ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Serum chloride and sodium concentration as a predictor of acute kidney injury in premature newborns

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SUMMARY

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

The aim of this study was to determine the correlation of sodium and chloride imbalance with the development of AKI, with consideration of 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, 23.97% 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 ± 412.1 g vs. $1,753.3 \pm 750.3$ g, $p < 0.05$); 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 (Cl_{max}: 114.1 ± 8.4 vs. 111.7 ± 4.6, $p = 0.029$) and maximum natremia (Na_{max}: 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 1.24–1.94). Mortality in neonates with AKI was higher than in neonates without AKI (19.4% vs. 92.7%, $p < 0.05$).

Conclusion Hyperchloremia and hypernatremia 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

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 extracellular 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 preterm infants or those with low birth weight or with intrauterine growth restriction [2]. The frequency of AKI in neonates in a neonatal intensive care unit (NICU) ranges from 8% to 24%, and a third of them are preterm. Mortality due to AKI is high, and AKI is most often nonoliguric (in about 60%) [1].

Attempts have been made recently to clarify the diagnostic criteria for AKI in neonatal population, especially in premature neonates, where 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 modifica-tion 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, the value of the infant's creatinine level correlates with that of the mother, and its value declines quickly during the 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 and higher normal urinary output were proposed by some studies [1, 3, 4]. Presently, there is no unique and completely reliable definition for AKI in neonates.

Significant association 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 has been confirmed in several

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studies [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 in the "third" space due to sepsis, perinatal hemorrhages, gastrointestinal losses, hypoalbuminemia or hypovolemia maintained due to cardiomyopathy and other reasons. If not treated in a timely manner, hypovolemia and ischemia progress and lead 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 has been much discussion 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, at the same time taking into consideration other risk factors for this disorder.

The objective of the present study is to determine the correlation of 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 37th week of gestation) hospitalized at the NICU of the Institute for Child and Youth Health Care of Vojvodina (ICYHCV) in the period from January 1, 2008 to December 31, 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), infants who died in the first 72 hours of treatment, nor 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 the first and the fifth minute, sex, 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 stayed at the NICU more than once during their 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 developed AKI, we calculated chloride and sodium values before the development of AKI. 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_{min}), and average (Na_{mean}) value.

AKI was diagnosed according to the modified AKIN criteria. Increase in serum creatinine of ≥ 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 of ≥ 26.4 mmol/l (≥ 0.3 mg/dl) within 48 hours 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, χ^2 test or Mann–Whitney U-test. Univariate and multivariate logistic regression models 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 after 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 ± 2.9 weeks, p < 0.05), as well as of a lower birth weight (971.31 ± 412.1 grams vs. 1,753.3 ± 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 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).

The neonates with AKI had significantly greater maximum values of chloride (Cl_{max} = 114.1 ± 8.4 vs. 111.7 ± 4.6, p = 0.029) and maximum values of sodium (Na_{max} = 147.9 ± 8.8 vs. 142.9 ± 4, p < 0.05) compared to the neonates

Table 1. Descriptive statistics and differences between 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 ± 2.8	31.7 ± 2.91	< 0.05
BW (gr)		1,565.9 ± 761	971.31 ± 412.1	1,753.3 ± 750.3	< 0.05
AS 1st min.		5.2 ± 2.5	3.2 ± 1.7	5.7 ± 2.4	< 0.05
AS 5th 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

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 Cl_{max}, 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: 1.005–1.141, 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 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 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 nephrotoxicity, were prematurity and low birth weight [1, 3].

In a retrospective study by Stojanović et al. [7], which analyzed 150 premature infants treated in the NICU, 26% of analyzed infants (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 lower birth weight (1,034 g vs. 1,620 g, 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, pat-

ent ductus arteriosus) in comparison with the preterm neonates without AKI. The final outcome was significantly worse in those with AKI, as the number of deaths was 69.2% vs. 13.5% (p < 0.001) in the neonates without AKI.

Koralkar et al. [8] analyzed newborns with low birth weight (≤ 1,500 g), treated at an NICU, in a prospective study. It was found that 18% of the neonates developed AKI and that they had lower values of Apgar score in the fifth minute and were of significantly lower birth weight (702 g vs. 1,039 g, 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).

In our group of neonates, AKI was registered in 23.97%, but only 19.4% of the patients survived. They were of significantly lower gestational age and lower birth weight, and had lower values of Apgar score in the first and fifth minute of life and needed more use of 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, significant volume replacement after major surgery or trauma has been shown to lead to hyperchloremia due to 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 various studies, both experimental and clinical, evidence suggests that hyperchloremia reduced renal perfusion and GFR.

Shaw et al. [6] showed that the use of 0.9% sodium chloride in 30,994 patients during open abdominal surgery carries a higher risk of complications than in the group of 926 patients who received a balanced crystalloid solution with a reduced content of chloride on the day of the operation. In patients who received only the infusion of 0.9% sodium chloride on the day of surgery, significantly more infections, electrolyte imbalance, development of acidosis, and the development of acute kidney failure were recorded and they had more need for renal replacement therapy, and more need for higher volume replacement and blood

transfusions. The mortality rate among patients who received 0.9% sodium chloride was 5.6%, compared with 2.9% in the group of patients who received balanced crystalloid. An unfavorable result in terms of higher percentage of hyperkalemia and acidosis was noted in the application of 0.9% sodium chloride in patients who underwent kidney transplantation, compared with those who received Ringer's lactate, until there was no significant difference in renal function [9]. Zhang et al. [10] in the study of 1,221 critically ill adult patients showed that those who had developed AKI (29.2%) during their stay in the intensive care unit had significantly higher values of chloremia compared with the patients without AKI, that there is a correlation between the Cl_{max} and Cl_{mean} values with the development of AKI, and that Cl_{max} was significantly higher in severe stages of AKI.

In our study group, we found that premature infants who developed AKI had significantly higher values of Cl_{max} and Na_{max} compared to the 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, as well as the presence of pathology. Immature neonates with lower birth weight lose more water through perspiration; another significant way of water loss among neonatal population is infection, when the fluid exceeds into "third space." Stojanović et al. [7] performed a study in which daily fluid intake in prematurely born neonates was monitored. For those who developed AKI, it was noted that they had higher levels of sodium in the third and fourth day of life. This major difference of sodium levels indicates a higher degree of dehydration in the premature neonates with AKI.

In the present study, in both groups we 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 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 12–24 hours [7]. Our assumption is that hyperchloremia in prematurely born infants with AKI occurred primarily because of parenteral rehydration with infusion solution rich in chloride.

An experimental study on the effect hyperchloremia has on kidneys on anesthetized dogs has was made a few decades ago. In the study, Wilcox [11] described renal vasoconstriction and GFR decline in the denervated kidneys dependent on the level of hyperchloremia. He applied captopril to block angiotensin II in an attempt to explain the mechanism of vasoconstriction. However, other studies have shown that angiotensin II vasoconstrictor is not important during infusion rich in sodium chloride because the application does not block renal vasoconstriction. The infusion of sodium chloride increases interstitial fluid more in comparison to balanced crystalloid solution. The result of this is that at relatively stretchable tissue, for example, in encapsulated organs, little accumulation fluid results with elevated intracapsular pressure, which then reduces tissue perfusion and slows down 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) in hypovolemic monkeys who underwent kidney decapsulation [12]. Namely, kidney decapsulation was prevented of secondary renal ischemia due to compartmental swelling. 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 kidney lesions, the connection between fluid intake and natriuresis is weak and the application of infusion is more likely to lead to water and sodium retention rather than to 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 was observed that there was a decrease of cortical perfusion and reducing flow rates in the renal artery after 2 l infusion of 0.9% sodium chloride compared with 2 l infusion Plasma-Lyte 148 solution [13]. Drummer et al. [14] have shown that in healthy volunteers, introduction of 2 l of 0.9% sodium chloride solution for 25 minutes was followed by increased excretion of urine and electrolytes for the next two days, with the biggest increase 3–22 hours after the infusion. Two days after the infusion they noted the suppression of RAAS, which corresponds to the influx of sodium, whereas atrial natriuretic peptide and urodilatin were raised 22 hours after the infusion, suggesting that they may represent a slower adaptive mechanism of the prolonged infusion with sodium chloride.

In their work, which involved 3,603 healthy 25–75-year-old individuals, Nakajima et al. [15] pointed out 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 through high concentration of sodium, but not to the correlation between the high concentrations of sodium and GFR decrease. Within one hour after sodium chloride infusion, 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 macula densa cells. Due to increased concentrations of sodium chloride in the renal tubules, more sodium and chloride enter macula densa cell through $NaCl_2K$ 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 adenosine triphos-

phate (ATP) and vasoconstriction of afferent and efferent arterioles. It is assumed that ATP has a direct effect, but also adenosine, a decomposition product of ATP, acting on 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, premature infants may be especially susceptible to the effects hyperchloremia. According to previous studies, more ATP was found in erythrocytes of infants than in those of adults, and more ATP in prematurely born infants than in term infants [18]. Hypothetically, if cells of macula densa in premature infants have more ATP, their depolarization probably involves more ATP release, and thus a stronger vasoconstriction of afferent and efferent arterioles. There are no clinical studies on the effects of hyperchloremia in neonates. Completion of the research in this area is certainly necessary to extend our knowledge.

CONCLUSION

In our group of neonates, premature infants with AKI had poor outcome. Lower gestational age, lower Apgar score in the first and fifth minute, lower birth weight, and the use of mechanical ventilation are significant 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 AKI. A larger study is needed to determine which fluid is most appropriate for use in premature newborns.

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

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САЖЕТАК

Увод/Циљ У студијама на одраслима утврђено је да након надокнаде течности физиолошким раствором долази до хиперхлоремије, која доводи до вазоконстрикције бубрежних крвних судова и развоја акутног оштећења бубрега (АОБ). Циљ рада је био да се утврди повезаност дисбаланса хлора и натријума у серуму са развојем АОБ-а, као и факторе ризика који предиспонирају АОБ.

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

Резултати Од укупног броја новорођенчади (*n* = 146), 23,97% је развило АОБ. Новорођенчад са АОБ-ом су имала значајно нижу гестацијску старост (26.3 ± 2.8 одн. 31,7 ± 2.90 недеља, *p* < 0.05), порођајну тежину (971,31 ± 412,1 *gr* тј. 1753,3 ± 750,3 *gr*, *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 АОБ-а. Новорођенчад са АОБ-ом су имала 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 према 142,9 ± 4, *p* < 0,05. Сваки од ових параметара је независни статистички значајан фактор ризика за развој АОБ-а, а гестацијска старост је најзначајнији (*OR* = 1/0,643 = 1,55, 95% *CI* 1,24 до 1,94). Морталитет је био значајно већи код новорођенчади са АОБ-ом у односу на децу без АОБ-а (19,4% тј. 92,7%, *p* < 0,05).

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

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