ISSN: 0975-833X

Available online at http://www.journalcra.com

International Journal of Current Research
Vol. 12, Issue, 02, pp.10080-10083, February, 2020

DOI: https://doi.org/10.24941/ijcr.37903.02.2020

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

RESEARCH ARTICLE

VIOLATION OF CELLULAR ENERGY IN PREMATURE NEWBORNS WITH RESPIRATORY DISTRESS SYNDROME

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ARTICLE INFO

Article History:
Received 04th November, 2019
Received in revised form
10th December, 2019
Accepted 29th January, 2020
Published online 28th February, 2020

Key Words:

Infants, Respiratory Distress Syndrome, Lactate, Pyruvate, Enzymes, Lymphocyte.

ABSTRACT

We examined 48 premature newborns with respiratory distress syndrome (RDS) and 20 healthy premature newborns. We determined the level of lactate and pyruvate in blood serum, as well as the activity of the Krebs cycle enzymes succinate dehydrogenase (SDH), α-glycerophosphate dehydrogenase (α-GPhDH) and lactate dehydrogenase (LDH) in peripheral blood lymphocytes using a quantitative cytochemical method by reaction with nitrofiolet tetrazolium. The development of RDS in premature newborns was accompanied by severe lactatacidosis on the background of hypoxemia and violations of bioenergetic processes at the cell level. These disorders were characterized by dissociation of the activity of peripheral blood lymphocyte dehydrogenases involved in the energy-forming process. There was a decrease in SDH and LDH activity with an increase in α-GPhDH activity in most newborns. To normalize the processes of bioenergy in infants with RDS, it is advisable to develop methods of pharmacological correction.

Citation: *Vladlena Vladimirovna Garmaeva, Dr. Maria Vasilievna Kushnareva Nina Vasilievna Kleymenova and Dr. Galina Mikhaylovna Dementyeva,* **2020.** "Violation of cellular energy in premature newborns with respiratory distress syndrome", *International Journal of Current Research*, 12, (02), 10080-10083.

INTRODUCTION

Respiratory distress syndrome (RDS) occupies one of the leading places in the structure of morbidity and mortality of premature infants (Cernada, 2014; Sukhanova, 2013). There are studies that focus on various aspects of this problem, including the fundamental work of a number of scientists. There are studies that are devoted to various aspects of this problem, including the fundamental work of a number of scientists (Cairns et al., 2004; Nasirova et al., 2018; O'Donnell, 2002).The introduction of these developments into the practice of neonatology and new methods of nursing premature babies has made it possible to achieve significant success in the diagnosis, prevention and treatment of RDS (Clark, 2017; Garmaeva, 2008; Ledyaev, 2017; Piksaykina, 2012). However, the development of severe complications of this disease ("fan-associated" pneumonia, sepsis, hypoxic-ischemic damage to the Central nervous system, disorders of the cardiovascular system) remains a serious problem in the neonatal and post-neonatal period.

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They can lead to the formation of chronic pathology and disability in the future (Cernada, 2014; Garmaeva, 2008; Ledyaev, 2017). It is known that the energy costs of the body increase significantly in severe respiratory failure, including in infants with RDS, especially against the background of the development of a bacterial infection. This is due to increased chest function and activation of antimicrobial protection (Garmaeva, 2008; Neudakhin, 2015; Shishchenko, 2013). The favorable outcome of RDS, especially with the development of complications, significantly depends on the adequate provision of the energy needs of infants, especially after the abolition of mechanical lung ventilation (ALV) (Cairns, 2000; Garmaeva, 2008; Maslovskaya, 2006). In this regard, the study of the bioenergy status of the body in premature babies with RDS is worthy of attention, using the determination of lactate and pyruvate levels in the blood serum (Garmaeva, 2008; Solovieva, 2018). A study of the activity of the Krebs cycle enzymes in blood lymphocytes will make it possible to indirectly judge the energetic activity of body tissues (Narcissov, 1978; Sukhorukov, 2004). This will help to further determine the pharmacological correction of the energy state of infants with respiratory failure.

The aim of the study was to determine the bioenergetic status in premature newborn infants with respiratory distress syndrome based on the study of the activity of Krebs cycle enzymes in peripheral blood lymphocytes (succinate dehydrogenase, alpha-glycerophosphate dehydrogenase and lactate dehydrogenase) and the level of lactate and pyruvate in blood serum.

MATERIAL AND METHODS

We examined 48 premature newborns with respiratory distress syndrome (the main group). All the infants were on artificial lung ventilation. The parameters of the studied enzymes, lactate and pyruvate obtained by us in 20 conditionally healthy preterm infants (control group) were used as control indicators. The infants were born with body weight from 1540 to 2500 g (M ± m = 2135.1 ± 77.82 g), body length from 42 to 47 cm (M ± m = 44.24 ± 0.43 cm) and gestational age from 30 to 37 weeks (M ± m = 33.9 ± 0.31 weeks). Groups of infants with RDS and of conditionally healthy infants were representative by body weight, body length, and gestational age at birth. We studied the activity of the Krebs cycle enzymes succinate dehydrogenase (SDH), alpha-glycerophosphate dehydrogenase (α-GPhDH) and lactate dehydrogenase (LDH) in peripheral blood lymphocytes using the quantitative Pierce cytochemical method modified by R. P. Narcissov in 1986 (Narcissov, 1978). The method is based on the reaction of formazan with nitro-violet tetrazolium. Depending on the detected enzyme, specific substrates were added to the basic medium. Formazan is a product of a cytochemical reaction and is detected using a light microscope in the cell in the form of colored granules. Formazan granules were counted in 50 peripheral blood lymphocytes. The activity of the enzyme was expressed in conventional units (granules/cell). The conventional unit corresponded to the average number of granules of formazan in one cell.

The study of the level of lactate and pyruvate in the blood was carried out by the enzymatic method Rollinghoff (1967) (mmol /L), as well as on the device ABL-735 (Radiometer, Denmark. Statistical data processing was performed using the Biostat application package, Ver / 3.03. We determined the mean values (M) and the errors of the mean values (M ± m). Comparison of indicators in the studied groups and between groups was carried out according to the criteria of Student (t-test) and of Pearson ($\chi 2$ - criterion).

RESULTS

Studies have shown that preterm infants with RDS revealed pronounced violations of oxygen homeostasis, as indicated by a decrease in blood $p0_2$ (54.14 ± 2.8 mmHg) and an increase in pCO_2 (50.7 ± 2.37 mmHg), despite the fact that the children were on additional oxygenation. Table 1 presents the concentration of lactic and pyruvic acids in the blood serum of premature infants with RDS and “conditionally” healthy premature infants. As can be seen from Table 1, a significant increase in the level of lactate and the ratio of lactate / pyruvate occurred in blood serum in infants with RDS. This indicated the presence of metabolic disturbances with changes in bioenergetic processes at the cell level, which were characterized by activation of anaerobic glycolysis processes under conditions of hypoxemia and hypoxia. Normal indicators of lactate, which we received in 20 "conditionally healthy" preterm infants of the control group, coincide with the literature data in healthy newborns (Maslovskaya, 2006; Solovieva, 2018). The results of a comparative cytochemical study of the activity of the enzymes LDH, SDH and α-GPhDH of peripheral lymphocytes in premature infants with RDS in comparison with "conditionally healthy" infants are presented in Table 2. As can be seen from Table 2, premature infants with RDS have a decrease in LDH activity, a tendency to decrease the activity of the SDH enzyme, and a significant increase in α-GPhDH, which is probably an indicator of the activation of the compensatory pathway - the glycerophosphate shunt, which is an element of the conjugation between glycolysis and respiration. We examined the state of lymphocyte enzyme activity, taking into account the severity of respiratory failure in infants with RDS. As can be seen from Table 2, in infants with RDS and severe respiratory failure who needed a ventilator for more than 5 days (6-8 days), there was a significant increase in the activity of α-GPhDH, while the activity of SDH and LDH did not differ from the norm. The data of individual analysis of the content of granules in blood lymphocytes in infants with RDS are presented in Table 3.

As can be seen from Table 3, the activity of enzymes in infants with RDS relative to the norm was ambiguous. However, in most infants (52%), the activity of SDH and LDH was higher than in healthy children (by one standard deviation) and ranged from 5.7 granules / cell to 11.3 granules / cell. The activity of α-GPHRH was increased in 25 children (52%), which was a compensatory reaction of the body to the violation of mitochondrial processes. This was manifested by a decrease in the activity of the SDH and LDH enzymes in the same number of newborns. We conducted a correlation analysis of the relationship of the activity of blood lymphocyte dehydrogenases on gestational age and body weight at birth in a group of healthy premature babies. These results are presented in Table 4. As can be seen from Table 4, the activity of SDH and LDH is negatively correlated with gestational age and birth weight in healthy premature infants, that is, the lower the gestational age and body weight, the higher the activity of SDH and LDH after birth, i.e. the more active the aerobic and anaerobic pathways of glucose utilization. The activity of α - GPhDH weakly directly correlates with gestational age and body weight at birth, i.e., the greater the body weight and gestational age, the higher the activity of α - GPhDH and the ability to switch to glycerophosphate shunt exchange. As a consequence, with an increase in postnatal age, α - GPhDH activity decreases. We compared the results of our study of the activity of lymphocyte dehydrogenases in conditionally healthy premature babies with those in healthy full-term newborns according to the results of the study Chugunova OL et al. (2003). The average activity of LDH and α-GPhDH in premature infants was 1.5 and 2.0 times lower than in full-term ones ($p < 0.05$) (Chugunova, 2003). Our studies showed that in RDS infants the activity of SDH, LDH and α-GPhDH of peripheral blood lymphocytes did not depend on gestational and postnatal age, as well as body weight at birth, in contrast to healthy premature infants.

DISCUSSION

The activity of lymphocyte dehydrogenases is dependent on gestational age and body weight at birth in healthy premature infants. The intensity of the aerobic and anaerobic pathways of glucose utilization is higher, the lower the gestational age and body weight at birth.

Table 1. The content of lactic, pyruvic acid in blood serum (mmol /L) in infants with RDS and in "conditionally" healthy premature infants

Indicator	Infants with RDS (n=48, main group)	"Conditionally" healthy infants (n=20, control group)	p
Lactate (mmol/L)	7.37±1.28*	1.44±0.51	0.004
Pyruvate (mmol/L)	0.26±0.04	0.16±0.08	0.220
Lactate/ Pyruvate	29.67±2.04*	11.02±3.72	0.001

Note. * - significant difference in infants with RDS compared with healthy infants.

Table 2. The average activity of the enzymes SDH, LDH and α-GPhDH (granules / cell) of peripheral blood lymphocytes

Day of life and duration of the ventilator	Activity of lymphocyte enzymes in infants with RDS (granules / cell)			Activity of lymphocyte enzymes in "conditionally healthy " infants (granules / cell)		
	SDH	LDH	α-GPhDH	SDG	LDG	α - GPhDH
3-5 days	10.7±0.56*	6.10±0.74	4.03±0.3*	13.52± ±0.65	7.85± ±0.35	2.45± ±0ю35
6 - 8 days	13.25±1.1	7.40±0,75	4.26±0.5*	-	-	-

Note. * - significant difference in infants with RDS compared with "conditionally healthy" infants.

Table 3. Distribution of infants with RDS taking into account the activity of the enzymes SDH, LDH, and α-GPhDH on the 3-5 day of life

Indicator	The number of infants with RDS (n = 48) with different enzyme activity on 3-5 days of life		
	Norm	Decreased enzyme activity	Enzyme activity increase
SDH	16	25	7
LDH	16	25	7
α - GPhDH	22	2	25

Table 4. Correlation coefficient "r" of the activity of peripheral blood lymphocyte dehydrogenases with gestational age and body weight at birth

Characteristics of newborns	The activity of enzymes of lymphocyte dehydrogenases		
	LDG	SDG	α - GPhDH
Gestational age	-0.376	-0.487	0.230
Body weight at birth	-0.544	-0.248	0.248

The intensity of the aerobic and anaerobic pathways of glucose utilization is higher, the lower the gestational age and body weight at birth. These data are consistent with studies that showed that premature babies, when a situation arises requiring increased energy costs, quickly strengthen the anaerobic route of glucose utilization as the main pathway that existed in the prenatal period (Maslovskaya, 2006). Normalization of LDH and SDH activity in lymphocytes in infants with long-term respiratory failure who had a ventilator for 6 or more days seems to be associated with increased glycolysis, energy correction of parenteral nutrition (Cairns, 2000; Neudakhin, 2015) and treatment (Baedilova, 2017; Garmaeva, 2008). The activity of peripheral blood lymphocyte dehydrogenases in infants with RDS did not depend on gestational and postnatal age, as well as birth weight, in contrast to healthy premature newborns. This is probably due to the fact that the activity of enzymes in cells fluctuated within very wide limits (decrease, norm, increase), corresponded to the individual maturity of the body in patients with neonatal pathology and depended on the severity of the pathological process (Maslovskaya, 2006; Neudakhin, 2015; Solovieva, 2018). It is known that the development of a pathological condition is characterized by a large amplitude of energy metabolism indicators in infants (Maslovskaya, 2006; Solovieva, 2018). One of the possible ways to correct energy metabolism disorders in newborns may be the use of the drug L-carnitine (Baedilova, 2017; Cairns, 2000; Clark, 2017). L-carnitine can normalize energy processes in mitochondria (Baedilova, 2017; Longo, 2006). It regulates the metabolism of non-esterified fatty acids (NEFA) (Clark et al., 2017; Longo, 2006). NEFA is the main endogenous source of energy (Maslovskaya, 2006; Shishchenko, 2013). There are positive experiences of using L-carnitine in premature infants with neurological (Ledyaev, 2017; Neudakhin, 2015), cardiovascular diseases (Baedilova, 2017; Piksaykina, 2012), hypoxia and malnutrition (Ledyaev, 2017; Neudakhin, 2015; O'Donnell, 2002).

Conclusion

The development of RDS in premature newborns was accompanied by a pronounced lactatacidosis on the background of hypoxemia, a violation of bio energetic processes at the cell level in the form of dissociation of the activity of peripheral blood lymphocyte dehydrogenases, which are involved in the energy generation. To normalize bioenergetic processes in babies with RDS and to prevent complications, it is advisable to develop methods of pharmacological correction with the use of drugs that regulate the energy balance in the body.

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