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Risk Factors Analysis for Acute Kidney Injury in the Newborn Infants, Predictive Strategies

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Original Paper

Introduction. Acute kidney injury (AKI) in the newborn infants is associated with increased mortality and morbidity. The purpose of this study was to investigate the prevalence, risk factors and outcome of AKI in the premature neonates.
Methods. Between January 2014 and January 2015, 206 premature neonates between 27 and 36 weeks gestations were studied in the newborn intensive care unit of Amir-AL Momenin Hospital, in Semnan, Iran. All neonates were followed-up for seven days after birth. The diagnosis of AKI was based on urine output (UOP) < 1.5 mL/kg/h for 24 hours and serum creatinine SCr > 0.3 mg/dL or increased by 150% to 200% from baseline value. Data collected included gestational age, gender, birth weight, first, and fifth-minutes Apgar scores, use of mechanical ventilation, continuous positive airway pressure (CPAP), sepsis, congenital heart disease, and respiratory distress syndrome (RDS).
Results. Gestational age (OR = 12.09, 95% CI = 3.51-41.63; $P < .001$), the use of mechanical ventilation (OR = 6.72, 95% CI = 1.44-31.41; $P < .05$), and the first and fifth minutes Apgar scores (OR = 0.65, 95% CI = 0.44-0.95; $P < .05$) were significantly related with AKI occurrence. Presence of congenital heart disease, sepsis, birth weight and RDS also had a significant relationship with AKI development ($P < .05$).
Conclusion. The most important risk factors associated with AKI development were prematurity and low-birth weight, low 1 and 5 minutes Apgar scores, and the need for mechanical ventilation, as well as the coexistent of sepsis.

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INTRODUCTION

Acute kidney injury (AKI) in newborn infants has been increasingly diagnosed globally during the last two decades.[1-3] Renal hypoperfusion secondary to various prenatal conditions is the major cause of neonatal AKI.[4-7]

The incidence of AKI in critically ill neonates varies from 24% to 50% worldwide.[8-10] Prenatal azotemia is the most common type of AKI in the infants and accounts for approximately 85% of all cases.[11,12]

Respiratory distress syndrome (RDS) is the most frequent cause of neonatal AKI due to renal hypoxemia.[13]

Newborn infants with AKI also are at increased risk for the development of chronic kidney disease (CKD), which can be associated with high mortality and morbidity.[14,15] One of the preventive strategies is to identify the comorbidity risk factors associated with the development of neonatal AKI.

Few randomized controlled clinical trials have examined and reported on the incidence and risk

factors associated with neonatal AKI.[16-18]

In a study reported by Gharebaghi and colleagues, the prevalence of intrinsic, prerenal, and postnatal AKI were 49.4%, 43.5%, and 7.1%; respectively.[19] The most prevalent predisposing factors for the AKI development were surgical procedures (43.5%), perinatal asphyxia (37%), sepsis (33%), RDS (26%), heart failure (20%), and nutritional problems (20%).[19] In another study by Walker *et al*.[20] low gestational age, and birth weight were the most important factors associated with renal dysfunction. Similarly, use of a vasopressor, male gender, intracranial hemorrhage, cyanotic heart disease, and use of indomethacin, infection and nephrotoxic antibiotics, and use of mechanical ventilation during the first few days of life were other causes of AKI.[20]

The present study was conducted to determine the risk factors associated with AKI development in the premature infants admitted to the neonatal intensive care unit (NICU).

MATERIALS AND METHODS

In this cross sectional study, premature Infants born between January 2014 and January 2015 in the NICU at Amie-Al Momenin Hospital in Semnan, Iran; were enrolled in.

Infants with gestational ages between 27 to 36 weeks who were admitted to NICU were included in the study. Infants who were transferred to other medical centers or those with congenital anomalies of the kidney and urinary tract system (high Cr and BUN on the first days of birth) were excluded from the study.

Given the wide range of neonatal AKI indecent, which varies from 20% to 54% and taking into account a standard deviation of 2.25 points, an alpha of 0.05, and a beta of 0.20 (power of 0.80); the number of subjects needed for the study was estimated to be 206 cases.

All patients were selected by simple random sampling. Preterm infants were classified into two subgroups of gestational ages including 27-30 and 31-36 and were followed for seven days after birth. Peripheral blood sample (1 mL) was obtained for blood chemistry analysis, which included creatinine (Cr), and blood urea nitrogen (BUN), electrolytes and arterial blood gas on the third and seventh days of life, and then every day as soon as AKI diagnosis was established. The diagnosis of AKI was based on the SCr plus urine output (UOP) criteria (SCr > 0.3 mg/dL or increased by 150% to 200% from baseline value and UOP < 1.5 mL/kg/h for 24 hours).[10] The estimated glomerular filtration rate (eGFR) was calculated using Schwartz formula on days 3 and 7 of life. Fractional excretion of sodium (FENa) and urine specific gravity (SG) were used to differentiate prerenal from intrinsic and postrenal failure. BUN/Cr ratio was considered greater than 30:1 in prerenal AKI and < 20 in intrinsic renal AKI. FENa ≤ 2.5%, urinary sodium ≤ 20 mEq/L, and SG > 1.022, defined as prerenal, and FENa ≥ 3 or urine to plasma osmolality ratio < 1.2 considered as intrinsic AKI.[4]

RDS scoring system is an index designed to objectively assess the clinical severity of hyaline membrane disease, in which intensity of five symptoms including cyanosis, retraction, grunting, air entry-make baby cry and listen to breath sounds while baby cries and respiratory rate were scored from 0 to 2 (Table 1). The score was measured after allowing the infant to stabilize for at least five minutes at a constant F1O2. A respiratory distress score more than 8 is defined as moderate to severe dyspnea.[21]

Sepsis was diagnosed based on clinical symptoms and confirmed by laboratory tests (white blood cell counts, CRP, blood and urine cultures). Heart disease was diagnosed based on clinical symptoms, physical exam, chest X-ray, and echocardiography.

The present research followed the recommendations of the declaration of Helsinki. The ethics committee of Semnan university of medical sciences approved the study protocol. The study

Table 1. Respiratory Distress Syndrome Scoring

Clinical Symptoms	0	1	2
Respiration Rates, minute	< 60	60 to 80	> 80
Cyanosis	No	Not under the hood	Yes under the hood
Intercostal Retraction	No	Average	Severe
Respiratory Sounds	Good	Reduced	Not heard
Granting	No	Audible with stethoscope	Audible without Stethoscope

objectives were explained to patients' parents before participation and written informed consent was obtained prior to the study (Ethical code # 92/409142).

Statistical Analysis

Data included in analysis were gestational age, gender, birth weight, first and fifth minutes Apgar scores, use of mechanical ventilation or continuous positive airway pressure (CPAP), surfactant therapy, sepsis, heart disease and RDS. Data analysis was performed using SPSS version 18 software (Chicago, Illinois). Kolmogorov-Smirnov, t student, Mann-Whitney U, Chi-square and logistic regression tests were applied. Significance level was set as the *P* value below .05.

RESULTS

A total of 206 premature neonates were studied. Of these, 50 (24.3%) had gestational age between 27 and 31 weeks and the remaining156 neonates (75.5%) had gestational age between 32-36 weeks.

There were 101(49%) girls and 105 (51%) boys. The birth weight of 53 (25.25%) of neonates was less than 1500 grams, 51 (24.8%) between1500 and 1999 grams, 59 (28.6%) between2000 and 2499 grams, and 43 (20.9%), 2500 grams or more. Among the neonates, 173 (84%) received oxygen through continuous positive CPAP and 12 (5.8%) via mechanical ventilation. Surfactant treatment was initiated in 80 (38%) of neonates. Sepsis was diagnosed in 30 (14.6%) and 34 (16%) had veracity of heart diseases.

Table 2 shows relationship between developing AKI and gestational age, gender, birth weight, receiving oxygen, CPAP and mechanical ventilation, surfactant treatment, sepsis, and heart disease. Among these variables, only gender did not show any significant relationship with AKI occurrence ($P > .05$). Gestational age, birth weight, receiving oxygen, CPAP and mechanical ventilation, surfactant treatment, sepsis and heart disease all had a significant relationship with developing AKI.

In order to evaluate the effects of gestational

Table 2. Relationship Between Developing AKI and Variables

Variables	Acute Kidney Injury			*P*
	Yes		No (n = 186)	
	Renal (n = 6)	Pre-renal (n = 14)		
Gestational Age, Weekweeks				
27-31	6 (12)	10 (20)	34 (68)	< .05
32-36	0 (0)	4 (2.6)	152 (97.4)	
Gender				
Boy	2 (1.9)	10 (9.5)	93 (88.6)	> .05
Girl	4 (4)	4 (4)	93 (92.1)	
Birth Weight, g				
< 1500	6 (11.3)	10 (18.9)	37 (69.8)	< .05
1500-1999	0 (0)	3 (5.9)	48 (94.1)	
2000-2499	0 (0)	1 (1.7)	58 (98.3)	
≤ 2500	0 (0)	0 (0)	43 (100)	
On Mechanical Ventilator				
CPAP	3 (1.7)	10 (5.8)	160 (92.5)	< .05
Ventilator	3 (25)	4 (33.3)	5 (41.7)	
No Oxygen	0 (0)	0 (0)	21 (100)	
Surfactant Treatment				
Yes	6 (7.5)	12 (25)	62 (77.5)	< .05
No	0 (0)	2 (1.6)	124 (98.4)	
Sepsis				
Yes	3 (10)	6 (20)	21 (70)	< .05
No	3 (1.7)	8 (4.5)	165 (93.8)	
Heart Disease				
Yes	5 (14.7)	6 (17.6)	23 (67.6)	< .05
No	1 (0.6)	8 (4.7)	163 (94.8)	

age, gender, heart disease, sepsis, first- and fifth-minute Apgar scores, birth weight, RDS severity, and impact of mechanical ventilation as potential independent variables and AKI as a dependent variable, logistic regression analysis was conducted. The results showed that the gestational age (OR = 12.09, 95% CI = 3.51-41.63; $P < .001$) and the use of mechanical ventilation (OR = 6.72, 95% CI = 1.44-31.41; $P < .05$) and also the first-minute Apgar (OR = 0.65, 95% CI = 0.44-0.95; $P < .05$) as independent risk factors were significantly related with AKI (Table 2). The AKI incidence in neonates with gestational age of 27-29 weeks was 12 times more than that of neonates with gestational age of 36-32 weeks. The chance of developing AKI in the neonates requiring ventilator support was 6.7 times more than those who did not need a ventilator.

DISCUSSION

The aim of this study was to determine the incidence of AKI and its related risk factors in premature infants admitted to NICU. The study results provide evidence that majority of neonates with AKI were born prematurely, had low birth weight, received oxygen, CPAP, mechanical ventilation, surfactant therapy and had sepsis or congenital heart diseases. In logistic regression analysis, AKI significantly correlated with first-minute and fifth-minute apgar scores, gestational age, birth weight, ventilation support, heart disease, presence of sepsis, or RDS severity (Table 3).

Youssef *et al.*[22] reported the AKI incidence in 250 term and preterm infants who were admitted in a NICU and showed 10.8% of patients had AKI and the incidence was higher in boys and preterm neonates (59.3%). They also found that AKI most frequently occurred as prerenal (96.3%) compared with intrinsic or post renal AKI, which was in agreement with the result of the present study. In a more recent and larger study, Momtaz *et al.*[23] reported the prevalence of AKI was 1.54% (49 out of 3166 patients admitted to NICU). The AKI was higher in girls and sepsis was the most common contributing factor of AKI. In the study by Momtaz, RDS and open artery duct were associated with higher incidence of AKI.[23] In another study reported by Vachvanichsanong *et al.*, consisting of 88 boys and 51 girls, 61% were premature and 56 % were under 2500 g. In their study, the most common cause of AKI was sepsis,[24] which was in contrast to the study by Mathur *et al.* who found out birth weight and AKI had a significant close relationship[25] but consistent with our study results. On the other hand, several investigators showed direct associations between sepsis and hypoxic events and AKI development.[26-9]

Koralkar *et al.* evaluated 229 neonates with a very low-birth weight (between 500-1500 g) from birth to the age of 36 weeks of gestation.[9] They found 18 % were affected by AKI and neonates with AKI seemed to have a low-birth weight, low gestational age, receiving mechanical ventilation and had lower Apgar scores, findings that were similar to those reported in our study. In another study, Stojanovic *et al.* conducted[30] on 150 premature neonates with birth weight less than 1500 g the authors showed that fifth minute apgar score less than 5, serum lactate level greater than 5 in the first day of life, central body temperature lower than 36°C in the first day of life, infection, intracerebral hemorrhage, open artery duct, necrotizing enterocolitis, and vancomycin or dopamine usage were potential risk factors for AKI.[30] Prematurity, low birth weight < 1500 g, need for mechanical ventilation and use of non-steroidal anti-inflammatory agents also have been reported as potential risk factors for AKI development by other investigators.[31,33]

Premature neonates, less than 36 weeks, have fewer number of nephrons, which may predispose them to AKI.[34,35] Further, low apgar scores cause hypoxia and acidosis, leading to hypotension,

Table 3. Respiratory Distress Syndrome and First- and Fifth- Minute Apgar Scores and Their Relationships with AKI (Mean ± SD)

Variables	AKI			*P*
	Yes		No (n = 186)	
	Renal (n = 6)	Pre-renal (n = 14)		
Respiratory Distress Syndrome	5.33 ± 1.75	5.20 ± 1.28	4.12 ± 1.71	< .005
First Minute Apgar Score	6.67 ± 2.34	6.14 ± 1.41	7.81 ± 1.21	< .001
Fifth Minutes Apgar Score	8.17 ± 1.72	8.21 ± 1.19	9.06 ± 0.87	< .001

decreased renal blood flow and kidney injury.[36] Likewise, patients receiving surfactant are at increased risk of acute AKI because of higher RDS score and lower gestational age.[37] Mechanical ventilation can cause pneumothorax, nosocomial pneumonia, cardiovascular complications, gastrointestinal bleeding, sepsis, and complicate the severity of AKI. Moreover, positive end-expiratory pressure (PEEP) by reducing cardiac output and therefore decreasing venous return and renal blood flow may accelerate the course of AKI.

CONCLUSION

Our study revealed that the most important risk factors associated with AKI development were prematurity and low-birth weight, low 1 and 5 minutes apgar scores, and the need for mechanical ventilation, as well as the coexistent sepsis.

LIMITATION OF THE STUDY

There are some limitations in our study; first, the neonates were examined during the first seven days of life. Second, the predisposing factors for AKI are much wider than what we have presented in this study.

ETHICAL CONSIDERATION

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

CONFLICT OF INTEREST

The authors declare no conflicts of interest regarding the contents of this article.

AUTHORS' CONTRIBUTION

MM contributed substantially to the concept, design, and data analysis of the work and edited and approved the final manuscript version for publication. MR contributed to the design of the study, collected and analyzed data and writing proposal. GR did the statistical analysis and provided first manuscript draft

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