

Cystatin C level and amikacin use in neonatal sepsis

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Abstract

Background Amikacin is the antibiotic of choice for eradicating bacteria in neonatal sepsis because of its effectiveness against Gram-negative bacteria. However, this drug has nephrotoxic effects. Monitoring kidney function in neonates is very important because amikacin can interfere with development of the kidney. Several studies have shown that serum cystatin C levels were closer to glomerular filtration rate (GFR) values compared to serum creatinine levels.

Objective To evaluate cystatin C levels before and after administration of amikacin in neonates with sepsis.

Methods This prospective cohort study was conducted in one group with a pretest and posttest design. Thirty neonatal sepsis patients who received amikacin therapy at Sanglah General Hospital, Denpasar, Bali, were included by consecutive sampling. Their cystatin C levels were measured before and after receiving amikacin therapy. Data were normally distributed and analyzed by paired T-test, with a value of $P < 0.05$ considered to be significant.

Results The mean difference was 0.23 [1.57 (SD 0.29) vs. 1.80 (SD 0.28)] mg/L with P value < 0.001 . There was different value of cystatin c level before and after amikacin therapy with deviation standard 0.25 with $P < 0.001$ (alfa 5%).

Conclusion Cystatin C levels are significantly higher in neonates with sepsis after administration of amikacin. [Paediatr Indones. 2020;60:1-5; doi: <http://dx.doi.org/10.14238/pi60.1.2020.1-5>].

Keywords: neonatal sepsis; cystatin C; renal function

Neonatal sepsis remains a worldwide health problem. Mortality and morbidity due to neonatal sepsis are high. Neonatal sepsis can lead to complications depending on its severity or the level of impairment of the organs involved. Data from the *World Health Organization* (WHO) estimated that neonatal sepsis causes four million deaths every year. The neonatal mortality rate (death in the first 28 days of life) is 34 per 1,000 live births, and 98% of these are from developing countries, including Indonesia.¹ The high rate of morbidity and mortality due to bacterial infection suggests that antibiotics be given immediately after an infection is suspected.^{1,2}

Neonates with suspected sepsis, antimicrobial therapy must be given immediately.³⁻⁵ Amikacin is drug of choice for neonatal sepsis but has a narrow therapeutic index which can be toxic to the kidney.⁶⁻⁸ Monitoring kidney function in neonates is very important where at that time is an important period

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of kidney development.⁹⁻¹⁰ Several studies have shown that serum cystatin c levels are closer to GFR values compared to serum creatinine levels,¹¹⁻²² but information on serum cystatin c in populations based on age especially neonates is still rare. We aimed to evaluate cystatin C levels before and after administration of amikacin in neonates with sepsis.

Methods

This was a prospective cohort, single group study with a pretest and posttest design. It was conducted in the Neonatal Ward (levels 2 and 3) of Sanglah Hospital, Denpasar, Bali, from August 2017 to August 2018. Examination of cystatin C levels was carried out in Prodia Laboratory, Denpasar, on the 10th days of amikacin dose. Subjects were septic neonates who received amikacin 7.5 mg/kg/dose for 10 days.²³⁻²⁸ They were included by consecutive sampling until the minimum required sample size was met. Inclusion criteria were neonates with a gestational age of ≥ 35 weeks, early-onset neonatal sepsis (EONS) or late-onset neonatal sepsis (LONS). Neonates with major congenital abnormalities, history of severe asphyxia at birth, as well as those who received amikacin or other nephrotoxic drugs (furosemide, vancomycin) before starting the study, those who did not complete the course of antibiotics due to discharge against medical advice, or those who died were excluded from this study. Calculation of the minimum required sample size was done with a sample formula to test the hypotheses against two mean groups in pairs, with $\alpha=0.05$, $\beta=0.10$, standard deviation of 0.5, and minimum average difference of 0.3, resulting in 29 subjects. To account for a 10% probability of loss to follow-up, the final sample size was deemed to require a minimum of 32 neonates.

The independent variable was amikacin therapy. The dependent variable was serum cystatin C level. The random variable was the adequacy of fluid intake. Data were analyzed using SPSS software. Subjects' characteristics are presented descriptively in the form of tables and narratives. Data normality was analyzed using Shapiro-Wilks test ($P>0.05$). Comparison of mean cystatin C levels before and after amikacin therapy was done with paired T-test. The analysis results are displayed in table form.²⁹

Results

During the study period, 30 patients was included in data analysis (2 samples was loss to follow up), half of them were male. The flow of subject recruitment is shown in **Figure 1**. Subjects' mean chronological age was 2 (SD 1.5) days, mean birth weight was 2,995 (SD 250.3) grams, and mean weight at admission was 2,991 (SD 248.5) grams. Of the 30 subjects, 21 were delivered by Caesarean section, 25 had EONS, and 27 received parenteral nutrition. In addition, 17/30 subjects used mechanical ventilators, 10/30 subjects used CPAP, and 3/30 subjects used high flow oxygen. Subjects' mean urine production during observation was 2.0 (SD 0.6) mL/kg/hour, with an average intake of 126.67 (SD 12.1) mL/kg/day.

The Shapiro-Wilk normality test had a value of $P=0.8$ with alpha 5%, hence the data were normally distributed. Clinical and septic work up performed every 3 days; during the treatment period, 18 patients

Table 1. Subjects' characteristics

Characteristics	(N=30)
Gender, n	
Male	15
Female	15
Age, n	
1-3 days	25
4-7 days	5
Median age (range), days	2 (1-7)
Mean birth weight (SD), grams	2,995 (250.3)
Mean weight at admission (SD), grams	2,991.67 (248.5)
Method of delivery, n	
Vaginal	9
Caesarean section	21
Type of sepsis, n	
Early-onset	25
Late-onset	5
Type of nutrition, n	
Parenteral	27
Enteral	3
Breathing assisted device, n	
Mechanical ventilator	17
CPAP	10
High flow oxygen	3
Mean urine output (SD), mL/kg/hour	2.01 (0.63)
Mean fluid intake (SD), mL/kg/day	126.67 (12.13)
Mean hemoglobin (SD), g/dL	16 (1.34)

showed clinical and laboratory improvement, those amikacin course was stopped on the day 7. For the rest 12 patients, amikacin course was stopped on day 10. Paired T-test revealed that mean cystatin C levels were significantly higher after amikacin treatment than before treatment. The difference in mean value before and after the administration of aminoglycosides was 0.23 (SD 0.25) mg/L, ($P < 0.001$) (Table 2). Cystatin C levels after administration of amikacin were significantly different, either evaluated on day 7 or day 10 (Table 3).

Discussion

We included only full-term neonates because the formation of nephrons is complete by 35 weeks of gestation, and new nephrons are not formed after birth. Disturbances in the urinary system, such as infection, reflux, or exposure to nephrotoxic substances after this period can interfere with kidney growth.³⁰⁻³³ The difference in mean values before and after amikacin therapy was 0.232 (SD 0.25) mg/L; ($P < 0.001$); at 5% alpha. Mean cystatin C level was significantly higher

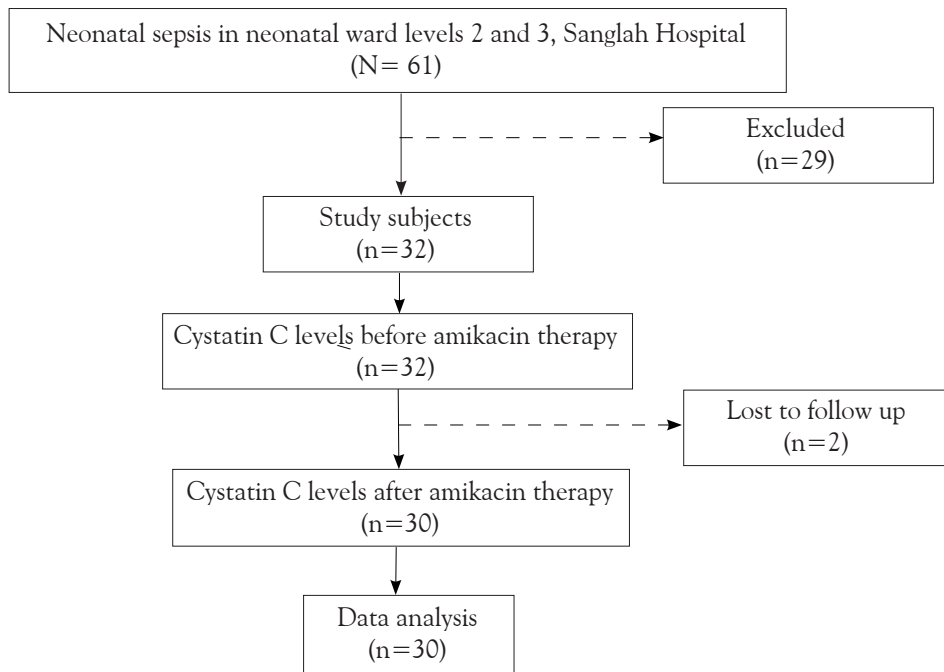


Figure 1. Flow chart of the study design

Table 2. Mean difference in cystatin C levels before and after amikacin therapy

Cystatin C	N	Mean (SD), mg/L	Mean difference	95%CI	P value
Pre-therapy	30	1.57 (0.29)	0.23	0.1439 to 0.326	<0.001
Post-therapy	30	1.80 (0.28)			

Table 3. Cystatin C levels on day 7 and day 10 post-amikacin therapy

	Cystatin C	N	Mean (SD)	Mean difference	95%CI	P value
Day 7	Pre-therapy	18	1.55 (0.25)	0.23	0.078 to 0.311	0.017
	Post-therapy	18	1.75 (0.23)			
Day 10	Pre-therapy	12	1.59 (0.34)	0.28	0.111 to 0.464	0.019
	Post-therapy	12	1.87 (0.32)			

after administration of amikacin. Cystatin C levels at the beginning of life are about 1.17 mg/L, normally decreasing at 3-5 days of age. The standard level at 1 year of age is 0.51-0.95 mg/L.³⁴⁻³⁸ In healthy neonates, the highest level of cystatin C was detected after birth, and was higher than maternal cystatin C levels [mean maternal cystatin C level (SD) 1.00 (0.20)].^{12,38} This finding suggests that cystatin C does not pass through the placenta.³⁹ Mean cystatin C levels in our study increased on day 7 or 10 after receiving amikacin therapy. This showed as an early marker that there was an abnormality in neonatal kidney function. In neonates with acute renal failure, a difference of 0.3 mg/L in mean cystatin C levels was observed on the first and third day of amikacin therapy.³⁸ Another study examined creatinine levels of neonatal subjects with sepsis who received aminoglycoside therapy, especially amikacin, before and after therapy (therapy given for 7-10 days) and found no increase in creatinine levels after therapy.^{11,38} This study did not compare cystatin c levels with other modalities for renal function examination.

In conclusion, there is a significant difference in cystatin C level before and after administration of amikacin in patients with neonatal sepsis.

Conflict of Interest

None declared.

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