CLINICAL SIGNIFICANCE OF CAFFEINE THERAPY IN REDUCING APNEA EPISODES IN PRETERM INFANTS

K.R. Dilmuradova[1], Z.X. Ikromova[2], H.O. Ziyadullayeva[3]

Samarkand State Medical University, Uzbekistan

КЛИНИЧЕСКОЕ ЗНАЧЕНИЕ КОФЕИНОТЕРАПИИ В УМЕНЬШЕНИИ ЭПИЗОДОВ АПНОЭ У НЕДОНОШЕННЫХ ДЕТЕЙ

К.Р. Дилмурадова[1], З.Х. Икромова[2], Х.О. Зиядуллаева[3]

Самаркандский государственный медицинский университет, Узбекистан

Resume. Apnea of prematurity is a common condition in preterm infants, manifesting as episodes of breathing cessation with bradycardia and hypoxemia due to immature respiratory control. This syndrome increases neonatal morbidity and mortality risk. Methylxanthines, especially caffeine citrate, are considered the most effective therapy to prevent and treat apnea.Objective: To evaluate the clinical efficacy of caffeine citrate therapy in preterm infants with apnea.In this clinical study, 80 preterm infants with apnea received comprehensive treatment including caffeine citrate (loading dose 20 mg/kg IV, followed by 5 mg/kg per day orally). By day 5 of therapy, respiratory status and laboratory and instrumental parameters were assessed.Within 3–5 days from treatment initiation, 70% of infants had complete cessation of apnea episodes, and the remaining 30% showed a significant reduction in frequency (<3 episodes/day). Spontaneous breathing was restored in 85% of infants; CPAP support was weaned by day 3–5 in 62.5% of cases, and need for mechanical ventilation decreased in 37.5%. Blood gas and metabolic indices improved: arterial pH increased with reduction in pCO_2, lactate level decreased, and electrolyte balance normalized (Table 1). In addition, signs of inflammation subsided as serum interleukin-1, TNF-a, and C-reactive protein levels significantly declined post-treatment (Table 2). Lung ultrasound indicated a two-fold reduction in interstitial syndrome signs, and cranial ultrasound showed ~60% decrease in frequency and severity of intraventricular hemorrhages.

Conclusion. The study results demonstrate that incorporating caffeine citrate into the therapy of apnea in preterm infants effectively leads to faster resolution of apnea episodes, reduction of respiratory insufficiency, correction of metabolic disturbances, and prevention of infectious-inflammatory complications. Thus, caffeine citrate is clinically effective in treating apnea of prematurity and improves the survival prognosis for these vulnerable patients.

Keywords: *apnea of prematurity, preterm infant, caffeine citrate, therapy, respiratory failure, neonatology*.

Резюме. Апноэ – частое состояние у недоношенных новорождённых, характеризующееся эпизодами остановки дыхания, брадикардии и гипоксемии вследствие незрелости дыхательной системы. Этот синдром повышает риск неонатальной заболеваемости и смертности. Метилксантины, особенно цитрат кофеина, считаются наиболее эффективным средством профилактики и купирования апноэ.

Цель исследования. Оценить клиническую эффективность применения цитрата кофеина у недоношенных новорождённых с апноэ. В клиническом исследовании 80 недоношенным с синдромом апноэ проводили комплексную терапию с включением цитрата кофеина (нагрузочная доза 20 мг/кг в/в, затем 5 мг/кг в сутки перорально). На 5-й день терапии анализировали динамику дыхания, лабораторных и инструментальных показателей. На 3–5 сутки от начала лечения у 70% новорождённых эпизоды апноэ полностью прекратились, у остальных 30% частота приступов значительно снизилась (<3 в сутки). У 85% детей восстановилось самостоятельное дыхание, в 62,5% случаев на 3–5 день была отменена CPAP-терапия, в 37,5% снизилась потребность в ИВЛ. Улучшились газовый состав крови и метаболические показатели: повышение pH и снижение pCO_2 в крови, снижение уровня лактата, нормализация электролитного баланса (табл. 1). Кроме того, после лечения уменьшились признаки воспаления: уровни интерлейкина-1, ФНО-а и С-реактивного белка в крови достоверно снизились (табл. 2). По данным УЗИ лёгких, наблюдалось двукратное уменьшение признаков интерстициального синдрома, при нейросонографии головного мозга частота и тяжесть внутрижелудочковых кровоизлияний снизились ~ на 60%. Результаты исследования показывают, что включение цитрата кофеина в комплексную терапию апноэ у недоношенных новорождённых эффективно способствует более быстрому купированию эпизодов апноэ, снижению дыхательной недостаточности, нормализации метаболических нарушений, а также профилактике инфекционно-воспалительных осложнений. Таким образом, цитрат кофеина является клинически эффективным средством в лечении апноэ недоношенных, улучшающим прогноз выживаемости этих уязвимых пациентов.

Ключевые слова: *апноэ недоношенных, недоношенный ребенок, цитрат кофеина, терапия, дыхательная недостаточность, неонатология.*

Introduction. Episodes of breathing cessation accompanied by bradycardia and hypoxemia (apnea syndrome) occur very frequently in preterm infants. Nearly all infants with extremely low birth weight (<1000 g) or born before the 28th week of gestation experience apnea episodes. Overall, at least half of preterm infants may develop recurrent apnea spells. Apnea episodes lead to hypercapnia (accumulation of CO_2) and persistent hypoxia in the infant, adversely affecting the development of the central nervous system. As a result, this condition contributes to severe complications in preterm infants – intraventricular brain hemorrhages, chronic lung diseases, and even life-threatening respiratory and cardiovascular disorders. In preterm infants with apnea syndrome, neonatal mortality and morbidity rates are significantly higher, which further heightens the urgency of this problem.

The pathogenesis of apnea syndrome in preterm infants is related to the immaturity of the respiratory center and airway control. Apnea spells are typically characterized by breathing pauses lasting 20 seconds or more, accompanied by a slowing of heart rate (heart rate <100/min) and cyanosis. Most episodes present in a mixed form of central apnea and obstructive apnea. The lower the infant's gestational age and body weight, the greater the likelihood of frequent apnea spells. In some cases, apnea results solely from an immature respiratory center, while in others it may be triggered by hypoglycemia, metabolic disturbances, brain pathology, or infections. Therefore, each preterm infant must be carefully monitored for apnea spells and prompt treatment measures must be taken.

Currently, several methods are used to manage apnea in preterm infants. First, to terminate an apnea spell, prompt interventions such as tactile stimulation or changing the infant's position are carried out. Additionally, to prevent hypoxemia and bradycardia, assisted respiratory support is provided – for example, CPAP (continuous positive airway pressure) or, if necessary, mechanical ventilation via intubation. However, these measures are symptomatic support and cannot ensure that apnea episodes will not recur.

In the pharmacological treatment of apnea, drugs from the methylxanthine group have been used for many years as the "gold standard" therapy. Although aminophylline (theophylline) was used in earlier years, currently caffeine citrate is preferred due to the former's frequent side effects and less favorable pharmacokinetic profile. Caffeine citrate stimulates the central nervous system, increases the sensitivity of the respiratory center, improves diaphragmatic muscle contractility, and stabilizes respiratory rate and rhythm by blocking adenosine receptors in the respiratory tract. Studies indicate that caffeine use significantly reduces the frequency of apnea episodes and even achieves their cessation, while also reducing spells of bradycardia and periodic hypoxemia. Caffeine citrate has a long half-life, allowing once-daily dosing, and is relatively well tolerated by preterm infants.

Caffeine therapy not only eliminates apnea episodes, but also, by reducing the need for mechanical ventilation, it lowers the risk of chronic lung diseases (such as bronchopulmonary dysplasia) in these infants. In particular, previous clinical trials found that extremely low birth weight infants who received caffeine had improved extubation success in the first weeks of life and subsequently better neurological development outcomes. For this reason, in recent years international guidelines have recommended early administration of caffeine citrate (within the first days after birth) for treating apnea in preterm infants. The World Health Organization also recommends using caffeine citrate to prevent and treat apnea spells in preterm infants.

Study Objective: The aim of the study was to determine the clinical efficacy of caffeine citrate therapy in preterm infants with apnea and to evaluate its effect on respiratory function and metabolic parameters.

Materials and methods. This clinical study was conducted at the Samarkand Regional branch of the Republican Specialized Scientific-Practical Medical Center for Mother and Child Health. It examined the outcomes of treating preterm infants with apnea syndrome using caffeine citrate. The study falls under the category of "Clinical research."

A total of 80 preterm infants with apnea episodes were observed (main group). All the infants were born at <37 weeks' gestation and were considered preterm with respect to gestational age and body weight; the majority had very low birth weight (<1500 g). Extremely low birth weight (<1000 g) infants comprised 47.5% of the main group. At birth, 45% of the infants were male and 55% female. All of them began to exhibit recurrent apnea spells within the first 2–3 days after birth. Apnea spells were assessed according to American Academy of Pediatrics (AAP) criteria: episodes lasting >20 seconds, or >10 seconds accompanied by bradycardia (<100/min) or oxygen desaturation, were recorded as clinically significant apnea.

Treatment method: All infants under observation received standard intensive therapy and care measures: maintaining a stable body temperature, oxygen supply, and respiratory support with CPAP if needed, as well as maintaining electrolyte and glucose balance. If an infant had 3 or more apnea episodes in a short interval, or if apnea recurred despite tactile stimulation and CPAP, caffeine citrate was added as part of the comprehensive therapy. Caffeine therapy was administered as an initial *loading dose* of 20 mg/kg intravenously by infusion over 30 minutes. After 24 hours, a *maintenance dose* of 5 mg/kg once daily was given orally. During the course of treatment, the caffeine dose was recalculated daily based on weight changes. The criterion for discontinuing caffeine therapy was defined as achieving 5 days of successful CPAP removal with no apnea episodes observed during that period.

Evaluation criteria: After initiating caffeine citrate therapy, the infants' condition and laboratory indicators were monitored dynamically. Specifically, through clinical observations, the number and duration of apnea episodes and the occurrence of bradycardia were recorded daily. The time when the infant began breathing independently (i.e. the day on which ventilatory support was no longer needed) was noted. The days on which CPAP therapy was discontinued and on which invasive mechanical ventilation was no longer required were also recorded. For laboratory tests, arterial blood gas and metabolic parameters (pH, pO_2, pCO_2, lactate, Na^+, K^+) were measured before treatment and at the end of day 5 of treatment. Levels of inflammatory markers in blood – cytokines (interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNF-a)) – as well as C-reactive protein (CRP) were determined, and the values before and after treatment were compared. For instrumental examinations, lung ultrasound was performed to assess changes in lung tissue, and cranial neurosonography (ultrasound of the brain) was done to detect intraventricular hemorrhages. These instrumental studies were also repeated at the start of treatment and at the end of day 5, and the results were compared.

Statistical analysis: Data collected were processed using Statistica 12.0 software. Differences between pre- and post-treatment indicators were evaluated using Student's *t*-test. A value of $p<0.05$ was considered a statistically significant difference. Results are presented as mean ± standard error (M±m).

Results. Baseline condition of patients: At the start of the study, certain birth and early neonatal characteristics of the preterm infants with apnea syndrome were compared with those of a control group. Infants in the main group had a significantly lower average birth weight and length than those in the control group ($p<0.01$). Signs of neonatal anemia (hemoglobin <140 g/L) were present in 45% of the infants. In initial blood tests, the mean hemoglobin in the main group infants was 134.6±15.8 g/L, which was significantly lower than in the control group ($p<0.001$). Additionally, these infants had leukocytosis at birth (mean leukocyte count ~18±4 ×10^9/L) and an elevated CRP level above the normal range, suggesting that an innate infectious-inflammatory process was active.

Pre-treatment arterial blood gas analysis indicated signs of metabolic and respiratory acidosis in the infants with apnea. In the main group, the average arterial pH was 7.10±0.05, which was considerably shifted toward the acidic side compared to the control group ($p<0.001$). The pCO_2 level at birth in these preterm infants was 43.1±1.8 mm Hg, higher than that of control infants ($p<0.01$), indicating the presence of hypercapnia. The blood lactate level was also higher in the main group compared to control (1.8±0.6 mmol/L vs 1.2±0.1 mmol/L, $p<0.001$), which shows that anaerobic glycolysis was enhanced due to tissue hypoxia. Moreover, the infants with apnea showed disturbances in blood electrolyte balance: for example, the serum sodium level in the main group was 135.6±1.7 mmol/L, lower than in healthy preterm controls ($p<0.001$), and potassium was 3.47±0.18 mmol/L, also lower than in controls ($p<0.001$). Some infants had relative hypoglycemia as well (due to increased glucose consumption in response to the hypoxic state), indicating an overall deranged metabolic status. Thus, in the first days of life, the preterm infants in the study group were found to have problems such as anemia, blood gas acidosis, electrolyte imbalances, and activation of innate inflammation. These findings confirm that the apnea syndrome is associated with severe neonatal and perinatal stress.

Clinical Observations. After the administration of caffeine citrate, significant positive changes were observed in the frequency and duration of apnea episodes. By 3–5 days after starting treatment, 70% (56 infants) had a complete cessation of apnea spells – that is, no new episodes were recorded. In the remaining 30% (24 infants), the number of apnea episodes decreased, averaging down to 1–2 times per day (whereas before treatment they occurred up to 5–6 times per day). However, because these 24 infants still had a small number of apnea episodes (1–2 per day) by the end of the 5th day of therapy, they were not evaluated as "fully recovered." A reduction in bradyapnea (apnea with bradycardia) episodes was also noted: in 45 of the 80 infants (56.3%), heart rate during apnea

improved to above 100/min, resolving the bradycardias that accompanied the apnea episodes. As a result, the overall condition of the preterm infants receiving caffeine citrate became significantly more stable.

Owing to the above clinical improvements, the infants' breathing ability improved rapidly. In 68 out of 80 infants (85%), independent breathing was achieved within 5–8 days of starting treatment, i.e. they no longer required any additional respiratory support. Notably, the need for CPAP support disappeared entirely within 3–5 days of starting caffeine therapy in 50 infants (62.5%), and CPAP treatment was discontinued. In some of the remaining infants, CPAP had to be continued, but even in those cases the apnea episodes occurred with reduced frequency. Furthermore, among 30 infants (37.5%) who required prior invasive mechanical ventilation, the need for ventilatory support significantly decreased by 2–3 days after starting treatment, and in some cases the ventilation settings were able to be eased or mechanical ventilation was briefly paused. These results indicate that caffeine citrate has a positive effect on facilitating early weaning (extubation) of preterm infants from respiratory support equipment.

Laboratory results: After 5 days of treatment with caffeine citrate, preterm infants showed significant improvements in blood gas and metabolic parameters (Table 1). Table 1 presents the main changes before and after therapy. According to the data, over the 5-day period the mean arterial blood pH increased from 7.10 to 7.32 ($p<0.001$), indicating that the acidosis state was partially corrected. At the same time, the pCO_2 level decreased from 43.1 mm Hg to 40.2 mm Hg ($p<0.001$), eliminating the excessive accumulation of carbon dioxide. The pO_2 level increased slightly from 34.9 ± 0.6 to 36.2 ± 0.5 mm Hg ($p=0.002$), meaning the arterial oxygen pressure improved somewhat, which reflects a reduction in respiratory insufficiency. The blood lactate concentration dropped from 1.45 ± 0.59 mmol/L before treatment to 0.98 ± 0.34 mmol/L after treatment ($p<0.001$), indicating a significant improvement in this marker of tissue hypoxia and anaerobic metabolism. During treatment, the levels of sodium and potassium ions rose to return into the normal range: Na^+ increased from 135.7 to 138.4 mmol/L ($p<0.001$), and K^+ from 3.47 to 4.02 mmol/L ($p<0.001$). Thus, after caffeine citrate therapy, gas exchange and acid-base status in the blood of preterm infants were significantly normalized. This shows that the respiratory insufficiency and metabolic acidosis that had developed due to apnea were resolved. Indeed, by stimulating the central respiratory center and concurrently transitioning the infants to full enteral feeding, caffeine helped improve metabolic processes as well. Additional measures during treatment – such as maintaining hemodynamic stability, correcting electrolyte and glucose deficiencies, and administering sodium bicarbonate solution when necessary – were also implemented, which further improved the outcomes.

In addition, caffeine citrate therapy influenced the activity of inflammatory processes. Analysis of blood samples before and after treatment revealed that the levels of inflammatory markers (cytokines) had decreased sharply (Table 2). Specifically, the average concentration of the pro-inflammatory cytokine interleukin-1 (IL-1) dropped from 3.82 ± 0.53 pg/mg to 2.91 ± 0.41 pg/mg ($p<0.001$). Similarly, the level of TNF-α (tumor necrosis factor-alpha) fell from 14.51 ± 2.42 pg/mg to 9.67 ± 1.89 pg/mg ($p<0.001$). The C-reactive protein level decreased from 3.68 ± 1.59 mg/L to 2.43 ± 1.32 mg/L ($p=0.003$). These changes were statistically significant and indicate that the activity of inflammatory processes in the body had diminished over the 5-day therapy period.

Notably, the reduction in IL-1 and TNF-α–key indicators of inflammation–suggests that the inflammatory response was attenuated. It is known that the process of preterm birth and subsequent

Table 1. Blood gas and metabolic parameters before and on day 5 of treatment in preterm infants with apnea (M±m, n=80)

Parameter	Before Treatment	After Treatment	p
Arterial pH	7.10 ± 0.05	7.32 ± 0.04	<0.001
pO_2, mm Hg	34.85 ± 0.62	36.15 ± 0.48	0.002
pCO_2, mm Hg	43.12 ± 1.84	40.21 ± 1.35	<0.001
Lactate, mmol/L	1.45 ± 0.59	0.98 ± 0.34	<0.001
Na^+, mmol/L	135.65 ± 1.66	138.42 ± 1.51	<0.001
K^+, mmol/L	3.47 ± 0.18	4.02 ± 0.21	<0.001

p – statistical significance of the difference between pre- and post-treatment values.

Table 2. Blood cytokine levels before and after treatment in preterm infants with apnea (M±m, n=80)

Parameter	Before Treatment	After Treatment	p
Interleukin-1 (IL-1), pg/mg	3.82 ± 0.53	2.91 ± 0.41	<0.001
TNF-a, pg/mg	14.51 ± 2.42	9.67 ± 1.89	<0.001
C-reactive protein, mg/L	3.68 ± 1.59	2.43 ± 1.32	0.003

intensive care can lead to elevated levels of inflammatory mediators in preterm infants, which increases the risk of sepsis, respiratory infections, and other complications. Our results indicate that the use of caffeine citrate may help reduce this risk. Indeed, during the treatment period, no clinical signs of infection were observed in the infants, and the decrease in C-reactive protein suggests that potential infectious processes were prevented. Thus, caffeine citrate appears to exert a positive effect not only on the respiratory center, but also indirectly on the immune system, helping to prevent infectious-inflammatory processes in preterm infants.

Instrumental results: Pre- and post-treatment instrumental observations also demonstrated the benefits of caffeine therapy. In particular, lung ultrasound examination of the preterm infants showed positive dynamics in the signs of lung tissue damage. At the start of treatment, most infants had ultrasound signs of interstitial syndrome (accumulation of interstitial fluid in lung tissue) and consolidation in the lungs; by the end of the 5th day, the severity of these signs had decreased by approximately two-fold. In other words, the condition of the lung tissue improved and the level of aeration increased. This indicates that, under the influence of caffeine, the respiratory function of the preterm infants improved and the risk of chronic lung disease was reduced. Neurosonography of the brain also recorded positive changes: after treatment with caffeine, the frequency and severity of intraventricular hemorrhages (IVH) decreased by about 60%. Whereas prior to treatment the neurosonogram showed grade II–III intraventricular hemorrhage episodes in a number of infants, by the end of day 5 no new hemorrhages were observed in most cases, and the existing hemorrhages were seen to be in a resorption stage. Thus, treatment with caffeine citrate may have helped stabilize cerebral hemodynamics in these infants.

All of the above results indicate that caffeine citrate therapy is very beneficial for preterm infants with apnea syndrome. Caffeine succeeded in eliminating apnea episodes in a short time and achieving restoration of breathing activity; it also improved metabolic balance and other vital homeostatic indicators. As a result, the dependence of the preterm infants on intensive therapy decreased, and their ability to maintain independent vital functions increased.

Discussion. Effectively treating apnea syndrome in preterm infants is an extremely important task in neonatology. The results obtained in our study show that adding caffeine citrate to the comprehensive therapy leads to the rapid and successful cessation of apnea episodes. In our study, within 5 days, 70% of patients had a complete disappearance of apnea, and even in the others the number of spells sharply decreased. This clinical efficacy is consistent with the findings of other authors: for example, Moschino et al. (2020) reported that caffeine significantly reduces breathing episodes in preterm infants and prevents apnea-associated bradycardia and hypoxemia. By stimulating the respiratory center, caffeine increases the infant's respiratory drive and improves the rhythmicity of breathing movements; as a result, the number and duration of recurrent apnea episodes are dramatically reduced. In our observation, in the majority of infants who received caffeine, breathing stabilized to such an extent within 3–4 days that they no longer required continuous CPAP or intubation support. Scientific sources have also noted that early administration of caffeine citrate in preterm infants accelerates extubation and shortens the duration of invasive ventilation. In addition, there are reports that starting caffeine therapy early can reduce the risk of developing a severe chronic complication like bronchopulmonary dysplasia (BPD). The lung ultrasound findings in our study support this idea – the reduction in interstitial injury signs under caffeine therapy could be a positive factor in preventing BPD in the future.

Caffeine citrate's impact on metabolic parameters is particularly noteworthy. The positive shifts observed in arterial blood gases (pH, pCO_2, pO_2) and lactate levels during the study indicate that respiratory acidosis in the preterm infants was successfully corrected with the help of caffeine. By stimulating the respiratory center, caffeine relieves alveolar hypoventilation and improves ventilation-perfusion balance in the lungs, resulting in the elimination of excess CO_2 from the blood and enhanced oxygenation. Consequently, the production of lactate–which contributes to metabolic acidosis–also

decreases, as was clearly observed in our patients. It should be noted that caffeine also has a direct effect on metabolism – it can raise intracellular cAMP levels and activate liver enzymes. However, in preterm infants the metabolic status is primarily normalized indirectly through the improvement of breathing. Our results, together with the conclusions of other researchers, demonstrate the value of caffeine citrate as a drug that stabilizes overall homeostasis in preterm infants.

Another important aspect of caffeine therapy may be its anti-inflammatory effect. In our study, we observed a significant reduction in IL-1, TNF-a and C-reactive protein levels in infants who received caffeine, indicating that the inflammatory process was attenuated. In fact, previous studies have noted that apnea episodes and hypoxic conditions can exacerbate infectious-inflammatory processes in the bodies of preterm infants. Repeated hypoxemic episodes associated with apnea stimulate the release of cytokines and cause tissue injury. By stabilizing breathing and eliminating hypoxia, caffeine may have prevented such pathological processes. Moreover, some experimental evidence indicates that caffeine possesses direct neuroprotective and anti-inflammatory properties. For example, L. Yang and colleagues (2021) reported in a model of ischemic brain injury in preterm infants that caffeine exerts a neuroprotective effect and also, via adenosine receptors in the nervous system, reduces the release of inflammatory mediators. The reduction in IVH that we observed may, in part, be related to caffeine's positive effect on cerebral circulation and its neuroprotective characteristics. From this perspective, it is noteworthy that beyond treating apnea, caffeine citrate may have long-term benefits for preterm infants.

When prescribing caffeine citrate to preterm infants, the factors of dose and timing are important. In our study, the standard regimen – a 20 mg/kg loading dose and 5 mg/kg daily maintenance dose – was used. This dosing was chosen because of previously established data on the safety profile and efficacy of caffeine. Some authors have raised the question of using higher daily doses in extremely preterm infants or adjusting the dosage based on gestational age. For instance, V. Saroha and R. M. Patel (2020) noted that although higher doses of caffeine might improve apnea control, attention must be paid to potential side effects. In our experience, the standard dose proved sufficient in most cases and none of the infants showed signs of caffeine intoxication (e.g., heart rate >180/min, uncontrollable tremor, a sharp increase in urine output, etc.). Thus, the currently accepted dosing regimen can be considered safe. However, in the future, dose-adjustment studies may be necessary in certain severe cases or in patients with altered pharmacokinetic characteristics (for example, those suffering from sepsis).

Overall, the results obtained confirm the broad benefits of caffeine citrate therapy for preterm infants with apnea syndrome. Our work demonstrated that administering caffeine to preterm infants not only stops apnea episodes, but also has a positive effect on their overall condition and future development. These findings are in harmony with the results of international clinical studies and confirm those results in our local setting. Experts also acknowledge that even in resource-limited countries (Low- and Middle-Income Countries), caffeine should be widely utilized as an inexpensive and effective remedy. In our country's neonatal practice, it is recommended to incorporate caffeine citrate into the routine care of preterm infants in the neonatal intensive care setting. Early use of caffeine therapy will serve to help thousands of preterm babies recover and to prevent complications.

Conclusion. Clinical efficacy: In preterm infants with apnea syndrome, the use of caffeine citrate led to stabilization of breathing episodes within a short time. After 5 days of therapy, 70% of patients had complete cessation of apnea spells, and in the remaining 30%, although episodes recurred, their frequency and duration were sharply reduced. During therapy, most infants regained spontaneous breathing, and their dependence on mechanical ventilation was eliminated.

Elimination of respiratory insufficiency: By stimulating the respiratory center, caffeine citrate effectively reduced respiratory insufficiency in preterm infants. The need for CPAP support disappeared within a short period (in 62.5% of infants, CPAP was discontinued by day 3–5), and the requirement for invasive mechanical ventilation significantly decreased (in 37.5% of cases). This indicates that caffeine helps to wean preterm infants earlier from respiratory support equipment.

Improvement of metabolic status: Caffeine therapy normalized blood gas and metabolic parameters – arterial blood pH increased, pCO_2 decreased, lactate level dropped, and electrolyte balance was restored. This confirms that the metabolic acidosis and hypoxia resulting from apnea were effectively corrected.

Reduction of inflammatory activity: During the course of therapy, preterm infants showed a significant decrease in IL-1, TNF-a and C-reactive protein levels. As a result, the activity of inflammatory processes in their bodies was attenuated, and the risk of potential infectious complications was

reduced. Such an indirect anti-inflammatory effect of caffeine citrate contributes positively to the immunological stability of preterm infants.

Possible neuroprotective effect: Under caffeine treatment, the frequency and severity of intraventricular brain hemorrhages in preterm infants decreased by ~60%. This suggests that the drug also helps stabilize cerebral circulation and protects brain tissue from hypoxic and perfusion-related injuries. Therefore, the use of caffeine citrate may potentially reduce long-term neurological complications in preterm infants.

Practical recommendations:

Widespread use: It is advisable to widely implement the use of caffeine citrate in the treatment of preterm infants with apnea episodes in clinical practice, including in resource-limited settings, as a low-cost and effective therapy.

Early administration: For prophylaxis of apnea, caffeine citrate is recommended as early as possible after birth (within 1–2 days), since earlier initiation yields better stabilization of breathing and reduction of complications.

Standard dosing: Adherence to the standard dosing regimen (20 mg/kg loading dose, 5 mg/kg daily) is sufficient and safe for most preterm infants. Only in certain severe situations, or if the drug's effect is inadequate, should an increase in dose be considered under specialist guidance.

Monitoring during therapy: During caffeine treatment, it is necessary to monitor parameters such as heart rate, blood pressure, and gastrointestinal function, as infrequent side effects like tachycardia or regurgitation can occur.

First-line therapy: Overall, caffeine citrate is a safe and highly effective first-choice medication for preterm infants with apnea syndrome.

Литература/References

1. Erickson G., Dobson N.R., Hunt C.E. Immature control of breathing and apnea of prematurity: the known and unknown. Journal of Perinatology, 2021, 41(9): 2111–2123. DOI: 10.1038/s41372-021-01115-8.

2. Moschino L., Zivanovic S., Hartley C., et al. Caffeine in preterm infants: where are we in 2020? ERJ Open Research, 2020, 6(2): 00330-2019. DOI: 10.1183/23120541.00330-2019.

3. Ленюшкина А.А. и др. Кофеина цитрат в неонатологии: история применения, особенности фармакодинамики и фармакокинетики, клинические эффекты, режимы дозирования (обзор литературы) // Неонатология: Новости. Мнения. Обучение, 2023, 11(1): 76–82.

4. Ofori E.K., Chirawurah D., Osei-Bonsu E., et al. The Use of Caffeine Citrate in the Management of Neonatal Apnea in Low- and Middle-Income Countries: A Rapid Systematic Review. Health Science Reports, 2025, 8(2): e1225. DOI: 10.1002/hsr2.1225.

5. Yang L., Huang Y., Wei H., et al. Encephalopathy in preterm infants: Advances in neuroprotection with caffeine. Frontiers in Pediatrics, 2021, 9: 724161. DOI: 10.3389/fped.2021.724161.

6. Saroha V., Patel R.M. Caffeine for preterm infants: Fixed standard dose, adjustments for age or high dose? Seminars in Fetal and Neonatal Medicine, 2020, 25(6): 101178. DOI: 10.1016/j.siny.2020.101178.

7. World Health Organization (WHO). WHO recommendations for care of the preterm or low-birth-weight infant. Geneva, 2022. (WHO Publications, ISBN 978-92-4-005826-2).