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DIAGNOSTIC VALUE OF ADDITIONAL MARKERS FOR ACUTE KIDNEY INJURY IN PRETERM NEONATES WITH PATENT DUCTUS ARTERIOSUS

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Summary

Acute kidney injury (AKI) is a common complication with high mortality rates among preterm infants at neonatal intensive care units. Identification of preterm newborns who are at risk for developing AKI is essential not only for early diagnosis and treatment, but also for prevention since AKI significantly worsens an outcome of any disease. Studying the information content of additional non-invasive markers for AKI, in particular, parameters of regional renal oxygen saturation ($RrSO_2$) and Doppler estimation of blood flow in the main renal vessels is interesting.

The aim of the study *was to evaluate the diagnostic performance of additional markers (measurements of $RrSO_2$ and blood flow in the main renal vessels using Doppler ultrasonography) in diagnosing of AKI and its degree of severity in preterm newborns with patent ductus arteriosus (PDA).*

Material and methods. *A single-center, open, prospective cohort study examined 66 preterm infants born at 29-36 weeks of gestational age (GA) undergoing treatment at the Department of Anesthesiology and Intensive Care for newborns. Inclusion criteria: preterm newborns born between 29-36 week's gestation with hemodynamically significant PDA (hsPDA), a written informed consent to participate in this study provided by parents. Exclusion criteria: congenital malformations, grades III-IV intracerebral or intraventricular hemorrhages, neonatal sepsis, severe perinatal asphyxia, skin diseases, fetal growth restriction. Clinical examination and treatment of children was carried out according to current guidelines. The modified neonatal KDIGO criteria were used to diagnose and characterize the severity of AKI.*

Doppler ultrasound measurements were done to reveal the presence, size, and hemodynamic significance of PDA. Color Doppler ultrasonography was performed to evaluate intrarenal hemodynamics upon hospital admission of children prior to prescribing ibuprofen, and in the case of hsPDA detection – on the 3rd and 10th days of life. Blood flow in the area from the main renal artery to the interlobar renal artery of the right kidney was measured including peak systolic velocity (PSV), end diastolic velocity (EDV), and the resistive index (RI) was calculated. $RrSO_2$ values were recorded using near-infrared spectroscopy (NIRS) and renal fractional tissue oxygen extraction (rFTOE) was estimated within 24 hours on the 1st, 3rd and 10th days of life.

The study received a positive conclusion of the Biomedical Ethics Commission of Dnipro State Medical University (minutes of the Commission meeting No. 8 dated 04.26.2023), which considered the scientific study as being consisted with generally accepted norms of morality, human rights requirements, interests and personal dignity of the study participants, bioethical standards of work with pediatric patients. There was no risk for study participants when performing examinations. Legal guardians of the children enrolled in the study were informed about all aspects related to the purpose, tasks, methods and expected benefits of the study. Laboratory and instrumental methods of examinations were generally adopted, medicines planned to be prescribed were licensed for use. Experiments with human subjects were not carried out.

Statistical processing of the results was realized using a software product STATISTICA 6.1® (StatSoft Inc., serial number AGAR909E415822FA). A set of statistical analysis methods based on parametric and non-parametric criteria was used for solving the tasks of testing a hypothesis on differences between mean values, methods of assessing the effect with an alternative form of a reaction result, correlation analysis (Spearman's rank correlation), cluster analysis.

The study was conducted within the bounds of complex research activities at the Department of Propaedeutics of Children's Diseases and Pediatrics No. 2 of 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), the study period 09.2019-12.2023.

Results. *Group 1 (with moderate renal impairment) included 43 patients with a GA of 33.27±0.43 weeks. AKI was detected in 12 patients (27.9%), of those, 10 (23.3%) children developed stage 1 AKI according to the modified neonatal KDIGO criteria, and stage 2 AKI were classified in 2 (4.7%) patients. Group 2 was composed of 5 patients (infants with severe renal impairment) with a GA of 31.60±0.75 weeks. All the children in this group had different stages of AKI (stages 1-3), which progressed to acute renal failure after 7 days. Mortality in this group was 60%. Group 3 consisted of 18 patients (infants with mild renal impairment) with a GA of 32.86±0.29 weeks. AKI stage 1 was diagnosed in 2 (11.1%) patients, and AKI was not detected in 16 (88.9%) of them. On the 1st day of life, the PSV and EDV values of the interlobar artery in children of the group with mild renal impairment were higher than those in children with a severe course of the disease ($p<0.05$). This trend regarding PSV continued on the 3rd day. Doppler parameters of renal blood flow, namely a decrease in EDV of the interlobar artery to 1.96 ± 2.22 cm/s and PSV to 8.14 ± 2.71 cm/s on the 1st day of life, as well as a decrease in PSV to 17,60 ±3.82 cm/s, EDV to 3.40±0.82 cm/s and increased*

RI up to 0.80±0.04 of the main renal artery were found to be early non-invasive predictors of severe AKI in preterm newborns on day of life 1 ($p<0.05$). Non-invasive monitoring of $RrSO_2$ and calculation of rFTOE revealed a decrease in renal oxygenation by NIRS in preterm infants with PDA on the 1st day of life to 53.60 ± 1.11%, as well as rFTOE values of 0.45 ± 0.01, that was prognostically unfavorable with regard to the course of AKI ($p<0.05$). The highest value of $RrSO_2$ on day 10 (91.8±0.81%) and the lowest rFTOE value (0.05 ± 0.01) ($p<0.05$) might indicate irreversible changes associated with reduced oxygen utilization due to destruction of cells and be used as a screening tool to detect and assess ductal steal phenomenon caused by hsPDA and the development of AKI.

Conclusions. *A decrease in the rate of diuresis within the first 5 days of life as well as a two fold increase in the level of serum creatinine on postnatal days 3 and 10 were the main, but late markers for the development of severe kidney impairment in preterm newborns. Doppler parameters of renal blood flow, namely decreased EDV and PSV in the interlobar artery on the 1st day of life, and decreased PSV, EDV and increased RI in the main renal artery has been found to be early non-invasive predictors of severe AKI in preterm newborns on the 1st day of life. Non-invasive monitoring of $RrSO_2$ and calculation of rFTOE can serve as screening tools for detection and assessment of hsPDA-related ductal steal phenomenon and the development of AKI.*

Key words: *Preterm Newborns; Renal Blood Flow; Regional Renal Oxygen Saturation (RrSO2); Renal Fractional Tissue Oxygen Extraction(rFTOE); Acute Kidney Injury.*

Introduction

Acute kidney injury (AKI) is a common complication with high mortality rates among preterm infants at neonatal intensive care units. The incidence of AKI detection has been reported at 70% in this category of patients with rates of mortality up to 60%. This issue is greatly exacerbated with the declining birthrate and increasing percentage of premature births [2, 3, 9]. Identification of preterm newborns who are at risk for developing AKI is fundamental not only for early diagnosis and treatment, but also for prevention since AKI significantly worsens outcomes of any disease.

According to the KDIGO neonatal modification, the criteria for AKI are determined by the magnitude of changes in serum creatinine concentration or urine output (oliguria) [9, 17, 29]. It is believed that the level of serum creatinine is not diagnostically sensitive enough to identify early stages of AKI, considering the occurrence of increased serum creatinine only with the development of irreversible morphological changes in the renal tissue. The functional decrease in glomerular filtration rate (GFR) does not reflect changes in real-time GFR, and the latter indicator can be 50% at the time of a noticeable increase in serum creatinine level [12, 15, 27]. Moreover, the diagnosis of AKI based on an increase in the serum creatinine level of more than 26.5 μmol/l within 48 hours is limited, since AKI can be documented no earlier than the 3rd postnatal day. Meanwhile, it increases the risk of mortality by 50% [24, 28].

Hence, there seems to be a constant search for new early and preferably non-invasive criteria for AKI, as well as an assessment of the criterion validity degree and selection of the most sensitive and specific ones. Aside from needing early diagnosis and appropriate treatment for kidney function decline in preterm newborns, an important factor that defines an approach to identifying additional diagnostic and prognostic markers for AKI is the necessity to provide potentially nephrotoxic therapy for such neonates.

In preterm newborns, especially with hemodynamically significant patent ductus arteriosus (hsPDA), AKI is most often a consequence of prerenal cause – systemic arterial steal syndrome [4, 30]. Clinical consequences of PDA functioning depend on the volume of left-right blood shunting and the capability of a newborn organism to compensate for hemodynamic disorders. Compensatory mechanisms are represented by an ability to increase left cardiac output due to enhancing myocardial contractility or increasing heart rate and to redistribute reduced blood flow by lowering diastolic pressure with consequent vasculature constriction and reduction of end-organ perfusion [6], which, in turn, can be a pathogenetic component of kidney damage and requires instrumental control, in particular ultrasound (US) examinations and measurements of regional tissue oxygen saturation using near-infrared spectroscopy (NIRS).

The Doppler ultrasound technique of blood flow examination allows the velocity of blood flow estimation in rather large-caliber vessels and indirect measurement of the oxygen uptake rate in tissues but does not indicate the degree of its utilization. NIRS measurement of regional tissue oxygen saturation, in particular, regional renal tissue oxygen saturation ($RrSO_2$), could be used to complement conventional monitoring (pulse oximetry, dopplerography) of end organ perfusion [8, 11, 13, 14, 21, 22]. Assessment of tissue oxygen supply and consumption is diagnostically significant, but its interpretation is constrained by changes in the cardiovascular system during postnatal adaptation, vasomotor immaturity, as well as anatomical and physiological features of preterm newborns [2, 16, 33].

All of the aforementioned areas still need to be further studied on the informativeness of additional non-invasive markers for AKI, especially parameters of regional renal tissue oxygen saturation and Doppler examination of blood flow in the main renal vessels.

The aim of the study was to evaluate the diagnostic performance of additional markers (measurements of $RrSO_2$ and blood flow in the main renal vessels using Doppler ultrasonography) in diagnosing of AKI and its degree of severity in preterm newborns with PDA.

Material and methods. A total of 66 preterm infants (gestational age (GA) of 29-36 weeks) undergoing treatment at the Department of Anesthesiology and Intensive Care for newborns of ME "Regional Medical Center of Family Health" DRC", Dnipro, were enrolled in the study.

The study was designed as open, single-center, prospective, cohort. Inclusion criteria: premature

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newborns with gestational age of 29-36 weeks with PDA who were in the intensive care unit due to respiratory distress syndrome (RDS), moderate asphyxia, signs of intrauterine infection (IUI) (pneumonia), presence of signed informed consent of parents for research. Exclusion criteria: congenital malformations, intracerebral and intraventricular hemorrhages of the III-IV degree, neonatal sepsis, severe asphyxia during childbirth, skin diseases, fetal growth retardation. The need to introduce such exclusion criteria is due to their severe impact on systemic and renal hemodynamics (the impossibility of isolating the effect of PDA) and the impossibility of using additional examination methods. Clinical examination and treatment of children was carried out according to current guidelines [25, 26].

To induce hsPDA closure, the following were used: fluid restriction (for all the children), ibuprofen (prescribed to 32 children at the end of the 1st day of life in doses of 10-5-5 mg/kg/day intravenously or 20-10-10 mg/kg/day rectally for a three-day course) [23].

The modified neonatal KDIGO criteria were used to diagnose and characterize the severity of AKI [29]. Diuresis was calculated every 6 hours daily, serum creatinine was measured on days 1, 3 and 10.

Doppler ultrasound measurements were done to reveal the presence, diameter, and hemodynamic significance of PDA [4, 30]. Color Doppler ultrasound scanning of the renal vascular bed was performed using a microconvex sensor with a frequency of 5-8 MHz ("TOSHIBA" Nemso XG model SSA-580A (Japan) from the main renal artery to the interlobar renal artery of the right kidney, which was visualized from the flank region in the child's position on the back immediately upon admission of the child to the department before prescribing ibuprofen, and in case of detection of GZVAP – on the third and tenth days of life. Blood flow in the area from the main renal artery to the interlobar renal artery of the right kidney was measured including peak systolic velocity (PSV), end diastolic velocity (EDV), and the resistive index (RI) was calculated.

$RrSO_2$ values were recorded using near-infrared spectroscopy (NIRS), and renal fractional tissue oxygen extraction (rFTOE) was estimated within 24 hours on the 1st, 3rd and 10th day of life using the "Somanetics INVOS 5100 C" device (USA). After localization of the kidney with the help of ultrasound examination and measurement of dopplerometric indicators, daily assessment of renal oxygenation (RrSO2) was carried out.

The study received a positive conclusion of the Biomedical Ethics Commission of Dnipro State Medical University (minutes of the Commission meeting No. 8 dated 04.26.2023), which considered the scientific study as being consisted with generally accepted norms of morality, human rights requirements, interests and personal dignity of the study participants, bioethical standards of dealing with pediatric patients. There was no risk for study participants when performing examinations. Legal guardians of the infants enrolled in the study were informed about all aspects related to the purpose, tasks, methods and expected benefits of the study. Laboratory and instrumental methods of examinations were generally adopted, medicines planned to be prescribed were licensed for use. Experiments with human subjects were not carried out.

A set of statistical analysis methods based on parametric and non-parametric criteria was used for solving the tasks of testing a hypothesis on differences between mean values, methods of assessing the effect with an alternative form of a reaction result, correlation analysis (Spearman's rank correlation), cluster analysis. Statistical processing of the results was realized using a software product STATISTICA 6.1® (StatSoft Inc., serial number AGAR909E415822FA).

The study was conducted within the bounds of complex research activities at the Department of Propaedeutics of Children's Diseases and Pediatrics No. 2 of 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), the study period 09.2019-12.2023.

Results and discussion

In total, 66 children with a GA of 27-35 weeks were included in the examination: 11 infants (16.6%) with GA of 27-31 weeks, 44 (66.8%) infants with GA of 32-34 weeks and 11 (16.6%) infants with GA of 35 weeks. The group had a predominance of boys (60.6%). A mean body weight of the examined infants was 1888.97±335.0 g: 11 infants (16.6%) weighing up to 1500 g, 55 infants (83.3%) weighing 1501-2700 g. A median 1-minute Apgar score was 6.03 (5-7) points in neonates, 5-minute – 6.85 (6-8) points. The main diagnoses were: RDS in 49 children (74.2%), moderate birth asphyxia in 7 (10.6%), IUI in 10 (15.2%).

On postnatal day 1, PDA without signs of hemodynamic significance was detected in 32 infants (48.5%), hsPDA was diagnosed in 34 (51.5%) infants. A PDA diameter (Me; Q1-Q3) was of 2.28 (1.6-2.5) mm on the 1st day. On postnatal day 3, PDA without signs of hemodynamic significance was identified in 5 infants (7.6%), hsPDA – in 3 (4.6%). A PDA diameter (Me; Q1-Q3) was of 0.29 (0-1.0) mm on the 3rd day.

Clinical and paraclinical parameters of kidney functions in the examined neonates are presented in Table 1.

The characteristics of renal blood flow were closely dependent on the size of PDA on the first day of life. Thus, peak systolic velocity (PSV) of blood flow had an inverse relationship between the size of PDA and this indicator on the first day of life in the main renal artery ($r_s = –0.483$, $p<0.01$) and interlobar renal artery ($r_s = –0.410$, $p< 0.000$).

Considering that the GA of the examined infants was different, at the first stage, the work was focused on analysis of associations (correlation analysis, Spearman's method) between the GA and the presented clinical and paraclinical parameters of kidney functions. Only significant ($p<0.05$) weak correlations were found between GA and indicators of diuresis on the 3rd day of life ($r_s=0.299$), $RrSO_2$ on the 1st day of life ($r_s=0.253$), RI in the interlobar artery on the 10th day of life ($r_s = –0.248$). Regarding the principal marker for the diagnosis of AKI in newborns, namely the level of serum creatinine, no significant correlations were found between this indicator and GA.

Table 1

Parameters of kidney functions in the examined newborns

Parameters, (M±m)	Values
Diuresis, (ml/kg/h)	
Day 1, 1-6 hours	1,08±0,05
Day 1, 6-12 hours	1,78±0,09
Day 3, 1-6 hours	2,34±0,14
Day 3, 6-12 hours	2,78±0,18
Day 10, 6-12 hours	3,47±0,18
Serum creatinine level, (μmol/L)	
Day 1	66,04±4,55
Day 2	80,66±6,68
Day 10	65,89±5,87
Regional renal oxygen saturation, $RrSO_2$, %	
Day 1	72,98±1,94
Day 2	80,26±0,92
Day 10	86,70±0,88
Renal fractional tissue oxygen extraction, rFTOE	
Day 1	0,24±0,02
Day 2	0,17±0,01
Day 10	0,11±0,01
Blood flow in the interlobar renal artery, (cm/s)	
PSV on day 1	15,33±0,51
EDV on day 1	4,66±0,30
IR on day 1	0,71±0,01
PSV on day 3	18,26±0,58
EDV on day 3	5,61±0,29
IR on day 3	0,69±0,02
PSV on day 10	22,39±0,60
EDV on day 10	6,89±0,38
IR on day 10	0,70±0,01
Blood flow in the main renal artery, (cm/s)	
PSV on day 1	24,03±0,69
EDV on day 1	7,82±0,50
IR on day 1	0,67±0,02
PSV on day 3	27,40±0,70
EDV on day 3	8,59±0,44
IR on day 3	0,68±0,01
PSV on day 10	30,67±0,61
EDV on day 10	9,84±0,43
IR on day 10	0,68±0,01

Given the clinical and paraclinical heterogeneity of the groups, a lack of clear correlations between GA and other AKI parameters, statistical processing of these data was carried out using cluster analysis (tree clustering to determine the number of clusters and a ball model to represent characteristics of clusters). Groups were allocated based on the same combination of clinical and paraclinical parameters of kidney functions, which differed significantly between groups ($p<0.05$) (table 2).

Group 1 included 43 patients with a GA of 33.27±0.43 weeks. Average weight 1826.33 ±0.346. RDS was present in 33 (76.7%) patients, asphyxia in 3 patients (7%), IUI in 7 (16.3%).AKI was detected in 12 patients (27.9%), of those, 10 (23.3%) infants developed stage 1 AKI according to the modified neonatal KDIGO criteria, and stage 2 AKI were classified in 2 (4.7%) patients. Loss of renal functions or mortalities were not documented in this group (moderate renal impairment group).

Group 2 was composed of 5 patients with a GA of 31.60±0.75 weeks. Average weight 1726.33 ±0.259. RDS was present in 4 (80%) patients, asphyxia in 1 patient (20%). All the infants in this group had different stages of AKI (stages 1-3), which progressed to acute renal failure after 7 days. Mortality in this group was 60% (3 infants with severe AKI died), that gave grounds to define this group as having severe renal impairment.

Group 3 consisted of 18 infants with a GA of 32.86±0.29 weeks. Average weight 1811.27 ±0.359. RDS was present in 12 patients (66.6%), asphyxia in 3 patients (16.7%), intrauterine infection in 3 (16.7%). AKI stage 1 was diagnosed only in 2 (11.1%) of them, and AKI was not detected in the other 16 (88.9%) infants. There were no mortalities in this group, the disease course was the most favorable, and all renal alterations were reversible (mild renal impairment group).

Table 2

Groups of preterm newborns with the same combination of clinical and paraclinical parameters of kidney functions

Parameters	Group 1 (n=43)	Group 2 (n=5)	Group 3 (n=18)
Regional renal oxygen saturation, $RrSO_2$ (%)			
Day 1	69,80 ± 2,41	53,60 ± 1,11	85,94 ± 1,42
Day 3	78,32 ± 1,11*	73,40 ± 1,83*	86,38 ± 1,12*
Day 10	87,67 ± 6,82 *^	91,80 ± 0,81*^	82,88 ± 1,62*^
Renal fractional tissue oxygen extraction, rFTOE			
Day 1	0,27 ± 0,02	0,45 ± 0,01	0,11 ± 0,02
Day 3	0,19 ±0,01*	0,24 ± 0,02*	0,10 ± 0,01*
Day 10	0,10 ±0,01*^	0,05 ± 0,01*^	0,14 ± 0,01*^
Blood flow in the interlobar renal artery, (cm/s)			
PSV on day 1	15,30 ± 0,62	8,14± 2,71	17,39 ± 0,63
EDV on day 1	4,50 ± 0,41	1,96 ± 2,22	5,77 ±0,41
PSV on day 3	18,66 ± 0,63*	9,60 ±1,21*	19,72 ± 1,11*
PSV on day 10	22,20 ± 0,64*^	15,20 ±1,62*^	24,83 ± 1,12*^
EDV on day 10	6,41± 0,42*	3,00 ±0,82*	9,11±0,73*
Blood flow in the main renal artery, (cm/s)			
PSV on day 1	23,57 ± 0,73	17,60 ±3,82	26,88 ± 1,31
EDV on day 1	7,06 ± 0,63	3,40 ± 0,82	10,833 ±0,83
RI on day 1	0,70 ± 0,02	0,80 ± 0,04	0,58 ± 0,03
EDV on day 3	8,00 ± 0,53*	6,60 ± 1,53*	10,55 ± 0,91*
Diuresis, (ml/kg/h)			
Day 1, 1-6 hours	1,11 ± 0,07	0,66 ± 0,12	1,10 ± 0,07
Day 1, 6-12 hours	1,81 ± 0,12	1,06 ± 0,33	1,90 ± 0,15
Day 3, 1-6 hours	2,17 ± 0,16*	1,04 ± 0,41*	3,10 ± 0,21*
Day 3, 6-12 hours	2,59 ± 0,21*	1,3 ± 0,72*	3,63 ± 0,21*
Day 10, 6-12 hours	3,79 ±0,21*^	1,4 ± 0,60^	3,28 ± 0,32^
Serum creatinine level, (μmol/L)			
Day 1	73,00 ± 6,74	72,60± 9,73	54,55± 6,64
Day 3	83,57 ±7,43*	151,80 ± 35,42*	54,72±8,81
Day 10	62,88±5,82*^	147,20± 9,83*	49,15±3,51

Notes:
**– significant differences from the corresponding parameters on the 1st day, p<0.05;*
^ – significant differences from the corresponding parameters on the 3rd day, p<0.05.

A mean PDA diameter was 1.54±0.2 mm in the group with moderate renal impairment on the 1st day of life, and it was the largest (3.30±1.2 mm, p<0.05) in the group with severe renal impairment compared to other groups (a large diameter as a manifestation of hemodynamic significance). In the group with mild renal impairment, the diameter of PDA was the smallest – 0.75 ± 0.20 mm. By the 3rd day of life, the ductal diameter did not exceed 1.54±0.1 mm, and PDA was not hemodynamically significant (p<0.05) in all the infants. That is, the maximum impact of hsPDA on hemodynamics in the form of ductal steal phenomenon affecting renal blood flow with the subsequent development of AKI was documented in Group 2 (with severe renal impairment). With hsPDA, the development of AKI directly depended on the size of PDA on the first day and its hemodynamic significance (r_s =0.593, p<0.001 and r_s =0.532, p<0.002, respectively).Currently, the literature contains evidence concerning hsPDA effects on the development of AKI due to a decrease in renal perfusion [31, 32].

The highest level of serum creatinine was detected in the group with severe renal impairment as compared to that in other groups (p<0.05) on the 3rd and 10th days of life. And at the same time, there was a significant increase in these values in groups with moderate and severe renal impairment as compared to the 1st day of life, but it was the group with severe renal impairment that the highest increase in creatinine level (151.80±35.42 μmol/l versus 72.60±9.73 μmol/l) was revealed on the 3rd day that demonstrated the progression of AKI into acute renal failure. The diagnosis of AKI has been proven to be based on an increase in serum creatinine level of more than 26.5 μmol/l within 48 hours thereby increasing the risk of death by 50% [28]. Thus, the increase in serum creatinine

on postnatal days 3 and 10 was directly correlated with the development of severe renal impairment in the group.

On the 1st day of life, the PSV and EDV values in the interlobar artery were greater in infants of the group with mild renal impairment than those in infants with a severe course of the disease ($p<0.05$). This trend regarding PSV continued on the 3rd day. However, the EDV values in the interlobar artery did not differ statistically on the 3rd day in the presented groups. But in the meantime, the systolic and diastolic blood flow parameters in the interlobar artery were increased in all the groups on the 10th day, as well as significant differences in PSV and EDV were found in the groups with the maximum values in Group 3 being maintained.

The lowest PSV values in the interlobar artery were noted in the group with severe renal impairment on the 1st (9.60±1.2 cm/s) and 3rd day (1.96±2.2 cm/s) of life ($p<0.05$). So, that could be considered to be a predictor of the AKI development (ischemic changes in arterial blood flow). Moreover, in the group with severe renal impairment on postnatal day 10, there were areas where absolutely no blood flow signal was detected in the interlobar artery, which had been reported in the literature as a symptom characteristic of nephrosclerosis [18].

In the group with moderate renal impairment, the blood flow parameters in the interlobar artery on the 1st day were higher compared to those in the group with severe renal impairment, but lower than in the group with mild impairment ($p<0.05$). Similar dynamics continued up to the 3rd day of life, and PSV did not differ significantly between groups with mild and moderate renal impairment on postnatal day 10.

The Doppler-derived renal RI assessing renal perfusion did not differ statistically between the groups when examining the interlobar artery, so it could not serve as a marker for AKI.

A similar trend occurred in the analysis of blood flow parameters of the main renal artery, namely, the highest values of systolic and diastolic blood flow on the 1st day of life were noted in the group with mild renal impairment (26.88±1.31 cm/s and 10.83± 0.83 cm/s, respectively) ($p<0.05$), the lowest blood flow parameters – in the group with severe manifestations of AKI (17.60±3.82 cm/s and 3.40±0.82 cm/s, respectively). In the group with moderate renal impairment, blood flow indicators were intermediate (23.57±0.68 cm/s and 7.06±0.63 cm/s, respectively). The blood flow in the renal artery did not differ statistically between groups on other days of life.

The most indicative was a change in Doppler RI in the main renal artery on the 1st day of life depending on the degree of renal impairment. The most severe renal impairment was revealed on postnatal day 1 (lethal outcomes were also registered) at RI 0.80±0.04 in the main renal artery, while moderate renal impairment was considered at RI 0.70±0.02. In the group with mild renal impairment on the 1st day, a RI value was of 0.58±0.03 (significantly less than in the other groups, $p<0.05$). Thus, increased RI values in the main renal artery on the 1st day were associated with the development of severe renal impairment.

$RrSO_2$ values were the highest (85.94±1.36%) in the group with mild renal impairment on the 1st day of life, while in Group 1 with moderate impairment, RrSO2 was 19% (69.80±2.36%) less, and the lowest values of $RrSO_2$ (53.60±1.11%) were observed in the group with severe impairment on the 1st day, which was 38% less than in the group with mild impairment. It is particularly noteworthy that all patients with daily mean $RrSO_2$ below 53.60 ± 1.12% later developed severe stages of renal impairment. By the 3rd day of life, $RrSO_2$ was on average 15% higher in Group 3 than that in Group 2 and 9% higher than that in Group 1. On postnatal day 10 (when PDA had been already functionally or medically closed in infants), the ratio of $RrSO_2$ values was radically changed since the indicator was the highest in the group with severe renal impairment, which was prognostically unfavorable (Table 2).

This may suggest that $RrSO_2$ values were decreased on postnatal day 1 in groups with severe and moderate renal impairment due to ischemic environment and reduced oxygen delivery to tissues due to PDA, and especially hsPDA. On the 10th day, after ductal closure, the ratio of $RrSO_2$ values was shifted completely, and this was probably driven by reduced oxygen utilization in tissues injured by reperfusion in infants with severe renal impairment.

$RrSO_2$ values and their prognostic significance have been much debated issues recently. The findings of the group with mild renal impairment are consistent with study results of $RrSO_2$ evaluations in healthy stable preterm infants during the first weeks of life [7]. Hypoxic conditions cause both inadequate tissue perfusion and oxygenation which, as a rule, are worsened by subsequently occurring reperfusion. Later, with sufficient blood flow, oxygen utilization by tissues improves, which brings a somewhat lower indicators of peripheral oxygenation (10-15%), that has also been proven by researchers in their studies [10, 19]. However, there are situations when a sufficient level of oxygen supply is unable to restore tissues, post-reperfusion alterations are occurred, manifesting in signs of impaired kidney functions (increased serum creatinine level), persistent blood flow disorders (areas with lack of blood flow in the interlobar artery), reduced utilization of oxygen by tissues with reactive oxygen species accumulation. The latter is a prognostically unfavorable sign.

In our opinion, increased values of rFTOE may indicate either a decrease in oxygen delivery to the renal tissue with constant oxygen uptake, or an increase in tissue oxygen uptake with a lack of its delivery, since rFTOE is the ratio of the two variables (arterial oxygen saturation and $RrSO_2$ values), so that is consistent with the data obtained in a study by Harer M. W. and Chock V. Y. [11]. The significant decrease in rFTOE may indicate an increase in renal blood flow and oxygen delivery to the renal tissue under condition of blood flow restoration in combination with a reduced oxygen utilization following cell destruction. While assessing oxygen delivery using $RrSO_2$, it can be expected that such dynamics of rFTOE represents an increase in oxygen supply with a simultaneous decrease in utilization during reperfusion, and reduced blood flow in some renal areas provides information on the minimal oxygen utilization in infants

with severe renal tissue injury accompanied by reactive oxygen species accumulation [5].

In the group with mild renal impairment, rFTOE fluctuated narrowly, increasing from 0.11±0.02 to 0.14±0.01 ($p<0.05$), which indicated an increase in tissue oxygen uptake during the first 10 days of life. In the group with moderate impairment, rFTOE values were more than half decreased over that period, indicating the normalization of blood flow with adequate oxygen consumption. And in the group with maximum renal impairment, rFTOE values were significantly decreased from 0.45±0.01 to 0.05±0.01, ($p<0.05$), and all the infants in this group had the maximum diameter of hsPDA. On postnatal day 10, $RrSO_2$ values were increased and rFTOE values were decreased in preterm infants who had the largest diameter of hsPDA on the 1st day of life. Our findings match the data of a study by M. W. Harer et al. [10, 11], where renal parameters measured with NIRS were shown to be predictors of the AKI development. Therefore, non-invasive monitoring of $RrSO_2$ and calculation of rFTOE could be used as screening tools to detect and assess ductal steal phenomenon caused by hsPDA and predict the development of AKI, that is consistent with the data obtained by Navikienė J. [22].

Conclusions.

1. A decrease in the rate of diuresis within the first 5 days of life as well as a twofold increase in the level of serum creatinine on postnatal days 3 and 10 were the main, but late markers for the development of severe kidney impairment in preterm newborns.

2. Doppler parameters of renal blood flow, namely decreased EDV to 1.96 ± 2.22 cm/s and PSV to 8.14 ± 2.71 cm/s in the interlobar artery on the 1st day of life; decreased PSV to 17.60 ± 3.82 cm/s and EDV to 3.40 ± 0.82 cm/s along with increased RI to 0.80 ± 0.04 in the main renal artery has been found to be early non-invasive predictors of severe AKI in preterm newborns on the 1st day of life.

3. Non-invasive monitoring of $RrSO_2$ and calculation of rFTOE can serve as screening tools for detection and assessment of hsPDA-related ductal steal phenomenon and the development of AKI. Reduced renal oxygenation to 53.60 ± 1.11% and rFTOE values to 0.45 ± 0.01 detected using NIRS in preterm infants with PDA on the 1st day of life were prognostically unfavorable regarding the course of AKI. Excessively high levels of $RrSO_2$ on postnatal day 10 (91.8±0.81%) and inappropriately low values of rFTOE (0.05 ± 0.01) could indicate irreversible impairments associated with decreased oxygen utilization due to cell destruction.

Prospects for further research – to study the incidence and severity of AKI according to the modified neonatal KDIGO criteria in preterm newborns with hsPDA, risk factors for the development of AKI and to develop criteria for early diagnosis of AKI in preterm newborns with hsPDA.

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ДІАГНОСТИЧНА ЗНАЧУЩІСТЬ ДОДАТКОВИХ МАРКЕРІВ ГОСТРОГО ПОШКОДЖЕННЯ НИРОК У НЕДОНОШЕНИХ ДІТЕЙ З ВІДКРИТОЮ АРТЕРІАЛЬНОЮ ПРОТОКОЮ

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Резюме

Вступ. Гостре пошкодження нирок (ГПН) – поширене ускладнення у передчасно народжених дітей, які перебувають у відділеннях інтенсивної терапії новонароджених з високою летальністю. Виявлення недоношених новонароджених, які схильні до ризику розвитку ГПН, важливе не тільки для ранньої діагностики та лікування, але й для профілактики, оскільки

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ГПН значно погіршує прогноз будь-якого захворювання. Вивчення інформативності додаткових неінвазивних маркерів гострого ураження нирок, зокрема показників регіонарного насичення тканин нирки киснем ($RrSO_2$) та допплерівського дослідження кровотоку в магістральних судинах нирки представляє інтерес.

Мета дослідження – вивчення діагностичної значущості додаткових маркерів (вимірювання $RrSO_2$ та допплерівського дослідження кровотоку в магістральних судинах нирки) у діагностиці ГПН та його ступеня тяжкості у недоношених новонароджених з відкритою артеріальною протокою.

Матеріал і методи дослідження. У відкритому, одноцентровому, проспективному, когортному дослідженні обстежено 66 недоношених новонароджених дітей (гестаційний вік 29-36 тижнів), які перебували на лікуванні у відділенні анестезіології та інтенсивної терапії для новонароджених. Критерії включення: передчасно народжені новонароджені у терміні гестації 29-36 тижнів з гемо динамічно значимою відкритою артеріальною протокою (ГЗВАП), наявність підписаної поінформованої згоди батьків на дослідження. Критерії виключення: вроджені вади розвитку, внутрішньомозкові та внутрішньошлуночкові крововиливи III-IV ступеня, сепсис новонароджених, важка асфіксія під час пологів, захворювання шкіри, затримка внутрішньоутробного розвитку. Клінічне обстеження та лікування дітей проводилося згідно чинних протоколів.

Діагностика та визначення тяжкості ГПН проводилось згідно неонатальної модифікації KDIGO. За допомогою допплерівської УЗД вивчали наявність та розміри відкритої артеріальної протоки, визначали її гемодинамічну значущість. Кольорове ультразвукове допплерівське сканування судинного русла нирок проводилось при надходженні дитини у відділення до призначення ібупрофену, а у разі виявлення ГЗВАП – на третю та десяту добу життя. Вивчали кровоток на ділянці від магістральної ренальної артерії до інтерлобарної ренальної артерії правої нирки, вимірювали показники пікової систолічної швидкості (PSV), кінцевої діастолічної швидкості (EDV) та розраховували індекс резистентності (RI). Дослідження насичення тканин нирок киснем NIRS ($RrSO_2$) та розрахунок фракційної екстракції кисню нирками (rFTOE) проводилось протягом доби на 1, 3 та 10 добу життя. Дослідження має позитивний висновок комісії з питань біомедичної етики Дніпровського державного медичного університету (протокол засідання комісії № 8 від 26.04.2023 року), яка постановила, що наукове дослідження вважати таким, що відповідає загальноприйнятим нормам моралі, вимогам дотримання прав, інтересів та особистої достойності учасників дослідження, біоетичним нормам роботи з хворими дитячого віку. Ризик для суб'єктів дослідження під час виконання роботи відсутній. Законних представників дітей, яких залучено до дослідження, інформують про всі аспекти, пов'язані з метою, задачами, методиками та очікуваною користю дослідження. Лабораторні та інструментальні методи дослідження є загальноприйнятими; препарати, що будуть використані, дозволені до застосування. Експерименти на людині не проводилися.

Статистичну обробку результатів проводили за допомогою програмного продукту STATISTICA 6.1® (StatSoft Inc., серійний № AGAR909E415822FA). Для вирішення поставлених завдань використовувався комплекс статистичних методів дослідження з використанням параметричних та непараметричних критеріїв перевірки гіпотези про різницю між середніми значеннями, методів оцінки ефекту при альтернативній формі результату реакції, кореляційного аналізу (рангової кореляції Спірмена), кластерного аналізу.

Робота виконана в межах комплексних науково-дослідних робіт 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) виконання 09.2019-12.2023 рр.

Результати дослідження. У першу групу (група з помірним ураженням нирок) ввійшли 43 пацієнти з гестаційним віком (ГВ) 33,27±0,43 тижнів. ГПН відзначалося у 12 пацієнтів (27,9%), з них у 10 (23,3%) дітей була I стадія ГПН згідно неонатальної модифікації KDIGO, у 2 (4,7%) – II стадія.

У другу групу включені 5 пацієнтів (група з тяжким ураженням нирок) з ГВ 31,60±0,75 тижнів. Усі діти групи мали різні стадії ГПН (до III стадії), які після 7 доби трансформувалися у гостру ниркову недостатність. Смертність у цій групі становила 60%.

У третю групу включили 18 пацієнтів (група з легким ураженням) з ГВ 32,86±0,29 тижнів. I стадія ГПН діагностована у 2 (11,1%) пацієнтів, у 16 (88,9%) пацієнтів ГПН не визначалось.

На першу добу життя показники пікового систолічного (PSV) та кінцевого діастолічного (EDV) кровотоку в інтерлобарній артерії у дітей групи з легким ураженням нирок були вищими, ніж у дітей з важким перебігом захворювання ($p<0,05$). Така тенденція стосовно PSV зберіглася і на 3 добу. Доплерографічні показники ниркового кровотоку, а саме зниження EDV кровотоку до 1,96±2,22 см/сек. та PSV до 8,14± 2,71 см/сек. в інтерлобарній артерії у першу добу життя, та зниження PSV до 17,60 ±3,82 см/сек., EDV до 3,40±0,82 см/сек. та підвищення RI до 0,80±0,04 у магістральні ренальній артерії виявились ранніми неінвазивними предикторами тяжкого ГПН у недоношених новонароджених першої доби життя.

Неінвазивний моніторинг насичення тканин нирок киснем та розрахунок rFTOE виявив зниження ренальної оксигенації при проведенні NIRS у недоношених дітей з відкритою артеріальною протокою у першу добу життя до 53,60 ± 1,11%, та rFTOE 0,45 ± 0,01 є прогностично несприятливим стосовно перебігу ГПН. Надвисокий рівень $RrSO_2$ на 10 добу (91,8±0,81%) та наднизький rFTOE (0,05 ± 0,01) можуть свідчити про незворотність змін, пов'язаних зі зниженням утилізації кисню при руйнуванні клітин та можуть використовуватися як інструмент скринінгу для виявлення та оцінки «протокового обкрадання» при ГЗВАП та розвитку ГПН.

Висновки. Зниження темпу діурезу в перші 5 діб життя, як і підвищення рівня креатиніну крові вдвічі на 3 та 10 добу життя основні, але пізні, маркери розвитку тяжких пошкоджень нирок у недоношених новонароджених дітей. Допплерографічні показники ниркового кровотоку, а саме зниження EDV кровотоку в інтерлобарній артерії у першу добу життя, та зниження PSV, EDV та підвищення RI у магістральні ренальній артерії виявились ранніми неінвазивними предикторами тяжкого ГПН у недоношених новонароджених першої доби життя. Неінвазивний моніторинг насичення тканин нирок киснем та розрахунок rFTOE можуть використовуватися як інструмент скринінгу для виявлення та оцінки «протокового обкрадання» при ГЗВАП та розвитку ГПН.

Ключові слова: недоношені діти; нирковий кровоток; насичення тканин нирок киснем (RrSO2); фракційна екстракція кисню нирками (rFTOE); гостре пошкодження нирок.

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