Paediatrica Indonesiana

VOLUME 53 July • 2013 NUMBER 4

Original Article

Acute kidney injury in asphyxiated neonates

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Abstract

Background Asphyxia neonatorum may result in multiorgan dysfunction including renal involvement. There is no consensus on the determination of acute kidney injury (AKI) in neonates making establishment of the diagnosis and its management becomes difficult. The Acute Kidney Injury Network (AKIN) recommends AKI criteria based on increased serum creatinine level and reduced urine output.

Objectives To identify the prevalence of AKI in asphyxiated neonates using the AKIN criteria, to compare the difference of AKI stages, and the glomerular filtration rates (GFR) between moderate and severe asphyxia.

Methods This was a cross-sectional analytical study conducted between July 2012 and January 2013. Subjects were all asphyxiated neonates (Apgar score <7 at fifth minute) with gestational age of ≥35 weeks delivered and hospitalized in Cipto Mangunkusumo Hospital and Koja District Hospital, Jakarta, Indonesia. Glomerular filtration rate was calculated using the components of urine creatinine, serum creatinine, and urine output; while AKI stages were determined according to AKIN criteria. Urinary output was measured via urethral catheterization.

Results Of 94 subjects, there were 70 neonates with moderate and 24 neonates with severe asphyxia, with the prevalence of AKI was 63%. Twenty one out of 24 neonates with severe asphyxia experienced AKI, while neonates with moderate asphyxia who experienced AKI was 38 out of 70 subjects (54%). Two third of neonates with severe asphyxia who experienced AKI had stage 3 of AKI. More severe AKI stages and lower median GFR were found in neonates with severe compared to moderate asphyxia (P<0.001).

Conclusion The prevalence of AKI in neonatal asphyxia is high (63%). The more severe degree of neonatal asphyxia, the more severe AKI stage and the lower median GFR. **[Paediatr Indones. 2013;53:232-8.]**

Keywords: *acute kidney injury, asphyxiated neonates, serum creatinine, urine output*

World Health Organization defines asphyxia as failure to breath spontaneous and regularly at birth.[1] The incidence of asphyxia in various countries ranges from 1 to 24% of live birth.[2,3] In Indonesia, estimated incidence of neonatal asphyxia is 3-5% of live birth.[4] A study performed at the Department of Child Health, University of Indonesia Medical School/Cipto Mangunkusumo Hospital (RSCM) in 2009 reports 5.9% neonatal asphyxia of all birth.[5] Hypoxia and acute ischemia due to asphyxia cause multiorgan dysfunction including renal dysfunction which reached 70% cases.[6] The occurrence of AKI in neonates with Apgar score on first minute <6 is 41.7% and in about 16.6% of them the kidney injury continues until 96 hours after birth.[7] Until now, no universal definition exists about AKI. Most studies used serum creatinine level of >1.5mg/dL as a cut-off point of AKI in neonates.[6,8] Acute Kidney Injury Network (AKIN) recommends criteria of AKI based on the increase of serum creatinine level and/or decrease of urine output and classifies AKI into three stages, stage 1 (mild), 2 (moderate), and 3 (severe).[9]

We aimed to identify the prevalence of AKI on neonatal asphyxia using AKIN criteria, to recognize

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for the relationship of AKI stages with the severity of asphyxia, and to identify the glomerular filtration rate (GFR) in neonates with moderate and severe asphyxia.

Methods

A cross-sectional analytical study was performed in the Neonatology Division of Cipto Mangunkusumo Hospital (RSCM) and District Hospital (RSUD) Koja Jakarta from Juli 2012 to Januari 2013. Subjects were all neonates with gestational age $\geq$35 weeks with Apgar score on the fifth minute <7 who were born and hospitalized in RSCM and RSUD Koja. We excluded neonates with major congenital malformation on physical examination at birth or detected previously by ultrasound on prenatal examination, neonates with syndromes, neonates who received vancomycin, furosemide, indomethacin, or ibuprofen; as well as neonates died before 48 hours; or parents did not give any consent to follow the study. Subjects were taken consecutively. A sample of 95 neonates was needed based on single sample formula to estimate a proportion of a population. A minimal subjects of each 29 neonates for each stage of asphyxia (moderate and severe) was needed, based on formula two independent group proportions.

Apgar score estimation was performed on minute 1st, 5th, and 10th by pediatricians, residents or by nurses/midwives based on reliability test with a Kappa score ≥0.8. Moderate asphyxia was defined as the Apgar score of 4 to 6 on the fifth minute, while severe asphyxia was the Apgar score of ≤3 on the fifth minute. The parents were informed about the study and were asked for the consent. The baseline characteristics of the neonates and mothers were recorded, anthropometries data were measured, and the estimation of gestational age was performed by using Ballard chart. The history of pregnancy and delivery, the diagnosis of hospitalization, and data of resuscitation in the delivery or operating room were recorded. Mothers' serum creatinine level before delivery was also recorded, but if the data was not available, then mother's serum creatinine level was measured in 24 hours after having birth.

An urethral catheter was performed in neonates to measure the time of first micturition, then the quantity of urine was collected by nurses until 48-72 hours of age. All neonates were using diapers, so that if there was a leak from the catheter, the diapers were weighted with a 10 gram sensitivity scale. The subject was excluded from this study if urine quantity was not measured in more than 6 hours. When the neonates aged 48-72 hours, a 2 ml blood sample was taken to measure serum creatinine level and urine was collected for 6 hours to measure urine creatinine. Blood and urine samples were taken simultaneously. The measurement of serum and urine creatinine level was performed by using *Enzymatic Creatinine_2 ADVIA 1800* machine with enzymatic method. Glomerular filtration rate (GFR) was calculated based on estimated creatinine clearance (eCCl) on 48-72 hours age using the following formula::

$$eCCl = \frac{UCr \times urine\ (mL/menit)}{SCr} \times \frac{1.73}{BSA}\ mL/minute/1.73\ m^2\ BSA$$

Acute kidney injury is defined as serum creatinine level increased by or more than 0.3 mg/dL measured by the difference between mother's and neonates' serum creatinine levels at 48-72 hours, or the increase of percentage neonate's serum creatinine levels at 48-72 hours by 50% compared to mother's serum creatinine levels, or a decrease in urine output <0.5 mL/kg/hour more than 6 hours after first urine.

Table 1. AKIN criteria[9]

Stage	Serum creatinine	Urine output
1	Increase >0.3 mg/dL or increase >150-200% baseline	<0.5 mL/kg/hour over 6 hours
2	Increase >200-300% baseline	<0.5 mL/kg/hour over 12 hours
3	Increase >300% baseline or > 4.0mg/dL with acute increase ≥ 0.5mg/dL	<0.3 mL/kg/hour over 24 hours or no urine for 12 hours

The AKI was determined based on AKIN criteria and AKI stage was chosen based on the worst stage of serum creatinine level increase or urine output decrease (**Table 1**).

Mother's serum creatinine level performed before delivery or 24 hours after delivery considered as the baseline serum creatinine level of the neonates. The normal cut-off point for mother's serum creatinine level was <1.0 mg/dL. The mean normal GFR on neonates with gestational age ≥35 weeks at age 2 and 4 days were 20.8 (SD 5) and 46.6 (SD 12.7) mL/min/1.73 m^2, consecutively.[7]

This study had approval from Ethical Committee of University of Indonesia Medical School. All parents gave consents for the study.

The difference between moderate and severe AKI were analyzed by using Chi-square or Kolmogorov-Smirnov where Chi square was not able to be applied. Mann-Whitney test was used for analyzing numerical data. The significance in this study was $P<0.05$.

Results

During the study period, there were 3,761 live birth with 97 neonates fulfilled the inclusion criteria, but 3 neonates were of incomplete data, therefore they expelled from the analysis. There were a total of 94 asphyxiated neonates recruited in this study, consisted of 70 neonates with moderate asphyxia and 24 neonates with severe asphyxia. Birth weight, birth length, sex, gestational age, degree of asphyxia, type of delivery, and age of first micturition are listed on **Table 2**. Mean and median of mother's serum creatinine level were 0.5 (SD 0.13) mg/dL and 0.5 (range 0.2-1.2) mg/dL, respectively.

Table 2. Characteristics of subjects

Characteristics	n=94
Mean birth weight (SD), gram	2.737 (581)
Median birth length (range), cm	48 (41-53)
Sex, n (%)	
Male	57 (61)
Female	37 (39)
Median gestational age (range), weeks	38 (35-43)
Degree of asphyxia, n (%)	
Moderate	70 (75)
Severe	24 (25)
Delivery type, n (%)	
Spontaneous	40 (43)
Vacuum extraction	8 (9)
Forceps extraction	1 (1)
Caesarian surgery	46 (47)
Median first micturition age (range), hours	7 (1-36)

Table 3. Prevalences and stages of acute kidney injury in all asphyxiated neonates

Variables	Numbers n=94	
Based on AKIN criteria, n (%)		
AKI	59 (63)	
Stages of AKI		
Stage 3		18 (31)
Stage 2		18 (31)
Stage 1		23 (38)
No-AKI	35 (37)	
Based on serum creatinine level, n (%)		
AKI	44 (47)	
Stages of AKI		
Stage 3		9 (21)
Stage 2		12 (27)
Stage 1		23 (52)
No-AKI	50 (53)	
Based on 24 hours urine output collected after first micturition, n (%)		
AKI	39 (42)	
Stages of AKI		
Stage 3		13 (33)
Stage 2		15 (39)
Stage 1		11 (28)
No-AKI	55 (58)	

The determination of AKI stages based on AKIN criteria was assessed based on the increase of serum creatinine level and/or decrease of 24 hours urine output collected after first micturition. Based on those two indicators, the prevalence of AKI was 59 subjects (63%). There were 23 (38%) neonates with AKI stage 1. Neonates with AKI based on increase of serum creatinine level only were 44 (47%), this was comprise of 23 (52%) neonates with stage 1 AKI. The neonates with AKI based on decrease of 24 hours urine output after first micturition was 39 (42%), amongst them 15 (39%) neonates had stage 2 of AKI (**Table 3**).

The comparison of prevalence and stage of AKI in moderate and severe asphyxia based on AKIN criteria, increase of serum creatinine level, and decrease of 24 hours urine output collected after first micturition are shown in **Table 4**.

Table 5 shows that neonates with severe asphyxia had a higher median (range) of serum creatinine level and a lower median (range) of GFR compared to the moderate asphyxia (P=0.005, P<0.001, respectively)

Discussion

The numbers of neonates with moderate and severe asphyxia were 74 (76%) and 24 (24%), consecutively. This is almost similar with other studies which reported the numbers of moderate and severe asphyxia were

Table 4. Prevalences and stages of AKI based on severity of asphyxia

Variables	Severe asphyxia group (n=24)	Moderate asphyxia group (n=70)	P value
Based on AKIN criteria, n (%)			
Yes	21	38	0.003#
No	3	32	
Stages			
Stage 3	14	4	<0.001#
Stage 2	5	14	
Stage 1	2	22	
Based on serum creatinine increasing level, n (%)			
Yes	16	28	0.025#
No	8	42	
Stages			
Stage 3	6	3	0.458*
Stage 2	4	8	
Stage 1	6	17	
Based on urine output 24 hours after first micturition, n (%)			
Yes	20	19	<0.001#
No	4	51	
Stages			
Stage 3	12	1	<0.001#
Stage 2	6	9	
Stage 1	2	9	

Chi-Square test; * Kolmogorov-Smirnov test

Table 5. Serum creatinine levels and glomerular filtration rates on moderate and severe asphyxia (n=94)

	48-72 hours		P value
	Moderate asphyxia (n=74) Median (range)	Severe asphyxia (n=24) Median (range)	
Serum creatinine level (mg/dL)	0.62 (0.42-1.88)	0.84 (0.40-3.32)	0.005*
GFR based on eCCl (mL/min/1.73m^2)	29.59 (9.46-115.53)	11.21 (2.11-43.8)	<0.001*

* Mann-Whitney test

53 (76%) and 17 (24%).[10] Almost all neonates with asphyxia had first micturition in 24 hours after birth. There was 1 neonate with severe asphyxia had its first micturition at 36 hours. Manoe *et al* reported 3 out of 33 neonates with asphyxia had their first micturition in 24-48 hours after birth.[11] In neonates with asphyxia, a paralysis of bladder might temporarily exist which may cause urine tardiness.[12] The low prevalence of neonates with asphyxia with first micturition >24 hours in this study might be because of the use of urinary catheter which ensure urine output, although there might be temporary bladder paralysis.

In this study, 59 (63%) neonates with asphyxia had AKI based on increase of serum creatinine level and/or decrease of urine output. The result is similar to a report from Aggarwal *et al* and Karlowicz *et al* who reported 56% and 61% neonates with asphyxia had acute renal failure, consecutively.[8,13] Askenazi *et al*[14] reported 16% neonates with asphyxia had AKI and Seleweski *et al*[15] reported 38% neonates with asphyxia who were treated with hypothermic method had AKI according to AKIN criteria. The high prevalence of AKI in this study might be due to severe and long hypoxia and hypoperfusion of the kidney. This in turn caused a disturbance in the nephrons which will increase the serum creatinine level and decrease of urine output. The low incidence of AKI in the study by Askenazi *et al* might be due to subject analysis was only performed on neonates with moderate asphyxia, while the low incidence of AKI in the study of Seleweski *et al* might be due to the effect of hypothermic therapy in the kidneys of neonates with asphyxia.

The prevalence of AKI based on increase of serum creatinine level only was 44 (47%). Manoe *et al* reported that 8 out of 33 (24%) neonates with fifth minute Apgar score <7 had an increase of serum creatinine level.[11] The assault of the nephrons due to hypoxia or hypoperfusion will lead to a decrease in creatinine clearance which in turn will increase serum creatinine level.[16] The problem of diagnosis of AKI based on serum creatinine level only in neonates is that neonate's serum creatinine level is still influenced by the creatinine level of the mother. The serum creatinine level was still similar to mother's.[17] In this study, the increase of serum creatinine level was measured by comparing neonate's serum creatinine level at 48-72 hours with mother's serum creatinine level. The low prevalence of AKI in the study by Manoe *et al* might be due to the difference of measurement of neonate's serum creatinine level compared to this study.

In this study, 39 neonates (42%) had AKI based on a decrease of 24 hours urine output collected after first micturition. Perlman *et al* reported that 14 out of 35 neonates with asphyxia had oliguria.[18] Mohan *et al* reported that 22 out of 36 neonates with asphyxia had oliguria.[19] Vasoconstriction of afferent arterioles which occurre at the time of hypoxemia leads to a decrease in urine output due to a decrease of blood flow to the kidneys.[20,21] Perlman's report was similar to this study, probably because of relatively similar subject criteria although they added the parameters of pH and pCO_2 of umbilical cord artery in diagnosing asphyxia.[18] The high incidence of oliguria in Mohan's report might be because of kidney injury occurred more severe than those in our study. Mohan used tighter criteria for neonatal asphyxia, those were lower Apgar score and the occurrence of hypoxic ischemic encephalopathy (HIE).[19] Hypoxic ischemic encephalopathy indicates the severity of hypoxia in the body which induces organs, including kidney, to have worse disruptions compared to asphyxia without HIE.

The prevalence of AKI in moderate and severe asphyxia based on the increase of serum creatinine level and/or the decrease of urine output was 40 (54%) and 21 (88%), consecutively. The difference of AKI prevalence between moderate and severe asphyxia was 34%. Radityo *et al* reported the difference of prevalence of 34%.[22] High prevalence of AKI in severe asphyxia probably due to the hypoxia and hypoperfusion conditions of the kidney are more severe and longer standing compared to moderate asphyxia. More nephron disruptions in severe asphyxia lead to more increase of serum creatinine level and decrease of urine output than moderate asphyxia. The findings that more AKI was found in severe asphyxiated neonates compared to moderate asphyxia are similar to other previous studies.[11,13]

This study also indicates that neonates with severe asphyxia are more likely to have more severe AKI stages compared to moderate asphyxia. This might be due to severe hypoxia on neonates with severe asphyxia which leads to disruption of blood flow to kidney compared to moderate asphyxia.

The median of serum creatinine level on neonates with severe asphyxia was higher than moderate asphyxia. This result is similar with other studies.[22-24] This might happen due to more nephron disruptions

in severe asphyxia than moderate asphyxia.

The median GFR on severe asphyxia was lower than moderate asphyxia. Two means comparison analysis for the difference of GFR in severe and moderate asphyxia reveals a significant difference. We can conclude that the more severe the asphyxia, the lower the value of GFR. Umboh[23] reports that there was a significant difference of GFR in mild-moderate asphyxia compared to severe asphyxia. The median GFR for moderate and severe asphyxia reported in that study was 28.9 (SD 6.9), and 22.2 (SD 6.4) mL/min/1.73 m^2, consecutively.[23] We found a larger difference between median GFR of neonates with severe asphyxia and moderate asphyxia compared to Umboh's study. This might be because the difference of diagnostic criteria of asphyxia used. Asphyxiated neonates in Umboh's study was defined as Apgar score <7 at the first minute while in our study we defined asphyxia as the Apgar score <7 at the fifth minute. Longstanding and severe hypoxia in this study compared to Umboh's probably has an effect to the lower GFR in severe asphyxia.

Limitations of this study were the criteria for asphyxia based only on Apgar score on fifth minute of <7, the neonates' serum creatinine level was examined once at 48-72 hours, and the etiology of AKI was not explored further. But, this study also has superiority, where urinary output was monitored carefully using urinary catheter therefore we could get exact amount of urine and the serum creatinine level was performed using an enzymatic method thus hemolysis, icteric serum, and albumin level did not disturb the result.

We conclude that AKI prevalence based of AKIN criterias on neonatal asphyxia is 63%; the more severe the asphyxia the more prevalence and severity of the AKI stages. The median of GFR based on eCCl in neonates with moderate asphyxia is higher than the severe asphyxia. Considering AKI prevalence is high in neonates with asphyxia and low GFR in severe asphyxia, medical professionals need to alert on the possibility of AKI in neonatal asphyxia, therefore prompt interventions can be made.

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