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INFLUENCE OF PAIN ON THE DEVELOPMENT IN PRETERM INFANTS

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Introduction. The influence of uncontrolled exposure to pain in newborns in the first days of life on the long-term consequences for both the brain and the development of the nervous system as a whole is of interest.

The aim of the study was to assess the intensity of pain in preterm infants who need respiratory care in the early neonatal period and to determine its impact on the development of the child by the end of the first month of life.

Materials and methods. From December 2018 to December 2019, 92 preterm infants requiring respiratory support in the early neonatal period were examined. Pain intensity was assessed on the EDIN6 scale, and neuro-muscular maturity was assessed on the J. Ballard scale. The preterm infants were divided into 2 groups: Group I – 34 children who underwent invasive ventilation (body weight 1120 [865; 1390] g, gestational age 29 [26; 31] weeks); group II – 58 newborns who used non-invasive respiratory therapy (CPAP) (body weight 1160 [875; 1400] g, gestational age 29 [28; 31] weeks). Group I newborns had a lower Apgar score at 5 minutes ($p = 0.001$) and a higher Silverman score ($p = 0.001$).

Results and discussions. In all newborns, the maximum pain intensity score on the EDIN6 scale was registered on the 3rd day of life: in group I, it was 9, and in group II – points ($p = 0.041$), which corresponds to moderate pain. Group I children underwent more manipulations (20.8 ± 2.14 vs 17.7 ± 2.05; $p = 0.016$). An increase in the average airway pressure of ⩾10 cm H_2O in group I children and ⩾6.5 cm H_2O in group II patients is accompanied by an increase in the intensity of pain to severe and moderate, respectively. In both groups of children, an inverse correlation was found between the number of manipulations, head circumference ($R = -0.64$; $p = 0.004$) and the J. Ballard score on the 28th day of life ($R = -0.57$; $p = 0.008$). The number of painful manipulations in the early neonatal period, exceeding 21 procedures per day, increases the risk of delayed child development by more than 3.5 ($p = 0.009$; OR = 3.68; CI = 1.12–8.36).

Conclusion. The number of manipulations performed and the value of the average airway pressure are the main factors affecting the intensity of pain in preterm infants and determining their development in the neonatal period.

Keywords: preterm infants; pain level; neuromuscular and physical development.

ВЛИЯНИЕ БОЛИ НА РАЗВИТИЕ ГЛУБОКО НЕДОНОШЕННЫХ НОВОРОЖДЕННЫХ

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Введение. Исследование долгосрочных последствий неконтролируемого воздействия боли у новорожденных первых дней жизни для развития нервной системы в целом и головного мозга в частности представляет научный и клинический интерес.

Цель исследования — оценить интенсивность боли у глубоко недоношенных новорожденных, нуждающихся в респираторной поддержке в раннем неонатальном периоде, и установить ее влияние на развитие ребенка к концу первого месяца жизни.

Материалы и методы. Обследовано 92 глубоко недоношенных новорожденных, нуждающихся в респираторной поддержке в раннем неонатальном периоде. Оценку интенсивности боли проводили по шкале EDIN6, оценку нейромышечной зрелости — по шкале J. Ballard. Новорожденные были разделены на 2 группы: I группа — 34 ребенка,

которым проводилась инвазивная ИВЛ (масса тела 1120 [865; 1390] г, срок гестации 29 [26; 31] недель); II группа — 58 новорожденных, у которых использовалась неинвазивная респираторная поддержка (НИП/CPAP) (масса тела 1160 [875; 1400] г, срок гестации 29 [28; 31] недель). Новорожденные I группы имели более низкую оценку по шкале Апгар на 5-й минуте (p = 0,001) и более высокую — по шкале Сильвермана (p = 0,001).

Результаты и обсуждение. У всех новорожденных максимальная оценка интенсивности боли по шкале EDIN6 была зарегистрирована на 3-и сутки жизни: в I группе она составила 9, а во II — 8 баллов (p = 0,041), что соответствует умеренной боли. Детям I группы было проведено большее количество манипуляций (20,8 ± 2,14 vs 17,7 ± 2,05; p = 0,016). Увеличение среднего давления в дыхательных путях ⩾10 см H_2O у детей I группы и ⩾6,5 см H_2O у пациентов II группы сопровождается увеличением интенсивности боли до сильной и умеренной соответственно. У детей обеих групп выявлена обратная корреляционная зависимость между количеством манипуляций, окружностью головы (R = –0,64; p = 0,004) и оценкой по шкале J. Ballard на 28-е сутки жизни (R = –0,57; p = 0,008). Количество болезненных манипуляций в раннем неонатальном периоде, превышающее 21 процедуру в сутки, увеличивает риск задержки развития ребенка более чем в 3,5 раза (p = 0,009; OR = 3,68; CI = 1,12–8,36).

Заключение. Количество выполняемых манипуляций и величина среднего давления в дыхательных путях — основные факторы, влияющие на интенсивность боли у глубоко недоношенных новорожденных, определяющие их развитие в неонатальном периоде.

Ключевые слова: глубоко недоношенные новорожденные; уровень боли; нейромышечное и физическое развитие.

Due to a significant increase in the survival rate of extremely premature infants, considerable attention is currently paid to reducing neurological deficits and long-term adverse consequences associated with immaturity of the central nervous system (CNS) and stress during the first days of life [17]. Since all extremely premature newborns require care and treatment in resuscitation and intensive care units (RICU), they require numerous diagnostic and therapeutic procedures much more frequently, many of which are very painful. All this happens in the presence of stress caused by the weaning of the child from the mother. The role of long-term exposure to stress and pain experienced by extremely premature infants in RICU remains unclear and requires detailed study. Although the CNS of extremely premature infants during the early neonatal period is in a critical period of development, it is apparent that these children can perceive pain [7]. Considering that the tactile sense threshold is lower, and the descending inhibitory pathways are immature, premature infants, especially extremely premature infants, are even more sensitive to painful stimuli [22].

Early life pain in newborns has long-term effects on both the developing brain and the nervous system. Experimental studies on animals have established that chronic stress in the mother during pregnancy causes excitotoxic brain damage in newborn mice [20]. In addition, several studies that attempted to create an environment aimed to reduce stress in premature infants showed improved short-term and long-term outcomes [5, 6]. Excessive pain can alter the structure and function of the developing brain in premature infants by contracting the white matter and the subcortical gray matter [8]. Therefore, such adverse effects may be associated with subsequent changes in the IQ levels of schoolchildren, which are mediated by microstructural changes in the brain [23]. Smith et al. [21] demonstrated that premature infants are exposed to many potentially stressful factors. The increased exposure to these factors in RICU is associated with decreases in the sizes of the frontal and parietal brain regions and changes in the microstructure in the temporal lobes. Also, developmental psychomotor disorders have been associated with early exposure to stress [21].

The study aims to assess pain intensity in extremely premature infants who require respiratory support during the early neonatal period and establish its effect on child development by the end of the first month of life.

MATERIALS AND METHODS

A non-randomized controlled comparative cohort study was performed from December 2018 to December 2019. The study included 92 extremely premature infants in the neonatal RICU of the V.N. Gorodkov Ivanovo Research Institute of Maternity and Childhood, the Ministry of Health of Russia. The study was approved by the local Ethics Committee (Protocol No. 2 of November 24, 2018), and the infants' parents signed a voluntary informed consent to participate in the study.

The study included children with respiratory distress syndrome, with a gestational age of 29 [range, 27–31] weeks and birth weight of 1150 [range, 875–1400] grams. All children received respiratory support in the early neonatal period, namely con-

tinuous positive airway pressure (CPAP) therapy or invasive artificial pulmonary ventilation (APV) [2]. The exclusion criteria for the mother were narcotic drug intake and alcohol abuse during pregnancy. Exclusions for the child were the presence of congenital malformations and diseases requiring surgical intervention, and severe hemorrhagic lesions of the CNS (degree III–IV intraventricular hemorrhage), and degree III cerebral ischemia in the early neonatal period, a change in the strategy of respiratory support. All children enrolled in the study had a NEOMOD score of 2 [range, 1–3] points to remove the influence of comorbidity and the presence/progression of multiple organ failure on pain intensity [15].

The degree of respiratory impairment was measured using the Silverman scale. The duration of respiratory support was also assessed. The follow-up of children was performed daily, including clinical, laboratory, and instrumental assessment of the state of organs and systems. Neuromuscular and physical maturity was assessed using the Ballard Scale on the first day of life and then every seven days until the end of the neonatal period. The pain level was assessed daily using the modified EDIN6 (Echelle Douleur Inconfort Nouveau-Né, 6) pain and discomfort scale in newborns [12, 19]. The number of manipulations performed was also counted daily. On day seven of life, children underwent an assessment of anthropometric data and neuromuscular and physical maturity according to the Ballard Scale.

Concerning the various methods of respiratory support, newborns were distributed into two groups. Group I consisted of 34 children who underwent invasive APV, and group II included 58 newborns, where CPAP therapy was used.

Table 1 presents the characteristics of the groups. The patients were comparable regarding anthropo-

Table 1 / Таблица 1

Characteristics of the examined preterm infants
Характеристика обследованных новорожденных

Indications / Показатели	Group I / Группа I (n = 34)	Group II / Группа II (n = 58)	p
Female/male, *n* / Женский/мужской пол, *n*	15/19	30/28	–
Gestational age, weeks / Гестационный возраст, нед.	29 [26; 31]	29 [28; 31]	0.081
Weight, g / Вес тела при рождении, г	1120 [865; 1390]	1160 [875; 1400]	0.320
Length, cm / Длина, см	36 [33; 39]	37 [34; 40]	0.071
Head circumference, cm / Окружность головы, см	26 [24; 28]	27 [25; 28]	0.067
Without prevention of RDS, *n* / Без профилактики респираторного дистресс-синдрома плода, *n*	16 (47.0%)	23 (39.7%)	0.480
Apgar score for 1 min, points / Оценка по шкале Апгар на 1-й минуте, балл	4 [3; 5]	4 [4; 5]	0.078
Apgar score for 5 min, points / Оценка по шкале Апгар на 5-й минуте, балл	5 [4; 6]	6 [5; 6]	0.001
Score for scale Silverman, points / Оценка по шкале Сильвермана, балл	6 [6; 7]	5 [5; 6]	0.001
Total time of primary resuscitation, min / Длительность первичной реанимации, мин	10 [10; 12]	5 [5; 10]	0.001
$FiO_{2\ max}$ when performing respiratory support in the delivery room / $FiO_{2\ max}$ при проведении респираторной поддержки в родильном зале	0.42 [0.3; 0.5]	0.21 [0.21; 0.3]	0.001

Note. $FiO_{2\ max}$ – the maximum fraction of oxygen in the oxygen-air mixture.
Примечание. $FiO_{2\ max}$ — максимальная фракция кислорода в кислородно-воздушной смеси.

metric parameters, gestational age, and antenatal prevention of fetal respiratory distress syndrome. The mothers' medical history was also comparable. Newborns of group I had a lower Apgar score at minute five ($p = 0.001$) and a higher score on the Silverman scale, which indicated that they had severe respiratory failure ($p = 0.001$).

Primary resuscitation care in the delivery room was provided according to current recommendations [2, 3]. In group I children, exogenous surfactant was administered through an additional port on the endotracheal tube in the delivery room. In contrast, the less invasive surfactant administration was used for children in group II.

Statistical data processing was performed using the Statistica v. 10.0 software package (Statsoft Ink, USA), the Open Epi system (http://www.openepi.com). Quantitative characteristics were presented as *Me* [Q_{25}; Q_{75}] for nonparametric samples and $M \pm m$ for parametric samples. The normal distribution of attribute values was tested using the Shapiro–Wilk *W*-test. The differences were assessed by the Mann–Whitney test for unconjugated samples, and Fisher's exact test was used for small samples. Correlation analysis was performed using Spearman's correlation coefficient. Differences were considered statistically significant at $p < 0.05$. The influence of individual risk factors on the studied groups was assessed by calculating the odds ratio (OR) with a 95% confidence interval (95% CI).

RESULTS

Analysis of primary resuscitation measures in the delivery room in children of group I revealed a significantly longer duration of primary resuscitation measures ($p = 0.001$). For children of group I from the first minutes of life, APV was started through an endotracheal tube, and CPAP was performed for the group II children. With respiratory support in newborns of group I, a significantly higher ($p = 0.001$) maximum oxygen fraction in the oxygen-air mixture ($FiO_{2\ max}$) was required. No children in either group required closed-chest cardiac massage or medication.

Upon admission to the RICU, all children continued respiratory therapy, the parameters of which are presented in Table 2. The maximum oxygen concentration in the oxygen-air mixture during APV in children of group I was statistically significantly higher ($p = 0.001$) than those in group II. Also, children in group I had a significantly longer duration of respiratory support ($p = 0.001$) than in children in group II.

Suppression syndrome was registered in the neurological status of children in both groups. The majority (67.6% in group I and 60.3% in group II) of infants had a delay in neuromuscular and physical development ($p > 0.05$) on the initial assessment with the Ballard Scale. Development corresponding to the gestational age was only 26.5% of newborns in group I and 29.3% in group II. The level of development exceeding the gestational age was registered in 5.9% of newborns in group I and 10.3% of patients in group II ($p > 0.05$).

From day 14 of life, newborns in group I had a statistically significant delay in neuromuscular and physical development according to the Ballard scale ($p = 0.002$). This tendency persisted until the end of the neonatal period ($p = 0.001$) (Fig. 1).

Table 2 / Таблица 2

The parameters of respiratory support for premature infants in the NICU in the early neonatal period
Параметры респираторной поддержки глубоко недоношенных новорожденных в отделении реанимации и интенсивной терапии в раннем неонатальном периоде

Indications / Показатели	Group I / Группа I ($n = 34$)	Group II / Группа II ($n = 58$)	*p*
$FiO_{2\ max}$	0.42 [0.3; 0.65]	0.25 [0.21; 0.3]	0.001
V_{te}, ml / V_{te}, мл	7 [6; 10]	–	–
MAP, cm H_2O / MAP, см вод. ст.	9 [8; 10]	6 [6; 7]	0.001
Duration of respiratory support, hours / Длительность респираторной поддержки, ч	185 [96; 297]	72 [48; 92]	0.001

Note. $FiO_{2\ max}$ – the maximum fraction of oxygen in the oxygen-air mixture; V_{te} – expiratory respiratory volume; MAP – average airway pressure.

Примечание. $FiO_{2\ max}$ — максимальная фракция кислорода в кислородо-воздушной смеси; V_{te} — экспираторный дыхательный объем; MAP — среднее давление в дыхательных путях.

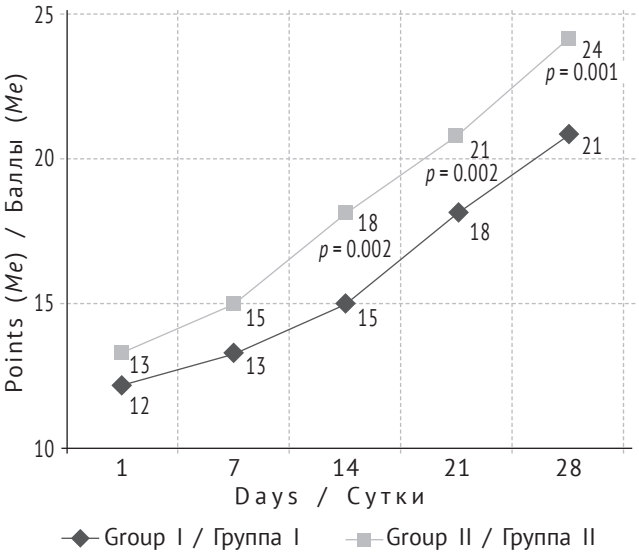

Fig. 1. Dynamics of neuromuscular and physical maturity in preterm infants according to the J. Ballard scale

Рис. 1. Динамика нейромышечной и физической зрелости у глубоко недоношенных новорожденных по шкале J. Ballard

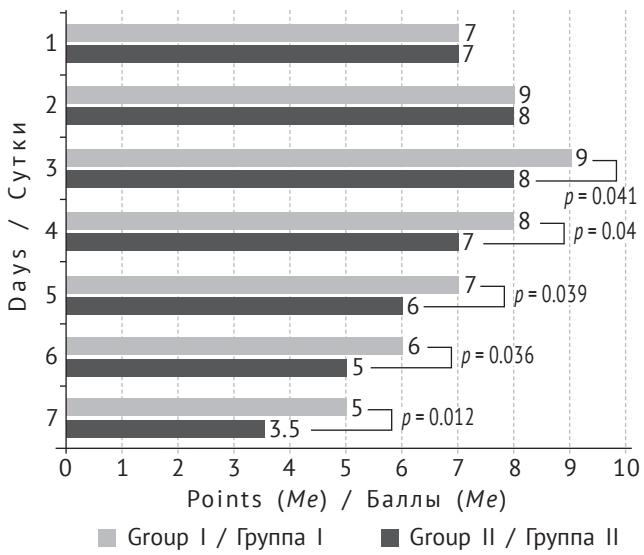

Fig. 2. Pain level on the EDIN6 scale in preterm infants in the early neonatal period

Рис. 2. Уровень боли по шкале EDIN6 у глубоко недоношенных новорожденных в раннем неонатальном периоде

The pain level on the first day of life was 7 [range, 7–9] points in group I and 7 [range, 6–9] points in group II ($p > 0.05$), which is interpreted as moderate pain. The daily assessment of pain intensity in extremely premature infants throughout the early neonatal period is presented in Fig. 2.

In the first two days, the pain level in patients of both groups was also statistically indistinguishable ($p > 0.05$). The maximum pain intensity in children of the group I was noted on the third day of life, and the EDIN6 score was 9. Starting from the third day of life until the end of the early neonatal period, the intensity of pain was significantly higher in children of group I ($p < 0.05$).

When analyzing the frequency of painful manipulations, children of group I in the early neonatal period underwent a significantly greater number of manipulations (20.8 ± 2.14 manipulations per day in group I versus 17.7 ± 2.05 manipulations per day in group II; $p = 0.016$) that caused pain or exerted stress. The most frequent procedures (% of the total number of manipulations) causing acute pain in extremely premature infants were changing baby linens and diapers (43%), changing body position (21%), puncturing the skin for taking tests (12%), manipulations for correct fixing the interface to provide CPAP therapy (9%), cleaning the trachea (6%), weighing (4%), cleansing the oral cavity and nasal passages (4%), inserting a naso- or orogastric tube for feeding children (3%), and others (10%). In addition, all newborns experienced the background effects of pain and/or stress during respiratory support using CPAP or APV. Depending on the group, these effects occurred from the placement of an endotracheal tube for APV in children of group I, the constant presence of an orogastric tube during respiratory support, continuous infusion through the deep venous line, and phototherapy.

The analysis of respiratory support revealed that in those children who, during APV (group I) required a mean airway pressure (MAP) of 10 cm H_2O or higher [$n = 6$ (17.6%)], the pain level was 11 [range, 10–11] points, which meets the criteria of severe pain on the EDIN6 scale and is significantly higher ($p = 0.001$) than in children on APV with a MAP lower than 10 cm H_2O (Fig. 3).

It was established that in children who required a MAP level of 6.5 cm H_2O or higher [$n = 9$ (15.5%)] for CPAP therapy, the pain level was recorded as an 8 [range, 7–9] points, the highest in the group, and met the criteria for moderate pain (Fig. 4).

Monitoring children over time showed that at the end of the neonatal period, body weight was 1450 [range, 1130–1610] g in children of group I, and 1520 [range, 1150–1650] g in children of group II ($p > 0.05$); body length of newborns was 35 [range, 31–38] cm in group I and 36 [range, 31–39] cm in children of group II ($p > 0.05$); head circumference was 28 [range, 27–31] cm in children of group II, and 27 [range, 26–29] cm

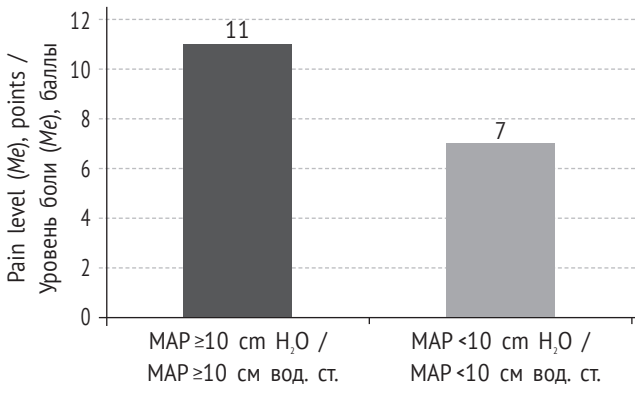

Fig. 3. The level of pain in preterm infants with mechanical ventilation (group I) depending on the MAP

Рис. 3. Уровень боли у детей, которым проводится ИВЛ (I группа), в зависимости от МАР

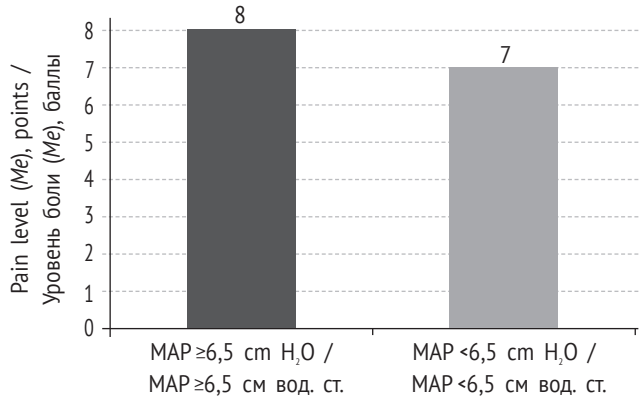

Fig. 4. The level of pain in preterm infants with CPAP (group II) depending on the MAP

Рис. 4. Уровень боли у детей, получающих CPAP (II группа) в зависимости от МАР

in children of group I ($p = 0.043$). A statistically smaller head circumference in children of group I at the end of the neonatal period may indicate significant influences of various factors acting in the early neonatal period (the presence of invasive ventilation, duration of APV, $FiO_{2\ max}$ during respiratory support, others), including the pain intensity.

An inverse correlation was revealed between the average number of manipulations in the early neonatal period in extremely premature infants of both groups and the head circumference by day 28 of life ($R = –0.64$; $p = 0.004$), and an inverse relationship between the average number of manipulations in the early neonatal period in extremely premature infants of both groups with a Ballard Score on day 28 of life ($R = –0.57$; $p = 0.008$).

DISCUSSION

Within the implementation of the concept of developing care for extremely premature newborns, much attention is paid to preserve the child's life successfully and reducing the incidence of late developmental disorders. Also, the influence of manipulations and actions of medical personnel during the first days of life affect long-term disease outcomes.

The study results demonstrated that the total number of painful procedures during the early neonatal period in extremely premature infants who received respiratory support averaged 18.8 ± 1.6 per day. The results obtained are comparable with the results of other authors, demonstrating that newborns can experience 10–18 painful manipulations per day [9, 11]. Although many procedures that we consider painful (diaper change, skin treatment in cases of local infection, use of nasal cannulas) are common in the neonatal RICU and most often are not defined as stressful by most doctors, their ability to influence other outcomes, in particular, the psychoneurological development of the child, must be considered in the future [1, 18, 25].

Particular attention should be paid during the first two days of life since there was no significant difference in pain intensity in children of both groups. The maximum pain intensity was noted in all children on the third day of life. Therefore, during the first two days of life, in extremely premature infants, protective mechanisms are activated, including the production of opioid peptides with analgesic and sedative effects and the presence of endogenous glucocorticoids [4, 14, 16]. However, in the presence of severe pathology, compensatory mechanisms are quickly depleted, and the pain intensity increases. The concentrations of endogenous active substances in extremely premature infants requiring respiratory support decrease over time. Therefore, one of the main tasks of the RICU personnel on the third day of life consists of controlling pain intensity by expanding the measures aimed at eliminating it [14, 16].

By the end of the early neonatal period, pain intensity tended to decrease in both groups ($p = 0.003$ and $p = 0.001$, respectively). In contrast, the mean values in group II on the seventh day of life bordered moderate and minimal pain levels. This result is probably due to the stabilization of patients and regression of the primary pathological process during therapeutic measures by the end of the early neonatal period. In children who underwent invasive APV, the intensity of pain, starting from the third day of life, was significantly higher

($p = 0.001$) than in newborns on CPAP therapy. Differences were revealed in pain intensity depending on the average airway pressure.

We believe that in the presence of signs of severe pain (an EDIN6 score greater than 10 points), both drug and non-drug methods of analgesia must be used to eliminate it [10, 16].

In children who required the MAP level of 6.5 cm H_2O or higher during CPAP therapy, pain intensity was recorded as the highest in the group ("moderate" pain on the EDIN6 scale). This can be explained by the negative effect of high flow and medium pressure on irritated receptors of the nasal passages [16].

When assessing neuromuscular and physical maturity according to the Ballard Scale (Fig. 1), a minimum increase ($p = 0.047$ in group I and $p = 0.031$ in group II) in points was registered in both groups by the end of the early neonatal period. This increase might be explained by the severity of the condition in children requiring intensive care. Also, there was further significant ($p = 0.001$ in both groups) improvement in development by day 28 of life. According to the results of the correlation analysis, many manipulations performed by extremely premature newborns contributed to a decrease in the increment in head circumference and a reduction in neuromuscular and physical development by the end of the neonatal period. Studies have revealed [13] that stressful events predict poorer development of motor skills, strength, and orientation in premature infants. Many painful procedures were directly associated with the subsequent decrease in head circumference growth and brain function in extremely premature infants. Also, recurring pain during the stabilization period can activate a stress signaling cascade that affects subsequent growth and development [24, 25]. The revealed differences in anthropometric parameters and the dynamics of neuromuscular and physical development (according to the Ballard Scale) of the newborns examined, depending on the pain level, will be necessary for the further neuropsychic development of an extremely premature child.

Based on the study, we calculated the risk of slowing down neuromuscular and physical development by day 28 of life in extremely premature infants who require respiratory support. When the number of painful manipulations during the early neonatal period exceeds 21 procedures per day, the risk of delayed development in a child increases by more than 3.5 times ($p = 0.009$; OR = 3.68; CI = 1.12–8.36).

CONCLUSIONS

1. The total number of painful manipulations in extremely premature infants requiring respiratory support is 18.8 ± 1.6 per day. The maximum pain intensity in the early neonatal period is typical for three days of life when most invasive procedures are performed.

2. Pain intensity in extremely premature infants requiring respiratory support is moderate, with the maximum EDIN6 score in infants requiring invasive APV.

3. MAP is one of the main factors determining pain intensity in extremely premature infants who require respiratory support. When conducting invasive APV, the "critical" MAP value is considered to be 10 cm H_2O or higher, and in patients who received CPAP therapy, it was 6.5 cm H_2O or higher.

ADDITIONAL INFORMATION

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