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Glomerular Function in Term Neonates

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Key words: *Glomerular Filtration, Barrier, Cystatin C, Creatinine, Newborn Infant, Pathology.*

Aim. With the aim to detect the condition of glomerular function in term neonates 53 newborns (infants) with clinical signs of pathological course of early neonatal period of severe and moderate degree, and 34 conditionally healthy babies were examined.

Methods and results. The results of the studies were indicative of the fact that in case of combined somatic and neurologic pathology term neonates develop clinical-paraclinical signs of renal dysfunction including disorders of glomerular filtration.

Conclusion. Reliable changes of serum creatinine and cystatine C levels as well as glomerular filtration rate calculated by the given markers are evidence of it. At the same time, certain literary data give evidence of higher information value of cystatine C as a marker of glomerular filtration in newborns as compared to the «gold» standard.

Гломерулярна функція в доношених новонароджених

А. Г. Бабінцева, Ю. Д. Годованець, А. Ф. Запотічна

З метою визначення стану гломерулярних функцій у доношених новонароджених обстежили 53 дитини із клінічними проявами патологічного перебігу ранньої постнатальної адаптації тяжкого та помірного ступенів тяжкості та 34 умовно здорових малюки. Результати дослідження показали, що за умов поєднаної соматичної та неврологічної патології в доношених новонароджених спостерігаються клініко-параклінічні прояви ренальної дисфункції, зокрема порушення гломерулярної фільтрації. Про це свідчать вірогідні зміни рівнів сироваткових креатиніну та цистатину С, а також швидкості гломерулярної фільтрації, що розраховані за цими маркерами. При цьому підтверджено дані фахової літератури щодо більшої інформативності цистатину С як маркера гломерулярної фільтрації в новонароджених дітей, порівнюючи із «золотим стандартом».

Ключові слова: *гломерулярна фільтрація, цистатин С, креатинін, новонароджений, патологія раннього неонатального періоду.*

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Гломерулярная функция у доношенных новорождённых

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С целью определения состояния гломерулярной функции у доношенных новорождённых исследовано 53 ребёнка с клиническими проявлениями патологического течения раннего неонатального периода тяжёлой и умеренной степеней тяжести и 34 условно здоровых малыша. Результаты исследований показали, что при сочетанной соматической и неврологической патологии у доношенных новорождённых наблюдаются клинико-параклинические проявления ренальной дисфункции, в том числе нарушения гломерулярной фильтрации. Об этом свидетельствуют достоверные изменения уровней сывороточных креатинина и цистатина С, а также скоростей гломерулярной фильтрации, которые рассчитаны по данным маркерам. При этом подтверждены литературные сведения о более высокой информативности цистатина С как маркера гломерулярной фильтрации у новорождённых детей в сравнении с «золотым» стандартом.

Ключевые слова: *гломерулярная фильтрация, цистатин С, креатинин, новорождённый, патология раннего неонатального периода.*

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Glomerular filtration is one of the main functions of the kidney which provides the output of water and low molecular weight components of plasma through glomerular filter. Glomerular filtration rate (GFR) defines the state of glomerular function. Placenta maintains the fluid and electrolyte balance, clearance of metabolic wastes in fetus; the circulation in fetal kidney is low and accordingly GFR is low too. GFR increases progressively during last months of intrauterine development until the 36th week of gestation, which is due to the increase in the number and size of nephrons. GFR is still relatively low after birth. In term infants, there is a large increase in GFR during the first 2 weeks after birth. Increases in systemic blood pressure and consequently hydrostatic pressure of the glomeruli, pore size of glomerular capillary wall, glomerular capillary surface area, ultrafiltration coefficient, and plasma flow rate secondary to increase in caliber of the afferent/efferent arterioles and the decrease in these arterioles resistance all play a certain role in maturation increase in early postnatal GFR [1–3].

Various methods have been used to measure GFR in neonates. One of these methods is the clearance measurement. In most neonatal intensive care units, GFR is measured by means of Schwartz formula, which is based on serum creatinine (SCr) level. But using creatinine as a GFR marker in neonates has some problems [1]. Several authors found that serum cystatin C (SCysC) is a better marker of GFR than creatinine, even in cases of sub-clinical renal dysfunction. Since the classic Schwartz formula for estimating GFR from SCr concentration shows considerable bias in children and GFR values derived from SCysC are only slightly overestimated, some authors have suggested replacing the Schwartz GFR formula with GFR calculated from serum SCysC [4].

The **objective** of this research is to study glomerular function in term neonates with clinical symptoms of disorders in early neonatal period on the basis of measuring levels of serum creatinine and cystatin C with calculation of glomerular filtration rate.

Materials and Methods

It is a hospital based, prospective case control study conducted during the period from January 2013 to July 2014. 84 term neonates were selected, 53 infants among them from whom received treatment in neonatal intensive care unit. The first group of observation included 30 ill term neonates who had clinical symptoms of severe disorders on their first week of life (I group). The second group of observation included 24 ill term newborn with clinical symptoms of moderate disorders of early neonatal period (II group). The control group included 34 apparently healthy term neonates (III group). All the infants were in physiological term of gestation, the groups under observation did not differ reliably in the body weight and length as well as gender signs. The exclusion criteria of the study were evidence-based early neonatal sepsis and major congenital anomalies of the kidney and urinary tract.

A predesigned and pretested proforma was used to collect the data such as gestational age, birth weight and relevant perinatal history. The ill neonates were grouped on the basis of Score for Neonatal Acute Physiology Perinatal Extension (SNAP-PE) and Neonatal Therapeutic Intervention Scoring System (NTISS) [5]. Immediate clinical assessment was made by recording respiratory rate, heart rate, capillary filling time, blood pressure, temperature, urine output, and body weight. Renal function parameters included SCr and SCysC which were monitored on 48 hours of life. SCr level was measured by photometric methods with picric acid. SCysC level was measured by immunonephelometric methods. Classically glomerular filtration rate (GFR) was calculated on the basis of G.J.Schwartz's formula: GFR (ml/min/1.73 m^2) = k · d (cm) / SCr (μmol/l) 0,0113, where k = 0,45 for term neonates [6]. Alternative method of calculation of glomerular filtration rate was based on A.Grubb's formula: GFR (ml/min) = 84,69 x cystatin $C^{-1,680}$ x 1,384 [7]. The analyses were conducted on the basis of the laboratory Gemeinschaftslabor Cottbus (Germany).

Informed written consent was obtained from parents prior to enrollment of their babies in the study. All studies were conducted in compliance with the basic provisions of the GCP (1996), Council of Europe Convention on Human Rights and Biomedicine (1997), Declaration of Helsinki of the World Medical Association about Ethical Principles for Medical Research Involving Human Subjects (1964)–(2008).

Statistical processing of mathematical data was performed by means of the program Statistica 7.0 (StatSoft Inc., USA) with the detection of median (Me) and interquartile range [Lq – lower quartile; Uq – upper quartile] for the selections with abnormal distribution. Non-parametric Mann-Whitney (MW) U-criterion was used for the comparison of two selections. The difference of the parameters was considered to be statistically significant with $p<0,05$.

Results and Discussion

The cause of renal function disorders in neonates is multifactorial and usually there are one or more associated contributing factors. Perinatal asphyxia, sepsis and surgical intervention are the most common associated conditions. Other causes associated with the development of renal dysfunction in early neonatal period are respiratory distress syndrome, dehydration, congestive heart failure and potentially nephrotoxic drugs [8–9].

The results of our studies showed that all infants from the first and second group of observation had more than 1 associated contributing condition which could lead to the development of renal function disorders. The frequency of each associated contributing condition is presented in *Table 1.*

Table 1

Associated Contributing Conditions to Renal Dysfunction in Newborns from I and II Groups of Observation

Factors	I group, N (%)	II group, N (%)
Sever asphyxia (score Apgar on fifth minute of life loss than 3 points)	10(33,3%)*	–
Moderate asphyxia (score Apgar on fifth minute of life 4-6 points)	5(16,7%)	10(41,1%)
Respiratory distress syndrome	12(39,9%)	4(16,7%)
Hemolytic disease of the newborn	–	4(16,7%)
Hypoxic-ischemic encephalopathy: - depression syndrome - excitation syndrome - convulsive syndrome - syndrome of vegetative-visceral disorders	30(100%) 18(59,9%) 5(16,7%) 7(23,3%)* 20(66,6%)	24(100%) 19(79,2%) 5(20,8%) – 10(41,7%)
Score SNAP-PE	54,0±2,11*	26,0±0,61
Mechanical ventilation	26(86.6%)*	–
Furosemide	10(33,3)*	2(8,3%)
Dobutamine	20(66,6%)*	2(8,3%)
Dopamine	5(16,7%)*	–
Ampicillin + amikacin	20(66,6%)*	24(100%)
Cefotaxime+ amikacin	10(33,3%)*	–
Score NTISS	24,0±0,55*	11,1±0,64

Note: * – significant difference between I and II groups of observation, $p<0,05$.

According to the data obtained the newborns from I group of observation had significantly more frequent pathological factors which had potentially negative influence on renal function. So, they had more lower Apgar score on the fifth minute of life, high frequency of severe hypoxic-ischemic encephalopathy, respiratory distress syndrome and also potentially nephrotoxic drugs. Renal involvement is frequent in neonates with perinatal asphyxia, which correlates with the severity of neurological damage. The newborn from III group of observation did not have pathological symptoms during early neonatal period.

We also examined classical clinical and paraclinical parameters of kidney injury in children from the groups of observation. The results are presented in *Table 2.*

Table 2

Clinical and Paraclinical Parameters to Renal Dysfunction in Newborns from I and II Groups of Observation

Parameters	I group N (%)	II group N(%)
Oedema	24(79,9%)	10(41,7%)
Oliguria (urinary output less than 1 ml/kg/h)	12(39,6%)*	–
Pathological increase body weight	21(69,9%)	10(41,7%)
Proteinuria	13(43,3%)	7(29,2%)
Hematuria	7(23,3%)	2(8,3%)
Leukocyturia	3(9,9%)	2(8,3%)
Bacteriuria	1(3,3)*	–

Note: * – significant difference between I and II groups of observation, $p<0,05$.

The results of our studies showed that newborns from I group of observation had significant tendencies of more frequent oedema, pathological increase of body weight, proteinuria, hematuria, leukocyturia and bacteriuria than those in the II group. Also 12 babies from I group had one of the criteria of acute kidney injury – abnormal urinary output less than 1 ml/kg/h. The newborns from III group of observation did not have pathological symptoms of renal disorders during early neonatal period.

Classical laboratory criteria for the study of glomerular function in newborn are SCr and GFR on the basis of G.J.Schwartz's formula. We measured these parameters in term neonates who had clinical symptoms of different disorders during the first week of life and healthy newborns. The results are presented on *Figure 1* and *Figure 2*.

In the infants of the first group of observation SCr was 50,0 μmol/l [43,0; 71,0], in the second group – 60,0 μmol/l [47,0; 78,0], in the control group – 43,0 μmol/l [41,0; 44,0], $p_{I-III}<0,05$, $p_{II-III}<0,05$. GFR accordingly to groups of observation was 42,22 ml/min/1,73m^2 [29,7; 51,87], 34,51 ml/min/1,73m^2 [29,59; 47,46] and 49,09 ml/min/1,73m^2 [47,07; 49,54], $p_{I-III}<0,05$, $p_{II-III}<0,05$. The results of the examinations conducted have shown considerable disorders of glomerular function in infants with pathological neonatal period as compared to healthy infants. But neonates from I and II groups did not have significantly difference between these parameters. It is indicative of low specificity and sensitivity of SCr and GFR on the basis of G.J. Schwartz's formula to indicate the degree of severity of renal dysfunction during the first week of life.

According to scientific literature the use of SCr as GFR marker in neonates has some problems. The clearance of creatinine underestimates the true GFR in neonates because of passive reabsorption of filtrated creatinine across immature non-hermetic renal tubules in neonates, and is more prominent in premature

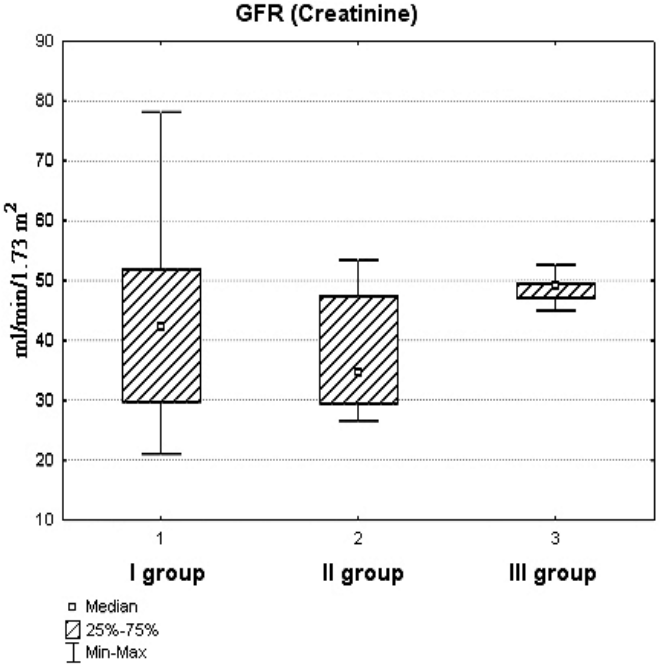

Fig. 1. SCR levels in groups of observation.

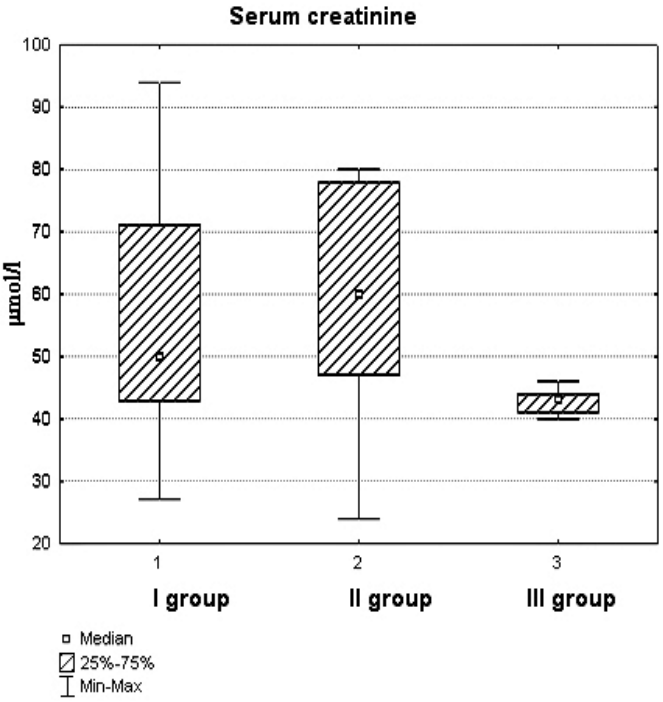

Fig. 2. GFR (G.J.Schwartz's formula) in groups of observation.

kidney. Also tubular secretion of creatinine (especially in the presence of low GFR) and secretion of creatinine into the intestine result in GFR overestimation. Jaffe method measuring SCr interfere with conditions such as hyperbilirubinemia, hypertryglyceridemia, hemolysis and ketone bodies in the blood. SCr creatinine is not sensitive to small changes of GFR. Growth and changes in muscle mass influence serum creatinine levels too. SCr at birth reflects maternal serum creatinine. As a result, SCr concentrations are influenced by some variables such as maternal kidney function, hydration, catabolic status and muscle mass. Thus, isolated SCr measurement cannot reveal the glomerular filtration status. It is better to measure serum creatinine periodically for GFR assessment [1,10].

The modern marker of kidney function in neonates is cystatin C. It is a proteinase inhibitor involved in intracellular catabolism of proteins, produced by all nucleated cells, freely filtrated across glomeruli, and completely catabolized and reabsorbed in the proximal tubule. Studies have shown that SCysC is a more specific and sensitive marker of GFR in both adults and children. The benefits of the use of SCysC in neonates as a kidney function marker are the following. There is no interference between SCysC and bilirubin, hemoglobin and ketone in laboratory findings. SCysC does not pass through the placenta, as a result, the values of SCysC reflect only neonatal GFR. SCysC level reflects maturation of the kidney better than other markers such as SCr. But there are limited studies available on reference values of SCysC in healthy and ill neonates [2,10].

In our study the level of SCysC and GFR on the basis of A.Grubb's formula in newborn with pathological neonatal period as compared to healthy infants have been examined. The results are presented on *Figure 3* and *Figure 4*.

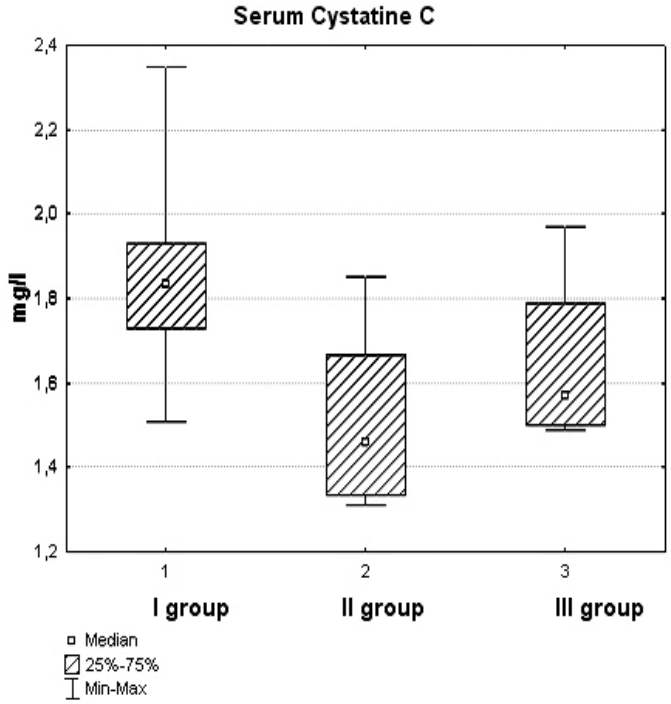

Fig. 3. SCysC levels in groups of observation.

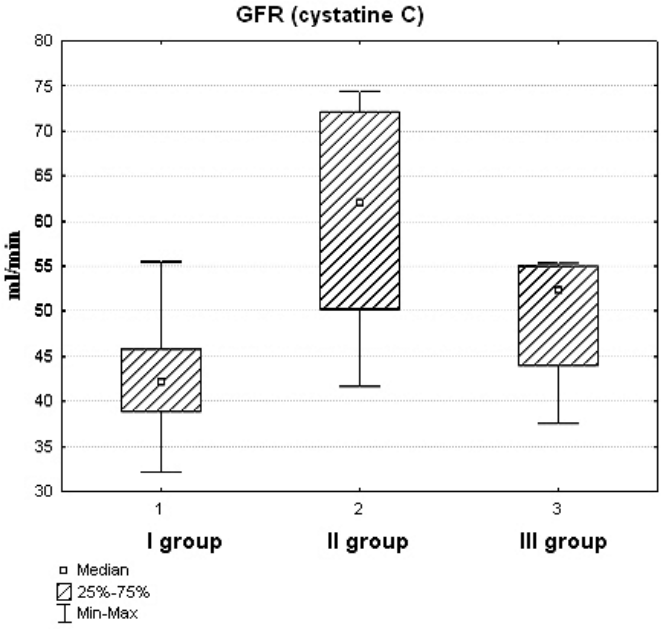

Fig. 4. GFR (A.Grubb's formula) in groups of observation.

In the newborns of the first group of observation SCysC 1,84 mg/l [1,73; 1,93], in the second group – 1,46 mg/l [1,34; 1,67], in the control group – 1,57 mg/l [1,5; 1,79], $p_{I-II}<0,05$, $p_{I-III}<0,05$, $p_{II-III}<0,05$. GFR accordingly to groups of observation was 42,07 ml/min [38,83; 45,78], 62,08 ml/min [50,31; 72,15] and 52,3 ml/min [44,07; 55,0], $p_{I-II}<0,05$, $p_{I-III}<0,05$, $p_{II-III}<0,05$. The levels of SCysC and GFR in infants with clinical symptoms of moderate disorders of early neonatal period are significantly higher than in healthy newborns. This is a result of the purpose sufficient volume of the infusion therapy, enteral nutrition, systemic blood pressure and consequently hydrostatic pressure of glomeruli. In neonates with clinical symptoms of severe disorders during the first week of life a significant decrease of SCysC and GFR as compared to the infants of II and control groups was diagnosed. This is due to the development of significant functional and anatomical renal disorders and multiorgan injuries in these babies.

Thus, our study have shown that serum Cys-C levels are superior, or at least equivalent, to SCr levels as an index of renal function of term neonates with disorders of early neonatal period and has been introduced as an alternative to SCr to monitor GFR.

Conclusions

1. The term newborns who were treated in neonatal intensive care unit had more than 1 associated contributing condition (severe asphyxia and hypoxic-ischemic encephalopathy, respiratory distress syndrome, mechanical ventilation, antibiotics, inotropic drugs) which could lead to the development of renal function disorders.

2. The term neonates with clinical symptoms of critical condition had classical paraclinical parameters of renal dysfunctions (oedema, pathological increase body weight, proteinuria, hematuria, leukocyturia and bacteriuria).

3. The measurement of SCr and GFR on the basis G.J.Schwartz's formula have shown a considerable disorders of glomerular function in infants with pathological neonatal period as compared with healthy infants, but they appeared to be low informative to indicate the degree of severity of renal dysfunction during the first week of life.

4. The measurement of SCysC and GFR on the basis of A.Grubb's formula has shown the increase in the intensity of glomerular filtration in neonates with moderate disorders of early neonatal period and, further, deterioration of this function in critically ill newborns. It is confirmed by recent evidence from clinical trials generally supporting the use of SCysC assays as a renal function test in neonatal patients.

The perspectives for future studies. Further studies with larger number of cases using concurrent gold standard tests are required to allow clarification of whether cystatin C and other modern biochemical markers can help diagnose early changes in kidney function among term neonates.

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