Comparative Results of Treatment and Complications: Pedea in Open Ductus Arteriosus in Premature Infants

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Abstract: The open ductus arteriosus (ODA) is the vessel through which the pathological communication between the aorta and the pulmonary artery persists after birth. Clinical manifestations depend on the size of the duct and the stage of hemodynamic disorders. The course of the defect varies from asymptomatic to extremely severe. With large duct sizes, the latter manifests itself from the first week of life with signs of heart failure. The current research is devoted to the choice of the optimal method of medical and surgical treatment in premature newborns with an unaffected ductus arteriosus. Drug therapy for pulmonary hypertension is recommended only for those patients who have irreversible pulmonary hypertension. Surgical closure of the ODA is recommended for overloads of the left heart or signs of pulmonary hypertension in the presence of blood discharge from left to right and after previously suffered endocarditis. The article analyzes current information about the treatment of premature infants with ODA.

Key Words: open ductus arteriosus, premature infants, Pedea, features of surgical treatment, complication

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INTRODUCTION

Open ductus arteriosus (ODA) is one of the most common malformations. The incidence of ODA is inversely proportional to gestational age and body weight at birth and is 10%–18% of all Congenital Heart Defects. Long-term functioning of the ductus arteriosus in premature infants is usually a sign of morpho-functional immaturity of the cardiovascular system.[1,2] The lower the gestational age of the newborn, the more often they have ODA. In newborns with a body weight of less than 2000 gm, ODA is detected in approximately 40%, and in children with a gestational age of 28–30 weeks, ODA is detected in approximately 80% of cases.[3,4]

Fanaroff et al reported on the frequency of hemodynamically significant functioning of the arterial duct in newborns with a very low body weight of 1251–1500 gm. In infants with a body weight of 501–750 gm, the mortality rate ranges from 13% to 49%.[5]

Despite the available information in the literature on this issue to date, there is no consensus on the methods of treatment of ODA in premature newborns. According to Ohlsson and Walia,[6] the optimal timing for surgical intervention for ODA ligation in premature infants remains uncertain.

Method of Drug Treatment

In ODA, the ideal treatment method has not yet been determined. Finding the optimal treatment for premature infants with a body weight of less than 2500 gm is challenging. At the same time, one of the best results of ODA treatment is associated with the identification and use of nonsteroidal anti-inflammatory drugs that have the property of inhibiting the synthesis of prostaglandins. For the first time in Kazakhstan, a drug (Pedea) for the treatment of ODA in premature infants was registered in

October 2018. According to the "clinical protocol for the diagnosis and treatment of ODA" of the Ministry of Health of the Republic of Kazakhstan, echocardiographic examinations are performed in all newborns at risk (gestational age <30 weeks, in the case of a ventilator, who received surfactant and had pulmonary bleeding during the first 48 hours of life). In the case of detection of hemodynamically significant functioning of open duct in accordance with this protocol, in the first 2–5 days of a child's life, the drug "Pedea" is administered intravenously in the amount of 10–5 mg/kg at intervals of 24 hours.[4,7]

However, the results of treatment with nonsteroidal anti-inflammatory drugs showed an increase in complications of the drug treatment. Because indomethacin and Pedea inhibit the synthesis of all prostaglandins in the body, they can cause various side effects and diseases such as intestinal perforation, necrotizing enterocolitis, renal failure, thrombocytopenia, and related gastrointestinal and ventricular bleeding.[8]

Preterm infants with a very low body weight (<1000 gm) are particularly susceptible to these complications, so surgery is often the method of choice, providing a clinical effect with low mortality.[9,10]

Little et al believed that the contraindications to the appointment of cyclooxygenase inhibitors are with a duct diameter of 2.5 mm and a child's weight of less than 1000 gm because the frequency of recanalization of the duct after the appointment of indomethacin was 55%.[8,10] According to the authors, the surgical method comes to the fore in the treatment of patients with a very low body weight. Gersony et al also found that 46% of children with an extremely low body weight recanalize ODA after the use of indomethacin.[11] In the group of children with a very low body weight, there is almost no evidence of the benefits of surgical treatment of ODA and drug treatment. The main reason for the lack of a large number of comparative studies is that in many neonatal centers, surgery is a backup method of treatment and makes it difficult to interpret the results. Only one randomized study was found in the Cochrane database. There are also results from the European Registry.[9] They compare the results of surgical and medical treatment. The data of this study did not allow us to conclude about any advantage of these 2 methods; however, despite the clinical effectiveness, it was concluded that thoracotomy contributes to an increase in the frequency of retinopathy, pneumothorax, and bronchopulmonary dysplasia. There is the risk of retinal damage in patients after open surgery, the occurrence of chronic lung disease and sensorineural deficits.[10]

In addition, conservative therapy is not always an effective method. This fact is confirmed by Gross and Hines and is explained by the observations made.[11,12] These scientists conducted a study of the mechanism of regulation of the obliteration of ODA in healthy full-term and premature infants. The results of the study showed that in premature infants, the process of narrowing of the ductal wall was too weak and did not lead to complete closure of its opening. In addition, ODA reduces the possibility of its reduction from cyclooxygenase inhibitors (because of a slowdown in metabolic processes and a decrease in the level of adenosine triphosphate in the muscle layer). These observations scientifically prove the ineffectiveness of conservative treatment of ODA.

The effectiveness of indomethacin and Pedea in relation to the closure of ODA is only relative, but Pedea has a significantly lower effect on the kidneys, mesenteric, and cerebral vessels and therefore causes fewer complications.[13] For example, a meta-analysis conducted by Little et al showed the development of transient renal failure by 9% and necrotizing enterocolitis by 4% when using Pedea.[14]

In addition, there are studies showing the successful use of paracetamol for the closure of ODA.[13,15] In a meta-analysis conducted by Huang, the advantage of paracetamol instead of Pedea was demonstrated. With relative efficacy, the risk of kidney failure and gastrointestinal bleeding in this study was low (5% and 6%, respectively).[15]

The effectiveness of the drug Pedea in premature infants with early use (in the first 3–4 days of life) is 75%–80%. The indication for the use of the drug Pedea is the treatment of a functioning arterial duct of hemodynamically significant functioning in premature infants with a gestational age of less than 34 weeks. The optimal procedure is considered to be the beginning of the course of treatment in the first 3–4 days after the diagnosis of ODA (in the absence of contraindications) and not later than 7 days of life.[16]

What Pedea Is and What It Is Used For

While a baby is inside its mother's womb it does not need to use its lungs. An unborn baby has a blood vessel called the ductus arteriosus near the heart that allows the baby's blood to bypass the lungs and circulate to the rest of the body. When the baby is born and starts using its lungs the ductus arteriosus normally closes. However, in some cases this does not happen. The medical term for this condition is <<patent ductus arteriosus>>, that is an ODA. This can cause heart problems in your baby. This condition is much more frequent in premature newborn than in full-term newborn infants. Pedea, when given to your baby, can help to close the ductus arteriosus. The active substance in Pedea is ibuprofen. Pedea closes the ductus arteriosus by inhibiting the production of prostaglandin, a naturally occurring chemical in the body that keeps the ductus arteriosus open.

Ecotoxicity/Environmental Risk Assessment

Art. 8 of Directive 2001/83/EC, as amended, requires the applicant to indicate any potential risks exhibited by the medicinal product for the environment and to perform an evaluation, if applicable, of the precautionary and safety measures to be taken during the storage of the product, the environmental release after the use in patients and the disposal of unused or waste products. Pedea is intended for the treatment of PDA in premature neonates. The maximum prevalence of this cardiac disorder in the EU was estimated to 2.13 per 10,000 persons by the COMP during the orphan designation procedure. If one considers that the overall PDA prevalence without any considerations of the gestational age is 31%, the total number of neonates in the EU presenting a PDA would be theoretically 80,000 in 2000. Therefore, if one considers that the maximum dosage for 2 full courses of treatment (ie, 3 injections × 2) is 40 mg/kg/patient [(10 + 5 + 5) × 2], and the maximum body weight of a neonate is 3 kg, the quantity of the medicinal product to be consumed per year

in the EU would not represent more than 9.6 kg of Pedea ($40.10 - 6 \times 80{,}000 \times 3$). The applicant therefore considers that it is not relevant to assess the environmental risk of Pedea and related compounds release in the water compartment. Indeed, this quantity, which is obviously overestimated, is very negligible compared with the large quantity of Pedea used in other nonorphan indications.

Pharmacodynamics

Mechanism of Action

A published review by Van Overmeire et al,[17] provides a good overview of the action mechanism of Pedea. The applicant has not performed any pharmacodynamics studies of Pedea. In the normal fetus, the DA connects the main pulmonary trunk to the descending aorta. This differs from other vessels of the fetal circulation in that the media is composed mainly of a spiral layer of muscle fiber and the intima is thicker and develops mounds or cushions in the third trimester of pregnancy; functionally, it could be regarded as a sphincter. Constriction of the musculature of the ductus is inhibited by local and circulating prostaglandins and by low oxygen tension of the blood. At birth, the lungs expand and arterial oxygen content rapidly rises and circulating prostaglandin levels fall: these changes will tend to initiate ductal closure. However, in premature infants, circulating prostaglandin levels are higher than at term and respiratory difficulties may lead to a state of hypoxia, both of which contribute to the failure of the ductus to close leading to abnormal hemodynamics. Nonsteroidal anti-inflammatory drugs reduce prostaglandin levels and promote closure of the DA. The incidence of PDA is inversely proportional to the gestational age and birth weight of the infant. For full-term babies, it is approximately 1:2000; for very low birth weight babies, it is approximately 35%, and for those with respiratory distress syndrome, it is approximately 45%–50%.

Ligation of the Open Ductus Arteriosus

The first surgical treatment of ODA was performed in 1938 for a 7-year-old girl by American doctors Robert Gross and John Hubbard. The left-sided anterolateral thoracotomy approach was used.[18] Although the first surgery was successful, Gross during the upcoming practice realized that the method is not perfect and needs to be improved. In some patients, the vessel ligation did not lead to its complete and reliable blockage. In addition, the ligature thread could lead to the vascular wall damage and, as a result, the development of such a dangerous complication as bleeding or the formation of a hematoma.

Gross began to use 2 ligatures, and since 1941, surgeries were performed by stitching the 2 ends of the arterial vessel. For the first time in 1963, the operation on a deep premature baby with hemodynamically significant functioning open duct was successfully completed. The most common method of treating ODA is correction by surgical bandaging.[14,18] Several modifications of this surgical approach are provided: double and triple ligation, separation of the vessel, stitching of the ends of the vessel, stitching of the vessel with a mechanical suture, and correction of the vessel in conditions of artificial blood circulation. The surgical method of dressing the ODA is performed mainly with the help of a left-sided thoracotomy without creating artificial blood circulation. In most cases, when sealing an open core, the double-binding method is used. In addition, this approach is simple and reliable and the result is high level. However, the binding method is prone to injuries during correction and will lead to complications during surgery in the early postoperative period.[19] Dangerous conditions that can occur during surgery are bleeding, pneumothorax, laryngeal nerve paralysis, chylothorax (due to the thoracic lymphatic nucleus damage), and scoliosis that forms after a long time.

In older studies, premature newborns at the gestational age of 28 weeks or less in the first 15 hours of life were given indomethacin for prophylactic purposes and corrected by surgical dressing for those who do not have success with open vessel blockage. As a result, their study concluded that after the surgical method of dressing, there is no risk of forming neurological complications. Currently, in medical institutions of various countries, the method of surgical dressing of the CAP is performed in the absence of results from the course of double drug treatment and with a late resumption of the open core. Ductus Arterial Communication has questions about how much the result of surgical treatment can prevent or protect against possible complications.[20]

Disadvantages of this method are surgical mortality associated with vessel wall damage and the development of intraoperative bleeding (according to Gross, in 1952, who operated on 525 patients, 43 of them were operated with ODA ligature and 482 were treated with blockade, with the mortality rate of 2%); because of incomplete ligation or recanalization, the formation of a high level of pathological blood flow along the arterial vessel after ligation is characteristic. According to various authors, residual blood circulation with ODA occurs in 0.4%–23% of patients; significant traumatization of interventions leads to unusual complications for thoracotomy such as chest deformity, rib overgrowth, scoliosis, and limited mobility of the shoulder joint. Because cosmetic results and length of the incision are important for patients, researchers began to look for effective minimally invasive techniques for the treatment of ODA at the end of the 20th century.[21]

The aim of the study was to determine the results of conservative therapy and surgical treatment with ODA in premature infants. We seek to optimize management tactics in premature newborns taking into account risk factors and its complications in neonatal cardiac surgery.

MATERIAL AND METHODS

All research procedures were conducted in accordance with the institutional recommendations of the Scientific and Clinical Center of Cardiac Surgery and Transplantology (Taraz, Kazakhstan).

During the period 2014–2020, 157 premature infants with a diagnosis of ODA were treated in the Regional Perinatal Center (Zhambyl, Kazakhstan). All children underwent a comprehensive examination: clinical and anamnestic,

electrocardiographic, chest x-ray, echocardiography, analysis of the gas composition, and acid–base status of the blood.

Patients

Depending on the gestational age, weight, and severity of the condition, the patients were divided into 2 groups. Newborns of the first group had gestational age, weight, and height at birth less than those in children of the second group.

Group 1 (80 children) included premature infants, where the average gestational age at birth was 28.8 ± 3.2 weeks and the average weight was 1.3 ± 0.62 kg. The above-mentioned patients needed surgical intervention for urgent indications. Indications for surgical intervention in preterm infants on a ventilator were dependence on a ventilator, severe circulatory insufficiency of IIb–III degree and respiratory failure, lack of effect from drug treatment, instrumental confirmation of the significance of ODA according to EchoCG, the presence of left–right blood discharge according to ODA, and volume overload of the left heart cavities. Concomitant pathology includes RDS in all newborns, requiring the use of Alveofact in 11 cases (55%), and intraventricular hemorrhage of II–III degree in 16 cases (85.7%).

Group 2 (77 children) preterm infants, where the average gestational age at birth was 30.1 ± 2.72 weeks and average weight was 1.5 ± 0.44 kg. Usually, they were on independent breathing, with a clinic of NC of varying degrees, without significant respiratory disorders. The characteristics of the groups are presented in Table 1.

Statistical Analysis

The results of the research were obtained and analyzed using Microsoft Excel 2016 and Statistica for Windows V.10.0 (StatSoft Inc). Statistical processing was performed using the application software system and statistical programs SPSS Statistics-20.The statistical analysis of the materials was performed using the methods of statistical analysis in advanced nonparametric biomedical research and the criteria of evidence-based medicine in accordance with modern requirements for the analysis of medical data. We present the Mann–Whitney *U* test to test the assumption of the involvement of the compared independent samples.

RESULTS

Conservative therapy for premature infants with ODA included fluid restriction in 100% of cases to 3–4 mL/kg/hour, diuretics (furosemide in 5.4% and verospiron in 2.7% of premature infants), and inotropic drugs (digoxin in 11.1% and dopamine in 24.3% of cases). The nonsteroidal anti-inflammatory drug was Pedea.

In group 1, ODA ligation was performed in 28 newborns (35%) and 52 newborns (65%) underwent conservative and medical treatment; of these, 43 (53.8%) received oxygen therapy and the drug Pedea, and the remaining 37 (46.2%) received oxygen therapy, inotropic drugs, and diuretics. In this group of premature newborns from 2 to 5 days of life, the drug Pedea (5–10 mg.) was taken in a 3-day course. The echocardiography revealed the average values of the following parameters: ODA d = 2.2 mm, FV = 60.75%, left ventricle (LV)/aorta (Ao) = 2.09, and left atrium (LA)/Ao = 1.52. In 31 preterm infants of 43 newborns at 5–10 days of life, repeated echocardiography revealed a decrease in the diameter of the ODA to 1.2 mm after conservative treatment, and in 10 preterm infants, repeated echocardiography revealed no changes.

All children were extubated at various times after surgery, on average after 7.4 ± 5.2 days (from 1 to 18 days). The relief of signs of NC after surgery made it possible to

TABLE 1. Characteristics and Risk Factors of the Groups of Premature Newborns Diagnosed With ODA

Indicators	I Group	II Group	Confidence Difference ($P \leq 0.05$) According to the Mann–Whitney *U* Test
No. of premature newborns	80	77	
Gestation period, wk (M ± SD)	28.8 ± 3.21	30.1 ± 2.72	0.003
Body weight at birth, kg (M ± SD)	1.3 ± 0.62	1.5 ± 0.44	0.037
Media mother's pregnancy sequence	3	3	
Diameter of the OAP (according to EchoCG), mm	2.6 ± 0.45	1.84 ± 0.64	0.042
Circulatory insufficiency (NC) IIa-IIb st., no. of newborns	80	40	
Respiratory failure (DN) IIIst, no. of newborns on Alveofact	80	5	
Endotracheal in the OPC, no. of newborns	42	35	
Duration of ventilator, h (M ± SD)	279 ± 74.45	178 ± 77.53	0.008
Concomitant pathology, RDS and BPD, no. of newborns	80	56	
Concomitant pathology, grade II–III VVC, no. of newborns	68	43	
Intrauterine infection and other infection	26	7	
Lethality (%)	12 (15%)	9 (11.7%)	

abandon, in most cases almost immediately, the use of cardiotonic drugs and diuretics. Of those who received conservative treatment with the drug Pedea, 6 children (14.2%) died from a complication of Bronchopulmonary dysplasia (BPD) with a severe course. After surgery, ligation of ODA, 4 (8.5%) of the children died from progressive cerebral edema caused by congenital hydrocephalus.

In children in the second group (N = 77), who were on independent breathing, 41 children (53%) were discharged from the hospital under the supervision of a cardiologist at the place of residence and 22 children (29%) were transferred to other hospitals for further observation and treatment. Of the total number of patients in group 2, 14 children (17.6%) needed digoxin and dopamine therapy. In this group of premature newborns, 12 children (15%) took the drug Pedea (5–10 mg) from day 2 to day 5 of life, 18 children (23.5%) underwent surgical interventions on a planned basis at various times (at 23–39 days of life). Indications for surgical intervention in these cases were circulatory insufficiency I-II A st and echocardiographic confirmation of progressive NC with significant ODA. The age of these children at the time of the surgery was up to 1 year. In this group of children who took the drug Pedea, 9 children (11.7%) died from complications of neonatal sepsis.

The analysis of the obtained data allowed us to determine the indications for surgical intervention in premature newborns. Decompensation of the condition of premature infants with hemodynamically significant ODA occurs in the first month of life (the neonatal period). The main volume of surgical interventions and all deaths in our observation were also recorded during this period. The main indications for the elimination of ODA in a premature baby are arranged in the descending order of their significance by instrumental confirmation, clinical manifestation (by the degree of circulatory insufficiency), and lack of effect from drug treatment.

In the first group, indications for surgical removal of ODA were the lack of effect from drug treatment in 6 children (30%) and circulatory insufficiency of varying severity in all children. In the second group, indications for ODA ligation were the lack of effect from drug treatment in 4 children (30.7%), circulatory insufficiency, and instrumental confirmation of the significance of ODA by ECHO-KG in 80% (the presence of unidirectional left–right blood discharge by ODA and volume overload of the left heart cavities). The comparative analysis of medical (Pedea) and surgical treatment of premature infants of groups 1 and 2 are presented in Table 2.

A comparative analysis of the echocardiographic criteria of children of groups 1 and 2 before and after surgery showed that in children of group 1, the values of most indicators were significantly higher (LV BWD = 75.64 ± 6.09 mL/m^2, LV = 64.4 ± 17.43%, LV/Ao = 2.51 ± 0.23) than those in children of group 2 (LV BWD = 72.1 ± 3.53 mL/m^2, LV = 62.21 ± 3.02%, LV/Ao = 2.18 ± 0.17). This can be explained by the duration of hemodynamic changes and compensatory processes occurring in the myocardium. Large values of the LP indicator/Ao in children of group 1 before surgery (group 1–1.58 ± 0.26, group 2–1.42 ± 0.28) was also explained by the duration of hemodynamic changes. By the time of surgery, most of the children in group 1 with hemodynamically significant ODA developed left ventricular hypertrophy.

After surgery, changes in echocardiographic parameters were less pronounced in children of group 1 [end-diastolic volume of the left ventricle (EDVLV)/LV = 69.5 ± 21.42 mL/m^2, ejection fraction (EF) = 69.7 ± 5.34%, LV/Ao = 2.29 ± 0.47] than those in children of group 2. In children of the second group, there was a decrease in EDVLV/LV (56.7 ± 23.01 mL/m^2), LP/Ao (1.40 ± 0.28), and LV/Ao (2.13 ± 0.64) with an almost unchanged LV ejection fraction, which, in our opinion, indicated the possibility of rapid regression of hemodynamic overload of the left heart in premature newborns. The comparative analysis of EchoCG criteria for preterm infants of groups 1 and 2 before are presented in Table 3.

When analyzing the gas composition of capillary blood in the examined children before surgery, there were an increase in pCO2 and a decrease in oxygenation of pO_2 and $SATO_2$, as well as pH and BE, which, in our opinion, is associated with pronounced DN (mixed acidosis) against the background of decompensation of the child's condition for Congenital Heart Defects.

Many children on the ventilator had an increase in pCO_2 (42.3 ± 0.28) and a decrease in oxygenation (pO_2 = 42.49 ± 0.42, $SATO_2$ = 72.4 ± 28.32) and pH (7.26 ± 0.09) with a deficiency of buffer bases (BE −2.67 ± 7.11). After ODA ligation, there was a positive dynamics of a decrease in pCO_2, an increase in pO_2 and SAT O_2, and normalization of pH and BE (pH = 7.35 ± 0.05, pCO_2 = 36.9 ± 1.48, pO_2 = 43.16 ± 1.83, $SATO_2$ = 90.3 ± 3.47; BE = −4.75 ± 3.72). The comparative analysis of the gas composition of the

TABLE 2. Comparative Analysis of Medical (Pedea) and Surgical Treatment of Premature Infants of Groups 1 and 2

Group	Absolute Number (n)	Conservative Treatment		Ineffective Medical Treatment		Surgical Treatment	
		Absolute Number, %	Lethality, %	Absolute Number, %	Lethality, %	Absolute Number, %	Lethality, %
I group N = 80	80	52 (65)	8 (10)	6 (30)	1 (0.8)	7 (35)	1 (5)
II group N = 77	77	59 (76.5)	9 (11.7)	4 (30.7)	0 (0)	4 (23.5)	0 (0)

TABLE 3. Comparative Analysis of EchoCG Criteria for Preterm Infants of Groups 1 and 2 Before Pedea

Main Echocardiography Criteria	Before			
	EDVLV/LV mL/m² M ± SD	EF % M ± SD	LV/Ao M ± SD	LA/Ao M ± SD
I group N = 80	75.64 ± 6.09	64.4 ± 3.02	2.51 ± 0.23	1.58 ± 0.26
II group N = 77	72.1 ± 3.53	64.21 ± 17.4	2.18 ± 0.17	1.42 ± 0.28

Main Echocardiography Criteria	After				Confidence Difference ($P \leq 0.05$) According to the Mann–Whitney *U* Test
	EDVLV/LV mL/m² M ± SD	EF % M ± SD	LV/Ao M ± SD	LA/Ao M ± SD	
I group N = 80	69.5 ± 21.42	69.7 ± 5.34	2.29 ± 0.47	1.54 ± 0.12	0.026
II group N = 77	56.7 ± 23.01	64.5 ± 4.17	2.13 ± 0.64	1.40 ± 0.28	0.012

capillary blood of premature infants of groups 1 and 2 before and after Pedea are presented in Table 4.

During the x-ray examination, we observed an increase in the pulmonary vascular pattern and an increase in CTI > 50% in most children [22 (59.4%)]. In the postoperative period, positive dynamics was radiologically noted.

DISCUSSION

In our work, we studied various risk factors (characteristics of the child's somatic state), which, according to our observations, had the greatest impact on the survival of children.

As a result, a group of factors was formed that is comparable with the aggravating signs studied in the literature. Each of them had a significant effect on mortality, the degree of prematurity, and the presence of concomitant disease ($P < 0.05$), early neonatal age up to 7 days of life ($P < 0.05$). The greatest significance was the combination of low weight (up to #1000 gm) and deep prematurity (28–30 weeks) (*P*, 0.00001), Intrauterine infection (*P*, 0.00001), ventilator before surgery (*P*, 0.00001), and somatic diseases (RDS, pneumonia, and VVC) (*P*, 0.0001). Our observations confirmed that in children without risk factors, the outcomes of surgical treatment are the most favorable, regardless of the type of intervention. However, characterizing the severity of the patient's somatic condition by the number of factors, regardless of their combination, each addition of one factor worsens the treatment outcomes ($P < 0.000001$). At the same time, the "critical" level can be confidently considered a combination of 3 risk factors. Based on the data obtained, specific dynamic steps were formulated in the treatment of children, depending on risk factors, which affected both an increase in the number of operated newborns over the years and a decrease in the overall surgical mortality in group I (up to 11.7%) than the comparison from group II (15%).

The results showed that the long-term functioning of the ODA directly affects the duration of stay on the ventilator, thus leading to the development of BPD (12.7% in the general group) and high mortality. If drug therapy is ineffective, such children need to undergo immediate surgical intervention, regardless of the severity of the initial condition—prematurity and low weight

TABLE 4. Comparative Analysis of the Gas Composition of the Capillary Blood of Premature Infants of Groups 1 and 2 Before and After Pedea

Main Criteria for the Gas Composition of Capillary Blood	Before				
	pH M ± SD	pO_2, mm Hg M ± SD	pCO_2, mm Hg M ± SD	BE M ± SD	$SATO_2$ % M ± SD
I group N = 20	7.26 ± 0.09	42.49 ± 0.42	42.3 ± 0.28	−2.67 ± 7.11	72.4 ± 28.32
II group N = 17	7.28 ± 0.08	44.89 ± 8.14	43.45 ± 11.35	−2.67 ± 7.11	76.32 ± 23.14

Main Criteria for the Gas Composition of Capillary Blood	After					Confidence Difference ($P \leq 0.05$) According to the Mann–Whitney *U* Test
	pH M ± SD	pO_2, mm Hg M ± SD	pCO_2, mm Hg M ± SD	BE M ± SD	$SATO_2$ % M ± SD	
I group N = 20	7.3 ± 0.06	43.16 ± 1.83	36.9 ± 1.48	−7.86 ± 0.49	90.3 ± 3.47	0.041
II group N = 17	7.35 ± 0.05	41.2 ± 3.6	39.8 ± 10.81	−4.75 ± 3.72	94.2 ± 2.23	0.044

—and the difficulties associated with transporting such patients to a specialized cardiac surgery hospital. Thus, a distinctive feature of cardiac surgery in the neonatal period is the "inability to wait" until the child gains weight, is cured of VUI, ventilator-associated pneumonia, is stabilized by heart failure after prolonged transportation, and so on. The expansion of indications for surgery with a confident positive outcome is possible with an increase in the quality of the surgery itself, anesthesia, and nursing, including the management of children in the early postoperative period.

CONCLUSIONS

Indications for surgical removal of ODA in premature newborns are the hemodynamic significance of ODA, the ineffectiveness of drug treatment (Pedea), and dependence on ventilators. Timely surgical removal of hemodynamically significant ODA in premature newborns reduces the duration of stay on a ventilator. Drug treatment with Pedea in a premature newborn with ODA is accompanied by a small number of complications and low postoperative mortality.

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