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Original Article

Efficacy of aminophylline vs. caffeine for preventing apnea of prematurity

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Abstract

Background Apnea of prematurity (AOP) usually occurs in neonates with a gestational age < 34 weeks. The *World Health Organization* has recommended the administration of caffeine or aminophylline to prevent AOP, but the efficacy of aminophylline remains unclear, and caffeine citrate is not available in Indonesia.

Objective To compare the efficacy of aminophylline to that of caffeine for preventing AOP.

Methods This single-blind, clinical trial was conducted on neonates (gestational age 28-34 weeks) who were able to breathe spontaneously within the first 24 hours of life and admitted to Sanglah Hospital from December 2012 to April 2013. Subjects were randomly allocated into two groups, namely groups of aminophyllin and caffeine. The aminophylline group received aminophylline dihydrate at an initial dose of 10 mg/kg body weight, then continued with a maintenance dose of 2.5 mg/kg body weight every 12 hours. The caffeine group received anhydrous caffeine at an initial dose of 10 mg/kg body weight, then continued with a maintenance dose of 1.25 mg/kg body weight every 12 hours. We followed subjects up until they were 10 days old. Subjects received per oral therapy for seven days. The efficacy comparison between the two groups was assessed by Chi-square test with 95% confidence interval (CI) and a statistical significance value of $P < 0.05$. We used multivariate test to analyze the confounding factors.

Results Ninety-six subjects participated in this study; 48 subjects received aminophylline therapy and the other 48 subjects received caffeine therapy. Twenty-eight subjects experienced apnea: 13 subjects from the aminophylline group (27.1%), and 15 subjects from the caffeine group (31.3%). It appeared that aminophylline was slightly better compared to caffeine, but the difference was not statistically significant, with a relative risk of 0.9 (95% CI 0.5 to 1.3; P=0.8). We found vomiting to be a side effect of both therapies, and not significantly different between groups. Sepsis and hyaline membrane disease were found to be confounding factors in this study.

Conclusion Aminophylline and caffeine have similar efficacy with regards to preventing AOP.

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Keywords: *prevent, apnea of prematurity, aminophylline, caffeine*

Infant prematurity is defined as a gestational age of < 37 weeks. Africa has the highest birth rate of premature infants of 11.9%, while that of Southeast Asia is approximately 11.1%.[1] The main issue that premature infants face is apnea. Apnea is caused by incomplete development of the respiratory center, and is known as apnea of prematurity (AOP). Several factors underlie the necessity of AOP prevention: an 85% incidence of AOP in infants with gestational age <34 weeks,[2] difficulty in diagnosing AOP, unpredictable onset, short- and long-term effects, long treatment length and requirement of intensive care. The *World Health*

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Organization (WHO) recommends the prevention of AOP by methylxanthine drug use, i.e., caffeine citrate or aminophylline.[3] These medicines work by competing with adenosine, a neurotransmitter in the synapse that inhibits neurons, hence, causing apnea in premature infants.[4] Caffeine citrate is not available in Indonesia at this time, however, aminophylline is available, but its efficacy remains unclear.[5]

In this study, we administered aminophylline and caffeine according to the WHO recommended dose, converted into an oral formula. A previous study showed that the WHO aminophylline dose resulted in a plasma theophylline level of 11.6 mg/L,[6] higher than in prior studies.[5] Therefore, the administration of aminophylline according to the WHO recommendation in our study was expected to prevent AOP. The aim of this study was to compare the efficacies of aminophylline and caffeine for the prevention of AOP.

Methods

This single-blind, clinical trial was conducted from December 2012 to April 2013 in the Level II Pediatric Ward and Neonatal Intensive Care Unit (NICU) of Sanglah General Hospital, Denpasar, Bali. Inclusion criteria were premature infants with gestational age 28 – 34 weeks, born in or admitted to Sanglah General Hospital since the first day of birth, and able to breathe spontaneously for the first 24 hours of life. Exclusion criteria were parents' refusal to participate or major congenital malformations. Subjects were distributed by block randomization using six permutations. The randomization was concealed. Sample size was calculated using Fleiss's sample size formula[7] for a two-proportion difference, with α = 5%, two tailed, β = 20%, P_2 = 52% and effect size = 30%. The minimum required sample size was calculated to be 44 neonates in each group.

We started by assessing the new Ballard score (NBS) for every patient admitted to Sanglah Hospital through the Maternity or Pediatric Emergency Room. The assessments were done by duty residents in each ward, and results were reported to the researcher. If the patient met the inclusion criteria, the reseacher provided an explanation to the parents and asked them to provide informed consent. The researcher then provided identity numbers to subjects. Medicine formulation was assisted by *Kimia Farma Pharmacy*. After the medicine was prepared, it was handed to the nurses in specific wards to be delivered to the subjects. The composition of the medicine was only known to the researcher. The medicine was prepared as 14 packages of medicine powder, with the first package as an initial dose, continued with a maintenance dose every 12 hours. The aminophylline group received aminophylline dihydrate at an initial dose of 10 mg/kg body weight, then continued with a maintenance dose of 2.5 mg/kg body weight every 12 hours. The caffeine group received anhydrous caffeine at an initial dose of 10 mg/kg body weight, then continued with a maintenance dose of 1.25 mg/kg body weight every 12 hours.

The medicine was administered by dissolving the medicine powder in 1 mL of sterile water, followed by immediate oral ingestion. For fasting subjects, the medicine was administered by orogastric tube (OGT) with continued oxygen therapy during administration. Medication was administered for seven days. If the subject went home before the full seven days of treatment, the remaining medicine was given to the family to be administered at home. Subjects who consumed less than 80% of the medicine in seven days were classified as dropped out (DO) of the study.

Observations of apnea were performed by residents, nurses or internship doctors without knowing the composition of medicine received by the sample who were blinded to treatment. Observations were conducted until subjects were 10 days old. Inpatient subjects were monitored for apnea, cyanosis or desaturation, using a pulse oximeter. Outpatient subjects aged less than 10 days were monitored by their mothers at home, by looking for apnea or blue lips, and monitored by the researcher once every three days via phone or during return visits to the Neonatal Polyclinic of Sanglah Hospital. During the observation period, administration of medication for subjects diagnosed with necrotizing enterocolitis (NEC) was stopped.

Residents, internship doctors, or nurses recorded medication side effects in inpatients by monitoring tachycardia, vomiting, or gastric aspirate, and seizures. However, parents observed medication side effects

in outpatients by monitoring vomiting or seizures. In the case of either occurrence, parents immediately contacted the researcher for further treatment.

Further management of apnea was conducted according to clinical guidelines in Sanglah General Hospital. We discontinued medication use in subjects who experienced tachycardia (200beats/min) as a side effect of treatment. For subjects with seizures, we administered active charcoal and discontinued further medication.

The researcher noted subjects' final diagnoses and hospital lengths of stay according to the register in the Neonatal Subdivision of Sanglah General Hospital, after discharge. All data were noted on observation forms and collected by the researcher. Data analysis was conducted after data collection of the minimum required sample size. Intention-to-treat analysis was performed for DO subjects with the worst possibility, i.e., for apnea.

The operational definition for prematurity was an infant gestational age of ≤ 37 weeks. Gestational age was the age of the infant according to measurement by NBS. Spontaneous breathing was defined as an able to breath without the help of ventilators for the first 24 hours of life. Apnea was defined as a cessation of breathing for 20 seconds, or for 10 seconds accompanied by cyanosis or oxygen desaturation. Cyanosis was defined as a bluish color occuring in the oral mucosa, also known as central cyanosis. Desaturation was defined as oxygen saturation of less than 80% and occurring for 5 seconds or more, as measured by oxymetry.

This study received ethical clearance from the Research and Development Board of Udayana University Medical School/Sanglah Hospital and a research permit from Sanglah General Hospital.

Descriptive data is presented in text and tables. Chi-square hypothetical test was used to compare the efficacy of aminophylline to that of caffeine, with P values < 0.05 considered to be statistically significant. If the data distribution or condition did not meet the requirements for Chi-square analysis, then Fisher's test was conducted. A relative risk (RR) analysis was also conducted, with 95% CI. Multivariate analysis with logistic regression was conducted to identify confounding variables in the study. Statistical calculations were assisted by *SPSS 17 for Windows*.

Results

During the study period, we identified 132 neonates with gestational age < 34 weeks. Four neonates had apnea within the first 24 hours of life, and 8 neonates were of gestational age < 28 weeks. A total of 120 neonates met the inclusion criteria, but 24 were excluded due to lack of parental consent. A total of 96 subjects were randomly allocated into two therapy groups, each group consisting of 48 subjects (**Figure 1**). Therapy was administered for 7 days and observations were conducted until subjects were 10 days old. During that period, 9 subjects consumed less than 80% of the medication, 6 from the aminophylline group and 3 from the caffeine group, due to death. These 9 subjects were considered to be DO. Subjects were treated according to their group from the beginning until the end of treatment, and no subjects switched therapy groups.

The initial subject characteristics of the two groups were similar in terms of numbers of males and females, median body weight, gestational age, and median length of medicine administration (**Table 1**). Subjects' clinical conditions were based on their final diagnoses upon hospital discharge. We found more severe clinical conditions in the aminophylline group than in the caffeine group, with regards to longer length of stay and higher death rate in the aminophylline group (**Table 2**).

Table 3 shows the comparison of the efficacies of aminophylline and caffeine, to prevent AOP. We found that the incidence of apnea in the aminophylline group was less than in the caffeine group, but this difference was not statistically significant (RR 0.9; 95%CI 0.5 to 1.6; P = 0.8).

We found vomiting to be the only side effect of methylxantine administration. There were no seizures or tachycardia observed. The proportion of vomiting was similar between the aminophylline and caffeine groups (RR 1.1; 95%CI 0.5 to 2.9; P = 1.0).

We conducted a multivariate analysis with logistic regression to test the clinical condition of subjects that can act as confounding variables. The analysis revealed that sepsis had an odds ratio (OR) of 8.3 (95%CI 2.4 to 29.2; P = 0.001), whereas hyaline membrane disease had an OR of 15.1 (95%CI 4.3 to 53.7; P = 0.0001). Both clinical conditions were confounding variables that could also cause apnea in this study (**Table 4**).

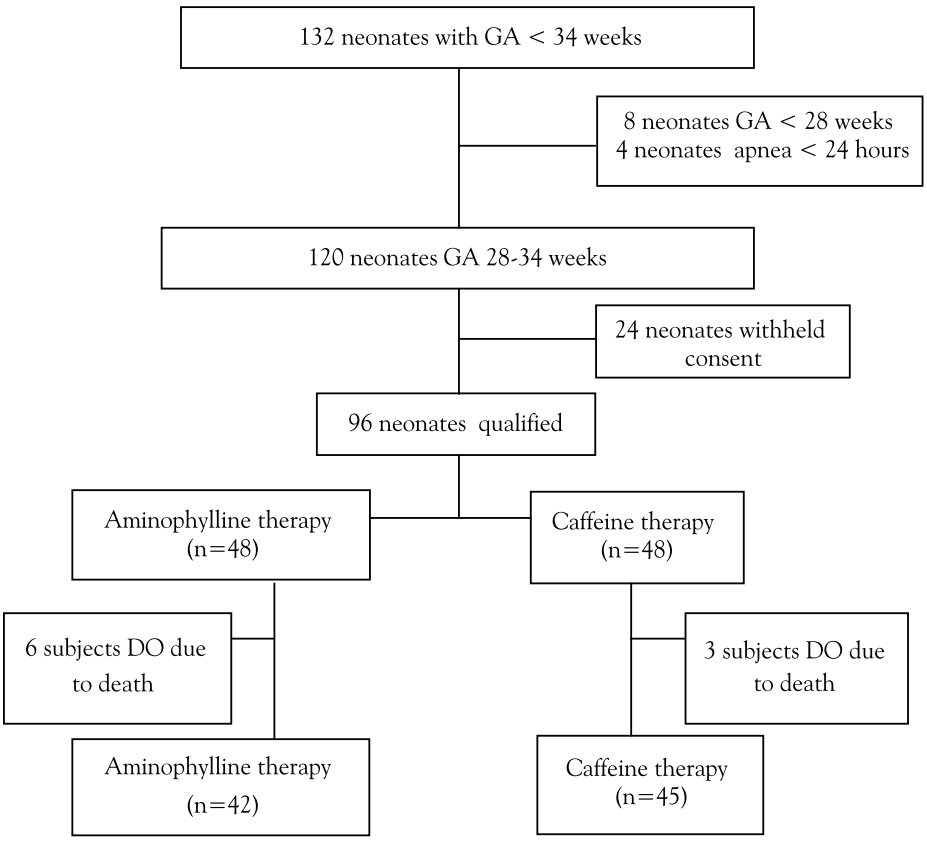

Figure 1. Study flowchart

Table 1. Subjects' characteristics

Characteristics	Therapy group	
	Aminophylline (n=48)	Caffeine (n=48)
Male gender, n	25	22
Mean birth weight (IQR), grams	1,850 (990 to 2,300)	1,975 (1,000 to 2,300)
Median gestational age (IQR), weeks	32 (28 to 33)	32 (28 to 33)
Median length of medication (IQR), days	7 (1 to 7)	7 (1 to 7)
Sepsis, n	16	14
Meningitis, n	8	7
Neonatal pneumonia, n	13	9
Hyaline membrane disease, n	15	13
Necrotizing enterocolitis, n	2	3
Anemia, n	10	10
Asphyxia, n	18	15
Hypoglycemia, n	2	1
Heart failure, n	3	0

IQR = interquartile range

Table 2. Use of ventilator, incidence of death, and length of stay in both therapy groups

Characteristics	Therapy group	
	Aminophylline (n=48)	Caffeine (n=48)
Use of CPAP, n (%)	15 (31.2)	13 (27.1)
Use of ventilator, n (%)	8 (16.7)	9 (18.8)
Died		
During therapy, n (%)		
Yes	7 (14.6)	5 (10.4)
No	19 (39.6)	25 (52.1)
After therapy, n (%)		
Yes	6 (12.5)	2 (4.2)
No	16 (33.3)	16 (33.3)
Median length of stay, days (IQR)	10 (1 to 49)	6.5 (1 to 50)

CPAP = continuous positive airway pressure; IQR = interquartile range

Table 3. Efficacy comparision of aminophylline and caffeine in preventing AOP

Therapy	Apnea (n=28)	No apnea (n=68)	RR	95% CI	P value
Aminophylline	13	35	0.9	0.5 to1.6	0.8
Caffeine	15	33			

Table 4. Multivariate analysis of clinical conditions

Step	Variable	B	OR	95% CI	P value
Step 1	Sepsis	1.8	6.2	1.2 to 31.9	0.03
	Hyaline membrane disease	2.7	15.5	4.3 to 56.3	0.0001
	Neonatal pneumonia	-0.9	0.4	0.09 to 1.9	0.3
	Meningitis	1.7	5.2	0.4 to 71.5	0.2
	Anemia	-1.0	0.4	0.03 to 3.8	0.4
	Constant	-2.5	0.1		0.0001
Step 2	Sepsis	1.7	5.3	1.1 to 24.9	0.04
	Hyaline membrane disease	2.7	15.1	4.2 to 54.5	0.0001
	Neonatal pneumonia	-1.1	0.3	0.07 to 1.5	0.2
	Meningitis	0.9	2.7	0.4 to 19.9	0.3
	Constant	-2.5	0.1		0.0001
Step 3	Sepsis	2.1	8.3	2.4 to 29.2	0.001
	Hyaline membrane disease	2.7	15.1	4.3 to 53.7	0.0001
	Neonatal pneumonia	-1.0	0.4	0.08 to 1.5	0.2
	Constant	-2.5	0.1		0.0001

Discussion

The initial characteristics of subjects of the two therapy groups were similar, but the development of clinical conditions during the observation and treatment period caused the aminophylline group to have greater risk of apnea by other causes, as compared to the caffeine group. This was confirmed by the longer length of stay and higher death rate in the aminophylline group after observation. Death rates in both groups during therapy were similar, hence deaths were not caused by methylxantine therapy.

We found apnea in 13/48 (27.1%) of subjects in the aminophylline group, and in 15/48 (31.3%) of

subjects in the caffeine group, however, this difference was not significant (RR 0.9; 95%CI 0.5 to 1.6; P = 0.8). We observed that aminophylline and caffeine had similar efficacies for preventing AOP. Similarly, a study found similar efficacy of aminophylline and caffeine in preventing AOP, although their aminophylline dose was lower than that of our study.[8] Aminophylline is from the same family of drugs as caffeine and has a similar mechanism of action, i.e., affecting the same adenosine receptors (adenosine A_1, A_{2A} and A_3 receptors).[9,10] Aminophylline is metabolized by the body into several active forms, but due to incomplete liver development in premature infants, several metabolites from aminophylline cannot be activated.[11] Active metabolites derived from aminophylline administration in premature infants include 25% caffeine[12] and 3-methylxanthine.[11] Therefore, aminophylline administered to premature infants was actually equivalent to a lower dose of caffeine, hence, administration of aminophylline at the right dose would have a similar effect as caffeine in premature infants for preventing AOP.

A previous study did not recommend aminophylline administration to prevent AOP, because the authors found an increased incidence of apnea following aminophylline administration.[5] In contrast, we found similar efficacies of aminophylline and caffeine in preventing AOP. This difference may have been due to the lower dose of aminophylline administered in their study, which resulted in a mean plasma theophylline level of 7.1 mg/L,[5] whereas the dose of aminophylline based on the WHO recommendation, resulted in a plasma theophylline level of 11.6 mg/dL.[6] Hence our higher dose of aminophylline may have prevented apnea.

Aminophylline use in premature infants may cause side effects and intoxication symptoms. A 1993 study reported that aminophylline prevented AOP. In that study, aminophylline dose was 25 mg/mL and was administered through a continuous intravenous infusion for five days and their mean plasma was 12.7 mg/L. Intoxication symptoms occurred in four subjects, with their plasma theophylline level reported to be 30.1 mg/L.[13] In our study, aminophylline was given orally every 12 hours according to the WHO recommendation.[3] A previous study showed that this dose resulted in a plasma theophylline level of 7.2 to 14.5 mg/L, a level that should not cause intoxication symptoms.[6] Another side effect is vomiting. We found the incidence of vomiting to be similar in both groups: 16.7% in the aminophylline group and 14.6% in the caffeine group. Vomiting in methylxantine-treated patients may be caused by a decrease of lower esophageal sphincter function,[14] gastric acid stimulation, and lower GABA activity.[4] Further assessment is needed as to whether vomiting is a major side effect of therapy, or a frequently-occurring physiological event in premature infants.[15]

The incidence of apnea in premature infants may be triggered by several factors.[16] Immaturity of the respiratory center is known as one of the causes of AOP.[4] Other factors may also play an important role in the incidence of apnea. Multivariate analysis revealed that apnea in our subjects could also be due to sepsis or hyaline membrane disease. Therefore, these two conditions cannot be ignored, despite therapy by administration of aminophylline or caffeine to prevent AOP.

A limitation of this study was the lack of facilities to conduct measurements of subjects' aminophylline or caffeine levels. Also, the single-blind study design may have led to bias. To minimize bias, the researcher did not participate in the observation of apnea. Information bias could also have occurred since some apnea data was acquired by parental observation during treatment at home.

In conclusion, aminophylline and caffeine have similar efficacies for preventing AOP. Aminophylline may be considered as a substitute for caffeine for prevention of AOP in Indonesia, if caffeine is unavailable. Patients undergoing methylxanthine treatment require monitoring of clinical conditions, such as sepsis and hyaline membrane disease.

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Conflict of interest

None declared

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