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The Serum Chloride and Sodium Concentration as a Predictor of Acute Kidney Injury in Premature Newborns

Концентрација хлора и натријума у серуму као предиктор развоја акутног бубрежног оштећења код превремено рођене новорођенчади

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Концентрација хлора и натријума у серуму као предиктор развоја акутног бубрежног оштећења код превремено рођене новорођенчади

SUMMARY

Introduction/Objective Hyperchloremia is often registered in adults' studies after administration with 0.9% sodium chloride. It contributes to the development of acute kidney injury (AKI) because it leads to vasoconstriction of renal blood vessels.

The aim of this study was to determine the correlation of the sodium and chloride imbalance with the development of AKI, with consideration of the other risk factors for this disorder.

Methods This retrospective study included 146 randomly selected preterm infants hospitalized at the Neonatal Intensive Care Unit from 2008 to 2015.

Results Among the patients registered for the study (n=146), 23.97% of them developed AKI, and they were of a significantly lower gestational age (26.3±2.8 weeks vs 31.7±2.90 weeks, p<0.05); birth weight (971.31±412.1g vs. 1753.3±750.3g, p<0.05); Apgar score in the first (3.2±1.7 vs 5.7±2.4, p<0.05) and fifth minute (5.3±1.7 vs 7.1±1.8, p<0.05) of life compared to those without AKI. The neonates with AKI had significantly higher maximum chloremia 114.1±8.4 vs 111.7±4.6, p=0.029, and maximum natremia 147.9±8.8 vs 142.9±4, p<0.05. Each of these parameters is (independently) a statistically significant risk factor for the development of AKI, and gestational age is the strongest (OR=1/0.643=1.55, 95%CI 1.24 to 1.94). Mortality in neonates with AKI was higher than in neonates without AKI (19.4% vs 92.7%, p<0.05).

Conclusion Hyperchloremia and hypernatre-mia are more common in the premature newborns with AKI compared to the premature newborns without AKI. Higher maximum sodium and chloride values are independent risk factors for AKI.

Keywords: acute kidney injury; hyperchloremia; hypernatremia; premature newborns

САЖЕТАК

Увод/Циљ У студијама на одраслима утврђено је да након надокнаде течношћу физиолошким раствором долази до хиперхлоремије, која доводи до вазоконстрикције бубрежних крвних судова и развоја акутног бубрежног оштећења (АБО).

Циљ рада је био да се утврди повезаност дисбаланса хора и натријума у серуму са развојем АБО, као и факторе ризика који предиспонирају АБО.

Методе У ретроспективну студију је укључено 146 насумично изабране превремено рођене деце лечене на Одељењу неонаталне интензивне неге од 2008. до 2015. године.

Резултати Од укупног броја новорођенчади (n=146), 23,97% је развило АБО. Новорођенчад са АБО су имали значајно нижу гестацијску старост (26.3±2.8 одн. 31.7±2.90 недеља, *p*<0.05), порођајну тежину (971.31±412.1гр тј. 1753.3±750.3гр, *p*<0.05), Апгар скор у првом (3.2±1.7 тј. 5.7±2.4, *p*<0.05) и петом минуту живота (5.3±1.7 тј. 7.1±1.8, *p*<0.05) у поређењу са децом без АБО. Новорођенчад са АБО су имали значајно веће максималне вредности хлора у серуму 114.1±8.4 тј. 111.7±4.6, *p*=0.029, као и максималне вредности натријума у серуму, 147.9±8.8 вс 142.9±4, *p*<0.05. Сваки од ових параметара је независни статистички значајан фактор ризика за развој АБО, а гестацијска старост је најзначајнији (ОР=1/0.643=1.55, 95% CI 1.24 то 1.94). Морталитет је значајно био већи код новорођенчади са АБО у односу на децу без АБО (19.4% тј. 92.7%, *p*<0.05).

Закључак Хиперхлоремија и хипернатремија су чешће код превремено рођене новорођенчади са АБО у поређењу са децом без АБО. Веће максималне вредности натријума и хлора у серуму су независни фактори ризика за развој АБО.

Кључне речи: акутно бубрежно оштећење; хиперхлоремија; хипернатремија; превремено рођено новорођенче

INTRODUCTION

Acute Kidney Injury (AKI) is a rapid decline of renal function, represented by reduction of glomerular filtration rate (GFR) with the accumulation of nitrogen substances and dysregulation of exstracellular fluid, electrolyte and acid-base balance [1]. Newborns have a low GFR which limits renal adaptation to different stress factors making them vulnerable to the development of AKI. The vulnerability is more pronounced in the preterm infants or those with low birth weight or with intrauterine growth restriction [2]. The frequency of AKI in neonates in Neonatal Intensive Care Unit

(NICU) ranges from 8-24%, and a third of them is preterm. Mortality due to AKI is high, and most often AKI is nonoliguric (about 60%) [1].

Attempts have been made recently, to clarify the diagnostic criteria for AKI in neonatal population, especially in the premature neonates, where the early detection can lead to improved outcomes. The current RIFLE criteria for the diagnosis of AKI by ADQI (Acute Dialysis Quality Initiative) are based on an increase in serum creatinine levels with or without changes in the urine output. Their modification for the pediatric population established lower levels of creatinine for diagnosis of AKI in children, but it still lacks clear levels of creatinine in neonatal age, especially in preterm neonates [1]. In the first three days of life, a value of creatinine correlates with mother's and its value declines quickly during first days of life. According to AKIN (Acute Kidney Injury Network) criteria for AKI diagnosing, the absolute value of creatinine is introduced, and AKI is classified into three stages of severity depending on the level of creatinine. Considering additional specificity of the neonatal population (especially preterm) and the immaturity of tubular cells, a higher percentage of body water, the higher normal urinary output were proposed by Bezerra de Melo et al [1,3,4]. Presently, there is no unique and completely reliable definition for AKI in the neonates.

The significant association is confirmed in several studies between lower birth weight and gestation age, perinatal asphyxia, respiratory distress syndrome, phototherapy, patent ductus arteriosus, lower Apgar score levels, use of drugs in mother and newborn (NSAIDs, antibiotics), sepsis with the development of AKI [1, 3]. The most common form of AKI in prematurely born infants is prerenal (85%) associated with ischemia, hypoxia and hypovolemia [1, 2]. Hypovolemia develops due to dehydration, fluid loss into the “third” space due to sepsis, perinatal hemorrhages, gastrointestinal losses, hypoalbuminemia or hypovolemia maintained due to cardiomyopathy and other reasons. If it's not treated in a timely manner, hypovolemia and ischemia progresses and leads to damage of nephrons [1, 2, 3].

Standard therapy of AKI includes maintaining the volume of circulating fluid through the infusion solution, but with caution against excessive compensation volume and electrolyte abnormalities, limiting intake of nephrotoxic drugs and other supportive therapy [1, 3]. Infusion therapy takes crucial place for the maintenance of renal perfusion and GFR, prevention and treatment of AKI. The standard infusion used in neonatology is 0.9% sodium chloride and 5% glucose.

There was a lot of talking in the past few decades about the negative effects of hyperchloremia registered with the infusion of 0.9% sodium chloride including the development of hyperchloremic acidosis and negative effect on renal blood vessels especially, leading to their vasoconstriction [5, 6]. This vasoconstriction further reduces GFR.

The aim of our study was to determine the value of chloride and sodium in the serum of premature infants, as well as association of electrolyte imbalances with the development of AKI, taking into consideration other risk factors for this disorder, at the same time. To determine the correlation of the sodium and chloride imbalance with the development of AKI, with consideration of the other risk factors for this disorder.

METHODS

The retrospective study included information from medical records of 146 randomly chosen premature newborns (born before the 37thweek of gestation) who were hospitalized at the NICU of the Institute for Child and Youth Health Care Vojvodina (ICYHCV) in the period from January 1st 2008, - December 31st 2015.

Access to medical records was approved by the Ethics Committee of ICYHCV.

The study does not include premature infants who had congenital malformation of the urinary tract or other congenital disorders that could directly or indirectly affect the serum sodium and chloride (congenital adrenal hyperplasia, Bartter syndrome, hydrocephalus, cardiomyopathy), the infants whohave died in the first 72 hours of treatment, as well as the infants with incomplete medical records.

All respondents were divided into two groups: those with AKI (n = 35) and infants without AKI (n = 111). The following information was gathered from medical records: gestational age, birth weight, Apgar score at first in the fifth minute, gender, the requirements for mechanical ventilation and for non-invasive respiratory support, the length of stay on NICU and entire hospital stay, outcome, and the serum chloride and sodium levels. The length of stay in the NICU is expressed as the sum for patients who have stayed more than once at the NICU during hospitalization and the length of hospital stay was calculated only for surviving patients.

For the assessment of possible correlation between serum chloride and sodium with AKI in the group of infants who have developed AKI, we calculated chloride and sodium values before the development of AKI while in the group without AKI throughout the entire hospitalization. We analyzed initial value of chloride on admission in NICU, marked Cl_0, the maximum recorded value of chloride Cl_{max}, minimum Cl_{min} and average Cl_{mean} value of chloride. The sodium levels were analyzed in the same way: initial Na_0, maximum Na_{max}, minimum Na_{mean} and average Na_{min}.

AKI was diagnosed according to the modified AKIN criteria. Increase in serum creatinine more than ≥ 26.4 mmol/l (≥ 0.3 mg/dl) compared to the baseline value of the third day of life or if the basal value was not determined, an increase of the serum creatinine ≥ 26.4 mmol/l (≥ 0.3 mg/dl) within 48h was defined as AKI.

The reference range of the chloride is 98-108 mmol/l and for sodium 135–145 mmol/l.

The parameters of descriptive statistics are presented through the mean value ± standard deviation or percentage and median and interquartile range (IQR). Statistical comparisons were made by Student's t-test, Chi-square test or Mann-Whitney U test. Univariate and amultivariate logistic regression model were conducted for evaluating the prediction for the development of AKI for all variables. For statistically significant difference, values with $p<0.05$ were taken.

RESULTS

Out of all of the preterm infants, (n=146) 35 (23.97%) had AKI. AKI was diagnosed on average 5.5±4.2 days of life. Compared with premature infants without AKI, neonates with AKI were of a significantly lower gestational age (26.3±2.8 weeks vs 31.7±2.90 weeks, p<0.05), as well as of a lower birth weight (971.31±412.1grams vs. 1753.3±750.3 grams, p<0.05), had lower values of Apgar score in the first (3.2±1.7 vs 5.7±2.4, p<0.05) and fifth minute (5.3±1.7 vs 7.1±1.8, p<0.05) of life. Mechanical ventilation was more frequently applied in a neonates with AKI compared to those without AKI (94.3% vs 67.8%, p <0.05), and the neonates without AKI were more often on a non-invasive respiratory support (67.8% vs 34.3%, p <0.05). Stay of the patients with AKI in the NICU was significantly longer (17 [14, 29.5] days vs 8 [4, 13] days, p= 0.006) and entire hospital stay (52 [42, 68] days vs 36 [20.5, 55] days, p=0.047) by analyzing only survivors in both groups. Survival was significantly higher in the neonates without AKI compared to the neonates with AKI (92.7% vs 19.4%; p <0.05) (Table 1).

Table 1. Descriptive statistics and differences between the groups of infants with and without AKI.

PARAMETERS		ALL (n=146)	AKI (n=35)	Without AKI (n=111)	*p*
GA (weeks)		30.6±3.5	27.0±2.8	31.7±2.91	**<0.05**
BW (gr)		1565.9±761	971.31±412.1	1753.3±750.3	**<0.05**
AS 1. min		5.2±2.5	3.2±1.7	5.7±2.4	**<0.05**
AS 5. min		6.8±1.8	5.3±1.7	7.1±1.8	**<0.05**
Gender (male, %)		88 (60.3)	20(55.6)	68(60.7)	0.188
Respiratory support	**MV (n,%)**	109 (74.6)	33 (94.3)	76 (67.8)	**<0.05**
	Noninvasive (n, %)	96 (65.7)	12(34.3)	76 (67.8)	**<0.05**
Survivor (n, %)		111 (76)	7(19.4)	103(92.7)	**<0.05**
Length of stay	**NICU (days;median, IQR)**	8.5(4.25,15)	17 (14,29.5)	8 (4,13)	**0.006**
	Entire hospital stay(days; median, IQR)	37 (21.25,55.75)	52 (42,68)	36 (20.5,55)	**0.047**

GA – gestational age; BW – birth weight; AS 1 and 5 – Apgar score in the first and fifth minute; MV – mechanical ventilation; IQR – interquartile range; NICU – Neonatal Intensive Care Unit.

The neonates with AKI had a significantly greater maximum values of chloride Cl_{max} (114.1±8.4 vs 111.7±4.6, p=0.029) and a maximum value of sodium Na_{max} (147.9±8.8 vs 142.9±4, p<0.05) compared to the neonates without AKI. Table 1 shows the initial, minimum and mean values of chloride and sodium levels in the neonates with and without AKI.

A univariate logistic regression model was developed for each variable for the prediction of AKI. It was found that the maximum value of chloride (Cl_{max}), the maximum value of sodium (Na_{max}), gestational age, Apgar score in the first and fifth minute, birth weight, and the use of mechanical ventilation were statistically significant independent risk factors for the development of AKI (Table 1). For each increased unit of Cl_{max}, the risk of AKI is 1.071 higher (OR 1.071, 95% CI: 1.005 to 1.141, p=0.036), and for each increased unit of Na_{max} 1.14 (OR 1.14, 95% CI: 1.068 -1225, p<0.05).

By switching off the parameters, which mutually demonstrated a strong correlation (gestational age in relation to the birth weight r=0.860, p=0.000; Apgar score in the first and fifth minute, r=0.860, p=0.000), and taking only one of them, such as gestational age and value of the Apgar score in the first minute, a multivariate logistic analysis showed that the strongest predictor of development AKI is gestational age. Decreasing the gestational age for one week increased the risk of AKI in premature infants up to 1.55 times (OR = 1/0.643 = 1.55, 95% CI: 1.24-1.94) (Table 1).

DISCUSSION

AKI is associated with a high mortality and occurs frequently in the NICU. The most important risk factors for the development of AKI, beside those which lead to poor renal perfusion and hypoxia or acts nephrotoxicity, were prematurity and low birth weight [1, 3].

In a retrospective study (Stojanović et al), that analyzed 150 premature infants treated in the NICU, 26% of them (39/150) developed AKI. In the group of neonates with AKI significantly lower gestational age was recorded (27.3 weeks vs 31.3 weeks, p <0.001) and a lower birth weight (1.034g vs 1.620g, p <0.001), lower Apgar score at birth in the first and in the fifth minute and significantly higher comorbidity (sepsis, high stage of intracranial hemorrhage, necrotizing enterocolitis, patent ductus arteriosus) in comparison with the preterm neonates without AKI. The final outcome was significantly worse in those with AKI, a number of deaths was 69.2% vs 13.5% (p <0.001) in the neonates without AKI [7].

Koralkar et al analyzed the newborns with low birth weight (≤1500g), treated in NICU, in a prospective study. It was found that 18% of the neonates developed AKI and that they have had lower values of Apgar score in the 5thminute and were of as significantly lower birth weight (702g vs 1039g, p <0.001), and lower gestational age (25 vs 28, p <0.001). As the gestational age was lower they had a higher stage of AKI by AKIN criteria. Mortality in neonates with AKI was significantly higher than in those without AKI (42% vs 5%, p<0.001) [8].

In our group of neonates, 23.97% were registered AKI, but only 19.4 % survived. They were of a significantly lower gestational age and lower birth weight, and had lower values of Apgar score in the first and fifth minute of life and they demanded more use of the mechanical ventilation. All of these parameters proved to be independent contributing factors for the development of AKI.

The role of hyperchloremia as a risk factor for AKI in neonates has not been studied. In adult intensive care units, a significant volume replacement after major surgery or trauma has been shown to lead to hyperchloremia due to a higher volume replacement with solutions rich in chloride, and this hyperchloremia has not been recorded in the volume replacement of the balanced solution [5]. Through both various studies, both experimental and clinical, evidence suggests that hyperchloremia reduced renal perfusion and GFR.

Shaw et al have shown that the use of 0.9% sodium chloride in 30994 patients during open abdominal surgery carries a higher risk of complications than in the group of 926 patients who have received a balanced crystalloid solution with a reduced content of chloride on the day of the operation. In patients who have received only the infusion of 0.9% sodium chloride on the day of the surgery significantly more infections, electrolyte imbalance, development of acidosis, and the development of acute kidney failure were recorded and they have had more need for renal replacement therapy, and more need for higher volume replacement and blood transfusions. The mortality rate among the patients who received 0.9% sodium chloride was 5.6% compared with 2.9% in the group of patients who received balanced crystalloid [6]. An unfavorable result in terms of a higher percentage of hyperkalemia and acidosis was noted in the application of 0.9% sodium chloride in patients who performed kidney transplantation compared with those who received Ringer's lactate, until there was no significant difference in renal function [9]. Zhang and others, in the study on the 1221 critically ill adult patients, showed that those who have developed AKI (29.2%), during their stay in the intensive care unit, had significantly higher values of chloremia compared with the patients without AKI, and there is a correlation between the maximum and mean values of chloride with the development of AKI, and the maximum chloride was significantly higher in the severe stages of AKI [10].

In our study group, we found that premature infants who developed AKI had significantly higher values of maximum chloride and sodium compared to the control group and that these parameters are independent risk factors for the development of AKI.

Hypernatremia indicates a state of dehydration caused by physiological predisposition of premature neonates and the presence of pathology. Immature neonates with lower birth weight lose more water through perspiration, and another significant way of water losses among the neonatal populations is infection, when the fluid exceeds into a "third space". Stojanović et al performed a study, in which daily fluid intake in prematurely born neonates had been monitored. For those who have developed AKI, it was noted that they had higher levels of sodium in the third and fourth day of life [7]. This major difference of sodium levels indicates a higher degree of dehydration in the premature neonates with AKI.

In both groups we had applied solution which contained 0.9% sodium chloride and 5% glucose, to maintain fluid balance. Recommendations for infusion therapy in neonatology suggest a better outcome with a restrictive fluid replacement because the GFR and concentration ability of kidneys in premature infants in the first days of life are reduced, and urine output is limited to 0.5 ml/kg/h in the first 12-24h [7]. Our assumption is that hyperchloremia in prematurely born infants who have developed AKI resulted primarily because of parenteral rehydration with infusion solution rich in chloride.

An experimental study, on anesthetized dogs, about the effect hyperchloremia has on kidneys has been made a few decades ago. In a study, Wilcox described renal vasoconstriction and GFR decline in the denervated kidneys dependent on the level of hyperchloremia. He applied captopril to block angiotensin II (AT II) in an attempt to explain the mechanism of vasoconstriction. However, other studies have shown that AT II vasoconstrictor is not important during infusion rich in sodium chloride because the application has not blocked renal vasoconstriction [11]. The infusion of sodium chloride increases of interstitial fluid more in comparison to balanced crystalloid solution. The result of this is that at a relatively stretchable tissue, for example, in encapsulated organs, a little accumulation fluid results with elevated intracapsular pressure which then reduces tissue perfusion and slows capillary flow [5]. This mechanism can serve as one of the explanations for the reduced diuresis after the infusion of sodium chloride. It was an experiment that demonstrated improvement of renal function and an increase in urine output during massive preoperative compensation volume crystalloid and blood transfusion at hypovolemic monkeys who underwent kidney decapsulation [12]. Hypovolemia, pain, and various stressful factors activate the sympathetic nervous system and the renin-angiotensin-aldosterone system (RAAS). Consequently, the activated and enhanced secretion of antidiuretic hormone leads to the retention of water and sodium. Even in conditions without damage or lesion of kidney, the connection between fluid intake and natriuresisis weak and the application of infusion more likely leads to water and sodium retention rather than diuresis [5]. Studies of the general population have been conducted in order to monitor physiological events in the intake of sodium chloride. In a double-blind controlled study that involved healthy volunteers, by using magnetic resonance imaging, it has been observed that there is a decrease of cortical perfusion and reducing flow rates in the renal artery after 2l infusion of 0.9% sodium chloride compared with 2l infusion Plasma-Lyte 148 solution [13]. Drummer et al have shown that in healthy volunteers, after entering 2l 0.9% sodium chloride solution for 25 minutes, followed by increased excretion of urine and electrolytes for next two days, with the biggest increase 3-22h after the infusion. Two days after the infusion they have noted the suppression of RAAS, which corresponds to the influx of sodium, whereas atrial natriuretic peptide and urodilatin were raised 22h after the infusion, suggesting that they may represent a slower adaptive mechanism of the prolonged infusion with sodium chloride [14]. Nakajima et al pointed out in his work, which involved 3603 healthy individuals, 25-75 years old, that there is a link between elevated levels of sodium and high blood pressure, but also that higher serum sodium is associated with reduced GFR independently of high blood pressure. Changes in serum chloride significantly contribute to high blood pressure throughout high concentration of sodium, but not the correlation between the high concentrations of sodium and decrease GFR [15]. Within one hour after the infusion of sodium chloride, RAAS is suppressed, but not after the infusion of sodium bicarbonate. In the experimental model of sodium sensitive hypertonic rats, hypertension was shown to be under the influence of sodium chloride, but not of sodium bicarbonate [16].

It is considered that mechanism by which hyperchloremia leads to vasoconstriction includes signaling of cells macules densa. Due to increased concentrations of sodium chloride in the renal tubules more sodium and chloride enter in the cell macula densa through NaCl2K cotransporter, then chloride exits through the chloride channels on the basolateral side of macule densa cell causing its depolarization which leads to the release of ATP and vasoconstriction of afferent and efferent arterioles. It is assumed that the ATP has a direct effect, but also adenosine, a decomposition product of ATP, acting at the A1 receptors leads to the vasoconstriction of afferent and efferent arterioles [5, 17]. There are also other possible mechanisms for negative effects of hyperchloremia [13].

Considering the specificities of the neonatal population, especially premature infants, may be more susceptible to the effects hyperchloremia. According to a previous study, more ATP was found in the erythrocytes of infants than in those of adults, and more ATP in the prematurely born infants in comparison to the term infants [18]. Hypothetically, if the cells of the macula densa in premature infants have more ATP their depolarization probably involve more ATP release, and thus a stronger vasoconstriction of afferent and efferent arterioles. There are not clinical studies on the effects of hyperchloremia in the neonate. Completion of the research in this area is certainly necessary to extend knowledge.

CONCLUSION

In our group of neonates, premature infants with AKI had a poor outcome. The lower gestational age, lower Apgar score in the first and fifth minute, a lower birth weight, and the use of mechanical ventilation are significantly independent risk factors for the development of AKI. A significant contribution to the development of AKI was found for the maximum value of chloride and sodium, which were significantly higher in the group of preterm infants who developed the AKI. A larger study is needed to determine which fluid is the most appropriate for use in premature newborns.

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