UDC 616.12-007.2:616-002.1]-053.32-07-036.4
DOI: 10.24061/2413-4260.XII.4.46.2022.7

THE DIAGNOSTIC VALUE OF URINE GELATINASE-ASSOCIATED LIPOCALIN AS A BIOMARKER FOR ACUTE KIDNEY INJURY IN PRETERM INFANTS WITH HEMODYNAMICALLY SIGNIFICANT PATENT DUCTUS ARTERIOSUS

O. Yu. Obolonska[1], T.P. Borysova[1], Vakulenko L.I.[1], O.I. Obolonsky[2]

Dnipro State Medical University[1],
CI "Regional Medical Center of Family Health DRC"[2]
(Dnipro, Ukraine)

Summary *Timely diagnosis of acute kidney injury (AKI) is problematic due to difficulties in using the "Kidney Disease: Improving Global Outcomes (KDIGO) guideline" modified for neonates, requiring the search for non-invasive markers and their diagnostic capacity assessment. Preterm infants with hemodynamically significant patent ductus arteriosus (HSPDA) are highly vulnerable to developing AKI. Renal biomarker neutrophil gelatinase-associated lipocalin (NGAL) in urine enables diagnosis of AKI, although literature data on the possibility of its use are somewhat contradictory.*

The aim of this study *was to identify diagnostic capacity of the renal biomarker NGAL in urine for the early diagnosis of AKI in preterm infants with HSPDA.*

Materials and methods *A total of 29 preterm infants (gestational age 29-36 weeks) with HSPDA were examined at the Department of Anesthesiology and Neonatal Intensive Care on the first, third and tenth day. The patients were assigned to groups depending on the development of AKI: the AKI group with any degree of severity - 14 children, and the group without AKI - 15 children. To determine the influence of HSPDA size on the level of urine NGAL, the children were further divided based on ductal size: HSPDA diameter ≥ 2 mm - 11 children, and HSPDA diameter ≤ 2 mm - 18 children. The urine NGAL level was quantitatively measured using sandwich enzyme-linked immunosorbent assay according to the manufacturer's licensed instructions (ELISA Kit, 96, USA).*

The study has a positive conclusion of the biomedical ethics commission of the Dnipro State Medical University (protocol of the commission meeting No. 2 dated October 19, 2022)/

A set of statistical research methods was used to solve the tasks and check the initial assumptions, namely: for independent samples - the Mann-Whitney test, for dynamic assessment - the Wilcoxon signed rank test. The test for the normality of the distribution of quantitative samples was carried out using the Kolmogorov-Smirnov test. Statistical processing of the results was carried out using the software product STATISTICA 6.1® (StatSoft Inc., serial number AGAR909E415822FA).

The work was carried out within the scope of complex research works of the Department of Propaedeutics of Children's Diseases and Pediatrics 2 of the Dnipro State Medical University "Development of criteria for early diagnosis and prediction of comorbid kidney damage in children with somatic and infectious diseases" (state registration number 0119U100836) execution 09.2019-12.2023.

Results. *In the group of children with AKI, the significant increase in the urine NGAL level was observed from the first to the tenth day. For example, the urine NGAL level was 2.2 times ($p<0.002$) and 2.4 times ($p<0.001$) increased on the third and tenth day, respectively, as compared to that on the first day, while in the group without AKI, urine NGAL level was 1.3 times ($p<0.04$) increased on the third day compared to that on the first day. On the tenth day, in the group without AKI, the urine NGAL level was increased by 1.6 times ($p<0.007$) compared to that on the first day and by 1.2 times ($p<0.04$) as compared to that on the third day.*

The data obtained were confirmed by the clear correlation between the urine NGAL level and the development of AKI. For instance, the urine NGAL level at the first day was significantly correlated with AKI on the third and on the fifth day: $\rho=0.72$, $p<0.001$ and $\rho=0.75$, $p<0.001$, respectively. On the third day, the urine NGAL level was also significantly correlated with AKI on the third and on the fifth day: $\rho=0.65$, $p<0.001$ and $\rho=0.73$, $p<0.001$, respectively. It was particularly important that the urine NGAL level on the first day was significantly correlated with the maximum stage of AKI: $\rho=0.76$, $p<0.001$.

In preterm infants with HSPDA size > 2 mm, the urine NGAL level on the first day of life was 1.7 times higher than that in children with HSPDA ≤ 2 mm ($p < 0.002$). It was also observed on the third day as in preterm infants with HSPDA size > 2 mm, the urine NGAL level was 2.3 times higher than that in children with HSPDA ≤ 2 mm ($p < 0.001$). On the tenth day, there was a 2.3-fold higher urine NGAL level in the group with ductal diameter > 2 mm as compared to the group with ductal diameter ≤ 2 mm ($p < 0.003$). The correlation between the urine NGAL level and the size of HSPDA has been found to be quite revealing. Notably, on the first day, urine NGAL level was significantly correlated with the HSPDA size: $\rho=0.66$, $p<0.001$, and on the 10th day, it was significantly correlated with the ductal size on the first day: $\rho=0.70$, $p<0.001$. In addition, the urine NGAL level on the first day was significantly correlated with the HSPDA size on the third day: $\rho=0.49$, $p<0.015$. The significant correlation between the urine NGAL level on the third day with the ductal size on the third day has also been revealed: $\rho=0.47$, $p<0.019$. Finally, on the 10th day, the urine NGAL level was significantly correlated with the HSPDA size on the third day: $\rho = 0.46$, $p < 0.022$.

Conclusions. *The elevated urine NGAL level has been found to be a reliable marker of the AKI development in preterm infants with HSPDA: it was 1.7 times ($p<0.001$), 2.8 times ($p<0.001$) and 2.6 times ($p<0.001$) increased on day one, three and ten, respectively, in children with AKI in comparison with those examined without AKI. In preterm infants with HSPDA diameter of > 2 mm on the first day, the urine level of NGAL was significantly increased on the first, third and tenth day.*

Key words: *Preterm Infants; Hemodynamically Significant Patent Ductus Arteriosus; NGAL Urine; Acute Kidney Injury.*

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

Introduction

Acute kidney injury (AKI) occurs in 29 - 70% of preterm infants at intensive care units and leads to a 50% increase in mortality rate [1,7,9,10,12]. Preterm infants with hemodynamically significant patent ductus arteriosus (HSPDA) are highly vulnerable due to left-to-right shunt across the ductus arteriosus, leading to hypoperfusion in end organs including the kidneys [2,3,16]. Timely diagnosis of AKI is problematic due to difficulties in using the "Kidney Disease: Improving Global Outcomes (KDIGO) guideline" modified for neonates, since its criteria are based solely on an elevated serum creatinine level and a decreased urine output. In fact, physiological postnatal oliguria may occur in newborns on the first day of life. In addition, an increase in serum creatinine level within the first 48 hours of life can be expected, and the diagnosis of AKI could not therefore be made until the third day of life in infants [9,19]. Taking into consideration that serum creatinine is relatively lacking sensitivity to AKI and does not reflect real-time changes in glomerular filtration rate, since its functional decrease can reach 50% before a valuable increase in serum creatinine level, new biomarkers for AKI are being currently studied [3,5]. Various markers are being presently proposed to diagnose AKI, but no one can serve as reliable. Neutrophil gelatinase-associated lipocalin (NGAL) is one of these renal biomarkers, which increases 2-4 hours after the development of AKI and enables its diagnosis in the early stages [4,13,22]. Meanwhile, data on the possibility of its use are somewhat contradictory, for example, A. Sellmer et al. [8,17,20,21] have found that urine NGAL was not useful diagnostic marker for AKI detection in extremely preterm neonates. The need for the use of nephrotoxic drugs in preterm infants causes an increase in urinary NGAL, which confirms damage to the kidneys [11]. All of the above requires further study of the informative value of this marker [6, 23].

The aim of this study was to identify diagnostic capacity of the renal biomarker NGAL in urine for the early diagnosis of AKI in preterm infants with HSPDA.

Materials and methods

A prospective, cohort study was conducted on the basis of the Department of Anesthesiology and Neonatal Intensive Care of the CI "Dnipro Regional Children's Clinical Hospital" and was approved by the Medical Ethics Board of the hospital. The study was carried out in accordance with the principles of the Declaration of Helsinki. Inclusion criteria were preterm infants with the gestational age of 29-36 weeks and HSPDA, informed written consent signed by parents for their child to participate in the study. Exclusion criteria were congenital malformations, grade III-IV intracerebral or intraventricular hemorrhages, neonatal sepsis, severe perinatal asphyxia, skin diseases, intrauterine growth retardation.

A total of 29 preterm infants with HSPDA were examined on the first, third and tenth day. The patients were assigned to groups depending on the development of AKI: the AKI group with any degree of severity - 14 children, and the group without AKI - 15 children. In order to determine the influence of HSPDA size on the level of urine NGAL, the children were further divided based on ductal size: HSPDA diameter ≥2 mm - 11 children, and HSPDA diameter ≤2 mm - 18 children. The urine NGAL level was quantitatively measured using sandwich enzyme-linked immunosorbent assay according to the manufacturer's licensed instructions (ELISA Kit, 96, USA).

Clinical examination and treatment of preterm infants were performed following accepted standard methods [14,15]. Medical therapy for HSPDA closure included ibuprofen in 24 preterm infants and restrictive fluid therapy in 5 preterm neonates [16].

Criteria for HSPDA were a large ductus arteriosus (>1.5 mm in neonates weighing <1500 g or > 1.4 mm/kg in neonates weighing >1500 g), a ductal left-to-right shunt and an increasing pulsatile trans-ductal shunt pattern, a left atrium-to-aortic root ratio >1.4, increased diastolic flow in the main pulmonary artery >0.2 m/s, retrograde diastolic flow in the post-ductal descending aorta, regional blood flow disorders [2].

AKI diagnosis and severity stratification was carried out according to the KDIGO stages by the criteria of its neonatal modification [19]. Serum concentrations of creatinine were measured on the first, third, fifth, seventh, tenth day, and urine output was assessed every 6-12 hours for this purpose.

A set of statistical research methods was used to address the tasks identified and check baseline assumptions, namely, for independent samples - the Mann-Whitney test, for assessing the dynamics - the Wilcoxon signed-rank test. All numerical data sets were tested for normality of distribution with the Kolmogorov-Smirnov test. Statistical analysis of the results was done using the STATISTICA 6.1®.

The study has a positive conclusion of the biomedical ethics commission of the Dnipro State Medical University (protocol of the commission meeting No. 2 dated October 19, 2022), which decided that the scientific research of Obolonska O.Yu. considered to be in accordance with generally accepted standards of morality, requirements for observing the rights, interests, and personal dignity of research participants, bioethical standards for working with pediatric patients. There is no risk for research subjects during the work. The legal representatives of the children involved in the research are informed about all aspects related to the purpose, tasks, methods and expected benefit of the research. Laboratory and instrumental research methods are generally accepted, the drugs to be used are approved for use. Experiments on humans were not conducted.

A set of statistical research methods was used to solve the tasks and check the initial assumptions, namely: for independent samples - the Mann-Whitney test, for dynamic assessment - the Wilcoxon signed rank test. The test for the normality of the distribution of quantitative samples was carried out using the Kolmogorov-Smirnov test. Statistical processing of the results was carried out using the software product STATISTICA 6.1® (StatSoft Inc., serial number AGAR909E415822FA).

The work was carried out within the scope of complex research works of the Department of Propaedeutics of Children's Diseases and Pediatrics 2 of the Dnipro State Medical University "Development

of criteria for early diagnosis and prediction of comorbid kidney damage in children with somatic and infectious diseases" (state registration number 0119U100836) execution 09.2019-12.2023.

Results and discussion

The mean gestational age was 32.69 ± 1.22 weeks. The mean body weight at birth was 1878.2 ± 54.55 g (Table 1).

Table 1

Clinical characteristics of the examined patients

Characteristics	Preterm infants with HSPDA, n=29
Gestational age, M±s (Me; Q1-Q3), weeks	32,69 ± 1,22 weeks
(33; 32-34)	1878,2 ± 54,55 (1920; 1620-2437,5)
Weight, M±s (Me; Q1-Q3), g	1878,2 ± 54,55
(1920; 1620-2437,5)	9 (31 %)
Male, n (P)	20 (69 %)
Female, n (P)	9 (31 %)
Apgar score at 1 min, M±s (Me; Q1-Q3), points	6,2±1,27 (7; 5-7)
Apgar score at 5 min, M±s (Me; Q1-Q3), points	6,7±1,05 (7; 6-8)
Respiratory distress syndrome	19 (65,5 %)
Asphyxia	5 (17,25 %)
Intrauterine infection	5 (17,25 %)
Patent ductus arteriosus size ≤ 2 mm on the 1st day	18 (62%)
Patent ductus arteriosus size > 2 mm on the 1st day	11 (38%)

The dynamics of the urine NGAL level depending on the development of AKI is presented in Table 2. The urine NGAL level at day one in preterm infants with HSPDA, who developed AKI on the third or fifth day of life, was 1.7 times higher than that in the group without AKI ($p<0.001$). On the third day, the urine NGAL level in children with AKI was already 2.8 times ($p<0.001$) higher than this indicator in the group without AKI. On the tenth day, this ratio was maintained: the urine NGAL level in AKI children was 2.6 times ($p<0.001$) higher than that in the group of children without AKI.

In the group of children with AKI, a significant increase in the urine NGAL level was observed from the first to the tenth day. For example, the urine NGAL level was 2.2 times ($p<0.002$) and 2.4 times ($p<0.001$) increased on the third and tenth day, respectively, as compared to that on the first day, while in the group without AKI, urine NGAL level was 1.3 times ($p<0.04$) increased on the third day compared to that on the first day. On the tenth day, in the group without AKI, the urine NGAL level was increased by 1.6 times ($p<0.007$) compared to that on the first day and by 1.2 times ($p<0.03$) as compared to that on the third day.

Table 2

Dynamics of the urine NGAL level in preterm infants with HSPDA depending on the presence of AKI, M±m (Me; Q1-Q3), ng/ml

Urine NGAL level	Total, n=29	Without AKI, n=15	With AKI, n=14	p<
On day 1	82,3±37,22 (67; 55,5-100)	61,2±23,36 (56; 53-61)	104,9±36,48 (98,5; 78-122,5)	0,001
On day 3	153,7±111,96 (91; 61,5-216)	82,8±74,55 (66; 53-77)	229,7±94,82 (208,5; 176-297,3)	0,001
On day 10	169,7±129,39 (111; 68-222)	95,7±97,00 (69; 61-84)	249,0±113,27 (210; 185,5-302)	0,001
P I-III <	0,001	0,04	0,002	
P I-X <	0,001	0,007	0,001	
P III-X <	no	no	no	

Note. *When comparing independent samples, the Mann-Whitney test was used; when comparing paired data, the Wilcoxon signed-rank test was used; ('no' - no significant difference was observed).*

The data obtained were confirmed by a clear correlation between the urine NGAL level and the development of AKI. For instance, the urine NGAL level at the first day was significantly correlated with AKI on the third and on the fifth day: $\rho=0.72$, $p<0.001$ and $\rho=0.75$, $p<0.001$, respectively. On the third day, the urine NGAL level was significantly correlated with AKI on the third and on the fifth day: $\rho=0.65$, $p<0.001$ and $\rho=0.73$, $p<0.001$, respectively. It was particularly important that the urine NGAL level on the first day was significantly correlated with the maximum stage of AKI: $\rho=0.76$, $p<0.001$.

An increase in the urine NGAL level on the first day in children with AKI may be interpreted as a result of damage to the proximal renal tubules with a decrease in NGAL reabsorption and an increase in its urine level.

The dysfunction of the proximal renal tubules with reduced NGAL reabsorption processes was evidenced by the progressive and significant increase

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)

in the urine NGAL level in infants with AKI identified on the third and tenth day. High levels of urine NGAL without a downward tendency on the tenth day in children with AKI could be explained by an increase in the synthesis of NGAL, which plays a central role in ensuring the survival of injured cells of the proximal tubules for their further proliferation [22].

Previous studies have found a relationship between the patent ductus arteriosus size and the development of AKI [3]. Therefore, it was important to examine the dynamics of the urine NGAL level in preterm neonates depending on the HSPDA size (Table 3).

Table 3

Dynamics of the urine NGAL level in preterm children depending on the HSPDA size on the first day, M±m (Me; Q_1-Q_3), ng/ml

Urine NGAL level	HSPDA size on the first day		p<
	≤ 2 mm, n=18	> 2 мм, n=11	
On day 1	> 2 mm, n=11	109,7±40,20 (101; 78-154)	0,002
On day 3	101,8±82,64 (66,5; 55,3-110)	238,7±103,36 (211; 179-334)	0,001
On day 10	114,4±96,80 (80; 65,5-130,3)	260,2±128,19 (233; 178-344)	0,03
p I-III <	0,02	0,004	
p I-X <	0,002	0,004	
p III-X <	no	no	

Note. *When comparing independent samples, the Mann-Whitney test was used; when comparing paired data, the Wilcoxon signed-rank test was used ('no' - no significant difference was observed).*

In both groups, regardless of the HSPDA size, the urine NGAL levels were increased from the first to the tenth day. In the group with HSPDA > 2 mm, the urine level of NGAL on the third day was 2.2 times ($p<0.004$) higher than that on the first day. On the tenth day, this index was 2.4 times higher compared to the first day ($p<0.004$). Meanwhile, in the group with HSPDA ≤ 2 mm, the urine NGAL level on the third day was 1.5 times ($p<0.02$) higher than that on the first day, and on the tenth day, the urine NGAL level was 1.7 times higher ($p <0.002$) as compared to the first day.

A correlation between the urine NGAL level and the size of HSPDA has been found to be quite revealing. Notably, on the first day, urine NGAL level was significantly correlated with the HSPDA size: $\rho=0.66$, $p<0.001$, and on the 10th day, it was significantly correlated with the ductal size on the first day: $\rho=0.70$, $p<0.001$. In addition, the urine NGAL level on the first day was significantly correlated with the HSPDA size on the third day: $\rho=0.49$, $p<0.015$. A significant correlation between the urine NGAL level on the third day with the ductal size on the third day has also been revealed: $\rho=0.47$, $p<0.019$. Finally, on the 10th day, the urine NGAL level was significantly correlated with the HSPDA size on the third day: $\rho = 0.46$, $p < 0.022$.

Thus, the data obtained by us have confirmed the fact that renal hypoperfusion associated with the HSPDA size during the first day resulted in the elevated urine NGAL level for ten days. In the early days, that was a manifestation of the proximal renal tubule injury, and on the tenth day, that was a sign of increased renal NGAL production for the proliferation of the injured proximal tubule epithelial cells.

Our data confirm the data of Zwiers A.J [24], that urine NGAL can be a marker of acute kidney injury in children and predict adverse prognostic consequences [18].

Conclusions.

1. The elevated urine NGAL level has been found to be a reliable marker of the AKI development in preterm infants with HSPDA: it was 1.7 times ($p<0.001$), 2.8 times ($p<0.001$) and 2.6 times ($p<0.001$) increased on day one, three and ten, respectively, in children with AKI in comparison with those examined without AKI.

2. In preterm infants with HSPDA diameter of > 2 mm on the first day, the urine level of NGAL was significantly increased on the first, third and tenth day.

Prospects for further research. To examine further the issues of early diagnosis of AKI in children born prematurely with HSPDA and associated comorbidities.

Conflict of interest. The authors declare no conflict of interest.

Sources of funding. The authors did not receive support from any organization for the submitted work. None of the authors obtained support from kit manufacturers.

Література

1. Askenazi DJ, Halloran BA, Heagerty PJ, Schmicker RH, Brophy P, Juul SE, et al. Gestational age, sex, and time affect urine biomarker concentrations in extremely low gestational age neonates. Pediatr Res. 2022;92(1):151-67. doi: 10.1038/s41390-021-01814-x

2. Бойченко АД, Гончарь МО, Кондратова ІЮ, Сенаторова АВ. Критерії діагностики гемодинамічно значущої відкритої артеріальної протоки у недоношених новонароджених. Neonatol. hìr. perinat. med. 2015;1(5):24-7. doi: 10.24061/2413-4260.V.1.15.2015.4

3. Борисова ТП, Оболонська ОО, Сурков ДМ. Гостре пошкодження нирок у недоношених дітей з гемодинамічно значу-

щою артеріальною протокою. Neonatol. hìr. perinat. med. 2020;4(38):26-34. doi: 10.24061/2413-4260.X.4.38.2020.2

4. Chen CN, Chou CH, Jeng SF, Tsai IJ, Chen PC, Chen CY, et al. Urinary Neutrophil Gelatinase-Associated Lipocalin Levels in Neonates. Pediatr Neonatol. 2016;57(3):207-12. doi: 10.1016/j.pedneo.2015.09.003

5. Li A, Yi B, Liu Y, Wang J, Dai Q, Huang Y, et al. Urinary NGAL and RBP Are Biomarkers of Normoalbuminuric Renal Insufficiency in Type 2 Diabetes Mellitus. J Immunol Res [Internet]. 2019[cited 2022 Nov 12];2019:5063089. Available from: https://www.hindawi.com/journals/jir/2019/5063089/ doi: 10.1155/2019/5063089

6. Capelli I, Vitali F, Zappulo F, Martini S, Donadei C, Cappuccilli M, et al. Biomarkers of Kidney Injury in Very-low-birth-weight Preterm Infants: Influence of Maternal and Neonatal Factors. In Vivo. 2020;34(3):1333-9. doi: 10.21873/invivo.11910

7. Годованець ЮД, Бабінцева АГ, Нікорич СІ. Гостре пошкодження нирок новонароджених: невирішені питання діагностики та стратифікації ступеня тяжкості патології. Neonatol. hìr. perinat. med. 2014;3(13):89-94. doi: 10.24061/2413-4260.IV.3.13.2014.16

8. Gunasekara TDK, De Silva PMC, Ekanayake EMD, Thakshila WAK, Pinipa RAI, Sandamini PMM, et al. Urinary biomarkers indicate pediatric renal injury among rural farming communities in Sri Lanka. Sci Rep [Internet]. 2022[cited 2022 Nov 12];12(1):8040. Available from: https://www.nature.com/articles/s41598-022-10874-w.pdf doi: 10.1038/s41598-022-10874-w

9. Jetton JG, Boohaker LJ, Sethi SK, Wazir S, Rohatgi S, Soranno DE, et al. Incidence and outcomes of neonatal acute kidney injury (AWAKEN): a multicentre, multinational, observational cohort study. Lancet Child Adolesc Health. 2017;1(3):184-94. doi: 10.1016/S2352-4642(17)30069-X

10. Majed B, Bateman DA, Uy N, Lin F. Patent ductus arteriosus is associated with acute kidney injury in the preterm infant. Pediatr Nephrol. 2019;34(6):1129-39. doi: 10.1007/s00467-019-4194-5

11. Martini S, Vitali F, Capelli I, Donadei C, Raschi E, Aiello V, et al. Impact of nephrotoxic drugs on urinary biomarkers of renal function in very preterm infants. Pediatr Res. 2022;91(7):1715-22. doi: 10.1038/s41390-021-01905-9

12. Макулова АИ. Острое почечное повреждение у новорожденных: современный взгляд на проблему. Педиатрия. 2018;97(1):147-52. doi: 10.24110/0031-403X-2018-97-1-147-152

13. Mikulić V, Rogić D, Mikulić I, Ljubić K, Ćuk A, Tomić V, et al. Urine neutrophil gelatinase-associated lipocalin concentration in healthy newborns during the first three postnatal days. Biochem Med (Zagreb) [Internet]. 2020[cited 2022 Nov 15];30(3):030706. Available from: https://www.biochemia-medica.com/en/journal/30/3/10.11613/BM.2020.030706 doi: 10.11613/BM.2020.030706

14. Про затвердження та впровадження медикотехнологічних документів зі стандартизації медичної допомоги з початкової, реанімаційної і післяреанімаційної допомоги новонародженим в Україні. Наказ МОЗ України від 28.03.2014р. № 225 [Інтернет]. Київ: МОЗ України; 2014 [цитовано 2022 Лис 18]. Доступно: https://zakon.rada.gov.ua/rada/show/v0225282-14#Text

15. Про затвердження Протоколу медичного догляду за новонародженою дитиною з малою масою тіла при народженні. Наказ МОЗ України від 29.08.2006р. № 584 [Інтернет]. Київ: МОЗ України; 2006 [цитовано 2022 Лис 18]. Доступно: https://zakon.rada.gov.ua/rada/show/v0584282-06#Text

16. Obolonskyi A, Snisar V, Surkov D, Obolonska O, Kapustina O, Dereza K. Management of patent ductus arteriosus in premature infants. Med. perspekt. 2019;24(2):33-40. doi:10.26641/2307-0404.2019.2.170125

17. Parravicini E, Locatelli C, Lorenz JM, Nemerofsky SL, Bateman DA. Is urinary neutrophil gelatinase-associated lipocalin able to predict acute kidney injury episodes in very low birth weight infants in clinical settings? Pediatr Res. 2016;80(5):663-7. doi: 10.1038/pr.2016.138

18. Saeidi B, Koralkar R, Griffin RL, Halloran B, Ambalavanan N, Askenazi DJ. Impact of gestational age, sex, and postnatal age on urine biomarkers in premature neonates. Pediatr Nephrol. 2015;30(11):2037-44. doi: 10.1007/s00467-015-3129-z

19. Selewski DT, Charlton JR, Jetton JG, Guillet R, Mhanna MJ, Askenazi DJ, et al. Neonatal Acute Kidney Injury. Pediatrics [Internet]. 2015[cited 2022 Nov 16];136(2):e463-73. Available from: https://publications.aap.org/pediatrics/article-abstract/136/2/e463/33766/Neonatal-Acute-Kidney-Injury?redirectedFrom=fulltext doi: 10.1542/peds.2014-3819

20. Sellmer A, Bech BH, Bjerre JV, Schmidt MR, Hjortdal VE, Esberg G, et al. Urinary Neutrophil Gelatinase-associated Lipocalin in the evaluation of Patent Ductus Arteriosus and AKI in Very Preterm Neonates: a cohort study. BMC Pediatr [Internet]. 2017[cited 2022 Nov 16];17(1):7. Available from: https://bmcpediatr.biomedcentral.com/counter/pdf/10.1186/s12887-016-0761-0.pdf doi: 10.1186/s12887-016-0761-0

21. Suchojad A, Tarko A, Smertka M, Majcherczyk M, Brzozowska A, Wroblewska J, et al. Factors limiting usefulness of serum and urinary NGAL as a marker of acute kidney injury in preterm newborns. Ren Fail. 2015;37(3):439-45. doi: 10.3109/0886022X.2014.996109

22. Suzuki M, Wiers KM, Klein-Gitelman MS, Haines KA, Olson J, Onel KB, et al. Neutrophil gelatinase-associated lipocalin as a biomarker of disease activity in pediatric lupus nephritis. Pediatr Nephrol. 2008;23(3):403-12. doi: 10.1007/s00467-007-0685-x

23. Wang Z, Jin L, Shen T, Zhan S. The Value of Urine NAG, NGAL Combined with Serum Cys-C in Early Diagnosis of Neonatal Hyperbilirubinemia-related Acute Kidney Injury. Signa Vitae. 2020;16(2);109-13. doi: 10.22514/sv.2020.16.0055

24. Zwiers AJ, de Wildt SN, van Rosmalen J, de Rijke YB, Buijs EA, Tibboel D, et al. Urinary neutrophil gelatinase-associated lipocalin identifies critically ill young children with acute kidney injury following intensive care admission: a prospective cohort study. Crit Care [Internet]. 2015[cited 2022 Nov 16];19(1):181. Available from: https://ccforum.biomedcentral.com/counter/pdf/10.1186/s13054-015-0910-0.pdf doi: 10.1186/s13054-015-0910-0

ДІАГНОСТИЧНА ЗНАЧУЩІСТЬ БІОМАРКЕРУ ЛІПОКАЛІН, АСОЦІЙОВАНИЙ З ЖЕЛАТИНАЗОЮ НЕЙТРОФІЛІВ, У СЕЧІ ПРИ ГОСТРОМУ ПОШКОДЖЕННІ НИРОК У НЕДОНОШЕНИХ ДІТЕЙ З ГЕМОДИНАМІЧНО ЗНАЧУЩОЮ ВІДКРИТОЮ АРТЕРІАЛЬНОЮ ПРОТОКОЮ

О. Ю. Оболонська [1], Т. П. Борисова [1], Л. І. Вакуленко [1], О. І. Оболонський[2]

Дніпровський державний медичний університет[1],
КП «Регіональний медичний центр родинного здоров'я » ДОР» [2]
(м. Дніпро, Україна)

Резюме

Вступ. Проблема своєчасної діагностики гострого пошкодження нирок (ГПН) за неонатальної модифікації KDIGO потребує пошуку та визначення діагностичної можливості неінвазивних маркерів. Особливо уразливою групою щодо ГПН є недоношені діти з гемодинамічно значущою відкритою артеріальною протокою(ГЗВАП). Ренальний біомаркер ліпокалін, ассоційований з желатиназою нейтрофілів (NGAL), у сечі дає можливість діагностувати ГПН, але можливості його використання є суперечливими за даними літератури.

Мета дослідження — визначити діагностичні можливості ренального біомаркеру NGAL в сечі для ранньої діагностики

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)

гострого пошкодження нирок у недоношених дітей з гемодинамічно значущою відкритою артеріальною протокою

Матеріали і методи дослідження. Обстежено 29 недоношених дітей з ГЗВАП (гестаційний вік 29-36 тижнів), що знаходились на лікування у відділенні анестезіології та інтенсивної терапії новонароджених, на першу, третю та десяту добу. Пацієнти були розподілені на дві групи залежно від наявності ГПН. Розподіл хворих проведено залежно від розвитку ГПН: група з ГПН різного ступеню тяжкості — 14 дітей, група без ГПН — 15 дітей. Для визначення впливу розміру ГЗВАП на рівень NGAL в сечі проведено розподіл дітей з розміром ГЗВАП більше 2 мм -11 дітей та 2 мм і менше -18 дітей.Досліджено рівень NGAL у сечі кількісним методом, заснованим на іммуноферментному аналізі за методом «сендвіч» за ліцензованими методиками виробника (ELISAKit, 96, USA).

Дослідження має позитивний висновок комісії з питань біомедичної етики Дніпровського державного медичного університету (протокол засідання комісії № 2 від 19 жовтня 2022 року).

Використовувався комплекс статистичних методів дослідження, зокрема: для незалежних вибірок – критерій Манна-Уїтні, для оцінки динаміки – критерій знакових рангів Вілкоксона. Перевірку на нормальність розподілу кількісних вибірок проведено з використанням критерію Колмогорова—Смірнова. Статистичну обробку результатів проводили за допомогою програмного продукту STATISTICA 6.1® (StatSoft Inc., серійний № AGAR909E415822FA).

Робота виконана в межах комплексної науково-дослідної роботи кафедри пропедевтики дитячих хвороб та педіатрії 2 Дніпровського державного медичного університету «Розробка критеріїв ранньої діагностики та прогнозування коморбідного ураження нирок у дітей з соматичними та інфекційними захворюваннями» (державний реєстраційний № 0119U100836), термін виконання 09.2019 р.-12.2023 р..

Результати дослідження. У групі дітей з ГПН спостерігається значне зростання рівня NGAL сечі з першої до десятої доби. Так, на третю добу показник NGAL сечі підвищився у 2,2 рази порівняно з першою добою ($p<0,002$), а на десяту добу - у 2,4 рази ($p<0,001$) відносно першої доби. Тоді як в групі без ГПН показник NGAL сечі на третю добу збільшився у 1,3 рази ($p<0,04$) порівняно з першою добою. На десяту добу в групі без ГПН NGAL сечі підвищився в 1,6 рази ($p<0,007$) у порівнянні з першою добою та 1,2 рази - з третьою добою.

Отримані дані підтверджуються чіткою кореляційною залежністю між рівнем NGAL сечі та розвитком ГПН. Так, рівень NGAL сечі на першу добу значуще корелює з ГПН на третю добу: $\rho=0,72$, $p< 0,001$, та на 5-ту добу: $\rho=0,75$, $p<0,001$. На третю добу NGAL сечі значуще корелює з ГПН на третю добу: $\rho=0,65$, $p<0,001$ та на 5-ту добу: $\rho=0,73$, $p<0,001$. Особливо важливо, що рівень NGAL сечі на першу добу значуще корелює з максимальною стадією ГПН: $\rho=0,76$, $p<0,001$.

У недоношених дітей з розміром ГЗВАП > 2 мм на першу добу життя рівень NGAL сечі був в 1,7 рази більший ніж рівень NGAL у дітей з ГЗВАП ≤ 2 мм ($p<0,002$). Це спостерігається і на третю добу: у недоношених дітей з розміром ГЗВАП > 2 мм рівень NGAL сечі був в 2,3 рази більший ніж рівень NGAL у дітей з ГЗВАП ≤ 2 мм ($p<0,001$). На 10 добу спостерігався в 2,3 рази вищий рівень NGAL сечі в групі з діаметром протоки > 2 мм ніж в групі з протокою ≤ 2 мм ($p<0,003$). Виявилася показовою кореляційна залежність показників NGAL сечі та розміру ГЗВАП. Так, NGAL сечі на першу добу значуще корелює з розміром ГЗВАП на першу добу: $\rho=0,66$, $p<0,001$, а на 10-ту добу значуще корелює з розміром протоки на першу добу: $\rho=0,70$, $p<0,001$. Також, NGAL сечі на першу добу значуще корелює з ГЗВАП на третю добу: $\rho=0,49$, $p<0,015$. Доведена значуща кореляція NGAL сечі на третю добу з розміром ВАП на третю добу: $\rho=0,47$, $p<0,019$. На 10-ту добу NGAL сечі значуще корелює з розміром ВАП на третю добу: $\rho = 0,46$, $p< 0,022$.

Висновки. Підвищений рівень NGAL сечі є достовірним маркером розвитку ГПН у недоношених дітей з ГЗВАП: він підвищувався в 1,7 рази ($p<0,001$) на першу добу, в 2,8 рази ($p<0,001$) на третю та в 2,6 рази ($p<0,001$) на десяту добу у дітей з ГПН в порівнянні з обстежуваними без ГПН. У недоношених дітей з діаметром ГЗВАП > 2 мм на першу добу рівень NGAL сечі демонструє значне підвищення на першу, третю та десяту добу.

Ключові слова: недоношені діти; гемодинамічно значуща відкрита артеріальна протока; NGAL сечі; гостре пошкодження нирок.

Contact Information:
Olha Obolonska - MD, PhD, assistant of Professor of the Department of pediatrics 2, Dnipro State Medical University (Dnipro, Ukraine)
e-mail o_obolonskaja@ukr.net
ORCID: https://orcid.org/0000-0001-9863-1828

Tamara Borysova - MD, Professor, Head of the department of Pediatrics 2, SI «Dnepropetrovsk Medical Academy of the Ministry of Health of Ukraine» (Dnipro, Ukraine)
e-mail: toma.inform@gmail.com
ORCID: https://orcid.org/0000-0001-8347-4348

Liudmyla Vakulenko - PhD, MD, Professor of the Department of pediatrics 2, Dnipro State Medical University (Dnipro, Ukraine)
e-mail: vakulenkol@ukr.net
ORCID: https://orcid.org/0000-0003-3823-6134

Oleksii Obolonskyi - DM, PhD, anesthesiologist of the neonatal intensive care unit with the field neonatology team of the Dnipropetrovsk Regional Children's Clinical Hospital (Dnipro, Ukraine)
e-mail: a_obolonskij@ukr.net
ORCID: https://orcid.org/0000-0002-3190-0402

Контактна інформація:
Оболонська Ольга Юріївна — доктор філософії, асистент кафедри педіатрії 2 Дніпровського державного медичного університету (м.Дніпро, Україна)
e-mail: o_obolonskaja@ukr.net
ORCID: https://orcid.org/0000-0001-9863-1828

Борисова Тамара Петрівна – доктор медичних наук, професор, завідувачка кафери педіатрії 2 Дніпровського державного медичного університету (м.Дніпро, Україна)
e-mail: toma.inform@gmail.com
ORCID:https://orcid.org/0000-0001-8347-4348

Вакуленко Людмила Іванівна - доктор медичних наук, професор кафедри педіатрії 2 Дніпровського державного медичного університету (м.Дніпро, Україна)
e-mail: vakulenkol@ukr.net
ORCID: https://orcid.org/0000-0003-3823-6134

Оболонський Олексій Іванович - к.мед.н., лікар анестезіолог дитячий відділення інтенсивної терапії новонароджених з виїзною неонатологічною бригадою КНП «Регіональний медичний центр родинного здоров'я » ДОР.
e-mail: a_obolonskij@ukr.net
ORCID: https://orcid.org/0000-0002-3190-0402

Надійшло до редакції 25.09.2022 р.
Підписано до друку 21.11.2022 р.