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MARKERS OF ACUTE KIDNEY INJURY IN CRITICALLY ILL PRETERM NEONATES

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Abstract. Early diagnosis of acute kidney injury (AKI) in very low birth weight (VLBW) and extremely low birth weight (ELBW) preterm infants is a serious problem due to the lack of specific clinical manifestations, metabolic features, immaturity of the renal tubular and tubule apparatus, and the intensive therapy provided. The aim of the study is to compare the diagnostic value of classical markers of AKI (diuresis and serum creatinine) and other biochemical parameters (serum cystatin C and urine b2-microglobulin) in children of this group in critical condition. A total of 100 neonates with VLBW and ELBW were included in the study, 28 of whom developed AKI during the first week of life (main group). Oliguria did not develop in any child, and a diagnostically significant increase in serum creatinine was noted on the third day of life. An increase in serum creatinine and urine b2-microglobulin levels in children of the main group compared to the comparison group was detected already on the first day, which allows us to consider them more sensitive markers. However, the reference values of the indicators in children with VLBW and ELBW need to be clarified.

Key words: acute kidney injury, creatinine, cystatin C, urine b2-microglobulin, preterm neonate, very low birth weight, extremely low birth weight

МАРКЕРЫ ОСТРОГО ПОВРЕЖДЕНИЯ ПОЧЕК У НЕДОНОШЕННЫХ НОВОРОЖДЕННЫХ В КРИТИЧЕСКОМ СОСТОЯНИИ

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Резюме. Ранняя диагностика острого повреждения почек (ОПП) у недоношенных с очень низкой (ОНМТ) и экстремально низкой массой тела (ЭНМТ) представляет собой серьезную проблему вследствие отсутствия специфических клинических проявлений, особенностей метаболизма, незрелости клубочкового и канальцевого аппарата почек, а также проводимой интенсивной терапии. Целью работы является сравнение диагностической ценности классических маркеров ОПП (диурез и сывороточный креатинин) и других биохимических показателей (сывороточный цистатин С и b2-микроглобулин мочи) у детей данной группы в критическом состоянии. В исследование были включены 100 новорожденных с ОНМТ и ЭНМТ, у 28 из которых развилось ОПП в течение первой недели жизни (основная группа). Олигурия не развилась ни у одного ребенка, диагностически значимое повышение сывороточного креатинина отмечалось на третьи сутки жизни. Увеличение уровня сывороточного цистатина С и b2-микроглобулина мочи у детей основной группы по сравнению с группой сравнения определялось уже в первые сутки, что позволяет считать их более чувствительными маркерами. Однако референсные значения показателей у детей с ОНМТ и ЭНМТ нуждаются в уточнении.

Ключевые слова: острое повреждение почек, креатинин, цистатин С, b2-микроглобулин, недоношенный новорожденный, очень низкая масса тела при рождении, крайне низкая масса тела при рождении

INTRODUCTION

Neonates with very low birth weight (VLBW) and extremely low birth weight (ELBW) are one of the most challenging groups of patients in intensive care units (ICU), requiring modern methods of respiratory and drug therapy, enteral and parenteral nutrition, careful monitoring and care [1]. At the same time, about 87% of premature neonates with VLBW and ELBW receive at least one nephrotoxic drug during hospitalization [2]. Asphyxia is another common factor in the development of the acute kidney injury (AKI) in preterm neonates, leading to AKI in 30–56% of cases [3, 4]. In addition, nephron development is not completed until 32–36 weeks of gestation, so the number of nephrons in extremely premature neonates is lower compared to premature neonates [5], which also predetermines the higher incidence of AKI. Various authors estimate that up to 50% of infants in ICUs have at least one episode of AKI [7], which, in turn, is an independent risk factor for morbidity and mortality in preterm neonates [8, 9].

Diagnosis of acute kidney injury in neonates with VLBW and ELBW is difficult due to non-specificity of symptoms, rapid development of decompensation, and the lack of generally accepted parameters for extremely premature neonates [6]. Currently, the KDIGO classification or its modified version pKDIGO, based on the assessment of serum creatinine level and diuresis rate, can be used to diagnose AKI [10].

The question of whether this classification can be used in preterm neonates remains debatable [11]. It is known that creatinine concentration can be affected by the catabolic orientation of metabolic processes, increased protein load, maternal creatinine level, the presence of hyperbilirubinae-

mia, and the method of testing [12]. In addition, diuresis in preterm newborns is influenced by their physiological tendency to polyuria and infusion therapy [13].

Serum cystatin C and urine b2-microglobulin can be used as alternative markers for AKI diagnosis. Cystatin C is a specific marker of renal tubular damage [14, 15]. Urine b2-microglobulin concentration reflects the functional status of tubules [16].

AIM

To compare the diagnostic value of serum creatinine levels and diuresis rate with serum cystatin C and urine b2-microglobulin levels for early diagnosis of acute kidney injury in critically ill premature neonates with VLBW and ELBW in the early neonatal period.

MATERIALS AND METHODS

This research was approved by the ethics committee of the Federal State Budgetary Educational Institution of Higher Professional Education "Volga Region Research Medical University" of the Ministry of Health of Russia. It is a primary prospective, non-randomized study. The research was carried out on the basis of the neonatal intensive care unit of the State Budgetary Institution of Neonatal Clinical Hospital No. 40 "Regional Perinatal Centre". The study included 100 premature newborns selected according to the following criteria: prematurity, birth weight less than 1500 g, absence of congenital malformations of the cardiovascular and genitourinary systems, life expectancy more than 168 hours, and informed voluntary parental consent for participation in the study.

28 patients were diagnosed with AKI regarding pKDIGO criteria. They formed the main group.

72 patients had no signs of AKI in the early neonatal period (comparison group).

Median weight of the examined neonates was 990 [820–1250] grams. The gestational age was 28 [27–30] weeks. The median APGAR score at the 1st minute was 4 [3–5] points, and 6 [5–6] at the 5th minute. All patients required respiratory support to varying degrees. 29 patients used nCPAP as respiratory therapy, 63 patients required ventilatory support and 8 patients required high-frequency oscillatory ventilation (HFOV).

Table 1 demonstrates characteristics of the main group (patients with AKI) and the comparison group (patients without diagnosed AKI).

All patients underwent necessary laboratory and diagnostic tests on the 1st, 3rd, and 7th day of life according to internal protocols of the clinical department. Blood sampling for biochemical analysis was taken in morning hours. Peripheral vein blood was taken by means of a disposable sterile vacuum tube with a clot activator. Determination of serum creatinine was performed on a MINDRAY BS-240pro apparatus. The remaining biological samples (serum, urine) were used for determination of cystatin C and b2-microglobulin. The examination was performed on a Thermo Scientific Konelab PRIME 60

analyzer. No additional blood and urine sampling was taken.

Statistical processing of the obtained data was performed by means of IBM SPSS Statistics v.26.0 and Prism 9 (Graphpad) software package. The obtained data was evaluated for conformity to the law of normal distribution in order to choose a method of parametric analysis. Kolmogorov–Smirnov criterion was used which is recommended when the number of subjects is more than 60. In addition, the Fisher's F-criterion was calculated to assess homoscedasticity of dispersions of the obtained data, which is one of the conditions for applicability of parametric analysis methods as well. According to the data obtained, all the compared distributions differed from the normal one; therefore, non-parametric analysis methods were used. In addition, asymmetry and kurtosis indices were estimated, which also confirmed the distribution was non-normal.

The data of descriptive statistics are presented in the form of Me [Q1; Q3], where Me is the median, Q1 and Q3 are the first (25%) and third (75%) quartiles, respectively. In this case, non-parametric Mann-Whitney U-test was used in assessing statistical significance of differences between two

Table 1. Characteristics of patients in the main group and comparison group

Таблица 1. Характеристика пациентов основной группы и группы сравнения

| Показатели / Indicators | Основная группа / Main group (n=28) | Группа сравнения / Comparison group (n=72) | p |
|--|-------------------------------------|--|----------------------------------|
| Вес при рождении, г / Birth weight, g | 990,0 [810,0–1100,0] | 1145,0 [945,0–1340,0] | p=0,008* |
| Длина тела при рождении, см / Body length at birth, cm | 35,0 [31,5–38,0] | 37,0 [34,5–40,0] | p=0,014* |
| Срок гестации / Gestation period | 26,50 [25,00–28,50] | 29,00 [27,50–31,00] | p=0,001* |
| Тяжелая асфиксия (оценка по APGAR 3 и менее на 1-й минуте) (абс., %) / Severe asphyxia (APGAR score 3 or less at 1st minute) (abs., %) | 9 (32,1%) | 15 (20,8%) | 0,234 |
| Инвазивная ИВЛ (абс., %) / Invasive AVL (abs., %) | 25 (89,3%) | 46 (63,9%) | 0,012* OR=6,32 |
| Инотропная поддержка (абс., %) / Inotropic support (abs., %) | 13 (46,4%) | 17 (23,6%) | 0,025* OR=4,99 |
| ЭНМТ (абс., %) / ELBM (abs., %) | 20 (71,4%) | 26 (36,1%) | 0,001* OR=0,226 |
| Дотация СЗП (абс., %) / FFP subsidy (abs., %) | 4 (14,3%) | 6 (8,3%) | 0,449 |
| Иммунотерапия (абс., %) / Immunotherapy (abs., %) | 6 (21,4%) | 18 (25%) | 0,401 |

* Значения статистически значимые. / Values are statistically significant.

Примечание: ИВЛ — искусственная вентиляция легких; СЗП — свежемороженая плазма; ЭНМТ — экстремально низкая масса тела.

* Values are statistically significant.

Note: AVL — artificial lung ventilation; ELBM — extremely low body weight; FFP — fresh frozen plasma

independent samples. In this case, nonparametric Mann-Whitney U-criterion was used to assess statistical significance of differences between two independent samples. Friedman criterion was used for "before-after" studies (when studying indices of OPP markers in dynamics on the 1st, 3rd, and 7th days) which is a nonparametric analog of repeated-measures analysis of dispersion. Nominal data were compared using Pearson's χ^2 criterion. Odds Ratio (OR) was used as a quantitative measure when comparing relative indices. OR is defined as the ratio of the probability (odds) of an event occurring in a group exposed to a risk factor to the probability of an event occurring in the control group.

Differences were considered statistically significant at a significance level of $p < 0.05$.

Since b2-microglobulin is supposed to be one of the main diagnostically important markers, the sample size of patients was based on the b2-microglobulin data. Required number of patients for comparing b2-microglobulin levels depending on AKI was determined by Lehr's formula for average values (at a given research power of 90%) and by the formula for calculating the sample size when comparing two averages.

The value of the minimal clinically significant difference of b2-microglobulin concentration in urine of patients with and without AKI as well as standard deviation (3.4) was substituted into the formula. The value was determined from the pilot study involving 20 patients, it was equal to 3.69 mg/L. Thus, the minimum sample size was calculated, which amounted to 19 patients for each group (main and comparison groups), so the sample size of 100 patients is sufficient.

RESULTS

Acute kidney injury was detected in 28 preterm neonates participating in the research. Newborns with AKI were significantly more frequently diagnosed with ELBW ($p=0.001$, $OR=0.226$), and had shorter gestational age (26.50 [25.00–28.50], ($p=0.001$)). The severity of their condition required more intensive care: artificial lung ventilation (ALV) in 89.3% ($p=0.012$, $LS=6.32$), inotropic support in 46.4% of cases ($p=0.025$, $LS=4.99$).

Commonly accepted criteria of AKI (diuresis and serum creatinine levels), as well as serum cystatin C and urine b2-microglobulin values were analyzed in dynamics (Table 2).

Diuresis remained normal in both groups, significantly increasing by the end of the early neonatal period. No cases of oliguria were observed. Meanwhile, all newborns received infusion therapy from the first day of life in accordance with clinical recommendations. In case of haemodynamic instability, drugs with inotropic action (mainly dopamine at a starting dose of 4–5 mcg/kg per minute) were prescribed.

The same children from the main group showed increased laboratory markers during the first week. However, timing and values of the first increase differed (Table 3).

However, there is no definite agreement on the normal value of serum creatinine in extremely premature neonates. In case of preterm newborns, the normal value of serum creatinine is less than 45 $\mu\text{mol/l}$, whereas normal values for neonates with a gestational age of less than 32 weeks are considered to be higher than 120 $\mu\text{mol/l}$ [17].

Therefore, dynamics is most important for diagnosing AKI, i.e., the increase in creatinine level in

Table 2. Diuresis dynamics (ml/kg/h)

Таблица 2. Динамика диуреза (мл/кг/час)

| Группа пациентов / Patient group | 1-е сутки / 1st day | 3-и сутки / 3rd day | 7-е сутки / 7th day | p |
|--|---------------------|---------------------|---------------------|--|
| Основная группа / Main group (n=28) | 3,10 [2,55–4,15] | 5,00 [4,50–5,80] | 5,70 [4,20–6,40] | <0,001* $p_{1-2}=0,001$ $p_{2-3}=0,419$ $p_{1-3}<0,001$ |
| Группа сравнения / Comparison group (n=72) | 3,75 [2,79–4,30] | 4,95 [4,40–5,45] | 5,65 [5,25–6,50] | <0,001* $p_{1-2}<0,001$ $p_{2-3}=0,007$ $p_{1-3}<0,001$ |

* Значения статистически значимые.

* Values are statistically significant.

Table 3. Dynamics of serum creatinine level ($\mu\text{mol/l}$)

Таблица 3. Динамика уровня сывороточного креатинина (мкмоль/л)

| Группа пациентов / Patient group | 1-е сутки / 1st day | 3-и сутки / 3rd day | 7-е сутки / 7th day | p |
|--|---------------------|----------------------|-----------------------|--|
| Основная группа / Main group (n=28) | 38,00 [28,00–42,50] | 91,00 [70,00–103,00] | 124,50 [79,00–155,00] | <0,001* $p_{1-2} < 0,001$ $p_{2-3} = 0,001$ $p_{1-3} < 0,001$ |
| Группа сравнения / Comparison group (n=72) | 42,50 [33,50–46,50] | 57,00 [52,00–70,0] | 52,50 [41,00–67,50] | 0,155 |

* Значения статистически значимые.

* Values are statistically significant.

Table 4. Serum Cystatin C level (ng/ml)

Таблица 4. Уровень сывороточного цистатина С (нг/мл)

| Группа пациентов / Patient group | 1-е сутки / 1st day | 3-и сутки / 3rd day | 7-е сутки / 7th day | p |
|--|---------------------|---------------------|---------------------|--|
| Основная группа / Main group (n=28) | 1,85 [1,72–2,02] | 2,06 [1,74–2,16] | 2,27 [2,07–2,66] | <0,001* $p_{1-2} < 0,001$ $p_{2-3} < 0,001$ $p_{1-3} < 0,001$ |
| Группа сравнения / Comparison group (n=72) | 1,57 [1,34–1,94] | 1,52 [1,32–1,90] | 1,84 [1,40–2,12] | <0,001* $p_{1-2} < 0,001$ $p_{2-3} = 0,014$ $p_{1-3} < 0,001$ |

* Значения статистически значимые.

* Values are statistically significant.

relation to the basal one. This approach is common for all classifications of acute kidney injury.

Serum creatinine levels did not exceed 50 $\mu\text{mol/l}$ in all patients on the first day. Controls had even a slightly higher creatinine level. Serum creatinine increased on average 2.5-fold by the third day of life, and by the end of the first week of life — 3-fold in controls. Serum creatinine remained stable in the comparison group.

Dynamics of serum cystatin C levels showed a different pattern (Table 4).

The cystatin C level was significantly higher in the main group as early as on the first day of life. Moreover, its values increased significantly in dynamics. At the same time, reference intervals of serum cystatin C, according to the literature, are 1.34–2.57 mg/l for premature newborns and 1.36–2.23 mg/l for full-term newborns [19].

Urine b2-microglobulin study was used to diagnose tubule abnormalities (Table 5).

Similar changes were also shown in the study of b2-microglobulin level. However, the differences between the main group and the comparison group were even more significant, and the dy-

namics within the group during the first week of life were less pronounced.

At the same time, the literature data on the level of b2-microglobulin in newborns are also limited. The level of b2-microglobulin equal to 1.5+0.8 mg/L at the age of 1–2 days and 1.8+0.3 mg/L at the age of 3–5 days in healthy newborns is considered normal [20]. Marker levels in extremely premature neonates must be clarified.

ROC-analysis was performed to determine the diagnostic significance of renal damage markers with the determination of sensitivity and specificity of the models, as well as separating values for each marker on the 1st, 3rd, and 7th day.

According to ROC-analysis, the creatinine level can be considered prognostically significant for AKI development not earlier than the third day of life. The area under the curve was 0.313; 0.824 and 0.924 on the 1st, 3rd, 7th day, respectively. The sensitivity of the models on the 3rd, 7th day was 75 and 71.4%, specificity was 72.2 and 72%. Separation value: 70.5 $\mu\text{mol/L}$; 92.5 $\mu\text{mol/L}$. Fig. 1 shows the results of ROC-analysis.

Table 5. Urine b2-microglobulin level (mg/L)

Таблица 5. Уровень б2-микроглобулина (мг/л)

| Группа пациентов / Patient group | 1-е сутки / 1st day | 3-и сутки / 3rd day | 7-е сутки / 7th day | p |
|--|---------------------|---------------------|---------------------|--|
| Основная группа / Main group (n=28) | 6,24 [4,16–11,56] | 6,66 [4,58–11,45] | 6,90 [5,33–12,50] | <0,001* p ₁₋₂ =0,053 p ₂₋₃ <0,001 p ₁₋₃ =0,003 |
| Группа сравнения / Comparison group (n=72) | 2,55 [1,05–5,65] | 4,27 [0,95–15,90] | 2,33 [0,94–6,92] | 0,026* p ₁₋₂ =0,808 p ₂₋₃ =0,004 p ₁₋₃ =0,273 |

* Значения статистически значимые.

* Values are statistically significant.

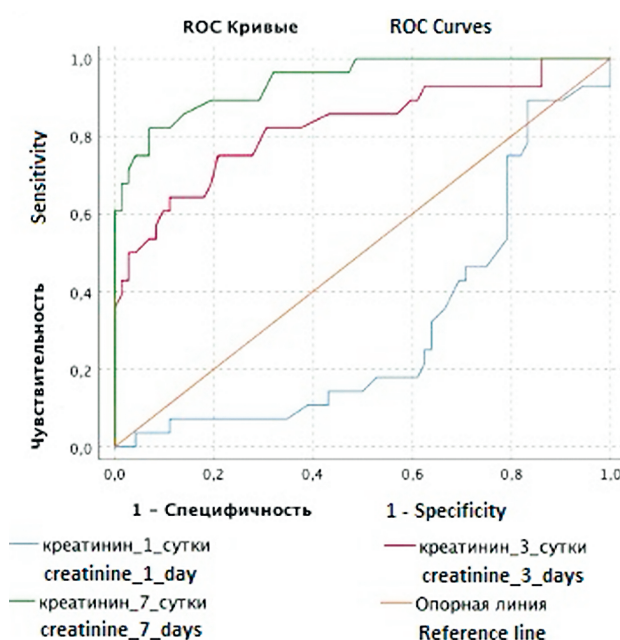


Fig. 1. ROC-curve of the prognostic significance of creatinine level at 1, 3 and 7 days of life in the diagnosis of AKI

Рис. 1. ROC-кривая прогностической значимости уровня креатинина на 1-е, 3-и, 7-е сутки жизни в диагностике ОПП

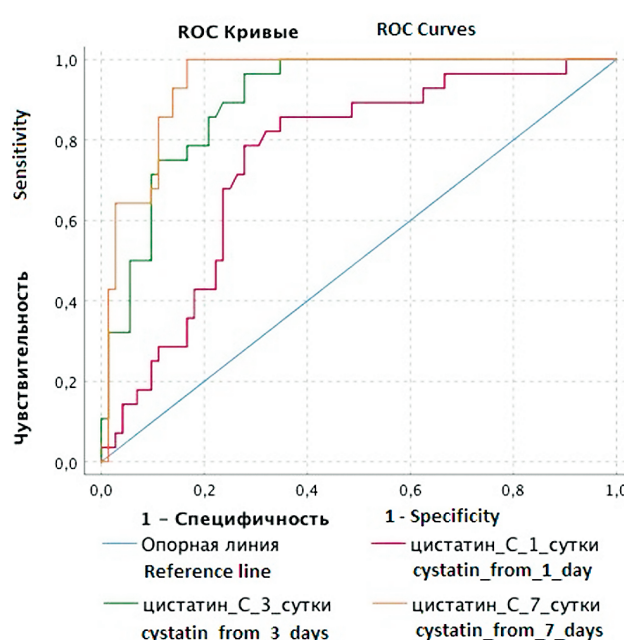


Fig. 2. ROC-curve of the prognostic significance of cystatin C levels at 1, 3 and 7 days of life in the diagnosis of AKI

Рис. 2. ROC-кривая прогностической значимости уровня цистатина С на 1-е, 3-и, 7-е сутки жизни в диагностике ОПП

When examining the diagnostic significance of cystatin C level, the area under the curve on the 1st, 3rd, and 7th days was 0.751, 0.901, and 0.943, respectively. The sensitivity of the models was 78.6, 82.1, and 92.9%. The specificity was 70.8, 79.2 and 86.1%. The separating value was 1.663 ng/mL; 1.733 ng/mL; 2.006 ng/mL. The result is presented in Fig. 2.

When examining the diagnostic significance of b2-microglobulin level, the area under the curve on the 1st, 3rd, 7th day was 0.725, 0.720, and 0.817, respectively. The sensitivity of the models was 60.7, 71.4, 82.1%. The specificity was 63.9,

62.5, 70.8%. The separating value was 4.638 mg/L; 5.245 mg/L; 5.280 mg/L. The obtained ROC curve is shown in Fig. 3.

According to the results of ROC-analysis, we can conclude that the most significant markers for the diagnosis of AKI starting from the first day of life are cystatin C and b2-microglobulin. Moreover, their diagnostic significance increases by the 7th day of life.

DISCUSSION

The number of patients diagnosed with acute kidney injury amounted to 28% in the research,

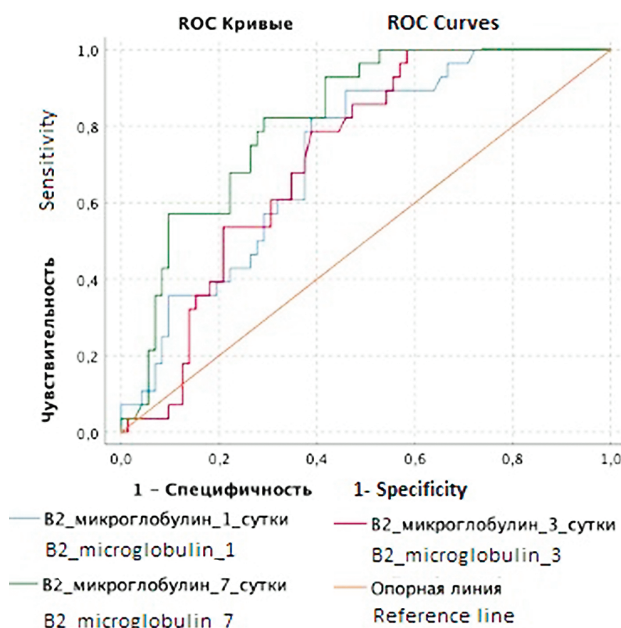


Fig. 3. ROC-curve of the prognostic significance of b2-microglobulin levels on days 1, 3 and 7 of life in the diagnosis of AKI

Рис. 3. ROC-кривая прогностической значимости уровня б2-микроглобулина на 1-е, 3-и, 7-е сутки жизни в диагностике ОПП

which does not exceed the average percentage of patients with AKI in other studies.

This pathology was more frequently detected in neonates with severe prematurity and birth weight less than 1000 g. It confirms the higher vulnerability and low compensatory capacity of kidneys due to morphological and functional immaturity, as well as the presence of a smaller number of functioning tubules. This group of patients also required more intensive therapy: invasive respiratory support, including high-frequency oscillatory ventilation, and inotropic drugs to maintain stable hemodynamics. The obtained data are consistent with the results of other studies [21], which revealed a close relationship between the progression of respiratory failure and the development of AKI in premature neonates. Acute injury makes a significant contribution to the development of multi-organ dysfunction syndrome.

All examined premature neonates did not show oliguria in the early neonatal period. Taking into account an inotropic drug which was added to treatment in case of hemodynamic instability, adequate renal blood flow and, accordingly, glomerular filtration were preserved. Similarly, the persistent high rate of diuresis in the early neonatal period might be associated with reduced water reabsorption at the tubule

apparatus. The results obtained indicated that diuresis had a low significance in diagnosing AKI in premature neonates in the first 7 days of life.

The levels of serum creatinine, serum cystatin C, and b2-microglobulin in urine were increased in the same patients at different periods of time. Thus, each laboratory parameter can be used to diagnose AKI in premature neonates, since it can reflect the damage of both the glomerular and tubule renal apparatus. The absence of generally accepted reference intervals for creatinine, cystatin C, and b2-microglobulin in preterm infants does not allow us to assume AKI. It is necessary to assess the increase of markers in dynamics in case of a single study. Creatinine had the lowest sensitivity among the markers analyzed in the research: its increase was detected in all premature neonates with AKI by the 7th day of life. Cystatin C and b2-microglobulin showed higher sensitivity. Determination of b2-microglobulin in urine should also be emphasized. Its concentration of was significantly higher in the main group starting from the first day of life, and it intensively increased in dynamics by the 7th day of life. No blood sampling is required for b2-microglobulin determination, which is especially important for patients with VLBW and ELBW.

CONCLUSION

1. Acute kidney injury. According to KDIGO criteria it was diagnosed in 28% of very low and extremely low birth weight infants in critical condition in the first week of life.

2. All patients in our study had non-oliguric AKI.

3. Cystatin C, creatinine and b2-microglobulin were increased in the same newborns with AKI, indicating pathological involvement of both glomerular and tubule renal apparatus.

4. Increase of serum creatinine in relation to basal creatinine. It started on the 3rd day of life in neonates with AKI.

5. Increase in serum cystatin C and urine b2-microglobulin levels in the main group in the first day of life and its subsequent growth allow to consider them as sensitive AKI markers.

6. It is necessary to determine normal levels of serum creatinine, cystatin C, and b2-microglobulin in premature infants with extremely low and very low birth weight in order to use them more effectively in the diagnosis of AKI.

ADDITIONAL INFORMATION

Author contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

Competing interests. The authors declare that they have no competing interests.

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ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

Информированное согласие на публикацию. Авторы получили письменное согласие законных представителей пациентов на публикацию медицинских данных.

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