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ALGORITHM OF A DIFFERENTIATED
APPROACH TO MANAGEMENT OF
PERSISTENT PULMONARY HYPERTENSION
IN PREMATURE INFANTS

T. Klymenko, M. Kononovych

Educational and Scientific Institute for Postgraduate
Training of the Kharkiv National Medical University
(Kharkiv, Ukraine)

Summary

Introduction. Oxidative stress (OS) is recognized as a contributing factor to the development of persistent pulmonary hypertension (PPH) in premature infants. In the modern scientific literature, there is a lack of unequivocal recommendations for the management of PPH, considering the levels of OS, what determines the need for the development of a differentiated approach for management to infants with pulmonary hypertension.

The aim of the study. To increase the efficacy of management of premature infants with persistent pulmonary hypertension with asphyxia and respiratory distress syndrome based on the development of the algorithm of a differentiated approach for management of pulmonary hypertension considering the levels of oxidative stress as determined by the urinary 8-hydroxy-2-deoxyguanosine (8-OHdG).

Material and methods. Were analyzed the observations of 96 infants born prematurely at gestational age of 26/1–34/6 weeks: group I consisted of 50 infants with respiratory distress syndrome (RDS), group II - 50 infants with RDS associated with perinatal asphyxia. PPH was determined by echocardiography on the 1st and on the 3rd-5th day of life, and quantitative determination of the urinary 8-OHdG (ng/ml) was performed on 44 neonates on the 1st and in dynamics on the 3rd-5th day of life using enzyme-linked immunosorbent assay (ELISA). For comprehensive radiographic assessment of PPH, all infants received chest X-Ray with determination of Moore's, Schwedel's, and cardiothoracic indexes (CTI).

Statistical analysis was performed using Microsoft Excel 2019 software. Under the conditions of normal distribution of quantities, parametric statistical methods were used to calculate the arithmetic mean (M) and the representativeness error of the mean (m). Using Fisher's exact test (φ) we analyzed the quantitative parameters. Using the heterogeneous sequential Wald procedure, development of diagnostic criteria was performed. The essence of the procedure is to determine both diagnostic (DC), prognostic coefficients (PC) and diagnostic informativeness (I) of the investigated indicators. The minimum informativeness of the feature required for addition to the developed algorithm was considered $I \geq 0.25$.

The algorithm was developed on the basis of diagnostic coefficients of clinical and anamnestic data of the examined groups of children, echocardiographic criteria for the presence and determination of the degree of PPH, the dynamics of OS levels and their comparison with the indicators of a comprehensive radiological assessment of pulmonary hypertension in prematurely born infants with RDS and perinatal asphyxia in association with RDS in gestational age of 26-34 weeks.

Design of a study was discussed and approved at a session of the Ethical commission of the Kharkiv Medical Academy of Postgraduate Education (Prot. № 5 from 18.12.2020). All parents gave an informed consent for examination of their children.

The study was carried out in accordance to the plan of the research work of the Department of Neonatology of the Kharkiv Medical Academy of Postgraduate Education "Study of features of the course of oxidative stress diseases in newborns" (January 2022 - December 2024), state registration number 0122U000025.

Results. Has been developed an algorithm of a differentiated approach to management of premature infants with RDS and asphyxia with PPH, the essence of which - is to improve and individualize the method of mechanical lung ventilation (MLV) for each individual case.

Conclusions. For prematurely born infants at gestational age 26-34 weeks, is important to determine the level of the urinary 8-OHdG on the 1st and 3rd-5th days of life to decide the severity of OS. For management of newborns with PPH, in the case of an increase of the level of 8-OHdG by the 3rd-5th day of life, is recommended to increase the ventilator parameters; in the case of a decrease - diminish the ventilation parameters or extubate an infant.

Keywords: Premature Infants; Persistent Pulmonary Hypertension; Oxidative Stress.

Introduction

Oxidative stress (OS) is recognized as a contributing factor to the development of persistent pulmonary hypertension (PPH) in premature infants [1-4]. One of the reliable biomarkers for determining the severity of OS in premature infants is the level of the urinary 8-hydroxy-2-deoxyguanosine (8-OHdG) [5-8], which correlates with mean pulmonary artery pressure (mPAP) and duration of respiratory support. The article presents the results of scientific work on the development of a differentiated approach to management of PPH. On the first step, an analysis of modern medical literature was provided and the need

to improve the management of patients with PPH was determined [9]. On the second step, was founded the correlation between OS and mPAP levels in premature infants with respiratory distress syndrome (RDS) and asphyxia [10, 11]. On the next step we analyzed the types and duration of respiratory support, their correlations with the dynamics of OS levels in prematurely born infants with PPH [12].

The aim of the study - to increase the efficacy of management of premature infants with persistent pulmonary hypertension with asphyxia and respiratory distress syndrome based on the development of the

algorithm of a differentiated approach for management of pulmonary hypertension considering into account the levels of oxidative stress as determined by the urinary 8-hydroxy-2-deoxyguanosine (8-OHdG).

Material and methods

Were analyzed the observations of 96 infants born prematurely at gestational age of 26/1–34/6 weeks, which were carried out in the intensive care unit for premature newborns at the Kharkiv City Perinatal Center in accordance with modern protocols.

In the presence of combined pathology, newborns were divided into two groups: group I consisted of 50 infants with respiratory distress syndrome (RDS), group II - 50 infants with RDS associated with perinatal asphyxia. Clinical characteristics of groups is presented in the table 1. The inclusion criteria for both groups were the presence of PPH.

The definitive diagnosis of PPH was established by echocardiography monitoring according to the method described in European recommendations [13].

A quantitative measurement of the value of the urinary 8-OHdG, ng/ml on the 1st day of life, and on the 3rd–5th day of life was provided by ELISA using the DNA Damage ELISA kit, Enzo Life Sciences (USA) as the manufacturer's instructions require.

In the comprehensive radiographic assessment of PPH, chest X-Ray was used with the determination of Moore's, Schwedel's, and cardiothoracic indexes (CTI) according to the method proposed by V.V. Spuzhak. with co-authors [14].

The algorithm was developed on the basis of clinical and anamnestic data of the examined groups

of children, echocardiographic criteria for the presence and determination of the degree of PPH, the dynamics of OS levels and their comparison with the indicators of a comprehensive radiological assessment of pulmonary hypertension in prematurely born infants with RDS and perinatal asphyxia in association with RDS.

Design of a study was discussed and approved at a session of the Ethical commission of the Kharkiv Medical Academy of Postgraduate Education (Prot. № 5 from 18.12.2020). All parents gave an informed consent for examination of their children.

Statistical analysis was performed using Microsoft Excel 2019 software. Under the conditions of normal distribution of quantities, parametric statistical methods were used to calculate the arithmetic mean (M) and the representativeness error of the mean (m). Using Fisher's exact test (φ) we analyzed the quantitative parameters. Using the heterogeneous sequential Wald procedure, development of diagnostic criteria was performed [15]. The essence of the procedure is to determine both diagnostic (DC), prognostic coefficients (PC) and diagnostic informativeness (I) of the investigated indicators.

The minimum informativeness of the feature required for addition to the developed algorithm was considered $I \geq 0.25$.

The study was carried out in accordance to the plan of the research work of the Department of Neonatology of the Kharkiv Medical Academy of Postgraduate Education "Study of features of the course of oxidative stress diseases in newborns" (January 2022 - December 2024), state registration number 0122U000025.

Table 1

Clinical characteristics of patient groups, n (%), $M \pm m$

Indicator	Group I (n=50)	Group II (n=50)
Gestational age, weeks	30,66±0,42	30,34±0,51*
Weight at birth (g)	1399 ±125	1520 ±155*
Boys, n (%)	26 (52%)	25 (50%)
Girls, n (%)	24 (48%)	25 (50%)

Note: * - $p > 0.05$ - no difference between groups

Results and discussion of the study

After studying the anamnesis data of the examined newborns, a high diagnostic significance ($5.0 \geq I \geq 1.0$) was established for the following coefficients: birth weight ($I=4.35$), presence of perinatal asphyxia ($I=3.60$), Apgar score on the 5th minute of life ($I=3.49$), gestational age ($I=3.24$), type of delivery ($I=1.68$), Apgar score on the 1st minute of life ($I=1.13$), appropriation for gestational age ($I=1.13$), the presence of placental dysfunction during pregnancy ($I=1.11$), child's gender ($I=1.04$). Moderate diagnostic significance ($1.0 \geq I \geq 0.50$) was characteristic of the presence of arterial hypertension during pregnancy ($I=0.60$).

To determine the possibility of using the OS biomarker in clinical practice for the management of premature infants with PPH, we analyzed the dynamics of the urinary 8-OHdG. It was established that a decrease in 8-OHdG levels on the 3rd-5th day

of life indicates a favorable course of PPH ($I=6.39$).

In our previous studies, it was established that the intensity of decreasing of the urinary 8-OHdG in prematurely born infants correlates with the duration of respiratory support [11]. Therefore, for including to the algorithm for the management of PPH in prematurely born infants in the early neonatal period, we analyzed the effect of the methods of the respiratory support on the course of PPH. High diagnostic significance was established ($5.0 \geq I \geq 1.0$) to the duration of high-frequency oscillatory ventilation (HFOV) – $I = 3.03$, traditional mechanical ventilation – $I = 2.49$, and non-invasive types of respiratory support – NIV and CPAP – $I = 1.56$.

For the effective management of PPH in premature infants in the early neonatal period, a comprehensive radiological assessment of pulmonary hypertension is important, which includes the determination of Moore's, Schwedel's, and CTI indices [16, 17] when

performing a chest X-ray examination on the 1st and 3rd-5th days of life. Among the above indices, the Schwedel index (I=4.22) has the highest diagnostic significance, which represents the diameter of the descending branch of the right pulmonary artery in its proximal section and is measured from the outer wall of the intermediate bronchus to the outer contour of the pulmonary artery [18].

Clinical recommendations for the treatment of persistent pulmonary hypertension in premature infants are controversial [19-22]. Modern trends of the management of PPH are passing over the need to optimize respiratory support in prematurely born infants with RDS and with RDS associated with perinatal asphyxia in the early neonatal period and improve the management of PPH [23-25].

The obtained results of the informativeness of prenatal and postnatal anamnesis, the level of OS, the

radiological assessment of pulmonary hypertension led us to the idea of developing a complex algorithm for the diagnosis of PPH in premature infants. According to the algorithm of the heterogeneous sequential procedure, all indicators were divided into gradations with further calculation of diagnostic coefficients (DC) and general diagnostic informativeness (I), which made it possible to form a multimarker diagnostic system (table 2). Management using the developed algorithm was carried out by algebraic summation of DC until the diagnostic threshold was reached, which for the 95% level of reliability was ≥ -13.0 , and for the 99% level - $DC \geq -20$. If there is a "-" sign next to the sum of DC of all indicators, there is a risk of developing PPH of a significant/severe degree, and the "+" sign indicates a favorable course of PPH. If the diagnostic threshold was not reached when adding DC of all algorithm indicators, the course was considered indeterminate.

Table 2

Algorithm of a differentiated approach to management of persistent pulmonary hypertension in premature infants

Indicator	Gradation	DC	I
mPAP on the 3rd – 5th day of life, mmHg	<40	+9.0	7.0
	≥40	-9.0	
Decrease of the 8-OHdG levels on the 3rd – 5th day of life	don't decreased	-7.8	6.39
	decreased	+9.3	
Birth weight, g	<1500	-3.8	4.35
	≥1500	+11.6	
Schwedel's index on the 3rd -5th day of life, cm	0,4-0.5	+8.5	4.22
	> 0.5	-5.0	
Perinatal asphyxia	present	-6.0	3.60
	not present	+6.0	
Apgar score on the 5th minute of life	1-3 points	-9.0	3.49
	4-6 points	-0.5	
	>6 points	+23.8	
Gestational age, weeks	26-29	-9.7	3.24
	30-34	+3.3	
Moore's index on the 3rd -5th day of life, %	36-40%	+6.7	3.23
	41-45%	-1.3	
	>45%	-6.3	
Duration of the HFOV, hours	<48	+3.1	3.03
	>48	-9.5	
Duration of TMV, hours	<72	+3.4	2.49
	>72	-6.9	
CTI on the 3rd -5th day of life, %	50-59	+3.4	2.49
	≥60	-6.9	
mPAP on the 1st day of life, mmHg	<40	+4.0	1.98
	≥40	-4.6	
Type of delivery	natural childbirth	-8.0	1.68
	Cesarean section	+1.9	
NIV/CPAP- the only one type of respiratory support	yes	+7.2	1.56
	no	-2.0	
Apgar score on the 1st minute of life	1-3 points	-4.3	1.13
	>3 points	+2.4	
Appropriation for gestational age	non-appropriative	-12.5	1.13
	appropriative	+1.8	
Placental disfunction during pregnancy	present	-2.6	1.11
	not present	+3.8	

Conclusions

1. The following clinical and diagnostic factors have a high diagnostic significance for the development of PPH of a significant/severe degree: birth weight <1500 g (I=4.35), perinatal asphyxia (I=3.60), Apgar score on the 1st minute of life 1-3 points (I=1.13), on the 5th minute of life < 7 points (I=3.49), gestational age < 30 weeks (I=3.24), natural childbirth (I=1.68), non-appropriate for gestational age (I=1.13), male gender (I=1.04), placental dysfunction during pregnancy (I=1.11), arterial hypertension during pregnancy (I=0.60).

2. Important to determine the level of the urinary 8-hydroxy-2-deoxyguanosine for premature infants born with RDS and perinatal asphyxia in the gestational age of 26-34 weeks, to decide the severity of oxidative stress on the 1st and on the 3rd -5th day of life. The levels of 8-OHdG have a high diagnostic value for determining the risk of developing PPH of a significant/severe degree on the 3rd-5th day of life (I=6.39): decreased levels of 8-OHdG in the urine indicates a favorable course of PPH, and increased - indicates the risk of developing PPH of a significant/severe degree.

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3. In the complex radiological assessment of the degree of severity of PPH in premature infants with perinatal asphyxia and RDS is important to use the X-ray index of Schwedel, which has a high diagnostic significance (I=4.22).

4. The high diagnostic value of the duration of types of respiratory support for the prognosis of the course of PPH in premature infants was established: the risk of developing PPH of a significant/severe degree is indicated by: duration of HFOV >48 hours (I=3.03) duration of TMV > 72 hours (I =2.49), or if NIV/CPAP is not the only type of respiratory support (I=1.56).

Prospects for further research. Prospects for further research are the study of diagnostic and prognostic factors for the development of persistent pulmonary hypertension in premature infants with perinatal pathology, considering the degree of oxidative stress.

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АЛГОРИТМ ДИФЕРЕНЦІЙОВАНОГО ПІДХОДУ ДО МЕНЕДЖМЕНТУ ПЕРСИСТУЮЧОЇ ЛЕГЕНЕВОЇ ГІПЕРТЕНЗІЇ У ПЕРЕДЧАСНО НАРОДЖЕНИХ ДІТЕЙ

Т.М. Клименко, М.І. Кононович

**Навчально-науковий інститут післядипломної освіти Харківського національного медичного університету
(м. Харків, Україна)**

Резюме.

Вступ. Оксидативний стрес (ОС) визнано фактором, що сприяє розвитку персистуючої легеневої гіпертензії (ПЛГ) у передчасно народжених дітей. Недостатність у сучасній літературі однозначних рекомендацій щодо менеджменту ПЛГ з урахуванням рівнів ОС визначає потребу в розробці диференційованого підходу до надання допомоги новонародженим із легеневою гіпертензією.

Мета дослідження. Підвищення ефективності надання медичної допомоги передчасно народженим дітям з персистуючою легеневою гіпертензією з асфіксією та респіраторним дистрес-синдромом на підставі розробки алгоритму диференційованого підходу до ведення легеневої гіпертензії з урахуванням рівнів оксидативного стресу за визначенням рівня 8-гідрокси-2-дезоксигуанозину (8-OHdG) в сечі.

Матеріал та методи дослідження.

Були проведені систематизовані спостереження над 96 передчасно народженими дітьми терміном гестації 26/1–34/6 тижнів: I групу склали 50 дітей з респіраторним дистрес-синдромом (РДС), групу II - 50 дітей з РДС у поєднанні з асфіксією при народженні. Проведено визначення наявності ПЛГ в першу та на 3-5 добу життя за допомогою ехокардіографії, а 44 дітям проведено кількісне визначення рівня 8-OHdG (нг/мл) на першу добу життя та повторно – на 3–5 добу методом імуноферментного аналізу (ІФА). Для комплексної променевої оцінки ПЛГ всім дітям було проведено Ro ОГК з підрахунком індексів Мура, Шведеля та кардіоторакального індексу (КТІ).

Статистичний аналіз проводився за допомогою програмного забезпечення Microsoft Excel 2019 року. За умов нормального розподілу величин застосовано параметричні методи статистики з розрахунком середньої арифметичної величини (M) та похибки репрезентативності середньої величини (m). Кількісні параметри аналізувалися за допомогою кутового критерію Фішера (φ). Для розроблення діагностичних критеріїв застосовувалася неоднорідна послідовна процедура Вальда. Суть процедури полягає в визначенні як діагностичних (ДК), прогностичних коефіцієнтів (ПК) і діагностичної інформативності (І) досліджуваних показників. Мінімальною інформативністю ознаки, необхідною для додавання до розробленого алгоритму вважали I ≥ 0,25.

Алгоритм створювався на основі діагностичних коефіцієнтів клініко-анамнестичних даних обстежених груп дітей, ультразвукових критеріїв наявності та визначення ступеню тяжкості ПЛГ, динаміки рівнів ОС та зіставлення їх з показниками комплексної променевої оцінки легеневої гіпертензії у передчасно народжених дітей з РДС та перинатальною асфіксією у поєднанні з РДС в гестаційному віці 26-34 тижні.

Дизайн дослідження був обговорений та схвалений на засіданні медико-етичної комісії Харківської медичної академії післядипломної освіти (протокол № 5 від 18.12.2020 р.). Усі батьки дали інформовану згоду на обстеження своїх дітей.

Дослідження проведено відповідно до плану науково-дослідної роботи кафедри неонатології Харківської медичної академії післядипломної освіти «Вивчення особливостей перебігу хвороб оксидативного стресу у новонароджених» (січень – грудень 2024 р.), номер державної реєстрації 0122U000025.

Результати дослідження. Розроблено алгоритм диференційованого підходу до ведення недоношених новонароджених з РДС та асфіксією з ПЛГ, сутність якого – у вдосконаленні та індивідуалізації вибору методики штучної вентиляції легень (ШВЛ) для кожного окремого випадку.

Висновки. Передчасно народженим дітям в терміні гестації 26-34 тижні для визначення тяжкості ОС важливо визначення рівня 8-OHdG в сечі в першу та в динаміці – на 3-5 добу життя. При веденні новонароджених з ПЛГ у випадку зростання рівню 8-OHdG к 3-5 добі життя рекомендовано підвищення параметрів ШВЛ; при зниженні – пом'якшення параметрів ШВЛ або екстубація дитини.

Ключові слова: передчасно народжені діти; персистуюча легенева гіпертензія; оксидативний стрес.

Contact Information:

Tetiana Klymenko – Doctor of Medical Science, Full Professor, Head of the Department of Pediatric №3 and Neonatology of Educational and Scientific Institute for Postgraduate Training of the Kharkiv National Medical University (Kharkiv, Ukraine)

e-mail: klimenko57.t@gmail.com

ORCID ID: <https://orcid.org/0000-0001-6936-8557>

Scopus Author ID: <https://www.scopus.com/detail.uri?authorId=6701325386>

Researcher ID: <https://www.researchrid.com/rid/H-3698-2017>

Mariia Kononovych – Postgraduate Student, Educational and Scientific Institute for Postgraduate Training of the Kharkiv National Medical University (Kharkiv, Ukraine)

e-mail: konon_92@ukr.net

ORCID ID: <https://orcid.org/0000-0002-4705-1444>

Scopus Author ID: <https://www.scopus.com/detail.uri?authorId=5784226250>

Контактна інформація:

Клименко Тетяна Михайлівна – доктор медичних наук, професор, в.о. завідувача кафедри педіатрії №3 та неонатології Навчально-наукового інституту післядипломної освіти Харківського національного медичного університету (м. Харків, Україна)

e-mail: klimenko57.t@gmail.com

ORCID ID: <https://orcid.org/0000-0001-6936-8557>

Scopus Author ID: <https://www.scopus.com/detail.uri?authorId=6701325386>

Researcher ID: <https://www.researchrid.com/rid/H-3698-2017>

Кононович Марія Ігорівна – аспірант кафедри педіатрії №3 та неонатології Навчально-наукового інституту післядипломної освіти Харківського національного медичного університету (м. Харків, Україна)

e-mail: konon_92@ukr.net

ORCID ID: <https://orcid.org/0000-0002-4705-1444>

Scopus Author ID: <https://www.scopus.com/detail.uri?authorId=5784226250>



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