Walsh J. T., Lukens J. R., Kipnis J.* Dealing with danger in the CNS: the response of the immune system to injury. *Neuron*. 2015; 87 (1): 47–62. DOI: 10.1016/j.neuron.2015.05.019. PMID: 26139369.
14. *Li S.-J., Liu W., Wang J.-L., Zhang Y., Zhao D.-J., Wang T.-J., Li Y.-Y.* The role of TNF-α, IL-6, IL-10, and GDNF in neuronal apoptosis in neonatal rat with hypoxic-ischemic encephalopathy. *Eur Rev Med Pharmacol Sci*. 2014; 18 (6): 905–909. PMID: 24706318.
15. *Locci E., Bazzano G., Demontis R., Chighine A., Fanos V., d'Aloja E.* Exploring perinatal asphyxia by metabolomics. *Metabolites*. 2020; 10 (4): 141. DOI: 10.390/metabo10040141. PMID: 32260446.
16. *Ahearne C. E., Chang R. Y., Walsh B. H., Boylan G. B., Murray D. M.* Cord blood IL-16 is associated with 3-year neurodevelopmental outcomes in perinatal asphyxia and hypoxic-ischaemic encephalopathy. *Dev Neurosci*. 2017; 39 (1–4): 59–65. DOI: 10.1159/000471508. PMID: 28490023.
17. *Xie D., Shen F., He S., Chen M., Han Q., Fang M., Zeng H., et al.* IL-1β induces hypomyelination in the periventricular white matter through inhibition of oligodendrocyte progenitor cell maturation via FYN/MEK/ERK signaling pathway in septic neonatal rats. *Glia*. 2016; 64 (4): 583–602. DOI: 10.1002/glia.22950. PMID: 26678483.
18. *Graham E. M., Everett A. D., Delpech J.-C., Northington F. J.* Blood biomarkers for evaluation of perinatal encephalopathy: state of the art. *Curr Opin Pediatr*. 2018; 30 (2): 199–203. DOI: 10.1097/MOP.0000000000000591. PMID: 29346139.
19. *Быкова Ю. К., Ушакова Л. В., Филиппова Е. А., Сугак А. Б., Ватолин К. В., Зубков В. В., Суворов И. А., с соавт.* Структурные особенности головного мозга глубоконе-

доношенных новорожденных при ультразвуковом исследовании. *Неонатология: новости, мнения, обучение*. 2023; 11 (2): 39–47. *Bykova Yu.K., Ushakova L. V., Filippova E. A., Sugak A. B., Vatolin K. V., Zubkov V. V., Suvorov I. A., et al.* Structural features of extremely and very preterm newborns' brains according to cranial ultrasound. *Neonatology: News, Opinions, Training = Neonatologiya: Novosti, Mneniya, Obucheniye*. 2023; 11 (2): 39–47. (in Russ.). DOI: 10.33029/2308-2402-2023-11-2-39-47.

20. *Пыков М. И., Ватолин К. В., Милованова О. А., Быкова Ю. К.* Детская ультразвуковая диагностика. Учебник, т. 3. Пыков М. И. (ред). Неврология. Сосуды головы и шеи. М.: Видар-М; 2015: 362. *Pykov M. I., Vatolin K. V., Milovanova O. A., Bykova Yu. K.* Pediatric ultrasound diagnostics. Textbook, vol. 3. Pykov M. I. (ed.). Neurology. Vessels of the head and neck. M.: Vidar-M; 2015: 362. (in Russ.).
21. *Володин Н. Н.* Неонатология. Национальное руководство. М: ГЭОТАР-Медиа; 2019: 896. *Volodin N. N.* Neonatology. National guidelines. M: GEOTAR-Media; 2019: 896. (in Russ.).
22. *Muniraman H. K., Song A. Y., Ramanathan R., Fletcher K. L., Kibe R., Ding L., Lakshmanan A., et al.* Evaluation of oxygen saturation index compared with oxygenation index in neonates with hypoxemic respiratory failure. *JAMA Netw Open*. 2019; 2 (3): e191179. DOI: 10.1001/jamanetworkopen.2019.1179. PMID: 30924897
23. *Allanson E.R., Waqar T., White C.R.H., Tunçalp Ö., Dickinson J.E.* Umbilical lactate as a measure of acidosis and predictor of neonatal risk: a systematic review. *BJOG*. 2017; 124 (4): 584–594. DOI: 10.1111/1471-0528.14306. PMID: 27704703.
24. *Neacsu A., Herghelegiu C., Voinea S., Dimitriu M., Ples L., Bohiltea R., Braila A. D., et al.* Umbilical cord lactate compared with pH as predictors of intrapartum asphyxia. *Exp Ther Med*. 2021; 21 (1): 80. DOI: 10.3892/etm.2020.9513. PMID: 33363591.
25. *Gjerris A. C., Staer-Jensen J., Jorgensen J. S., Bergholt T., Nickelsen C.* Umbilical cord blood lactate: a valuable tool in the assessment of fetal metabolic acidosis. *Eur J Obstet Gynecol Reprod Biol* 2008; 139 (1): 16–20. DOI: 10.1016/j.ejogrb.2007.10.004. PMID: 18063469.
26. *Tuuli M. G., Stout M. J., Shanks A., Odibo A. O., Macones G. A., Cahill A. G.* Umbilical cord arterial lactate compared with pH for predicting neonatal morbidity at term. *Obstet Gynecol*. 2014; 124 (4): 756–761. DOI: 10.1097/AOG.0000000000000466. PMID: 25198278.
27. *Volpe J. J.* Neurology of the Newborn. 6th ed. Elsevier; Philadelphia, PA, USA; 2018: 325–698.
28. *Hollebrandse N. L., Spittle A. J., Burnett A. C., Anderson P. J., Roberts G., Doyle L. W., Cheong J. L. Y.* School-age outcomes following intraventricular haemorrhages in infants born extremely preterm. *Arch Dis Child Fetal Neonatal Ed*. 2021; 106 (1): 4–8. DOI: 10.1136/archdischild-2020-318989. PMID: 32732377.
29. *Costa F. G., Hakimi N., Van Bel F.* Neuroprotection of the perinatal brain by early information of cerebral oxygenation and perfusion patterns. *Int J Mol Sci*. 2021; 22 (10): 5389. DOI: 10.3390/ijms22105389. PMID: 34065460.
30. *Vesoulis Z. A., Whitehead H. V., Liao S. M., Mathur A. M.* The hidden consequence of intraventricular hemorrhage: persistent cerebral desaturation after IVH in preterm infants. *Pediatric Res*. 2020; 89 (4): 869–877. DOI: 10.1038/s41390-020-5. PMID: 33038871.
31. *Krediet T. G., Kavelaars A., Vreman H. J., Heijnen C. J., van Bel F.* Respiratory distress syndrome-associated inflammation is related to early but not late peri/intraventricular hemorrhage in preterm infants. *J Pediatr*. 2006; 148 (6): 740–746. DOI: 10.1016/j.jpeds.2006. 01.037. PMID: 16769379.
32. *Villamor-Martinez E., Fumagalli M., Rahim O. M., Passera S., Cavallaro G., Degraeuwe P., Mosca F., et al.* Chorioamnionitis is a risk factor for intraventricular hemorrhage in preterm infants: a systematic review and meta-analysis. *Front. Physiol*. 2018; 9: 1253. DOI: 10.3389/fphys.2018.01253. PMID: 30271352.
33. *Atienza-Navarro I., Alves-Martinez P., Lubian-Lopez S., Garcia-Alloza M.* Germinal matrix-intraventricular hemorrhage of the preterm newborn and preclinical models: inflammatory considerations. *Int J Mol Sci*. 2020; 21 (21): 8343. DOI: 10.3390/ijms21218343. PMID: 33172205.
34. *Kontos H. A., Raper A. J., Patterson J. L.* Analysis of vasoactivity of local pH, PCO_2 and bicarbonate on cat pial arterioles. *Stroke*. 1977; 8 (3): 226–234. DOI: 10.1161/01.STR.8.2.226. PMID: 16363.
35. *Dix L. M. L., Weeke L. C., de Vries L. S., Groenendaal F., Baerts W., van Bel F., Lemmers P. M. A.* Carbon dioxide fluctuations are associated with changes in cerebral oxygenation and electrical activity in infants born preterm. *J. Pediatr*. 2017; 187: 66–72.e1. DOI: 10.1016/j.jpeds.2017.04.043. PMID: 28578157.
36. *Alderliesten T., Lemmers P. M. A., Smarius J. J. M., van de Vosse R. E., Baerts W., van Bel F.* Cerebral oxygenation, extraction, and autoregulation in very preterm infants who develop peri-intraventricular haemorrhage. *J.*

Pediatr. 2013; 162 (4): 698–704. DOI: 10.1016/j.jpeds.2012.09.038. PMID: 23140883.
37. *Hoffman S. B., Cheng Y. J., Magder L. S., Shet N. S., Viscardi R. M.* Cerebral autoregulation in premature infants during the first 96 hours of life and relationship to adverse outcomes. *Arch Dis Child Fetal Neonatal Ed*. 2019; 104 (5): F473-F479. DOI: 10.1136/archdischild-2018-315725. PMID: 30385514.
38. *Piccolo B., Marchignoli M., Pisani F.* Intraventricular hemorrhage in preterm newborn: predictors of mortality. *Acta Biomed*. 2022; 93 (2): e2022041. DOI: 10.23750/abm.v93i2.11187. PMID: 35546030.
39. *Quade B. N., Parker M. D., Occhipinti R.* The therapeutic importance of acid-base balance. *Biochem Pharmacol*. 2021; 183: 114278. DOI: 10.1016/j.bcp.2020.114278. PMID: 33039418.
40. *Wyss M. T., Jolivet R., Buck A., Magistretti P. J., Weber B. In vivo* evidence for lactate as a neuronal energy source. *J Neurosci*. 2011; 31 (20): 7477–7485. DOI: 10.1523/JNEUROSCI.0415-11.2011. PMID: 21593331.
41. *Zheng Y., Wang X.-M.* Expression changes in lactate and glucose metabolism and associated transporters in basal ganglia following hypoxic-ischemic reperfusion injury in piglets. *Am J Neuroradiol*. 2018; 39 (3): 569–576. DOI: 10.3174/ajnr.A5505. PMID: 29326137.
42. *Mota-Rojas D., Villanueva-García D., Solimano A., Muns R., Ibarra-Ríos D., Mota-Reyes A.* Pathophysiology of perinatal asphyxia in humans and animal models. *Biomedicines*. 2022; 10 (2): 347. DOI: 10.3390/biomedicines10020347. PMID: 35203556.
43. *Groenendaal F., Benders M. J. N. L., de Vries L. S., van Bel F.* Neuroprotective drugs and perinatal brain injury. In: *Aranda J. V., van den Anker J. N. (eds.)*. Neonatal and Pediatric Pharmacology: Therapeutic Principles in Practice. 5th ed. Wolter Kluwer Pub-Licers. Philadelphia, PA, USA; 2021: 171–182.

Received 20.03.24
Accepted 10.09.24

https://doi.org/10.15360/1813-9779-2024-5-15-23

The Effect of Corticosteroids on the Progression and Outcomes of Polytrauma in Children

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For citation: *Konstantin V. Pshenisnov, Yury S. Aleksandrovich, Andrey S. Lipin.* The Effect of Corticosteroids on the Progression and Outcomes of Polytrauma in Children. *Obshchaya Reanimatologiya = General Reanimatology.* 2024; 20 (5): 15–23. https://doi.org/10.15360/1813-9779-2024-5-15-23 [In Russ. and Engl.]

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Summary

Polytrauma in children is among the most common causes of death in the pediatric intensive care unit (ICU).

The aim of this study was to evaluate the effect of systemic corticosteroids (SCS) on the progression, laboratory parameters, and outcomes of severe multiple injuries in children requiring ICU.

Materials and methods. A retrospective, observational, multicenter (case-control and cross-sectional) study included 203 patients from pediatric ICUs across the Russian Federation. The Abbreviated Injury Scale (AIS) score was 36.81 (25–48), and the Pediatric Trauma Score (PTS) was 5.2 (2–8). SCS were administered to 113 (55.7%) children, 19 (9.36%) of whom died.

Results. The most severe changes in laboratory parameters, such as an increase in amylase (35.3 vs. 18.3; $P<0.001$) and activated partial thromboplastin time (APTT) (28.9 vs. 25.8; $P<0.001$), were documented upon admission of children with multiple traumatic injuries to the hospital compared with subsequent days of treatment in the ICU. The average fluid volume (as a percentage of age-related fluid requirements) on the first day of treatment in the ICU was 118.53% and did not exceed 84.42% on subsequent days ($P<0.001$). Higher systolic blood pressure (SBP) during the first three days of ICU treatment was observed in children treated without SCS. SBP tended to decrease by day 5, and then a tendency toward arterial hypertension emerged on days 6–7. In children treated with SCS, blood pressure remained stable during the first seven days in the ICU, contributing to a favorable outcome.

Conclusion. The use of SCS in children with severe polytrauma from the first day of ICU treatment contributed to the stabilization of hemodynamic parameters and improved control of shock signs. A positive response to SCS in these patients can be considered a marker for a favorable disease course during ICU treatment.

Keywords: corticosteroids; multiple injuries in children; intensive care unit; outcome

Conflict of interest. The authors declare no conflict of interest.

Introduction

Severe polytrauma is one of the leading causes of death in children, and the younger the child, the higher the likelihood of an adverse outcome [1, 2]. It often results in irreversible brain damage and brain death due to underlying systemic hypoxia. Although there are many guidelines for the treatment of both adults and children with polytrauma, most provide only basic principles of intensive care and do not adequately address the subtleties and details of individual therapeutic strategies that significantly affect outcome [3–13].

Currently, international guidelines for hemodynamic and respiratory support in pediatric polytrauma are lacking, highlighting the need to find optimal solutions to this problem.

One therapeutic strategy widely used in clinical practice for patients with polytrauma and shock of various etiologies is the use of systemic corticosteroids (CS). However, the efficacy of their use raises many questions and requires multicenter randomized trials. This is particularly true for severe combined spinal trauma, where methylprednisolone is commonly used, but the need for and timing of its administration remains controversial.

In 2017, clinical guidelines for the use of methylprednisolone in adult patients with spinal cord injury were published, noting that methylprednisolone had no significant beneficial effect on motor recovery; however, patients prescribed it within the first 8 hours of injury had better motor recovery at 6 and 12 months. The authors do not recommend administering high-dose methylprednisolone to adults after 8 hours of injury, but continuous infusion of high-dose methylprednisolone for 24 hours is warranted in patients hospitalized within the first 8 hours of injury. Continuous infusion for 48 hours is not recommended. Similar results have been reported in pediatric practice [14]. Caruso M. C. et al (2017) found that the use of high doses of methylprednisolone is associated with a high probability of complications, indicating the need to abandon this therapeutic strategy, especially in the absence of convincing evidence of severe spinal injury and late hospitalization of the child [15].

Nonetheless, in the presence of refractory septic shock-often a result of severe polytrauma in children-the use of systemic corticosteroids is one

of the life-saving techniques since patients have critical acute adrenal insufficiency [16–18].

Based on the above, it can be concluded that the use of systemic glucocorticoids in children with polytrauma requires further study.

The aim of this study was to evaluate the effects of systemic corticosteroids on clinical and laboratory parameters and outcomes of polytrauma in children requiring intensive care.

Patients and Methods

We performed a retrospective observational multicenter study (case-control and cross-sectional type) based on the pediatric intensive care units of the Northwest Federal District of the Russian Federation, the Voronezh Regional Children's Clinical Hospital No. 1, the V. D. Seredavin Samara Regional Clinical Hospital, and the Republican Children's Clinical Hospital of the Republic of Bashkortostan.

Inclusion criteria: 1) age up to 18 years; 2) presence of polytrauma; 3) need for ICU treatment; 4) duration of ICU treatment at least 10 days.

Exclusion criteria: 1) organic brain damage; 2) congenital and hereditary comorbidities.

The study included 203 children with severe polytrauma who required ICU treatment between 2010 and 2019. The mean age of the children included in the study was 9.5 [4–14] years. There were 129 boys (65.55%) and 74 girls (36.45%). Patient characteristics are shown in Table 1.

The parameters studied were systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), heart rate (HR), shock index (HR/SBP ratio), capillary hemoglobin oxygen saturation (SpO_2), blood chloride and lactate levels, serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels, activated partial thromboplastin time (APTT), fluid infusion volume (as a percentage of age-specific fluid requirements), catecholamine index, body surface area, urine output, and disease outcome. The catecholamine index was calculated using the formula:

Dopamine, μg/kg/min +
dobutamine, μg/kg/min +
epinephrine, μg/kg/min × 100 +
norepinephrine, μg/kg/min × 100.

The study included several phases evaluated using cross-sectional analysis and case-control evaluation.

The study was conducted using open-source software Linux OS (Fedora 33), Python 3, analytical libraries (pandas, matplotlib, sklearn), and graphical data presentation tools (matplotlib, seaborn).

Normality of the data set distribution was tested using the Shapiro–Wilk test. Since the data set distribution was not normal, all results were presented as median *(Me)* and lower *(LQ)* and upper *(UQ)* quartiles. Non-parametric statistical methods were used to analyze the significance of differences between groups. The Wilcoxon test was used to test the significance of differences between two independent groups, and the Kruskal–Wallis test was used to evaluate indicators in three or more independent groups. The Friedman test was used to assess the significance of differences between two or more dependent groups (with repeated observations). Two-sided *P*-values were used in all tests, and the critical level of significance was set at $P<0.05$.

The results of the statistical analysis and the executable Python notebook code are publicly available at https://github.com/docinit/hormone_therapy_in_children_with_multiple_injuries.

Results

When analyzing the changes in the studied parameters over the entire treatment period in the ICU, we found that 11 out of 14 parameters had statistically significant differences ($P<0.05$) compared to the mean values for the following 10 days of treatment (Table 2).

The differences found indicate that patients remained unstable and required intensive care on day 1 of treatment in the hospital. There were fewer significant differences on days 2 and 3–10, as well as on days 3 and 4–10 of treatment.

In the second phase of the study, we created nine groups of patients according to CS use and disease outcome: 1 — all patients; 2 — all patients who did not receive CS; 3 — all patients who received CS; 4 — surviving patients; 5 — surviving patients who did not receive CS; 6 — surviving patients who received CS; 7 — non-survivors; 8 — non-survivors who did not receive CS; 9 — non-survivors who received CS.

On different days of observation in each group there was a varying number of significant differences: the maximum number of significant differences in parameters ($P<0.05$) was found in groups 1, 3, 4 and 6 on admission to the ICU. In the following days, the number of parameters with significant differences decreased.

Thus, we rejected the hypothesis that the use of CS does not affect clinical and laboratory parameters in children with polytrauma and accepted an alternative hypothesis, which implied that the surviving patients who received CS had significant intragroup differences in the studied parameters on the first and subsequent observation days (Table 3).

The next phase of the study revealed intergroup differences in the relationship between immediate outcomes and the use of CS during the first seven days of ICU treatment (Table 4).

In most cases, a significant difference was found between the clinical and laboratory parameters of survivors and non-survivors who received CS, as well as the group of non-survivors who did not receive CS.

Table 1. Patient characteristics, *N* (%) or *Me (LQ–HQ)*.

Parameter	Value
Sex	
Male	129 (63.55)
Female	74 (36.45)
Characteristics of injuries	
AIS, points	36.81 (25–48)
PTS, points	5.2 (2–8)
Traumatic brain injury + thoracic trauma + abdominal trauma + skeletal trauma	45 (22.16)
Traumatic brain injury + thoracic trauma + abdominal trauma	47 (23.15)
Traumatic brain injury + thoracic trauma + skeletal trauma	69 (33.99)
Traumatic brain injury + abdominal trauma + skeletal trauma	84 (41.3)
Traumatic brain injury + thoracic trauma	71 (34.9)
Traumatic brain injury + abdominal trauma	92 (45.32)
Traumatic brain injury + skeletal trauma	174 (85.71)
Multiple musculoskeletal injuries	181 (89.16)
Motor vehicle injury	63 (31.03)
Fall from a height	58 (28.57)
Intracranial hematoma	28 (13.79)
Subarachnoid hemorrhage	48 (23.64)
Intraventricular hemorrhage	10 (4.23)
Use of corticosteroids	
Administered	113 (55.67)
Not administered	90 (44.33)
Used only during day 1 of treatment in ICU	12 (5.91)
Outcome	
Survived	184 (90.64)
Died	19 (9.36)
Duration of mechanical ventilation, hours	3.11 (0–4.06)
Duration of treatment in the ICU, days	6.93 (1–8)

Note. AIS — Abbreviated Injury Scale; PTS — Pediatric Trauma Score.

Table 2. Clinical and laboratory parameters in children with polytrauma.

Parameter	Values during ICU stay		*P*-value
	On day 1	During days 2–10	
Systolic blood pressure, mm Hg	110.0 (102.7–117.2)	108.0 (95.0–120.0)	0.005
Diastolic blood pressure, mm Hg	64.33 (58.9–70.0)	61.0 (55.0–70.0)	0.0194
Mean blood pressure, mm Hg	79.78 (73.3–84.78)	77.33 (68.3–86.7)	0.0080
Heart rate, per minute	105.71 (94.0–115.6)	110.0 (92.0–125.0)	<0.001
Shock index	0.95 (0.83–1.11)	1.0 (0,83–1.24)	<0.001
SpO_2, %	98.78 (98.0–99.8)	99.0 (98,0–100.0)	0.6846
Chloride, mmol/L	108.9 (104.6–112.9)	108.74 (104.0–112.0)	0.6023
Lactate, mmol/L	1.2 (0.0–1.7)	1.1 (0.0–2.6)	0.0013
Amylase, IU/L	35.3 (0.0–94.0)	18.3 (0.0–49.7)	<0.001
Alanine aminotransferase, IU/L	39.48 (18.98–77.55)	39.6 (15.2–101.5)	<0.001
Aspartate aminotransferase, IU/L	55.81 (34.06–110.0)	62.5 (28.5–163.4)	<0.001
Activated partial thromboplastin time, s	28.9 (0.0–33.09)	25.8 (0.0–31.0)	<0.001
Fluid infusion volume, % of age-related requirement	118.53 (98.96–138.8)	84.42 (60.99–130.5)	<0.001
Catecholamine index	0.0 (0.0–5.3)	0.0 (0.0–5.0)	0.0721

We further compared the values of the studied parameters for all patients on the first and subsequent days of treatment, forming groups for pairwise comparison (Table 5).

We found that the values of clinical and laboratory parameters differed significantly between patients who received CS only on the first day of treatment and those who received it in later periods; these differences were not characteristic of non-survivors, unlike survivors. The groups of patients were similar in terms of outcome (Table 6).

When CS were administered on any of the days of treatment in the ICU, significant differences in all analyzed parameters were observed between non-survivors and survivors. We also found significant differences in the width of the ranges of values of the studied clinical and laboratory parameters between the created groups of patients, with a narrower range of values in children who received CS. The most pronounced differences between patients who received CS on different days of treatment in the ICU were observed when comparing children who received CS only on day 1 (on admission to the hospital). In particular, differences were found in chloride levels, volume of fluid infusion, and frequency of catecholamine use (all of which were lower in children who received CS on day 1).

Systolic blood pressure levels with the use of CS in children with fatal polytrauma deserve special attention (see Figure). Children who did not receive

Table 3. Analysis of paired samples of patients in the first seven days of treatment in ICU.

Values	Values in groups		
	1 (all)	**2 (all without steroids)**	**3 (all with steroids)**
Chloride, mmol/L	110.0 (106.0–116.75) *P=0.0002	110.85 (106.75–116.0) P=0.2838	110.0 (105.3–117.0) P=0.0007
Alanine aminotransferase, IU/L	41.3 (21.21–93.0) P=0.0029	44.8 (22.0. 103.55) P=0.0242	40.9 (21.02. 85.64) P=0.176
Aspartate aminotransferase, IU/L	58.75 (36.0–120.65) p<0.001	60.4 (40.04–125.0) p<0.001	57.0 (35.3–118.52) P=<0.001
Amylase, IU/L	51.3 (0.0–120.69) p<0.001	50.5 (19.22–101.1) P=0.0019	51.3 (0.0–140.43) p<0.001
Diastolic blood pressure, mm Hg	62.0 (55.0–70.0) P=0.0019	63.0 (58.0–72.0) P=0.0938	61.0 (55.0. 70.0) P=0.0078
Urine output, mL/kg	48.0 (33.24–75.5) P=0.0009	48.23 (34.75–79.17) P=0.2918	47.83 (32.94–74.5) P=0.0011
Shock index	0.91 (0.76–1.09) P=0.0001	0.97 (0.74–1.11) P=0.7597	0.9 (0.77–1.08) p<0.001
Fluid infusion volume, % of age-related requirement	118.33 (96.21–147.46) P=0.0	119.03 (99.96. 147.58) P=0.1117	118.26 (94.2. 145.08) P=0.0001
Catecholamine index	5.0 (0.0–7.5) P=0.0057	2.75 (0.0–7.5) P=0.4063	5.0 (0.0–7.5) P=0.0233
Lactate, mmol/L	1.2 (0.15–1.9) P=0.0004	1.4 (1.0–1.8) P=0.6424	1.2 (0.0–2.08) P=0.0001
Systolic blood pressure, mm Hg	110.0 (100.0–120.0) P=0.0002	112.0 (100.0–120.25) P=0.1962	110.0 (100.0–120.0) P=0.0002
Mean blood pressure, mm Hg	78.33 (71.33–87.67) P=0.0003	80.0 (71.33–88.67) P=0.0638	78.33 (71.42–87.33) P=0.0011
Heart rate, per minute	102.0 (88.0–118.0) P=0.0118	102.5 (89.0–116.25) P=0.6667	102.0 (85.25–118.0) P=0.0149
Parameter	**4 (survivors)**	**5 (survivors not receiving steroids)**	**6 (survivors receiving steroids)**
Chloride, mmol/L	110.0 (105.0–115.0) p<0.001	110.0 (105.5–116.0) P=0.0523	110.0 (105.0–115.0) P=0.0001
Alanine aminotransferase, IU/L	38.48 (19.95–89.52) P=0.0004	44.4 (22.25–117.35) P=0.0117	33.7 (19.3–71.0) P=0.0738
Aspartate aminotransferase, IU/L	60.4 (43.85–112.95) p<0.001	60.4 (43.85–112.95) p<0.001	50.6 (33.2–95.0) p<0.001
Amylase, IU/L	63.85 (27.0–143.52) p<0.001	55.7 (27.5–102.85) P=0.0019	69.4 (27.0–171.2) p<0.001
Diastolic blood pressure, mm Hg	65.0 (60.0–72.0) P=0.4422	65.0 (60.0–72.0) P=0.4422	61.0 (55.0–70.0) P=0.0001
Urine output, mL/kg	47.83 (32.98–75.0) P=0.0033	48.46 (34.52–79.17) P=0.3763	47.5 (32.22–73.33) P=0.0078
Shock index	0.93 (0.73–1.09) P=0.8015	0.93 (0.73–1.09) P=0.8015	0.89 (0.75–1.06) p<0.001
Catecholamine index	116.16 (94.27–144.06) p<0.001	114.7 (98.83–145.83) P=0.093	117.23 (92.59–143.75) P=0.0001
Lactate, mmol/L	1.3 (0.0–5.0) P=0.6135	1.3 (0.0–5.0) P=0.6135	5.0 (0.0–7.0) P=0.0144
Systolic blood pressure, mm Hg	1.3 (0.9–1.9) P=0.0003	1.3 (1.0–1.7) P=0.3905	1.3 (0.8–2.0) P=0.0002
Mean blood pressure, mm Hg	115.0 (100.0–120.0) P=0.332	115.0 (100.0–120.0) P=0.332	110.0 (100.0–120.0) P=0.0
Heart rate, per minute	78.83 (72.0–87.33) P=0.0	81.0 (73.17–88.67) P=0.2954	78.33 (71.67–86.67) P=0.0
Catecholamine index	100.0 (88.0–115.0) P=0.6786	100.0 (88.0–115.0) P=0.6786	100.0 (84.0–116.0) P=0.0015
Parameter	**7 (non-survivors)**	**8 (non-survivors receiving steroids)**	**9 (non-survivors receiving steroids)**
Activated partial thromboplastin time, s	24.5(0.0–36.15) P=0.0035	25.0 (0.0–31.5) P=0.0983	24.0 (0.0–37.0) P=0.1185
Catecholamine index	7.5 (4.0–14.0) P=0.0073	14.0 (14.0–30.0) P=0.1265	5.0 (2.5–10.0) P=0.0364

Note. * — all P-values are presented as comparisons between the parameters of the first day and those of the following seven days of observation.

Table 4. Comparative analysis of patient samples during the first seven days of ICU treatment.

Values	Values in groups			*P*-value
	6 (survivors receiving steroids)	9 (non-survivors receiving steroids)	8 (non-survivors not receiving steroids)	
Catecholamine index, LQ	5.571	7.7819	14.9828	0.0000
Lactate, LQ	1.2085	0.5157	0.3655	0.0000
SpO_2, UQ	98.7448	98.2378	99.3208	0.0001
Activated partial thromboplastin time, LQ	26.9007	15.3725	14.1115	0.0004
Systolic blood pressure, LQ	109.361	101.8029	96.7571	0.0060
Diastolic blood pressure, LQ	62.127	57.9126	53.8308	0.0111
Chloride, LQ	110.3991	112.8445	112.6637	0.0159
Mean blood pressure, LQ	77.9618	72.7039	68.4225	0.0174
Aspartate aminotransferase, LQ	87.0879	118.9305	62.3428	0.0194
Amylase*, UQ	167.2604	31.2796	90.0558	0.0213
Amylase*, LQ	117.0766	0.6165	6.2633	0.0248
Lactate, UQ	1.6116	1.7959	1.2822	0.0373
Catecholamine index, UQ	9.5239	26.322	32.2077	0.0382
Systolic blood pressure, UQ	112.6329	112.3789	113.3381	0.0383
Alanine aminotransferase, LQ	64.2138	74.3447	41.1377	0.0437

Note. UQ — upper quartile; LQ — lower quartile.

Table 5. Clinical and laboratory in relation to the use of corticosteroids in ICU.

Parameter	Values in relation to the time of steroid administration		*P*-value
	Only on day 1	On any day	
Activated partial thromboplastin time, s	27.8 (0–34.05)	29.2 (26.96–33.68)	0.0461
Amylase	49.3 (0–172.03)	33 (0–64.48)	0.0215
Urine output, mL/kg	42.5 (28–58.15)	51.42 (29.06–83.33)	0.0475
Catecholamine index	4.5 (0–7.5)	0 (0–4.38)	<0.001
Lactate	1.2 (0–1.9)	0 (0–1.3)	0.0001
Parameter	**Only on day 1**	**Any day except for day 1**	
Chloride	108 (102.3–110.75)	111 (106–121)	<0.001
Activated partial thromboplastin time, s	29.2 (26.96–33.68)	32 (28.78–34.8)	0.0100
Amylase	33 (0–64.48)	72 (50.08–129.7)	<0.001
Shock index	0.87 (0.78–1.07)	0.97 (0.81–1.11)	0.0900
Fluid infusion volume, % of age-related requirement	107.43 (82.25–131.56)	129.79 (109.69–160.27)	<0.001
Catecholamine index	0 (0–4.38)	5 (1.25–7.5)	<0.001
Lactate	0 (0–1.3)	1.1 (0–1.6)	<0.001
Parameter	**Only on day 1**	**Not administered**	
Catecholamine index	0 (0–4.38)	0 (0–5)	0.0200
Lactate	0 (0–1.3)	1.1 (0–1.7)	<0.001
Parameter	**Any day**	**Not administered**	
Amylase	61 (0–141.5)	39 (0–78.98)	<0.001
Catecholamine index	5 (0–7)	0 (0–5)	<0.001

CS had higher blood pressure values during the first three days of treatment in the ICU, with a decrease on day 5 and a tendency to hypertension on days 6–7. When CS were administered, the patients' blood pressure levels remained stable during the first seven days after trauma.

Clinical and laboratory signs in patients who received CS only on day 1 of treatment in the ICU were as close as possible to age-related reference values, in contrast to patients who received CS on other days of treatment in the ICU.

Discussion

Corticosteroids are among the few drugs that are widely used despite the lack of clear evidence of their efficacy and safety, especially in pediatric practice. In recent years, several studies have focused on the evaluation of steroid levels in patients after trauma and the efficacy of their administration for stabilization, indicating the relevance of the issue under consideration and the need for a thorough reassessment of the available data [19–24].

The results obtained suggest that the use of steroids provides primary stabilization of the patient and promotes the restoration of key biochemical parameters. The administration of corticosteroid therapy on the first day has the greatest effect, and its efficacy can serve as a criterion for a favorable outcome, since no significant differences were observed in the group of non-survivors regardless of the use of corticosteroids, whereas a significant positive evolution of the evaluated parameters was observed in the group of survivors with the use of corticosteroids. We suggest that the use of corticosteroids led to a stabilization of homeostasis. In particular, the lower limit of the interquartile range of systolic blood pressure was lower in patients

Table 6. Treatment outcomes in ICU in relation to the use of corticosteroids.

Parameter	Values in relation to the time of steroid administration		*P*-value
	Survivors	Non-survivors	
Chloride	108.72 (104–114)	111.2 (108.74–124)	0.0001
SpO_2, %	99 (98–100)	98 (98–99)	<0.001
Alanine aminotransferase	36.75 (20.5–71.1)	71 (39.375–113)	0.0108
Activated partial thromboplastin time, s	30 (24–35)	24 (0–38)	0.0022
Amylase	61 (19.6625–129.775)	0 (0–0)	<0.001
Diastolic blood pressure	65 (60–73)	59.5 (46.75–70)	0.0005
Catecholamine index	2.5 (0–5)	8 (5–20)	<0.001
Lactate	1.2 (0–1.8)	0 (0–1.1)	<0.001
Systolic blood pressure	110 (104–120)	103 (86.5–117)	0.0063
Mean blood pressure	81.333 (73.3333–88.3333)	73.333 (60–86.8333)	0.0011
	Not administered on day 1		
SpO_2, %	99 (98–100)	98 (98–99)	0.0491
Catecholamine index	2.5 (0–5)	8 (5–20)	0.0058
	Administered on any day		
Chloride	108.87 (105–115)	120 (108.74–139)	<0.001
SpO_2, %	99 (98–100)	98 (98–99)	<0.001
Alanine aminotransferase	36.75 (20.5–71.1)	71 (39.375–113)	<0.001
Aspartate aminotransferase	48.3 (30–83.3875)	111 (42.1–183)	<0.001
Amylase	61 (19.6625–129.775)	0 (0–0)	<0.001
Diastolic blood pressure	65 (60–73)	59.5 (46.75–70)	0.0005
Urine output, mL/kg	46.733 (30.5956–72.5)	45.685 (32.75–70.8576)	0.2074
Shock index	0.933 (0.7727–1.1)	0.991 (0.8385–1.1919)	0.0272
Fluid infusion volume, % of age-related requirement	116.583 (95.027–142.743)	125.884 (93.714–147.917)	0.3323
Catecholamine index	2.5 (0–5)	8 (5–20)	<0.001
Lactate	1.2 (0–1.8)	0 (0–1.1)	<0.001
Systolic blood pressure	110 (104–120)	103 (86.5–117)	<0.001
Mean blood pressure	81.333 (73.333–88.3333)	73.333 (60–86.8333)	0.0001
Heart rate	106 (90–120)	106 (90–121.25)	0.6672
	Administered on day 1		
SpO_2, %	99 (98–100)	98 (98–99)	0.0080
Diastolic blood pressure	65 (60–73)	59.5 (46.75–70)	0.0189
Fluid infusion volume, % of age-related requirement	116.6 (95.03–142.7)	125.9 (93.7–147.9)	0.0100
Catecholamine index	2.5 (0–5)	8 (5–20)	0.0070
Systolic blood pressure	110 (104–120)	103 (86.5–117)	0.0415
Mean blood pressure	81.333 (73.3–88.3)	73.333 (60–86.83)	0.0239
Catecholamine index	5 (0–7)	0 (0–5)	<0.001

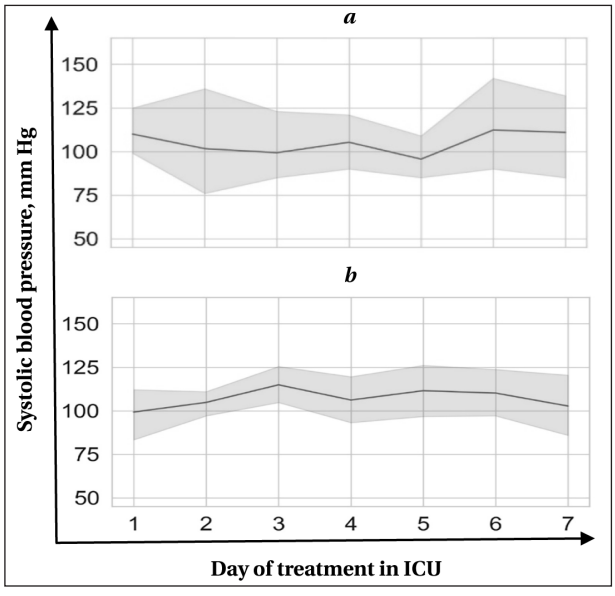

Fig. Systolic blood pressure in children with fatal polytrauma in relation to corticosteroid use (shaded area corresponds to 95% confidence interval).
Note. *a* — no corticosteroids administered; *b* — corticosteroids were administered.

who did not receive corticosteroids than in those who did, both in survivors and non-survivors (*P*=0.006).

Most likely, this was due to the maximum intensity of the therapeutic effect of CS on the first day after the trauma. The forced use of CS later in the post-traumatic period indicates instability of the patient's condition, has minimal therapeutic effect and serves as a diagnostic marker of unfavorable outcome in children with polytrauma.

The necessity of using CS and their effectiveness in patients with severe traumatic brain injury is demonstrated by the work of Prasad G. L., who showed that the use of dexamethasone at an initial dose of 12 mg/day in adult patients with mild to moderate traumatic brain injury for six days, with a gradual reduction of the dose, helps prevent delayed cerebral edema. The author noted sustained improvement in all patients: the mean time from the first dexamethasone injection to resolution of neurological symptoms was 3.8 days. No complications related to the use of CS were reported [19].

In the 2023 publication, Prasad G. L. discusses the need to re-evaluate the efficacy of CS use in

cerebral edema that cannot be controlled with osmotic diuretics [20].

The role of CS in the development of the stress response and its potential use in the treatment of severe polytrauma is also supported by the study by Bentley C. et al. who examined the levels of adrenal hormones in adult patients during the first hour after injury and found that the levels of cortisol and 11-hydroxyandrostenedione increase rapidly and significantly [23].

Kwok A. M. et al. (2020) also demonstrated that low cortisol concentrations in severe adult polytrauma are associated with the need for large volumes of blood products, vasopressors, and increased mortality. They suggest that testing blood cortisol concentrations on admission to hospital may be useful in identifying high-risk patients [24].

In 2023, a literature review on the early use of CS for hemorrhagic shock in adult patients reported a lack of research on this topic in recent years, despite the wide availability of steroids and their use in routine clinical practice, suggesting the need for modern multicenter studies [22].

The positive therapeutic effects of CS in pediatric ICU patients are also confirmed in the study by Corbet Burcher G. et al. (2018), which showed that their use contributes to the reduction of post-traumatic stress in children with sepsis and meningoencephalitis, although it is associated with a decrease in evening salivary cortisol concentration [21].

Conclusion

The administration of corticosteroids in children with severe polytrauma on the first day of treatment in the ICU helped to stabilize hemodynamic parameters and reduce signs of shock. A positive response to steroids in children with polytrauma can be considered a marker of favorable prognosis throughout their treatment in the ICU.

References

1. *Юнусов Д. И., Александрович В. Ю., Миронов П. И., Пшениснов К. В., Ульрих Г. Э., Пастухова Н. К., Незабудкин С. Н. с соавт.* Алгоритм оказания помощи детям с сочетанной травмой. *Ортопедия, травматология и восстановительная хирургия детского возраста.* 2019; 7 (4): 67–78. *Yunusov D. I., Aleksandrovich V.Yu., Mironov P. I., Pshenisnov K. V., Ulrich G. E., Pastukhova N. K., Nezabudkin S. N. et al.* Algorithm of medical care for children with polytrauma. *Orthopedics, Traumatology and Pediatric Reconstructive Surgery = Ortopedia, Travmatologiya i Vosstanovitelnaya Khirurgiya Detskogo Vozrasta.* 2019; 7 (4): 67–78. (in Russ.). DOI: 10.17816/PTORS7467-78.
2. *Пшениснов К. В., Александрович Ю. С., Липин А. С., Казиахмедов В. А., Козубов М. Ю., Пастухова Н. К.* Предикторы исхода тяжелой политравмы у детей: ретроспективное когортное мультицентровое исследование. *Вестник интенсивной терапии имени А. И. Салтанова.* 2022; 4: 69–78. *Pshenisnov K. V., Aleksandrovich Yu.S., Lipin A. S., Kaziakhmedov V. A., Kozubov M. U., Pastukhova N. K.* Predictors of the outcome of severe polytrauma in children: a retrospective cohort multicenter study. *Ann Crit Care = Vestnik Intensivnoy Terapii im AI Saltanova.* 2022; 4: 69–78. (in Russ.). DOI: 10.21320/18-474 X-2021-4-69-78.
3. *Колыхалкина И. А., Чернышева Т. А., Амчеславский В. Г., Исхаков О. С., Иванова Т. Ф., Бережной Ю. Ю.* Безопасность применения протокола пошаговой терапии острой внутричерепной гипертензии у детей с тяжелой механической травмой. *Медицинский алфавит.* 2013; 2 (14): 57–58. *Kolykhalkina I. A., Chernysheva T. A., Amcheslavsky V. G., Iskhakov O. S., Ivanova T. F., Berezhnoy Yu.Yu.* Safety of the protocol of step-by-step therapy of acute intracranial hypertension in children with severe mechanical injury. *Medical Alphabet = Meditsinskiy Alfavit.* 2013; 2 (14): 57–58. (in Russ.). eLIBRARY ID: 20788023.
4. *Кондратьев А. Н.* Нейротравма глазами анестезиолога-реаниматолога. М.: Медицина; 2014: 204. *Kondratiev A. N.* Neurotrauma through the eyes of an anesthesiologist-reanimatologist. M.: Medicine; 2014: 204. (in Russ.).
5. Лечение пострадавших детей с черепно-мозговой травмой. Клинические рекомендации. Ассоциация нейрохирургов России, Ассоциация детских нейрохирургов России. М.; 2015: 36. Management of injured children with traumatic brain injury. Clinical guidelines. Association of Neurosurgeons of Russia, Association of Pediatric Neurosurgeons of Russia. M.; 2015: 36. (in Russ.). https: //rusans.org/Text/Guidelines/head_injury_children.pdf
6. Лечение пострадавших с тяжелой черепно-мозговой травмой. Ассоциация нейрохирургов России, Ассоциация детских нейрохирургов России. М.; 2014: 21. Treatment of victims with severe traumatic brain injury. Association of Neurosurgeons of Russia, Association of Pediatric Neurosurgeons of Russia. Moscow; 2014: 21. (in Russ.). http: //neuro-online.ru/biblioteka/stati/klinicheskie-rekomendacii-lechenie-postradavshih-s-tjazheloi-cherepno-mozgovoi-travmoi.html?ysclid = m06d25z5pf822711708
7. *Тулупов А. Н., Афончиков В. Ю., Чикин А. Е., Тания С. Ш.* Организация оказания медицинской помощи пострадавшим с сочетанной травмой в травмоцентрах Санкт-Петербурга. *Скорая медицинская помощь.* 2014; 15 (1): 67–71. *Tulupov A. N., Afonchikov V. Yu., Chikin A. E., Tanya S. Sh.* Organization of medical care for victims with combined trauma in trauma centers in St. Petersburg. *Emergency Medical Care = Skoraya Meditsinskaya Pomoshch.* 2014; 15 (1): 67–71. (in Russ.). DOI: 10.24884/2072-6716-2014-15-1-67-71.
8. *Колыхалкина И. А., Чернышева Т. А., Амчеславский В. Г., Карасева О. В., Иванова Т. Ф., Багаев В. Г., Бережной Ю. Ю., с соавт.* Профилактика и лечение внутричерепной гипертензии у детей с тяжелой черепно-мозговой травмой. *Медицинский Алфавит.* 2014; 1 (5): 16–19. *Kolykhalkina I. A., Chernysheva T. A., Amcheslavsky V. G., Karaseva O. V., Ivanova T. F., Bagaev V. G., Berezhnoy Yu.Yu., et al.* Prevention and treatment of intracranial hypertension in children with severe traumatic brain injury. *Medical Alphabet = Meditsinskiy Alfavit.* 2014; 1 (5): 16–19. (in Russ.). eLIBRARY ID: 21500188.
9. *Семенова Ж. Б., Мельников А. В., Саввина И. А., Лекманов А. У., Хачатрян В. А., Горелышев С.К* Рекомендации по лечению детей с черепно-мозговой травмой. *Российский вестник детской хирургии, анестезиологии и реаниматологии.* 2016; 6 (2): 112–131. *Semenova Zh.B., Melnikov A. V., Savvina I. A., Lekmanov A. U., Khachatryan V. A., Gorelyshev S.* Recommendations for treatment of children with craniocerebral trauma. *Russian Bulletin of Pediatric Surgery, Anesthesiology and Intensive Care = Rossiyskiy Vestnik Detskoy Khirurgii Anesteziologii i Reanimatologii.* 2016; 6 (2): 112–131. (in Russ.). eLIBRARY ID: 26376244.
10. *Савин И. А., Горячев А. С.* Водно-электролитные нарушения в нейрореанимации. М.: «Аксиом Графикс Юнион»; 2015; 332. *Savin I. A., Goryachev A. S.* Hydroelectrolytic disorders in neuro-intensive care. M.: «Axiom Graphics Union»; 2015; 332. (in Russ.).

11. *Савин И. А.* Рекомендации по интенсивной терапии у пациентов с нейрохирургической патологией. Савин И. А., Фокин М. С., Лубнин А. Ю. (ред.). М.: НИИ нейрохирургии им. акад. Н. Н. Бурденко РАМН; 2014: 168. *Savin I. A.* Intensive care guidelines in patients with neurosurgical pathology. Savin I. A., Fokin M. S., Lubnin A. Yu. (ed.). M.: Research Institute of Neurosurgery named after Academician N. N. Burdenko of the Russian Academy of Sciences; 2014: 168. (in Russ.). https://www.volgmed.ru/uploads/files/2014-11/33850-rekomendacii_po_intensivnoj_terapii_u_pacientov_s_nejrohirurgicheskoj_patologiej_2014_nii_nejrohirurgii_im_akad_n_n_burdenko_ramn_otdelenie_reanimacii_i_intensivnoj_terapii_http_nsicu_ru.pdf?ysclid = m06fgzgnz7181360953.
12. *Феличано Д. В., Маттокс К. Л., Мур Э. Е.* Травма. М.: Издательство Панфилова; БИНОМ. Лаборатория знаний; 2013; 2: 496. *Feliciano D. V., Mattox K. L., Moore E. E.* Trauma. M.: Panfilov Publishing House; BINOM. Laboratoriya Znaniy; 2013; 2: 496.
13. *Kochanek P. M., Tasker R. C., Bell M. J., Adelson P. D., Carney N., Vavilala M. S., Selden N. R., et al.* Management of pediatric severe traumatic brain injury: 2019 consensus and guidelines-based algorithm for first and second tier therapies. *Pediatr Crit Care Med*. 2019; 20 (3): 269–279. DOI: 10.1097/PCC.0000000000001737. PMID: 30830015.
14. *Fehlings M. G., Wilson J. R., Tetreault L. A., Aarabi B., Anderson P., Arnold P. M., Brodke D. S., et al.* A clinical practice guideline for the management of patients with acute spinal cord injury: recommendations on the use of methylprednisolone sodium succinate. *Global Spine J*. 2017; 7 (3 Suppl): 203S–211S. DOI: 10.1177/2192568217703085. PMID: 29164025.
15. *Caruso M. C., Daugherty M. C., Moody S. M., Falcone R. A., Bierbrauer K. S., Geis G. L.* Lessons learned from administration of high-dose methylprednisolone sodium succinate for acute pediatric spinal cord injuries. *J Neurosurg Pediatr*. 2017; 20 (6): 567–574. DOI: 10.3171/2017.7.PEDS1756. PMID: 28984538.
16. *Davis A. L., Carcillo J. A., Aneja R. K., Deymann A. J., Lin J. C., Nguyen T. C., Okhuysen-Cawley R. S., et al.* American college of critical care medicine clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock. *Crit Care Med*. 2017; 45 (6): 1061–1093. DOI: 10.1097/CCM.0000000000002425. PMID: 28509730.
17. *Nandhabalan P., Ioannou N., Meadows C., Wyncoll D.* Refractory septic shock: our pragmatic approach *Crit Care*. 2018; 22 (1): 215. DOI: 10.1186/s13054-018-2144-4. PMID: 30231909.
18. *Annane D., Pastores S. M., Rochwerg B., Arlt W., Balk R. A., Beishuizen A., Briegel J.,* et al. Guidelines for the diagnosis and management of critical illness-related corticosteroid insufficiency (CIRCI) in critically ill patients (Part I): Society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM) 2017. *Intensive Care Med*. 2017; 43 (12): 1751–1763. DOI: 10.1007/s00134-017-4919-5. PMID: 28940011.
19. *Prasad G. L.* Steroids for delayed cerebral edema after traumatic brain injury. *Surg Neurol Int*. 2021; 12: 46. DOI: 10.25259/SNI_ 756_2020. PMID: 33654549.
20. *Prasad G. L.* Steroids and traumatic brain injury: time to revisit? *Indian J Neurotrauma*. 2023; 20: 63–64.DOI: 10.1055/s-0043-1769804.
21. *Burcher G. C., Picouto M. D., Als L. C., Cooper M., Pierce C. M., Nadel S., Garralda M. E.* Post-traumatic stress after PICU and corticosteroid use. *Arch Dis Child*. 2018; 103 (9): 887–889. DOI: 10.1136/archdischild-2017-314157. PMID: 29175821.
22. *Hogarty J. P., Jones M. E., Jassal K., Hogarty D. T., Mitra B., Udy A. A., Fitzgerald M. C.* Review article: Early steroid administration for traumatic haemorrhagic shock: a systematic review. *Emerg Med Australas*. 2023; 35 (1): 6–13. DOI: 10.1111/1742-6723.14129. PMID: 36347522.
23. *Bentley C., Hazeldine J., Bravo L., Taylor A. E., Gilligan L. C., Shaheen F., Acharjee A., et al.* The ultra-acute steroid response to traumatic injury: a cohort study. *Eur J Endocrinol*. 2023; 188 (3): lvad024. DOI: 10.1093/ejendo/lvad024. PMID: 36809311.
24. *Kwok A. M., Davis J. W., Dirks R. C., Sue L. P., Wolfe M. M., Kaups K.* Prospective evaluation of admission cortisol in trauma. *Trauma Surg Acute Care Open*. 2020; 5 (1): e000386. DOI: 10.1136/tsaco-2019-000386. PMID: 32072017.
25. *Толочко М. В., Лейдерман И. Н., Хохунов О. А., Мазурок В. А., Ржеутская Р. Е.* Анализ клинической эффективности дексаметазона у пациентов со среднетяжелым течением COVID-19. *Общая реаниматология*. 2022; 18 (1): 11–16. *Tolochko M. V., Leyderman I. N., Khokhunov O. A., Mazurok V. A., Rzheutskaya R. E.* Assessment of clinical efficacy of dexamethasone in patients with moderate COVID-19. *General Reanimatology = Obshchaya Reanimatologiya*. 2022; 18 (1): 11–16. (in Russ.&Eng.). DOI: 10.15360/1813-9779-2022-1-11-16.

Received 04.03.2024
Accepted 18.09.2023

https://doi.org/10.15360/1813-9779-2024-5-24-30

Effect of Succinate Crystalloid Solution on Hemostasis in Children with Severe Community-acquired Pneumonia

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For citation: *Vladimir V. Lazarev, Pavel E. Anchutin, Manuel M. Megeryan, Mikhail V. Bykov, Dmitry A. Smirnov, Tatiana A. Pchelicnceva, Nikolay S. Frolov, Khurzada M. Makhachilaeva, Boris I. Golubev, Elena A. Spiridonova.* Effect of succinate crystalloid solution on hemostasis in children with severe community-acquired pneumonia. *Obshchaya Reanimatologiya = General Reanimatology.* 2024; 20 (5): 24–30. https://doi.org/10.15360/1813-9779-2024-5-24-30 [In Russ. and Engl.]

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Summary

Aim of the study. To improve outcomes in children with severe community-acquired pneumonia (CAP) by including succinate-containing crystalloid solution (SCCS) in the treatment plan.

Materials and methods. The study included 100 patients diagnosed with CAP. SCCS was administered to 24 patients from the prospective (main) group, divided into 2 equal subgroups of 12 subjects who received SCCS with the infusion rate of 2.5 ml/kg/h (subgroup 1) and 5.0 ml/kg/h (subgroup 2). Treatment of 76 patients in the retrospective (control) group did not include SCCS.

Results. Greater decreases in D-dimer (by 418.5 ng/mL vs. 137.0 ng/mL, P=0.026) by day 3 and in fibrinogen (by 1.7 g/L vs. 0.2 g/L, P<0.001) by day 3 and (3.8 g/L vs. 0.5 g/L, P=0.002) by day 5 of hospitalization were found in children from the main group vs. the control group. Fibrinogen levels decreased in both study subgroups, although subgroup 1 had significantly higher fibrinogen levels on day 2 of ICU stay (P=0.034). A significant increase in activated partial thromboplastin time (aPTT) of 9.7 seconds was observed on day 3 in the main group versus 2.9 seconds in the control group (P<0.001). There was a direct correlation between fibrinogen level and neutrophil count on day 2 of ICU stay (R=0.479, P=0.033).

Conclusion. The use of SCCS in the treatment of severe CAP helps to prevent thrombotic complications, reduces hypoxia-induced changes in the coagulation system, and enhances the effects of unfractionated heparin. SCCS infusion at a rate of 5.0 mL/kg/h effectively reduces the levels of hypercoagulation markers, while its administration at a rate of 2.5 ml/kg/h potentiates the effects of unfractionated heparin. The effects of SCCS on hemostasis in severe CAP are equivalent to those of a moderate anticoagulant.

Keywords: succinate-containing crystalloid solution; inflammation; pediatric community-acquired pneumonia; hypercoagulation; meglumine sodium succinate; Reamberin

Conflict of interest. The authors declare no conflict of interest. NTFF POLYSAN LLC had no influence on the study design, analysis of the obtained data, interpretation of the results and writing the manuscript.

Introduction

Hypoxia is a common pathophysiological process that occurs in any critical illnesses, including infectious inflammation.

During inflammation and hypoxia, the energy metabolism of body cells undergoes a systemic rearrangement with suppression of aerobic glycolysis and oxidative phosphorylation [1]. This response is a defense mechanism found in all body cells, including immune cells and platelets, and is not designed for long-term function.

Inflammation and hypoxia lead to an increase in endogenous succinate (EnS) levels, which typically reach 20 μmol/L under normal conditions. EnS is a major pro-inflammatory signaling molecule that accumulates as a result of Krebs cycle arrest [2–4]. Regulation of the immune response is compromised under hypoxic stress conditions, resulting in coagulopathy, uncontrolled coagulation activation and thrombotic microangiopathy [5–7].

Cells of the immune system play an important role in the regulation of blood coagulation, in particular by promoting platelet thrombus formation [8-11]. Platelets are essential for the regulation of blood coagulation. Platelet aggregation is activated when endogenous succinate concentrations reach 300–500 μmol/L [12–15]. Monocytes [16, 17], neutrophils [18], lymphocytes and dendritic cells [19] are also important coagulation regulators.

Some clotting factors, such as thrombin, can directly activate immune cells, leading to increased production of proinflammatory cytokines [20]. Fibrin helps to recruit and activate immune cells at the site of injury or infection [21].

According to the World Health Organization, pneumonia is the leading cause of death in children

under the age of five worldwide. Severe pneumonia accounts for about 20% of deaths in children in the first five years of life. Deaths in children with pneumonia are more common during the active inflammatory phase [22].

Severe pneumonia is always associated with a high inflammatory response and an increased risk of arterial and venous thrombosis, including pulmonary embolism [23].

Normalizing the energy supply to the cell suppresses the production of inflammatory mediators, preventing an excessive immune response and, as a result, coagulation disorders. Exogenous succinate, as part of a succinate-containing crystalloid solution (SCCS), freely enters the cell and regulates energy metabolism, which benefits the coagulation system [23].

The aim of the study was to increase the efficacy of the treatment of children with severe community-acquired pneumonia (CAP) by adding a succinate-containing crystalloid solution (SCCS) to the treatment regimen.

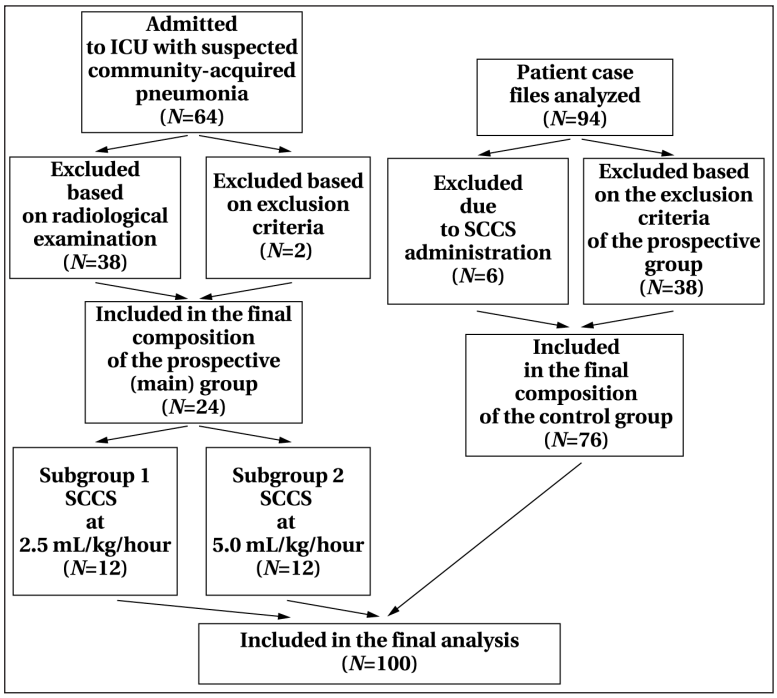

Fig. 1. Study flowchart.

Materials and Methods

We performed a retrospective-prospective, open-label, parallel-group, comparative study with patient stratification according to the mode of SCCS administration.

The study was conducted at the Podolsk Clinical Hospital from November 2021 to August 2023. The study included patients of both sexes aged 2 to 16 years with a confirmed diagnosis of severe community-acquired pneumonia who were admitted to the intensive care unit and required fluid therapy. Informed consent was obtained from the patient's legal representative.

Individual intolerance to the study drugs, traumatic brain injury with cerebral edema, renal dysfunction with changes in blood plasma electrolytes, urea, and creatinine, impaired blood acid-base balance such as alkalosis, pregnancy, lactation, and documented immunosuppression, both congenital and acquired, were non-inclusion criteria.

The prospective (main) group consisted of 24 patients with a confirmed diagnosis of CAP and indications for fluid therapy, which included an infusion of SCCS, meglumine sodium succinate (Reamberin 1.5%, OOO NTFF POLISAN), administered once daily at a total dose of 10 mL/kg per day, but not more than 400 mL.

Patients in the main group were divided into subgroups according to the rate of SCCS infusion using a random number table:

- Subgroup 1 (*N*=12): 2.5 mL/kg per hour
- Subgroup 2 (*N*=12): 5.0 mL/kg per hour.

The first SCCS infusion in each subgroup was given at the time of admission to the ICU, immediately after laboratory tests. Subsequent infusions were given once a day between 10:00 and 14:00. If necessary, the infusions of both subgroups were supplemented with 10% glucose and isotonic Sterofundin® solutions. The total daily fluid volume was limited to a maximum of 75% of the physiological requirement calculated according to the Holliday-Segar formula by continuous intravenous infusion throughout the day, with the exception of the SCCS administration.

The retrospective (control) group included 76 patients aged 2 to 16 years with a confirmed diagnosis of CAP and indications for fluid therapy who were previously treated in the intensive care unit between 2020 and 2023. Solutions containing 10% glucose and isotonic Sterofundin® were administered intravenously. The total amount of fluid infused each day was also limited to 75% of physiologic requirements.

To prevent venous thromboembolic complications, both groups received a continuous intravenous infusion of heparin sodium at a rate of 10 units/kg/hour from admission until transfer from the ICU, with the syringe changed every 6 hours.

Complete blood count and coagulation parameters such as activated partial thromboplastin time (APTT), international normalized ratio (INR), prothrombin index (PI), D-dimer, and fibrinogen were evaluated daily. Coagulation parameters were measured using a four-channel coagulation ana-

lyzer CoaTest-4 (Astra Research and Development Center, Russia).

Statistical analysis of the study results was performed using IBM SPSS Statistics v.26 and Microsoft Office Excel 2017 (Microsoft Corp., USA).

Due to non-normal distribution, quantitative parameters were presented as median and 25th and 75th quartiles *[Me (Q25; Q75)]*. Categorical variables were reported as absolute values and percentages (number, %).

Differences in qualitative parameters were evaluated using the Pearson χ^2 test or Fisher's exact test when the number of observations in a cell of the four-way table was <5.

Differences in quantitative parameters were calculated using the Mann–Whitney *U*-test. Multiple correlation analysis was performed using Spearman's rank correlation coefficient. To eliminate the influence of sex and age, additional pseudorandomization was performed by propensity score matching (PSM), resulting in the formation of groups comparable on these parameters. Differences were considered significant at $P<0.05$.

Results and Discussion

The groups were comparable in age (main group, 5.0 [2.8; 9.0] years; control group, 6.0 [4.0; 9.3] years, $P=0.298$); median body weight (main group, 19.5 [13.8; 28.3] kg; control group, 21.0 [16.0; 28.3] kg, $P=0.555$). The groups (main vs. control) were also comparable in the incidence of cerebral dysfunction (8.3% vs. 0.0%, $P=0.056$), circulatory disorders (4.2% vs. 0.0%, $P=0.240$), and metabolic disorders (4.2% vs. 0.0%, $P=0.240$). Male gender was predominant in the control group, 33.3% (8 patients) vs. 60.5% (46 patients) in the main group ($P=0.020$).

All patients in both groups had CAP (100.0%) and respiratory dysfunction (100.0%). The incidence of left-sided CAP in the main group was 20.8% (5 patients) and 21.1% (16 patients) in the control group ($P=1.0$); the incidence of right-sided CAP was 45.8% (11 patients) and 47.4% (36 patients), respectively ($P=0.895$); bilateral CAP was diagnosed in 33.3% (8 patients) and 31.6% (24 patients), respectively ($P=1.0$).

All patients in both groups received steroid, antibacterial, antiviral, and anticoagulant therapy with equivalent dosages and routes of administration.

Patients receiving SCCS had a more significant decrease in fibrinogen concentration on day 3 (by 1.7 g/L vs. 0.2 g/L, $P<0.001$) and day 5 of hospitalization (by 3.8 g/L vs. 0.5 g/L, $P=0.002$) compared to the control group (Fig. 2, *a*).

The main group also showed a more significant decrease in D-dimer concentration (by 418.5 ng/mL vs. 137.0 ng/mL, $P=0.026$) by day 3 of ICU stay compared to the control group (Fig. 2, *b*).

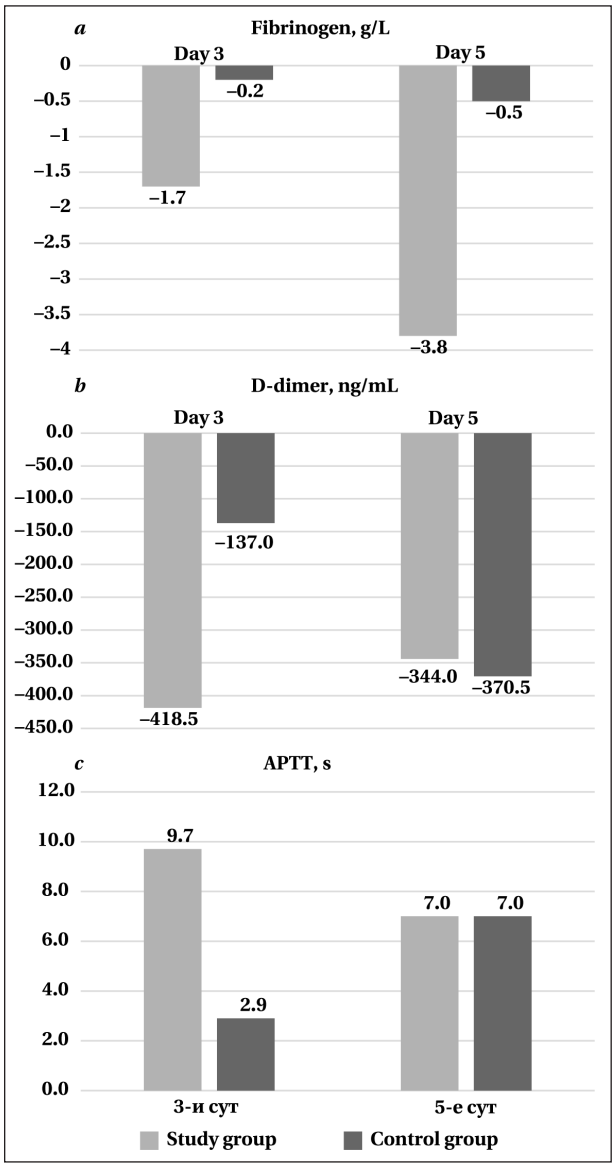

Fig. 2. Intergroup comparison of levels of fibrinogen *(a)*, D-dimer *(b)*, and APTT *(c)* on days 3 and 5 of hospital stay.

We found a significant increase in APTT on day 3 in the main group — by 9.7 seconds vs. 2.9 seconds ($P<0.001$) in the control group (Fig. 2, *c*).

PI values decreased by 25.6% in the main group and increased by 0.5% in the control group by day 5 ($P=0.018$).

Platelet count decreased by 63,000 cells in the main group and increased by 25,500 cells in the control group by day 3 ($P=0.045$), but by day 5 the decrease in platelet count was not statistically significant in either group.

Changes in coagulation parameters in the groups from the first to the fifth day of ICU stay are shown in Table 1.

Considering the significant sex differences between the groups, pseudorandomization was performed, resulting in the selection of 24 patients

Table 1. Changes in coagulation parameters in the study groups, *Me [Q1; Q3]*.

Day of ICU stay	Values in groups		*P*-value
	Main, *N*=24	Control, *N*=76	
Platelet count, 10^9/L			
1	316.0 [235.0; 361.3]	241.5 [204.0; 376.8]	0.236
2	308.5 [356.0; 344.0]	270.0 [202.8; 343.3]	0.053
3	312.0 [272.5; 418.0]	272.0 [190.5; 327.8]	0.026
4	354.0 [288.0; 398.0]	272.0 [187.5; 311.0]	0.014
5	296.5 [219.8; 335.8]	221.0 [183.0; 298.0]	0.373
Fibrinogen, g/L			
1	5.0 [4.5; 6.0]	4.1 [3.1; 5.3]	0.029
2	4.2 [3.6; 4.5]	4.1 [3.1; 5.1]	0.980
3	3.6 [2.7; 4.2]	4.2 [3.0; 4.9]	0.122
4	3.4 [2.9; 4.2]	4.0 [3.4; 4.4]	0.243
5	3.4 [2.9; 3.9]	4.0 [3.5; 4.7]	0.123
D-dimers, ng/mL			
1	624.0 [466.3; 819.8]	655.0 [441.0; 1140.5]	0.573
2	768.0 [590.5; 945.5]	1221.5 [1066.5; 1441.3]	0.267
3	225.0 [213.8; 254.5]	631.0 [476.0; 863.0]	0.001
4	115.0 [115.0; 115.0]	756.0 [482.5; 1131.5]	0.167
5	197.0 [192.5; 201.5]	991.0 [512.0; 1105.0]	0.095
APTT, s			
1	25.5 [22.1; 30.4]	28.4 [24.5; 34.2]	0.108
2	30.5 [28.5; 35.5]	30.4 [26.8; 34.1]	0.304
3	33.5 [32.0; 45.2]	32.3 [27.6; 35.3]	0.063
4	34.9 [29.0; 41.4]	33.9 [29.1; 36.4]	0.494
5	35.8 [31.5; 43.5]	33.9 [30.9; 37.6]	0.568
INR			
1	1.04 [0.95; 1.18]	1.1 [1.01; 1.18]	0.304
2	1.04 [0.95; 1.10]	1.11 [0.98; 1.16]	0.026
3	1.0 [0.9; 1.12]	1.05 [0.86; 1.14]	0.866
4	1.01 [1.0; 1.09]	1.04 [0.91; 1.12]	0.740
5	1.03 [0.96; 1.19]	1.01 [0.92; 1.1]	0.644
PI, %			
1	91.9 [86.5; 106.4]	97.0 [84.0; 108.0]	0.874
2	90.5 [84.8; 96.9]	94.5 [84.0; 104.0]	0.416
3	87.0 [83.0; 104.0]	93.0 [83.0; 104.0]	0.313
4	86.2 [85.0; 98.3]	97.5 [89.3; 105.0]	0.234
5	84.0 [78.9; 97.3]	97.5 [92.0; 105.3]	0.087

Note. For tables 1, 2, 3: APTT — activated partial thromboplastin time; INR — international normalized ratio; PI — prothrombin index.

from the control group who were comparable to the main group in terms of sex, age, and body weight. There were 33.3% (8 patients) males in the main group and 41.7% (10 patients) males in the comparison group (*P*=0.766). The median age was 5.0 [2.8; 9.0] and 6.0 [3.8; 10.4] years, respectively (*P*=0.220). The median body weight was 19.5 [13.8; 28.3] and 22 [14; 33] kg, respectively (*P*=0.687).

After pseudorandomization, there was an even more significant decrease in fibrinogen concentration (by 1.7 g/L vs. 0.8 g/L, *P*=0.040) and an increase in APTT (by 9.7 sec vs. 3.3 sec, *P*=0.007) in the main group compared with the control group on day 3 of hospitalization. We also observed a trend toward a reduction in PI in the main group by day 5 of hospitalization. However, the intensity of the decrease in D-dimer level (*P*=0.533), platelet count at day 3 (*P*=0.155), and fibrinogen at day 5 of ICU stay (*P*=0.144) did not differ between groups.

After adjustment for sex, the prospective group of children also maintained higher median platelet levels on days 2 (308.5 vs. 233.0×10^9/L, *P*=0.004), 3 (312.0 vs. 240.0×10^9/L, *P*=0.003), and 4 (354.0 vs. 231.0×10^9/L, *P*=0.010) of ICU stay. No decrease in platelet count below reference values was observed in either study group.

Subgroups of patients with different rates of SCCS infusion differed significantly in platelet counts on day 1 of observation: higher counts were observed in the subgroup with a lower rate of SCCS infusion (*P*=0.010, Table 2). On day 4, however, higher platelet counts were observed in the subgroup with a higher rate of SCCS infusion (*P*=0.010, Table 2).

A decrease in fibrinogen concentration was observed in both subgroups. However, on the 2nd day of ICU stay, lower values were recorded in the 2nd subgroup of the main group than in the 1st subgroup (*P*=0.034, Table 2).

The main group subgroups differed in APTT only on day 4: APTT was higher in subgroup 1 than in subgroup 2 (*P*=0.019, Table 2).

The subgroups of the main group differed in PI values only on day 1: it was higher in subgroup 2 than in subgroup 1 (*P*=0.027, Table 2).

There were no differences in INR values between the subgroups of the main group (Table 2).

Table 2. Changes in coagulation parameters in the subgroups of the study group, *Me [Q1; Q3]*.

Day of ICU stay	Subgroup of the study group		*P*-value
	1, *N*=12	2, *N*=12	
	Platelet count, 10^9/L		
1	345.0 [324.0; 371.8]	235.0 [199.0; 296.8]	0.010
2	315.0 [260.5; 411.3]	306.0 [255.3; 321.0]	0.443
3	315.0 [286.0; 463.5]	308.0 [275.3; 350.0]	0.397
4	290.0 [259.8; 313.5]	479.5 [398.0; 567.0]	0.010
5	273.0 [221.0; 296.5]	341.0 [271.5; 404.5]	0.4
	Fibrinogen, g/L		
1	5.5 [4.7; 6.1]	4.8 [3.8; 5.0]	0.283
2	4.4 [4.2; 4.6]	3.6 [3.2; 4.2]	0.034
3	4.0 [3.1; 4.2]	3.3 [2.4; 3.9]	0.397
4	3.1 [2.8; 3.5]	4.6 [4.3; 4.9]	0.143
5	2.9 [2.6; 3.4]	3.9 [3.4; 4.2]	0.4
	D-dimers, ng/mL		
1	624.0 [438.0; 887.5]	614.5 [563.5; 665.8]	1.0
	APTT, s		
1	27.3 [21.7; 31.1]	25.3 [22.5; 29.5]	0.976
2	31.1 [29.5; 38.5]	30.5 [28.5; 33.9]	0.456
3	40.1 [32.9; 45.3]	33.3 [29.6; 35.1]	0.299
4	40.0 [36.7; 43.0]	28.2 [27.1; 29.6]	0.019
5	40.0 [35.8; 42.3]	31.4 [29.6; 38.3]	0.7
	INR		
1	1.14 [0.95; 1.21]	1.03 [0.97; 1.11]	0.235
2	1.05 [0.95; 1.09]	1.04 [0.96; 1.11]	0.771
3	0.95 [0.89; 1.16]	1.0 [0.92; 1.12]	0.669
4	1.03 [1.0; 1.09]	1.01 [0.99; 1.1]	1.0
5	1.0 [0.91; 1.12]	1.05 [1.0; 1.21]	0.700
	PI, %		
1	87.5 [83.0; 104.3]	104.0 [91.5; 110.0]	0.027
2	88.5 [84.0; 93.9]	94.5 [87.0; 101.5]	0.346
3	90.0 [84.5; 104.0]	85.5 [83.5; 90.0]	0.417
4	85.2 [85.0; 93.3]	93.0 [79.0; 101.8]	0.610
5	79.0 [78.9; 92.5]	89.0 [73.5; 94.5]	1.0

Note. Rate of infusion of the SCCS: subgroup 1, 2.5 mL/kg/hour; subgroup 2, 5 mL/kg/hour.

Table 3. Correlation analysis of the relationship between neutrophil count and coagulation parameters.

Coagulation parameters	Neutrophil count		
	Day 1	Day 2	Day 3
Platelets	*R*=–0.185, *P*=0.409	*R*=–0.048, *P*=0.828	*R*=0.089, *P*=0.754
Fibrinogen	*R*=0.229, *P*=0.317	*R*=0.479, *P*=0.033	*R*=0.496, *P*=0.071
D-dimers	*R*=0.236, *P*=0.511	—	*R*=–0.400, *P*=0.600
APTT	*R*=–0.195, *P*=0.385	*R*=–0.206, *P*=0.370	*R*=–0.359, *P*=0.188

Correlation analysis was performed to assess the relationship between inflammation and coagulation parameters. The data are presented in Table 3.

There was a direct correlation between fibrinogen levels and neutrophil counts on day 2 of ICU stay, with a similar trend observed on day 3. The increase in fibrinogen levels not only reflects a tendency toward hypercoagulability, but also serves as an indicator of the intensity of the inflammatory response.

The complex interaction between the coagulation system and inflammation has important scientific and clinical implications. Infection-associated coagulopathy is closely related to the systemic inflammatory response syndrome, which is characterized by excessive release of cytokines and chemokines, increased production of interleukin-6 and -7, tumor necrosis factor-alpha, inflammatory chemokines, and hyperactivation of monocytes and macrophages [24, 25]. Accumulation of EnS leads to stabilization of hypoxia-inducible factor-1 alpha [26]. One way to correct an excessive inflammatory response and consequently hypercoagulation is to treat cellular hypoxia with exogenous succinate (ExS). As a component of SCCS, ExS normalizes the energy supply of immune cells and platelets, restores electron transfer chain function, suppresses glycolysis, and helps regulate hypoxia-inducible factor-1 alpha stability [27, 28].

Administration of SCCS was associated with potentiation of the effect of heparin. A similar therapeutic result was observed by other authors, who did not find potentiation of antiplatelet antibody production [29].

The use of SCCS as an adjuvant treatment for severe pneumonia in children helps to effectively eliminate systemic cellular energy deficiency.

Conclusion

Positive changes in coagulation parameters confirm the efficacy of SCCS (meglumine sodium succinate) in the intensive treatment of children with severe CAP. SCCS administration at a rate of 2.5 mL/kg/hour enhances the effect of prophylactic doses of unfractionated heparin (10 units/kg/hour). SCCS infusion at a rate of 5.0 mL/kg/hour results in a decrease in fibrinogen concentration.

References

1. *Keiran N., Ceperuelo-Mallafré V., Calvo E., Hernández-Alvarez M. I., Ejarque M., Núñez-Roa C., Horrillo D., et al.* SUCNR1 controls an anti-inflammatory program in macrophages to regulate the metabolic response to obesity. *Nat Immunol.* 2019; 20 (5): 581–592. DOI: 10.1038/s41590-019-0372-7. PMID: 30962591
2. *Hamel D., Sanchez M., Duhamel F., Roy O., Honoré J. C., Noueihed B., Zhou T., et al.* G-protein-coupled receptor 91 and succinate are key contributors in neonatal postcerebral hypoxia-ischemia recovery. *Arterioscler Thromb Vasc Biol.* 2014; 34 (2): 285–93. DOI: 10.1161/ATVBAHA.113.302131. PMID: 24285580.
3. *De Castro-Fonseca M., Aguiar C. J., da Rocha Franco J. A., Gingold R. N., Leite M. F.* GPR91: expanding the frontiers of Krebs cycle intermediates. *Cell Commun Signal.* 2016; 14: 3. DOI: 10.1186/s12964-016-0126-1. PMID: 26759054.
4. *Li T., Hu J., Du S., Chen Y., Wang S., Wu Q.* ERK1/2/COX-2/PGE2 signaling pathway mediates GPR91-dependent VEGF release in streptozotocin-induced diabetes. *Mol Vis.* 2014; 20: 1109–1121. PMID: 25324681.
5. *Palta S., Saroa R., Palta A.* Overview of the coagulation system. *Indian J Anaesth*. 2014; 58 (5): 515–523. DOI: 10.4103/0019-5049.144643. PMID: 25535411.
6. *Golebiewska E. M., Poole A. W.* Platelet secretion: from haemostasis to wound healing and beyond. *Blood Rev.* 2015; 29 (3): 153–162. DOI: 10.1016/j.blre.2014.10.003. PMID: 25468720.
7. *Chapin J. C., Hajjar K. A.* Fibrinolysis and the control of blood coagulation. *Blood Rev.* 2015; 29 (1): 17–24. DOI: 10.1016/j.blre.2014.09.003. PMID: 25294122.
8. *Delvaeye M., Conway E. M.* Coagulation and innate immune responses: can we view them separately? *Blood.* 2009; 114 (12): 2367–2374. DOI: 10.1182/blood-2009-05-199208. PMID: 19584396.
9. *Dahlbäck B., Villoutreix B. O.* Regulation of blood coagulation by the protein C anticoagulant pathway: novel insights into structure-function relationships and molecular recognition. *Arterioscler Thromb Vasc Biol.* 2005; 25 (7): 1311–1320. DOI: 10.1161/01.ATV. 0000168421.13467.82. PMID: 15860736.
10. *Popescu N. I., Lupu C., Lupu F.* Disseminated intravascular coagulation and its immune mechanisms. *Blood.* 2022; 139 (13): 1973–1986. DOI: 10.1182/blood.2020007208. PMID: 34428280.
11. *Tsantes A. G., Parastatidou S., Tsantes E.A, Bonova E., Tsante K. A., Mantzios P. G., Vaiopoulos A. G., et al.* Sepsis-induced coagulopathy: an update on pathophysiology, biomarkers, and current guidelines. *Life (Basel)*. 2023; 13 (2): 350. DOI: 10.3390/life13020350. PMID: 36836706.
12. *Hanby H. A., Bao J., Noh J. Y., Jarocha D., Poncz M., Weiss M. J., Marks M. S.* Platelet dense granules begin to selectively accumulate mepacrine during proplatelet formation. *Blood Adv.* 2017; 1 (19): 1478–1490. DOI: 10.1182/bloodadvances.2017006726. PMID: 28936487.
13. *Sharda A., Flaumenhaft R.* The life cycle of platelet granules. *F1000Res.* 2018; 7: 236. DOI: 10.12688/f1000research.13283.1. PMID: 29560259.
14. *Kim D. A., Ashworth K. J., Di Paola J., Ku D. N.* Platelet α-granules are required for occlusive high-shear-rate thrombosis. *Blood Adv.* 2020; 4 (14): 3258–3267. DOI: 10.1182/bloodadvances.2020002117. PMID: 32697818.
15. *Scridon A.* Platelets and their role in hemostasis and thrombosis- from physiology to pathophysiology and therapeutic implications. *Int J Mol Sci.* 2022; 23 (21): 12772. DOI: 10.3390/ijms232112772. PMID: 36361561.
16. *Shahneh F., Probst H. C., Wiesmann S. C., A-Gonzalez N., Ruf W., Steinbrink K., Raker V. K., et al.* Inflammatory monocyte counts determine venous blood clot formation and resolution. *Arterioscler Thromb Vasc Biol.* 2022; 42 (2): 145–155. DOI: 10.1161/ATVBAHA. 121.317176. PMID: 34911360.
17. *Hirayama D., Iida T., Nakase H.* The phagocytic function of macrophage-enforcing innate immunity and tissue homeostasis. *Int J Mol Sci*. 2017; 19 (1): 92. DOI: 10.3390/ijms19010092. PMID: 29286292.
18. *Shirakawa K., Sano M.* Neutrophils and neutrophil extracellular traps in cardiovascular disease: an overview and potential therapeutic approaches. *Biomedicines.* 2022; 10 (8): 1850. DOI: 10.3390/biomedicines10081850. PMID: 36009397.
19. *Tobon G. J., Izquierdo J. H., Canas C. A.* B lymphocytes: development, tolerance, and their role in autoimmunity-focus on systemic lupus erythematosus. *Autoimmune Dis.* 2013; 2013: 827254. DOI: 10.1155/2013/827254. PMID: 24187614.
20. *Keragala C. B., Draxler D. F., McQuilten Z. K., Medcalf R. L.* Haemostasis and innate immunity — a complementary relationship: a review of the intricate relationship between coagulation and complement pathways. *Br J Haematol.* 2018; 180 (6): 782–798. DOI: 10.1111/bjh.15062. PMID: 29265338.
21. *Hohlstein P., Gussen H., Bartneck M., Warzecha K. T., Roderburg C., Buendgens L., Trautwein C., et al.* Prognostic relevance of altered lymphocyte subpopulations in critical illness and sepsis. *J Clin Med.* 2019; 8 (3): 353. DOI: 10.3390/jcm8030353. PMID: 30871101.
22. Global Health Observatory. Proportions of child death by cause. (http://www.who.int/gho/child_health/en/index.html), WHO, Geneva Accessed on 24 July 2014.
23. *Violi F., Cangemi R., Calvieri C.* Pneumonia, thrombosis and vascular disease. *J Thromb Haemost.* 2014; 12 (9): 1391–1400. DOI: 10.1111/jth. 12646. PMID: 24954194.
24. *Lin J., Yan H., Chen H., He C., Lin C., He H., Zhang S., et al.* COVID-19 and coagulation dysfunction in adults: a systematic review and meta-analysis. *J Med Virol.* 2021; 93 (2): 934–44. DOI: 10.1002/jmv. 26346. PMID: 32706426.
25. *Frazer J. S., Tyrynis Everden A. J.* Emerging patterns of hyperco-agulability associated with critical COVID-19: A review. *Trends Anaesth Crit Care.* 2020; 34 (6): 4–13. DOI: 10.1016/j.tacc.2020.07.004. PMID: 38620391.
26. *Palazon A., Goldrath A. W., Nizet V., Johnson R. S.* HIF transcription factors, inflammation, and immunity. *Immunity.* 2014; 41 (4): 518–528. DOI: 10.1016/j.immuni. 2014.09.008. PMID: 25367569.
27. *Vilar R., Fish R. J., Casini A., Neerman-Arbez M.* Fibrin (ogen) in human disease: both friend and foe. *Haematologica.* 2020; 105 (2): 284–296. DOI: 10.3324/haematol. 2019.236901. PMID: 31949010.
28. *Jin M., Fuller G. G., Han T., Yao Y., Alessi A. F., Freeberg M. A., Roach N. P., et al.* Glycolytic enzymes coalesce in G bodies under hypoxic stress. *Cell Rep.* 2017; 20 (4): 895–908. DOI: 10.1016/j.celrep.2017. 06.082. PMID: 28746874.
29. *Лукьянова Л. Д.* Сигнальные механизмы гипоксии. М.: РАН; 2019. *Lukyanova L. D.* Signaling mechanisms of hypoxia. M., RAS; 2019. (In Russ)
30. *Симутис И. С., Бояринов Г. А., Юрьев М. Ю., Петровский Д. С., Коваленко А. Л., Парфенов С. А.* Возможности коррекции гипервоспаления при Covid-19. *Антибиотики и химиотерапия.* 2021; 66 (3–4): 40–48. *Simutis I. S., Boyarinov G. A., Yuriev M. Yu., Petrovsky D. S., Kovalenko A. L., Parfenov S. A.* Possibilities of hyperinflammation correction in COVID-19. *Antibiotics and Chemotherapy = Antibiotiki i Khimioterapiya.* 2021; 66 (3–4): 40–48. (In Russ). DOI: 10.37489/0235-2990 -2021-66-3-4-40-48.
31. *Михайлова Е. В., Чудакова Т. К.* Грипп у детей. Гематологические показатели интоксикации, детоксикационная терапия. *Экспериментальная и клиническая фармакология.* 2015; 78 (5): 33–36. *Mikhailova E. V., Chudakova T. K.* Influenza in children: clinical picture, hematological indicators of intoxication, detoxification therapy. *Experimental and Clinical Pharmacology = Eksperimentalnaya i Klinicheskaya Farmakologiya.* 2015; 78 (5): 33–36. (In Russ).
32. *Стоева Т. В., Титкова Е. В., Сытник В. В., Карташова В. А., Синенко В. В., Радюк Л. П.* Коррекция метаболических нарушений при вторичном ацетонемическом синдроме в условиях острой респираторной вирусной инфекции у детей. *Здоровье ребенка.* 2018; 13 (8): 736–742. *Stoeva T. V., Titkova E. V., Sytnik V. V., Kartashov V. A., Sinenko V. V., Radyuk L. P.* Correction of metabolic disorders in secondary acetonemic syndrome in children with acute respiratory infection. *Child's Health = Zdorovie Rebenka.* 2018; 13 (8): 736–742. (In Russ).

Received 22.01.2024
Accepted 16.08.2024

https://doi.org/10.15360/1813-9779-2024-5-31-36

Pancreatic Ultrasound in High-risk Neonates

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For citation: *Safaa A. ELMeneza, Naglaa F. Hassan, Aisha R. Mohamed.* Pancreatic Ultrasound in High-risk Neonates. *Obshchaya Reanimatologiya = General Reanimatology.* 2024; 20 (5): 31–36. https://doi.org/10.15360/1813-9779-2024-5-31-36 [In Engl.]

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Summary

Pancreatic ultrasound is employed to assess the structure of the organ and diagnose various conditions. However, analyses of pancreatic images of high-risk newborn infants are scarce.

Aim of the study: to investigate pancreatic echogenicity in high-risk neonates and evaluate the association between pancreatic echogenicity and clinical diagnosis.

Materials and methods. This prospective observational case-control ultrasound study included 105 neonates admitted to the neonatal intensive care unit or outpatient. The patients were divided into two groups: group 1 (high-risk), which included 55 high-risk neonates, and group 2 (control), which included 50 neonates of comparable age with no history of high-risk pregnancy or delivery who were presented for medical consultation. Abdominal ultrasound examinations were performed, with a focus on the pancreas. Pancreatic echogenicity was classified as hyperechoic, isoechoic, or hypoechoic, relative to the liver.

Results. No significant difference in pancreatic size was observed between the high-risk and control groups. A significant predominance of hyperechogenicity over hypoechogenicity or isoechogenicity was found in the high-risk group. A significant difference in echogenicity was found between the high-risk and control groups (P=0.0001). Neonates in the control group were more likely to have pancreatic isoechogenicity (60%) compared to hyperechogenicity (34%) or hypoechogenicity (6%). In the high-risk group, neonates had a higher frequency of pancreatic hyperechogenicity (72.72%) compared to hypoechogenicity (10.9%) or isoechogenicity (16.36%). Notably, 83.3% of infants born to diabetic mothers had a hypoechogenic pattern. Certain high-risk infants, such as preterm infants and those with perinatal asphyxia, had a higher frequency of hyperechogenicity (83.3%). The percentage of hypoechoic pattern was comparable in male and female newborns (50%); isoechoic pattern was more prevalent in females (77.3%) than in males (22.2%), while males had a more frequent hyperechoic pattern (57.5%).

Conclusion. Evaluation of the pancreas in high-risk neonates and monitoring of long-term outcomes are of critical importance, especially in the infants of diabetic mothers.

Keywords: high-risk neonates; pancreas; ultrasound; hyperechogenicity; isoechogenicity; hypoechogenicity; neonates

Conflict of interest. The authors declare no conflict of interest.

Financial support. This study did not receive financial support.

Acknowledgments. We thank the parents of the neonates for their cooperation in this study.

Introduction

The pancreas, an organ located in the abdomen, performs both endocrine and exocrine functions. It produces hormones that regulate blood glucose levels and secretes fluids containing bicarbonate and enzymes for digestion. While pancreatic disorders are difficult to detect using imaging techniques, ultrasound can detect a variety of conditions including pancreatitis, pancreatic insufficiency, cystic formations, and pancreatic tumors [1]. Pancreatic insufficiency is a condition in which the pancreas does not produce enough digestive enzymes to break down food in the digestive system [2].

Although challenging, imaging of the pancreas can provide valuable information about morbidity and mortality. Ultrasound is particularly useful for examining the pancreas in children because it is non-invasive, does not require sedation, and does not expose children to ionizing radiation. The effectiveness of ultrasound in evaluating the pediatric pancreas is well documented, with children having an optimal acoustic window due to their minimal adipose tissue and large left hepatic lobe [3].

The pancreas can be affected by a variety of diseases, both focal and diffuse.

Transabdominal ultrasound can detect acute pancreatitis, congenital anomalies, cysts, and tumors. However, assessing the pancreatic images may be limited because of the variation of pancreatic area in echogenicity and size. Although the ultrasound investigation provides a rapid, noninvasive, and safe method of examining multiple organs in the NICU, the knowledge of the neonatal pancreas remains limited. Studies on the echogenicity of the neonatal pancreas are still limited. While the echogenicity of a normal adult pancreas increases with age [4], it may appear isoechoic or hypoechoic in children [3]. A marked increase in echogenicity in children may indicate conditions such as cystic fibrosis [5]. High-risk infants, including those born

prematurely or with health problems at birth, have an increased risk of morbidity and mortality regardless of gestational age or birth weight. These newborns are vulnerable to both immediate and long-term health and developmental problems. Although high-risk neonates may present with varying degrees of pancreatic disease, few studies have focused on pancreatic imaging in NICU patients. Understanding the diverse pancreatic imaging patterns in high-risk neonates may facilitate early detection of a pancreatic pathologic pattern(s) and personalize treatment to improve outcomes.

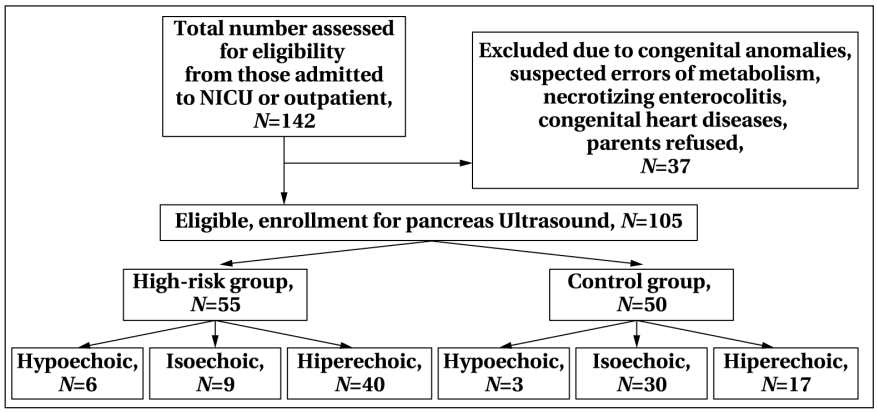

Fig. Study flow diagram.

The aim of the study was to investigate pancreatic echogenicity in high-risk neonates and evaluate the association between pancreatic echogenicity and clinical diagnosis in high-risk neonates.

Material and Methods

The study was conducted at AL Zhrraa University Hospital. It was an observational case-control study. The study was approved by the Ethics Committee of the Faculty of Medicine for Girls (registration number RHDIRB 2018122002 and OHHP Reg.No. IRB00012239 / study number 2461).

Informed consent statement. Informed consent was obtained from the parents of the neonates enrolled in the study.

The study period was from November 2023 to June 2024. We hypothesized that neonates and high-risk neonates have specific patterns of pancreatic echogenicity and that high-risk neonates may have a different pattern than other normal neonates that can be detected by US examination. The power was set at 0.8 (80%) to avoid false-negative results, with 80% representing a reasonable balance between alpha and beta risk.

Sample size was estimated using the equation:

$$n = \frac{z^2 \times \hat{p}(1-\hat{p})}{\varepsilon^2}$$

A minimum sample size of 101 patients was required to achieve a 95% confidence level. The study prospectively enrolled 105 patients, including neonates admitted to the NICU and controls brought in for consultation. Participants were divided into two groups: Group 1 (high-risk) with 55 neonates and Group 2 (control) with 50 neonates. The high-risk group included preterm infants, infants of diabetic mothers (IDM), and those with perinatal asphyxia (PA), jaundice, meconium aspiration (MA), sepsis, intrauterine growth retardation (IUGR), and neonates from post-date pregnancies. To ensure optimal abdominal visualization, infants with major congenital anomalies, liver disease, and necrotizing enterocolitis were excluded [6]. The control group consisted of normal neonates of comparable age with no history of high-risk pregnancy or delivery who were presented for medical consultation. The patient selection process is illustrated in a flow chart (Figure).

In addition, laboratory tests were performed for blood gases, electrolytes, blood glucose, complete blood count, and C-reactive protein (CRP).

Pancreatic ultrasound examinations were performed using a SIEMENS Sonoline Elegra unit with a 3.5 curvilinear transducer. Patients were positioned in the supine position with the option to move to either side for improved visualization. The echogenicity of the pancreas was assessed in relation to the liver, which served as a reference point [7–8]. Pancreatic images were categorized as hyperechoic, isoechoic, or hypoechoic compared to the liver at a similar depth. The examining radiologist was blinded to the clinical diagnoses of the patients.

Data analysis. The collected data were coded and processed. All analyses were performed with IBM SPSS version 25.

Qualitative variables were presented as numbers and percentages, while quantitative variables were expressed as means with standard deviations *(SD)*.

The data exhibited a normal distribution, allowing the use of Student's *t*-test to compare group means. Chi-squared test was used to determine statistical significance between categorical variables.

A *P* value of less than 0.05 was considered statistically significant. The study used a 95% confidence interval and accepted a 5% margin of error. Therefore, two-tailed *P* values of 0.05 or less were considered statistically significant.

Results

The results are presented in Tables 1–6.

Demographic and clinical features of the groups. While no significant differences were observed between high-risk and control infants with respect to gestational age, sex, body length, head circumference, and mode of delivery, significant differences were found in birth weight, postnatal age, and Apgar scores at 1 and 5 minutes in high-risk infants.

Table 1. The characteristics of the studied groups.

Parameters	Values in groups		*P*-value
	High-risk, *N*=55	Control, *N*=50	
Gestational age, weeks	38.15±3.05 30–44	38.5±1.5 37–41	t=0.734*, *P*=0.46
Birth weight, kg	3.07±0.61 1.800–4.300	3.34±0.18 3.100–3.500	3.012*, *P*=0.003
Gender, male/female	28/27	30/20	χ^2=0.8671, *P*=0.35
Postnatal age, day	5.89±3.02 3–11	7.9±3.73 3–5	t=3.047*, *P*=0.0029
Body length, cm	48.82±1.44	49.1±0.88	1.188*, *P*=0.237
Head circumference, cm	34.33±0.68	34.5±0.47	t=1.476*, *P*=0.143
Mode of delivery			
Normal vaginal	39	28	t=2.4970, *P*=0.114
Cesarean section	16	22	
Apgar score at 1 min	4.8±2.03	7.9±1.34	9.137*, *P*=0.0001
Apgar score at 5 min	6.49±1.95	8.5±1.35	t=6.082*, *P*=0.0001

Note. * — *t*-Student *t*-test; χ^2 — chi-square test.

The corresponding *P* values were 0.003, 0.0029, 0.0001, and 0.0001 (Table 1).

Table 2 shows the clinical diagnoses and their frequencies among the patients. In the high-risk group, each of the following conditions accounted for 10.9% of cases: preterm birth, infants born to diabetic mothers, perinatal asphyxia, meconium aspiration, sepsis, intrauterine growth retardation, and post-term pregnancy. In addition, jaundice was observed in 12.72% of the high-risk infants (Table 2).

Table 2. Diagnoses of high-risk newborns and their frequency.

Diagnoses	Values, *N* (%)
Hyperbilirubinemia	7 (12.72)
Infant of diabetic mother	6 (10.9)
Perinatal asphyxia	6 (10.9)
Meconium aspiration	6 (10.9)
Premature rupture of membranes	6 (10.9)
Sepsis	6 (10.9)
Prematurity	6 (10.9)
Intrauterine growth retardation	6 (10.9)
Postdate pregnancy	6 (10.9)

Laboratory findings. The high-risk group had significant decreases in hemoglobin, RBCs, platelets, and blood glucose (*P*=0.0001, 0.0001, 0.023, and 0.0001, respectively). In contrast, the control group showed significant increases in WBCs and bilirubin (*P*=0.039 and 0.0001, respectively) (Table 3).

Ultrasonographic evaluation of the pancreas. Ultrasonography revealed that the pancreas of the studied neonates had well-demarcated borders and consistent echogenicity. Pancreatic dimensions did not differ significantly between the high-risk and control groups (Table 4).

In the control group, isoechogenicity was observed in 60% of patients, while hyperechogenicity and hypoechogenicity were observed in 34% and 6%, respectively. Conversely, high-risk infants had a higher proportion of hyperechogenicity (72.72%), followed by isoechogenicity (16.36%) and hypoechogenicity (10.9%). The high-risk group showed a significant prevalence of hyperechogenicity compared to the other patterns. Post hoc power analysis for dichotomous data (alpha=0.05) in high-risk infants showed 100% power for hyperechogenicity versus isoechogenicity and hypoechogenicity. However, a low power of 12.9% was observed between hypoechoic and isoechoic patterns.

A significant difference in echogenicity was found between the high-risk and control groups (*P*=0.0001). The control group showed predominantly isoechogenicity compared to hyper- and hypoechogenicity. Post hoc power analysis for dichotomous

Table 3. Laboratory findings in the studied groups.

Parameters	Values in groups		*P*-value
	High-risk, *N*=55	Control, *N*=50	
Hemoglobin, g/dL	14.74±1.5	16.8±1.9	t=6.194, *P*=0.0001
RBC, 10^6/mm^3	4.39±0.85	5.01±0.04	t=5.150, *P*=0.0001
WBC, 10^6/mm^3	14.32±6.27	12.42±1.46	t=-2.091, *P*=0.039
Platelets, 10^3/μL	192.93±85.71	225.8±56.23	t=2.299, *P*=0.023
Blood glucose, mg/dL	56.89±9.75	67.3±4.08	t=7.010, *P*=0.0001
Serum bilirubin, mg/dL	6.03±4.56	1.69±0.096	t=-6.726, *P*=0.0001

Note. t — Student's *t*-test.

Table 4. Comparison of pancreatic dimensions between the control and high-risk groups.

Parameters	Values in groups		*P*-value
	High-risk, *N*=55	Control, *N*=50	
Head, cm	1.1±0.4	0.94±0.4	t=1.28, *P*=0.2
Body, cm	0.6±0.04	0.6±0.15	t=0.00, *P*=1.00
Tail, cm	0.97±0.14	1 ±0.14	t=–1.09, *P*=0.27

Note. t — Student's *t*-test.

Table 5. The echogenicity of pancreas in the studied groups.

Groups	Values in groups, *N* (%)			*P*-value
	Hypoechoic	Isoechoic	Hyperechoic	
High-risk:				
Hyperbilirubinemia	1 (14.3)	1 (14.3)	5 (71.4)	χ^2= 38.06, *P*=0.0001
Infants of diabetic mother	5 (83.3)	0 (0)	1 (16.7)	
Perinatal asphyxia	0 (0)	1 (16.7)	5 (83.3)	
Meconium aspiration	0 (0)	2 (33.3)	4 (66.7)	
Premature rupture of membranes	0 (0)	0 (0)	6 (100)	
Sepsis	0 (0)	2 (33.3)	4 (66.7)	
Prematurity	0 (0)	1 (16.7)	5 (83.3)	
Intrauterine growth retardation	0 (0)	0 (0)	6 (100)	
Post-date pregnancy	0 (0)	2 (33.3)	4 (66.7)	
Total	6 (10.9)	9 (16.36)	40 (72.72)	
Control	3 (6)	30 (60)	17 (34)	χ^2 =20.9818, *P*=0.0001
High risk — Control	χ^2= 21.3988			*P*=0.0001

data (alpha=0.05) in the control group showed a 100% probability for isoechogenicity versus hypoechogenicity and hypo- and hyperechogenicity combined. In addition, there was a 96.8% probability for isoechogenicity versus hyperechogenicity.

However, the hypoechoic pattern was prevalent (83.3%) in infants born to diabetic mothers. Certain high-risk infants, including those born prematurely or with perinatal asphyxia, had a higher frequency of hypoechoic patterns (83.3%) (Table 5).

The occurrence of hypoechoic patterns was equally distributed between male and female newborns (50%). Isoechoic patterns were more common in females (77.3%) than in males (22.2%), whereas hyperechoic patterns were more common in males (57.5%) than in females (42.5%) (Table 6).

Table 6. The echogenicity of the pancreas concerning sex in the high-risk group.

Sex	Values, *N* (%)		
	Hypoechoic	Isoechoic	Hyperechoic
Male	3 (50)	2 (22.2)	23 (57.5)
Female	3 (50)	7 (77.3)	17 (42.5)
Total	6 (100)	9 (100)	40 (100)

Discussion

Ultrasound examination of the pancreas has proven valuable in both adults and children. The pancreas develops around the fifth week of pregnancy, arising from the endodermal lining of the duodenum as separate ventral and dorsal buds. As a result, this organ is susceptible to several intrauterine risk factors, including infection, blood glucose fluctuations, and oxygen deprivation. Limited research has focused on the pancreas during the neonatal period, with no studies specifically examining high-risk neonates, except for a 1990 investigation of premature infants [9]. Our study aimed to characterize the sonographic features of the pancreas in high-risk neonates admitted to the NICU.

The study found no significant differences in pancreatic dimensions in the head, body, and tail regions between the high-risk and control groups. These findings are consistent with previous research in healthy neonates [10–11], although D. S. Raut et al. [12] reported lower values.

The study revealed a marked prevalence of pancreatic hyperechogenicity in the high-risk neonatal group, whereas isoechogenicity predominated in the control neonatal group. Pancreatic echogenicity was assessed using the liver as a reference point.

In the high-risk group, 72.72% of patients had hyperechogenic pancreas, 16.36% had isoechogenic pancreas, and 10.9% had hypoechogenic pancreas. In the control group, 34% of neonates had hyperechogenic pancreas, 60% had isoechogenic pancreas, and 6% had hypoechogenic pancreas. A previous study found that 60% of healthy newborns had a hyperechogenic pancreas [9], while another study of newborns, infants, and children up to 19 years of age revealed low echogenicity in 10%, isoechoic pancreas in 53%, and high echogenicity in 37% [10]. Typically, the pancreas in neonates and infants is described as slightly more echogenic than the liver. However, one study contradicted this and reported that the neonatal pancreas was relatively hypoechoic [11].The echogenicity and tissue reflectivity of the pancreas may be influenced by the interaction of external and internal factors. Increased pancreatic echogenicity is attributed to the amount of intra- and peripancreatic fat, connective tissue septa between lobules, and reticular tissue [13]. In addition, the densely packed cellular elements in the pancreas of newborns and infants contribute to increased echogenicity, as it occurs in the kidneys [14]. In older children and adults, increased echogenicity may result from fibrosis, lipomatosis, hemosiderosis, medications, congestive changes, fatty infiltration, and calcification [11].

Hyperechogenicity may not necessarily indicate disease, especially in preterm infants. A study by E. Walsh showed that pancreatic hyperechogenicity changes to an isoechoic pattern with age [9]. In this study, analysis of echogenicity in various high-risk infants showed that preterm infants, neonates with perinatal asphyxia or delivered after premature rup-

ture of membranes, and infants with IUGR had a predominance of hyperechoic pancreatic parenchyma. This may be due to exposure to risk factors during the intrauterine and perinatal period that could affect blood flow and tissue perfusion or cause energy depletion and oxidative stress that alter organ structure and metabolism. Pancreatic echogenicity in children is related to the volume of parenchymal tissue [15].

Preterm infants have relatively small amounts of subcutaneous tissue and intra-abdominal fat, which facilitates the examination of abdominal organs. The pancreas was hyperechoic in 83.3% of preterm infants and isoechoic in 17.7%, which is comparable to the data of E. Walsh et al. who reported that normal pancreatic parenchyma in preterm and term infants is hyperechoic with respect to the liver [9]. This appearance is related to prominent septa within the lobules, large amounts of glandular tissue, and supportive reticular tissue within the lobules. The shift from predominantly hyperechoic patterns in preterm infants to isoechoic patterns in term infants observed in our study may be explained by near-term changes, including a reduction in these tissues and the development of a more obvious lobular structure with tightly packed glandular components [16]. Follow-up ultrasound of premature infants and neonates showed isoechoic transformation of the pancreas in some premature infants who initially had hyperechogenicity. The study concluded that hyperechogenicity relative to the liver is common in premature infants and neonates [9].

The present study also identified a high occurrence of hypoechoic patterns in infants born to diabetic mothers, observed in 83.3% of IDM cases. While the reason for this predominant hypoechogenicity in these infants remains unclear, it may be attributed to intrauterine metabolic changes causing various structural alterations, and diabetic fetopathy, which is closely linked to the intensity and the time of onset of maternal hyperglycemia. According to J. Pedersen's hypothesis, elevated maternal blood glucose results in fetal hyperglycemia, leading to beta cell hypertrophy and subsequent hyperinsulinemia [17]. An alternative explanation suggests that compromised placental blood flow affects fetal and pancreatic development, potentially resulting in long-term health issues such as diabetes mellitus, hypertension, or cardiovascular disease, as proposed by Barker et al [18].

Recent studies on fetal liver have demonstrated that venous circulation reflects the impact of maternal hyperglycemia. The umbilical return from the placenta is disproportionately directed to the fetal liver (exceeding that of normal fetuses). The fetal liver is solely responsible for initial fetal fat accumulation, regulated by the volume of umbilical liver perfusion [19–20]. Hepatic fat deposition causes the liver to appear hyperechoic in comparison to the pancreas. Additional factors contributing to a hypoechoic pancreas include edema, fluid accumulation, and exposure to intravenous fluids.

Ultrasound imaging provides a simple and safe method of examining abdominal organs in neonates, allowing measurement of the dimensions of the liver, pancreas, and spleen [21]. While research on the neonatal pancreas is limited, our investigation provides important insight into pancreatic disease in high-risk infants in the NICU. Study limitations include the impact of multiple risk factors and the lack of follow-up of the patients studied. Further research is needed that focuses on individual risk factors and includes follow-up assessments.

Conclusion

High-risk neonates have a predominantly hyperechoic pattern of the pancreas, whereas normal neonates have an isoechoic pancreas. There was no significant difference in pancreas size between the normal and high-risk neonates. Preterm infants, as well as those with perinatal asphyxia, premature rupture of membranes, and intrauterine growth retardation, presented with pancreatic hyperechogenicity, whereas infants of mothers with diabetes presented with pancreatic hypoechogenicity. It is important to evaluate the pancreas in high-risk neonates and monitor long-term outcomes, especially in the infants of diabetic mothers.

References

1. *Low G., Panu A., Millo N., Leen E.* Multimodality imaging of neoplastic and nonneoplastic solid lesions of the pancreas. *Radiographics*. 2011; 31 (4): 993–1015. DOI: 10.1148/rg.314105731. PMID: 21768235.
2. *Mehta V., Hopson P. E., Smadi Y., Patel S. B., Horvath K., Mehta D. I.* Development of the human pancreas and its exocrine function. *Front Pediatr*. 2022; 10: 909648. DOI: 10.3389/fped.2022.909648. PMID: 36245741.
3. *Di Serafino M., Vitale V., Severino R., Barbuto L., Vezzali N., Ferro F., Rossi E., et al.* Pediatric ultrasonography of the pancreas: normal and abnormal findings. *J Ultrasound*. 2019; 22 (3): 261–272. DOI: 10.1007/s40477-018-0348-8. PMID: 30552664.
4. *Möller K., Jenssen C., Braden B., Hocke M., Hollerbach S., Ignee A., Faiss S., et al.* Pancreatic changes with lifestyle and age: What is normal and what is concerning? *Endosc Ultrasound*. 2023; 12 (2): 213–227. DOI: 10.4103/EUS-D-22-00162. PMID: 37148135.
5. *Engjom T., Kavaliauskiene G., Tjora E., Erchinger F., Wathle G. Lærum B. N., Njølstad P. R., et al.* Sonographic pancreas echogenicity in cystic fibrosis compared to exocrine pancreatic function and pancreas fat content at Dixon-MRI. *PLoS One*. 2018; 13 (7): e0201019. DOI: 10.1371/journal.pone.0201019. PMID: 30048483.
6. *ELMeneza S. A., Arafat N. M., El-Bagouri I. M., Gaber A.* Inter-alpha inhibitory proteins as a predictor of necrotizing enterocolitis in newborns. *General Reanimatology = Obshchaya Reanimatologiya*. 2023; 19 (2): 33–39. (in Eng.&Russ.). DOI: 10.15360/1813-9779-2023-2-2304.
7. *Oh H., Park H. J., Oh J., Lee E. S., Park S. B., Cha M. J., Ahn S.* Hyperechoic pancreas on ultrasonography: an analysis of its severity and clinical implications. *Ultrasonography*. 2022; 41 (2): 335–343. DOI: 10.14366/usg.21099. PMID: 34743485.
8. *Trout A. T. Patel R., Nathan J. D., Lin T. K., Vitale D. S., Nasr A., Zhang B., et al.* Ultrasound findings of acute pancreatitis in children. *Pediatr Radiol*. 2022; 52 (12): 2342–2347. DOI: 10.1007/s00247-022-05381-z. PMID: 35554642.
9. *Walsh E., Cramer B., Pushpanathan C.* Pancreatic echogenicity in premature and newborn infants. *Pediatr Radiol*. 1990; 20: 323–325. DOI: 10.1007/BF02013164.
10. *Robben S., Rijn R. V., Smithuis R.* Normal values in pediatric ultrasound. *Radiology assistant*. Radiology Department of the Maastricht University Hospital, Academical Medical Centre in Amsterdam and the Alrijne Hospital in Leiderdorp, the Netherlands. Publication date 2018-02-09. Available at: https: //radiologyassistant.nl/pediatrics/normal-values/normal-values-ultrasound#pancreas.
11. *Riccabona M.* Spleen and pancreas in pediatric US. In: Pediatrics Ultrasound Requisites and Applications: Springer Heidelberg New York Dordrecht London. (eds); 2014: 257–288. ISBN 978-3-642-39155-2 ISBN 978-3-642-39156-9 (eBook). DOI 10.1007/978-3-642-39156-9.
12. *Raut D. S., Raje D. V., Dandge V. P., Singh D.* Percentile reference curves for normal pancreatic dimensions in Indian children. *Indian J Radiol Imaging*. 2018; 28 (4): 442–447. DOI: 10.4103/ijri.IJRI_189_18. PMID: 30662207.
13. *Raut D. S., Desai S. A., Raje D. V., Singh D., Dandge V. P.* Enlargement of the pancreas in children diagnosed with acute pancreatitis: an approach based on P/V ratio. *Indian J Radiol Imaging*. 2022; 32 (4): 488–496. DOI: 10.1055/s-0042-1754368. PMID: 36451952.
14. *Hricak H., Slovis T. L., Callen C. W., Callen P. W., Romanski R. N.* Neonatal kidneys: sonographic anatomic correlation. *Radiology*. 1983; 147 (3): 699–702. DOI: 10.1148/radiology.147.3.6844606. PMID: 6844606.
15. *Hryhorczuk A. L., Paltiel H. J.* Pancreas, adrenal glands, and retroperitoneum. In: *Paltiel H. J., Lee, E. Y.* (eds) Pediatric Ultrasound. Springer, Cham. 2021: 563–628. Print ISBN 978-3-030-56801-6. Online ISBN 978-3-030-56802-3. DOI: 10.1007/978-3-030-56802-3_14.
16. *Valdeìs-Dapena Marie A.* Histology of the fetus and newborn. Saunders, Philadelphia (eds); 1979: 270.ISBN: 0721689485, 9780721689487. http: //pi.lib.uchicago.edu/1001/cat/bib/329439.
17. *Pedersen J.* Weight and length at birth of infants of diabetic mothers. *Acta Endocrinol*. (Copenh). 1954; 16 (4): 330–342. DOI: 10.1530/acta.0.0160330. PMID: 13206643.
18. *Barker D. J., Hales C. N., Fall C. H., Osmond C., Phipps K., Clark P. M.* Type 2 (non-insulin-dependent) diabetes mellitus, hypertension and hyperlipidaemia (syndrome X): relation to reduced fetal growth. *Diabetologia*. 1993; 36 (1): 62–67. DOI: 10.1007/BF00399095. PMID: 8436255.
19. *Kiserud T.* Diabetes mellitus impact on fetal liver circulation, and new diagnostic options. *Revista Médica Clínica Las Condes*. 2023; 34 (1) 8–17. DOI: 10.1016/j.rmclc.2023.01.003.
20. *Al Salam H., Jones J., Bell D., et al.* Generalized increase in hepatic echogenicity. Reference article; Radiopaedia.org (Accessed on 29 July 2024). DOI: 10.53347/rID-12509. https: //radiopaedia.org/ articles/12509.
21. *Perepelitsa S. A., Alekseeva S. V., Vozgoment O.V.* Early ultrasound signs of splenomegaly in neonates. *General Reanimatology = Obshchaya Reanimatologiya*. 2019; 15 (4): 58–66. (in Russ.&Eng.). DOI: 10.15360/1813-9779-2019-4-58-66.

Received 30.07.2024
Accepted 27.08.2024

https://doi.org/10.15360/1813-9779-2024-5-37-43

Ultrasound-Based Cardiac Output Monitoring During Pediatric Open-Heart Surgery

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For citation: *Nikolay A. Soloviev, Mikhail M. Rybka, Jumber Ya. Khinchagov, Sofya M. Tsoi, Gleb E. Gorbunov, Denis A. Dibin, Zera A. Kodzokova, Madina Yu. Chomaeva.* Ultrasound-Based Cardiac Output Monitoring During Pediatric Open-Heart Surgery. *Obshchaya Reanimatologiya = General Reanimatology.* 2024; 20 (5): 37–43. https://doi.org/10.15360/1813-9779-2024-5-37-43 [In Russ. and Engl.]

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Summary

Aim of the study. To evaluate the feasibility of using non-invasive hemodynamic monitoring technology based on Doppler ultrasound during open-heart surgery in children.

Material and methods. Prospective, observational, single-center cohort study included 20 patients aged 10 to 34 months undergoing surgery for congenital heart defects. Ten patients underwent atrial septal defect closure (ASD group), other 10 patients had ventricular septal defect closure (VSD group). Cardiac output (CO) was measured in all patients to guide inotropic and infusion therapy adjustments at three control time points: (1) after intubation and before skin incision, (2) during the immediate post-bypass period with the chest open after weaning from cardiopulmonary bypass (CPB), and (3) after sternal closure and before transfer to the intensive care unit (ICU).

Results. At time point 1, the CO values for both the ASD and VSD groups were within the normal reference range: 5.2 L/min [4.7; 5.5] and 5.1 L/min [4.6; 5.6], respectively. At time point 2, CO was measured in 15 of 20 patients, including 8 patients in the ASD group and 7 in the VSD group. Coverage was 75% because of the challenges of measuring 5 patients on the operating table. In the immediate post-bypass period, two patients with VSD (25%) developed hypotension with CO reduced to 3.6 L/min, which is lower than the age-related hemodynamic reference value (5.1 L/min). Inotropic support in these two patients was increased by switching from dopamine, 7 mcg/kg/min, to adrenaline at a dose of 0.05 mcg/kg/min, resulting in improvement of hemodynamic parameters and an increase in CO to 5.2 L/min and 5.0 L/min, respectively, compared to normal age-related reference values (4.1; 6.1 L/min). After sternal closure, CO values in both groups did not differ significantly from age-related reference values.

Conclusion. The USCOM cardiac output monitoring device can be used to manage intraoperative hemodynamics and adjust inotropic therapy even during open chest surgery. However, its routine use in all stages of surgery with median sternotomy is difficult because it requires more time to align the aortic valve projection.

Keywords: pediatric cardiac surgery; open heart surgery in children; hemodynamic monitoring; intensive care; fluid therapy; USCOM device

Conflict of interest. The authors declare no conflict of interest.

Introduction

During cardiac surgery, hemodynamics are directly dependent on fluid and inotropic support [1]. In this case, a reliable method to determine the need for volume loading is required. The use of invasive techniques to determine cardiac output (CO) (prepulmonary and transpulmonary thermodilution) in children with congenital heart disease (CHD) is limited due to the complexity of the circulatory system (the presence of intracardiac shunts). Several researchers confirm that the difference between invasive techniques and echocardiography can be as much as 30% [2].

At the A. N. Bakulev National Medical Research Center for Cardiovascular Surgery, ultrasound examination methods, especially transesophageal echocardiography, are performed by a qualified ultrasound specialist, including during surgery.

An Austrian pharmacologist Adolf Jarisch (1891–1965) once expressed a view that is still relevant today: «It is a source of regret that measurement of flow is much more difficult than measurement of pressure. This has led to an undue interest in blood pressure measurements. Most organs, however, require flow rather than pressure».

Currently, the diagnostic value of central venous pressure (CVP) measurement is declining [3]. It should be noted that CVP depends on intravascular volume, total peripheral vascular resistance (TPVR), right ventricular compliance, total pulmonary vascular resistance (TPulmVR), and intrathoracic pressure. CVP may also be elevated in hypovolemia

due to right ventricular failure, pulmonary embolism, cardiac tamponade, tension pneumothorax, and hypervolemia [4]. Therefore, its values depend on multiple factors and cannot serve as a «gold standard» for the assessment of volemia [5]. In cardiothoracic surgery after sternotomy, there is an opportunity to visually assess ventricular filling and contractility.

Currently, many tests and indices have been developed to determine the relationship between cardiac output and preload and to predict response to fluid therapy [6, 7]. All of these tests are reliable only under strict conditions that limit their use in different clinical situations [8]. Non-invasive methods of hemodynamic monitoring are usually more accessible and reduce the number of potentially dangerous invasive procedures [9,10]. However, for monitoring blood pressure in cardiac surgery, it is more appropriate to use an invasive method that does not «mask» hypotension. A left atrial catheter can be used for intraoperative measurement of left heart pressure without the use of a Swan–Ganz catheter. In young children, the use of single-channel 18–22 G catheters placed intraoperatively into the left atrium via an interatrial communication (IAC) is preferred. This is an invasive procedure that in some cases requires creation of a fenestration in the interatrial septum and is therefore used in radical repair of severe congenital heart disease (CHD), such as persistent common atrioventricular canal (PCAC). The use of such a procedure is inappropriate in radical surgery for septal malformations [11,12]. During open-heart surgery, continuous measurement of CVD is performed and direct measurement of left atrial (LA) pressure is used. With the direct method, it is possible to measure pressures in all chambers and major vessels of the heart. This technique can also be used in patients with severe pulmonary hypertension diagnosed by echocardiography without aortocoronary angiography.

Ultrasound can be used to diagnose left or right ventricular failure. However, we found no studies on the applicability and reliability of USCOM measurements in the right ventricular region. USCOM measures the velocity of blood flow through the aortic and pulmonary valves. Using predetermined internal algorithms based on patient height data, it calculates the diameters of the aortic and pulmonary valves and their cross-sectional areas. Based on the valve cross-sectional area and the measured blood flow velocity, the USCOM device determines the volume of blood pumped by the heart in one minute [13]. N. Patel et al. found that the reliability of USCOM derived values in neonates is quite high [14]. A.U. Lekmanov et al. concluded that the parameters of central hemodynamics in children with severe burn injuries obtained by invasive and non-invasive methods were comparable [15]. Boronina I. V. et al. reported that bedside training under instructor supervision is sufficient to learn practical skills in USCOM monitoring, with an average of 50 independent studies required to master the technique [16]. The statistical significance of data obtained using the USCOM technique in children compared to older age groups may be attributed to the lower incidence or absence of obesity, increased sternal thickness, aortic calcification associated with luminal narrowing and thickening of the arterial wall, and age-related vascular changes that affect signal quality and, consequently, the statistical significance of the results obtained [17].

In 2019, a meta-analysis by Yun Zhang [18] analyzed 26 scientific articles involving 772 patients. This meta-analysis found no significant difference between cardiac output (CO) and cardiac index (CI) measurements using the USCOM device and transpulmonary thermodilution: the mean difference in CO values was –0.06 [95% CI, –0.17 to 0.05; P=0.31], and the mean difference in CI values was –0.04 [95% CI, –0.13 to 0.05; P=0.38].

In 2018, Yu-wei Cheng [19] included 60 children in her study and measured parameters after cardiac surgery for CHD.

The parameters (HR, CVP, stroke volume index, cardiac index, stroke volume change) reflecting left ventricular preload obtained by hemodynamic testing using PiCCO catheter, TE echocardiography, and USCOM were compared. The results showed that volume load sensitivity best reflected stroke volume change, with noninvasive hemodynamic monitoring showing a sensitivity of 84.4% and a specificity of 60.7%. This suggests that the USCOM can reliably predict the response to ongoing fluid therapy in children after correction of CHD, making the device essential for the selection of individualized fluid therapy. There are no studies on the intraoperative use of the USCOM device in cardiac surgery. Intraoperative TE echocardiography is highly informative but requires more time than direct measurements. Intraoperative measurement of basic hemodynamic parameters using the USCOM device is likely to aid in the assessment for the correct choice of cardiac support and fluid therapy.

The aim of the study was to evaluate the feasibility of a non-invasive hemodynamic monitoring technique based on ultrasound Doppler evaluation during open heart surgery in children.

Materials and methods

A single-center, prospective, randomized study was conducted with the approval of the local ethics committee of the Bakulev National Medical Center of Cardiovascular Surgery (protocol No. 002 dated April 28, 2022). The study was not pre-registered on the Clinical Trials platform.

Inclusion criteria:

— children 11 months to 3 years of age;

— informed consent from parents or legal guardians to participate in the study;

— septal heart defect requiring surgical correction under cardiopulmonary bypass via midline access;

— no history of previous open heart surgery.

Exclusion criteria:

— severe genetic abnormality;

— massive blood loss;

— severe comorbidities;

— repeated sternotomy in the early postoperative period.

Of the 41 young children with CHD who underwent surgery between March and April 2022, 20 patients were included in the study. Of these, 10 patients underwent correction of the atrial septal defect (ASD group) and 10 patients underwent correction of the ventricular septal defect (VSD group). No complications were observed in the early postoperative period. All children were extubated on postoperative day 1. All patients were transferred from the ICU to the specialized departments the next day. The structure of all surgical procedures is shown in Table 1 and the study flow chart is shown in Fig. 1.

Patients with septal malformations were selected for the study as the most hemodynamically stable patients requiring the shortest duration of cardiopulmonary bypass (CPB).

All patients were evaluated three times intraoperatively with the USCOM device, and the mean value was used for analysis. Three control time points were selected: when the patient was admitted to the operating room, at the end of cardiopulmonary bypass, and before transfer to the ICU. At the first time point, measurements were taken after tracheal intubation and before skin incision while in deep sedation (RASS, 5 points). At the second time point, measurements were taken with the sternum open, after the end of CPB. At this stage, it was not possible to perform measurements in five patients due to the peculiarities of their positioning on the operating table (Fig. 1). At the third time point, measurements were performed before transfer to the ICU.

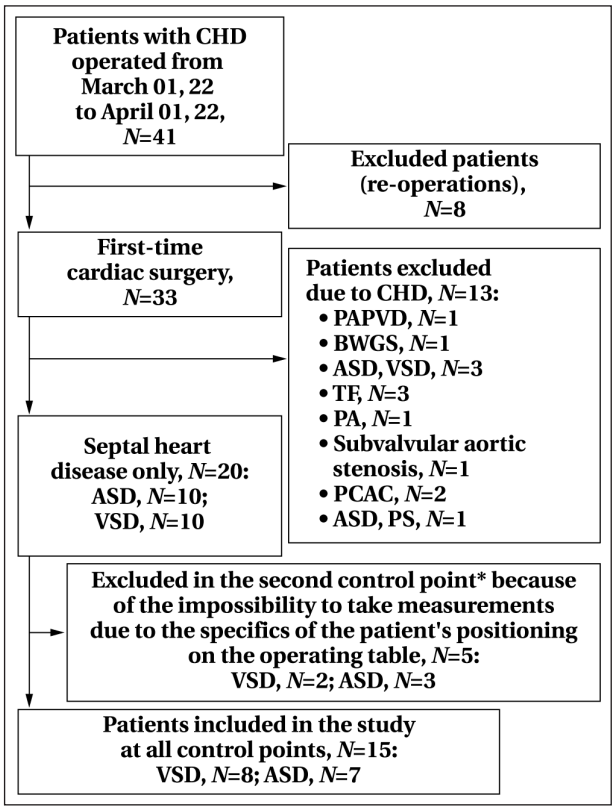

Fig. 1. Flowchart of patient inclusion in the study.
Note. * — control points are detailed in the text.

Patients in both groups were classified as ASA risk group 3 or 4 and NYHA class I–II. The groups were comparable in terms of the duration of CPB, the duration of aortic clamping, the complexity of the surgical procedure, and the time to cardiac recovery in the postperfusion period. A brief description of patient characteristics is presented in Table 2.

SPSS version 11.5 for Windows (SPSS Inc., Chicago, IL) and the analytical add-on for Excel 2016 were used for data analysis. The sample size was not predetermined.

Data distribution was checked using the Shapiro–Wilk test. For normally distributed data, the arithmetic mean *(M)* and the standard error of the mean *(m)* were calculated, and the statistical significance of the differences between the means

Table 1. Surgical interventions in the patient population, *N*=41.

Intervention	Cases, *N*
VSD repair	10
ASD repair	10
Repeated open-heart surgery	8
Simultaneous repair of atrial and ventricular septal defects	3
Radical repair of tetralogy of Fallot (TF)	3
Resection of subvalvular aortic stenosis	2
ASD repair with resection of pulmonary stenosis (PS)	1
Palliative surgery for pulmonary atresia (PA)	1
Radical surgery of persistent common atrioventricular canal (PCAC)	1
Surgical correction of Bland-White-Garland syndrome (BWGS)	1
Radical surgery for partial anomalous pulmonary vein drainage and atrial septal defect repair (PAPVD, ASD)	1

Table 2. Summary of patient characteristics.

Parameter	Values in groups		*P*-value*
	VSD, *N*=8	ASD, *N*=7	
Age, months	20.2±8.6	19.8±8.8	0.9
Height, cm	85.2±7.9	80.5±7	0.9
Body weight, kg	11.17±1.9	10.7±2.1	0.5
Duration of cardiopulmonary bypass, min	48±3	43±10	0.3
Aortic clamping time, min	23±8	21±8	0.4
Volume of blood loss, mL	140±27	150±1	0.2

Note. Results by age are presented as *Me*±σ, others as *M*±*m*. * — Mann–Whitney test.

was assessed using a one-sample Student's *t*-test. Non-parametric descriptive statistics, such as median *(Me)* calculation and the Mann–Whitney test, were also employed. The critical two-sided significance level was set at *P*=0.05.

The limited number of patients in the study resulted from the number of surgeries performed during the analyzed period.

Results

In 15 of 20 (75%) patients, aortic valve area measurements were possible during the surgical phase with the sternum open (time 2). CO varied within the age-standardized range: 5.2 L/min [4.7; 5.5] in patients with ASD and 5.1 L/min [4.6; 5.6] in patients with VSD. After CPB, hypotension was observed in two patients (17%) with VSD, with CO decreasing to 3.6 L/min, below the age-standardized reference value (5.1 L/min) (*P*=0.032). These patients were switched from dopamine 7 μg/kg/min to adrenaline 0.05 μg/kg/min. During serial measurements, stabilization of hemodynamic parameters was observed with an increase in CO up to 5.2 L/min. After sternal closure, CO parameters were not significantly different from age-related reference values.

The mean CO was 4.9 L/min [4.7; 5.0] in the ASD group (*P*=0.849) and 4.7 L/min [4.6; 5.0] in the VSD group (*P*=0.622).

The clinical presentation was consistent with the values obtained.

Notably, the accuracy of the measurements was influenced by the condition of the patient (calm/crying) and the positioning of the sensor.

For example, in a 2-year-old patient with a body weight of 12.5 kg diagnosed with CHD (atrial septal defect), CI was 5.1 L/min/m² when calm (Fig. 2, *a*), 4.1 L/min/m² while crying (Fig. 2, *b*), and 2.8 L/min/m² with incorrect sensor positioning (Fig. 2, *c*).

Discussion

The problem of hypervolemia in pediatric cardiac surgery requires special attention. The study by Sinitsky L. et al. demonstrated a pattern of development of organ dysfunction and prolonged duration of mechanical ventilation with a positive fluid balance exceeding 13% of initial body weight [20, 21].

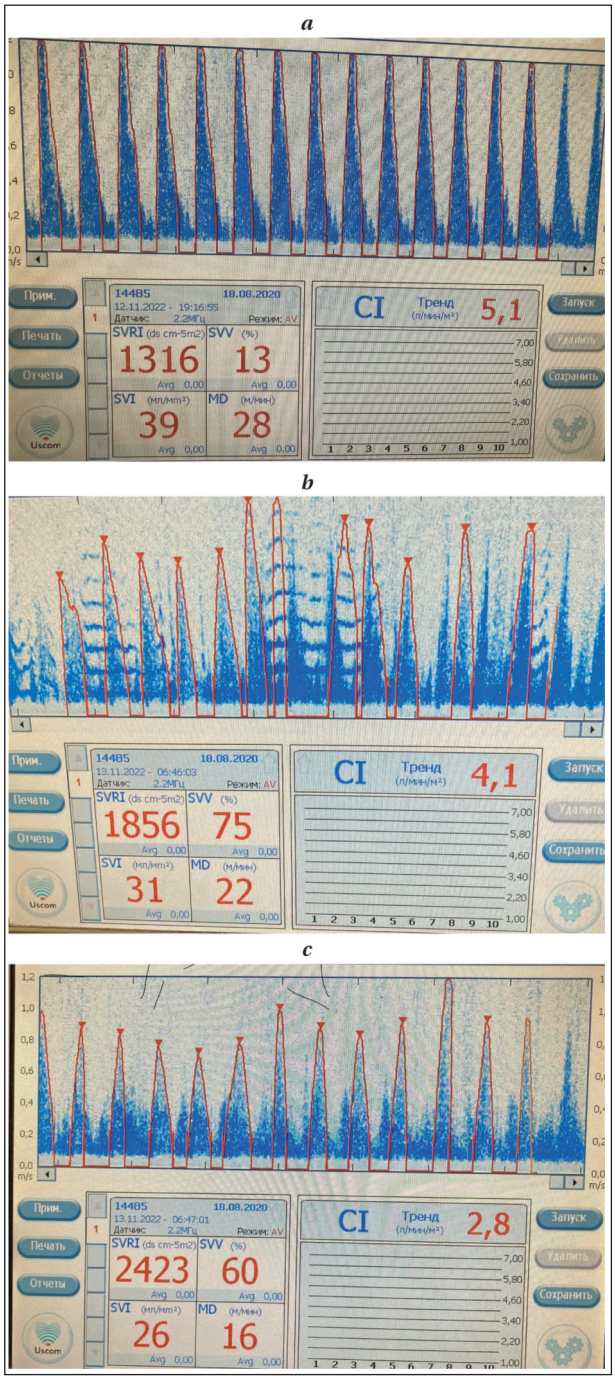

Fig. 2. Example of SI measurement when calm *(a)*, while crying *(b)*, and with incorrect sensor positioning *(c)*.

The use of noninvasive methods for CO monitoring, when properly applied and interpreted, may replace the routine use of invasive CO monitoring [22, 23]. The USCOM device, when used intraoperatively, reliably shows changes in cardiac output but requires time for correct positioning of the sensor. In particular, measurements were performed after stabilization of systemic pressure and CPB, as it was difficult to obtain measurements at earlier stages.

Correct positioning of the transducer, especially during surgery, may not always be feasible in all patients. In addition, the ultrasound method is operator dependent.

Pulmonary valve measurements were not performed in this study because of the difficulty of intraoperative transducer positioning. During sternotomy, the area of the pulmonary artery valve, which is difficult to access for measurements even under normal conditions, is displaced.

During the study, the transducer could not be positioned correctly in 5 patients (25%); however, in 15 patients (75%), the data obtained were consistent with the clinical picture.

The use of the USCOM device may be useful in pediatric cardiac surgery as an adjunct or alternative to the routine use of transpulmonary and prepulmonary thermodilution. The effectiveness of its use in the pediatric intensive care unit has also been confirmed by previous studies [15, 24].

Training in ultrasound techniques takes little time and can be done at the patient's bedside, allowing more staff to master it [16]. The USCOM device is already widely used in pediatrics because the use of noninvasive methods to monitor cardiac output in children reduces the risk of complications [14–16].

Conclusion

The USCOM device can be used for intraoperative hemodynamic assessment and selection of cardiac support therapy even during open heart surgery. However, its routine use in all stages of surgery with median sternotomy is challenging because optimal visualization of the aortic valve requires proper patient positioning.

References

1. Интенсивная терапия: национальное руководство в 2 т. Заболотских И. Б., Проценко Д. Н. (ред.). М.: ГЭОТАР-Медиа; 2021; I: 1152. (Серия «Национальные руководства»). ISBN 978-5-9704-6258-4. Intensive care: national guidelines in 2 vols. Zabolotskikh I. B., Protsenko D. N. (ed). M.: GEOTAR-Media; 2021; I: 1152. (The «National Guidelines» series). (in Russ.). ISBN 978-5-9704-6258-4.
2. *Кодзокова З. А., Ломакин М. В., Рыбка М. М., Дибин Д. А.* Интраоперационное измерение центральной гемодинамики методом холодовой термодилюции при помощи катетера Свана–Ганца у пациента с корригированной транспозицией магистральных артерий. *Клиническая физиология кровообращения.* 2020; 17 (2): 142–147. *Kodzokova Z. A., Lomakin M. V., Rybka M. M., Dibin D. A.* Intraoperative measurement of central hemodynamics by cold thermodilution using a Swan–Ganz catheter in a patient with corrected transposition of the great arteries. *Clinical Physiology of Blood Circulation = Klinicheskaya Fiziologiya Krovoobrashcheniya.* 2020; 17 (2): 142–147. (in Russ.). DOI: 10.24022/1814-6910-2020-17-2-142-147.
3. *Хинчагов Д. Я., Рыбка М. М.* Центральная гемодинамика при операциях реваскуляризации коронарных артерий без искусственного кровообращения. *Клиническая физиология кровообращения.* 2021; 3 (18): 201–211. *Khinchagov D. Ya., Rybka M. M.* Central hemodynamics in coronary artery revascularization surgery without cardiopulmonary bypass. *Clinical Physiology of Blood Circulation = Klinicheskaya Fiziologiya Krovoobrashcheniya.* 2021; 3 (18): 201–211. (in Russ.). DOI: 10.24022/1814-6910-2021-18-3-201-211.
4. *Юдин Г. В., Айдашев Ю. Ю., Рыбка М. М., Хинчагов Д. Я., Мещанов Б. В., Гончаров А. А.* Центральная гемодинамика, потребление кислорода и оксигенирующая функция легких при рестриктивной и либеральной периоперационной инфузии у больных с приобретенными пороками сердца. *Клиническая физиология кровообращения.* 2021; 1 (18): 60–72. *Yudin G. V., Aidashev Yu. Yu., Rybka M. M., Khinchagov D.Ya., Meshchanov B. V., Goncharov A. A.* Central hemodynamics, oxygen consumption and oxygenating lung function in restrictive and liberal perioperative infusion in patients with acquired heart defects. *Clinical Physiology of Blood Circulation = Klinicheskaya Fiziologiya Krovoobrashcheniya.* 2021; 1 (18): 60–72. (in Russ.). DOI: 10.24022/1814-6910-2021-18-1-60-72.
5. *Fu Y., He C., Bai Y., Zhang N., Zhao H.* Value of the combination of renal resistive index and central venous pressure to predict septic shock induced acute kidney injury. *Zhonghua Wei Zhong Bing Ji Jiu Yi Xue.* 2020; 32 (4): 473–477. Chinese. DOI: 10.3760/cma.j. cn121430-20191014-00062. PMID: 32527356.
6. *Shostak E., Shochat T., Manor O., Nahum E., Dagan O., Schiller O.* Fluid Responsiveness predictability in immediate postoperative pediatric cardiac surgery. Is the old slandered central venous pressure back again? *Shock.* 2021; 56 (6): 927–932. DOI: 10.1097/SHK.0000000000001786. PMID: 33882511.
7. *De Backer D., Vincent J. L.* Should we measure the central venous pressure to guide fluid management? Ten answers to 10 questions. *Crit Care.* 2018; 22 (1): 43. DOI: 10.1186/s13054-018-1959-3. PMID: 29471884.
8. *Monnet X., Shi R., Teboul J. L.* Prediction of fluid responsiveness. What's new? *Ann Intensive Care.* 2022; 12 (1): 46. DOI: 10.1186/s13613-022-01022-8. PMID: 35633423.
9. *Jozwiak M., Monnet X., Teboul J. L.* Prediction of fluid responsiveness in ventilated patients. *Ann Transl Med.* 2018; 6 (18): 352. DOI: 10.21037/atm.2018.05.03. PMID: 30370279.
10. *Смёткин А., Хуссейн А., Захаров В., Изотова Н., Кузьков В., Киров М.* Точность неинвазивного измерения сердечного выброса на основе оценки времени транзита пульсовой волны при аортокоронарном шунтировании на работающем сердце. *Патология кровообращения и кардиохирургия.* 2016; 20 (2): 104–110. *Smyotkin A., Hussein A., Zakharov V., Izotova N., Kuzikov V., Kirov M.* Accuracy of noninvasive measurement of cardiac output based on the estimation of pulse wave transit time during coronary artery bypass grafting on a beating heart. *Pathology of Blood Circulation and Cardiac Surgery = Patologiya Krovoobrashcheniya i Kardiokhirurgiya.* 2016; 20 (2): 104–110. (in Russ.). DOI: 10.21688/1681-3472-2016-2-104-110.
11. *Lee J. H., Kim E. H., Jang Y. E., Kim H. S., Kim J. T.* Fluid responsiveness in the pediatric population. *Korean J Anesthesiol.* 2019; 72 (5): 429–440. DOI: 10.4097/kja.19305. Erratum in*: Korean J Anesthesiol.* 2021; 74 (2): 188. PMID: 31591858.
12. *Кузибаева Н. К.* Распространенность врожденных пороков сердца у детей. *Лечащий Врач.* 2021; 9 (24): 48–52. *Kuzibaeva N. K.* Prevalence of congenital heart defects in children. *The Attending Physician = Lechashchiy Vrach.* 2021; 9 (24): 48–52. (in Russ.). DOI: 10.51793/OS.2021.24.9.009.
13. *Изотова Н. Н., Ильина Я. Ю., Фот Е. В., Сметкин А. А., Кузьков В. В., Киров М. Ю.* Оценка ультразвукового мониторинга сердечного выброса после реваскуляризации миокарда без искусственного кровообращения. *Анестезиология и реаниматология.* 2019; (2): 48–55. *Izotova N. N., Ilyina Ya. Yu., Fot E. V., Smyotkin A. A., Kuzkov V. V., Kirov M. Yu.* Ultrasound monitoring of cardiac output after off-pump coronary artery bypass grafting. *Russian Journal of Anaesthesiology and Reanimatology / Anesteziologiya i Reanimatologiya.* 2019; (2): 48–55. (in Russ.). DOI: 10.17116/anaesthesiology201902148.
14. *Patel N., Dodsworth M., Mills J. F.* Cardiac output measurement in newborn infants using the ultrasonic cardiac output monitor: an assessment of agreement with conventional echocardiography, repeatability and new user experience. *Arch Dis Child Fetal Neonatal Ed.* 2011; 96 (3): F206–11. DOI: 10.1136/adc.2009.170704. PMID: 20605971.
15. *Лекманов А. У., Азовский Д. К., Пилютик С. Ф.* Сравнение методов трансторакальной допплерографии и транспульмональной термодилюции при анализе гемодинамических показателей у детей с тяжелой термической травмой. *Вестник анестезиологии и реаниматологии.* 2017; 14 (1): 42–50. *Lekmanov A. U., Azovsky D. K., Pilyutik S. F.* Comparison of Doppler ultrasonography and

transpulmonary thermodilution when analyzing hemodynamics in the children with severe thermal injury. *Messenger of Anesthesiology and Resuscitation = Vestnik Anesthesiologii i Reanimatologii*. 2017; 14 (1): 42–50. (in Russ.). DOI: 10.21292/2078-5658-2017-14-1-42-50.

16. *Боронина И. В., Александрович Ю. С., Шмаков А. Н., Ошанова Л. С.* Возможность использования ультразвукового монитора неинвазивного контроля гемодинамики у новорожденных. *Российский вестник детской хирургии, анестезиологии и реаниматологии.* 2017; 7 (3): 69–73. *Boronina I. V., Alexandrovich Y. S., Shmakov A. N., Oshanova L. S.* The possibility to use the ultrasound monitor of noninvasive control of hemodynamic in newborns. *Russian Bulletin of Pediatric Surgery, Anesthesiology and Intensive Care = Rossiyskiy Vestnik Detskoy Khirurgii Anesteziologii i Reanimatologii.* 2017; 7 (3): 69–73. (in Russ.). https: //rps-journal.ru/jour/article/viewFile/336/335.
17. *Ruste M., Jacquet-Lagrèze M., Fellahi J.-L.* Advantages and limitations of noninvasive devices for cardiac output monitoring: a literature review. *Curr Opin Crit Care*. 2023; 29 (3): 259–267. DOI: 10.1097/MCC.0000000000001045.PMID: 37078642.
18. *Zhang Y., Wang Y., Ji D., Qian J., Xu J., Shi J.* Ultrasound cardiac output monitor and thermodilution for cardiac function monitoring in critical patients: a meta-analysis. *Zhonghua Wei Zhong Bing Ji Jiu Yi Xue*. 2019; 31 (12): 1462–1468. Chinese. DOI: 10.3760/cma.j.issn. 2095-4352.2019.12.006. PMID: 32029030.
19. *Cheng Y. W., Xu F., Li J.* Identification of volume parameters monitored with a noninvasive ultrasonic cardiac output monitor for predicting fluid responsiveness in children after congenital heart disease surgery. *Medicine (Baltimore)*. 2018; 97 (39): e12289. DOI: 10.1097/MD.0000000000012289. PMID: 30278500.
20. *Sinitsky L., Walls D., Nadel S., Inwald D. P.* Fluid overload at 48 hours is associated with respiratory morbidity but not mortality in a general PICU: retrospective cohort study. *Pediatr Crit Care Med.* 2015; 16 (3): 205–209. DOI: 10.1097/PCC.0000000000000318. PMID: 25581632.
21. *Cardoso F. S., Pereira R., Laranjo A., Gamelas V., Bagulho L., Germano N., Karvellas C. J.* Positive fluid balance was associated with mortality in patients with acute-on-chronic liver failure: a cohort study. *J Crit Care.* 2021; 63: 238–242. DOI: 10.1016/j.jcrc.2020.09.012. PMID: 32988683.
22. *Argaiz E. R., Koratala A., Reisinger N.* Comprehensive assessment of fluid status by point-of-care ultrasonography. *Kidney* 360. 2021; 2 (8): 1326–1338. DOI: 10.34067/KID.0006482020. PMID: 35369665.
23. *Pliauckiene A., Liubsys A., Vankeviciene R., Usonis V.* Ultrasonic cardiac output monitor provides effective non-invasive bedside measurements of neonatal cardiac output. *J Clin Monit Comput.* 2022; 36 (3): 803–807. DOI: 10.1007/s10877-021-00711-2. PMID: 33929641.
24. *Koratala A., Ronco C., Kazory A.* Diagnosis of fluid overload: from conventional to contemporary concepts. *Cardiorenal Med.* 2022; 12 (4): 141–154. DOI: 10.1159/000526902. PMID: 36096121.

Received 06.03.2024
Accepted 05.09.2024

https://doi.org/10.15360/1813-9779-2024-5-44-54

Efficacy and Safety of a Standardized CPAP Protocol in the Delivery Room in Late Preterm Infants with Infectious and Non-Infectious Lung Diseases

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For citation: *Eugene V. Shestak, Olga P. Kovtun, Ekaterina A. Mylarshikova, Yulia I. Nechaeva.* Efficacy and Safety of a Standardized CPAP Protocol in the Delivery Room in Late Preterm Infants with Infectious and Non-Infectious Lung Diseases. *Obshchaya Reanimatologiya = General Reanimatology.* 2024; 20 (5): 44–54. https://doi.org/10.15360/1813-9779-2024-5-44-54 [In Russ. and Engl.]

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Summary

The aim of this study was to evaluate the efficacy and safety of a standardized protocol of delivery room CPAP therapy in late preterm infants with acute neonatal respiratory failure (ARF) caused by various conditions.

Material and methods. A retrospective comparative study of the efficacy of the standardized CPAP protocol in the cohorts of late preterm infants (34–36 weeks) was conducted at the Yekaterinburg Perinatal Center. The comparison group (C, *N*=256) included infants who received CPAP therapy in the delivery room during 12 months in 2020 before the introduction of the standardized protocol. The study group (S, *N*=169) included infants treated with standardized CPAP in April-December, 2022. The following subgroups were identified in groups C and S based on the cause of ARF: transient tachypnea of the newborn (TTN; C: *N*=100; S: *N*=89), respiratory distress syndrome (RDS; C: *N*=84; S: *N*=39), and congenital infection (CI; C: *N*=54; S: *N*=37). Other causes of ARF in groups C and S were found in 18 and 4 infants, respectively.

Results. Switching to the standardized CPAP protocol reduced the duration of mechanical ventilation by an average of 24 h (*P*=0.013), the incidence of documented cerebral ischemia (CI) from 64.1% to 53.2% in all subgroups (*P*=0.022), the length of stay in the neonatal ward from 12 to 11 days (*P*=0.001), and the length of stay in the hospital from 16 to 14 days (*P*=0.001) as well as the incidence of CI in the STTN subgroup vs CTTN (38.2% vs. 61.0%, *P*=0.002). No significant differences were found in the RDS and CI subgroups. The frequency and duration of binasal CPAP and lung ventilation in the neonatal ICU did not differ between subgroups. Pneumothorax within the first 24 h occurred in one patient in group C and in two patients in group S (*P*=0.339), all of whom were diagnosed with congenital infection. No damage to the nasal passages was observed in any group.

Conclusion. The use of a standardized protocol of CPAP therapy for neonates born after 35 weeks of gestation with respiratory failure of any etiology can significantly reduce the severity and duration of illness and should be considered as a basic respiratory strategy in the delivery room when indicated.

Keywords: newborn; late preterm infants; CPAP; transient tachypnea of the newborn; neonatal respiratory distress syndrome; congenital infection

Conflict of interest. The authors declare no conflict of interest.

Introduction

Birth is characterized by a series of preparatory changes in the body, first in the fetus and then in the newborn. These changes include a decrease in the production of fetal lung fluid and activation of its reabsorption, as well as the production of sufficient surfactant to maintain surface tension in the open alveoli after the first breath [1]. Stress hormones (adrenaline, cortisol, etc.) produced by both the mother and fetus in response to natural term delivery significantly influence fluid clearance from the lungs [2, 3].

However, delivery at late preterm gestation age ($34^{0/7}$–$36^{6/7}$ weeks), especially via cesarean section, disrupts the neonatal adaptation to extrauterine life, which may manifest as acute respiratory failure immediately after birth or during the first hours of life [4]. Transient tachypnea of the newborn (TTN) [5, 6] and surfactant deficiency can lead to respiratory distress syndrome (RDS) [5, 7], which is associated with fetal fluid retention in the lungs. Most neonatal conditions are characterized by nonspecific acute respiratory failure (ARF), which is also observed in congenital infection (CI) [7–9]. When ARF develops in the delivery room, differentiating between TTN, RDS, and CI is extremely difficult [5]. Not only are the signs and symptoms of these conditions similar, but the morphologic changes in the lungs are as well. One study showed that hyaline membranes were found in the lungs of 93.5% of neonates with an average gestational age (GA) of 28.9±5.3 weeks, a birth weight of 1404±945 g, and a median life expectancy of 72 hours [10]. The causes of hyaline membranes were varied and included true surfactant deficiency, pneumonia, asphyxia, aspiration, shock, hemorrhagic syndrome, and others. Regardless of the etiology of ARF, the infant requires prompt and appropriate respiratory therapy. In particular, sepsis and acute respiratory distress syndrome are the

leading causes of multiorgan failure and mortality in neonates [11]. The primary method of respiratory support for neonates of any gestational age with moderate ARF is continuous positive airway pressure (CPAP) therapy [12–14].

Russian guidelines, such as the Methodological Letter of the Ministry of Health of the Russian Federation on Resuscitation and Stabilization of Neonates in the Delivery Room (2020) [15] and the National Guidelines for Neonatology (2019) [16], recommend CPAP therapy for children older than 32 weeks of gestation when ARF develops, but do not specify the criteria for initiating therapy, its continuation, efficacy, or the technique itself, including the required parameters of respiratory support. In our previous studies, we analyzed the severity of TTN in full-term neonates and the type of respiratory support used [17]. Based on these data, we developed a standardized protocol for CPAP therapy in the delivery room.

In a subsequent prospective study, the protocol was found to be highly effective in reducing the severity, duration, and incidence of brain ischemia (BI) in TTN [18].

The aim of this study was to evaluate the efficacy and safety of a standardized protocol for delivery room CPAP therapy in late preterm neonates with acute respiratory failure caused by various conditions.

Material and Methods

A single-center, retrospective cohort study was conducted on late preterm neonates ($34^{0/7}$–$36^{6/7}$ weeks of gestation) born at the Yekaterinburg Clinical Perinatal Center (YCPC) who underwent CPAP therapy in the delivery room.

The standardized protocol for CPAP therapy in preterm neonates with TTN was approved by the local ethics committee of the YCPC (Protocol No. 2 dated July 2, 2021). The protocol for CPAP therapy in the delivery room for ARF in late preterm and term neonates was implemented at the YCPC on March 11, 2022 (Decision No. 147). Parents of all neonates signed an informed consent for diagnosis and therapy, including the use of data obtained for scientific purposes.

The control group (C, *N*=256) included children treated in 2020, before the implementation of the protocol. The study group (S, *N*=169) included children hospitalized from April to December 2022, after the implementation of the protocol.

Inclusion and exclusion criteria were the same for groups C and S.

Inclusion criteria:

— Late preterm birth (GA $34^{0/7}$–$36^{6/7}$ weeks);

— Development of ARF within the first 60 minutes after birth;

— CPAP therapy in the delivery room.

Exclusion criteria:

— congenital malformations presenting with ARF;

— chromosomal abnormalities;

— any other condition that could influence the results of the study.

In groups C and S, subgroups of patients were identified according to the cause of respiratory disorders in the delivery room: for T_{TN}, the subgroups C_{TTN} (*N*=100) and S_{TTN} (*N*=89); for RDS, the subgroups C_{RDS} (*N*=84) and S_{RDS} (*N*=39); for CI, the subgroups C_{CI} (*N*=54) and S_{CI}(*N*=37).

In addition to T_{TN}, RDS, and CI, the following causes of ARF in the delivery room were identified in the control group: moderate to severe birth asphyxia (*N*=10), polycythemia (*N*=3), anemia (*N*=3), and interventricular septal defect (*N*=2).

In addition to T_{TN}, RDS and CI, the causes of ARF in the study included moderate to severe birth asphyxia (*N*=4).

All other causes of ARF in the delivery room in groups C and S were documented in infants at 34 weeks' gestation.

Inclusion and exclusion criteria were consistent between control and study subgroups (C_{TTN} and S_{TTN}, C_{RDS} and S_{RDS}; C_{CI} and S_{CI}).

Inclusion criteria:

- for the TTN subgroup, a diagnosis of TTN;
- for the RDS subgroup, a diagnosis of RDS;
- for the CI subgroup, a diagnosis of congenital infection.

Exclusion criteria: none.

The flowchart of group and subgroup recruitment is shown in Fig. 1.

Description of medical intervention. Standardized protocol for delivery room CPAP therapy. The use of a standardized protocol for delivery room CPAP therapy was first studied and described in a cohort of preterm infants with TTN [18] and subsequently in those with congenital infection [19]. The protocol was developed based on the analysis of respiratory therapy in this population [17] and the prognosis of the disease [20].

CPAP equipment and methodology. We used conventional equipment and supplies available in all delivery and operating rooms of the perinatal center. When indications were present (described below), CPAP was initiated with mask-based CPAP, followed by a transition to mononasal CPAP (hereafter referred to as CPAP) for 5 minutes. This was delivered via an endotracheal tube (ETT) inserted into the child's nasal passage to a depth equal to the midpoint of the distance between the earlobe and the nasal ala (corresponding to the level of the nasopharynx). The transition from mask-based CPAP to mononasal CPAP was prompted by the need to free the clinician's hands for further assistance to the patient. CPAP was delivered using a T-shaped resuscitation breathing circuit (Fisher &

Paykel Healthcare Limited, New Zealand), respiratory therapy devices integrated into open resuscitation stations (ORS), such as the Giraffe Warmer (General Electric, USA), BLR-2100 (MEDICOR, Hungary), or a separate device capable of titrating oxygen fraction and monitoring airway pressure, such as the Neopuff™ (Fisher & Paykel Healthcare Limited, New Zealand). Within 5 minutes of starting CPAP, the clinician placed an orogastric tube in the child and left it open. If indicated, ventilation was performed with a face mask, with transition to tracheal intubation and invasive ventilation as needed. Starting ventilation parameters were PiP 20 cm H_2O, PEEP 5 cm H_2O, FiO_2 0.21, and a rate of 40–60/min.

During the transfer of the patient from the delivery room to the NICU, the mode and parameters of respiratory support were not changed. Binasal CPAP parameters in the NICU were 4–8 cm H_2O, with an initial FiO_2 of 0.21. The respiratory support device used during transport of the infant to the NICU for CPAP or ventilation was the Stephan Reanimator F120 (Stephan GmbH, Germany) with a breathing circuit (Kometaline, Russia). Respiratory support devices for CPR in the NICU included the Infant Flow CPR (VIASYS Healthcare Inc., USA) and the Infant Flow circuit with a set of consumables (humidifier chamber, cap, nasal cannulae) (Vincent Medical, China). Respiratory support devices for NICU ventilation included the Avea (VIASYS Healthcare Inc., USA) and the SLE-5000 (SLE Limited, UK). CPAP equipment and technique did not differ between groups C and S.

CPAP parameters. The initial mean airway pressure (MAP) was set at 8 cm H_2O with an oxygen fraction (FiO_2) of 21%. The oxygen concentration could be gradually increased or decreased to maintain the saturation (SpO_2) on the right arm in the range of 91–95%. CPAP parameters and indications for its initiation in the groups are listed in Table 1.

Indications for initiation of CPAP therapy and routing of patients in the delivery room according to the protocol. CPAP was initiated according to the protocol when the neonate developed ARF with Downes score ⩾3 points.

After 20 minutes of CPAP, the Downes score of ARF was assessed:

- if the score was <3 points, the endotracheal tube was removed from the nose and the child was monitored by the physician for 5 minutes:
- if the ARF score remained <3 during this period and no other organ or system dysfunction was observed, the infant was transferred to the neonatal unit (NNU);
- if the ARF score increased to 3 or higher, the clinician resumed CPAP using the MAP and FiO_2 parameters described above;
- CPAP was continued without changing the initial parameters if the ARF score remained at the baseline level of 3–5 points;
- if the ARF score increased from 3–4 to 5 or more points, or from 5 to 6 or more points, the infant was transferred to the NICU with the appropriate type of respiratory support (CPAP or ventilation);
- if the ARF score remained at the baseline level of 6 points or increased, the infant was transferred to the NICU with the appropriate type of respiratory support (CPAP or ventilation).

Similar actions were performed 40 and 60 minutes after CPAP initiation. At the same time, the infant was transferred to the NICU if the Downes score at

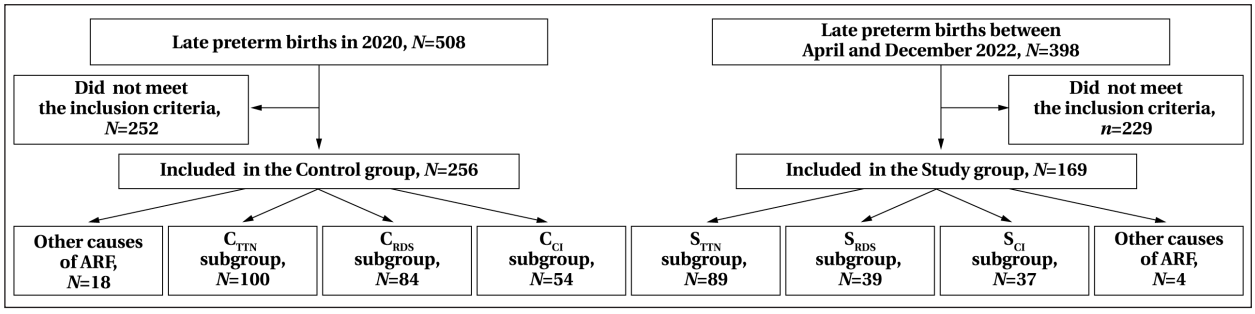

Fig. 1. Study flowchart.
Note. C — control group; S — study group; TTN — transient tachypnea of newborns; RDS — respiratory distress syndrome; CI — congenital infection.

Table 1. CPAP parameters and indications for CPAP in the delivery room.

Criterion	Control group	Study group
Interface	Face mask with switch to nasal mask CPAP	
CPAP therapy when Downes score ⩾4 points	Always	
CPAP therapy when Downes score = 3 points	At doctor's discretion	Always
CPAP therapy when Downes score = 2 points	At doctor's discretion	Never
MAP, cm H_2O	5–10	8
FiO_2, %	21	
Duration of CPAP, min	5–30	20–60
Orogastric tube placement within 5 minutes after CPAP initiation	Always	

Note. MAP — mean airway pressure; FiO_2 — fraction of inhaled oxygen; CPAP — continuous positive airway pressure

60 minutes remained the same (3–5 points at 40 minutes) or increased (Fig. 2). Neonates were transferred from the neonatal unit (NNU) and NICU to the neonatal pathology unit (NPU) if they required additional treatment and monitoring.

Study Outcomes.

— Frequency of brain injury (brain ischemia and IVH)

— Frequency and duration of mechanical ventilation

— Frequency and duration of NICU admission

— Total length of hospital stay

Methods of outcome assessment. Study outcomes were determined by analyzing data from primary medical records, such as the neonate's medical chart.

CPAP therapy safety parameters:

— Air leak syndrome diagnosed by radiological examination within the first 24 hours after birth

— Damage to the nasal passages (swelling, bleeding) diagnosed by clinical examination.

All study parameters were recorded throughout the hospital stay at the participating medical center.

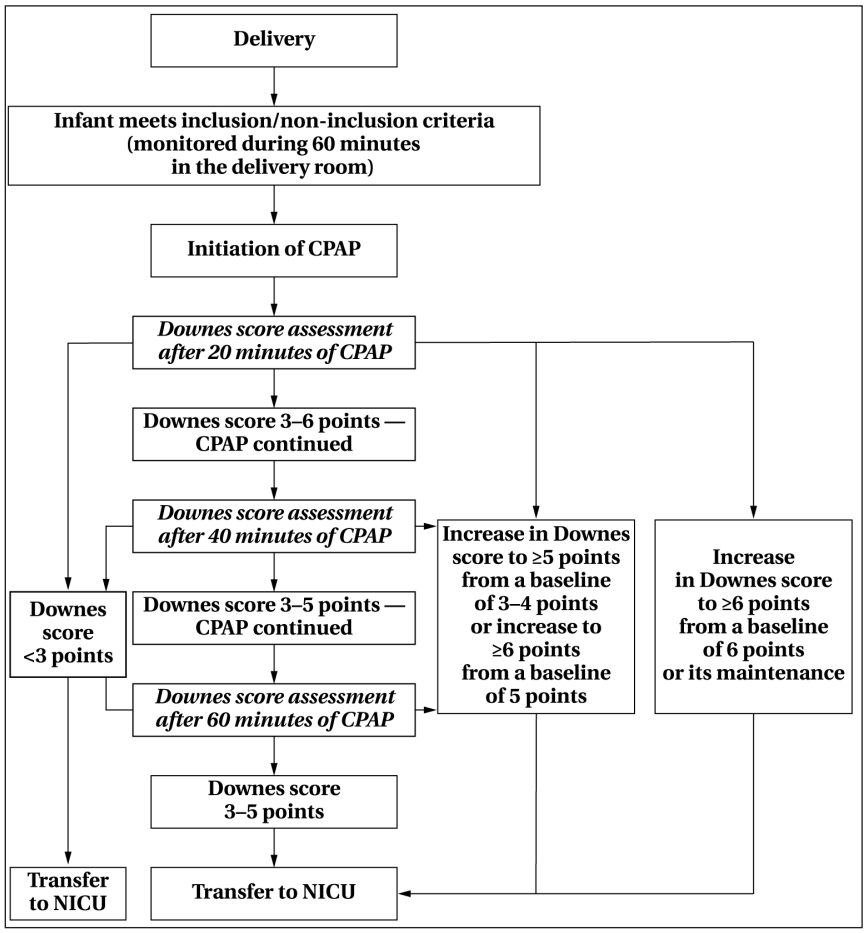

Fig. 2. Routing of neonates during CPAP therapy in the delivery room according to protocol (study group)

Note. CPAP — continuous positive airway pressure; NICU — neonatal intensive care unit; NNU — neonatal unit.

Diagnostic criteria:

— The diagnosis of TTN was made when other causes of ARF were excluded.

— The diagnosis of RDS was made on the basis of characteristic ground-glass opacities in the lungs and the absence of clinical and laboratory evidence of infection

— Congenital infection was defined by manifestations of infection within the first 72 hours after birth; the exact diagnoses were made based on the standard definition of cases according to the local YCPC protocol: early neonatal sepsis (ICD-10 P36), congenital pneumonia (ICD-10 P23), infection specific to the perinatal period (ISPP) (ICD-10 P39). The diagnosis of infection was made both with and without a positive bacterial culture from the site of infection, based on a combination of clinical, instrumental, and laboratory data

— Prolonged time between rupture of membranes and delivery was defined as amniorrhea occurring more than 18 hours before delivery

— The diagnosis of BI was made based on clinical presentation, neurosonography, and a report from a pediatric neurologist; the severity of BI was classified according to the Classification of Perinatal Neural System Lesions in Newborns (ICD-10 P91.0).

Principles of sample size calculation. Sample size was not calculated in advance. A continuous sampling design was employed.

Methods of statistical analysis. Accumulation, correction, systematization of the initial information, and visualization of the obtained results were performed using Microsoft Office Excel 2016. Statistical analysis was conducted with IBM SPSS Statistics v.27 (IBM Corporation) and BioStat (AnalystSoft Inc.) software. The normality of the distribution of quantitative parameters was assessed using the Shapiro–Wilk test (for samples with fewer than 50 values) or the Kolmogorov-Smirnov test (for samples with 50 or more values). Non-normally distributed variables were described by the median *(Me)* and lower and upper quartiles *(LQ; UQ)*. Nominal data were represented as absolute values and percentages. The Mann–Whitney *U*-test was used to compare quantitative data in independent groups, while Pearson's χ^2 test was applied for qualitative variables. When the frequency of a parameter was

less than 10, the χ^2 test with Yates' correction was used. The arithmetic mean *(M)*, standard deviation *(SD)*, and Student's *t*-test were utilized to describe numerical parameters with a normal distribution. Differences were considered significant at $P<0.05$; a two-sided *P* level of significance was applied.

Results and Discussion

When analyzing the general characteristics of the neonates, we found that GA and Apgar scores at 1 and 5 minutes were comparable in groups C and S (Table 2). There were significantly fewer boys in group C, and patients in this group were characterized by lower birth weight.

There were no significant differences in birth weight, sex, GA, and Apgar scores at 1 and 5 minutes ($P>0.05$) among the compared subgroups of patients with TTN, RDS, and CI.

Comparative analysis of the incidence of brain injury showed that children in the control group were diagnosed with brain injury significantly more often overall; however, there was no significant difference in the incidence of mild-to-moderate and severe brain injury. The frequency of IVH did not differ significantly between groups, including IVH grades 1–2 and 3–4: 1 case was recorded in the control group and none in the study group (Table 3).

Comparative analysis of respiratory therapy (Table 4) in the patient groups showed that CPAP therapy in the delivery room was significantly longer in group C, in accordance with the implemented protocol. Surfactant was administered to a comparable number of patients in both groups. The frequency of binasal CPAP (BinCPAP) in the NICU and its duration did not differ between groups. Lung ventilation in the NICU was performed in a similar number of patients in both groups, but it was significantly longer in group C. The frequency of hospitalization in the NPU and NICU, as well as the duration of hospitalization in the NICU, did not differ between the groups; however, the duration of stay in the NPU and the total length of hospitalization were significantly shorter in group S. One case of pneumothorax was recorded in group C

Table 2. Patient characteristics in groups, *Me (LQ; UQ)*, *N* (%).

Parameter	Values in groups		*P*-value
	Group C, *N*=256	Group S, *N*=169	
Gestational age, weeks	35 (34; 36) *Me*=34.792 *SD*=±0.826	35 (34; 36) *Me*=34.9 *SD*=±0.803	0.063 *t*-test (0.058)
Male sex	116 (45.3)	97 (57.4)	0.015*
Birth weight, grams	2310 (2035; 2640)	2480 (2140; 2780)	0.019*
Apgar score at 1 minute, points	6 (6; 7)	6 (6; 7)	0.395
Apgar score at 5 minute, points	7 (7; 8)	7 (7; 8)	0.919

Note. * — significant difference between groups.

Table 3. Comparison of the incidence of brain injury in patients, number (%)

Parameter	Values in groups		*P*-value
	Group C, *N*=256	Group S, *N*=169	
BI, total	164 (64.1)	90 (53.2)	0.022*
BI, mild and moderate severity	157 (95.7)	89 (98.8)	0.169
BI, severe	7 (4.3)	1 (1.2)	
IVH, total	60 (23.4)	33 (19.5)	0.340
IVH, grade 1–2	59 (98.3)	33 (100.0)	0.456
IVH, grade 3–4	1 (1.7)	0 (0)	

Note. * — significant difference between groups. For Tables 3, 5, 6, 8: BI — brain ischemia; IVH — intraventricular hemorrhage.

Table 4. Respiratory therapy and hospital stay in the groups of patients, *Me (LQ; UQ)*, *N* (%).

Parameter	Values in groups		*P*-value
	Group C, *N*=256	Group S, *N*=169	
Duration of CPAP in the delivery room, min	15 (10; 15)	40 (20; 40)	<0.001*
Administration of surfactant	40 (15.6)	21 (12.4)	0.357
BinCPAP in NICU	177 (69.1)	120 (71.0)	0.682
Duration of BinCPAP, days	1 (1; 1)	1 (1; 1)	0.222
Lung ventilation in NICU	40 (15.6)	24 (14.2)	0.688
Duration of ventilation, days	3 (1; 5)	2 (1; 3)	0.013*
Admitted to NICU	180 (70.3)	120 (71.0)	0.878
Duration of NICU stay, days	1 (1; 3)	1 (1; 2)	0.217
Admitted to NPU	242 (94.5)	154 (91.1)	0.173
Duration of NPU stay, days	12 (10; 18)	11 (9; 14)	0.001*
Total length of hospital stay, days	16 (12; 21)	14 (11; 18)	0.001*
Pneumothorax within the first 24 hours	1 (0.3)	2 (1.1)	0.339
Death	2 (0.7)	0 (0.0)	0.250

Note. * — significant difference between groups. For Tables. 4, 5, 6, 8: CPAP — continuous positive airway pressure; BinCPAP — binasal CPAP; NICU — neonatal intensive care unit, NPU — neonatal pathology unit.

compared to two cases in group S. One case of pneumothorax during the first 24 hours after birth was observed in each subgroup, as well as two deaths in subgroup C.

Subgroup analysis of patients with TTN. Analysis of the incidence of brain injury showed that mild and moderate BI were diagnosed more frequently in the C_{TTN} subgroup, and no statistically significant difference was found in the incidence of grade 1–2 IVH between the compared subgroups. No severe BI or grade 3–4 IVH was observed in either subgroup (Table 5).

CPAP therapy in the delivery room was statistically longer in the S_{TTN} subgroup. There were no significant differences between subgroups in the frequency and duration of BinCPAP use in the NICU, or in the frequency and duration of ventilation (Table 6).

There were no significant differences between subgroups in the frequency of NICU admission, NPU admission, or NICU length of stay. Length of stay in the NPU and total length of stay in the perinatal center were significantly lower in the S_{TTN} subgroup.

Only one neonate with TTN was identified at $34^{0/7}$–$34^{6/7}$ weeks of gestation in the S_{TTN} subgroup, and there were no neonates with TTN and CPAP in the delivery room in the C_{TTN} subgroup at this gestational age.

Subgroup analysis of patients with RDS. Analysis of the frequency of detection of brain injury showed no differences in the overall frequency of

Table 5. Comparison of incidence of brain injury, respiratory therapy parameters, and hospitalization characteristics of patients in the TTN subgroup, *Me (LQ; UQ)*, number (%).

Parameter	Values in groups		*P*-value
	C_{TTN}, *N*=100	S_{TTN}, *N*=89	
BI, total	61 (61.0)	34 (38.2)	0.002*
BI, mild and moderate severity	61 (100)	34 (100)	
BI, severe	0 (0)	0 (0)	
IVH, total	18 (18.0)	15 (16.9)	0.836
IVH, grade 1–2	18 (100)	15 (100)	
IVH, grade 3–4	0 (0)	0 (0)	
Duration of CPAP in the delivery room, min	15 (15; 20)	40 (20; 40)	<0.001*
BinCPAP in NICU, *N*	57 (57.0)	47 (52.8)	0.563
Duration of BinCPAP, days	1 (1; 1)	1 (1; 1)	0.976
Lung ventilation in NICU, *N*	1 (1.0)	2 (2.2)	0.493
Duration of lung ventilation, days	1 (1; 1)	1 (1; 1)	1.0
Admitted to NICU, *N*	58 (58.0)	47 (52.8)	0.473
Duration of NICU stay, days	1 (1; 1)	1 (1; 1)	0.725
Admitted to NPU, *N*	91 (91.0)	75 (84.3)	0.158
Duration of NPU stay, days	10 (8; 13)	9 (7; 12)	0.022*
Total length of hospital stay, days	13 (11; 15)	12 (9; 14)	0.018*

Note. * — significant difference between groups.

Table 6. Comparison of incidence of brain injury, respiratory therapy parameters, and hospitalization characteristics of patients in the RDS subgroup, *Me (QL; QU), N* (%).

Parameter	Values in groups		*P*-value
	C_{RDS}, *N*=8	$И_{RDS}$, *N*=39	
BI, total	57 (67.9)	28 (71.8)	0.660
BI, mild and moderate severity	54 (94.7)	7 (96.4)	0.843#
BI, severe	3 (5.3)	1 (3.6)	
IVH, total	24 (28.6)	8 (20.5)	0.343
IVH, grade 1–2	24 (100)	8 (100)	
IVH, grade 3–4	0 (0)	0 (0)	
Duration of CPAP in the delivery room, min	15 (12,5; 15)	20 (20; 40)	<0.001*
Intubated in the delivery room	1 (1.2)	0	0.494
Administration of surfactant	21 (25.0)	10 (25.6)	0.939
Surfactant using the INSURE technique	20 (23.8)	10 (25.6)	0.826
Surfactant through the endotracheal tube	1 (1.2)	0	0.494
Surfactant 1 time	20 (23.8)	9 (23.1)	0.929
Surfactant 2 times	1 (1.2)	1 (2.6)	0.575
BinCPAP in NICU, n	68 (81.0)	39 (100)	0.003*
Duration of BinCPAP, days	1 (1; 1)	1 (1; 1)	0.302
Lung ventilation in NICU, n	2 (2.4)	2 (5.1)	0.424
Duration of lung ventilation, days	2 (1; 3)	1 (1; 1)	0.617
Admitted to NICU, n	69 (82.1)	39 (100)	0.005*
Duration of NICU stay, days	1 (1; 1)	1 (1; 1)	0.171
Admitted to NPU, n	84 (100)	39 (100)	1.0
Duration of NPU stay, days	15 (12; 22)	16 (12; 23)	0.662
Total length of hospital stay, days	19 (14.5; 25)	20 (16; 25)	0.342

Note. # — Chi-square test with Yates correction. * — significant difference between subgroups. For Tables 6, 8: INSURE — surfactant administration technique including tracheal intubation, surfactant administration, tracheal extubation.

brain injury, including mild, moderate, and severe BI, among the subgroups. No significant differences were found in the incidence of grade 1–2 IVH. No grade 3–4 hemorrhage was observed in any of the subgroups (Table 6). Comparative analysis of respiratory therapy parameters showed that the duration of CPAP in the delivery room was significantly shorter in the C_{RDS} subgroup; the frequency of BinCPAP use in the NICU was lower in the C_{RDS} subgroup, with the same median duration of 1 day, and the frequency of ventilation and its duration were comparable between the subgroups. Only 1 infant in the C_{RDS} subgroup was intubated in the delivery room. Surfactant was administered in 25% of patients in both subgroups. Analysis of the methods and frequency of surfactant administration showed no statistically significant differences. The frequency of NICU admission was higher in the S_{RDS} subgroup, with the same median NICU length of stay of 1 day. All patients in both subgroups were treated in the NICU with a comparable length of stay, while the total length of stay in the perinatal center was 19 (14.5; 25) days in the C_{RDS} subgroup and 20 (16; 25) days in the S_{RDS} subgroup, with no statistically significant difference. Eighty-two (97.6%) infants in the C_{RDS} subgroup and all 39 (100%) infants in the S_{RDS} subgroup were enrolled during week $34^{0/7}$–$34^{6/7}$ of GA.

Subgroup analysis of patients with CI. No statistically significant subgroup differences were found in the incidence of congenital pneumonia, early neonatal sepsis, and infections specific to the perinatal period (Table 7).

The frequency of CI was comparable in the subgroups, including mild, moderate, and severe. Twenty-five percent of patients in both subgroups had IVH, including grade 1–2 IVH. Only one case of grade 3–4 IVH was observed in the C_{CI} subgroup (Table 8).

CPAP duration was significantly shorter in the C_{CI} subgroup; the frequency of BinCPAP use in the NICU and its duration did not differ. Surfactant was administered to a similar number of patients in both subgroups. The percentage of patients receiving mechanical ventilation did not differ, but the duration of mechanical ventilation was significantly longer in the C_{CI} subgroup (Table 9). The frequency of admission to the NICU did not differ between the subgroups, but the duration of treatment for children in the NICU was longer in the C_{CI} subgroup. A similar number of patients were admitted to the NPU in both subgroups, though the hospital stay was longer in the C_{CI} subgroup, without a statistically significant difference.

Two deaths were documented in the C_{CI} subgroup (*P*=0.241). The hospital stay was significantly longer in this subgroup.

Adverse events. Pneumothorax during the first 24 hours occurred in one patient in the control group and in two patients in the study group (*P*=0.339); all 3 patients were diagnosed with infection. No damage to the nasal passages was observed in the studied groups.

Table 7. Diagnoses in patients of CI subgroups, *Me (LQ; UQ), N* (%)

Parameter	Values in groups		*P*-value
	C_{CI}, *N*=54	S_{CI}, *N*=37	
Congenital pneumonia	23 (42.5)	17 (45.9)	0.752
Early neonatal sepsis	17 (31.4)	9 (24.3)	0.458
Infection specific for the perinatal period	14 (25.9)	11 (29.7)	0.690

Table 8. Comparison of incidence of brain injury, respiratory therapy parameters, and hospitalization characteristics of patients in the CI subgroup, *Me (LQ; UQ)*, number (%).

Parameter	Values in groups		*P*-value
	C_{CI}, *N*=54	S_{CI}, *N*=37	
BI *(N)*, of them:	34 (62.9)	26 (70.2)	0.471
BI, mild and moderate severity *(N)*	30 (88.2)	26 (100)	0.198
BI, severe *(N)*	4 (11.8)	0 (0)	
IVH *(N)*, of them:	14 (25.9)	9 (24.3)	0.863
IVH, grade 1–2 *(N)*	13 (92.8)	9 (100)	0.820
IVH, grade 3–4 *(N)*	1 (7.2)	0 (0)	
Duration of CPAP in the delivery room, min	15 (10; 15)	40 (20; 40)	<0.001*
Administration of surfactant, *N*	19 (35.1)	11 (29.7)	0.587
BinCPAP in NICU, *N*	52 (96.2)	34 (91.8)	0.366
Duration of BinCPAP, days	2 (1; 3)	1 (1; 2)	0.064
Lung ventilation in NICU, *N*	37 (68.5)	20 (54.0)	0.162
Duration of lung ventilation, days	3 (2; 5)	2 (1; 3)	0.032*
Admitted to NICU, *N*	53 (98.1)	34 (91.8)	0.153
Duration of NICU stay, days	5 (3; 7)	3 (2; 6)	0.024*
Admitted to NPU, *N*	49 (90.7)	36 (97.2)	0.216
Duration of NPU stay, days	14 (10; 18)	11 (9; 14.5)	0.075
Death, *N*	2 (3.7)	0	0.241
Total length of hospital stay, days	19,5 (16; 23)	16 (13; 19)	0.037*

Note. * — significant difference between subgroups.

Discussion

BI was diagnosed less frequently in the study group than in the control group, 53.2% vs. 64.1% (*P*=0.022). However, a significant difference in BI was found only in patients with TTN, 38.2% vs. 61.0% (*P*=0.002). After the implementation of a standardized protocol for CPAP therapy in the routine work of the perinatal center, the frequency of CPAP use in the delivery room significantly decreased in this cohort of children (*P*=0.018). In the group of premature neonates who received CPAP therapy according to the protocol, positive results were observed regarding the severity and duration of the diseases that caused ARF, namely a decrease in the frequency of BI and the total length of hospital stay from 16 to 14 days (*P*=0.049).

Treatment of patients with TTN according to the CPAP therapy protocol had a significant effect on their clinical status: the duration of mechanical ventilation was reduced by an average of 1 day (*P*=0.013), the frequency of BI was reduced from 64.1% to 53.2% (*P*=0.022), the length of stay in the NPU decreased from 12 to 11 days (*P*=0.001), and the total length of hospital stay was reduced from 16 to 14 days (*P*=0.001).

In the group of patients with RDS, the CPAP protocol was not effective but was associated with an increase in the frequency of NICU admission from 82.1% to 100% of patients (*P*=0.005).

In patients with CI, the use of the protocol resulted in a decrease in severity and duration of illness: a decrease in duration of mechanical ventilation from 3 to 2 days (*P*=0.032), a decrease in duration of NICU stay from 5 to 3 days (*P*=0.024), and a decrease in total hospital stay from 19.5 to 16 days (*P*=0.037).

Analysis of diagnoses and GA showed that at $34^{0/7}$–$34^{6/7}$ weeks, 121 (98.3%) out of 123 infants with RDS were enrolled in the control and study groups, and only 1 (0.5%) infant with TTN out of 189 patients in the control and study groups. In contrast, patients with CI were observed at all gestational ages, but their numbers were significantly lower compared to those with TTN and RDS. A large national multicenter study showed that 80–100% of neonates admitted to the NICU at $34^{0/7}$–$36^{6/7}$ weeks' gestation required respiratory support, and the most common cause of ARF in this study was RDS [21]. The median GA in this study was 34.0 (34.0; 35.0) weeks, which correlates with our findings.

Due to the proven efficacy of the CPAP protocol in patients with TTN and the lack of a positive effect in patients with RDS, we decided to change the protocol indications for CPAP therapy, specifically by increasing the minimum GA to $35^{0/7}$ weeks.

Comparison of the control and study groups showed that the main causes of ARF in the delivery room in late preterm neonates with GA of $35^{0/7}$–$36^{6/7}$ weeks (*N*=247) were:

— TTN (*N*=188; 76.1%);
— CI (*N*=57; 23.1%);
— RDS (*N*=2; 0.8%).

According to previous studies, the incidence of TTN increases with decreasing GA at birth: 0.2–0.6% in preterm neonates [22, 23], 5% in neonates at GA 35–36 weeks, and up to 10% in neonates at 33–34 weeks gestation [24–26]. Intrauterine fetal infection is the most established factor for premature rupture of membranes and preterm birth [27, 28], and stillbirths due to congenital infection can be as high as 10–25%, even in countries with high socioeconomic levels [29–31]. The concept of early neonatal infection is typically defined by the onset of symptoms in the first 72 hours after birth [32]. In the delivery room, when the primary respiratory disorder develops, the differential diagnosis of TTN and CI is challenging. The clinical presentation of ARF in newborns is not specific, and both conditions do not have characteristic symptoms. Laboratory diagnosis of CI in the delivery room is limited due to the absence of changes in complete blood count and inflammatory markers (C-reactive protein and procalcitonin) in most cases in the first hours after birth, and radiologic examination is cumbersome [6, 7, 32]. The need for immediate care of the infant prompted us to conduct several studies to develop and evaluate the efficacy of a standardized respiratory therapy protocol, regardless of the primary condition, based solely on the assessment of ARF. Taking into account the above data, the developed protocol for CPAP therapy can be considered as a universal method for the treatment of ARF in the delivery room for preterm and premature infants from 35 weeks of gestation, provided the protocol criteria are met.

Brain ischemia resulting from respiratory disorders and hypoxemia has been described as a consequence of RDS and infection [33], but no studies have been found to suggest an association between brain damage and TTN in late preterm infants.

Our previous studies on TTN in preterm infants have shown an association of this condition with functional and biochemical changes in the brain, characterized by a low level of cerebral oxygenation after birth and its gradual increase [34], as well as lower levels of nerve growth factor beta (NGF-β) 6–12 hours after birth compared to healthy preterm infants [35]. Furthermore, the use of a standardized protocol of CPAP therapy in the delivery room in preterm infants with TTN reduced the incidence of BI (from 85.5% to 29.1%, *P*=0.001), the incidence of infant admission to the NICU (from 70.3% to 18.2%, *P*=0.001), and the total length of hospital stay (from 10 (7; 12) to 3 (2; 7) days, *P*=0.001) [16]. On the other hand, the use of the same CPAP protocol in preterm infants with infections did not affect the

incidence of the above outcomes but also did not worsen their condition [19].

Considering that TTN is the most common cause of ARF in the delivery room in neonates born over $35^{0/7}$ weeks of gestation, and that TTN and CI together account for 95–99% of ARF cases, the application of the CPAP protocol in late preterm neonates at GA over $35^{0/7}$ weeks with ARF of any etiology is justified from both a scientific and practical perspective as a standardized method that significantly reduces the severity of the disease and the duration of treatment.

Study limitations:

1. Single-center, retrospective nature of the study.

2. Significant differences in baseline characteristics of the control and study groups regarding sex and birth weight, which may have a confounding effect.

Conclusion

The developed standardized protocol of CPAP therapy in the delivery room has demonstrated high efficacy and safety and can be recommended as a basic method of therapy for late preterm neonates. The maximum efficacy of the protocol was achieved in patients with TTN, which is the predominant cause of ARF in this cohort.

References

1. *Hooper S. B., Te Pas A. B., Kitchen M. J.* Respiratory transition in the newborn: a three-phase process. *Arch Dis Child. Fetal Neonatal Ed.* 2016; 101 (3): F266–271. DOI 10.1136/archdischild-2013-305704. PMID: 26542877.
2. *Brown M. J., Olver R. E., Ramsden C. A., Strang L. B., Walters D. V.* Effects of adrenaline and of spontaneous labour on the secretion and absorption of lung liquid in the fetal lamb. *J Physiol.* 1983; 344: 137–152. DOI 10.1113/jphysiol.1983.sp014929. PMID: 6655575.
3. *Umran R. M. R., Khalil R. M.* Association between low cord serum cortisol level and transient tachypnea of the newborn in late preterm and term neonates delivered by elective cesarean section. *Am J Perinatol.* 2022; 39 (11): 1254–1260. DOI: 10.1055/s-0040-1722603. PMID: 33454947.
4. *Mahoney A. D., Jain L.* Respiratory disorders in moderately preterm, late preterm, and early term infants *Clin Perinatol.* 2013; 40 (4): 665–678. DOI 10.1016/j.clp.2013.07.004. PMID: 24182954.
5. *Овсянников Д. Ю., Бойцова Е. В., Жесткова М. А., Кршеминская И. В., Ашерова И. К., Украинцев С. Е., Межинский С. С.* Неонатальная пульмонология: Монография. (ред. Овсянников Д. Ю.). М.: Севен-Принт; 2022: 168. *Ovsyannikov D. Yu., Boitsova E. V., Zhestkova M. A., Krsheminskaya I. V., Asherova I. K., Ukraintsev S. E., Mezhinsky S. S.* Neonatal pulmonology: Monograph. (ed. Ovsyannikov D. Yu.). M.: Seven-Print; 2022: 168. (in Russ.). ISBN 978-5-91556-757-2. EDN NGFFJV.
6. *Шестак Е. В., Ковтун О. П., Ксенофонтова О. Л.* Транзиторное тахипноэ у новорожденных: монография; ред. Ковтун О. П. д-р мед. наук, проф., акад. РАН; М-во здравоохранения РФ, Урал. гос. мед. ун-т. Екатеринбург : УГМУ; 2023: 144. *Shestak E. V., Kovtun O. P., Ksenofontova O. L.* Transient tachypnea in newborns: monograph; ed. Kovtun O. P. Doctor of Medical Sciences, Professor, acad. RAS; Ministry of Health of the Russian Federation, Ural State Medical University Yekaterinburg: USMU; 2023: 144. (in Russ.). ISBN 978-5-00168-047-5.
7. *Овсянников Д. Ю., Володин Н. Н.* Заболевания легких новорожденных: трудности диагностики, диагностические критерии и последствия. *Педиатрия. Журнал им. Г. Н. Сперанского.* 2022; 101 (3): 170–177. *Ovsyannikov D. Yu., Volodin N. N.* Lung diseases in newborns: diagnostic difficulties, diagnostic criteria and consequences. *Pediatrics. G.N Speransky J. = Pediatria. Zhournal im. G. N. Speranskogo*. 2022; 101 (3): 170–177. (in Russ.). DOI: 10.24110/0031-403X-2022-101-3-170-177.
8. *Антонов А. Г., Байбарина Е. Н., Балашова Е. Н., Дегтярев Д. Н., Зубков В. В., Иванов Д. О., Ионов О. В., с соавт.* Врожденная пневмония: клинические рекомендации. *Неонатология: новости, мнения, обучение.* 2017; 4: 133–148. *Antonov A. G., Baibarina E. N., Balashova E. N., Degtyarev D. N., Zubkov V. V., Ivanov D. O., Ionov O. V., et al.* Congenital pneumonia: clinical recommendations. *Neonatology: News, Opinions, Training = Neonatologiya: Novosti, Mneniya, Obucheniye.* 2017; 4: 133–148. (in Russ.). DOI 10.24411/2308-2402-2017-00049.
9. *Шестак Е. В.* Кистозно-аденоматозная мальформация легкого II типа у новорожденного, проблемы ранней диагностики. *Уральский медицинский журнал.* 2022; 21 (1): 77–84. *Shestak E. V.* Cystic adenomatous lung malformation of type II in the newborn, problems of early diagnosis. *Ural Medical Journal = Uralskiy Meditsinskiy Zhurnal.* 2022; 21 (1): 77–84. (in Russ.). DOI: 10.52420/2071-5943-2022-21-1-77-84.
10. *Перепелица С. А.* Острый респираторный дистресс-синдром у недоношенных новорожденных (морфологическое исследование). *Общая реаниматология.* 2020; 16 (1): 35–44. *Perepelitsa S. A.* Acute respiratory distress syndrome in preterm newborns (morphological study). *General Reanimatology = Obshchaya Reanimatologiya.* 2020; 16 (1): 35–44. (in Russ.&Eng.). DOI: 10.15360/1813-9779-2020-1-35-44.
11. *Голомидов А. В., Григорьев Е. В., Мозес В. Г., Мозес К. Б.* Патогенез, прогнозирование и исходы синдрома полиорганной недостаточности у новорожденных (обзор). *Общая реаниматология.* 2022; 18 (6): 37–49. *Golomidov A. V., Grigoriev E. V., Moses V. G., Moses K. B.* Pathogenesis, prognosis and outcomes of multiple organ failure in newborns (review). *General Reanimatology = Obshchaya Reanimatologiya.* 2022; 18 (6): 37–49. (in Russ.&Eng.). DOI: 10.15360/1813-9779-2022-6-37-49.
12. *Osman A. M., El-Farrash R. A., Mohammed E. H.* Early rescue Neopuff for infants with transient tachypnea of newborn: a randomized controlled trial. *J Matern Fetal Neonatal Med.* 2019; 32 (4): 597–603. DOI 10.1080/14767058.2017.1387531. PMID: 28965435.
13. *Gizzi C., Klifa R., Pattumelli M. G., Massenzi L., Taveira M., Shankar-Aguilera S., De Luca D.* Continuous positive airway pressure and the burden of care for transient tachypnea of the neonate: retrospective cohort study. *Am J Perinatol.* 2015; 32 (10): 939–943. DOI: 10.1055/s-0034-1543988. PMID: 25811328.
14. *Migliori C., Motta M., Angeli A., Chirico G.* Nasal bilevel vs. continuous positive airway pressure in preterm infants. *Pediatr Pulmonol.* 2005; 40 (5): 426–430. DOI: 10.1002/ppul.20276. PMID: 16155882.
15. Реанимация и стабилизация состояния новорожденных детей в родильном зале: методическое письмо Министерства Здравоохранения Российской Федерации от 4 марта 2020 г. № 15–4/И/2–2570 под редакцией профессора Е. Н. Байбариной; 2020: 55. Resuscitation and stabilization of newborns in the delivery room: Methodical instructions of the Ministry of Health of the Russian Federation dated March 4, 2020 No. 15-4/I/2-2570 edited by Professor E. N. Baibarina; 2020: 55. (in Russ.). URL: http: //niiomm.ru/attachments/article/370/Реанимация%20и%20стабилизация%20состояния%20новорожденных%20детей%20в%20родильном%20зале%202020.pdf.
16. Неонатология: национальное руководство: краткое издание. ред. Володин Н. Н. Москва: ГЭОТАР–Медиа; 2019: 896. Neonatology: National guidelines: short edition. ed. Volodin N. N. Moscow: GEOTAR–Media; 2019: 896. (in Russ.). ISBN 978–5–9704–4877–9.
17. *Шестак Е. В., Ковтун О. П., Ксенофонтова О. Л., Додров Д. С., Калякова Н. В.* Респираторные стратегии, влияющие на тяжесть течения транзиторного тахипноэ новорожденных. *Врач.* 2022; (1): 56–60. *Shestak E. V., Kovtun O. P., Ksenofontova O. L., Dodrov D. S., Kalyakova N. V.* Respiratory strategies affecting the severity of transient tachypnea in newborns. *Doctor = Vrach.* 2022; (1): 56–60. (in Russ.). DOI: 10.29296/25877305-2022-01-09.
18. *Шестак Е. В., Ковтун О. П., Ксенофонтова О. Л., Додров Д. С.* Эффективность и безопасность стандартизированного протокола CPAP-терапии доношенных новорожденных в родовом зале при транзиторном тахипноэ: клиническое ис-

следование с историческим контролем. *Вопросы современной педиатрии*. 2022; 21 (4): 320–330. *Shestak E. V., Kovtun O. P., Ksenofontova O. L., Dodrov D. S.* Efficacy and safety of a standardized protocol of CPAP therapy for full-term newborns in delivery room at transient tachypnea: clinical trial with historical control. *Issues of Modern Pediatrics = Voprosy Sovremennoy Pediatrii*. 2022; 21 (4): 320–330. (in Russ.). DOI: 10.15690/vsp.v21i4.2445.

19. *Шестак Е. В., Ковтун О. П.* Стандартизированный подход к CPAP-терапии в родовом зале у доношенных детей с врожденной инфекцией: наблюдательное исследование. *Российский педиатрический журнал*. 2023; 4 (3): 85–93. *Shestak E. V., Kovtun O. P.* Standardized approach to CPAP therapy in the delivery room in full-term infants with congenital infection: observational research. *Russian Pediatric Journal/ Rossiyskiy Pediatricheskiy Zhurnal*. 2023; 4 (3): 85–93. (in Russ.). DOI: 10.15690/rpj.v4i3.2618.
20. *Шестак Е. В., Ковтун О. П.* Прогнозирование тяжести течения транзиторного тахипноэ у доношенных новорожденных в родовом зале. *Российский педиатрический журнал*. 2022; 25 (2): 91–95. *Shestak E. V., Kovtun O. P.* Predicting the severity of the course of transient tachypnea in full-term newborns in the delivery room. *Russian Pediatric Journal/ Rossiyskiy Pediatricheskiy Zhurnal*. 2022; 25 (2): 91–95. (in Russ.). DOI: 10.46563/1560-9561-2022-25-2-91-95.
21. *Мостовой А. В., Карпова А. Л., Володин Н. Н., Петрова А. С., Милева О. И., Захарова Н. И., Дмитриев А. В., с соавт.* Оценка клинической практики проведения респираторной терапии и ее исходов у недоношенных новорожденных гестационного возраста 34–36 недель с респираторным дистресс-синдромом. *Анестезиология и реаниматология*. 2021; (4): 67–72. *Mostovoy A. V., Karpova A. L., Volodin N. N., Petrova A. S., Mileva O. I., Zakharova N. I., Dmitriev A. V., et al.* Evaluation of the clinical practice of respiratory therapy and outcomes in late preterm (34–36 weeks) with respiratory distress syndrome. *Russian Journal of Anesthesiology and Reanimatology/ Anesteziologiya i Reanimatologiya*. 2021; (4): 67–72. (in Russ.). DOI: 10.17116/anaesthesiology202104167.
22. *Kumar A., Bha B.V* Epidemiology of respiratory distress of newborns. *Indian J Pediatr*. 1996; 63 (1): 93–98. DOI: 10.1007/BF02823875. PMID: 10829971.
23. *Ryan C. A. Hughes P.* Neonatal respiratory morbidity and mode of delivery at term: influence of timing of elective caesarean section. *Br J Obstet Gynaecol*. 1995; 102 (10): 843–844. DOI: 10.1111/j.1471-0528.1995.tb10861.x. PMID: 7547751.
24. *Kasap B., Duman N., Ozer E., Tatli M., Kumral A., Ozkan H.* Transient tachypnea of the newborn: predictive factor for prolonged tachypnea. *Pediatr Intl*. 2008; 50 (1): 81–84. DOI: 10.1111/j.1442-200X.2007.02535.x. PMID: 18279211.
25. *Jain L.* Respiratory morbidity in late–preterm infants: prevention is better than cure! *Am J Perinatol*. 2008; 25 (2): 75–78. DOI: 10.1055/s–2007–1022471. PMID: 18214813.
26. *Raju T. N. K., Higgins R.D, Stark A. R., Leveno K. J.* Optimizing care and outcome for late–preterm (near–term) infants: a summary of the workshop sponsored by the National Institute of Child Health and Human Development. *Pediatrics*. 2006; 118 (3): 1207–1214. DOI: 10.1542/peds.2006–0018. PMID: 16951017.
27. *Gomez-Lopez N., Galaz J., Miller D., Farias-Jofre M., Liu Z., Arenas-Hernandez M., Garcia-Flores V., et al.* The immunobiology of preterm labor and birth: intra-amniotic inflammation or breakdown of maternal-fetal homeostasis. *Reproduction*. 2022; 164 (2): R11–R45. DOI: 10.1530/REP-22-0046. PMID: 35559791.
28. *Jiang M., Mishu M. M., Lu D., Yin X.* A case control study of risk factors and neonatal outcomes of preterm birth. *Taiwan J Obstet Gynecol*. 2018; 57 (6): 814–818. DOI: 10.1016/j.tjog.2018.10.008. PMID: 30545533.
29. *Gibbs R. S.* The origins of stillbirth: infectious diseases. *Semin Perinatol*. 2002; 26 (1): 75–78. DOI: 10.1053/sper.2002.29839. PMID: 11876570.
30. *Rawlinson W. D., Hall B., Jones C. A., Jeffery H. E., Arbuckle S. M., Graf N., Howard J., et al.* Viruses and other infections in stillbirth: what is the evidence and what should we be doing? *Pathology*. 2008; 40 (2): 149–160. DOI: 10.1080/00313020701813792. PMID: 18203037.
31. *Goldenberg R. L., Thompson C.* The infectious origins of stillbirth. *Am J Obstet Gynecol*. 2003; 189 (3): 861–873. DOI: 10.1067/s0002-9378 (03)00470-8. PMID: 14526331.
32. *Puopolo K. M., Benitz W. E., Zaoutis T. E.*; Committee on Fetus and Newborn; Committee on Infectious Diseases. Management of neonates born at ⩾ 35 0/7 weeks‘ gestation with suspected or proven early-onset bacterial sepsis. *Pediatrics*. 2018; 142 (6): e20182894. DOI: 10.1542/peds.2018-2894. PMID: 30455342.
33. *Greco P., Nencini G., Piva I., Scioscia M., Volta C. A., Spadaro S., Neri M., et al.* Pathophysiology of hypoxic-ischemic encephalopathy: a review of the past and a view on the future. *Acta Neurol Bel*. 2020; 120 (2): 277–288. DOI: 10.1007/s13760-020-01308-3. PMID: 32112349.
34. *Шестак Е. В., Ковтун О. П., Ксенофонтова О. Л.* Оценка церебральной оксигенации при развитии транзиторного тахипноэ у новорожденных. *Педиатрия. Журнал им. Г. Н. Сперанского*. 2023; 102 (1): 27–35. *Shestak E. V., Kovtun O. P., Ksenofontova O. L.* Assessment of cerebral oxygenation in the development of transient tachypnea in newborns. *Pediatrics. G. N. Speransky J. = Pediatria. Zhournal im. G. N. Speranskogo*. 2023; 102 (1): 27–35. (in Russ.). DOI: 10.24110/0031-403X-2023-102-1-27-35.
35. *Шестак Е. В., Ковтун О. П., Базарный В. В., Полушина Л. Г., Максимова А. Ю.* Диагностическая оценка уровня нейротрофических факторов VEGF, BDNF, β-NGF у новорожденных с транзиторным тахипноэ и церебральной ишемией в сравнении со здоровыми детьми. *Педиатрия. Журнал им. Г. Н. Сперанского*. 2024; 103 (1): 49–57. *Shestak E. V., Kovtun O. P., Bazarny V. V., Polushina L. G., Maksimova A.Yu.* Assessment of the level of neurotrophic factors VEGF, BDNF, β-NGF in newborns with transient tachypnea and cerebral ischemia in comparison with healthy children. *Pediatrics. G.N Speransky J. = Pediatria. Zhournal im. G. N. Speranskogo*. 2024; 103 (1): 49–57. (in Russ.). DOI: 10.24110/0031-403X-2024-103-1-49-57.

Received 11.08.2023
Accepted 10.09 2024

https://doi.org/10.15360/1813-9779-2024-5-55-69

Procedural Complications of Central Venous Catheter Placement in Pediatric Oncology Practice (a Clinical Case Series)

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For citation: *Vladislav V. Shchukin, Nikolay P. Leonov, Elena A. Spiridonova, Vladimir V. Selivanov, Ekaterina V. Dergunova, Galina A. Novichkova, Natalia V. Myakova, Nikolay S. Grachev, Mikhail V. Bykov, Anastasia A. Bystrova, Rina S. Grigoryan, Nune V. Matinyan, Anton V. Petrushin, Ugo Loaisa.* Procedural Complications of Central Venous Catheter Placement in Pediatric Oncology Practice. *Obshchaya Reanimatologiya = General Reanimatology.* 2024; 20 (5): 55–69. https://doi.org/10.15360/1813-9779-2024-5-55-69 [In Russ. and Engl.]

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Summary

The availability of central venous access is the cornerstone of contemporary pediatric oncology and hematology. As a result, the percentage of pediatric patients receiving infusion chemotherapy who require a central line remains high. Central venous catheter insertion can be associated with procedural complications, including life-threatening ones.

Aim to investigate the potential factors leading to complications during central venous catheterization in order to develop preventive strategies.

Materials and methods. The study included 1,512 original cases of patients aged 1 month to 20 years treated at the D. Rogachev National Research Medical Center between 2019 and 2022. The following 10 complications were examined: failed first venipuncture attempt, guidewire/catheter malpositioning, guidewire knotting, life-threatening arrhythmias, guidewire entrapment in the trabecular network of the right ventricle, arterial puncture, pneumothorax, hemothorax, puncture of lung parenchyma, Horner's syndrome. In addition, four rare complications were noted, including phrenic nerve injury, cardiac tamponade, alveolar hemorrhage, and arterial pseudoaneurysm.

Results. The primary cause of all complications was direct mechanical injury to anatomical structures by a needle or guidewire/catheter. When inadvertent vascular injury and bleeding occur, the resulting hematoma may lead to further damage by compressing soft tissues. Excessively deep insertion of the guidewire may cause its knotting or cardiac arrhythmias. Adequate physician training and strict adherence to procedural protocols are essential to avoid these complications.

Conclusion. Central venous catheterization remains a procedure with potential complications. Although ultrasound guidance does not eliminate all risks, it increases the likelihood of successful venipuncture at the first attempt, thereby reducing complication rates. Recognizing the potential causes of procedural complications during central venous access placement, including uncommon ones, facilitates early diagnosis and appropriate medical intervention.

Keywords: central venous catheter; central venous catheterization in children; complication of central venous catheter placement in children; pneumothorax; hemothorax; neurological disorders in children; cardiac tamponade; pseudoaneurysm; pediatric oncology practice.

Conflict of interest. The authors declare no conflict of interest.

Introduction

Central venous access is essential in pediatric oncology and hematology, and the frequency of central venous catheterization in this patient population remains high.

The insertion and operation of venous access devices can lead to complications of varying severity, with thrombosis, infections, and pneumothorax or hemothorax being the most common.

Rare but life-threatening complications can also occur during central venous catheterization, and late recognition of these complications can result in patient death [1]. Based on the timing of clinical manifestation, complications are classified

as early (detected within 24 hours) and late (detected after 24 hours post-catheterization).

Since 2013, the Dmitry Rogachev NMRC National Medical Research Center of Pediatric Hematology, Oncology and Immunology (NMRC PHOI) has been recording all problems that occur during the insertion of vascular devices. Since 2018, new software has made it possible to analyze these complications. In addition to complications identified since 2018, we have highlighted several rare but relevant complications noted before 2018 or outside the NMRC PHOI.

The aim was to evaluate the potential causes of complications of central venous access insertion in order to develop strategies to prevent complications.

Material and Methods

In 2019–2022, we identified 1512 complications that occurred during 6690 central venous catheterizations in patients aged 1 month to 20 years treated at the Dmitry Rogachev Center.

Ultrasound and C-arm data were recorded during all catheterizations. The catheterization protocol included a complete list of possible complications of catheterization. Timeliness and accuracy of protocol completion were checked daily.

One anesthesiologist was permanently involved in central venous catheterization, and four staff members temporarily replaced him or assisted in catheterization. Training in catheterization (implantation) using ultrasound navigation was conducted semi-annually. Data were collected centrally. An audit was performed. The cumulative risk of all adverse events during venous catheterization and the relative incidence of the most common catheterization complications were calculated. The cumulative risk was defined as the ratio of a given catheterization complication per year to the number of catheterizations per year and expressed as a percentage. Relative incidence was calculated as the ratio of new cases of catheterization complications per year to the estimated rate of catheterizations during the study period and reported as the number of cases per 100 catheterizations per year. The average number of catheterizations per year was calculated as the arithmetic mean of all catheterizations over the 4 years of the audit. The audit results for 2019–2022 are shown in Table 1.

Informed consent for the publication of anonymized observations was obtained from all adult patients or legal representatives of pediatric patients.

A total of 1,512 original observations were included in the analysis. We reviewed 10 complications: failed first venipuncture attempt, guidewire/catheter malposition, guidewire knotting, life-threatening arrhythmias, guidewire entrapment in the trabecular meshwork of the right ventricle, arterial puncture, pneumothorax, hemothorax, puncture of lung parenchyma, and Horner syndrome. In addition, four rare complications were identified: phrenic nerve injury, cardiac tamponade, alveolar hemorrhage, and arterial pseudoaneurysm.

All photographs are from the author's archive.

Complications Related to Insertion of a Central Venous Access Device

Failed insertion on the first attempt. The most common complication of catheterization attempts (8.5 to 11.7% of all catheterizations) was re-puncture. The main reasons included:

— in young children, the similar diameter of the patient's veins and the needle makes it difficult to accurately position the needle in the vein lumen, and when attempting to change the syringe to a J-shaped guide, needle displacement with partial exit of the needle from the vein or puncture of the posterior wall of the vein occurs more frequently;

— insufficient operator proficiency in ultrasound-guided puncture technique (relative incidence rate decreased by 2–3 cases per 100 catheterization-years as operators gained experience).

The significance of the patient's anatomical peculiarities combined with poor proficiency in ultrasound guidance for the risk of iatrogenic complications was confirmed by Vartanova I. V. et al [2].

Malposition of the guidewire or catheter (displacement of the guidewire into the contralateral subclavian or jugular vein, placement of the catheter into the inferior vena cava, or placement of the catheter into the azygos vein). According to our data, the cumulative risk of malposition was 7.7–11.5%. Changes in the direction of guidewire movement could be caused by, among other things, intravascular structures (valves, thrombotic deposits) (Fig. 1, *a*).

Guidewire placement in the unilateral jugular vein during subclavian vein puncture was also frequently observed when the needle entry point was near the jugular-subclavian vein confluence (Fig. 1, *b*).

Anatomical features such as the dilated azygos vein entry site may contribute to incorrect guidewire and catheter positioning.

Fig. 2, a shows a tunneled catheter placed in a 10-year-old patient A. with a history of multiple venous catheterizations and catheter-associated thrombosis. At the time of insertion, no attention was paid to the «tortuous» course of the catheter. The next day, the patient underwent a chest CT, which showed that the catheter was in the azygos vein (Fig. 2, *b*). The catheter was replaced.

Despite the seemingly «harmless» misplacement of the catheter, it should be noted that if the catheter tip is outside the central veins or the right atrium, its location should be considered peripheral, and the administration of irritating

Table. Complications during central venous catheterization in 2019–2022 (data from the Dmitry Rogachev Center).

	v.femoralis	v. jugularis interna	v. subclavia	Total, 2019		v. femoralis	v. jugularis interna	v. subclavia	Total, 2020		v. femoralis	v. jugularis interna	v. subclavia	Total, 2021		v. femoralis	v. jugularis interna	v. subclavia	Total, 2022	
				Number, *N*	CR, %				Number, *N*	CR, %				Number, *N*	CR, %				Number, *N*	CR, %
Air embolism		1		1	0.06				0	0.00			2	2	0.12				0	0.00
Acute arrhythmia			1	1	0.06				0	0.00		2		2	0.12			1	1	0.06
Malposition, including	1	18	117	136	7.76	2	43	108	153	9.54	4	43	153	200	11.51		23	129	152	9.52
Migration of the guidewire into the contralateral subclavian vein		6	32	38	2.17		31	19	50	3.12		26	25	51	2.93		12	21	33	2.07
Migration of the guidewire into the jugular vein	1	7	81	89	5.08		7	87	94	5.86	3	6	125	134	7.71		9	107	116	7.26
Displacement of the catheter into the contralateral subclavian vein		3		3	0.17				0	0.00		8		8	0.46				0	0.00
Insertion of the catheter into the right ventricular cavity			1	1	0.06				0	0.00		2		2	0.12				0	0.00
Incorrect positioning of the catheter		2	3	5	0.29	2	5	2	9	0.56	1	1	3	5	0.29		2	1	3	0.19
Multiple puncture attempts	9	49	147	205	11.70	12	38	106	156	9.73	14	58	116	188	10.82	10	27	98	135	8.45
Bleeding from the puncture site			1	1	0.06		1	1	2	0.12		2	2	4	0.23				0	0.00
Hematoma at the puncture site		2	1	3	0.17			2	2	0.12			2	2	0.12		3	3	6	0.38
Puncture of the homonymous artery with clinically significant bleeding				0	0.00				0	0.00	1			1	0.06				0	0.00
Puncture of the homonymous artery without clinically significant bleeding	5	7	23	35	2.00	7	12	7	26	1.62	4	7	21	32	1.84	1		6	7	0.44
Vascular wall injury with guidewire displacement		3	9	12	0.68	1	2	3	6	0.37		7	12	19	1.09	1	5	5	11	0.69
Catheter extravasation		1	1	2	0.11				0	0.00				0	0.00				0	0.00
Vascular/heart chamber thrombosis	1			1	0.06		1		1	0.06				0	0.00			1	1	0.06
Catheter occlusion not related to thrombosis		1		1	0.06				0	0.00				0	0.00				0	0.00
Pneumothorax		1	2	3	0.17				0	0.00				0	0.00				0	0.00
Nerve plexus injury			1	1	0.06				0	0.00				0	0.00				0	0.00
Pneumomediastinum				0	0.00				0	0.00			1	1	0.06				0	0.00
Total complications				402	22.95				346	21.58				451	25.95				313	19.60
Total catheterizations				1752					1603					1738					1597	

Note. Cumulative risk (CR) values for complications located in areas: femoral vein, internal jugular vein, subclavian vein; *n* — absolute number of patients.

and harmful solutions through it is either limited by the infusion rate or not recommended [3]. In addition, the direction of the catheter tip against the blood flow during fluid therapy inevitably leads to regional slowing of blood flow, which is one of the components of Virchow's triad for the early development of catheter-associated thrombosis.

Because incorrect guidewire placement during catheter insertion using the Seldinger technique results in catheter malposition [4, 5], it is important to timely diagnose this issue. Fluoroscopy during catheterization allows for opportunely visualization of guidewire advancement but increases the radiation exposure for the patient and staff. The use of ultrasound visualization of catheter position, such as the ECHOTIP algorithms available in adult, pediatric, and infant versions (ECHOTIP-PED, NEO-ECHOTIP), serves as an alternative [6–8].

The relative frequency of guidewire (catheter) misplacement decreased by 3 per 100 catheterizations per year after additional hands-on training in the simulation center.

Guidewire knotting. Displacement of part or all of the needle lumen outside the vessel after blood sampling results in an extravascular position of the J-tip, with the operator capable of forcing most of the guidewire into the vasculature (Fig. 3). This complication can result in vein injury, knotting, or guidewire damage, especially during forceful manipulation. In our practice, fluoroscopy revealed guidewire knotting in three patients. In two cases, the knot was disentangled by manipulation under fluoroscopic control. One case, shown in Fig. 4, required surgical access to the subclavian vein and release of the guidewire. Fig. 5 shows the retrieved guidewire with the knot. Deep guidewire

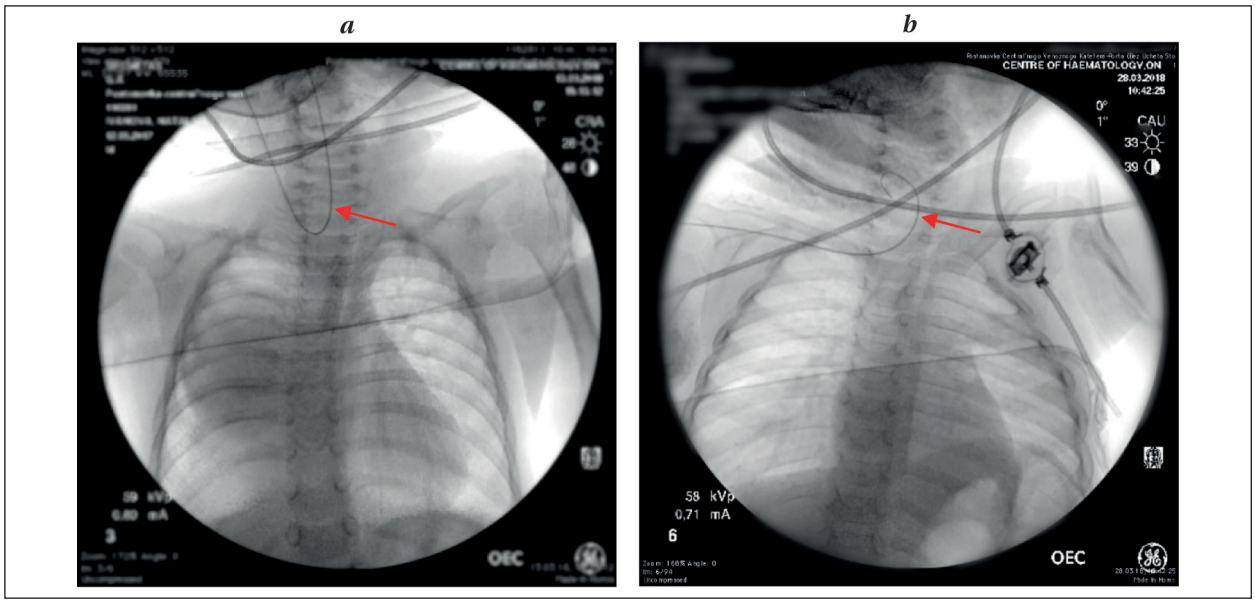

Fig. 1. Change the direction of guidewire advancement.

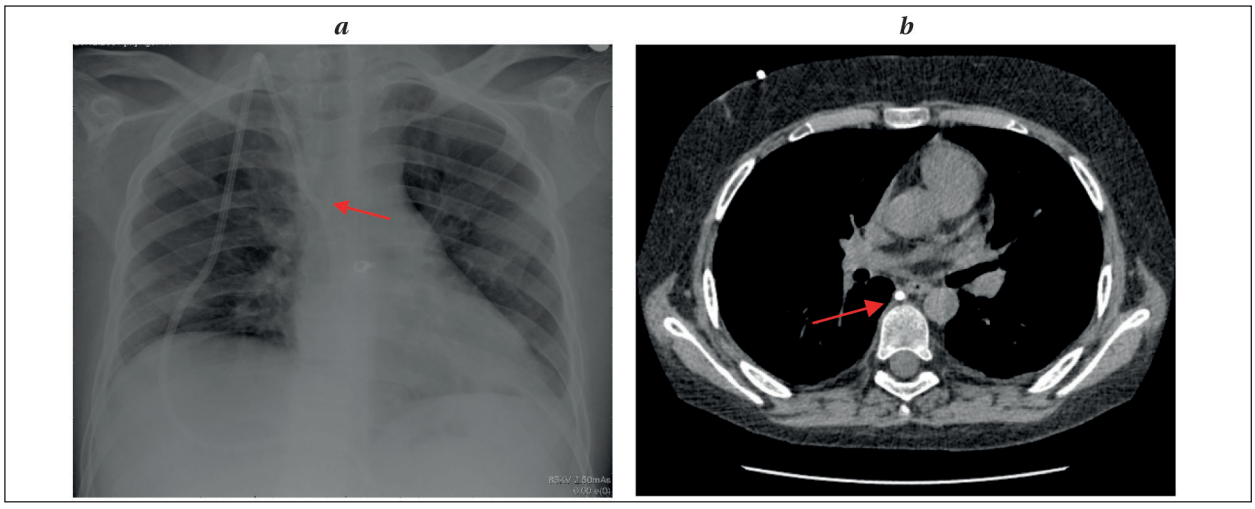

Fig. 2. The catheter placed in the azygos vein (indicated by the arrow).

insertion and rapid guidewire advancement were observed in all three cases.

Life-threatening arrhythmias (ventricular tachycardia, ventricular fibrillation). Introducing the guidewire or catheter too deeply can lead to various complications, including life-threatening ones. In our center, the cumulative risk of acute arrhythmias associated with catheterization was 0.06–0.12%.

Clinical case 1. Patient B., 16 years old, was admitted to the operating room for the placement of a Hickman-type tunnel catheter under sevoflurane inhalation anesthesia. Airway patency was maintained with a second-generation supraglottic airway device. After guidewire insertion and endocardial contact, frequent ventricular extrasystoles developed, progressing to ventricular tachycardia and ventricular fibrillation. Resuscitation, including indirect chest compressions and defibrillation, successfully restored rhythm following the first 150 J discharge.

Guidewire entrapment in the trabecular meshwork of the right ventricle.

Clinical cases 2 and 3. In Patient B., 5 years old, in 2016, and Patient G., 8 years old, in 2018, deep insertion of the guidewire into the right ventricular projection was accompanied by J-tip entrapment (presumably in the myocardial trabeculae). The guidewire could not be withdrawn. Attempts to pull back the guidewire caused it to oscillate in tandem with the heartbeat, and extrasystoles were recorded on the ECG. In both cases, insertion of the catheter through the guidewire and «straightening» of the J-tip of the guidewire in the catheter lumen proved effective, allowing the catheter to be withdrawn to the desired level.

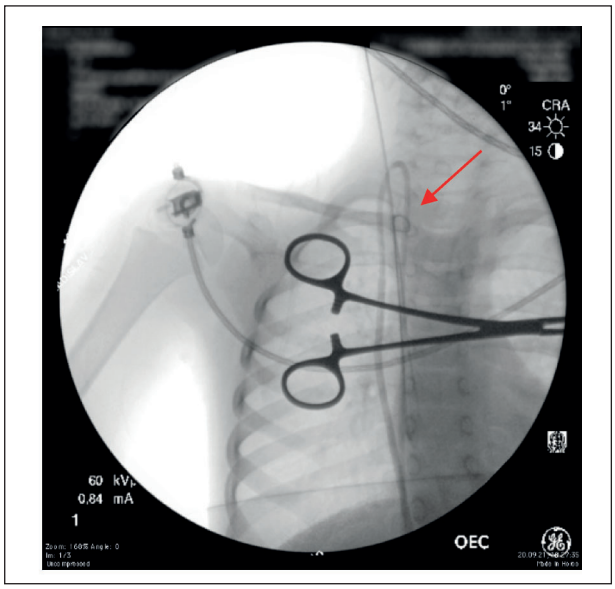

Fig. 3. Extravasation of the J-shaped guidewire (arrow). The guidewire itself is in the venous lumen.

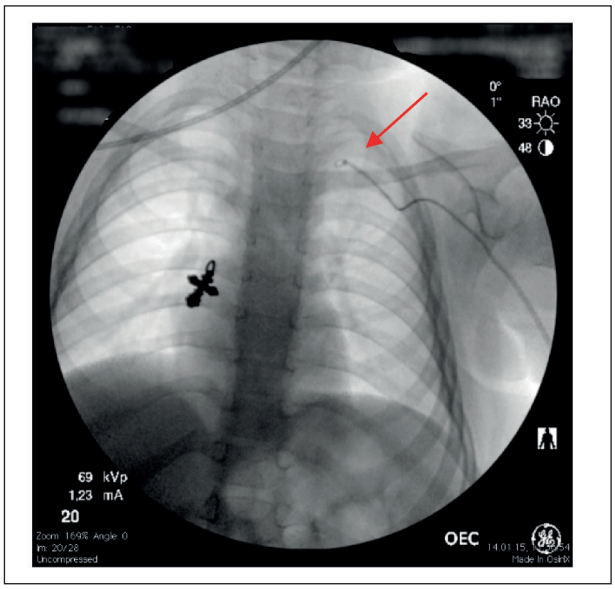

Fig. 4. Knotting of the guidewire in the lumen of the vein (indicated by the arrow).

In 2020, Verma A. et al. reported a similar case in which guidewire retrieval was achieved without additional devices by rotating the guidewire counterclockwise while gently pulling in sync with cardiac contractions [9]. The authors of this report reasonably noted that to avoid complications associated with deep guidewire insertion, it is essential not to insert the guidewire beyond the endpoint of the catheter.

To retrieve the guidewire in such situations, either through the introducer or directly, while preserving the integrity of the flexible catheter tip, Unnikrishan et al. proposed the J-tip straightening technique. This involves pressing the guidewire firmly against the palm with the middle, ring, and little fingers while simultaneously applying force to the guidewire as if «stretching» it with the thumb and index finger of the same hand. This method straightens the J-shaped tip and, as a result, does not require significant force to extract the guide. According to the authors, this method not only avoids complications related to the position of the guidewire, but also preserves the integrity of the J-tip for its eventual reinsertion and prevents vein displacement [10].

If the guidewire and catheter are located in the projection of the right atrium (as seen on x-ray), they may actually be in the inferior vena cava. This misplacement may also be associated with an increased incidence of thrombotic occlusion of the catheter due to the catheter pushing against the blood flow or migration of the catheter into the veins draining into the inferior vena cava. Such a case is shown in Fig. 6. At the time of insertion, the catheter was positioned in the projection of the right atrium. Later, the catheter tip was found to be in the hepatic vein.

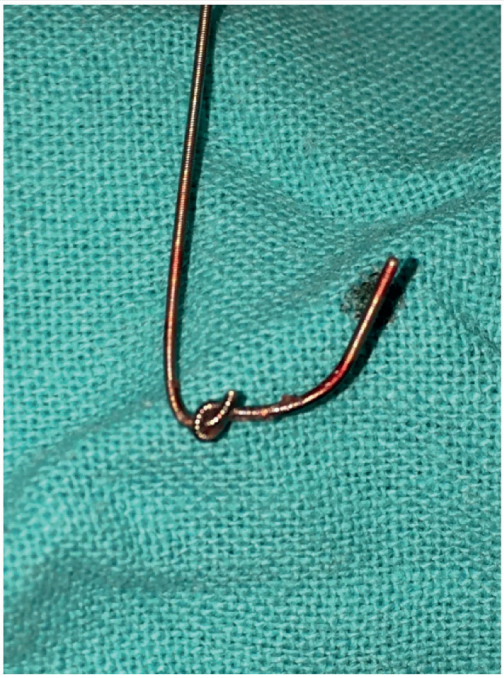

Fig. 5. Knotted guidewire after removal.

To avoid such complications, it is important to follow the rule: «Do not insert the guidewire deeper than the planned catheter location. To control the insertion depth, some guidewire models have markings that indicate both the distance from the catheter tip in centimeters and the length of the guidewire. In the absence of markings, the following method is used. As the needle tip passes the J-tip, the operator's tactile sensation changes. The operator then continues to insert the guidewire, grasping it with the fingers approximately 1 cm from the needle hub. In this way, the approximate

depth of guidewire insertion can be estimated and stopped in time, depending on the anatomical characteristics of the patient and the puncture site.

It is also important to remember the dangers of removing the guidewire through the needle or applying excessive physical force to the guidewire. These actions can cause damage and fragmentation (Fig. 7) [11].

Arterial puncture. According to a review [12], the incidence of arterial puncture is 6.3–9.4% during jugular vein catheterization, 3.1–4.9% during subclavian vein catheterization, and 9–15% during femoral vein catheterization. Romanenko N. A. et al. report that the frequency of arterial puncture reaches 3%; the authors attribute this complication to the technique of catheter insertion [13].

In our center, the cumulative risk of inadvertent arterial puncture and catheterization ranged from 0.44% to 2.00%. Arterial puncture occurred more frequently during subclavian vein catheterization, which we believe is due to the significant difficulty of ultrasound guidance. In the absence of ultrasound guidance, inadvertent arterial puncture can be attributed to anatomical variability in the location of arteries and veins in individual patients [14–16]. In addition, when puncturing the subclavian region, the proximity of the skin puncture site to the clavicle causes the needle to pass close to the clavicle. Consequently, as the needle tip is advanced under the clavicle, the bony base acts as a fulcrum, preventing the needle tip from reaching the vein directly. As a result, despite attempts to lower the needle, the needle trajectory becomes more vertical, directing the needle tip toward the artery below the vein (Fig. 8).

Ultrasound navigation may increase the rate of first attempt venipuncture and decrease the rate of inadvertent arterial puncture, but it does not reduce the overall number of complications [17]. The main causes of inadvertent arterial puncture when using ultrasound navigation are poor visualization of the needle tip, which may result from excessive body weight, defects in the imaging technique, and low operator experience.

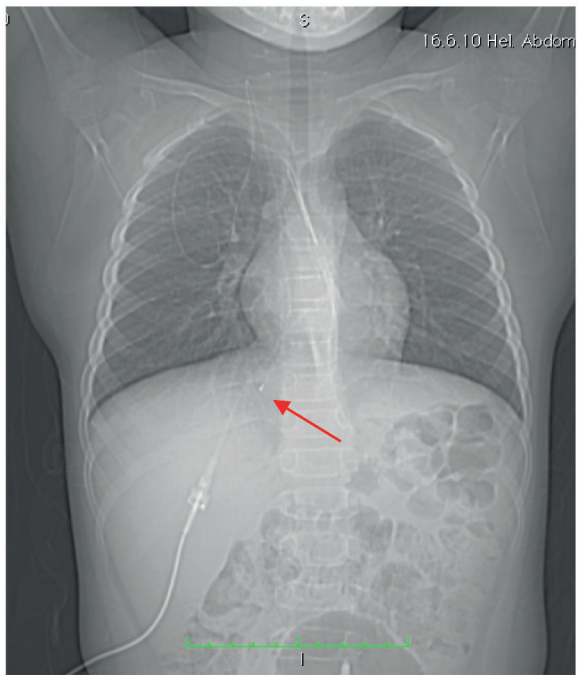

Fig. 6. The tip of the catheter placed in the hepatic vein (indicated by the arrow).

One of the early signs of an arterial puncture is the color of the leaking blood and its pulsatile flow, but these signs may be inconclusive in unstable patients [18]. Radiologic imaging allows detection of the guidewire position on the left side of the vertebral column and may suggest arterial catheterization (Fig. 9).

There was no significant change in the relative incidence of inadvertent punctures (catheterizations). However, by improving the practical skills of ultrasound navigation and training just one staff member in central venous catheterization, this parameter was reduced by 1.5 cases per 100 catheterizations per year.

Another cause of vein wall injury and perforation of adjacent structures, in our opinion, is the attempt to pass a relatively rigid catheter or dilator through the guidewire without properly securing it (Fig. 10).

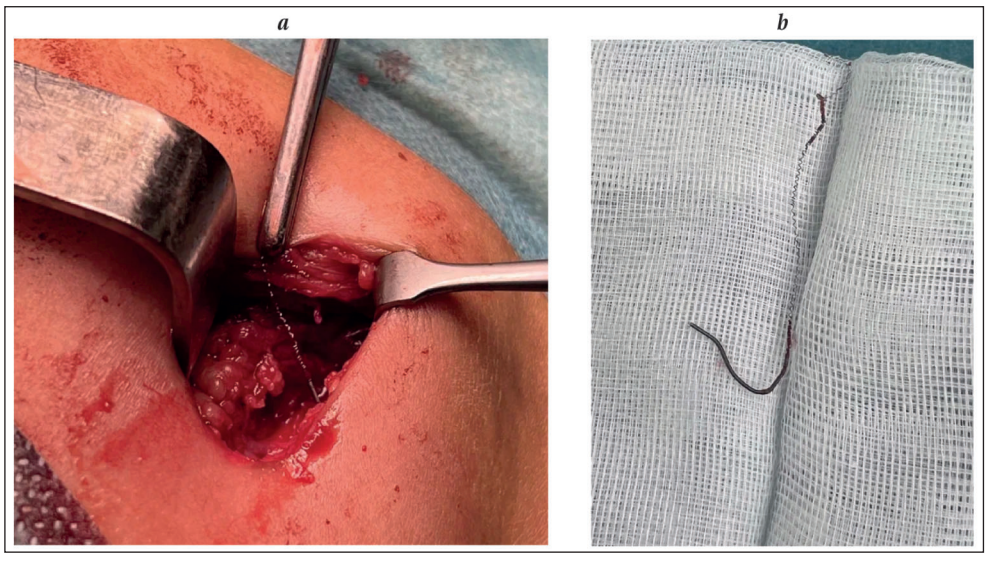

Fig. 7. Guidewire damage: surgical retrieval *(a)* and retrieved guidewire *(b)*.

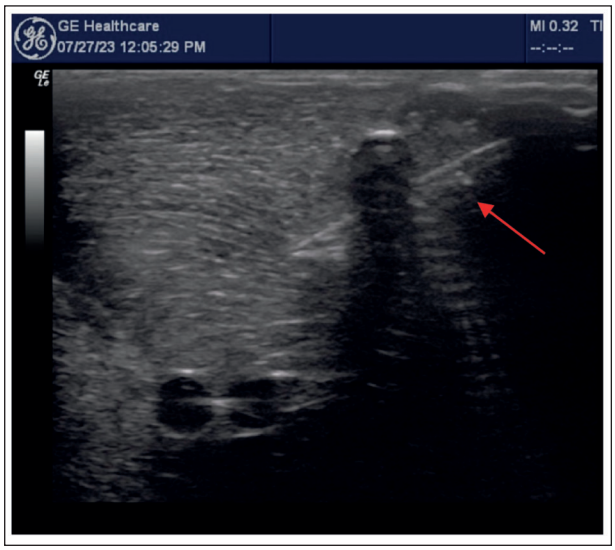

Fig. 8. Needle deflection during puncture through a bony obstruction (simulation) (arrow indicates the needle).

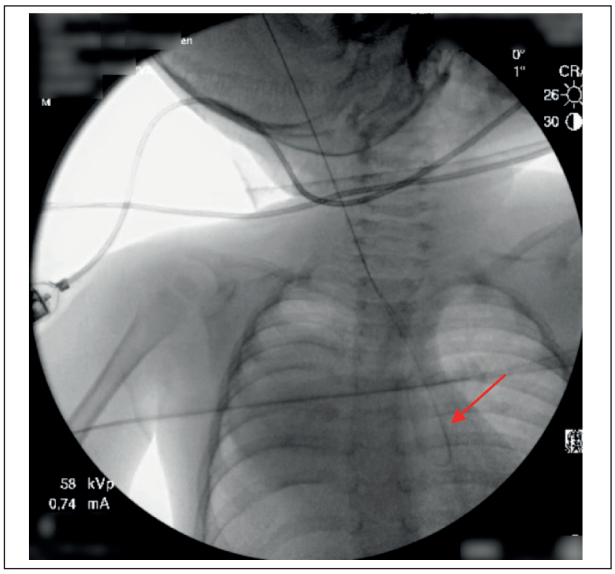

Fig. 9. Arterial puncture; the guidewire (indicated by the arrow) is positioned to the right of the vertebral column.

In this case, the device, which is stiffer than the guidewire, does not slide along the trajectory of the guidewire, but instead moves along its own trajectory, «grabbing» and deforming the guidewire and pulling it behind it. Fig. 10 shows the change in direction of movement of the guidewire and introducer when the outer end of the guidewire is accidentally released.

Similarly, the esophagus was injured during angiography when an introducer was inserted through a guidewire placed in the right internal jugular vein. After contrast injection, the esophageal injury and catheter malposition were confirmed (Fig. 11).

A case of perforation of the internal jugular vein and esophagus during placement of a central line through the left internal jugular vein was also reported in 2020 [19]. According to Wang et al, even deep structures such as the epidural space can be damaged during manipulation with a needle, guidewire, dilator, or catheter, potentially resulting in an epidural hematoma [18].

Cardiac tamponade. A rare but potentially fatal complication is cardiac tamponade. Because the pericardium merges with the adventitia of the great vessels just above the sternal angle (approximately at the level of the second costo-clavicular junction), perforation of the vein can lead to penetration of the catheter into the pericardium. Such

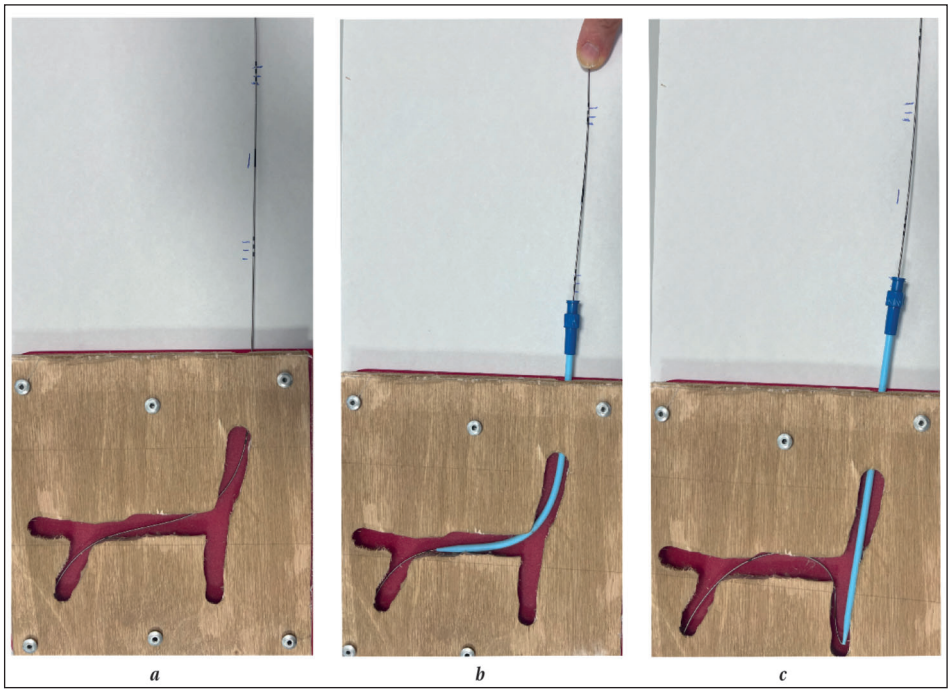

Fig. 10. Change of guidewire direction (simulation).
Note. *a* — the guidewire is inserted into the desired vein (e. g., from the left jugular vein to the superior vena cava); *b* — if the guidewire is held in place (the markings on the guidewire do not move relative to the simulator), the catheter will follow the direction of the guidewire; *c* — if the guidewire is not held in place, the catheter will pull the guidewire behind it due to friction and, with sufficient rigidity, may perforate the vein wall.

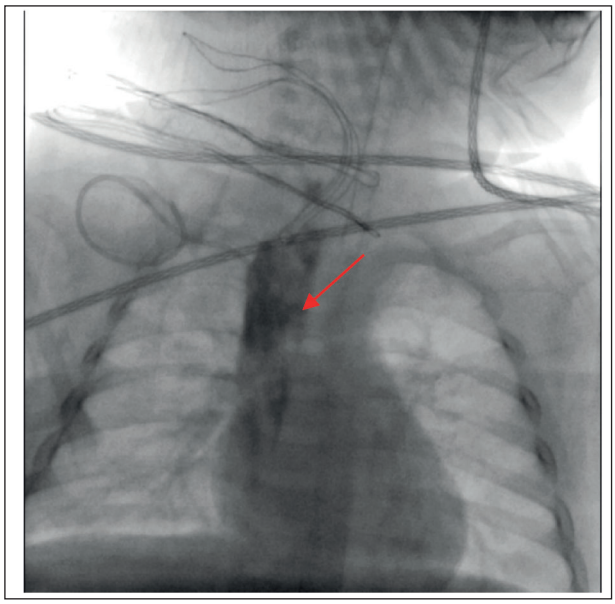

Fig. 11. Perforation of the esophagus by a catheter (contrast medium is visible in the esophagus after the end of its injection). The arrow indicates the esophagus with contrast.

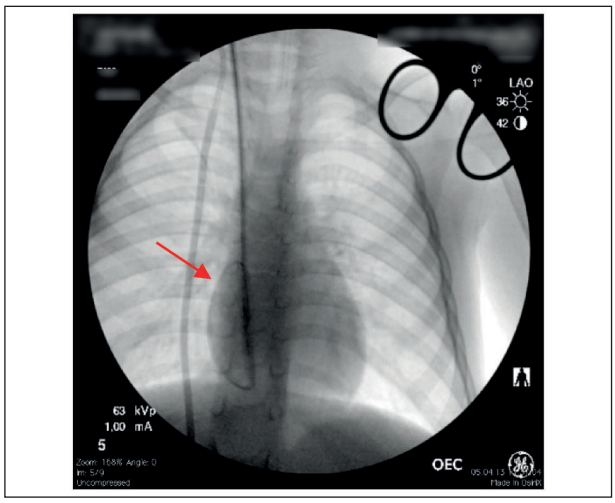

Fig. 12. Guidewire deformation following the shape of the heart.

an injury mechanism usually leads to the «sudden» development of tamponade a few hours after the start of fluid therapy [20].

Another cause of tamponade development is mechanical damage directly to the myocardium, which typically manifests immediately during catheter insertion.

Clinical case 4. Patient D., 2 years old, was admitted to the operating room for tunnel catheterization. A guidewire was inserted into the superior vena cava and its position was confirmed at the junction of the superior vena cava and the right atrium. During insertion of the splittable introducer, the operator did not securely fix the outer end of the guidewire and did not notice the change in its configuration on fluoroscopy (Fig. 12).

After catheter insertion, hypotension to 40/20 mmHg and bradycardia to 30 bpm were observed, and fluoroscopy showed that the borders of the heart were dilated compared to previous images. Chest compressions were initiated and an intraosseous line was placed. Echocardiography revealed hemopericardium with signs of cardiac tamponade. During cardiopulmonary resuscitation, thoracotomy and pericardiotomy were performed, a myocardial defect in the right atrial region was detected, and after suturing, hemodynamic parameters were stabilized. However, the patient continued to have a significant neurological deficit.

Pneumothorax, hemothorax, puncture of lung tissue, alveolar hemorrhage. The anatomic location of the subclavian, jugular, and brachiocephalic veins may increase the risk of damage to the punctured vein and the development of pneumothorax or hemothorax. The subclavian vein, brachiocephalic vein, and superior vena cava are directly adjacent to the pleural cavity (Fig. 13). According to the literature, the incidence of pneumothorax ranges from 0.8 to 3.0% when ultrasound guidance cannot be used [21, 22]. Unfortunately, even the use of ultrasound guidance in the case of loss of needle visualization does not prevent the development of these complications.

When puncturing at the Aubaniac point (1 cm below the border of the inner and middle third of the clavicle), the needle is directed toward the sternoclavicular junction, i.e., puncture is performed in the area of the junction of the subclavian vein with the jugular vein and their transition into the brachiocephalic vein. The apex of the lung is also located in this area, which creates conditions for the development of either pneumothorax and/or alveolar hemorrhage.

Clinical case 5. Patient G., 6 years old. She was admitted to the operating room for the placement of a tunnel catheter. At the time of placement, the guidewire and catheter were positioned in the superior vena cava projection. The operator did not notice their unusual position (Fig. 14). Six hours later, after starting fluid infusion, the attending physician noted decreased breath sounds on the right side of the chest. Control radiography confirmed a right-sided hemothorax (Fig. 15). Aspiration from the catheter produced a pale fluid. After fluid aspiration was stopped, the catheter was removed, and the pleural cavity was drained.

Control radiography in this case was performed after the onset of clinical signs of hydrothorax, because the operator believed that the absence of signs of pneumo- or hydrothorax on intraprocedural radiography was sufficient to exclude this complication.

The main method for timely diagnosis of hydrothorax is chest radiography within 6 hours of

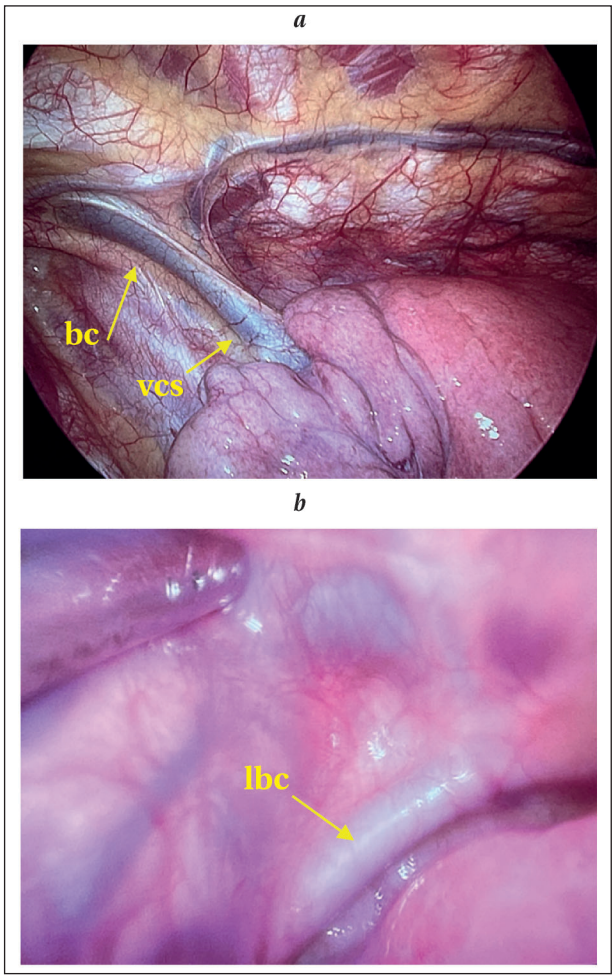

Fig. 13. ***a*** **— right brachiocephalic vein (bc) and vena cava superior (vcs) on thoracoscopy;** ***b*** **— left brachiocephalic vein (lbc) on thoracoscopy.**

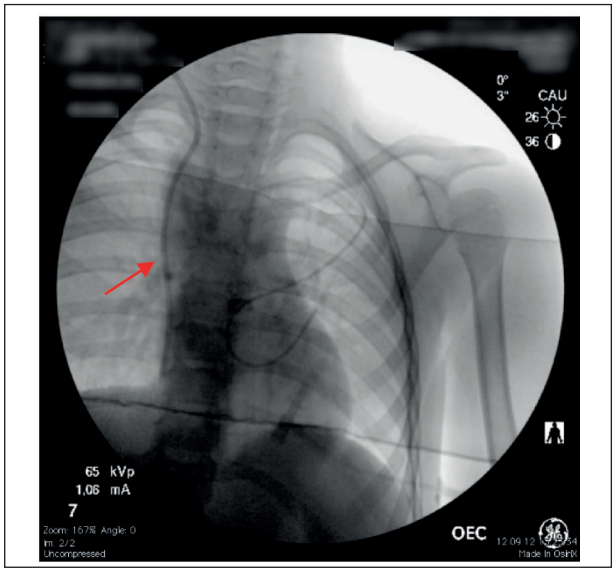

Fig. 14. Catheter in the pleural cavity (indicated by arrow).

catheterization. Ultrasound of the pleural cavity may be used to minimize radiation exposure.

Another option to control catheter position and avoid complications may be to preplan central

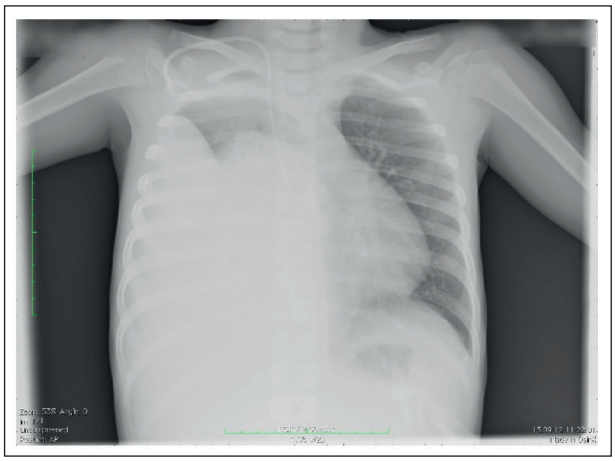

Fig. 15. Right-sided hydrothorax.

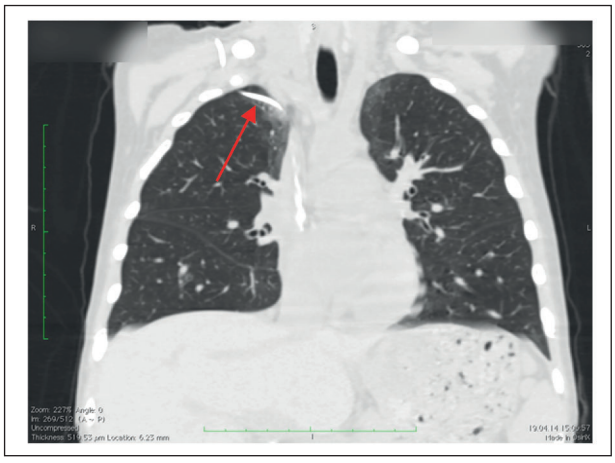

Fig. 16. Catheter passing through lung tissue (indicated by arrow).

venous catheterization before routine chest CT. However, this option is primarily applicable to routine catheterization.

Patient Z., 5 years old, was admitted with a catheter previously inserted through the right subclavian vein. Prior to catheter replacement, a chest CT scan was performed, which revealed puncture and catheterization of the upper lobe of the right lung (Fig. 17).

Catheter removal was performed without the expected development of pneumothorax, most likely because the catheter was covered with a fibrin sheath at that time.

Clinical case 6. Patient I., 12 years old, was admitted for surgical treatment. Prior to surgery, a central line was placed through the right subclavian vein. Long-axis ultrasound guidance was used at the time of puncture. Due to difficulty in visualizing the needle, the operator was guided by the movement of the tissue surrounding the needle. Venous puncture and guidewire insertion were successful on the first attempt. Catheter insertion was uneventful. On control radiography, the catheter was located in the superior vena cava region. Thoracoscopy showed that

the catheter emerged from the subclavian vein, passed through the lung tissue, and entered the right brachiocephalic vein (Fig. 18). The catheter was removed by the surgeon during thoracoscopy.

In this case, poor visualization of the needle led to compression of the subclavian vein by the needle and unnoticed puncture of both vein walls, followed by further advancement of the needle and puncture of the brachiocephalic vein, from which blood flow was obtained. A catheter was then inserted through the guidewire and advanced through the subclavian vein, pleural cavity, and lung apex tissue into the brachiocephalic vein.

Lung injury may be associated with alveolar hemorrhage, which can be fatal.

Clinical case 7. Patient K., 9 years old, with acute lymphoblastic leukemia. Catheterization of the right subclavian vein was performed using anatomical landmarks without ultrasound. Arterial puncture was successful on the first attempt and venous puncture was successful on the third attempt. After guidewire catheter placement, SpO_2 decreased to 83%. Pleural ultrasound showed no evidence of pneumothorax or hemothorax. At the time of examination, blood was noted in the oral cavity and bradycardia progressed to asystole. Cardiopulmonary resuscitation was initiated with positive results. Tracheal intubation was performed and dark blood was drained from the tracheobronchial tree. Chest radiography revealed bilateral polysegmental infiltration, more pronounced on the right side (Fig. 19). Repeated pleural ultrasonography showed free fluid in the right pleural cavity in the posterior and inferior parts, with separation of the pleural layers up to 6–7 mm and up to 10 mm in the right pleural sinus. Respiratory support was continued. After 7 hours, a second pulmonary hemorrhage occurred, accompanied by hypoxia and bradycardia, leading to cardiac arrest. At autopsy, the lumen of all bronchi was found to be obstructed by blood clots.

The development of alveolar hemorrhage as a result of lung puncture has also been described by Yeldec, Bagchi, Bawa, Goldberg, and Kossaify [22–26]. Yeldec et al. suggested that the main mechanisms include damage to lung tissue or arteries (including both the subclavian artery and the pulmonary artery or their branches) [27]. In cases of isolated lung injury, such complications are usually benign [22]. According to Goldberg et al., when lung injury is associated with arterial injury, a fistula often forms between the blood vessel and the bronchus [25]. In these cases, the outcome can be fatal, especially if the patient has concomitant heart failure, chronic respiratory failure, or coagulopathy [22, 27].

Neurological Disorders Associated with Central Venous Catheterization

Horner's syndrome, characterized by the triad of ptosis, miosis, and enophthalmos, was first de-

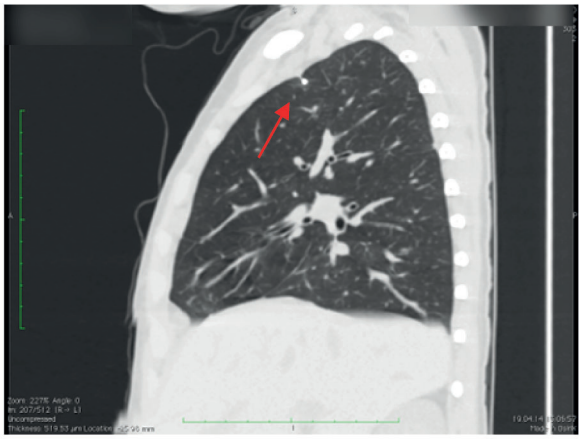

Fig. 17. Catheter passing through lung tissue (indicated by arrow).

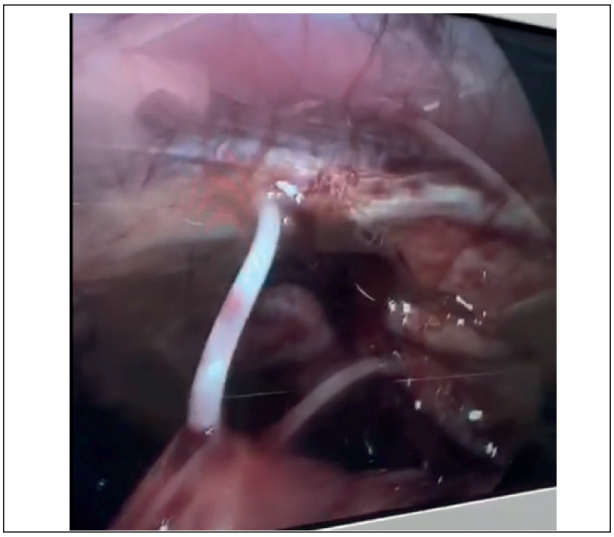

Fig. 18. The catheter exits the subclavian vein and enters the brachiocephalic vein after passing through the lung.

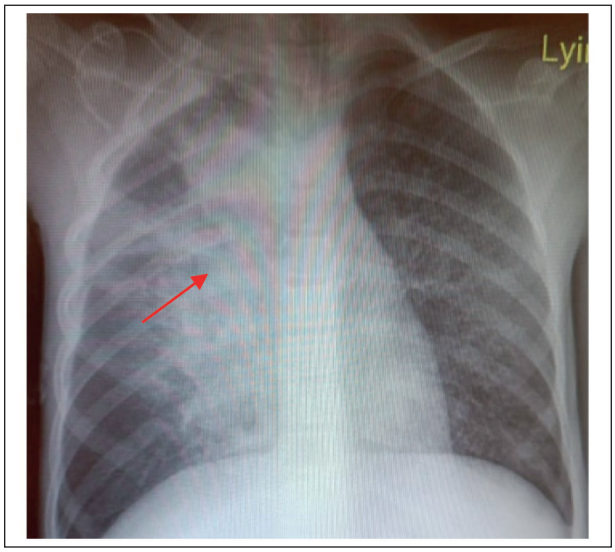

Fig. 19. Infiltration due to pulmonary hemorrhage (indicated by arrow).

scribed by J. F. Horner in 1869. Horner attributed it to impaired sympathetic innervation of the eye [28]. Any disorder affecting the oculosympathetic tract, which consists of three groups of neurons, can cause Horner's syndrome. First-order neurons originate in the posterolateral hypothalamus, pass through the brainstem, and enter the mid-lateral gray column of the spinal cord at the C8–Th1 level. Second-order neurons travel through the apex of the lung into the cervical sympathetic chain near the carotid adventitia. Third-order neurons originate in the upper cervical ganglion, from where they pass through the sheath of the internal carotid artery into the skull, where they divide into the short ciliary nerves (innervating the Müller muscle) and the long ciliary nerves (innervating the pupil dilator) [29].

Clinical case 8. Patient L., 4 years old, underwent the insertion of a tunnel catheter through the left internal jugular vein under ultrasound guidance. During the first catheterization attempt, blood was obtained. Extravasation of the guidewire and the development of a hematoma at the puncture site were observed during the attempt to insert the guidewire. The second catheterization attempt was successful. After 5 hours, ptosis of the left eyelid was noted by the patient's parents (Fig. 20). The patient was examined by an ophthalmologist, and Horner's syndrome was diagnosed. Follow-up continued, and the left-sided ptosis resolved 2 months after catheterization.

After central vein catheterization, Horner's syndrome may develop as a result of direct damage to the sympathetic circuit, direct damage to the periclavicular nerve tracts, or compression of nerve bundles by a hematoma. Clinical signs can appear within a few hours up to 19 days [30]. Since there is no specific treatment for Horner's syndrome, the primary way to avoid this complication is through prevention.

To this end, several authors have made the following recommendations [29, 30]:

1. Venipuncture should be performed under high-resolution ultrasound guidance. The cervical sympathetic chain can be identified medial to the scalene muscles, lateral to the longus colli muscle, esophagus and trachea, superior to the subclavian artery, and posterior to the pleura and vertebral vessels [31].
2. To avoid puncturing the carotid artery and damaging the sympathetic chain, the needle angulation should not be too steep.
3. The patient's head should be rotated less than 30 degrees.
4. Avoid multiple puncture attempts.
5. If the carotid artery is injured, apply compression to prevent hematoma formation.

Phrenic nerve injury. Depending on its anatomical location, the phrenic nerve can be injured under certain conditions, such as needle insertion, compression by a hematoma or catheter, or nerve block with local anesthesia. The phrenic nerve is formed primarily by the C3–5 roots. It descends along the anterior surface of the anterior scalene muscle, behind the prevertebral fascia, then crosses the subclavian artery behind the subclavian vein and enters the thorax. In some cases, the phrenic nerve may pass through the wall of the subclavian vein. Within the thorax, the nerve contacts the mediastinal pleura all the way to the diaphragm. The right phrenic nerve also contacts the superior vena cava [32].

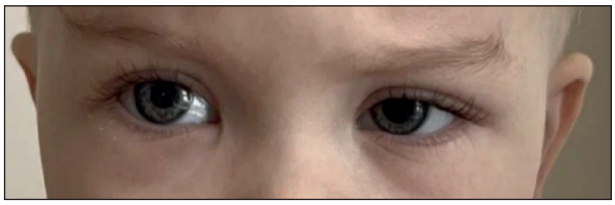

Fig. 20. Horner's sign (ptosis of the left eyelid).

Clinical case 9. Patient M, 3 years old, was admitted to the operating room for catheterization of the right subclavian vein prior to surgery. The puncture was performed under ultrasound guidance. In the first attempt, the subclavian artery was punctured. On the second attempt, the right subclavian vein was successfully punctured and catheterized. The catheter was placed without difficulty. After 20 hours, the right side of the chest was lagging on physical examination, and auscultation revealed decreased breath sounds on the right side. A control radiograph showed elevation of the right hemidiaphragm, suggesting phrenic nerve paresis on the right side. The phrenic nerve paresis resolved 12 days after catheterization. This transient condition was considered to be the result of compression of the phrenic nerve by a hematoma.

In 2001, a case of right phrenic nerve paresis due to compression through the thin wall of the superior vena cava by a catheter inserted during catheterization of the left subclavian vein was described [33].

In 2017, Bykov M. et al. described a paresis of the vagus nerve located in close proximity to the internal jugular vein. Presumably, the cause of the paresis was a hematoma [34]. Because the mechanism of injury to the phrenic and vagus nerves is the same as that of other nerve trunks, recommendations to reduce the risk of phrenic nerve injury are similar.

Arterial pseudoaneurysm. A pseudoaneurysm is an accumulation of blood that communicates with the arterial lumen but is not surrounded by the arterial wall [35,36]. Iatrogenic pseudoaneurysms occur when the puncture site is not closed and arterial blood is released into the surrounding tissue, forming a pulsatile hematoma. Clinically, they manifest as varying degrees of pain, the formation of a pulsatile hematoma, and the appearance of a mur-

mur or thrill over the hematoma. Untreated pseudoaneurysms may be complicated by rupture, distal embolization, neuropathy, chronic local pain, and local skin ischemia [37, 38].

Clinical case 10. Patient N., 17 years old, was admitted to the operating room for catheterization of the left femoral vein with a 12F catheter under ultrasound guidance for apheresis. The first catheterization attempt resulted in an arterial puncture. Compression of the puncture site was performed for approximately 3 minutes, after which the left femoral vein was successfully catheterized. A 20 cm catheter was inserted into the vein without incident. The next day, 3 hours after apheresis, the catheter was removed. No compression was applied to the puncture site. Four days after catheter placement, the patient complained of pain at the puncture site and noticed an elastic pulsating mass. Ultrasonography revealed a pseudoaneurysm of the right femoral artery (Fig. 21).

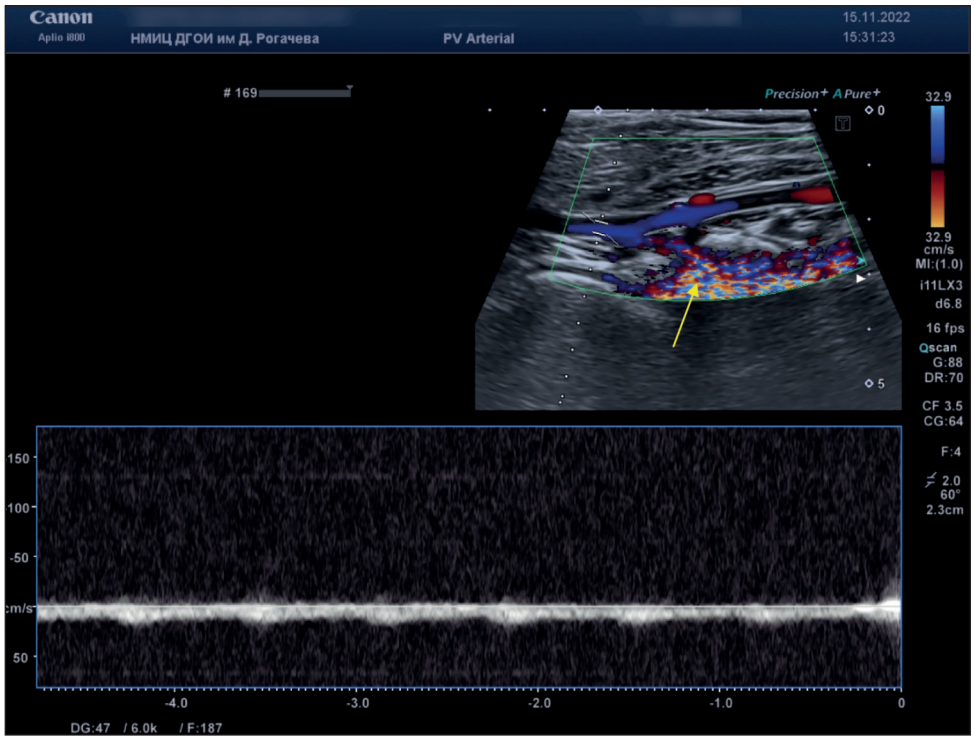

Fig. 21. Pseudoaneurysm of the femoral artery (indicated by the arrow).

A compression bandage was applied for 4 days, after which the clinical manifestations resolved.

Several cases of pseudoaneurysm formation after attempts to puncture and catheterize the veins in the superior vena cava territory have been reported, resulting in brachial plexus paresis. In one case, a carotid artery puncture occurred during an attempt to catheterize the internal jugular vein, resulting in brachial plexus paresis due to compression [39]. In the second case, a pseudoaneurysm developed after puncture of the subclavian artery, also leading to brachial plexus paresis [40].

When treating patients with pseudoaneurysms, open surgical methods, aneurysm compression with or without ultrasound control, and thrombin or collagen injection into the pseudoaneurysm, as well as endovascular stenting, can be used [37–41]. Each of these methods has advantages and disadvantages [38].

A report by Balethbail et al. [42] described the development of thrombosis of a vertebral artery pseudoaneurysm on day 4 after inadvertent puncture of the vertebral artery with a retrieval needle. This patient was not treated because thrombin injection was contraindicated, and surgical intervention was refused by the relatives.

Thus, central venous catheterization remains a procedure with the potential for complications. The use of ultrasound guidance does not currently eliminate the risk of complications, both because of the skill of the operator and the anatomic characteristics of the patient. However, the use of ultrasound guidance and robotic devices that allow automated venipuncture increases the likelihood of successful venipuncture on the first attempt, which helps to reduce the risk of complications [43, 44].

Conclusion

Understanding the causes of various complications of puncture and venous catheterization, including rare ones, allows for timely diagnosis and necessary treatment. A system for recording, controlling, and auditing complications during central venous access placement, as well as improving manual skills and preventing identified causes on simulators in the simulation laboratory, could reduce the incidence of complications related to puncture and venous catheterization.

References

1. *Askegard-Giesmann J. R., Caniano D. A., Kenney B. D.* Rare but serious complications of central line insertion. *Semin Pediatr Surg*. 2009; 18 (2): 73–83.
2. *Вартанова И. В., Вартанов В. Я., Родина Н. А.* Прикладные анатомо-клинические аспекты катетеризации центральных вен. Санкт-Петербург: Военно-медицинская академия им. С. М. Кирова; 2024: 46–51. *Vartanova I. V., Vartanov V. Ya., Rodina N. A.* Applied anatomical and clinical aspects of central vein catheterization. St. Petersburg: S. M. Kirov Military Medical Academy; 2024: 46–51. (in Russ.).
3. *Pittiruti M., Boxtel T. V., Scoppettuolo G., Carr P., Konstantinou E., Miluy G. O., Lamperti M., et al.* European recommendations on the proper indication and use of peripheral venous access devices (the ERPIUP consensus): A WoCoVA project. *J Vasc Access*. 2021: 24 (1): 165–182. DOI: 10.1177/11297298211023274. PMID: 34088239.
4. *Seldinger S. I.* Catheter replacement of the needle in percutaneous arteriography; a new technique. *Acta radiol*. 1953; 39 (5): 368–376. DOI: 10.3109/00016925309136722. PMID: 13057644.
5. *Каледа В. И.* Свен Ивар Сельдингер (1921–1998 гг.) и его метод катетеризации артерий. *Диагностическая и интервенционная радиология*. 2016; 10 (1): 64–67. *Kaleda V. I.* Sven Ivar Seldinger (1921–1998) and his method of catheterization of arteries. *Diagnostic and Interventional Radiology = Diagnostricheskaya i Iinterventsionnaya Radiologiya*. 2016; 10 (1): 64–67. (in Russ.).
6. *Barone G., Pittiruti M., Biasucci D. G., Elisei D., Iacobone E., La Greca A., Marinosci G. Z., et al.* Neo-ECHOTIP: A structured protocol for ultrasound-based tip navigation and tip location during placement of central venous access devices in neonates. *J Vasc Access*. 2022; 23 (5): 679–688. DOI: 10.1177/11297298211007703. PMID: 33818191.
7. *La Greca A., Iacobone E., Elisei D., Biasucci D. G., D'Andrea V., Barone G., Marinosci G. Z., et al.* ECHOTIP: A structured protocol for ultrasound-based tip navigation and tip location during placement of central venous access devices in adult patients. *J Vasc Access*. 2023; 24 (4): 535–544. DOI: 10.1177/11297298211044325. PMID: 34494474.
8. *Marinosci G. Z., Biasucci D. G., Barone G., D'Andrea V., Elisei D., Iacobone E., La Greca A., et al.* ECHOTIP-Ped: A structured protocol for ultrasound-based tip navigation and tip location during placement of central venous access devices in pediatric patients. *J Vasc Access*. 2023; 24 (1): 5–13. DOI: 10.1177/11297298211031391. PMID: 34256613.
9. *Verma A., Chitransh V., Jaiswal S., Vishen A., Sheikh W. R., Haldar M., Ahuja R., et al.* Guidewire entrapped in the right ventricle: a rare complication of hemodialysis catheter insertion. *Indian J Crit Care Med*. 2020; 24 (1): 80–81. DOI: 10.5005/jp-journals-10071-23334. PMID: 32148357.
10. *Unnikrishnan K. P., Sinha P. K., Nalgirkar R. S.* An alternative and simple technique of guidewire retrieval in a failed Seldinger technique. *Anesth Analg*. 2005; 100 (3): 898–899. DOI: 10.1213/01.ANE. 0000146654.99367.DD. PMID: 15728092.
11. *Park S. K., Yi I.-K., Lee J.-H., Kim D.-H., Lee S.-Y.* Fracture of J-tipped guidewire during central venous catheterization and its successful removal under fluoroscopic guidance — a case report. *Korean J Anesthesiol*. 2012; 63 (5): 457–460. DOI: 10.4097/kjae.2012.63.5.457. PMID: 23198042.
12. *McGee D. C., Gould M. K.* Preventing complications of central venous catheterization. *N Engl J Med*. 2003; 348 (12): 1123–1133. DOI: 10.1056/NEJMra011883. PMID: 12646670.
13. *Романенко Н. А., Шилова Е. Р, Алборов А. Э., Волошин С. В., Чеботкевич В. Н.* Тромботические, геморрагические и другие осложнения, констатируемые в процессе и после катетеризаций центральной вены у пациентов онкогематологического профиля. *Вестник Гематологии*. 2020; 16 (4): 54–55. *Romanenko N. A., Shilova E. R., Alborov A. E., Voloshin S. V., Chebotkevich V. N.* Thrombotic, hemorrhagic and other complications detected during and after catheterization of the central vein in patients with hematological profile. *Bulletin of Hematology = Vestnik Gematologii*. 2020; 16 (4): 54–55. (in Russ.)
14. *Быков М. В.* Ультразвуковые исследования в обеспечении инфузионной терапии в отделениях реанимации и интенсивной терапии. Тверь: ООО «Издательство «Триада»; 2011: 36. *Bykov M. V.* Ultrasound examinations in providing infusion therapy in intensive care units. Tver: LLC «Publishing House «Triada»; 2011: 36.
15. *Soleimanpour H.* Inadvertent arterial puncture during central venous catheter insertion. *Ann Clin Anal Med*. 2016; 7 (161). DOI: 10.4328/JCAM.1699
16. *Wierstra B., Au S. S., Cantle P. M., Romens K.* Arterial placement of central venous catheters: beyond prevention to management. *Can J Gen Intern Med*. 2020; 159 (3): 45–48.
17. *Saugel B., Scheeren T. W. L., Teboul J.-L.* Ultrasound-guided central venous catheter placement: a structured review and recommendations

for clinical practice. *Crit Care*. 2017; 21 (1): 225. DOI: 10.1186/s13054-017-1814-y. PMID: 28844205.
18. *Wang L., Liu Z.-S., Wang C.-A.* Malposition of central venous catheter: Presentation and management. *Chin Med J (Engl)*. 2016: 129 (2): 227–234. DOI: 10.4103/0366-6999.173525. PMID: 26830995.
19. *Chen W.-M., Chiang M.-S., Wang P. C., Wei K.-L., Tung S.-Y., Chang T. S., Hung C.-H.* Esophageal perforation caused by a central venous catheter: A case report and literature review. *Adv Dig Med*. 2020; 7 (2): 93–96. DOI: 10.1002/aid2.13160.
20. *Kayashima K.* Evaluation of mechanical complications during pediatric central venous catheter placement from 1994 to 2013. *Int J Anesthesiol Res*. 2013; 1 (1): 34–36. DOI: 10.14205/2310-9394.2013.01.01.5
21. *Karapinar B., Cura A.* Complications of central venous catheterization in critically ill children. *Pediatr Int*. 2007; 49 (5): 593–599. DOI: 10.1111/j.1442-200X.2007.02407.x.PMID: 17875082.
22. *Yelgeç N. S., Osken A., Turkkan C., Alper A. T.* Subclavian vein puncture-induced massive pulmonary hemorrhage and hemoptysis during pacemaker implantation. *North Clin Istanb*. 2018; 5 (3): 254–255. DOI: 10.14744/nci.2017.86619.PMID: 30688923.
23. *Bagchi A., Agarwal R. K., Talwar K. K.* Hemoptysis after subclavian vein puncture for pacemaker implantation: a case report. *J Cardiol Cardiovasc Med*. 2019; 4 (3): 192–194. DOI: 10.29328/journal.jccm. 1001065.
24. *Bawa A. S., Jain V., Gutierrez G.* Local pulmonary hemorrhage as a complication of subclavian vein catheterization. *Chest*. 2007; 132 (4): 695A. DOI: 10.1378/chest.132.4_MeetingAbstracts.695a
25. *Goldberg A., Rosenfeld I., Marmor A.* Hemoptysis — a rare complication of pacemaker implantation. *Indian Pacing Electrophysiol J*. 2008; 8 (1): 75–76. PMID: 18270606.
26. *Kossaify A., Nicolas N., Edde P.* Hemoptysis after subclavian vein puncture for pacemaker implantation: importance of wire-guided venous puncture. *Clin Med Insights Case Rep*. 2012; 5: 119–122. DOI: 10.4137/CCRep.S10006. PMID: 22859867.
27. *Truong A. T., Brown D. L.* Catastrophic hemothorax from lobar pulmonary artery puncture during attempted subclavian vein catheterization: the fallibility of venous blood aspiration. *J Clin Anesth*. 2009; 21 (5); 377–378. DOI: 10.1016/j.jclinane.2008.10.005. PMID: 19700295.
28. *Horner F.* On a form of ptosis. *Arch Neurol*. 1968; 19 (5): 541–542. 10.1001/archneur.1968.00480050111013.
29. *Khan T. A., Zameer S., Ijaz U., Zahid M. A., Zameer N. U. A.* Iatrogenic Horner's syndrome after insertion of a central venous catheter: recommendations for clinical practice. *Egypt J Intern Med*. 2022; 34 (1): 55. DOI: 10.1186/s43162-022-00144-6.
30. *Zou Z. Y., Yao Y. T.* Horner syndrome caused by internal jugular vein catheterization. *J Cardiothorac Vasc Anesth*. 2020; 34 (6): 1636–1640. DOI: 10.1053/j.jvca.2019.06.031. PMID: 31350153.
31. *Narouze S., Vydyanathan A., Patel N.* Ultrasound-guided stellate ganglion block successfully prevented esophageal puncture. *Pain Physician*. 2007; 10 (6): 747–752. PMID: 17987096.
32. *Paraskevas G. K., Raikos A., Chouliaras K., Papaziogas B.* Variable anatomical relationship of phrenic nerve and subclavian vein: clinical implication for subclavian vein catheterization. *Br J Anaesth*. 2011; 106 (3): 348–351. DOI: 10.1093/bja/aeq373. PMID: 21233111.
33. *Takasaki Y., Arai T.* Transient right phrenic nerve palsy associated with central venous catheterization. *Br J Anaesth*. 2001; 87 (3): 510–511. DOI: 10.1093/bja/87.3.510. PMID: 11517143.
34. *Быков М. В., Лазарев В. В., Багаев В. Г., Мадорский К. С., Быкова Л. В.* Повреждение блуждающего нерва при пункции и катетеризации внутренней яремной вены — одно из редко выявляемых осложнений катетеризации центральных вен. *Российский вестник детской хирургии анестезиологии и реаниматологии*. 2017; 7 (3): 54–62. *Bykov M. V., Lazarev V. V., Madorsky K. S., Bagaev V. G., Bykova L. V.* Injure to the vagus nerve in the puncture and catheterization of the internal jugular vein: *Russ J Pediatr Surg Anesth Intensive Care = Rossiyskiy Vestnik Detskoy Khirurgii Anesteziologii i Reanimatologii*. 2017; 7 (3): 54–62. (in Russ.&Eng.). DOI: 10.17816/psaic334.
35. *Leone V., Misuri D., Console N.* Radial artery pseudoaneurysm after a single arterial puncture for blood-gas analysis: a case report. *Cases J*. 2009; 2: 6890. DOI: 10.4076/1757-1626-2-6890. PMID: 19829877.
36. *Levis J. T., Garmel G. M.* Radial artery pseudoaneurysm formation after cat bite to the wrist. *Ann Emerg Med*. 2008; 51 (5): 668–670. DOI: 10.1016/j.annemergmed.2007.11.031. PMID: 18325629.
37. *Eisenberg L., Paulson E. K., Kliewer M. A., Hudson M. P., DeLong D. M., Carroll B. A.* Sonographically guided compression repair of pseudoaneurysms: further experience from a single institution. *AJR Am J Roentgenol*. 1999; 173 (6): 1567–1573. DOI: 10.2214/ajr.173.6. 10584803.PMID: 10584803
38. *Lenartova M., Tak T.* Iatrogenic pseudoaneurysm of femoral artery: case report and literature review. *Clin Med Res*. 2003; 1 (3): 243–247. DOI: 10.3121/cmr.1.3.243. PMID: 15931315.
39. *Mol T. N., Gupta A., Narain U.* Brachial plexus compression due to subclavian artery pseudoa-

neurysm from internal jugular vein catheterization. *Indian J Nephrol.* 2017; 27 (2): 148–150. DOI: 10.4103/0971-4065.179334. PMID: 28356671.

40. *Al-Thani H., Hussein A., Sadek A., Barah A., El-Menyar A.* Balloon-assisted percutaneous thrombin injection for treatment of iatrogenic left subclavian artery pseudoaneurysm in a critically ill COVID-19 patient. *Case Rep Vasc Med.* 2021; 2021: 4245484. DOI: 10.1155/2021/ 4245484. PMID: 34659861.
41. *Weger N., Klaassen Z., Slurt C., Hertz S.* Endovascular treatment of a pseudoaneurysm after an iatrogenic axillary artery injury. *Ann Vasc Surg.* 2010; 24 (6): 826. e9–12. DOI: 10.1016/j.avsg.2009.12.019. PMID: 20471203.
42. *Balethbail S., Singha S. K., Gayatri P.* Vertebral artery pseudoaneurysm a complication after attempted internal jugular vein catheterization in a neurosurgical patient. *J Neurosurg. Anesthesiol.* 2011; 23 (1): 53. DOI: 10.1097/ANA.0b013e3181f20616. PMID: 21252709.
43. *Scholten H. J. Pourtaherian A., Mihajlovic N., Korsten H. H. M., Bouwman R. A.* Improving needle tip identification during ultrasound-guided procedures in anaesthetic practice. *Anaesthesia.* 2017; 72 (7): 889–904. DOI: 10.1111/anae.13921. PMID: 28542716.
44. *Лахин Р. Е., Антипин Э. Э., Баутин А. Е., Корячкин В. А., Уваров Д. Н., Теплых Б. А., Ульрих Г. Э., с соавт.* Клинические рекомендации по катетеризация сосудов под контролем ультразвука. Общероссийская общественная организация «Федерация Анестезиологов и Реаниматологов». 2015. *Lakhin R. E., Antipin E. E., Bautin A. E., Koryachkin V. A., Uvarov D. N., Teplykh B. A., Ulrikh G. E., et al.* Clinical guidelines for catheterization of blood vessels under ultrasound control. All-Russian public organization «Federation of Anesthesiologists and Intensive Care Specialists». 2015. (in Russ.). eLIBRARY ID: 26002350.

Received 04.03.2024
Accepted 14.08.2024

https://doi.org/10.15360/1813-9779-2024-5-70-76

Effective Ventilation Mode in Early Neonatal Sepsis, Bilateral Pneumonia, and Pulmonary Hypertension in a Very Low Birth Weight Newborn (Case Report)

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For citation: *Konstantin V. Lukashev, Alexander I. Nuzhdin, Alexey T. Emikh, Anna N. Grishina, Elena B. Zorina, Nikolay V. Shleikher, Sergey L. Kan, Yulia V. Kovaleva.* Effective Ventilation Mode in Early Neonatal Sepsis, Bilateral Pneumonia, and Pulmonary Hypertension in a Very Low Birth Weight Newborn (Case Report). *Obshchaya Reanimatologiya = General Reanimatology.* 2024; 20 (5): 70–76. https://doi.org/10.15360/1813-9779-2024-5-70-76 [In Russ. and Engl.]

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Summary

The aim was to demonstrate an alternative approach to respiratory therapy in respiratory failure complicated by pulmonary hypertension when conventional ventilation and high-frequency oscillatory ventilation are ineffective.

Patient and study methods. We analyzed laboratory data, ventilatory parameters and hemodynamic parameters during ventilation in a child with birth weight of 1300 grams and respiratory failure complicated by pulmonary hypertension. Dynamic selection of parameters and modes of pulmonary ventilation with transition to Airway Pressure Release Ventilation (APRV) mode is presented. Chest radiography and echocardiography were used.

Results. The use of APRV mode when traditional approaches were ineffective allowed «stabilization» of the lungs by alveolar recruitment without deep sedation and muscle relaxation. On day 20 after birth, the infant was weaned. On day 29, the infant was transferred to the neonatal pathology unit for further management, and on day 49, the infant was discharged in stable condition.

Conclusion. In neonates with severe respiratory failure, the use of the APRV mode as an alternative to ineffective conventional ventilation requires further investigation and the development of guidelines for its use.

Keywords: Bi-Vent; APRV; high-frequency oscillatory ventilation; neonatal pneumonia; early neonatal sepsis; neonatal pulmonary hypertension; low birth weight neonate; neonatal distress syndrome

Conflict of interest. The authors declare no conflict of interest.

Introduction

Congenital pneumonia is an acute infectious disease with predominant lower respiratory tract damage and accumulation of inflammatory exudate inside the alveoli, detected by physical and radiologic examination, usually within the first 72 hours after birth [1]. Congenital pneumonia may be complicated by neonatal sepsis, which clinically manifests as a systemic infection in the first 28 days of life. It is usually classified as early (<48–72 h) or late (>48–72 h) sepsis, depending on the child age on onset [2].

A recent meta-analysis by Fleischmann S. et al. reported an incidence of neonatal sepsis of 2,824 cases per 100,000 live births for the period January 1979 to May 2019 [3].

The European guidelines for the treatment of neonatal respiratory distress syndrome (NRDS) published in 2022 recommend non-invasive ventilation combined with surfactant administration for premature infants with respiratory distress and, if indicated, subsequent transition to lung ventilation (LV) or high-frequency oscillatory ventilation (HFOV) if non-invasive ventilation is ineffective [4]. However, the Russian NRDS guidelines recommend non-invasive ventilation combined with surfactant administration and when indicated transition to lung ventilation and followed by, if ineffective, transition to HFOV [5].

Thus, both European and Russian guidelines for NRDS do not provide alternative ventilation options when traditional methods are ineffective.

One ventilation option in the treatment of adult respiratory syndrome in the clinical guidelines of the Russian Federation of Anesthesiologists and Reanimatologists is airway pressure release ventilation (APRV) [6, 7]. APRV is proposed as a method to improve gas exchange in severe RDS and was first described in 1987 by M. Stock et al. [8]. Opinions on the effectiveness of the APRV mode are mixed due to limited data on its use and unclear criteria for selecting mode settings [9–11]. In 2019, the first systematic review on the use of this mode in adults was published; however, the authors themselves acknowledge the

challenge of interpreting clinical data due to the lack of clear approaches [12]. In 2023, Shreyas A. et al. published a study comparing APRV and HFOV in 90 infants and concluded that APRV is an effective rescue method of lung ventilation. The study showed comparable survival rates for infants ventilated with either APRV or HFOV mode, with APRV mode achieving similar ventilation and oxygenation goals. However, the need for further studies was confirmed [13].

The possibility of spontaneous breathing by the patient in any phase of the respiratory cycle in this ventilation mode is similar to the «Bi-Vent» mode with two pressure levels, where the lower pressure level (PEEP) and the upper pressure level (P_{high}) are set [14, 15]. The difference between the APRV mode and the Bi-Vent mode is the inverted inhalation/exhalation (I:E) ratio, which promotes alveolar recruitment, opening, and stabilization of the volume of the recruited alveoli [16, 17].

The aim of our work was to demonstrate an alternative approach to respiratory therapy in respiratory failure complicated by pulmonary hypertension with ineffective conventional and HFO ventilation.

In this clinical situation, we encountered respiratory failure in a child complicated by pulmonary hypertension, resistant to conventional and HFOV, requiring the search for alternative ventilation options to stabilize his condition. APRV (Airway Pressure Release Ventilation) was chosen as a «last resort» therapy because this mode of ventilation reduces the risk of barotrauma due to optimized PIP control and does not require deep sedation and the use of muscle relaxants.

Medical History

The child was from the first pregnancy, the mother was regularly examined in the antenatal clinic from the 7th week of pregnancy. In the first half of the pregnancy, marginal placenta previa was noted. In the second half of the pregnancy, edema, hypertension, and proteinuria were observed from the 27th week of gestation, and prenatal fetal lung stimulation was done at the 28th week of gestation. Magnesium administration and antihypertensive therapy (methyldopa 2,000 mg/day, nifedipine 10 mg three times a day) were started at 28 weeks' gestation.

At 31 weeks' gestation, the patient was admitted to the perinatal center with elevated blood pressure (BP) up to 170/100 mmHg, progressive edema of the lower extremities, and decreased urine output during the previous 3 days. Delivery was performed by cesarean section due to severe pre-eclampsia and lack of conditions for natural delivery.

Diagnosis during labor: Premature operative labor at 31 weeks and 5 days gestation. Complication: Severe pre-eclampsia with underlying chronic hypertension. Fetal growth retardation, grade I. Breech presentation of the fetus. Associated: Obesity, 1st degree; myopia, 1st degree; urolithiasis. Surgery: Emergency cesarean section.

Clinical Case and Discussion

The child was born by cesarean section with a body weight of 1,300 grams, Apgar score of 5/6/6 points, Silverman score of 4–5 points, mask ventilation was performed in the delivery room with transition to CPAP, after which the child was transported to the neonatal intensive care unit (NICU).

Clinical diagnosis of the infant. Very low birth weight (1,300 grams). Early neonatal sepsis (severe condition, multiorgan failure syndrome, onset in the first 72 hours after birth). Neonatal infection of undetermined etiology. Congenital bilateral pneumonia (radiologic findings, severe respiratory failure, onset in the first 72 hours of life).

Associated: Respiratory distress syndrome (based on radiologic findings, need for respiratory support and administration of surfactant). Pulmonary hypertension (pulmonary artery pressure 50 mmHg).

Complication: Multiple organ failure syndrome (cardiovascular + respiratory + intestinal), nSOFA score 11 points.

Background: Prematurity 31 weeks.

Risk factors for neonatal infection included very low birth weight, prematurity, and cesarean delivery [18].

On admission to the NICU, we continued respiratory support in the mode of non-invasive lung ventilation (NIV) with pressure control through DragerBabyFlowProng size «L» nasal cannulas (MaquetServoI device). Ventilation parameters are listed in Table 1. Taking into account the gestational age of the infant, the need for NIV respiratory therapy, Silverman score > 3 points in the first 3–6 hours of life, and the need for FiO_2 up to 0.4, surfactant was administered endotracheally by INSURE, after which the oxygen fraction (FiO_2) was reduced to 0.25. NIV was continued in the previous mode.

Antibiotic therapy was administered according to the «starting» protocol (ampicillin + amikacin). Clinical deterioration was observed within 8 hours. Despite NIV, respiratory insufficiency increased, tachypnea up to 90/min and SpO_2 80–82% were recorded. With persistent respiratory distress syndrome (RDS) according to the radiological data, tachypnea on ventilatory support, SpO_2 decrease, the child was transferred to lung ventilation: tracheal intubation was performed with ETT 3.0 mm to a depth of 7 cm from the upper lip, and ventilation was started in intermittent mode with pressure control (MaquetServoI) (Table 1).

On the 2nd day after birth there were episodes of desaturation up to 80%, ultrasound screening of the lungs showed signs of right-sided non-tension pneumothorax, we started therapy according to the protocol

Table 1. Mechanical ventilation modes during the observation period.

Ventilation mode	Lung ventilation settings								
	F, inspirations/s	PEEP, cm H_2O	PIP, cm H_2O	I:E, inspiration/expiration ratio	T_{ins}, s	T_{ins}, %	MAP, cm H_2O	FiO_2	SpO_2, %
Day 1									
nSIMV	30 (60)	5	15	1:2	0.60	20	8	0.4	99
nSIMV	30 (60)	5	15	1:2	0.60	20	8	0.25	82
SIMV	30 (60)	5	18	1:2	0.33	5	10	0.25	99
Day 1									
SIMV	30 (60)	5	18	1:2	0.33	5	10	0.25	80
PC	60 (60)	4	21	1:2	0.33	5	12	1.0	99
Day 3, before 5:30 p.m.									
PC	60 (60)	6	26	1:2	0.33	5	14	1.0	65
PC	60 (60)	7	30	1:2	0.33	5	16	1.0	75
PC	60 (60)	8	35	1:2	0.33	5	20	1.0	70
Day 3, after 5:30 p.m.									
HFOV	P_{mean} 20–22 cm H_2O, △P 35 cm H_2O, Respiratory rate 12–15/min							1.0	70–78
Day 3, from 8:30 p.m.									
APRV / BiVent	P_{high} 35–30 cm H_2O, PEEP 3 cm H_2O (auto PEEP 9 cm H_2O), TP high 0.45 s, PS more than P_{high} 14 cm H_2O, T_{PEEP} 0.15 s, PS higher than PEEP 24 cm H_2O, RR 100 per minute, I:E 3:1, Inspiratory rise time 0.15 s, $V_{t\,ins}$ 20 mL, $V_{t\,exp}$ 25 mL, $V_{t\,exp}$ 3.1 L/min						25–20	1.0	90–95
Day 14									
PC	50 (60)	6	18	1:2	0.40	5	11	0.3	99

of air leak syndrome with FiO_2 100%. Ventilation was performed in pressure control mode (Table 1).

Chest x-ray (Fig. *a*) and echocardiography (Table 2) were performed.

On day 3 after birth, at 15:30, a dramatic negative change in the child's status was observed. Chest x-ray (Fig. *b*) and echocardiography (Table 2) were performed again.

Thus, the pre-existing respiratory failure of parenchymal type was complicated by pulmonary hypertension. It was treated according to current clinical guidelines [19]. Levosimendan was administered as a loading dose of 12 μg/kg followed by a maintenance dose of 0.1 μg/kg/min in combination with sildenafil 1.5 mg/kg twice daily. Cardiotonic support with dobutamine was started at 2 μg/kg/min and gradually increased to 10 μg/kg/min. Vasopressor support with epinephrine was also provided, starting at 0.1 μg/kg/min and gradually increasing to 0.7 μg/kg/min to maintain cardiac output and mean arterial pressure, taking into account «rigid» ventilatory parameters. Nitric oxide was not used.

Low SpO_2 parameters (65–75%) persisted during pressure-controlled ventilation (Table 1).

Taking into account the severity of the disease, increasing deterioration, high risk of death, multiorgan failure syndrome, ongoing neonatal infection, persistent low blood oxygenation, antibiotic therapy was revised, «reserve» antibiotics (meropenem + vancomycin) were prescribed, and non-specific immunoglobulin was added to the treatment.

At 17.30, taking into account the failure of ventilation in pressure control mode with «rigid» parameters, the need for high PIP up to 35 cm H_2O, MAP up to 20 cm H_2O, FiO_2 of 1.0, the patient was transferred to HFOV (Table 1). After that, SpO_2 increased slightly (up to 70–78%). A chest x-ray was performed (Fig. *c*).

In view of transfer to HFOV, sedation was started with fentanyl 0.005% in an age-appropriate dosage. Blood acid-base balance (ABB) showed compensated metabolic acidosis and normocapnia (Table 3). ABB was monitored in capillary blood.

At 20:30, due to the ineffectiveness of HFOV, negative radiological changes, low blood oxygenation (SpO_2 70–78%), high risk of barotrauma, and high probability of death, BiVent/APRV mode was used as an alternative method of ventilation (Table 1). A distal flow sensor was placed in the ventilation circuit. Normalization of SpO_2 to 90–95% was observed within a few minutes. Chest radiography was performed (Fig. *d*).

This mode of ventilation was chosen because of available literature data on its use in pediatric and adult practice [9, 20–24].

After stabilization of the child's condition, the previous therapy was continued.

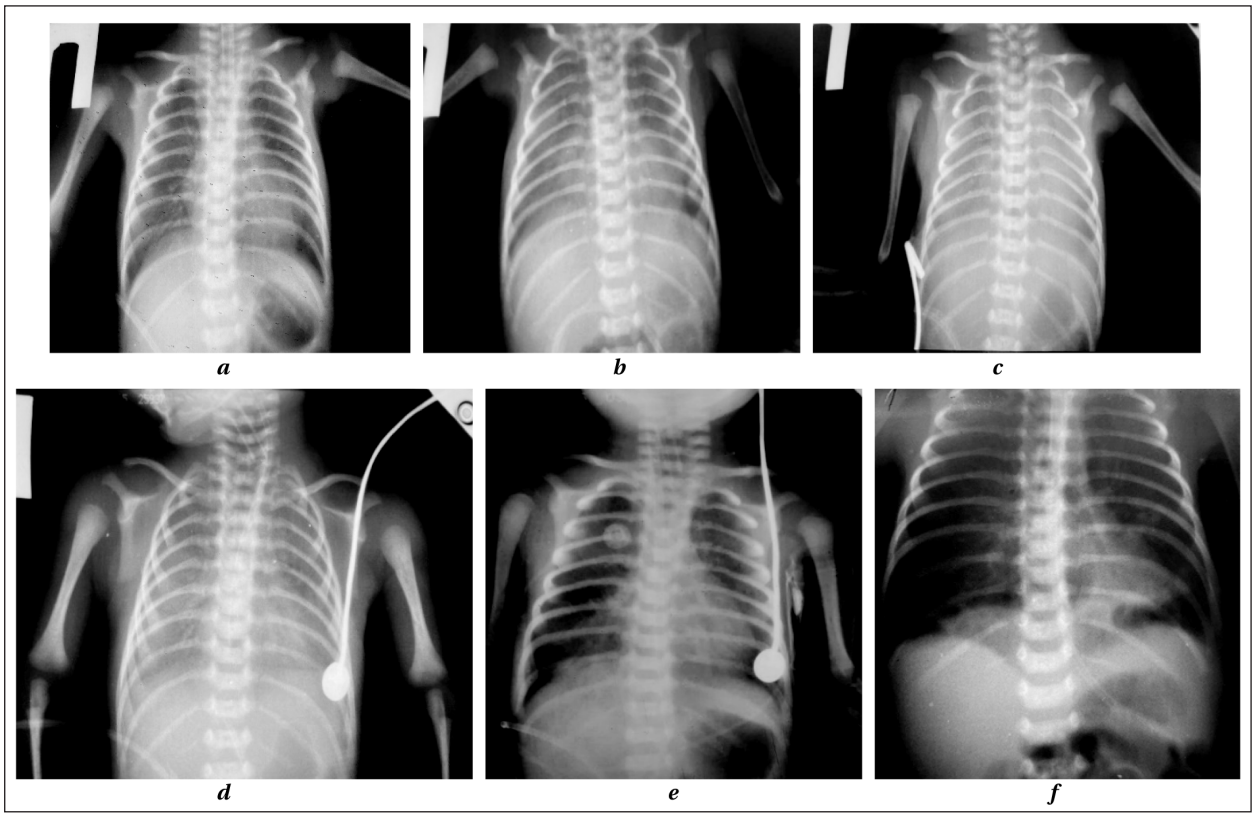

Fig. Chest radiography during the study stages.
a — PC mode ventilation (day 2); *b* — PC mode ventilation (day 3); *c* — HFOV (day 3); *d* — 3 h after switching to APRV mode; *e* — 22 h after switching to APRV mode; *f* — PC mode ventilation (day 14).

Table 2. Change of echocardiographic parameters during study stages.

Parameter	Values		
	Day 2	Day 3	Day 4
Right ventricle diameter, cm	0.7	1	0.6
Interventricular septum, cm	0.28	0.22	0.25
Left ventricular end diastolic diameter, cm	1.2	1.1	1.1
Left ventricular end systolic diameter, cm	0.7	0.6	0.7
Left ventricular posterior wall, cm	0.21	0.2	0.2
Ejection fraction, %	>65	>65	>65
Pulmonary artery pressure, mm Hg	<30	=50	=34

On day 4, echocardiography (Table 2) and chest radiography were performed (Fig. *e*).

In this case, the APRV ventilation mode allowed the setting of a sufficient PIP level corresponding to *P*-high, which was at the same time much lower than in «assisted» and pressure-controlled «classical» ventilation, but allowed to maintain a high MAP, and the inspiratory inversion allowed to prolong the inspiratory phase in the respiratory cycle at a stable frequency, which promoted alveolar recruitment without changing the respiratory volume, which further allowed to smoothly reduce PIP (*P*-high) and MAP with subsequent reduction of gas flow and the risk of barotrauma. High AutoPEEP (due to prolonged inspiratory and expiratory phases and inversion of the I:E ratio) helped to increase functional residual capacity (FRC). Such a long period of APRV mode use was based on the results of acid-base balance and chest x-ray.

Further improvement of the patient's condition was observed with normalization of glycemia, lactate and procalcitonin levels (Tables 3, 4). The evolution of the complete blood count values is shown in Table 5.

A chest x-ray was performed (Fig. *f*).

Metabolic acidosis was corrected with 4% sodium bicarbonate and 2 mL/kg cytoflavin in 5% glucose solution in a 1/5 ratio (this combination was chosen to prevent hypernatremia and encephalopathy) [25]. Respiratory alkalosis was corrected by gradually decreasing P-high and adjusting the I:E ratio with a «shift» from reversible APRV mode to Bi-vent mode (E:I 3:1; 2:1; 1:1; 1:1; 1:2) and further transition to conventional ventilation under blood ABB control (Table 3).

On postnatal day 14, the mode of ventilation was changed from endotracheal tube to pressure-controlled support (Table 1).

Table 3. Changes in blood ABB.

Time of measurement	Values						
	pH	pCO_2, mm Hg	pO_2, mm Hg	BE(B), mmol/L	HCO_3(std), mmol/L	Glucose, mmol/L	Lactate, mmol/L
Day 1							
14:59	7.35	34	44	–5.5	20.2	5.3	4.8
21:05	7.29	43	42	–5.5	19.4	8.3	3.2
21:42	7.34	35	48	–6.1	19.9	5.6	3.1
Day 2							
05:36	7.39	31	42	–4.8	20.7	4.5	3.9
15:33	7.38	26	32	–7.7	18.3	7.9	4.9
Day 3							
13:23	7.32	34	41	–7.4	17.6	5.0	2.4
15:33	7.30	36	35	–7.8	17.7	5.8	3.5
17:30	7.30	41	20	–5.6	20.7	6.9	2.9
19:05	7.38	41	24	–1.1	24.3	8.6	2.6
20:55	7.24	39	31	–10.1	16.3	13.0	8.0
23:05	7.28	32	30	–10.6	15.2	14.5	12.3
02:16	7.26	38	29	–9.0	17.5	17.1	14.9
05:26	7.37	38	35	–3.1	22.0	13.1	12.6
Day 4							
13:11	7.53	42	112	11	33.5	10.3	4.5
19:43	7.65	35	109	16.6	37.8	6.2	3.4
1:51	7.57	38	93	11.7	34.0	5.0	2.4
Day 8							
13:00	7.46	24	48	–5.1	20.8	3.8	1.8
Day 13							
13:00	7.43	25	72	–6.2	20.0	4.7	1.5

Table 4. Changes in inflammatory markers.

Day in NICU	Values	
	Procalcitonin, ng/mL	C-reactive protein, mg/L
1	—	0
4	>10	24
8	0.5–2.0	7
17	0	5

Note. Procalcitonin was measured by immunochromatographic analysis.

Table 5. Changes in CBC

Parameter	Values on days of study				
	1	2	4	8	14
WBC, 1×10^9/L	14.4	24.3	24.6	25.9	17.3
RBC, 10×10^{12}/L	4.29	4.73	3.71	2.94	5.16
HGB, g/L	179	194	150	112	154
HCT, %	51.2	55.1	42.0	32.2	45.7
PLT, 10×10^{12}/L	256	270	185	220	378
WBC differential, %					
Eosinophils	2	2	2	1	1
Bands	7	7	9	8	7
Segments	39	51	46	61	58
Lymphocytes	41	30	30	22	22
Monocytes	11	10	13	8	12

On postnatal day 20, the infant was weaned from the ventilator, and on postnatal day 29, the infant was transferred to the neonatal pathology unit for further management.

After reaching 49 days after birth, the infant was discharged in stable condition at 38 weeks postconceptional age.

Conclusion

When traditional ventilation approaches proved ineffective in a neonate with very low birth weight, early neonatal sepsis, bilateral pneumonia, pulmonary hypertension, and severe respiratory failure, the use of the airway pressure release ventilation (APRV) mode allowed «stabilization» of the lungs by alveolar recruitment. Adaptation of the ventilated infant and stabilization of central hemodynamics and pulmonary blood flow were achieved without the use of «harsh» and dangerous methods such as deep sedation and administration of muscle relaxants. Further research into the APRV mode as an alternative to ineffective conventional ventilation is needed, as well as the development of recommendations for its use.

References

1. *Овсянников Д. Ю., Бойцова Е. В., Жесткова М. А., Кршеминская И. В., Ашерова И. К., Украинцев С. Е., Межинский С. С.* Глава 2. Пневмонии новорожденных. В кн.: НЕОНАТАЛЬНАЯ ПУЛЬМОНОЛОГИЯ. М.; 2022. ISBN: 978-5-91556-757-2. *Ovsyannikov D.Yu., Boitsova E. V., Zhestkova M. A., Krsheminskaya I. V., Asherova I. K., Ukraintsev S. E., Mezhinsky S. S.* Chapter 2. Pneumonia in newborns. In the book: NEONATAL PULMONOLOGY. M.; 2022. ISBN: 978-5-91556-757-2. (in Russ.).
2. *Shane A. L., Sanchez P. J., Stoll B. J.* Neonatal sepsis. *Lancet*. 2017; 390 (10104): 1770–1780. DOI: 10.1016/S0140-6736 (17)31002-4. PMID: 28434651.
3. *Fleischmann S., Reichert F., Cassini A., Horner R., Harder T., Markwart R., Trondle M., et al.* Global incidence and mortality of neonatal sepsis: a systematic review and meta-analysis. *Arc Dis Child*. 2021; 106 (8): 745–752. DOI: 10.1136/archdischild-2020-320217. PMID: 33483376.
4. *Sweet D. G., Carnielli V. P., Greisen G., Hallman M., Klebermass-Schrehof K., Ozek E., Pas A., et al.* European consensus guidelines on the management of respiratory distress syndrome: 2022 Update. *Neonatology*. 2023; 120 (1): 3–23. DOI: 10.1159/000528914. PMID: 36863329.
5. *Володин Н. Н. (ред).* Ведение новорожденных с респираторным дистресс-синдромом. Клинические рекомендации 2016 год. (РФ). *Volodin N. N. (ed.).* Management of newborns with respiratory distress syndrome. Clinical recommendations 2016. (Russian Federation). (in Russ.). https: //raspm.ru/files/0236-rds-br2.pdf.
6. *Klingenberg C., Kornelisse R. F., Buonocore G., Maier R. F., Stocker M.* Culture-negative early-onset neonatal sepsis — at the crossroad between efficient sepsis care and antimicrobial stewardship. *Front Pediatr*. 2018; 6: 285. DOI: 10.3389/fped.2018.00285. PMID: 30356671.
7. *Ярошецкий А. И., Грицан А. И., Авдеев С. Н., Власенко А. В., Еременко А. А., Заболотских И. Б., Зильбер А. П., с соавт.* Диагностика и интенсивная терапия острого респираторного дистресс-синдрома. *Анестезиология и реаниматология*. 2020; 2: 5–39. *Yaroshetsky A. I., Gritsan A. I., Avdeev S. N., Vlasenko A. V., Eremenko A. A., Zabolotskikh I. B., Zilber A. P., et al.* Diagnostics and intensive therapy of acute respiratory distress syndrome. (Clinical guidelines of the Federation of Anesthesiologists and Reanimatologists of Russia). *Russian Journal of Anesthesiology and Reanimatology = Anesteziologiya i Reanimatologiya*. 2020; 2: 5–39. (in Russ.). DOI: 10.17116/anaesthesiology20200215.
8. *Stock M. C., Downs J. B., Frolicher D. A.* Airway pressure release ventilation. *Crit Care Med*. 1987; 15 (5): 462–466. DOI: 10.1097/00003246-198705000-00002. PMID: 3552443.
9. *Henzler D.* What on earth is APRV? *Crit Care*. 2011; 15 (1): 115. DOI: 10.1186/cc9419. PMID: 21345265
10. *Sato R., Hamahata N., Daoud E. G.* Are we really preventing lung collapse with APRV? *Crit Care*. 2019; 23 (1): 178. DOI: 10.1186/s13054-019-2463-0. PMID: 31097005.
11. *Mireles-Cabodevila E., Kacmarek R. M.* Should airway pressure release ventilation be the primary mode in ARDS? *Respiratory Care*. 2016; 61 (6): 761–773. DOI: 10.4187/respcare.04653. PMID: 27235312.
12. *Carsetti A., Damiani E., Domizi R., Scorcella C., Pantanetti S., Falcetta S., Donati A., et al.* Airway pressure release ventilation during acute hypoxemic respiratory failure: a systematic review and meta-analysis of randomized controlled trials. *Ann Intensive Care*. 2019; 9 (1): 44. DOI: 10.1186/s13613-019-0518-7. PMID: 30949778.
13. *Arya S., Kingma M. L., Dornette S., Weber A., Bardua C., Mierke S., Kingm P. S.* Comparison of airway pressure release ventilation to high-frequency oscillatory ventilation in neonates with refractory respiratory failure. *Int J Pediatr*. 2022; 2022: 7864280. DOI: 10.1155/2022/7864280. PMID: 35546962.
14. *Горячев А. С., Савин И. А.* гл. 3.12. В кн.: Основы ИВЛ. М.: АКСИОМ ГРАФИКС ЮНИОН; 2019. *Goryachev A. S., Savin I. A.* Chapter 3.12. In the book: Fundamentals of mechanical ventilation. M.: AXIOM GRAPHICS UNION; 2019. (in Russ.).
15. *Полупан А. А., Горячев А. С., Савин И. А.* Асинхронии и графика ИВЛ. Руководство для врачей. М.: АКСИОМ ГРАФИКС ЮНИОН; 2017: 281–282. *Polupan A. A., Goryachev A. S., Savin I. A.* Asynchrony and mechanical ventilation graphics. Physician's manual. M.: AXIOM GRAPHICS UNION; 2017: 281–282. (in Russ.).
16. *Савеленок М. И., Ярошецкий А. И., Райкин И. Д., Конаныхин В. Д., Захарченко И. А.* Персонализированная Airway Pressure Release Ventilation при остром респираторном дистресс-синдроме: патофизиологическое обоснование, клинические исследования и перспективы применения. *Анестезиология и реаниматология*. 2019; 6: 52–64. *Savelenok M. I., Yaroshetsky A. I., Raikin I. D., Konanykhin V. D., Zakharchenko I. A.* Personalized Airway Pressure Release Ventilation for acute respiratory distress syndrome: pathophysiological rationale, clinical trials and application prospects. *Russian Journal of Anesthesiology and Reanimatology = Anesteziologiya i Reanimatologiya*. 2019; 6: 52–64. (in Russ.). DOI: 10.17116/anaesthesiology201906152.
17. *Kollisch-Singule M., Ramcharran H., Satalin J., Blair S., Gatto L. A., Andrews P. L., Habashi N. M., et al.* Mechanical ventilation in pediatric and neonatal patients. *Front Physiol*. 2022; 12: 805620. DOI: 10.3389/fphys.2021.805620. PMID: 35369685.
18. *Самсыгина Г. А.* Глава 7. Факторы риска развития сепсиса новорожденных. В кн.: Неонатальный сепсис. Руководство. М.; 2022. *Samsygina G. A.* Chapter 7. Risk factors for neonatal sepsis. In: Neonatal sepsis. Manual. M.; 2022. (in Russ.).
19. Легочная гипертензия у детей. Клинические рекомендации РФ 2013–2017 (Россия). Pulmonary hypertension in children. Clinical recommendations of the Russian Federation 2013–2017 (Russia). (in Russ.). https://diseases.medelement.com/disease/16752?ysclid=m0y6nni03l824636866.
20. *Li J., Luo Z., Li X., Huang Z., Han J., Li Z., Zhou Z., et al.* Effect of different transpulmonary pressures guided mechanical ventilation on respiratory and hemodynamics of patients with ARDS: a prospective

randomized controlled trial. (in Chinese). *Zhonghua Wei Zhong Bing Ji Jiu Yi Xue*. 2017; 29 (1): 39–44. DOI: 10.3760/cma.j.issn.2095-4352.2017.01.009. PMID: 28459402.
21. *Li J.-Q., Li N., Han G.-J., Pan C.-G., Zhang Y.-H., Shi X.-Z., Xu J.-Y., et al.* Clinical research about airway pressure release ventilation for moderate to severe acute respiratory distress syndrome. *Eur Rev Med Pharmacol Sci*. 2016; 20 (12): 2634–2641. PMID: 27383316.
22. *Gupta S., Joshi V., Joshi P., Monkman S., Vaillancourt K., Choong K.* Airway pressure release ventilation: a neonatal case series and review of current practice. *Can Respir J*. 2013; 20 (5): e86–e91. DOI: 10.1155/2013/734729. PMID: 24093118.
23. *Kollisch-Singule M., Jain S. V., Satalin J., Andrews P., Searles Q., Liu Z., Zhou Y., et al.* Limiting ventilator-associated lung injury in a preterm porcine neonatal model. *J Pediatr Surg*. 2017; 52 (1): 50–55. DOI: 10.1016/j.jpedsurg.2016.10.020. PMID: 27837992.
24. *Yener N., Üdürgücü M.* Airway pressure release ventilation as a rescue therapy in pediatric acute respiratory distress syndrome. *Indian J Pediatr*. 2020; 87 (11): 905–909. DOI: 10.1007/s12098-020-03235-w. PMID: 32125661.
25. Гипоксическая ишемическая энцефалопатия новорожденного вследствие перенесенной асфиксии при родах. Клинические рекомендации (проект). Hypoxic ischemic encephalopathy of the newborn due to asphyxia during childbirth. Clinical guidelines. (draft). (in Russ.). https: //www.raspm.ru/files/encefalopatiya.pdf.

Received 01.12.2023
Accepted 13.09.2024

https://doi.org/10.15360/1813-9779-2024-5-77-80

The Effect of Extracorporeal Membrane Oxygenation in the Management of Refractory Ventricular Tachycardia Developed after Fontan Procedure (Case Report)

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For citation: *Olga S. Anikina, Ilya A. Soynov, Ilya A. Velyukhanov, Olga A. Suzdalova, Yuri Yu. Kulyabin, Stanislav A. Sergeev, Alexey N. Arkhipov, Igor A. Kornilov.* The Effect of Extracorporeal Membrane Oxygenation in the Management of Refractory Ventricular Tachycardia Developed after Fontan Procedure. *Obshchaya Reanimatologiya = General Reanimatology.* 2024; 20 (5): 77–80. https://doi.org/10.15360/1813-9779-2024-5-77-80 [In Russ. and Engl.]

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Summary

Aim: to evaluate the effect of extracorporeal membrane oxygenation (ECMO) as a life support in the treatment of a patient with refractory ventricular tachycardia developed after Fontan procedure.

Patient and treatment. A 4-year-old child developed refractory ventricular tachycardia (up to 250 bpm) and hemodynamic depression 18 hours after the Fontan procedure. After the failure of cardiopulmonary resuscitation and antiarrhythmic therapy, resternotomy with central venoarterial (VA) ECMO support was performed, followed by diagnostic angiocardiography. Contrast-enhanced cavopulmonary angiography revealed stenosis of the left pulmonary artery, which was treated with balloon angioplasty and stenting.

Results. Ventricular tachycardia resolved and sinus rhythm was restored within 24 hours after left pulmonary artery stenting, supported by continuous ECMO and antiarrhythmic therapy. On day 3, transthoracic echocardiography showed good single ventricle contractility after a trial weaning from ECMO. As a result, the ECMO support was removed and the sternum sutured. The patient was discharged from the hospital on day 47 in stable condition.

Conclusion. The prompt initiation of VA ECMO support in a 4-year old patient with refractory ventricular tachycardia post-Fontan procedure along with the complex management of post-procedural residual tachycardia using a combination of antiarrhythmic agents helped restoring sinus rhythm and could contribute to preventing neurological complications.

Keywords: ECMO; refractory ventricular tachycardia in children; Fontan procedure

Conflict of interest. The authors declare no conflict of interest.

Funding. This study was performed under the State Contract No. 124022500251-0 of the Russian Ministry of Health.

Introduction

Refractory ventricular tachycardia (VT) is a rare and life-threatening complication after cardiac surgery [1]. The main causes of postoperative refractory VT in children with congenital heart disease include ineffective myocardial protection and residual lesions after cardiac surgery [2, 3]. The only emergency treatment option is the use of venoarterial extracorporeal membrane oxygenation (ECMO), which can serve as a bridge to either recovery or heart transplantation [1, 2].

Here we present a clinical case of sinus rhythm restoration as a result of effective use of venoarterial ECMO for refractory ventricular tachycardia in a patient 4 years after cardiac surgery.

The aim was to evaluate the outcome of a patient with refractory ventricular tachycardia receiving ECMO.

Clinical Report

A 4-year-old patient with a body weight of 16 kg was admitted to E. N. Meshalkin Research and Medical Center for Fontain's surgery with the initial diagnosis of congenital heart disease: hypoplastic left heart syndrome. Echocardiography showed normal contractility of the systemic ventricle, bidirectional cavopulmonary anastomosis without deformation, interatrial communication of 3.4 cm, accelerated flow in the neoaorta. A stent was identified in the descending aorta; peak gradient at this level was 54 mmHg. Significant tricuspid regurgitation and a vena contracta width of 0.79 cm were noted.

The child underwent a complete extracardiac cavopulmonary anastomosis with a Gore-Tex 18 mm vascular graft (GORE-TEX® Vascular Grafts, W. L. Gore & Associates, Inc, Flagstaff, AZ, USA) with a 4 mm fenestration, we performed pulmonary artery branch repair, aortic arch repair with a Vascutek vascular prosthesis flap (Terumo, Renfrewshire, United Kingdom), De Vega suture angioplasty of the tricuspid valve. Aortic arch reconstruction was performed under antegrade cerebral perfusion (total time 43 minutes). Cardioplegic solution Custodiol (650 ml Custodiol, Dr. Franz Köhler Chemie GmbH, Ger-

many) was used for myocardial protection. There was spontaneous recovery of cardiac activity. Cavopulmonary anastomosis was performed under parallel cardiopulmonary bypass (CPB) for 189 minutes. Weaning from CPB was performed with the infusion of minimal doses of norepinephrine and epinephrine without cardiac arrhythmias. Intraoperative transesophageal echocardiography (TEE) demonstrated a functional cavopulmonary anastomosis without accelerated blood flow. Single ventricle contractility was normal (ejection fraction 58%).

18 hours after surgery, the child developed ventricular tachycardia with ventricular rate up to 250 beats/min and hemodynamic compromise. Cardiopulmonary resuscitation was performed with multiple electrical defibrillations at 5-minute intervals.

Antiarrhythmic therapy with a triple bolus injection of amiodarone 5 mg/kg followed by infusion at 5 mg/kg/h and a double bolus of lidocaine 1 mg/kg was administered without beneficial effect. Blood electrolytes were within normal ranges. At the time of resuscitation, the inotropic index was 34 points with high doses of dopamine, epinephrine, norepinephrine, and phenylephrine. During refractory ventricular tachycardia, echocardiography was performed and showed reduced contractility of the single ventricle. During cardiopulmonary resuscitation, resternotomy with central veno-arterial extracorporeal membrane oxygenation (ECMO) was performed, followed by diagnostic angiocardiography. A cavopulmonary contrast study revealed a left pulmonary artery stenosis (Fig., *a*), and balloon angioplasty was performed with a CP Stent L 34–45 mm (NuMED Inc, Hopkinton, New York, USA) (Fig., *b*). Coronary angiography showed no deformation or abnormal compression of the coronary arteries.

Results

After 24 hours on ECMO and continuous infusion of amiodarone 5 mg/kg/h, sinus rhythm was restored. No arrhythmias were observed for the next 3 days. On day 3, VA-ECMO was discontinued and transthoracic echocardiography showed good contractility of the single ventricle. The patient was then weaned from ECMO and the chest was sutured. The total ICU stay was 10 days and no neurological abnormalities were noted in the child. The patient was discharged from the hospital on day 47 in stable condition.

Discussion

The conventional approach to the treatment of pediatric VT is medical therapy [4]. However, VT refractory to medical therapy and triple ineffective defibrillation often leads to hemodynamic compromise and the need for cardiopulmonary resuscitation [1–3]. In such cases, the only emergency treatment option is ECMO [2]. The causes of refractory VT or ventricular fibrillation include ineffective myocardial protection, electrolyte disorders, and congenital heart rhythm disorders such as long QT syndrome, short QT syndrome, and Brugada syndrome, as well as residual lesions after cardiac surgery [2, 5]. In our case, electrolyte disturbances and myocardial ischemia (absence of ST-segment elevation in the early postoperative period and normal recovery of sinus rhythm after surgery) were excluded. Veno-arterial ECMO with central cannulation was initiated during cardiopulmonary resuscitation to stabilize hemodynamics and to identify further causes of arrhythmias. According to the ECMO protocol used in our center, the diagnosis of residual lesions is performed after cardiac surgery [5].

Echocardiography is the gold standard for ruling out residual lesions [6], but in single ventricle patients on ECMO, diagnosis can be challenging and invasive diagnostic modalities are more effective [7]. Additional tests, such as computed tomography or

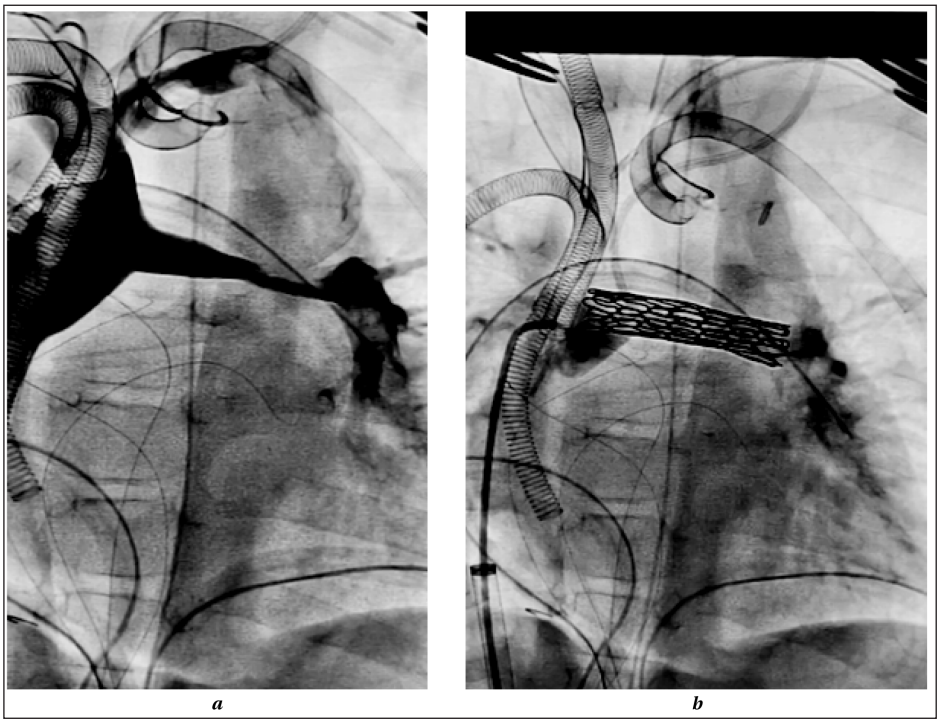

Fig. Cardiac catheterization in a patient on VA-ECMO: stenosis *(a)* and stenting *(b)* of the left pulmonary artery.

cardiac catheterization, can identify the causes of arrhythmias and the need for veno-arterial ECMO [5, 8]. Cardiac catheterization revealed an extensive stenosis of the left pulmonary artery and compression by the aorta.

After stenting of the left pulmonary artery within 24 hours, the ventricular tachycardia resolved and sinus rhythm was restored.

ECMO helped to maintain stable hemodynamics throughout its administration and to identify the cause of the residual lesion. Once the abnormal conditions have been corrected in patients with a single ventricle heart, the time to weaning from ECMO depends on several factors, such as the duration of cardiopulmonary resuscitation, global systolic and diastolic ventricular function, and the presence of ECMO-related complications [9,10]. The use of a preconditioned ECMO circuit shortened the duration of cardiopulmonary resuscitation and reduced the risk of neurological complications. Single ventricle ejection fraction was restored immediately after control of the rhythm disturbance, and careful surgical hemostasis helped to avoid ECMO-related complications. The implemented action algorithm allowed to discontinue venoarterial ECMO after 56 hours and to discharge the patient in stable condition in sinus rhythm and without neurological deficit.

Conclusion

The timely initiation of venoarterial ECMO in the treatment of refractory ventricular tachycardia, together with detection and elimination of postoperative residual lesions and combined drug antiarrhythmic therapy, allows restoration of normal heart rhythm and helps to avoid neurological complications.

References

1. *Bhandary S. P., Joseph N., Hofmann J. P., Saranteas T., Papadimos T. J.* Extracorporeal life support for refractory ventricular tachycardia. *Ann Transl Med.* 2017; 5 (4): 73. DOI: 10.21037/atm.2017.01.39. PMID: 28275618.
2. *Bosson N., Kazan C., Sanko S., Abramson T., Eckstein M., Eisner D., Geiderman J., et al.* Implementation of a regional extracorporeal membrane oxygenation program for refractory ventricular fibrillation out-of-hospital cardiac arrest. *Resuscitation.* 2023; 187: 109711. DOI: 10.1016/j.resuscitation.2023.109711. PMID: 36720300.
3. *Chen C-.Y., Tsai J., Hsu T. Y., Lai W.-Y., Chen W.-K., Muo C.-H., Kao C.-H.* ECMO used in a refractory ventricular tachycardia and ventricular fibrillation patient: a national case-control study. *Medicine (Baltimore).* 2016; 95 (13): e3204. DOI: 10.1097/MD.0000000000003204. PMID: 27043684.
4. *Crosson J. E., Callans D. J., Bradley D. J., Dubin A., Epstein M., Etheridge S., Papez A., et al.* PACES/HRS expert consensus statement on the evaluation and management of ventricular arrhythmias in the child with a structurally normal heart. *Heart Rhythm.* 2014; 11 (9): e55–78. DOI: 10.1016/j.hrthm.2014.05.010. PMID: 24814375.
5. *Soynov I. A., Kornilov I. A., Kulyabin Y. Y., Zubritskiy A. V., Ponomarev D. N., Nichay N. R., Murashov I. S., et al.* Residual lesion diagnostics in pediatric post-cardiotomy extracorporeal membrane oxygenation and its outcomes. *World J Pediatr Congenit Heart Surg.* 2021; 12 (5): 605–613. DOI: 10.1177/21501351211026594. PMID: 34597209.
6. *Agarwal H. S., Hardison D. C., Saville B. R., Donahue B. S., Lamb F. S., Bichell D. P., Harris Z. L.* Residual lesions in postoperative pediatric cardiac surgery patients receiving extracorporeal membrane oxygenation support. *J Thorac Cardiovasc Surg.* 2014; 147 (1): 434–441. DOI: 10.1016/j.jtcvs.2013.03.021. PMID: 23597724.
7. *Boscamp N. S., Turner M. E., Crystal M., Anderson B., Vincent J. A., Torres A. J.* Cardiac catheterization in pediatric patients supported by extracorporeal membrane oxygenation: a 15-year experience. *Pediatr Cardiol.* 2017; 38 (2): 332–337. DOI: 10.1007/s00246-016-1518-0. PMID: 27872993.
8. *Abdelmohsen G., Al-Ata J., Alkhushi N., Bahaidarah S., Baho H., Abdelsalam M., Bekheet S., et al.* Cardiac catheterization during extracorporeal membrane oxygenation after congenital cardiac surgery: a multi-center retrospective study. *Pediatr Cardiol.* 2022; 43 (1): 92–103. DOI: 10.1007/s00246-021-02696-w. PMID: 34328521.
9. *Polimenakos A. C., Wojtyla P., Smith P. J., Rizzo V., Nater M., El Zein C. F., Ilbawi M. N.* Post-cardiotomy extracorporeal cardiopulmonary resuscitation in neonates with complex single ventricle: analysis of outcomes. *Eur J Cardiothorac Surg.* 2011; 40 (6): 1396–1405. DOI: 10.1016/j.ejcts.2011.01.087. PMID: 21507672.
10. *Dyamenahalli U., Tuzcu V., Fontenot E., Papagiannis J., Jaquiss R. D., Bhutta A., Morrow W. R., et al.* Extracorporeal membrane oxygenation support for intractable primary arrhythmias and complete congenital heart block in newborns and infants: short-term and medium-term outcomes. *Pediatr Crit Care Med.* 2012; 13 (1): 47–52. DOI: 10.1097/PCC.0b013e3182196cb1. PMID: 21516054.

Received 29.05.2023
Accepted 03.09.2024

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3. Герасимов Л.В., Марченков Ю.В., соавт. «Возможности коррекции метаболических нарушений с использованием реамберина в остром периоде травмы», Анестезиология и реаниматология № 6, 2015

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