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Original Article

Comparison of oral caffeine and oral theophylline for apnea of prematurity: A randomized clinical trial

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Abstract

Background Caffeine and theophylline are methylxanthine compounds that have been widely used in the treatment of apnea of prematurity (AOP). Previous studies comparing the two agents have shown inconsistent results and have mostly used intravenous preparations.

Objective To assess the effectiveness of oral administration of caffeine compared to oral theophylline as therapy for apnea of prematurity.

Methods Fifty consecutively recruited premature neonates (gestational age 28-34 weeks, birth weight <2,500 g) with AOP who were able to tolerate at least 10 mL/kg of enteral feeding were randomized to receive either oral caffeine or oral theophylline for seven days. The main outcome was the daily frequency of apnea after treatment. Secondary outcomes were duration of oxygen or CPAP administration, duration of oxygen fraction (FiO_2) taper to reach 21%, time to achievement of full feeding tolerance, length of hospital stay, and side effects.

Results We randomized 25 subjects into each group. The distribution of baseline characteristics (gender, gestational age, mode of delivery, birth weight and length, age at onset of AOP, and initial frequency of AOP) was similar between both groups. The mean daily number of apnea episodes after treatment was significantly higher in the caffeine group compared to the theophylline group [3.16 (SD 1.31) *vs.* 2.28 (SD 1.40); P=0.031]. The caffeine group, compared to the theophylline group, also had a longer mean duration of oxygen or CPAP use [12.56 (SD 7.67) days *vs.* 8.40 (SD 6.41) days; P=0.030] and duration of FiO_2 taper [5.76 (SD 2.68) *vs.* 4.08 (SD 2.54); P=0.035]. There were no significant differences in mean time to full feeding and mean length of hospital stay. There was no significant difference in the occurrence of side effects between the two groups.

Conclusion In premature neonates with AOP, oral theophylline is slightly more effective than oral caffeine in reducing the frequency of apnea and is associated with a shorter duration of oxygen or CPAP use and duration to reach 21% FiO_2. **[Paediatr Indones. 2024;64:350-5; DOI: 10.14238/pi64.4.2024.350-5].**

Keywords: *apnea of prematurity; neonates; methylxanthine; caffeine; theophylline*

Apnea of prematurity (AOP) is a common respiratory disorder in premature infants and is a cause of intermittent bradycardia and hypoxemia. It occurs in more than 50% of infants with birth weight <1,500 grams and in 80% of infants with birth weight <1,000 grams. The incidence of apnea is inversely related to gestational age. At <34 weeks of gestation, 25% of neonates require pharmacological intervention and ventilation because of recurrent apnea. At 30-31 weeks of gestation, the incidence of apnea is 50%, and increases to 80% in infants 30 weeks and almost 100% in very premature neonates. In very very low birth weight babies (VVLBW), the incidence of apnea is 84%.[1,2]

Methylxanthines (theophylline and aminophylline) have been used in the treatment of AOP. Caffeine, a methylxanthine and a non-specific adenosine receptor blocker, has been used for more than 40 years. It is one of the most frequently prescribed drug in neonatal medicine.[3] However, until 2006, there were only a few relatively small, short-term studies supporting its use.[4] Existing studies suggest that caffeine is one of the most effective

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therapies for apnea of prematurity. Several clinical trials have demonstrated the effectiveness of caffeine in reducing apneic episodes and reducing the need for mechanical ventilation in premature infants.[5] Although the mechanism of action of caffeine in apnea of prematurity is unknown, several mechanisms have been hypothesized.[6] One study reported that the benefits of caffeine were more significant than theophylline in premature neonates of <33 weeks' gestation in the first week, but theophylline does not require routine monitoring of serum concentrations unless there is toxicity.[7] Another study concluded that aminophylline is as effective as caffeine for preventing apnea spells in preterm neonates.[8] In contrast, some other studies concluded that caffeine is more effective than theophylline in AOP therapy.[9,10] Yet another study found no significant difference between the groups receiving caffeine and aminophylline.[11] Caffeine can be administered orally or intravenously. Various dose regimens have been used, but a systematic review could not determine the optimal dose of caffeine due to the low level of evidence available.[12]

Theophylline is a weak, non-selective phosphodiesterase isoenzyme (PDE3) inhibitor and an adenosine receptor antagonist. In premature infants, theophylline improves ventilation, increases tidal volume, decreases arterial blood hydrogen concentration and carbon dioxide tension, and increases the ventilatory response to CO_2. Theophylline may also increase lung maturation.[3]

To our knowledge, no study has compared the effectiveness of oral caffeine with theophylline for the treatment of apnea of prematurity in Indonesia. As such, we aimed to examine the effectiveness of caffeine compared to theophylline as a therapy for apnea of prematurity.

Methods

This randomized controlled trial was done at the Perinatology Unit of Dr. Kariadi Hospital, Semarang, Indonesia, from October 2021 to October 2022. We randomized premature infants born at 28-34 weeks' gestation who were diagnosed with AOP into either the caffeine or the theophylline treatment group. Using a consecutive sampling method, newborns who met the inclusion criteria were enrolled until the minimum sample size was reached. Inclusion criteria were premature infants with gestational age of 28-34 weeks and birth weight <2,500 grams who were diagnosed with AOP and who were able to receive at least 10 mL/kg/day of breast milk enterally. The treatment was given until the infant was apnea-free. Infants with congenital malformations, severe AOP (requiring mechanical ventilation), and who had previously received aminophylline therapy were excluded. Randomization was carried out by the pharmacist using simple randomization when the infant was diagnosed with AOP (**Figure 1**).

Infants in the caffeine group received oral caffeine citrate with an initial dose of 20 mg/kg BW (equivalent to 10-12.5 mg caffeine base/anhydrous), followed 24 hour later by a maintenance dose of 5-10 mg/kg BW/day (equivalent to 2.5-5 mg caffeine base/anhydrous) for seven days. In the theophylline group, infants were given oral theophylline with an initial dose of 5-8 mg/kg, followed by 4-22 mg/kg BW every 6-8 hours for seven days.

We also recorded the subjects' demographic and clinical data, including maternal education, maternal occupation, family socioeconomic status, date of birth, date of admission, type of delivery, gender, gestational age, birth weight, birth length, age at apnea, and frequency of apnea. The study treatment received by the subjects was unknown to the investigator assessing the outcomes.

The main outcome was frequency of apnea, defined as the frequency of respiratory arrest of >20 seconds or <20 seconds accompanied by bradycardia (<100 beats/minute) and decreased oxygen saturation (<85%), calculated at midnight each day and reported as the number of episodes per 24 hours. Secondary outcomes were oxygen fraction (FiO_2), duration of oxygen supplementation or continuous positive airway pressure (CPAP) use, feeding tolerance, length of hospital stay, and side effects (e.g., tachycardia, vomiting). FiO_2 was typically started at 40% or 30%, then gradually tapered until it reached 21%. We noted the time needed for the FiO_2 taper to reach 21%. Feeding tolerance was the infant's tolerance to enteral diet, which was started at 10 mL/kg and gradually increased until full feeding was achieved. We recorded the time needed until the infant reached full enteral feeding. Side effects

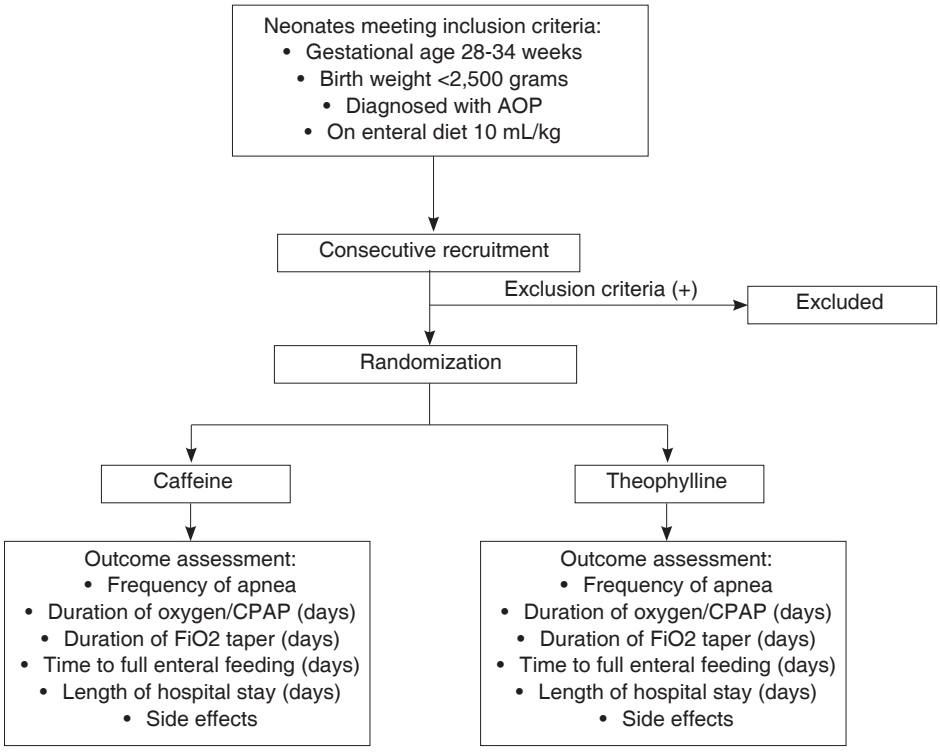

Figure 1. Study procedure

(tachycardia or gastrointestinal complaints of nausea and vomiting) were reported as absent or present. We noted complications or comorbidities that could serve as confounding variables, such as sepsis, hypothermia, and hypoglycemia.

Categorical variables were analyzed using the chi-square test. Numerical variables were analyzed for normality using the Shapiro-Wilk test. Comparisons between numerical data were analyzed using the independent samples T-test if they were normally distributed and using the Mann-Whitney test otherwise. A P value of <0.05 was considered significant. Statistical analyses were aided by *SPSS software version 26* (*IBM*, Armonk, New York).

Parents were given a thorough explanation of the study and asked to sign a written informed consent before their infants were enrolled. The study protocol was approved by the Health Research Ethics Committee of the Faculty of Medicine, Universitas Diponegoro.

Results

We randomized 50 neonates; 25 in each group. There were slightly more male than female subjects. Baseline subject characteristics were similar in the two groups (**Table 1**).

Comparison of outcomes between the caffeine and theophylline groups can be seen in **Table 2**. The main outcome, mean frequency of apnea after treatment, was significantly higher in the caffeine group compared to the theophylline group [3.16 (SD 1.31) *vs.* 2.28 (SD 1.40) episodes/24 hours; P=0.031], despite the initial mean apnea frequency being similar between the two groups [3.12 (SD 0.72) in the caffeine group and 3.4 (SD 0.91) in the theophylline group]. With regards to secondary outcomes, mean duration of oxygen or CPAP use was significantly higher in the caffeine group than in the theophylline group [12.56 (SD 7.67) days *vs.* 8.40 (SD 6.41) days; P=0.030]. Mean duration of FiO_2 taper was significantly higher in the caffeine group than in the theophylline group [5.76 (2.68) days vs. 4.08 (2.54) days; P=0.035]. Mean time to reach full feeding tolerance and mean

length of hospital stay did not differ significantly between the two groups.

Side effects of tachycardia, nausea, or vomiting were reported in 18/25 or infants in the caffeine group and 20/25 of infants in the theophylline group; this difference was not significant (P=0.741). Two subjects had sepsis; none of them experienced hypothermia and hypoglycemia.

Discussion

We studied infants with AOP to compare the effectiveness of treatment using caffeine vs. theophylline. We noted that subjects who received caffeine had a significantly longer duration of O2 or CPAP administration than those who received theophylline [12.56 (SD 7.67) days *vs.* 8.40 (SD 6.41) days; P=0.030]. In contrast, a previous study reported no significant difference between the mean duration of CPAP use [1.9 (SD 3.3) days in the caffeine group *vs.* 3.5 (SD 2.1) days in the caffeine group; P=0.08], mechanical ventilation [4.6 (SD 5.3) days in the caffeine group *vs.* 3.6 (SD 7.2) days in the theophylline group; P=0.29], or supplemental oxygen use [15.2 (SD 13.9) days in the caffeine group vs. 14.3 (SD 6.0) days in the theophylline group; P=0.74].13 Another study comparing caffeine and aminophylline showed that caffeine significantly reduced the duration of mechanical ventilation or oxygen supplementation, as well as the duration of hypothermia which may prolong oxygen or CPAP use.[14] In our study, no subject experienced hypothermia.

The mean duration of FiO2 taper to reach 21% was significantly longer (P=0.035) in the caffeine group [5.76 (SD 2.68) days] than in the theophylline group [4.08 (SD 2.54) days], in contrast to a previous study reporting that the duration and concentration of inhaled oxygen required for infants treated with caffeine was shorter (2.5 days) and lower (4%) than

Table 1. Baseline characteristics of subjects

Characteristics	Groups	
	Caffeine (n=25)	Theophylline (n=25)
Gender, n (%)		
Male	13	14
Female	12	11
Mean gestational age (SD), weeks	30.36 (2.05)	31.36 (0.5)
Mode of delivery, n (%)		
Vaginal	4	6
Cesarean section	21	19
Mean birth weight (SD), gram	1,474.4 (350.8)	1,501.96 (356.7)
Mean birth length (SD), cm	10.02 (3.62)	39.72 (2.98)
Mean age at AOP onset (SD), days	12.28 (16.73)	9.68 (10.51)
Mean frequency of initial AOP (SD), episodes/24 hours	3.12 (0.72)	3.4 (0.91)

Table 2. Outcomes of the caffeine and theophylline groups

Variables	Groups		P value
	Caffeine (n=25)	Theophylline (n=25)	
Frequency of apnea (SD), episodes/24 hours	3.16 (1.31)	2.28 (1.40)	0.031*+
Mean duration of oxygen or CPAP use (SD), days	12.56 (7.67)	8.40 (6.41)	0.030*+
Mean duration of FiO_2 taper (SD), days	5.76 (2.68)	4.08 (2.54)	0.035*+
Mean time to full feeding (SD), days	18.04 (10.60)	14.00 (9.84)	0.120+
Mean length of hospital stay (SD), days	20.16 (11.28)	16.36 (10.37)	0.200+

*significant (P<0.05), +Mann-Whitney test

infants treated with aminophylline (P<0.05).[14] Premature babies are at high risk for breathing problems due to insufficiency of surfactant to keep the alveoli open.[15] For this reason, the choice of oxygen supplementation method must be considered carefully.

We found no significant differences in feeding tolerance between the caffeine and the theophylline group, as shown by the time required to full feeding [18.04 (SD 10.60) days *vs.* 14.00 (SD 9.84) days; P=0.120]. In contrast, a 2010 study reported that there was less feeding intolerance necessitating medication dose change in neonates receiving caffeine compared to theophylline [risk ratio (RR) 0.17; 95%CI 0.04 to 0.72].[3] A study also reported less feeding intolerance in the caffeine group than in the theophylline group (P=0.027), but there was no significant difference regarding when full enteral feeding after birth was achieved.[13] Feeding intolerance in infants born prematurely can be affected by conditions of respiratory distress. Premature babies often experience difficulty in feeding due to immaturity of their gastrointestinal function, which affects motility and secretion of digestive enzymes so that temporary cessation of oral feeding may be required, which ultimately leads to prolonged parenteral feeding.[16-17]

Length of hospital stay was not significantly different between the caffeine and the theophylline group [20.16 (SD 11.28) days *vs.* 16.36 (SD 10.37) days; P=0.200]. This finding was in agreement with a previous study which stated mean durations of treatment of 30.0 (SD 17.4) days for the caffeine group and 29.7 (SD 10.1) days for the theophylline group (P=0.91).[13] The length of hospital stay is determined by improvement in apnea and other clinical conditions, such as premature administration of oxygen.[18] It is also heavily affected by other factors, including the different complications and comorbidities present in each neonate, which were not compared in this study.

There was no difference in side effects in the caffeine and theophylline groups (P=0.741). Previous studies reported that caffeine and theophylline can produce side effects in premature infants with AOP, most commonly in the form of tachycardia and gastrointestinal complaints (nausea and vomiting), but that caffeine had fewer side effects than theophylline did. A Cochrane review reported that caffeine had fewer side effects than theophylline (RR 0.17; 95%CI 0.04 to 0.72). Caffeine also has a larger margin between therapeutic and toxic doses, monitoring of serum caffeine levels can be done less frequently than theophylline levels. On the other hand, theophylline is easier to absorb and has a longer half-life, so it can be given only once per day. Administering caffeine only once per day is associated with fewer gastrointestinal side effects compared to administering theophylline more than once per day.[3] Research on side effects by Jeong et al. stated that 90.6% of subjects in the caffeine group had difficulty feeding (such as presence of residual volume, abdominal distention, regurgitation, or vomiting) compared to the theophylline group (98.9%) (P=0.027). The same study found no significant difference in tachycardia between the two groups.[13] We did not find any difference in the occurrence of side effects. This could have been due to the oral administration of the drugs in our study. In previous studies, caffeine and theophylline were given intravenously, which may have increased the likelihood of side effects.[7-11]

In our study, the group receiving caffeine had a higher mean frequency of apnea after treatment than the theophylline group. The Cochrane review reported that both of caffeine and theophylline were equally effective in reducing the frequency of AOP.[3] The difference of our results may have been due to the difference in the drug regimen used or due to the presence of unmeasured confounding variables that affected subject outcomes.

Previous research also mentioned that giving both caffeine and theophylline can reduce the frequency of apnea of prematurity. Jeong et al. reported that there was a significant, gradual decrease in the frequency of apnea in each sequential day of therapy with caffeine or theophylline, with no significant difference in the frequency decrease between the two groups.[13] Another study also showed that caffeine and theophylline both reduced the incidence of apnea in premature infants, but caffeine was superior to theophylline because caffeine can act both as treatment to reduce apnea frequency and as prophylaxis to prevent apnea (P=0.001), while theophylline was effective only in as treatment (P=0.012), but not as prophylaxis.[7] A similar, more recent study concluded that caffeine is more effective than theophylline in the treatment of AOP.

Based on our study results, we conclude that in premature neonates with AOP, oral theophylline is slightly more effective than oral caffeine in reducing the frequency of apnea, and is associated with a shorter duration of oxygen or CPAP use and duration of FiO_2 taper. There is no difference in the effect of caffeine and theophylline on the time required to achieve full feeding and length of hospital stay. These agents can be given safely without any notable side effects.

Conflict of interest

None declared.

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