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ORIGINAL ARTICLE

Physiologic changes of serum creatinine level following aminoglycoside exposure in neonatal sepsis

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ABSTRACT

BACKGROUND: The study aimed to assess the pattern of serum creatinine levels changes and prevalence of AKI after aminoglycoside treatment for seven days in neonatal sepsis.

METHODS: This prospective cohort study included preterm and full-term newborns admitted with suspected sepsis and received aminoglycosides. SCr levels were measured before and after aminoglycoside treatment for seven days using the Jaffe method, and the results were compared between the two groups of newborns. AKI was determined according to the Kidney disease: Improving Global Outcome (KDIGO) criteria.

RESULTS: A total of 37 preterm and 35 full-term newborns were included in the study. SCr levels before and after aminoglycoside treatment for seven days, were 0.78 *vs.* 0.57 mg/dL (P=0.008) in preterm, and 0.60 *vs.* 0.44 mg/dL (P=0.124) in full-term newborns. In both groups, SCr levels decrease despite treatment with an aminoglycoside, but only in preterm, the decrease was significant. After aminoglycoside treatment, there was no significant difference in SCr levels between the two groups. The prevalence of AKI in preterm and full-term newborns was 18.9% *vs.* 15.3% (P=0.598). There was no significant correlation between AKI and gestational age, chronological age, birth weight, type of aminoglycoside, and urine output.

CONCLUSIONS: SCr level changes after aminoglycoside treatment appear to follow a pattern of physiological decline and have not been affected by gestational age. AKI occurrence is a sign that aminoglycoside should be administered with caution, especially in newborns with high-risk underlying diseases.

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KEY WORDS: Aminoglycosides; Creatinine; Infant, newborn.

Aminoglycosides are the most used antibiotics in newborns with high suspicion of sepsis in neonatal intensive care units (NICUs) combined with ampicillin.[1] Streptomycin was the first aminoglycoside introduced in 1944, followed by neomycin (1949), kanamycin (1957), gentamycin (1963), tobramycin (1968), amikacin (1972), and netilmicin (1975). The most widely used aminoglycosides in NICUs are gentamicin and amikacin. Despite their high efficacy profile, aminoglycosides have the potential to cause nephrotoxicity and ototoxicity. Tubular damage has been reported in up to 50% of neonates exposed to aminoglycosides.[1-4] Aminoglycoside use may lead to the manifestation of non-oliguric renal impairment, with elevated serum creatinine levels and hypoosmolar urinary output that develops 7-10 days after administration. Toxic effects occur because a small portion of aminoglycosides accumulates in the epithelial cells, mainly of the proximal tubules, following glomerular filtration. This accumulation can also occur in the distal and col-

lecting tubules for an extended period, leading to intracellular alterations and damage ranging from losing the brush border to complete tubular necrosis. Furthermore, the functional kidney damage could be through the mechanism involved in water and soluble transportation, obstructing the lumen tubules. Other contributing factors are the generation of free radicals and the decrease of renal blood flow through local enhancement of vasoconstrictors and blocking vasodilators. Treatment with gentamicin may induce oxidative stress of renal tubules mediated by hydrogen peroxide and superoxide anions, a group of reactive oxygen species (ROS).[2, 5, 6] In neonates, aminoglycoside elimination is affected by age and maturity. The kidneys of preterm newborns, which are still going through structural and functional development stages, behave differently from those of mature newborns. This difference in elimination ability leads to differences in drug toxicity to the kidneys. Prematurity is associated with a higher risk of aminoglycoside nephrotoxicity and may impair renal function with long-term use. Several studies have shown that aminoglycoside exposure may result in morphological and functional changes in developing kidneys and puts the infant at risk for AKI. The studies also reported that the side effects of aminoglycosides on glomeruli and renal tubules are greater in preterm than in full-term newborns.[2, 7-9] Therefore, it is essential to assess the renal function of newborns receiving aminoglycoside, based on their level of maturity/gestational age, to determine the safety of aminoglycoside use in preterm and full-term newborns. It is well known that serum creatinine (SCr) is one of the biomarkers used to assess renal function. Although SCrs levels may not change until 25-50% of renal function has been impaired,[10] this biomarker is still obtainable and the most widely used, including in the neonatal intensive care setting.[11] This prospective cohort study was conducted to assess the effect of different gestational ages on SCr levels by comparing SCr levels changes before and after aminoglycoside treatment for seven days in each and between groups of preterm and full-term newborns. The secondary outcomes were the prevalence of AKI and the evaluation of factors related to AKI in the two groups.

Materials and methods

Study design and study population

This study was observational with a prospective cohort approach, conducted in the Neonatal Intensive Care Unit (NICU) of Dr. Wahidin Sudirohusodo Hospital, Makassar, Indonesia, from February to April 2017. All suspected sepsis newborns ≥24 hours of age admitted to the NICU and who have never received antibiotics before were asked their guardian to participate in the study. Exclusion criteria were determined to reduce confounding factors predisposed to AKI, namely small for gestational age, asphyxia, use nonsteroidal anti-inflammatory drugs (NSAIDs) and glucocorticoid therapy, shock, major congenital anomalies, and who survived less than seven days after admission. The data relating to the research was recorded.

Ethical issues

The study protocol was approved by Institutional Review Board of the ethical committee of Faculty of Medicine, Hasanuddin University, Makassar, Indonesia.

Data collection

Newborns who met the inclusion criteria were examined and recorded at the time of admission for the gestational age, sex, birth weight, birth length, chronological age (an age when aminoglycoside was administered), and the type of aminoglycoside used. Urine output was measured after seven days of aminoglycoside treatment. SCr levels were measured before and after being treated with an aminoglycoside for seven days in a chemical blood analyzer (Pentra 400, ABX, Horiba Medical Montpellier, France), and the results were grouped based on gestational age (preterm and full-term groups). The SCr decline was calculated by estimating the percentage of SCr decline before and after aminoglycoside treatment. The subjects were defined as having neonatal AKI (nAKI) according to the kidney disease: Improving Global Outcomes (KDIGO) definition, which defines nAKI as a rise in SCr level ≥0.3 mg/dL within 48 hours or a ≥1.5-1.9 fold from baseline.[12]

Aminoglycoside administration

According to our NICU protocol, the first choice of aminoglycoside to treat neonatal sepsis is gentamycin (combined with ampicillin), and then it will be replaced with amikacin as the second choice if there is a clinical deterioration or no clinical improvement within 48 hours. The protocol for aminoglycoside administration in our NICU follows the guideline developed by Young in 2010. Briefly, intravenous dose of gentamycin at gestational age ≤29 weeks 5 mg/kg/48 hours, gestational age 30-34 weeks 4.5 mg/kg/36 hours, gestational age ≥35 weeks 4 mg/24 hours; while an intravenous dose of amikacin at gestational age ≤29 weeks 18 mg/kg/48 hours, gestational age 30-34 weeks 18 mg/kg/36 hours, gestational age ≥35 weeks 15 mg/24 hours.[13]

Outcomes

The primary outcomes were comparing SCr levels changes before and after aminoglycoside administration for seven days within each group of preterm and full-term newborns and comparing the two groups. The secondary outcomes were prevalence of AKI and factors related to AKI in the two groups (gestational age, chronological age, the type of aminoglycoside used, birth weight, and urine output).

Statistical analysis

All statistical analyses were conducted using the SPSS software for Windows, version 25.0 (IBM Corp., Armonk, NY, USA). Normally distributed data were presented as the mean and standard deviation of 95% confidence interval (95% CI), whereas non-normally distributed data were presented as the median and minimum-maximum range. For comparison, Student's *t*-test, Mann Whitney U Test, and Wilcoxon signed-rank test were used for continuous data, and the chi-square test and Fisher's Exact Test were used for categorical data. A P value of <0.05 was considered statistically significant.

Results

A total of 128 newborns with suspected sepsis and who received aminoglycoside were enrolled

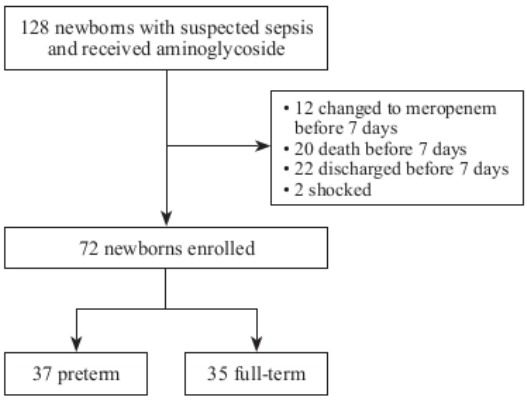

Figure 1.—Flowchart of subjects' enrolment and reasons for exclusion.

in this study. After excluding some subjects base on the exclusion criteria, only 72 subjects remained. Of them, 37 subjects and 35 subjects were classified into preterm group and full-term group, respectively (Figure 1).

Characteristic of the study subjects

Table I summarizes the demographic characteristic of each group. A total of 72 newborns were divided into two groups, 37 were preterm and 35 were full-term newborns. Gestational age in the preterm group had a median value of 32 weeks. Birth weight was ranged between 830-2400 grams with a median value of 1525 grams. In the full-term group, the median gestational age was 38 weeks. Birth weight was ranged between 2500-4110 grams with a median value of 2900 grams. The characteristics were similar in the two groups, and no statistically significant differences concerning sex and type of aminoglycoside used. Age at the time of aminoglycoside administration was significantly different between the two groups (P=0.02). In the preterm group, the distribution of age less than seven days was 99%, while it was 77% in full-term. Urinary output after administration of aminoglycoside for seven days was significantly higher in the preterm group than in the full-term group. However, the values in both groups were still within normal limits.

Serum creatinine level

In preterm newborn, the mean (SD) SCr levels before aminoglycoside treatment was signifi-

TABLE I.—*Demographic characteristics.*

N.	Variables	Groups		P value
		Preterm (N.=37)	Full-term (N.=35)	
1	Sex			
	Male (N.)	23	22	0.951*
2	Aminoglycosides, N. (%)			
	Gentamicin	14 (37.8),	17 (48.6)	0.316*
	Gentamicin+amikacin	23 (56.8)	18 (51.4))	
3	Age, days			
	Median (min-max)	1 (1-11)	3 (1-17)	0.002**
4	Urine output after 7 days of aminoglycoside, mL/kg/h			
	ean (SD)	3.69 (1.07)	3.02 (0.89)	0.005***
5	Gestational age, weeks			
	Median (min-max)	32 (27-36)	38 (37-40)	
6	Birth weight, g			
	edian (min-max)	1525 (830-2400)	2900 (2500-4110)	
7	Birth length, cm			
	Median (min-max)	40 (36-50)	48 (45-51)	

*χ^2 test; **Mann-Whitney Test; ***independent student *t*-test.

TABLE II.—*Serum creatinine levels in preterm and full-term newborns before and after seven days of aminoglycoside treatment.*

Serum creatinine level (mg/dL)	Preterm newborns*		Full-term newborns**	
	Before (N.=37)	After (N.=37)	Before (N.=35)	After (N.=35)
Mean (SD)	0.78 (0.37)		0.60	-
an (min-max)	-	0.57 (009-1.86)	-	0.44(0.04-2.40)

*Wilcoxon signed rank test P=0.008 (<0.01); **Wilcoxon signed rank test P=0.124 (P>0.05).

TABLE III.—*Comparison of serum creatinine levels between preterm and full-term newborns before and after aminoglycoside therapy.*

Creatinine level (mg/dL)	Before treatment*		After treatment**	
	Preterm (N.=37)	Full-term (N.=35)	Preterm (N.=37)	Full-term (N.=35)
Mean (SD)	0.78 (0.37)	0.60 (0.25)	0.60 (0.33)	0.58 (0.54)
Median (range)	0.86 (0.01-1.39)	0.62 (0.22-1.40)	0.57 (0.09-1.86)	0.44 (0.04-2.44)

*Student's *t*-test P=0.017 (P<0.05); ** Mann-Whitney U-Test P=0.085 (P>0.05).

cantly higher than the median (min-max) levels after treatment for seven days (0.78 [0.37] *vs.* 0.60 [0.09-1.86] mg/dL; P=0.008) (Table II). In full-term newborns, the mean (SD) SCr levels before aminoglycoside treatment was not significantly different with the median (min-max) levels after treatment for seven days (0.59 [0.25] mg/dL *vs.* 0.44 [0.04-2.40] mg/dL; P=0.124) (Table II, III). The mean (SD) SCr levels in preterm group before treatment was significantly higher than full-term groups (0.78±0.37 mg/dL, *vs.* 0.60±0.25 mg/dL, respectively; P=0.015). In comparison, after seven days treatment the SCr median (min-max) levels was not significantly different between the two groups (0.57 [0.09-1.86] mg/dL *vs.* 0.44 [0.04-2.40 mg/dL, respectively]; P=0.085). In both groups, SCr levels decreased despite treatment with an aminoglycoside, but only in preterm, the decrease was significant (Table IV; Figure 2). After AKI subjects were excluded, the percentage decline in SCr levels before and after treatment was 34% in preterm and 32% in the full-term group.

Acute kidney injury

The prevalence of AKI after seven days of aminoglycoside treatment in the preterm group was 7 (18.9%), while in the full-term group was 5 (14.3%). This prevalence was not significantly different between the two groups, with a

TABLE IV.—*Possible contributing factors for acute kidney injury.*

N.	Variables	Groups		P value
		AKI (N.=37)	Non-AKI (N.=35)	
1	Gestational age, weeks Median (min-max)	34.5 (28-38)	36.5 (27-40)	0.343*
2	Birth weight, g Mean (SD)	2108.7 (811.52)	2320 (854.56)	0.426**
3	Chronological age, days Median (min-max)	2 (1-11)	1 (1-17)	0.388**
4	Urine output after seven days of aminoglycoside, mL/kg/h Mean (SD)	3.06 (0.98)	3.42 (1.04)	0.270*
5	Type of aminoglycosides, N. (%) Gentamicin	3 (25)	28 (46.7)	0.166***
	Gentamicin + amikacin	9 (75)	32 (53.3)	

*Mann Whitney U-Test; **Student's *t*-test; ***χ^2 test.

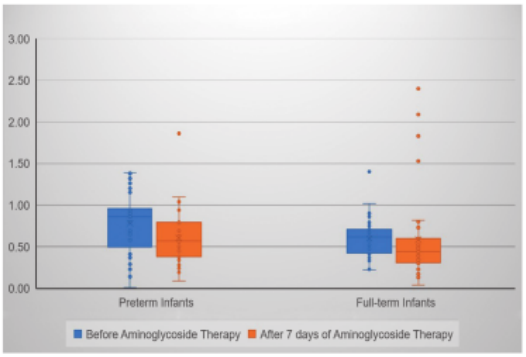

Figure 2.—Comparison of serum creatinine levels of preterm and full-term newborns before and after seven days of aminoglycoside treatment.

P value = 0.598. There were no significant differences between newborns with AKI and without AKI concerning gestational age, birth weight, chronological age, the type of aminoglycoside used, and the urine output (Table IV).

Discussion

This prospective study was conducted to compare the SCr levels changes before and after seven days of aminoglycoside administration between preterm and full-term newborn who suffered from sepsis, and the prevalence of AKI in the two groups. The results revealed that changes in SCr levels before and after treatment were equally decreased within normal range in both group although only in the preterm group which decreas[10] significantly. Furthermore, the SCr levels was not significantly different between the two groups after receiving aminoglycos[41] for seven days. The prevalence of AKI also not significantly different between the two groups. At birth the biochemical values of newborns are often influenced by maternal values and the adaptation process during the transition into the extra-uterine life, as well as SCr levels. Numerous stu[65] have shown that infant SCr levels are highest on the first day of life as a reflection of maternal SCr, then generally decreases to a stable level as the kidney adapt.[14-16] Innate kidney function is the primary determinant for the ability of the newborns to reach their own SCr steady state. One of the studies that proves this phenomenon is study by Bueva *et al*. They found that SCr levels of 66 physiologically stable preterm and full-term newborns were high in early life, then decreased rapidly until it reaches a stable value in the third week of life.[17] SCr levels reflect a balance between creatinine production by muscle and clearance by glomerular filtration.[15, 16, 18] The decrease in SCr levels after one week of life is the result of physiological processes. As age increases, the glomerulus become mature and its ability to filtrate creatinine improved.[9, 16, 18, 19] Higher values of SCr levels were found in preterm newborns.[17, 20, 21] The more premature the baby, the higher the creatinine levels.[14, 16, 20] As expected, in our study, the SC[45] evels before aminoglycoside treatment was significantly higher in preterm than the full-ter[17] group. Immature kidney in preterm newborns was associated with a low glomerular filtration rate resulting in creatinine not being fully excreted in the urine that indicates poor creatinine clearance. Furthermore,

poor creatinine clearance is also evidenced by the high SCr levels though the preterm newborns have a small muscle mass. Higher SCr levels in early life also occur secondary to the passive reabsorption of creatinine through leakage of renal tubular cells due to immature tubular and vascular structures in preterm newborns.[11, 22] In contrast, full-term newborns have a mature tubular function that can respond appropriately to maintain homeostasis.[16, 18, 19] The results of our study also showed a physiological changes of the SCr levels both in the two groups, similar with some previous study by Bateman *et al* and Boer *et al*. Bateman *et al*. found that SCr levels in preterm newborns in early life were 0.9 (0.79-1.15) mg/dL, then after one week slowly decreased until reaching a stable average value of 0.27-0.32 mg/dL after the age of 5-9 weeks, depending on gestational age.[14, 23] Boer *et al*. reported that SCr levels of full-term newborns were higher in early life and then gradually decreased with age, with reference value of 0.62 mg/dL in early life and 0.38 mg/dL in the first week.[23] These values were almost identic to our findings of 0.60 mg/dL initial SCr level, and 0.44 mg/dL after 7 days. Similar results also shown from previous study that the mean SCr level at birth of preterm newborns with gestational age between 23-35 weeks was 0.82 (0.76-0.88) mg/dL, decreased to 0.58 (0.52-0.65) mg/dL when the SCr was measured prior to discharge.[16] As well known that sepsis and nephrotoxic medications, including aminoglycoside (in this context, gentamycin and amikacin), are risk factors for neonatal AKI and AKI as a side effect of antibiotic treatment is most evident when administered during the first week of life.[24, 25] Interestingly, our subjects were neonatal sepsis treated with an aminoglycoside for seven days, but the changes of SCr levels seemed physiologic. There was another study that also had similar results with our study. They found the preterm initial SCr levels were 0.94 (0.36) mg/dL, but after aminoglycoside therapy decreased by 0.6 (0.37) mg/dL (P=0.000).[15] Our finding may have been due to adjusting doses and intervals of aminoglycoside administration for gestational and postnatal age, following Neofax guidelines.[13] Thus, drug accumulation in the kidney tubule was minimal, and the toxicity can be avoided.[1] Moreover, the mean gestational age in the preterm group was 32 weeks, at which nephrogenesis is almost complete, as tubular ability to excrete creatine is better than lower gestational age. Another possibility is that the kidney damage was still minimal, as SCr levels may not change until 25-50% of renal function has been impaired.[10] According to studies by Gupta *et al*. and Perazzo *et al*., one reason could assume that percentage of SCr declining could identify the newborn who already had impairment kidney function (IKF) before AKI occurred.[26, 27] They found that SCr decline associated with IKF was <31% by the seventh day of life, combined with an SCr threshold of ≥0.7 mg/dL in 31-40 weeks newborns. They mention that newborns with IKF had a more prolonged hospital stay, prolonged mechanical ventilation, vasoactive drugs, and a higher mortality rate.[26, 27] Our study showed that in both groups, the SCr decline was not following the IKF criteria made by Perazzo *et al*.[27] (32% in full-term, 34% in preterm newborn). Although the SCr changes before and after treatment of aminoglycoside seemed physiologic, the low rate of SCr decline can be a warning for neonatal management in NICU, especially for those at risk for AKI. Normal diuresis of a newborn is 1-3 mL/kg/hr. The percentage of total body fluid in newborns is greater than in adults, especially in preterm newborns, whose total body fluids can reach 80% of the baby's weight. The differences in fluid content in the body along with tubular cell immaturity may explain why normal urine production in newborns is greater than in adults.[7, 28] In addition, preterm newborns tend to have negative sodium balance in the first three weeks of life, leading to hyponatremia (<130 mEq/L) because of they have lower sodium reabsorptive capacity in renal tubules. This condition is one of the causes of higher urine production in the preterm newborns[17] as also shown in our study that urine output in preterm significantly higher than full-term group. Karlowicz *et al*. reported aminoglycoside treatment is one of some factors contribute to non-oliguric renal failure and up to one-third of neonates with acute renal failure may have non-oliguric renal failure that can only be detected by the finding of elevated serum creatinine or

cystatin C levels.[29, 30] Although, on average, the SCr levels were decreased following aminoglycoside therapy in both groups, some subjects experienced elevated SCr levels and suffered from AKI stage 1; 7 (18.9%) in preterm and 5 (14.3%) in the full-term group. This elevation is reasonable because these newborns are already at high risk for AKI due to their underlying sepsis, then multiplied by nephrotoxic drugs which should be given to treat the sepsis. Neonatal sepsis is one of high-risk factors for developing AKI, as proven by previous studies that reported a high incidence of sepsis in up to 78% of AKI cases.[19, 31] In contrast Gallo *et al*. reported a low incidence as 2.8% but with different criteria of AKI.[32]

Limitations of the study

Our study has several limitations, including the length of observation was only seven days and a small sample size. The severity of sepsis and outcome of the patients were not recorded, such as length of stay and mortality after seven days. The strength of our study is this is a prospective study, and the confounding factors for AKI risk were excluded to assess the only effect of different gestational ages on aminoglycoside exposure in sepsis newborns.

Conclusions

In conclusion, gestational age does not affect SCr levels changes following aminoglycoside treatment, suggesting that their use in preterm and full-term newborns for seven days is safe if proper and interval dosages are used. In addition, preterm and full-term newborns with the same underlying disease seem to have the same risk for AKI. Further studies on larger populations of different gestational ages with more extended observation are necessary to convince whether aminoglycoside treatment must administer based on gestational age to avoid toxicity.

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