International Journal of Contemporary Pediatrics
Haque MA et al. Int J Contemp Pediatr. 2025 Nov;12(11):1773-1777
http://www.ijpediatrics.com
pISSN 2349-3283 | eISSN 2349-3291

DOI: https://dx.doi.org/10.18203/2349-3291.ijcp20253480

Original Research Article

Safety and efficacy of use of aminophylline and caffeine in management of apnea of prematurity

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Received: 09 September 2025
Accepted: 10 October 2025

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ABSTRACT

Background: Both aminophylline and caffeine have been used to manage apnea of prematurity in various NICUs. We aimed to investigate the efficacy and safety of these two drugs in the mentioned scenario.
Methods: This randomized controlled trial was carried out from July 2024 to June 2025 in the ICMH, Dhaka. All the preterm newborns with ≤ 34 completed weeks of GA were enrolled. Those having major congenital anomalies, respiratory depression from medications and patent ductus arteriosus (PDA) as a cause of apnea were excluded. Among 53 participants, 27 received caffeine and 26 received aminophylline.
Results: In the caffeine group average gestational age was 33.1 days and the birth weight was 1330 grams. On average, treatment was started at 2.5 days and was continued for 18 days. While in the aminophylline group average gestational age was 32.8 days and the birth weight was 1402 grams. On average, treatment was started at 4.1 days and was continued for 21 days. The aminophylline group observed relatively more apneic spells and other adverse effects. Except for treatment starting days, neither of the changes in these groups was statistically significant.
Conclusions: Regarding effectiveness and safety, caffeine exerted as much performance as aminophylline without any superiority of one over the other.

Keywords: Apnea, Aminophylline, Caffeine, Prematurity

INTRODUCTION

Apnea of premature infants is a cessation of breathing for >15 seconds, accompanied by hypoxia or bradycardia or both. It is a very common problem encountered in the NICU throughout the world. A developing brain is always at risk of being insulted by apnea, with a risk of future consequences.[1,2] Apnea has a documented propensity to occur in earlier ages, like 30-31 weeks of gestation and usually resolves by the time the infant approaches term age. Evidence suggests that at least 85% of infants born at less than 34 weeks of gestation develop apnea.[3,4] Apnea is classified into central, obstructive and mixed types. A pause in breathing due to a lack of respiratory effort results in central apnea. When the airway blockage occurs despite ongoing respiratory effort, it is called obstructive apnea. A combination of mechanisms results in mixed apnea and it accounts for half of the apneic spells.[5] The pathogenesis of the apnea of prematurity is indistinct. Previous studies have directed the derangement in CNS development with a linkage to the inability to control breathing in preterm infants.[6,7] The management of the apnea of prematurity involves a combination of two major therapies, a pharmacological treatment and the supply of O2.6 Although caffeine citrate and aminophylline have been

the primary treatments of infant apnea within clinical practice, a comparison of the efficacy and safety of both drugs in the treatment of apnea remains to be performed, particularly for those who underwent different strategies of O_2 supply.[8] It has been reported that continuous positive airway pressure and nasal intermittent positive pressure ventilation are safe and effective in improving the respiratory function and decreasing bradycardia.[9,10] Despite the improvement of respiratory support to treat hypoxia, there is considerable uncertainty regarding the performance of these two drugs in the treatment of apnea in infants receiving different strategies of O_2 delivery.[1]

There are limited trials emphasizing the effectiveness and safety of caffeine versus aminophylline in developing countries. Besides, small for gestation age (SGA) growth category or intrauterine growth retarded (IUGR) babies are a significant problem in many developing and underdeveloped countries and the effect of methylxanthines in them is incompletely understood.[9]

Evidence suggests that caffeine is the preferred treatment for neonatal apnea over aminophylline because it has fewer adverse effects, a longer half-life and a wider therapeutic range. Equal efficacy has been shown in reducing apnea frequency by these two drugs. Caffeine has fewer adverse effects than aminophylline as well. It is more practical to administer orally and is compatible with breastfeeding. Caffeine-treated infants have a lower risk of complications like PDA and BPD than aminophylline-treated infants.

Caffeine-treated infants have a lower rate of apnea recurrence than aminophylline-treated infants, a lower median heart rate on day 3, fewer tachycardia and less gastric aspirate. Aminophylline has been used conventionally as a treatment option for apnea of prematurity. The use of caffeine is relatively limited and newer in our settings.[10] The current study was performed to investigate the efficacy and safety of caffeine and aminophylline in the treatment of the apnea of premature infants.

METHODS

A Randomized controlled trial was carried out at the department of neonatology, Institute of Child & Mother Health (ICMH), Dhaka, from July 2024 to June 2025. All the preterm newborns with ≤34 completed weeks of GA were enrolled in the study. Those having major congenital anomalies, respiratory depression from medications and PDA as a cause of apnea (defined as– ductus diameter of 1.5 mm and absent/retrograde diastolic flow in the post-ductal aorta) were excluded.

The following mathematical formula was used to determine the sample size for this study.

n= (p1×(100-p1)+p2×(100-p2))/(p1-p2)2)×(zα+zβ) 2= (70×(100-70)+85× (100-85)/ (70–85)2)× (1.96+1.67) 2 =197

(p1= efficacy of aminophylline in treating apnea= 70%, P2= efficacy of caffeine in treating apnea= 85%, Zα= z value at 95% confidence level =1.96, Zβ =z value at 0.95 power =1.64)

But due to time and financial constraints, we included 53 neonates in our study. 27 participants received caffeine and rest, 26 received aminophylline. Infants allocated to the Caffeine group received a loading dose of 20 mg/kg of caffeine citrate diluted in 5% dextrose given for 30 minutes with a maintenance dose of 5 mg/kg 24-hourly. Neonates allocated to the aminophylline group received a loading dose of 5 mg/kg of aminophylline, diluted in 5 % dextrose, followed by a maintenance dose of 1.5 mg/ kg every 8 hours.

Independent t-tests compared continuous variables. Pearson's correlation coefficient assessed the relationship. The Chi-square test was used to examine associations between categorical variables. A p value of less than 0.05 was considered statistically significant. All analyses were conducted using SPSS software v 26.0.

Written consent was obtained from each legal guardian. All data were recorded in a pre-tested semi-structured questionnaire. Ethical clearance was taken from the institutional review board of ICMH.

RESULTS

Gestational ages, birth weight, male gender, use of antenatal steroids, cesarian section and APGAR score at 1st and 5th minutes were analyzed as baseline characteristics among the two groups and yielded no significant differences (Table 1). The effectiveness of two drugs was compared with respect to the age of treatment start with duration, apnea duration, time to full feed and duration of intubation. The average age of treatment start with aminophylline was 4.1 days, while that with caffeine was 2.5 days.

This finding was statistically significant. Neonates in the aminophylline group had more treatment duration, longer duration of apnea, more days to full feed and prolonged intubation than the caffeine group, though the findings were not statistically significant (Table 2). 8 neonates (30.8%) had frequent apneic spells in the aminophylline group, while 5 neonates (18.5%) of caffeine group had frequent apnea. This change was not statistically significant. Respiratory function was assessed by the mode of oxygen supply.

Oxygen hood and ventilation were more needed in the aminophylline group (19.2% and 11.5 % respectively), while 81.5% participants in the caffeine group received CPAP therapy. This finding was not statistically

significant as well (Table 3). The major adverse effects encountered by the drugs were tachycardia, polyuria, GI problems (necrotizing enterocolitis or intolerance), seizure and hyperglycemia. Apart from hyperglycemia, the aminophylline groups had shown more adverse effects, but the changes were not statistically significant. (Table 4).

Table 1: Baseline characteristics of the participants.

Characteristics	Caffeine group (n=27)	Aminophylline group (n=26)	P value
Gestational age	33.1	32.8	0.12
Birth weight (gram)	1330	1402	0.09
Male gender	13	12	0.15
Antenatal steroid	15	14	0.72
Cesarian section	18	20	0.07
APGAR at min 1	4.2	4.8	0.12
APGAR at min 5	5.7	6.1	0.09

Table 2: Comparison of effectiveness in two groups.

	Caffeine (n=27)	Aminophylline (n=26)	P value
Age at treatment start (day)	2.5	4.1	0.04
Duration of treatment	18	21	0.52
Duration of apnea	15	18	0.22
Time to full feed	8	9	0.09
Duration of intubation	6	8	0.23

Table 3: Comparison of primary outcomes between caffeine and aminophylline groups.

Variable		Caffeine (n=27)	Aminophylline (n=26)	P value
Frequency of apnea in 72 hours	Yes	5 (18.5%)	8 (30.8%)	0.56
	No	22 (81.5%)	18 (69.2%)	
Respiratory function	Oxyhood	3 (11.1%)	5 (19.2%)	0.12
	CPAP	22 (81.5%)	18 (69.2%)	
	Ventilation	2 (7.4%)	3 (11.5%)	

Table 4: Comparison of adverse effects between caffeine and aminophylline groups.

Variable	Caffeine (n=27)	Aminophylline (n=26)	P value
Tachycardia	20 (74.1%)	22 (84.6%)	0.17
Polyuria	12 (44.4%)	14 (53.9%)	0.36
NEC/ GI intolerance	0	1 (3.8%)	0.56
Seizure	2 (7.4%)	3 (11.5%)	0.08
Hyperglycemia	2 (7.4%)	1 (3.8%)	1.2

DISCUSSION

This RCT explored the efficacy and safety of caffeine and aminophylline in treating apnea of prematurity among preterm neonates. The findings reflect that both drugs are effective for clinical practice to treat the apnea of prematurity.

The effectiveness of both drugs is found to be supported by other studies as well, though no statistically significant difference was found between caffeine and aminophylline while exploring their effectiveness and safety level in this trial.[4,5,7,8,12,13,15,17-19] Caffeine seems to have fewer adverse effects than aminophylline after exploring the adverse outcomes for the two groups in this trial. This finding is similar to many other clinical trials done at different times in different countries.[4,5,7,14,18,20] This trial found that the group of neonates receiving caffeine showed slightly higher effectiveness, though its difference with the aminophylline group didn't show any statistical significance. Treatment initiation with caffeine was earlier than with aminophylline, which was a significant indicator of effectiveness for caffeine. Notably, a higher number of neonates from the caffeine group experienced no apnea episodes in the last 72 hours, reflecting faster therapeutic action, similar to other studies, even though the difference was found to be not statistically significant in our study.[4,5,7,8,16,18] The neonates who experienced apnea episodes in the last 72 hours were found to be higher in the aminophylline group in our study, which is contradictory to two other trials done to compare the

efficacy between aminophylline and caffeine.[11,19] The respiratory support required in both groups was CPAP in the majority. A few cases were revealed in the caffeine group in terms of requiring oxygen and ventilatory support. Though it was not statistically significant, different trials support this evidence.[1,4,17,20]

Both the drugs exert some adverse effects, while caffeine seems to have a greater safety profile as it exerts fewer adverse effects than aminophylline, overall. Tachycardia, the most common adverse effect, was less frequent with caffeine. Also, Polyuria was higher in the aminophylline group, though not statistically significant. These findings are similar to some other trials conducted to compare the methylxanthines.[4,5,13-19] No cases of NEC or GI intolerance were found in the caffeine group of our study, which is also supported by other studies reporting very few such cases for caffeine therapy.[5,13,15] Seizures and hyperglycemia cases were very few in both the groups, but again slightly higher in the aminophylline group and caffeine group, respectively. Other studies also found these adverse outcomes were rarely or statistically insignificant.[4,13,15]

Although none of these differences reached statistical significance, the consistent favorable trend towards caffeine suggests it's more effective and safer than aminophylline. Some studies reported having no adverse effects after using caffeine to treat apnea.[3]

Limitations

The study included a relatively small sample size. A further multicenter study, comprising of larger sample size, is recommended.

CONCLUSION

Both caffeine and aminophylline were same effective in treating the apnea of prematurity in preterm neonates. The adverse effects observed in the two groups were also statistically similar.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Haque MA, Rahman MM, Adnan MA, Rumi AY, Ahmed M, Islam MT. Safety and efficacy of use of aminophylline and caffeine in management of apnea of prematurity. Int J Contemp Pediatr 2025;12:1773-7.