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Urinary Melatonin Metabolite in Premature Infants with Extremely and Very Low Birth Weight

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The aim. Determination of daily urinary 6-sulfatoxymelatonin in premature infants with extremely and very low birth weight.

Materials and methods. A non-invasive, descriptive, single-centered study involving data of 96 premature infants with weight less than 1500 g : 46 infants with extremely and 50 infants with very low birth weight.

The study included a detailed scrutiny of history and objective examinations, data from medical records, anthropometric measurements, and daily urine collection. Determination of 6 - SM in the 24-hours urine collection from premature infants was performed by enzyme immunoassay on the analyzer "Labline-90" (Austria) using a commercial test system manufactured by "LDR" (LABOR DIAGNOSTIKA NORD GmbH & Co.KG, Germany) according to the provided instruction. 166 portions of urine were collected during the examination in time intervals: 96 portions of urine in premature infants at 1st day of life and 70 portions at 10th – 14th day of life.

Results. Ante- and intranatal periods for the infants enrolled in the study were characterized by conditions: premature rupture of membranes 37 (38.5%), multiple pregnancy 16 (16.6%), preeclampsia 15 (15.6%), isthmic-cervical insufficiency 11 (11.5%), placental abruption 8 (8.3%), extra corporal fertilization 5 (5.2%), chorioamnionitis 4 (4.2%); caesarean section urgent 33 (34.4%) and planned 24 (25.0%). There was no any significant difference in frequency of ante – and intranatal pathology between ELBW and VLBW. Antenatal administration of corticosteroids for reduce the severity of neonatal respiratory distress syndrome occurred in all mothers of infants enrolled in the study.

There was significant low urinary 6-sulfatoxymelatonin level in extremely low birth weight infants (median 120.0 pg /mL) on the 1st day of life compared with very low birth weight (median 348.5 pg / mL). There was no difference at 10 – 14th days. The predictive level of lethal outcome in infants with extremely low birth weight is ≤ 84 pg / mL with sensitivity 84.62% and specificity 70.0%.

Conclusion. In infants with extremely and very low birth weight the determining the urinary 6-sulfatoxymelatonin is a non-invasive method. The significant decrease level of urinary 6-sulfatoxymelatonin in infants with extremely low birth weight on the first day of life was found. The measurement of urinary 6-sulfatoxymelatonin will allow to establish the prediction of perinatal outcomes. Its levels <87 pg / mL is associated with lethal outcomes. Authors speculate than it will the way for future supplement of melatonin to premature infants and study of its effect on perinatal outcomes.

Keywords: premature infants, melatonin, urinary 6-sulfatoxymelatonin.

Connection of the study with scientific programs, plans, topics. The work is a fragment of the research work of the Department of Neonatology of the Kharkiv Medical Academy of Postgraduate Education «Study of the peculiarities of the course of the pathology of newborns at the stage of modern development of perinatal care in the Kharkiv region», state registration number 0116U004791.

Intoduction. One of the main functions of melatonin is the regulation of sleep-wake rhythm, i.e., the realization of the chronobiotic effect such as "light-dark". Melatonin, or N-acetyl-5-methoxytryptamine, is an Indoleamine that is formed from amino acid Tryptophan [1, 2]. But the biological effects of this molecule are not limited to sleep-wake regulation, as much evidence has recently been obtained of the effects of melatonin on many aspects of human health, such as counteracting certain pathological conditions, regulating nerve tissue, endocrine organs, immune cells, antioxidants and inactivation of some pathogens [1-5].

The main metabolite of melatonin in urine is 6-sulfatoxymelatonin (6 – SM or aMT6s). It is a reliable surrogate biomarker reflecting the blood melatonin concentration [6]. The urinary 6-SM secretion in sample of premature infants is very importent for studing for the further testing in clinical trials of melatonine administration [7]. However, publications have a lack of information of urinary 6-SM secretion in premature infants with extremely low birth weight (ELBW) and very low birth weight (VLBW).

The aim. Determination of daily urinary 6 - SM in premature infants with ELBW and VLBW. Hypothesis: the urinary 6 – SM level is different in ELBW and VLBW infants.

Materials and methods. A non-invasive, descriptive, single-centered study was conducted. We evaluated clinical and demographic data, determined the level of urinary 6 - SM excretion. This study was

approved by the Ethics Committee (The protocol No 9 16.10.2018), which was conducted with the involvement of underage patients and did not contain measures that could harm their health. The patients' parents were informed about the methods and scope of the study and gave their consent to participation of their children in this study.

The cohort of 96 premature infants with ELBW and VLBW were involved in the study. Inclusion criteria: 46 of ELBW (≤ 999 g) and 50 of VLBW (≤ 1499 g) infants. Exclusion criteria: body weight ≥ 1500 g, small for gestational age, congenital and intrauterine infections, degenerative and congenital diseases of the nervous system, chromosomal diseases; diseases with impaired renal function; orphan diseases and those who did not agree to participate in the study.

The study included a detailed scrutiny of history and objective examinations, data from medical records, anthropometric measurements, and daily urine collection [7]. Determination of 6 - SM in the 24-hours urine collection from premature infants was performed by enzyme immunoassay on the analyzer "Labline-90" (Austria) using a commercial test system manufactured by "LDR" (LABOR DIAGNOSTIKA NORD GmbH & Co.KG, Germany) according to the provided instruction. 166 portions of urine were collected during the examination in time intervals: 96 portions of urine in premature infants at 1st day of life and 70 portions at 10th – 14th day of life.

Statistical analysis was performed with the program MedCalc version 14.8 - © 1993 - 2014 MedCalc Software bvba (Acacialaan 22 B - 8400 Ostend, Belgium). Descriptive analysis with Median (Me) and comparison of two proportions by Fisher test were performed. We used Mann-Whitney test (MW test) to compare of two independent samples and Wilcoxon Rank-Sum Test (WRST) to compare of two dependent samples. The Receiver Operating Characteristic (ROC) curve analysis for calculating sensitivity and specificity, relative risk (RR) and their 95% confidence interval (CI) were used. The difference in parameters was considered statistically significant at $p < 0.05$.

Results. Ante- and intranatal periods for the infants enrolled in the study were characterized by conditions: premature rupture of membranes 37 (38.5%), multiple pregnancy 16 (16.6%), preeclampsia 15 (15.6%), isthmic-cervical insufficiency 11 (11.5%), placental abruption 8 (8.3%), extra corporal fertilization 5 (5.2%), chorioamnionitis 4 (4.2%); caesarean section urgent 33 (34.4%) and planned 24 (25.0%). There was no any significant difference in frequency of ante– and intranatal pathology between ELBW and VLBW. Antenatal administration of corticosteroids for reduce the severity of neonatal respiratory distress syndrome occurred in all mothers of infants enrolled in the study. The general clinical and demographic characteristics of the premature infants with ELBW and VLBW are present in **table 1**.

Despite that there was no significant difference in frequency of IVH between ELBW and VLBW, in the infants with ELBW the frequency of much severe III level of IVH (RR = 15.2; 95% CI 2.1 – 66.8) were significantly increased while in the infants with VLBW I and II level.

There was significant difference between urinary 6 – SM distribution in ELBW and VLBW on the

Table 1. – Connection of the study with scientific programs, plans, topics. The general clinical and demographic characteristics of the premature infants with ELBW and VLBW

Data	Infants with ELBW, n=46	Infants with VLBW, n=50	P
*Body weight, g Me (min; max)	900 (560; 990)	1350 (1070; 1490)	0.0001
Extremely preterm: <28 weeks abs., (%)	38 (82.6)	-	<0.0001
Very preterm: 28 weeks to <32 weeks abs., (%)	8 (17.4)	35 (70.0)	<0.0001
Moderate preterm: 32 weeks to <34 abs., (%)	-	15 (30.0)	0.0002
Male abs., (%)	17 (36.9)	28 (56.0)	0.0665
Female abs., (%)	29 (63.0)	22 (44.0)	0.0991
Severe asphyxia abs., (%)	26 (56.5)	9 (18.0)	0.0001
Neonatal sepsis abs., (%)	14 (30.4)	11 (22.0)	0.3733
Respiratory distress syndrome abs., (%)	46 (100)	50 (100)	1.0000
Intraventricular haemorrhage abs., (%)	22 (47.8)	17 (34.0)	0,1664
Bronchopulmonary displasia abs., (%)	7 (15.2)	3 (6,0)	0.1508
Anemia of premature abs., (%)	15 (32.6)	29 (58.0)	0.0159
Retinopathy of Premature abs., (%)	20 (43.4)	7 (14.0)	0.0016
Sensorioneural Hearing Loss abs., (%)	16 (34.7)	13 (26.0)	0.3403
Lethal outcome abs., (%)	19 (41.3)	2 (4.0)	0.0001

Note: *MW test.

1st day of life (**Fig. 1**). On the 1st day urinary 6 – SM was statistically significant lower in premature infants with ELBW compare VLBW (MW test, p=0.0010) with Me 120,0 (95% CI 78,55 - 238,16) pg / mL and 348,5 (95% CI 208,61 - 448,50) pg / mL respectively. There was no difference of urinary 6 – SM on the 10 – 14th days (MW test, p=0,0806) in infants with ELBW and VLBW: Me 97,5 (95% CI 58,54 – 102,15) pg / mL and 70,5 (95% CI 54,73 - 136,00)) pg / mL respectively.

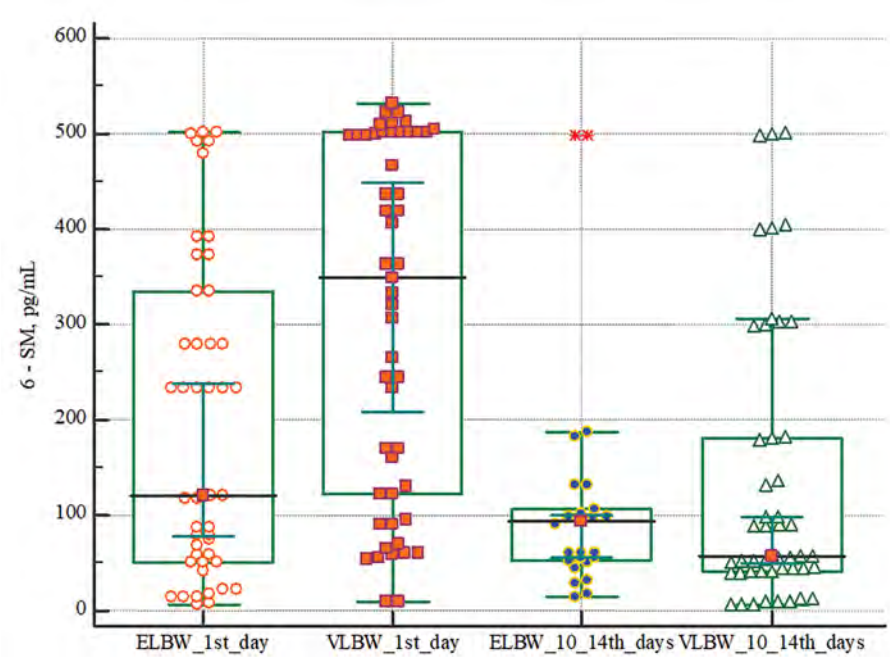

Figure 1 – The urine 6 – SM distribution in ELBW and VLBW infants on 1st day and on 10-14th days of life

Compare the urinary 6 – SM distribution on the 1st day and on the 10-14th days of life in both separately we found the significance lower urinary 6 – SM at 10-14th days of life in premature infants with ELBW (WRST, p=0.0019) and in premature infants with VLBW (WRST, p=0.0001).

Among 96 prematurely born children, 22 (22.9%) had lethal outcomes in neonatal period (**Table 1**). Moreover, 20 of them were infants ELBW. The number of dead infants with VLBW was small. The main causes of death were intraventricular hemorrhage in 12 (54.5%), severe asphyxia in 7 (31.8%), neonatal sepsis in 2 (91.0%), and necrotizing enterocolitis in 1 (4.5%). We compared of the urinary 6 - SM on the 1st day of life in premature infants with ELBW depending on the lethal outcomes. We have demonstrated a statistically significant decrease of the urinary 6 - SM dead infants (MW test, p=0.0006): Me 65.5 (95% CI 22.07 – 106.42) pg/ml compare who surviving Me 180.6 (95% CI 180.66 – 352.14) pg / mL.

We used ROC-analysis to predict the neonatal outcomes with urinary 6 -MS at 1st day in premature infants with ELBW. The predictive level of urinary 6 – SM for lethal outcome is ≤ 84.0 pg / mL (p =0.0001 with sensitivity 84.62 (95% CI 65.1 – 95.6)% and specificity 70.0 (95% CI 45.7 – 88.1)%.

It should be noted that we obtained statistically significant relationships only in urinary 6-SM excretion at the first day of life and did not obtain relationships between perinatal pathology and the level of its excretion at 10-14th days of life.

Discussion. The pathological conditions and their course, morbidity and mortality of premature infants, mostly related to immaturity of organs and systems and maternal health [8]. Perinatal conditions as a cause of mortality in neonates are a result of brain damage by oxidative stress injury and free radical-mediated damage [9, 10]. And over the past decades, medical science has paid more and more attention to the prevention of hypoxic brain injury in neonatal population, especially premature [5, 11]. One such protector is melatonin. The role of melatonin in the circadian sleep-wake rhythm disorders in adults and adolescents is known. The determination of melatonin levels is not routinely used in clinical practice, its determination can still be useful in complex cases [12]. In addition to regulating circadian sleep-wake rhythms, melatonin and its metabolites are effective antioxidants and free radical scavengers. This function provides neuroprotection in cerebral ischemia not only in adults but also in children [5, 13]. One such metabolite of melatonin is urinary 6 – SM (aMT6s) [14]. The object of our study was measurement of daily urinary 6 - SM in premature infants with ELBW and VLBW. We have also found of its predictive function. Published research demonstrated changes in the level of melatonin and urinary 6 - SM in term and preterm infants [15, 16]. Research covered different gestational age categories and different conditions. Thus, the development of rhythmic excretion of urinary 6-SM in healthy full-term and premature infants during the first 12 months of life was studied. It has been shown arrhythmic excretion of 6-SM in full-term infants up to 9-12 weeks, and in premature infants up to 21 weeks [15]. A significant effect of the summer birth season on urinary 6 - SM production at the age of 8 week was

found in term neonates [16]. Our study differs from the previous ones in that we studied urinary 6 – SM in the earliest period of life of premature infants with ELBW and VLBW: on the first day and on days 10-14th of life. We got low values of urinary 6 – SM in premature infants with ELBW compared with VLBW at 1st day. On days 10-14 of life, urinary 6 - SM was lower than on the first day but did not depend on the birth weight of the child. Like our study, a prospective, longitudinal, multicenter study to assess of urinary 6 – SM at 1st and 3rd day of life in 110 preterm infants with gestational age less than 34 weeks and 99 ones more than 34 weeks was published [7]. Urinary 6 –SM was significantly lower in infants with gestational age less than 34 weeks at 1st and 3rd days (230 ng/L vs 533 ng/L and 197 ng/L vs 359 ng/L). The level of urinary 6 - SM decreases every day, which was also obtained by our study. However, the design of this study used the radioimmunoassay method and not randomized premature infants based on birth weight.

Deficiency of the powerful antioxidant melatonin was the basis for studying the effect of increasing in blood levels in premature infants by oral supplementation [17]. The study included 36 premature weighing more than 1700 g. However, outcomes have not been studied. Therefore, the authors believe that melatonin supplementation for preterm infants may be a potential strategy for nursing these infants.

The all cited above studies do not clearly describe relationships of perinatal pathology with the blood melatonin or urinary 6 - SM. The all perinatal specific diseases of premature infants, are called “free radical diseases of premature infants” due to common pathways [18].

The next important point for discussion is determination of the predictor role of urinary 6 – SM level in infants with ELBW and VLBW. One published study about prognostic role of low urinary 6 - SM levels in full-term newborns showed delayed psychomotor development at 3 and 6 months of age [19]. This once again proves the effect of melatonin on the development of the nervous system and its protective role in brain damage. We did not study long-term outcomes and especially child development.

At the same time, the originality of our study lies in the investigation of lethal outcomes in premature infants with ELBW with correlation of urinary 6 -SM. We did not find similar results in the available literature. Of course, the more the infants affected by various pathological conditions and the less oxidative protection, the worse was the prognosis.

We have shown that urinary 6 - SM less than 87 pg/mL on the 1st day of life in infants with ELBW is associated with lethal outcomes.

It is believed than oxidative stress is the result of many events, including hyperoxia due to mechanical ventilation, and plays a role in their sustainable damage: epithelial damage, surfactant inactivation, inflammation [20]. Although oxygen therapy is critical in the treatment of respiratory diseases, it can cause damage to endothelial and epithelial cell barriers, thereby contributing to the development of BPD [21]. The role of melatonin in this mechanism remains open and requires further study especially in ELBW and VLBW infants [22, 23]. Interesting there will be studies about relationship between melatonin and hearing loss. Some studies and recommendations show that infants in the neonatal intensive care unit are at greater risk of hearing loss than healthy infants [24, 25].

We suppose that significant associations between high urinary 6 - SM deafness have the same mechanisms as other perinatal pathology due to hyperoxidative stress. Since there are few studies on the relationship between s SNHL and melatonin levels in premature babies, our results also open prospects for further research. And trials of melatonin supplements in this category of children can not only change their nursing strategies, but also, with positive results, prevent mortality and disability.

The results of our study confirmed the null hypothesis that urinary excretion of 6-SM in premature infants with ELBW and VLBW are different at the 1st day of life only. Moreover, the urinary 6-SM can be a predictive marker of lethal outcomes.

There were some inherent limitations associated with this study: firstly, the sample size. Our model was based on single-center descriptive study and was limited by the time and the number of premature infants. We investigated of the urinary 6 – SM only at the 1st and at the 10 - 14th days of life in infants with ELBW and VLBW. Secondly, there were very few prior researches and there are some gaps in the studies relevant to the urinary 6 – SM, which influenced the methodology of our study. The limitation of our study also lies in urinary 6 - SM analyses was carried out in a cohort, among which were infants who died before 10 – 14th days of life. Thirdly, we did not establish the relationship between long-term outcomes and urinary 6 – SM at 1st day and 10 - 14th days of life in ELBW and VLBW infants. Forthly, urinary 6 -SM depends on maturity of renal function despite the fact that we excluded infant with kidney insuficiensy. As a result, ROC-analysis detected a relationship between urinary 6 – SM and lethal outcomes only at 1st day, which may be as bias.

Conclusion and perspectives of further research. In premature infants with extremely and very low birth weight the determining the melatonin metabolite in urine 6-sulfatoxymelatonin is a non-invasive method. There was found the significant decrease level of urinary 6-sulfatoxymelatonin in infants with

extremely low birth weight infants on the first day of life. The measurement of urinary 6-sulfatoxymelatonin will allow to establish the prediction of perinatal outcomes. Its levels <87 pg / mL is associated with lethal outcomes. Authors speculate than it will the way for future supplement of melatonin to premature infants and study of its effect on perinatal outcomes.

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МЕТАБОЛІТ МЕЛАТОНІНУ В СЕЧІ У НЕДОНОШЕНИХ ДІТЕЙ З НАДЗВИЧАЙНО ТА ДУЖЕ МАЛОЮ ВАГОЮ ПРИ НАРОДЖЕННІ

Кузєнкова Г. А., Клименко Т. М.

Резюме. *Мета.* Визначення добового 6-сульфатоксимелатоніну в сечі у недоношених дітей з екстремально та дуже малою масою тіла при народженні.

Матеріали та методи. Неінвазивне, описове, одноцентрове дослідження, що охоплює дані 96 недоношених немовлят із вагою менше 1500 г: 46 немовлят із надзвичайною та 50 немовлят із дуже низькою вагою. 6-сульфатоксимелатонін в сечі досліджували на 1-шу та 10-14-ту добу життя.

Результати. Анте- та інтранатальний періоди дітей, залучених до дослідження, характеризувались такими станами: передчасний розрив плодових оболонок 37 (38,5%), багатоплідна вагітність 16 (16,6%), прееклампсія 15 (15,6%), істміко-цервікальна недостатність 11 (11,5%).), відшарування плаценти 8 (8,3%), екстракорпоральне запліднення 5 (5,2%), хоріоамніоніт 4 (4,2%); кесарів розтин терміновий 33 (34,4%) і плановий 24 (25,0%). Не було жодної значущої різниці в частоті анте- та інтранатальної патології між ELBW та VLBW. Антенатальне введення кортикостероїдів для зменшення тяжкості неонатального респіраторного дистрес-синдрому відбулося у всіх матерів немовлят, які брали участь у дослідженні.

Визначено суттєво низький рівень 6-сульфатоксимелатоніну в сечі у немовлят з надзвичайно низькою вагою при народженні (медіана 120,0 пг/мл) на 1-й день життя порівняно з дуже низькою вагою при народженні (медіана 348,5 пг/мл). На 10-14 добу різниці не було. Прогностичний рівень летального результату у немовлят із надзвичайно низькою вагою при народженні становить ≤84 пг/мл із чутливістю 84,62% і специфічністю 70,0%.

Висновки. У немовлят з надзвичайно та дуже низькою вагою при народженні визначення 6-сульфатоксимелатоніну в сечі є неінвазивним методом. Виявлено достовірне зниження рівня 6-сульфатоксимелатоніну в сечі у новонароджених з екстремально малою масою тіла на першу добу життя. Вимірювання 6-сульфатоксимелатоніну в сечі дозволить встановити прогноз перинатальних наслідків. Його рівень <87 пг/мл асоціюється з летальним наслідком. Автори припускають, що це буде шлях до майбутнього додавання мелатоніну недоношеним дітям і вивчення його впливу на перинатальні результати.

Ключові слова: недоношені діти, мелатонін, 6-сульфатоксимелатонін сечі.

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