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THE SIGNIFICANCE OF CLINICAL AND LABORATORY SIGNS IN ASSESSING THE EFFECTIVENESS OF NUTRITIONAL SUPPORT FOR CRITICALLY ILL NEWBORNS

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Abstract. ***Introduction.*** The choice of starting nutritional support in newborns depends on the severity of multiple organ failure and the initial metabolic process in the early neonatal period. ***The purpose*** is to study the prognostic value of clinical and laboratory parameters in assessing the metabolic status of newborns in need of nutritional support. ***Materials and methods***. 125 newborns are included in the study. They are divided into 2 groups: 69 children with the somatic disorder symptoms, 55 with surgical pathology. Prognostic assessment of biochemical markers and their relationship with nosological profile and nutritional corrected types is performed using statistical methods of data processing. ***Results and conclusion.*** In patients with somatic disorders cardiorespiratory hypoxia affects the nutritional status in the short term. The tolerance to full enteral nutrition is restored within a week. Surgical trauma is associated with the hypercatabolic syndrome, dysproteinemia and fluctuations in body weight. The prognostic value of death is determined in groups: in the surgical one with C-reactive protein growth (AUC >0,9, p=0,000), the elevated of blood urea nitrogen after surgery (AUC >0,8, p=0,000) and lactate on the 7th day (AUC=0,989, p=0,000); in newborns with the somatic disorder C-reactive protein growth is valuable in ICU admission and glucose concentration is on the 7th day (AUC=0,88 and AUC=0,94, p=0,000 respectively). For nutritional support, the values of C-reactive protein are relevant in the somatic group. There are actual levels of glucose, blood urea nitrogen, albumin on the first postoperative day. The duration of parenteral nutrition is significantly affected by surgical treatment and albumin transfusion (p=0.000), η^2=26.4% (ANOVA method). In the choice of nutritional support the personalized approach is important to determine metabolic status.

Keywords*: newborns, metabolic status, parenteral nutrition, intensive care*

ЗНАЧИМОСТЬ КЛИНИКО-ЛАБОРАТОРНЫХ ПРИЗНАКОВ В ОЦЕНКЕ ЭФФЕКТИВНОСТИ НУТРИТИВНОЙ ПОДДЕРЖКИ У НОВОРОЖДЕННЫХ В КРИТИЧЕСКОМ СОСТОЯНИИ

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Резюме. ***Введение.*** Выбор нутритивной поддержки и ее начало у новорожденных зависит от тяжести полиорганной недостаточности, характера патологии, исходного метаболического статуса. ***Цель исследования*** — изучение прогностической ценности клинико-лабораторных показателей в оценке метаболического статуса у новорожденных, нуждающихся в нутритивной поддержке. ***Материалы и методы.*** Исследование проведено у 125 новорожденных, распределенных на 2 группы: соматическая — 69 детей, хирургическая — 56 детей. Прогностическая оценка биохимических маркеров и их взаимосвязь с патологией и видами нутритивной коррекции выполнена статистическими методами обработки данных. ***Результаты и выводы.*** У соматических пациентов гипоксия вследствие кардиореспираторной депрессии влияет на нутритивный статус краткосрочно с восстановлением толерантности к полному энтеральному питанию в течение недели. Операционная травма сопряжена с развитием гиперкатаболического синдрома, проявляющегося тяжелой диспротеинемией колебаниями массы тела. Прогностическую ценность неблагоприятного исхода определили: в хирургической группе рост С-реактивного белка AUC >0,9, p=0,000, уровень азотемии после операции AUC >0,8, p=0,000, лактата на 7-е сутки AUC=0,989, p=0,000; в соматической группе — С-реактивный белок при поступлении и концентрации глюкозы на 7-е сутки (соответственно, AUC=0,88 и AUC=0,94, p=0,000). Для проведения нутритивной поддержки актуальны значения С-реактивного белка в соматической группе, в хирургической — уровни глюкозы, мочевины, альбумина в 1-е сутки послеоперационного периода. На длительность парентерального питания значимо влияют проведенное хирургическое лечение и трансфузия альбумина (p=0,000), η^2=26,4 % (метод ANOVA). Персонифицированный подход определения метаболического статуса остается актуальным в выборе нутритивной поддержки.

Ключевые слова: *новорожденные, метаболический статус, парентеральное питание, интенсивная терапия*

INTRODUCTION

Counteracting critical conditions requires significant metabolic demands from patients, especially in the neonatal period [1, 2]. Nutritional deficiency significantly hinders the metabolic effects of nutrients, moreover, it is a universal component of multiorgan failure syndrome and requires comprehensive clinical and laboratory monitoring [2, 3]. The developed clinical protocols for parenteral and enteral nutrition in newborns do not take into account the peculiarities of dysmetabolism in newborns in critical condition associated with gastrointestinal insufficiency in the postoperative period, the presence of congenital malformations of the gastrointestinal tract and intrauterine developmental delay [3–5]. According to studies [6, 7], more than 70% of neonates operated during the neonatal period had a body weight deficit below the 50th centile and required nutritional correction. The need for a better understanding of the changes in the metabolic status of neonates in critical condition determined the relevance of the study.

AIM

To study a prognostic value of clinical and laboratory parameters in the assessment of metabolic status in neonates requiring nutritional support.

MATERIALS AND METHODS

The observational study was conducted at the paediatric intensive care unit (ICU) of the State Novosibirsk Regional Clinical Hospital approved by the Local Ethics Committee of the State Novosibirsk Regional Clinical Hospital (protocol No. 1 of 09.03.2021). The total study sample consisted of 125 newborns hospitalized from 2020 to 2022. Gender distribution: boys — 72 (58%), girls — 53 (42%). Newborns were divided into two groups depending on the presence or absence of surgical pathology requiring surgical treatment for urgent and emergency indications: somatic — 69 (group 1), surgical — 56 (group 2). 50 patients (40%) had gestational age less than 37 weeks, 18 patients (14%) had fetal growth restriction (FGR). There were 7 (5.6%) deaths: 4 in the somatic group and 3 in the surgical group.

Inclusion criteria: Group 2 required surgical treatment of intestinal pathology. All participants were included in the study in case of the neonatal period (up to 28 days of life at admission), absence of cardiovascular insufficiency with shock development, indications for long-term parenteral nutrition. Nosological characteristics of the groups: Somatic group- presence of intrauterine infection (pneumonia, enterocolitis stage I–II) — 15 (22%), congenital heart defect — 13 (19%), early neonatal sepsis — 8 (12%), respiratory distress syndrome of prematurity — 23 (33%), other — 8 (12%); Surgical group — oesophageal atresia — 14 (36%), high intestinal obstruction — 5 (9%), low intestinal obstruction — 15 (27%), gastroschisis — 2 (3.6%), diaphragmatic hernia — 4 (7%), necrotising enterocolitis (NEC) grade III — 5 (9%), other — 9 (16%). Complications in the somatic group: infectious ones — 26 (38%), haemorrhagic — 3 (4%), in the surgical group: infectious — 21 (37.5%), haemorrhagic — 4 (7.1%).

There were no significant intergroup differences in mortality and number of complications. Intensive therapy was performed according to the generally accepted algorithm: respiratory therapy to achieve target ventilation/oxygenation parameters; hemodynamic therapy: to ensure the volume of daily hydration according to physiological needs with recalculation per day of life (for preterm neonates — from 40 ml/kg to reach 130 ml/kg, less than 37 weeks of gestation — from 60 to 140 ml/kg). Isotonic saline solutions, components of parenteral nutrition, and dilutions were included in the calculation. When enteral nutrition (EN) had been tolerated, the volume of intravenous infusion was reduced. The algorithm and composition of parenteral nutrition (PN) were performed according to modern protocols [1, 5]. PN was performed in 101 neonates (81%), albumin transfusion — in 60 patients (48%). The substrate-energy composition of nutritional support is presented in Table 1. The need for parenteral nutrition in the surgical group was 211 hours (138; 301) and 118 hours (89; 160) in the somatic group, p=0.000. The somatic group achieved adequate volume of enteral nutrition earlier at all stages ($p < 0.05$).

The studied parameters were recorded over 3 stages: for surgical patients: stage 1 — the first day after surgical treatment (when administered to ICU), 2 — the third day, 3 — the sixth-seventh day. The same time stages were used for somatic patients according to the time of stay in ICU. The study included general clinical parameters (leukocyte (Le), haemoglobin (Hb), haematocrit (Ht) levels), biochemical monitoring (ionised calcium (Ca^{2+}), potassium (K), C-reactive protein (C-RP), total protein (Prot), lactate (Lac), glucose (Glu), albumin (Alb.), urea (Ur), creatinine (Cr), anthropometric data.

Statistical processing of the material was performed using IBM SPSS Statistics 20 program, USA. Taking into account the non-normal nature of data distribution (Kolmogorov–Smirnov criterion), mathematical processing was carried out using nonparametric statistics methods. The results are presented in tables and graphs in the form of median with values of lower and upper quartile (Q25; Q75). Two independent signs were compared by the Mann–Whitney test, dependent pairs of signs — by the Wilcoxon test, dependent 3 signs and more — by the Friedman test, correlation analysis — by the Spearman rank test. Predictive analytics was performed by ROC-analysis methods (calculation of area under the ROC-curve (AUC), overall model characterization (SE standard error, CI 95%: confidence interval) and decision tree construction (CHAID method). The influence of factors was assessed by multivariate analysis of variance (ANOVA), η^2%. The null hypothesis was rejected at $p < 0.05$.

RESULTS AND DISCUSSION

The neonates were compared in terms of the fetal growth restriction (FGR) incidence (Table 2). Odds Ratio (OR) = 1 (95% CI 0.4–2.7), preterm infants were 3.5 times more common in the somatic group: p=0.001, OR 3.5 (95% CI 1.5–4.7).

Table 1. Substrate provision and enteral nutritive initiation in groups at stages

Таблица 1. Субстратное обеспечение и начало энтерального питания в группах на этапах

Этап / Stage	Показатель / Indicator				
	№ гр. / gr. №	белок, г/кг/сутки / protein, g/kg/day	углеводы, г/кг/сутки / carbohydrates, g/kg/day	энергия, ккал/кг/сутки / energy, kcal/kg/day	ЭП, % / EN, %
1	1	1,5 (1; 2)	6,3 (4,7; 8,6)	38 (36; 48)	0
	2	1,25 (0,5; 2)	6,2 (4; 8,4)	40 (22; 50)	0 (0; 20)
2	1	2,8 (2; 3)	11,3 (8; 13)	68 (49; 74)	0 (0; 20)
	2	2 (1,6; 3)	9,2 (7; 12,4)	60 (40; 72)	20 (0; 50)
3	1	2,5 (1,3; 3)	10 (5,5; 13,3)	65 (30; 75)	30 (10; 70)
	2	2 (1; 2,5)	9,3 (6,3; 11,6)	60 (41; 71)	60 (30; 80)

Table 2. Anthropometric characteristics of groups

Таблица 2. Антропометрические характеристика групп

Показатель / Indicator	Группа 1 / Group 1 (n=69)	Группа 2 / Group 2 (n=56)	Критерий Манна–Уитни / Mann–Whitney test
Масса тела, г / Body weight, g	2690 (2440; 3180)	3120 (2455; 3470)	p=0,105
Возраст, дни / Age, days	1 (1; 8)	2 (1; 6)	p=0,664
Апгар, балл / Apgar, score	7/7 (6/7; 7/8)	7/8 (7/8; 8/9)	p=0,002
Срок гестации, недели / Gestation period, weeks	35 (33; 38)	38 (37; 39)	p=0,021

Table 3. General clinical and carbohydrate status in two groups at stages

Таблица 3. Общеклинический и углеводный статус в двух группах на этапах

Этап / Stage	Показатель / Indicator					
	№ гр. / gr. №	Le, 10^9/л / Le, 10^9/l	Hb, г/л / Hb, g/l	Ht, % / Ht, %	Lac, ммоль/л Lac, mmol/l	Glu, ммоль/л / Glu, mmol/l
1	1	13 (11; 18)	147 (128; 170)	44 (40; 52)	*2,2(1,6; 4,4)*	3,8 (3; 4,6)
	2	15 (12; 17)	155 (142; 175)	47 (41; 51)	*1,6(1,3; 2,3)**	4 (3,5; 4,7)
2	1	12 (9; 15)	150 (135; 187)	43 (39; 55)	1,5 (1,2; 2)	4,7 (3,9; 5,4)
	2	13 (10; 19)	148 (130; 171)	45 (38; 49)	1,5 (1,2; 1,9)	4,3 (3,7; 5,1)
3	1	10 (9; 14)	142 (125; 167)	45 (38; 52)	1,8 (1,5; 2,1)	4,7 (4,4; 5)
	2	13 (9; 19)	147 (127; 154)	42 (37; 46)	1,5 (1,2; 1,8)	4,5 (4; 4,9)

* Значимость критерия Манна–Уитни p=0,021.
* Significance of the Mann–Whitney test p=0.021.

The dynamics study of body weight is presented in Figure 1. A significant loss of the parameter was detected in newborns in the postoperative period (Friedman's criterion χ^2=8.11, p=0.04) while the parameter was stable in the somatic group (a trend was detected between the 2nd and 3rd stages, not reaching the accepted level of significance; Wilcoxon's criterion, p=0.065).

When comparing the results of general clinical and biochemical analyses in the groups at stages, the results are generally comparable (Tables 3, 4). Differences in lactate and creatinine concentrations were noted on arrival; multidirectional dynamics in azotaemia remained by the end of the week.

Correlation analysis of different markers have been performed in groups according to Apgar score. It revealed the fact that there is a direct significant association between creatinine at all stages with Apgar score (ρ=0.7, p=0.000; ρ=0.67, p=0.000; ρ=0.54, p=0.000, respectively) and lactate level at admission (ρ=0.72, p=0.000) in the somatic group. The surgical group showed a direct

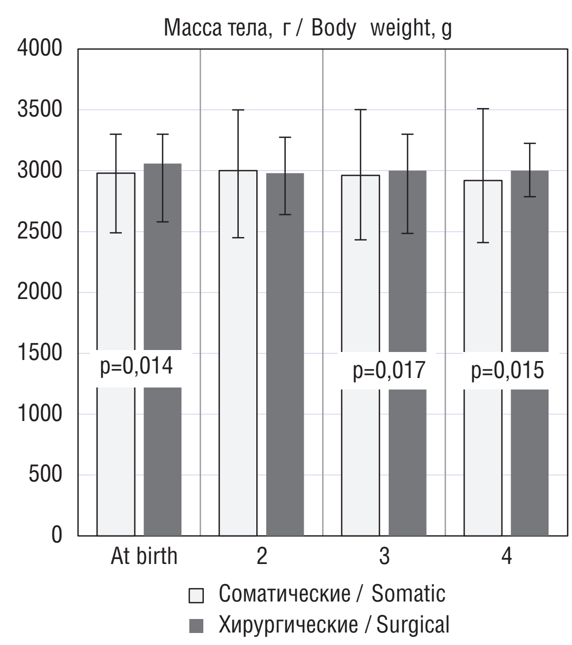

Fig. 1. Dynamics of body weight in groups at the study stages. The Mann–Whitney's test significance

Рис. 1. Динамика массы тела в группах на этапах исследования. Указана значимость критерия Манна–Уитни

Table 4. Biochemical parameters in groups at stages

Таблица 4. Биохимические параметры в группах на этапах

Этап / Stage	Показатель / Indicator							
	№ гр. / gr. №	Ca^{2}+, ммоль/л / Ca^{2}+, mmol/l	K+, ммоль/л / K+, mmol/l	C-RP, мг/л / C-RP, mg/l	Prot., г/л / Prot., g/l	Alb., г/л / Alb., g/l	Ur, ммоль/л / Ur, mmol/l	Cr, мкмоль/л / Cr, µmol/l
1	1	1 (0,9; 1,3)	4 (3,8; 4,6)	2 (0,5; 13)	44 (41; 48)	31 (28; 32)	5 (3,4; 8,3)	77 (67; 97)
	2	1 (0,9; 1,2)	4,1 (3,8; 4,8)	6 (1,5; 20)	44 (40; 48)	30 (28; 32)	5,3(3,7; 6,2)	73 (58; 82)*
2	1	1,1 (0,9; 1,3)	4,2 (3,9; 4,5)	2 (1; 7)	45 (42; 47)	31 (29; 32)	6,1 (4,6; 9)	68 (64; 84)
	2	1,2 (1,1; 1,4)	4,4 (3,9; 4,7)	10 (4; 21)	47 (43; 50)	31 (28; 35)	6 (4,8; 9)	59 (52; 78)*
3	1	1,3 (1,1; 1,4)	4,5 (4,1; 4,6)	2 (1,5; 4)	46 (44; 49)	31 (30; 33)	5,2 (4,1; 7,5)	57 (51; 66)
	2	1,3 (1,2; 1,4)	4,5 (4,2; 4,7)	5 (3; 9)	48 (44; 51)	33 (30; 36)	6,9 (5,3; 8,1)*	54 (48; 67)*

* Значимость критерия Манна–Уитни Ur_3 p=0,016, Cr_1 p=0,008; Cr_2 p=0,005, Cr_3 p=0,03.
* Significance of the Mann–Whitney test Ur3 p=0.016, Cr1 p=0.008; Cr2 p=0.005, Cr3 p=0.03.

Table 5. ROC-analysis of indicators in groups at stages (prediction of death)

Таблица 5. ROC-анализ показателей в группах на этапах (прогнозирование летального исхода)

Этап/ Stage	Показатель / Indicator	№ гр. / gr. №	AUC	SE	p	95% ДИ	
	Возраст, дни / Age, days	1	0,814	0,083	0,000	0,651	0,978
		2	0,675	0,075	0,020	0,528	0,822
1	C-RP, мг/л / C-RP, mg/l	1	0,879	0,076	0,000	0,730	0,99
		2	0,917	0,044	0,000	0,831	0,99
3	C-RP, мг/л / C-RP, mg/l	1	0,686	0,098	0,058	0,494	0,878
		2	0,983	0,013	0,000	0,97	0,992
1	Ur, ммоль/л / Ur, mmol/l	1	0,979	0,022	0,000	0,936	0,993
		2	0,883	0,064	0,000	0,757	0,99
1	Cr, мкмоль/л / Cr, µmol/l	1	0,686	0,090	0,039	0,509	0,862
		2	0,803	0,092	0,002	0,610	0,973
3	Glu, ммоль/л / Glu, mmol/l	1	0,943	0,039	0,000	0,866	0,99
		1	0,663	0,088	0,059	0,499	0,838
3	Lac, ммоль/л / Lac, mmol/l	1	0,393	0,095	0,261	0,206	0,580
		2	0,989	0,012	0,000	0,966	0,992

Table 6. ROC-analysis of indicators in groups (prediction of the parenteral nutrition initiate)

Таблица 6. ROC-анализ показателей в группах (прогнозирование начала парентерального питания)

Этап / Stage	Показатель / Indicator	№ гр. / gr. №	AUC	SE	p	95% ДИ	
1	C-RP, мг/л / C-RP, mg/l	1	0,413	0,096	0,362	0,225	0,600
		2	0,898	0,076	0,000	0,749	0,986
2	Alb., г/л / Alb., g/l	1	0,487	0,086	0,878	0,319	0,655
		2	0,819	0,074	0,000	0,673	0,964
1	Ur, ммоль/л / Ur, mmol/l	1	0,499	0,083	0,993	0,337	0,661
		2	0,902	0,070	0,000	0,796	0,993

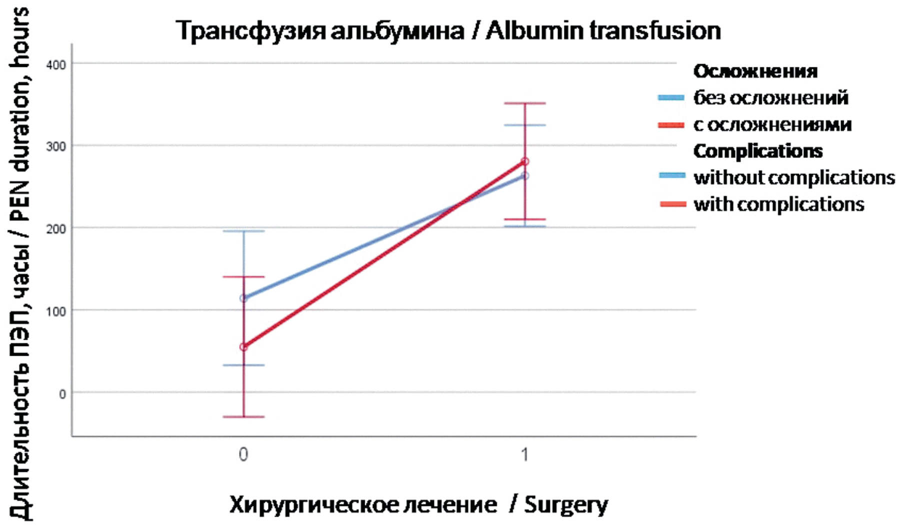

Fig. 2. Interaction of factors (albumin transfusion and complications) and their influence on the duration of parenteral nutrition in groups

Рис. 2. Взаимодействие факторов (трансфузия альбумина и осложнений) и их влияние на длительность парентерального питания в группах

correlation only between urea and creatinine at stage 3 (ρ=0.537, p=0.000).

Prediction of outcome (fatal outcome) and the need for parenteral nutrition was performed by ROC analysis. The ignificant AUC is ≥0.8. Prognostic markers of target variables are presented (Table 5).

The predictive indicators of lethal outcome in the surgical group were C-reactive protein concentrations over 93 mg/l (Se 89%, Sp 85%) in the first three days and lactate concentrations over 5 mmol/l on the 7th day (Se 91%, Sp 83%). Neonates with somatic pathology showed validity of urea concentration on admission greater than 9.4 mmol/l (Se 87%, Sp 82%) and glycaemia less than 3.1 mmol/l (Se 84%, Sp 89%) on the 7th day.

Parenteral nutritional support was initiated in neonates after surgical treatment with C-reactive protein concentrations less than 33 mg/L (Se 83%, Sp 87%) and urea levels less than 4.7 mmol/L (Se 84%, Sp 90%). Albuminemia of more than 24 g/l (Se 86%, Sp 81%) determined tolerance to substrate load on the 3rd day in the somatic group (Table 6). ROC analysis was not informative for predicting complications (factor sign 0/1). The method of multifactorial analysis of variance ANOVA revealed isolated and bifactorial influence of albumin transfusion after surgical treatment of complications during parenteral nutrition (Fig. 2). Both surgical treatment and the need for albumin transfusion appeared to have a statistically significant influence on the duration of PN (p=0.006 and p=0.047 respectively). The correlation of these factors between each other was statistically significant (p=0.000) and had a maximum contribution to the variance of η^2=26.4%.

Taking into account the comparability of the groups in terms of outcome category (χ^2=0.011, p=0.09) and the majority of metabolic indices at the stages, the decision tree method was used to create a prognostic model of unfavourable outcome (lethal outcome) and to identify significant markers of intensive care for the whole sample. Unfavourable signs were anaemia on admission (haemoglobin less than 149 g/l) and kalaemia less than 3.8 mmol/l on the 7th day (Fig. 3).

The present study revealed the nature of pathology on metabolic status in neonates. The influence of initial hypoxia on cardiorespiratory maladaptation and metabolism has been confirmed in neonates with somatic pathology [8]. However, regression is noted within a week without critical catabolic shifts and no weight loss, despite priority restriction of hydration volumes. The literature confirms [9, 10] that surgical trauma is associated with profound metabolic disorders, the development of hypercatabolic syndrome which manifests in severe dysproteinaemia. The number of albumin transfusions was significantly higher in the surgical group χ^2=13, p=0.000, OR=3.8 (95% CI 1.8–8.2). Hypoalbuminaemia in somatic neonates was associated with pre- and postnatal nutrient deficiency (correlation with hypoglycaemia on admission was found). As for sur-

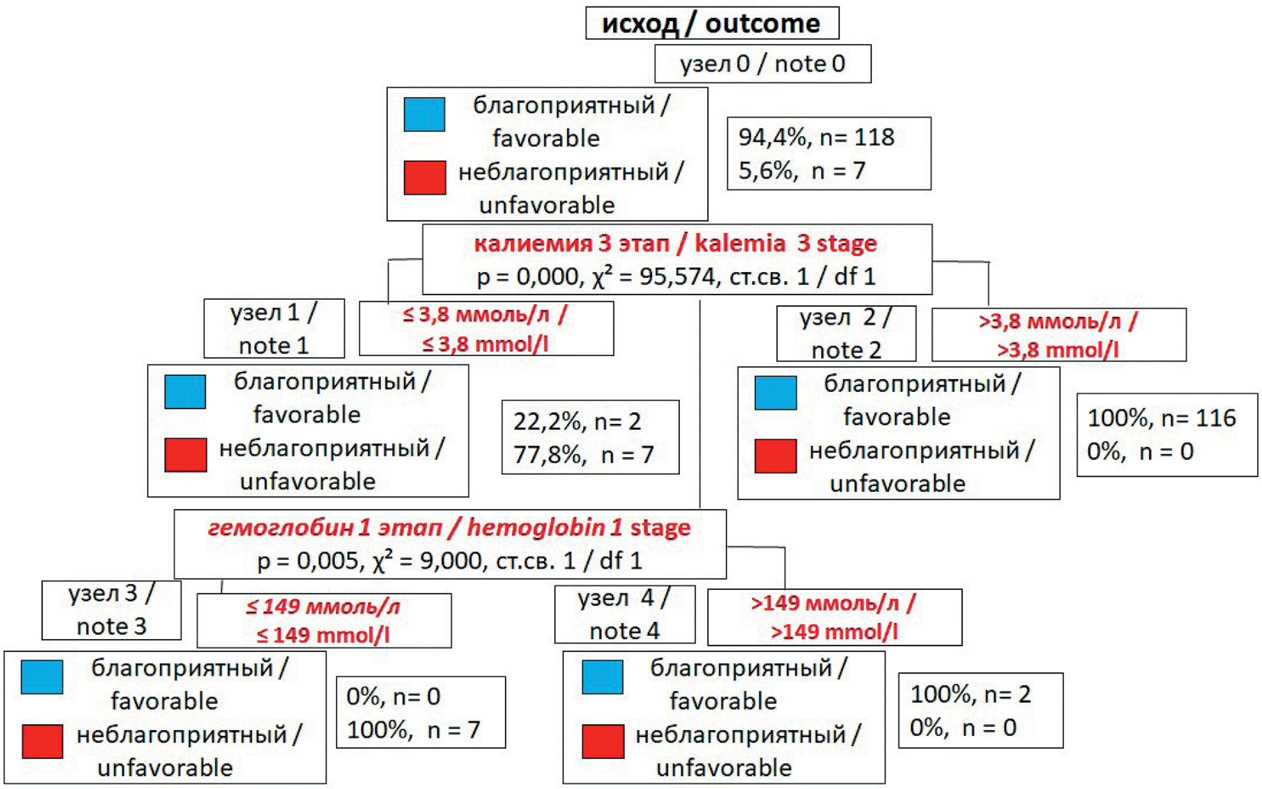

Fig. 3. Decision tree method CHAID (Chi-squared Automatic Interaction Detection)

Рис. 3. Дерево решений, метод CHAID (Chi-squared Automatic Interaction Detection)

gical neonates, it was associated with C-reactive protein concentration, i.e. with intensity of an inflammatory response to surgical aggression. The growth of azotaemia in the postoperative period is associated with the duration of post-stress protein hypercatabolism on the background of replacement therapy. The revealed metabolic shifts in neonates with abdominal surgical pathology confirmed the data presented by the authors [9]. The sergical group was supplied with lower daily amino acid intake during the early postoperative period compared to the somatic group, which was characterised by rapid increase in the volume of enteral nutrition and the amount of substrate-energy support [11, 12]. Studies have confirmed the importance to control the nutrient requirements in neonates after surgical treatment [13, 14]. The opportunity to achieve adequate enteral nutrition determined the stability of the body weight index in this group.

The increase in the enteral nutrition rate was associated with a positive difference in body weight by the 7th day (direct, weak correlation ρ=0.35, p=0.035). The studied groups were compared in relation to the number of unfavourable outcomes (χ^2=0.01, p=0.9, OR=0.9 (95% CI 0.1–4.2) and complications (χ^2=0.09, p=0.8, OR= ,1 (95% CI 0.5–2.3). The structure of complications coincided in the groups. However, an infection component was significant in the somatic pathology during the eraly period, while it apeared in the surgical group remotely. The prognostic unfavourable shifts of indices were revealed: the presence of hemoglobin deficiency on admission (less than 149 g/l) and kalaemia on the 7th day (less than 3.8 mmol/l).

CONCLUSIONS

1. Inflammatory response (C-reactive protein less than 33 mg/L) and decreased azotemia less than 4.7 mmol/L were the criteria for initiation of parenteral nutritional support in neonates in early period after surgical treatment.

2. The rate of initiation of parenteral nutrition in neonates with cardiopulmonary maladaptation was associated with an albuminemia level of more than 24 g/L.

3. C-reactive protein concentration of more than 93 mg/l in the first three days and lactate concentration of more than 5 mmol/l by the end

of the week were determined as prognostic indicators of lethal outcome in newborns after surgical treatment. Azotemia of more than 9.4 mmol/l on admission and glycaemia of less than 3.1 mmol/l were associated with an unfavourable outcome in neonates with somatic pathology. For all neonates, anaemia (haemoglobin less than 149 g/l) and potassium level (less than 3.8 mmol/l) at 7th day were considered as prognostic unfavourable shifts in parameters.

4. A personalized approach to the development and control of metabolic status and nutritional support remains relevant in treating neonates in critical conditions and requires further research.

ADDITIONAL INFORMATION

Author contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

Competing interests. The authors declare that they have no competing interests.

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Consent for publication. Written consent was obtained from legal representatives of the patients for publication of relevant medical information within the manuscript.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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