KEY TITLE: NEONATOLOGIÂ, HÌRURGIÂ TA PERINATAL'NA MEDICINA (ONLINE)
ABBREVIATED KEY TITLE: NEONATOL. HÌR. PERINAT. MED. (ONLINE)
ISSN 2226-1230 (PRINT) ISSN 2413-4260 (ONLINE)

РЕЗУЛЬТАТИ ДИСЕРТАЦІЙНИХ ТА НАУКОВО-ДОСЛІДНИХ РОБІТ/ RESULTS OF DISSERTATION AND RESEARCH WORKS

UDC: 616.8-009.7-071.4-053.32
DOI: 10.24061/2413-4260.XIII.1.47.2023.1

PECULIARITIES OF CHRONIC PAIN AND PAIN-RELATED STRESS MARKERS IN PRETERM INFANTS

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Summary

Preterm infants are a special cohort of newborns that require long-term treatment in the neonatal intensive care unit (NICU). NICU stay, accompanied by numerous excessive stimuli, painful procedures, and separation from parents leads to a high risk of chronic pain and stress.

The aim of research *was to study the level of chronic pain and pain-related stress markers in preterm infants with a gestational age of less than 34 weeks, and their associations with various factors.*

Materials and methods. *The study involved 104 preterm infants with gestational age (GA) less than 34 weeks who were treated in the NICU. The level of chronic pain and pain-related stress markers (dopamine, β-endorphin, serotonin) in urine samples was determined by an enzyme-linked immunosorbent assay using kits for the quantitative determination of dopamine (Dopamine Elisa kit, Elabscience, Wuhan, China), β-endorphin (β-endorphin Elisa kit, Elabscience, Wuhan, China), serotonin (Serotonin Elisa kit, Elabscience, Wuhan, China). Samples were analyzed in duplicate, and assays were performed using provided controls according to the manufacturer's instructions.*

Ethics approval was obtained from the appropriate local ethics committee and research was conducted under the World Medical Association's Helsinki Declaration. Informed consent was obtained from all the participants who took part in the study.

All computations were performed using StatSoft STATISTICA Version 13 (Tulsa, OK). Quantitative data are presented as the median and interquartile range (IQR; 25th to 75th percentiles). For qualitative parameters, absolute and relative frequencies are presented. The Mann-Whitney U-test (for two independent groups) and Kruskal-Wallis test (for three groups) were used to compare numerical data. Significance was assumed at $p<0.05$. Correlations were analyzed using Spearman's rank correlation coefficient.

The study is a part of the scientific research: Implementation of the neuro-developmental care elements for preterm infants and their follow-up observation (0120U104281, 01.01.2020-12.31.2022).

Research results and their discussion. *Dopamine level in the urine of preterm infants was 132.20 [104.80; 183.70] pg/ml. It was significantly higher in children who underwent mechanical ventilation compared to non-ventilated neonates (164.60 [110.00; 253.70] pg/mL vs. 123.20 [98.65; 158.70] pg /ml), $p=0.030$, and was associated with the severity of respiratory disorders ($H=5.84$; $p=0.049$). Dopamine level was significantly lower in twins compared to singleton infants (113.70 [78.75; 164.70] vs. 145.10 [111.80; 208.50], $p=0.017$.*

β-endorphin level in the urine of preterm newborns was 29.87 [20.61; 46.94] pg/ml. It was significantly higher in twins compared to singletons (38.30 21.97; 59.61] vs. 27.80 [19.66; 39.16], $p=0.046$). β-endorphin level was significantly lower in children with neonatal seizures ($p=0.039$).

Serotonin level in the urine of preterm infants was 23.49 [16.13; 32.19] pg/ml. It was significantly higher in neonates born by caesarean section compared to those born naturally (25.62 [18.87; 38.53] ng/ml vs. 17.41 [13.36; 27.89] ng/ml, $p=0.017$), and it was higher in twins compared to singletons (27.19 [18.87; 41.75] ng/ml vs. 21.98 [14.41; 29.70] ng/ml), however, with no statistical significance ($p=0.073$).

The study revealed the positive correlation between serotonin and β-endorphin levels ($r=0.68$; $p<0.001$) in infants who required mechanical ventilation and in newborns with neonatal seizures ($r=0.59$; $p<0.001$). Positive correlation between β-endorphin and serotonin levels in twins also was found ($r=0.72$, $p<0.001$).

Conclusion. *This prospective cohort study showed that severe respiratory disorders in preterm infants were associated with decreased dopamine level, while serotonin and β-endorphin levels were correlated in this case. Neonatal seizures were associated with decreased β-endorphin level, while a positive correlation was found between β-endorphin and serotonin levels. Dopamine levels were significantly lower and β-endorphin levels significantly higher in twins compared to singleton preterm neonates. Serotonin level was significantly higher in neonates born by caesarean section. Gestational age, birth weight, gender, early-onset sepsis, and intraventricular hemorrhage were not associated with increased or decreased levels of pain and pain-related stress markers in preterm infants.*

Key words: *Chronic Pain; Pain-related Stress; Preterm Infants; Dopamine; β-endorphin; Serotonin.*

Introducion

Preterm infants are a special cohort of newborns with functional immaturity, multisystem disorders and high morbidity that require long-term treatment in the neonatal intensive care unit (NICU). NICU stay, accompanied by numerous excessive stimuli, painful procedures, and separation from parents leads to a high risk of chronic pain and stress. The International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience

associated with, or described in terms of, actual or potential tissue damage." Because the basis of this definition is the subjective assessment and reporting of pain sensations, it has long been considered impossible to assess the severity of neonatal pain. However, the inability to communicate verbally does not negate the possibility that the infants feel pain and require appropriate pain management [1, 2, 3].

The perception of pain and the response to stress in preterm infants can be even more pronounced than in full-term babies. This is due to the fact that the ascending nociceptive pathways are formed and begin to function fully from the 24th week of pregnancy, while the descending inhibitory pathways are still immature. In this regard, preterm neonates, on the one hand, have a lower threshold of pain sensitivity, poor localization of the pain stimulus, which leads to a diffuse distribution of pain sensation, and on the other hand, the pain modulation and overcoming processes are insufficient and immature [4, 5, 6, 7]. In addition, preterm infants experience long-term hyperalgesia and allodynia after tissue damage or another painful event, which leads to chronic pain and pain-related stress [7].

Recently, more and more attention has been paid to the research of pain that persists after an acute painful procedure in neonates [8, 9]. To date, there is no clear and unambiguous definition of chronic pain in infants [2]. The International Association for the Study of Pain defines chronic pain in adults as pain that persists or recurs for more than 3-6 months after an injury [10]. However, this definition of chronic pain in newborn infants cannot be used in neonatal practice [8], and a specific time criterion cannot be applied to newborns [2].

Thus, the purpose of our research was to study the level of chronic pain and pain-related stress markers in preterm infants with a gestational age (GA) of less than 34 weeks, and their associations with various factors.

Materials and methods

Single-center, cohort and prospective study was performed at the level III NICU of the Ternopil regional perinatal center. The research included 140 preterm infants with GA of less than 34 weeks. Newborns with the chromosomal disorders, congenital malformations, and surgical pathology were excluded from the research. A laboratory study of pain in preterm infants in the NICU included determination of markers (dopamine, serotonin, and β-endorphin) associated with chronic pain and stress.

Sample collection and urinary dopamine, serotonin, and β-endorphin assay. Urine was collected using cotton sponges, after that was extracted from the sponges by centrifugation (2 minutes at 2000×g). After extraction, urine samples were centrifuged for 20 min at 1000×g at 2-8℃ and after that were frozen and stored at -80°C. Enzyme immunoassay kits for the quantitative determination of dopamine (Dopamine Elisa kit, Elabscience, Wuhan, China), β-endorphin (β-endorphin Elisa kit, Elabscience, Wuhan, China), serotonin (Serotonin Elisa kit, Elabscience, Wuhan, China) were used to analyze the levels of pain and pain-related stress markers in the urine samples. Samples were analyzed in duplicate, and assays were performed using provided controls according to the manufacturer's instructions.

Ethics approval was obtained from the appropriate local ethics committee and research was conducted under the World Medical Association's Helsinki Declaration. Informed consent was obtained from all the participants who took part in the study.

All computations were performed using StatSoft STATISTICA Version 13 (Tulsa, OK). Quantitative data are presented as the median and interquartile range (IQR; 25th to 75th percentiles). For qualitative parameters, absolute and relative frequencies are presented. The Mann-Whitney U-test (for two independent groups) and Kruskal-Wallis test (for three groups) were used to compare numerical data. Significance was assumed at $p<0.05$. Correlations were analyzed using Spearman's rank correlation coefficient.

The study is a part of the scientific research: Implementation of the neuro-developmental care elements for preterm infants and their follow-up observation (0120U104281, 01.01.2020-12.31.2022).

Research results and their discussion

A total of 19 extremely preterm infants (13.6%), 52 very preterm (51.4%), and 49 moderate preterm infants (35%) were included in the study. There were 74 boys (52.9%) and 66 girls (47.1%), fig. 1. The mean GA was (31.1±2.4) weeks. There were 54 twins (38.6%) and 86 singletons (61.4%).

The mean maternal age was (29.5±5.5) years, with no significant difference depending on the GA of the children ($p=0.25$). There was no significant difference in history of pregnancy and delivery in newborns of different GA groups. Only gestational hypertension and preeclampsia were more often observed in mothers of moderate preterm neonates compared to extremely and very preterm (48.98% compared to 21.05 % and 18.06 %, $\chi2=14.18$; $p<0.001$), and anemia was present more often in mothers of extremely and very preterm infants (47.37% and 47.22 % vs 24.49 %, $\chi2=6.92$; $p=0.031$). One hundred one child (72.14%) was born by cesarean section, with no difference depending on the gestational age.

Seventy-four (52.85%) and twenty-one (15.00%) children had Apgar scores of less than 7 points at the 1st and 5th minutes respectively. The mean birth weight was (1591.46±439.51) grams, birth length - (39.96±4.25) cm, head circumference (HC) - (28.92±2.37) cm. Fourteen (10%) infants were born small for gestational age. Anthropometric indicators of the study population depending on the GA are presented in the table. 1. Enteral nutrition was started on average on the first day of life in all newborns. All children received parenteral nutrition from the first hours of life.

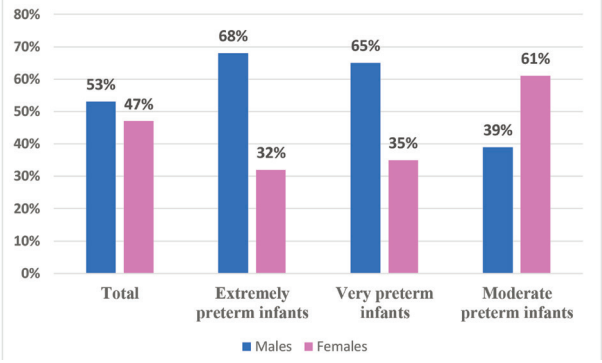

Figure 1. Gender distribution of the study population

ISSN 2226-1230 (PRINT) ISSN 2413-4260 (ONLINE)
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Table 1

Anthropometric indicators of the study population

Indicator		Statistical indicator	Extremely preterm infants, n=19	Very preterm infants, n=72	Moderate preterm infants, n=49	p
Birth weight	g	Mean±SD	917.37 ± 207.14	1559.72 ±281.42	1899.49±384.58	p_{1-2}<0.001* p_{1-3}<0.001* p_{2-3}<0.001*
	percentile	Mean±SD	53.68±27.93	59.17±25.43	44.31±29.51	p_{1-2}=0.715 p_{1-3}=0.410 p_{2-3}=0.009*
Birth length	cm	Mean±SD	33.47±3.5	39.5±3.0	43.2±2.5	p_{1-2}<0.001* p_{1-3}<0.001* p_{2-3}<0.001*
	percentile	Mean±SD	42.11±29.86	40.29±24.31	42.35±26.69	p_{1-2}=0.916 p_{1-3}=0.999 p_{2-3}=0.905
Birth head circumference	cm	Mean±SD	25.4±1.6	29.0±2.0	30.2±1.6	p_{1-2}<0.001* p_{1-3}=0.0042* p_{2-3}<0.001*
	percentile	Mean±SD	78.81±24.79	64.24±24.95	48.38±25.05	p_{1-2}=0.791 p_{1-3}=0.006 p_{2-3}<0.001*
Note. * – statistically significant results						

Respiratory disorders of varying degrees were diagnosed in all infants. Thus, severe respiratory disorders predominated in extremely preterm infants, moderate and severe respiratory disorders - in very preterm infants, and moderate respiratory disorders in moderate preterm neonates. Surfactant replacement therapy was performed in 43 (30.71%) newborns. A total of 45 children required mechanical ventilation, with a significant predominance in the group of extremely preterm infants (p<0.001).

Respiratory distress syndrome (71.43 %), early-onset neonatal sepsis (23.57 %), intraventricular hemorrhages (23.57 %), hypoxic-ischemic encephalopathy (22.14 %) were the most frequent diseases of the study population. Twenty-six infants (18.6%) had neonatal seizures.

The dopamine level in the urine of preterm infants was 132.20 [104.80; 183.70] pg/ml. It was significantly higher in children who underwent mechanical ventilation compared to non-ventilated neonates (164.60 [110.00; 253.70] pg/mL vs. 123.20 [98.65; 158.70] pg /ml), p=0.030. The level of dopamine was associated with the severity of respiratory disorders (H=5.84; p=0.049). It was found that high levels of dopamine were associated with severe respiratory disorders in preterm infants (Table 2, Fig. 2). The dopamine levels in the study population depending on neonatal diseases are presented in Table 3.

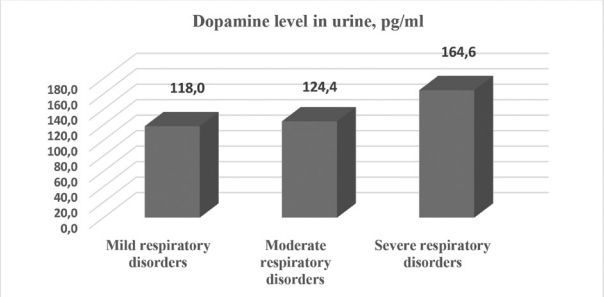

Figure 2. The level of dopamine in urine in preterm infants depending on the degree of respiratory disorders

***Note.** * – statistically significant results*

Table 2

Pain and pain-related stress markers in preterm infants depending on the severity of respiratory disorders

Index	Mild respiratory disorders (n=18)	Moderate respiratory disorders (n=77)	Severe respiratory disorders (n=45)	Kruskel-Wallis test	p
Dopamine in urine, pg/ml	118,00 (110,40; 185,00)	124,35 (95,26; 156,95)	164,60 (110,90; 264,65)	H=5,84; p=0,049*	p_{1-2}=1,000 p_{1-3}=1,000 p_{2-3}=0,047*
β-Endorphin in urine, pg/ml	37,10 (15,75;52,10)	28,96 (20,74; 46,77)	35,15 (19,66; 59,05)	H=0,04; p=0,978	p_{1-2}=1,000 p_{1-3}=1,000 p_{2-3}=1,000
Serotonin in urine, ng/ml	42,46 (12,38; 57,85)	23,17 (18,22; 31,65)	23,23 (14,41; 33,32)	H=0,85; p=0,654	P_{1-2}=1,000 P_{1-3}=1,000 P_{2-3}=1,000
Note. * – statistically significant results					

Table 3

Pain and pain-related stress markers in preterm infants depending on diseases

Neonatal disease		Dopamine in urine, pg/ml		β-Endorphin in urine, pg/ml		Serotonin in urine, ng/ml	
		Me (Lq; Uq)	p	Me (Lq; Uq)	p	Me (Lq; Uq)	p
Respiratory distress syndrome	+	125.50 (104.80; 165.30)	0.209	28.99 (20.47; 45.79)	0.607	22.30 (15.13; 30.15)	0.188
	–	156.55 (91.87; 269.30)		30.09 (21.50; 52.10)		27.19 (16.13; 44.48)	
Early-onset sepsis	+	124.90 (91.43; 209.50)	0.994	32.04 (17.27; 65.31)	0.715	16.81 (14.41; 33.32)	0.509
	–	132.20 (107.20; 183.70)		29.87 (21.12; 45.19)		23.75 (18.22; 32.08)	
Neonatal seizures	+	164.85 (107.40; 264.65)	0.174	24.88 (15.61; 35.15)	0.039*	22.18 (13.82; 29.55)	0.239
	–	127.70 (101.60; 165.10)		32.80 (21.97; 54.78)		25.50 (17.41; 34.72)	
IVH	+	136.10 (105.10; 253.70)	0.497	28.88 (21.50; 37.10)	0.664	22.30 (17.41; 29.70)	0.910
	-	128.25 (101.60; 170.00)		30.60 (20.47; 47.11)		24.03 (16.13; 32.19)	
Note. * – statistically significant results							

It was found that dopamine level was significantly lower in twins compared to singleton infants (113.70 [78.75; 164.70] vs. 145.10 [111.80; 208.50], p=0.017, Fig. 3. There was no difference in dopamine level depending on gender (p=0.331), mode of delivery (p=0.424), gestational age (H=3.44; p=0.179), and birth weight (H=0.26; p=0.877). Dopamine levels in preterm neonates of different GA are presented in Table 4.

Table 4.

Pain and pain-related stress markers in preterm infants depending on the severity of respiratory disorders

Index	GA 24-28 weeks (n=19)	GA 29-32 weeks (n=72)	GA 33-34 weeks (n=49)	Kruskel-Wallis test	p
Dopamine in urine, pg/ml	136.10 (111.80; 163.90)	121.80 (91.43; 165.20)	159.55 (112.50; 238.90)	H=3.44; p=0.179	p_{1-2}=1.000 p_{1-3}=1.000 p_{2-3}=0.216
β-Endorphin in urine, pg/ml	26.48 (14.23; 44.60)	32.80 (21.99; 50.95)	23.80 (18.94; 37.81)	H=2.06; P=0.357	p_{1-2}=1.000 p_{1-3}=1.000 p_{2-3}=0.594
Serotonin in urine, ng/ml	22.7 (14.77; 26.73)	24.03 (17.55; 32.08)	18.76 (14.26; 36.31)	H=0.68; p=0.712	P_{1-2}=1.000 P_{1-3}=1.000 P_{2-3}=1.000
Note. * – statistically significant results					

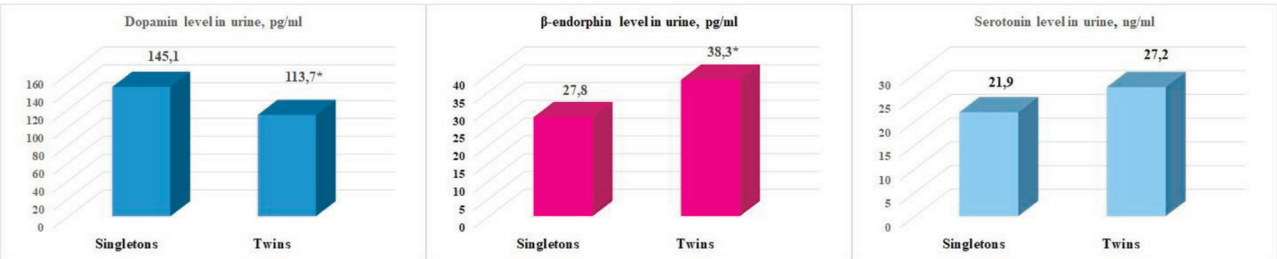

Figure 3. Dopamine, β-endorphin and serotonin levels in twins and singleton infants

***Note.** * – statistically significant results*

The β-endorphin level in the urine of preterm neonates was 29.87 [20.61; 46.94] pg/ml. It was significantly higher in twins compared to singletons (38.30 21.97; 59.61] vs. 27.80 [19.66; 39.16], p=0.046, Fig. 3). It was found that the β-endorphin level was significantly lower in children with neonatal seizures (p=0.039, table 3), and was not associated with gender (p=0.650), mode of delivery (p=0.136), mechanical ventilation (p=0.780). The level of β-endorphin in urine depending on neonatal diseases are presented in Table 3. The β-endorphin level did not depend on the GA (H=2.06; p=0.357, Table 4) and birth weight (H=4.42; p=0.106).

The serotonin level in the urine of preterm infants was 23.49 [16.13; 32.19] pg/ml. It was not associated with gestational age (H=0.18; p=0.913, Table 4) and birth weight (H=0.21; p=0.901). It was found that neonates born by caesarean section had significantly higher levels of serotonin compared to those born naturally (25.62 [18.87; 38.53] ng/ml vs. 17.41 [13.36; 27.89] ng/ml, p=0.017). Serotonin level was higher in twins compared to singletons (27.19 [18.87; 41.75] ng/ml vs. 21.98 [14.41; 29.70] ng/ml), however, statistical

ISSN 2226-1230 (PRINT) ISSN 2413-4260 (ONLINE)

significance was not established (p=0.073), fig. 3. It was also higher in females (27.54 [19.58; 34.72] ng/ml) compared to males (21.79 [14.05; 28.82] ng/ml, p=0.054. Serotonin levels in urine depending on neonatal diseases did not differ significantly (p>0.05), and are presented in Table 3.

The study revealed the positive correlation between serotonin and β-endorphin levels (r=0.68; p<0.001) in infants who required mechanical ventilation and in newborns with neonatal seizures (r=0.59; p<0.001), Fig. 4. It was also found a positive correlation between β-endorphin and serotonin levels in twins (r=0.72, p<0.001), Fig. 5.

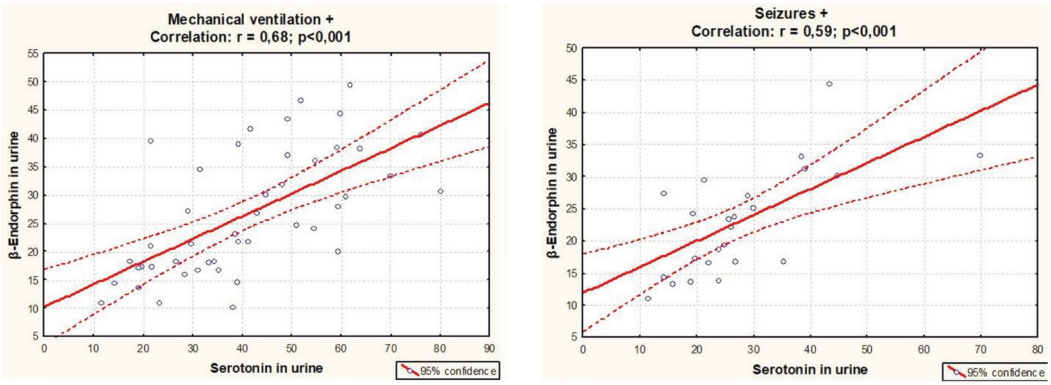

Figure 4. Correlation between β-endorphin and serotonin levels in preterm infants who required mechanical ventilation and in case of neonatal seizures

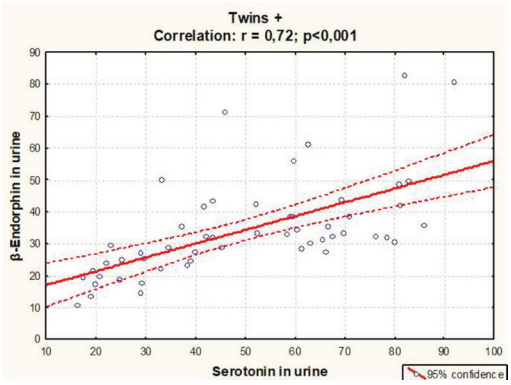

Figure 5. Correlation between β-endorphin and serotonin levels in twins

This is the first national and international research that studied the level of pain and pain-related stress markers in premature infants during their treatment in the intensive care unit, depending on various factors. We found that such factors as severe respiratory disorders and the need for mechanical ventilation in preterm infants were more often associated with elevated levels of dopamine as one of the pain markers. B-endorphin and serotonin levels were not significantly different in infants who required mechanical ventilation compared to non-ventilated patients, however, these analgesic and anti-stress markers were interrelated (r=0.76; p<0.001) in children who required mechanical ventilation.

All infants with severe respiratory disorders required mechanical ventilation. Elevated levels of dopamine and positive correlations between analgesic and anti-stress markers in ventilated infants laboratory confirm that mechanical ventilation is stressful for preterm neonates and accompanied by pain. Whit Hall R. et al. noted that mechanical ventilation is a stressful experience for newborns, which leads to neuroendocrine disorders, pain, and changes of physiological reactions [11]. There are no data on how painful and stressful invasive ventilation is, but it is clear that it is accompanied by a huge number of painful interventions, such as intubation, reintubation, frequent endotracheal aspirations, skin damage during the changes of adhesive materials [12]. Assisted lung ventilation in neonates is thought to lead to chronic recurrent pain, which is associated with adverse long-term outcomes [11]. In addition, different modes of ventilation can potentially increase stress levels. In particular, mandatory modes can lead to patient-ventilator asynchronies, when infants need to "fight the ventilator" [13].

Our study showed that the β-endorphins level was associated with the neonatal seizures, indicating that neuropeptide systems play a crucial role in modulating neuronal excitability [14, 15] in addition to its direct analgesic and sedative effects [16]. The level of serotonin was not associated with the neonatal seizures, however, it was found the positive correlation between serotonin β-endorphin levels (r=0.60; p<0.001) in preterm infants who had it. According to the literature, natural opioid peptides have both proconvulsant and anticonvulsant effects, participating in spontaneous seizures. Anticonvulsant action is described more often [17, 18]. Since the seizure phenomenon is often associated with severe electrical discharges in the brain, it is believed that most neurohumoral transmitters play a role in the events before or after the seizure [19]. A significant increase in β-endorphin level in plasma was found in adults with convulsive syndrome, and it was also proved that its level was associated with the frequency of convulsive attacks and the duration of the disease [19]. At the same time, when studying the level of β-endorphin in the cerebrospinal fluid of children with infantile spasms (West syndrome), the authors found its significant decrease [20].

The level of pain and pain-related stress indices

significantly differed in twins compared to singletons. So, the dopamine levels were significantly lower, and the β-endorphin level was significantly higher in the twins. Serotonin level was also slightly higher in twins with no statistical significance (p=0.073), however, there was a positive correlation between β-endorphin and serotonin levels in twins (p<0.001).

Our data are consistent with the results of Badiee's et al. study, which showed that cobedding of twins was associated with a significant reduction in neonatal pain. The authors showed that acute pain scores checked with Premature Infant Pain Profile scale and salivary cortisol levels during the heel lance were significantly lower in the cobedding group [21]. Cobedding is thought to improve twins' co-regulation, improve physiologic stability, reduce oxygen demand, improve growth and development, and reduce the duration of hospital stay [22]. In addition, cobedding provides tactile, olfactory, and auditory stimulation and may reduce pain responses in preterm infants [23, 24]. We did not aim to study the effect of cobedding on pain and pain-related stress markers in our research, however, the twins were often together, which likely influenced the intensity of chronic pain and stress. During the fetal life twins share a small, comfortable intrauterine space where their bodies are very close to each other. Thus, having a co-twin nearby can have a calming effect on the preterm infants [21].

Conclusion

This prospective cohort study showed that severe respiratory disorders in preterm infants were associated with decreased dopamine level, while serotonin and β-endorphin levels were correlated in this case. Neonatal seizures were associated with decreased β-endorphin level, while a positive correlation was found between β-endorphin and serotonin levels. Dopamine levels were significantly lower and β-endorphin levels significantly higher in twins compared to singleton preterm neonates. Serotonin level was significantly higher in neonates born by caesarean section. Gestational age, birth weight, gender, early-onset sepsis, and intraventricular hemorrhage were not associated with increased or decreased levels of pain and pain-related stress markers in preterm infants.

Conflict of interest: the authors have declared no conflict of interest.

Sources of funding: self-financing.

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ОСОБЛИВОСТІ МАРКЕРІВ ХРОНІЧНОГО БОЛЮ ТА СТРЕСУ У ПЕРЕДЧАСНО НАРОДЖЕНИХ НЕМОВЛЯТ

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Резюме

Передчасно народжені діти – це особлива когорта новонароджених із функціональною незрілістю, мультисистемними порушеннями та високою захворюваністю, які потребують тривалого лікування у відділенні інтенсивної терапії новонароджених (ВІТН). Перебування у ВІТН, що супроводжуються численними надмірними стимулами, болючими процедурами та відокремлення від батьків призводить до високого ризику хронічного болю та стресу.

Метою дослідження було вивчити рівень маркерів хронічного болю та стресу у передчасно народжених немовлят із гестаційним віком менше 34 тижнів, а також їх зв'язок з різними факторами.

Матеріали та методи. У дослідженні взяли участь 104 недоношених новонароджених із гестаційним віком (ГВ) менше 34 тижнів, які перебували на лікуванні у відділенні інтенсивної терапії. Рівень маркерів хронічного болю та стресу (дофамін, β-ендорфін, серотонін) у зразках сечі визначали за допомогою імуноферментного аналізу з використанням стандартних наборів (Dopamin Elisakit, Elabscience, м. Ухань, Китай; Serotonin Elisakit, Elabscience, м. Ухань, Китай; β-endorphin Elisakit, Elabscience, м. Ухань, Китай). Зразки аналізували в дублікатах, а аналізи проводили з використанням наданих контролів відповідно до інструкцій виробника.

Дослідження було проведено відповідно до Гельсінської декларації Всесвітньої медичної асоціації про етичні принципи проведення наукових медичних досліджень за участю людини. На проведення досліджень отримано дозвіл біоетичної комісії Тернопільського національного медичного університету імені І.Я. Горбачевського. Інформована згода була отримана від усіх батьків, діти яких брали участь у дослідженні.

Статистичний аналіз даних проводили за допомогою програми „STATISTICA 13.0. FOR WINDOWS" (Tulsa, OK). Результати дослідження представляли у вигляді абсолютних та відносних значень. Кількісні показники представлено у вигляді медіани (Me) та міжквартильного діапазону (нижнього (Lq) та верхнього (Uq) квартилів). Для порівняння числових характеристик використовували U-тест Манна-Уітні (для двох незалежних груп), тест Крускала-Уолліса (для трьох незалежних груп). Відмінності між групами вважали статистично достовірними при $p<0,05$. Ступінь взаємозв'язку між кількісними показниками визначали за допомогою коефіцієнта кореляції Спірмена (r).

Дослідження є фрагментом науково-дослідної роботи на тему: «Впровадження елементів нейро-розвиткового догляду за передчасно народженими дітьми та їх катамнестичне спостереження» (шифр 0120U104281, терміни виконання 01.01.2020-31.12.2022).

Результати дослідження та їх обговорення. Рівень допаміну у сечі немовлят становив 132,20 [104,80; 183,70] пг/мл. Він був значно вищим у дітей, яким проводилася ШВЛ порівняно з тими, які не потребували інвазивної вентиляційної підтримки (164,60 [110,00; 253,70] пг/мл проти 123,20 [98,65; 158,70] пг/мл), $p=0,030$, та асоціювався із ступенем тяжкості дихальних розладів ($H=5,84$; $p=0,049$). Виявлено, що показники допаміну були значно нижчі у двійнят у порівнянні із немовлятами, що народилися від одноплідної вагітності (113,70 [78,75; 164,70] пг/мл проти 145,10 [111,80; 208,50] пг/мл), $p=0,017$.

Рівень β-ендорфіну у сечі передчасно народжених немовлят становив 29,87 [20,61; 46,94] пг/мл. Даний показник був значно вищим у двійнят у порівнянні із немовлятами, які народилися від одноплідної вагітності (38,30 [21,97; 59,61] пг/мл проти 27,80 [19,66; 39,16] пг/мл), $p=0,046$. Рівень β-ендорфіну був значно нижчим у дітей із судомним синдром ($p=0,039$).

Рівень серотоніну у сечі передчасно народжених немовлят становив 23,49 [16,13; 32,19] нг/мл. Немовлята, народженні шляхом кесарського розтину, мали значно вищі показники серотоніну порівняно з тими, хто народився природнім шляхом (25,62 [18,87; 38,53] нг/мл проти 17,41 [13,36; 27,89] нг/мл, $p=0,017$). Рівень серотоніну був дещо вищим у двійнят у порівнянні із немовлятами, які народилися від одноплідної вагітності (27,19 [18,87; 41,75] нг/мл проти 21,98 [14,41; 29,70] нг/мл), однак статистичної достовірності не встановлено ($p=0,073$).

Дослідження встановило позитивні кореляційні зв'язки між рівнем серотоніну та β-ендорфіну у дітей, які потребували механічної вентиляції ($r=0,68$; $p<0,001$) та при наявності неонатальних судом ($r=0,59$; $p<0,001$). Також виявлено позитивний кореляційний зв'язок між рівнями β-ендорфіну та серотоніну у передчасно народжених двійнят ($r=0,72$, $p<0,001$).

Висновки. Це проспективне когортне дослідження показало, що важкі дихальні розлади у передчасно народжених дітей асоціювалися зі зниженням рівня допаміну, при цьому рівні серотоніну та β-ендорфіну були взаємопов'язаними. Неонатальні судоми були пов'язані зі зниженням рівня β-ендорфіну, при цьому був виявлений позитивний кореляційний зв'язок між рівнем β-ендорфіну та серотоніну. Показники допаміну були значно нижчі, а рівень ендорфіну вірогідно вищим у двійнят порівняно з немовлятами, народженими від одноплідної вагітності. Рівень серотоніну був значно вищим у дітей, народжених шляхом кесаревого розтину. Гестаційний вік, маса при народженні, стать, ранній сепсис та ВШК не були пов'язані з підвищенням або зниженням рівню маркерів хронічного болю та стресу у передчасно народжених немовлят.

Ключові слова: хронічний біль; стрес; передчасно народжені немовлята; дофамін; β-ендорфін; серотонін.

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Received for editorial office on 17/12/2022
Signed for printing on 15/02/2023