CORRELATION OF THE PROGNOSTIC INDICATORS OF A BRAIN INJURY AT THE BIRTH AND THE OUTCOME OF THE NEWBORNS

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SUMMARY

Background: *To investigate the impact of blood acid-base disorders and elevated lactate during birth on the final outcome of the newborn.*

Subjects and methods: *The study include 110 children born with acid-base imbalance and increased level of lactates at the admission. We also took into account the assessment of the vitality of newborns at birth, need for resuscitation procedures and mechanical ventilation, ultrasound scanning of the brain, treatment methods and final outcome.*

Results: *Research has shown that 80% of the newborns had the disorder of acid-base status of blood on admission and 76.3% had high lactates. On admission, 53.60% of the newborns had clinical features of hypoxic ischemic encephalopathy. Ultrasound scanning images of brain have been pathologically changed in 92.70% and mechanical ventilation was necessary at 90.90% of the newborns.*

Conclusion: *After completed treatment, all examinees have survived. These indicators of hypoxic ischemic injury at our patients had no significant impact on the treatment outcome.*

Keywords: *hypoxic-ischemic encephalopathy, lactic acid, metabolic acidosis, acid-base imbalance*

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INTRODUCTION

Perinatal hypoxic ischemic injury is unfortunately a common diagnosis in neonatal intensive care units. If it lasts, hypoxemia stimulates centralisation of blood circulation towards vital organs and consequently ischemia of tissue at peripheral part. Ischemia further leads to the cellular oedema, inflammation and necrosis, resulting in the end in a damaged tissue. Neonatal hypoxic ischemic encephalopathy is a syndrome in which the disorder in the function of a central nervous system takes place in the first days of a child's life. It occurs as a consequence of an insufficient oxygen saturation of blood and it is manifested in the disorder of consciousness, difficulties in establishing and maintaining independent breathing, disorder of tonus and reflex of muscles, manifesting in the lack of primitive reflexes, poor spontaneous motor system together with frequent occurrence of convulsions. Within those pathological events as the consequence of anaerobic metabolism, the carbon dioxide is increased as well as the lactates in blood with the decrease of pH-value of blood (Gunn & Thoresen 2019). Several studies showed that the increased level of lactates above the reference values might be applied as an early marker of the tissue hypoxia and disease severity as well as the predictor of the outcome at seriously diseased patients. The newborns with hyperlactatemia (above 4mmol/L) and lower lactate clearance had a significantly worse clinical outcome, and these parameters are also serious predictive indicators of mortality at the diseased newborns (Chaudhry et al. 2022). Lactic acidosis at the patients is connected with a worse clinical outcome and increased mortality (Sun et al. 2017). The most frequent disorder of acid-base status (ABS) in hypoxia is metabolic acidosis. The hyperlactatemia in neonatal age is significantly connected to the reanimation procedures, receptions at neonatal intensive care units, complications of treatment and early neonatal death (Kumar & Yadav 2022). Since we have not done any similar researches in our hospital on this topic so far and since the hypoxic ischemic injuries are serious conditions, which might severely affect the life and health of the patient, it was our goal to determine the existence of the correlation between the prognostic indicators of hypoxic injury at birth and the outcome of the treatment of the newborns at our department to be able to approach in as much responsible manner as possible to the resolving of these problems with the aim of preventing the long-term consequences and the

lethal outcome at this vulnerable population of patients.

SUBJECTS AND METHODS

We carried out a retrospective study in which we involved 110 term infants with acid-base imbalance and increased level of lactates at the admission. In that analysis we took into account also the pathology of mothers during the pregnancy, evaluation of vitality of the newborns (Apgar score) at birth, referral diagnoses of the newborns, need for reanimation procedures and mechanical ventilation, ultrasonic scanning of brain, treatment methods and outcome.
The research was carried out at our Department of Intensive Care Treatment and Neonatology, Paediatric Clinic, University Clinical Hospital (UCH) Mostar.

natal age who had been received at our department mostly on the first day of their life and they had shown acid-base imbalance and hyperlactatemia. There were more boys (68.18 %) than girls. The most of them had the birth weight above 2500 grams (86.36 %). The research showed that 54.2% of the examinees from this group had been delivered by Caesarean section, and 59.8% of the newborns had been delivered from previous normal pregnancy. The most common pathological conditions in pregnancy of mothers, who had complications, were infections. The mothers, who gave birth in this period, are mainly primipara (36.36%) with single pregnancies (90.00%). In most cases, women in labour did not receive any therapy at the time of delivery (65.45%). The most common therapy of mothers with pathological conditions in pregnancy were antibiotics

Table 1. The most common referral diagnoses of the newborns who had hyperlactatemia at the reception

| | | Lactates | | | | | | | |
| | | Normal | | Moderately increased (2-4) | | Extremely increased (above 4) | | Total | |
		n	%	n	%	n	%	n	%
Referral diagnosis	cerebral disorder	1	12.5	5	62.5	2	25.0	8	100.0
	encephalopathy	10	26.3	21	55.3	7	18.4	38	100.0
	haematology disorder	2	50.0	2	50.0	0	0.0	4	100.0
	infection	0	0.0	1	33.3	2	66.7	3	100.0
	cardiac disorder	0	0.0	2	50.0	2	50.0	4	100.0
	convulsions	0	0.0	2	50.0	2	50.0	4	100.0
	congenital anomalies	1	33.3	2	66.7	0	0.0	3	100.0
	reanimation/ encephalopathy	4	19.0	11	52.4	6	28.6	21	100.0
	Respiratory disorder	7	30.4	12	52.2	4	17.4	23	100.0
	other	1	50.0	1	50.0	0	0.0	2	100.0

The research included the newborns of gestational age from 37 + 0/7 weeks to 41 + 6/7 weeks of all mothers who gave birth in our hospital in the period from the beginning of 2021 to 2023. The results of the statistical analysis are presented in the absolute and relative frequencies. The significance of differences was tested by $\chi 2$ test (in the lack of the expected frequencies by Fisher's exact test). The results of statistical tests are interpreted at the significance level of 0.05. P values, which could not be presented up to three decimal places, are presented as P<0.001. Statistical analysis of collected data was made in the following programmes: IBM SPSS Statistics (version 25.0, SPSS Inc, Chicago, Illinois, USA) and Microsoft Excel 2019 (Microsoft Corporation, Redmond, WA, USA).

RESULTS

Our study was carried out on 110 examinees of early neo-

(9.09%), antidiabetics (7.27%), L-thyroxine (6.36%) and antihypertensives (4.55%). The most common pathological conditions before birth were the infections (9.09%), diabetes type II (8.18%), hypothyroidism (6.36%) and hypertension (5.45%). At the admission, there were 77.27% of the newborns in acidosis. The repeated pH was mostly normal (80.81%), and in 19.09% even the repeated pH was lower than the reference values. Although 70.90% - 90.90% of the newborns had normal evaluation of vitality in the 1st and 5th minute of postnatal life. 77.2% newborns had the disorder of ABS of blood at the admission in the form of metabolic, respiratory or mixed acidosis and 76.30% of the newborns had lactates above reference values. The most often referral diagnoses were encephalopathy (34.55%) and respiratory disorder (20.91%) (Table 1). At the admission, 53.60% of the newborns had clinical features of encephalopathy. Ultrasound examination of the brain was pathologically changed in 92.70% of our subjects. The image of the respiratory insufficiency was presented at 20.91% examin-

ees and mechanical ventilation was necessary at 90.90% of the examinees with the increased lactates. The control measuring of lactates after the first day of life showed significant decrease of their concentration (77.27%). At 25 newborns (22.73%), the control values of lactates remained discreetly increased, whereof the most was delivered by natural birth (36.7%). After the completed treatment (Table 2), 98.20% of patients were discharged for home care with normal somatic and neurological status. The most common first discharge diagnosis was hypoxic ischemic encephalopathy (52.73%). Two patients were relocated to higher centres for further diagnostic evaluation. All patients have survived (100 %).

DISCUSSION

Lactate is a final product of the degradation of glucose under conditions of anaerobic metabolism and therefore it is considered as a valuable indicator of tissue hypoxia (Wu et al. 2018). The determination of lactate concentration under those conditions is one of the basic biochemical markers (Salvanos 2020). In this research the lactates and ABS were done at 110 term infants referred to our department with the following diagnoses: encephalopathy, respiratory disorder, reanimation, disorder of cerebral status, haematological disorders, convulsions, cardiac disorders, perinatal infection and congenital anomalies. ABS is a reflection of

Table 2. Clinical features, ABS and outcome of treatment in comparison to the level of lactates in blood

		Normal		Lactates Moderately increased (2-4)		Extremely increased (above 4)		Total	
		n	%	n	%	n	%	n	%
Sex	Male	18	24.0	41	54.7	16	21.3	75	100.0
	Female	8	22.9	18	51.4	9	25.7	35	100.0
Gestational age	37+0/7 - 37+6/7	16	38.1	20	47.6	6	14.3	42	100.0
	38+0/7 - 38+6/7	4	14.8	19	70.4	4	14.8	27	100.0
	39+0/7 - 39+6/7	3	20.0	7	46.7	5	33.3	15	100.0
	40+0/7 - 40+6/7	2	9.5	11	52.4	8	38.1	21	100.0
	41+0/7 - 41+6/7	1	20.0	2	40.0	2	40.0	5	100.0
Apgar score in the 1st minute	0-3	1	11.1	4	44.4	4	44.4	9	100.0
	4-7	5	21.7	10	43.5	8	34.8	23	100.0
	8-10	20	25.6	45	57.7	13	16.7	78	100.0
Apgar score in the 5th minute	0-3	1	50.0	0	0.0	1	50.0	2	100.0
	4-7	0	0.0	3	37.5	5	62.5	8	100.0
	8-10	25	25.0	56	56.0	19	19.0	100	100.0
Birth weight	<2500	8	53.3	4	26.7	3	20.0	15	100.0
	>2500	18	18.9	55	57.9	22	23.2	95	100.0
Date of reception at the department	1 hour	7	21.2	18	54.5	8	24.2	33	100.0
	within the first 24 hrs	19	28.4	35	52.2	13	19.4	67	100.0
	after 24 hrs.	0	0.0	6	60.0	4	40.0	10	100.0
ABS	Normal	5	22.7	14	63.6	3	13.6	22	100.0
	respiratory acidosis	4	18.2	17	77.3	1	4.5	22	100.0
	metabolic acidosis	10	25.6	18	46.2	11	28.2	39	100.0
	mixed acidosis	7	25.9	10	37.0	10	37.0	27	100.0

Table 2. Continuous

Day of the beginning of feeding	1	25	22.9	59	54.1	25	22.9	109	100.0
	2	1	100.0	0	0.0	0	0.0	1	100.0
Method of feeding	normal	21	25.0	48	57.1	15	17.9	84	100.0
	gastric tube	5	19.2	11	42.3	10	38.5	26	100.0
US scanning of brain	normal	0	0.0	7	87.5	1	12.5	8	100.0
	HIC 1	20	24.7	43	53.1	18	22.2	81	100.0
	HIC 2	6	31.6	8	42.1	5	26.3	19	100.0
	HIC 3	0	0.0	1	50.0	1	50.0	2	100.0
Duration of treatment	1-7	18	23.7	44	57.9	14	18.4	76	100.0
	8-14	3	15.0	12	60.0	5	25.0	20	100.0
	15-30	5	38.5	3	23.1	5	38.5	13	100.0
	31 and more	0	0.0	0	0.0	1	100.0	1	100.0
Outcome	relocated	1	50.0	1	50.0	0	0.0	2	100.0
	discharged	25	23.1	58	53.7	25	23.1	108	100.0
	lethal outcome	0	0.0	0	0.0	0	0.0	0	0.0

complex processes, keeping the stability of extracellular pH for optimal cell function. Keeping of balance between the production and the neutralisation of acids in tissue is a big challenge for the newborn because of a higher production of acids as compared to the adults. The disorders of acid-base balance at the newborn may be developed fast, as at the problem with breathing, or they can be developed gradually (Quigley & Baum 2004). In this research 77.27% newborns were at the admission in acid-base imbalance, and it was mainly about the metabolic acidosis (60%). Acidosis in the newborn age is a sensitive and specific parameter for determining the seriousness of the hypoxic injury and it used as the predictor of possible development of hypoxic ischemic encephalopathy, convulsions and other abnormalities in neonatal period (Sabol & Caughey 2016). According to the literature the afore mentioned complications are more often at metabolic acidosis which is confirmed also by this research (Lorain et al. 2022). This research determined a significantly higher incidence of ABS disorder and lactate concentration at male newborns (68.18%) as compared to the female ones (31.83%). There are very few studies that investigated the ABS disorder and lactate concentrations compared to the gender, but in two researches a higher frequency of ABS disorder was determined as well as the occurrence of neurological complications at male newborns (Kumar & Yadav 2022, Simchen et al. 2014). Ultrasonography of brain is the examination of the choice that is used on a daily basis in diagnostics and monitoring of all children endangered in a perinatal period, and especially at the suspicion of intracranial hypoxic ischemic injury (Alfaifi 2023). Ultrasonography of brain in our study was pathologically changed at 92.73% examinees. The most frequent pathological test result was intracranial

bleeding of the 1stdegree (73.64%), which correlates with one Polish research from the past years. Intracranial bleeding is a serious cause of death in newborns, and children who survive very often have permanent consequences such as cerebral palsy, retardation in psychomotor development, visual and hearing impairments. Periventricular bleeding with a progress to the intraventricular bleeding is the most common type of bleeding. This type of bleeding mostly occurs at the premature babies, whereas at the term babies it occurs as the consequence of the birth trauma and hypoxia (Hong & Lee 2018, Wu et al. 2018). Risk factors for development of intraventricular bleeding are vaginal birth, low evaluation of vitality at birth, respiratory distress syndrome (RDS), hypoxia, convulsions, pneumothorax. All those conditions cause fluctuations in blood flow in brain and increasing the risk of bleeding (Condo et al. 2017). Clinically, milder bleeding (degree I. and II.) go mostly asymptomatically, and they are detected by ultrasound scanning of brain. About 25 – 50 % of all intracranial bleeding at the newborns is of this type. More severe bleeding with dilatation of ventricle or with parenchyma bleeding (degree III. and IV.) are manifested in severe clinical signs, and most often they are the convulsions, respiratory insufficiency and need for mechanical ventilation (Wu et al. 2018). The most frequent cause of respiratory failure at the newborn age is a shortened gestational age, but the risk factors include also the twin pregnancy, C-section birth, unregulated diabetes of a mother, perinatal hypoxia and asphyxia, hyposurfactosis and male gender (Condo et al. 2017). Clinically, the respiratory failure is presented in the first hours of life as tachypnoea, dyspnoea, nostrils widening, use of secondary musculature, nodding, silent moaning and cyanosis. If no required treatment measures are taken in time,

then circulation failure takes place as well as oliguria and retention of water with occurrence of oedema and occurrence of brain symptoms that indicate sever hypoxia and ischemia of brain (Edwards et al. 2013, Wu et al. 2018).

The treatment of RDS includes specific interventions such as application of oxygen, exogenous surfactant and mechanical ventilation with general supportive measures (Wu et al. 2018). Some of the modes of mechanical ventilation were necessary at majority of our examinees. Such ventilation support is an invasive procedure which requires clear indications and objectives (Solberg et al. 2018). The fact that the lactate and ABS disorder at the admission is a serious bad prognostic indicator of clinical outcome of the patient is confirmed by the results of one Croatian research from 2018, where the mortality rate reached even 21.1% (Heibel et al. 1993). Looking at the parameters of mothers in this research, it turned out that it was mostly about the primipara (36.36 %) at the age of 30-39 years. Earlier researches did not prove the connection between the older age of the mother with the higher probability of acidosis and hypoxic ischemic encephalopathy at the newborns (Peebles et al. 2020). With regard to the type of a birth, C-section is somewhat more represented (55.46%) as compared to the natural birth (44.55 %), and this research determined statistically significant differences in value of control lactates between the children who were delivered by natural birth and by C-section. The results of the researches in Switzerland and Croatia showed that the higher value of lactates was more common at the vaginal birth as compared to the urgent and elective C-section (Gaertner et al. 2021, Souza et al. 2016). According to our research the ABS and lactate disorders were most often recorded at previously controlled, normal pregnancies (60%), whereas the researches in America and Croatia showed that the pathological conditions of mothers in pregnancies were related to the significantly higher risk of development of neonatal complications, which is more logical and more expected conclusion (Nelson et al. 2012).

CONCLUSION

Our research showed that the increased lactate levels and disorder of ABS of blood of the newborn upon the birth was in correlation with the input pathological conditions of pregnant women and newborns. The increased prognostic indicators of hypoxic brain injury at our patients had no significant impact on the outcome of treatment. The obtained results determined a good outcome of treatment of the newborns with disturbed ABS and lactates as well as pathological ultrasound scanning of brain, opposite to the expectations though. We believe that it is exactly the case because of the fast lactate's clearance, timely, individualised and prompt therapeutic response to the bad initial clinical status. The timely recognition of these disorders and the adjusted early therapeutic intervention can substantially reduce the neuro-developmental disorders and improve the

quality of life of children and their families.

Contribution of individual authors:
Marija Novaković Bošnjak: study design, literature search, statistical analyses.
Nina Knezović: literature search, manuscript writing, data collection.
Anita Kolobarić: study design, literature search, manuscript writing.
Marjana Jerković Raguž: study design, data collection, literature search.
All the authors have approved the final version

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