



## Comparing the efficacy of Aminophylline and Caffeine in treatment of apnea of prematurity; A Randomized Clinical Trial

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### Abstract

**Introduction:** The apnea of prematurity usually occurs at the end of the first week of life in premature infants. In most cases, apnea of premature infants occurs when they reach the appropriate age to be born. The present study aims to compare the effectiveness and adverse effects of caffeine with aminophylline on apnea of prematurity in infants.

**Methods:** The present clinical trial has been conducted on 64 premature infants. They were hospitalized in the NICU of Najmiyeh Hospital and divided into 2 groups. 30 infants received a loading dose of 5mg/kg aminophylline followed by a maintenance dose of 1.5mg/kg 3 times a day while 34 infants received a loading dose of 20 mg/kg caffeine followed by a maintenance dose of 5mg/kg once a day. Clinical symptoms and complications of infants, mechanical ventilation time, length of stay and frequency of apnea during treatment were gathered.

**Results:** Eventually 64 premature infants were investigated ( $p=0.185$ ). Mean of gestational age in infants who received caffeine (group A) was 31.27 weeks and in infants who received aminophylline (group B) was 31.07 weeks ( $p=0.806$ ). The mean duration of mechanical ventilation was  $2.78\pm 1.43$  days in group A infants. This was  $2.57\pm 1.53$  in group B infants. Mean duration of hospitalization was  $18.42\pm 17.18$  days in group A and  $14.50\pm 9.86$  days in group B ( $p=0.582$ ). There was no significant difference between caffeine and aminophylline in decreasing apnea attacks ( $p=0.428$ ).

**Conclusion:** There was no significant difference in decreasing apnea attacks, length of stay and mechanical ventilation time between the two groups.

#### Keywords:

Aminophylline,  
Caffeine,  
Apnea of prematurity

### Introduction

Apnea of prematurity (AOP) is a common problem in preterm infants which also involves term infants less commonly. AOP occurs in infants with gestational ages of lower than 37 weeks without precise reason and is one of the most common causes

of medication therapy in infants (3-1). AOP may be hereditary or associated with other conditions such as sepsis, anemia, pneumonia, metabolic disorders, GERD or neurologic disorders. Prevention of preterm labor is the most effective method for anticipating prematurity

complications such as respiratory distress syndrome, intraventricular hemorrhage, bronchopulmonary dysplasia, retinopathy of prematurity as well as apnea (8-4 ,1).

Caffeine, Theophylline, and Aminophylline have been used for treatment of AOP as respiratory stimulators. Previously, Theophylline was the most common standard treatment for AOP and needed serial serum level monitoring. Since FDA approval of Caffeine for infants, it has been widely replaced for Theophylline as the first medication for management of AOP (4). Methylxantines improve duration of ventilation, CO<sub>2</sub> sensitivity, hypoxia, respiratory depression, diaphragmatic activity and fatigue and decrease apnea incidence in 7-2 days after prescription (4 10 ,9).

In the present study we aimed to compare effectiveness and adverse effects of Aminophylline versus Caffeine in apnea of prematurity as a randomized clinical trial.

### Patients and methods

This randomized clinical trial study was conducted between March and September 2017 at NICU ward of Najmiyeh University Hospital, Tehran, Iran. Study protocol was registered at ethics committee of Baqiyatallah University of Medical Sciences. Figure 1 shows the flowchart of the trial. Premature infants who were hospitalized in NICU ward of Najmiyeh Hospital due to apnea were assessed for eligibility. Diagnosis was confirmed by a neonatologist and through symptoms such as heart rate, cyanosis, bradycardia and apnea. Patients were selected using simple random selection. Infants with gestational age of less than 35 weeks and birthweight of less than 1800 gr were included in the trial. Patients with craniomaxillofacial or chromosomal anomalies as well as those who did not develop apnea in first 5 days of birth were excluded from the study. Demographic information as well as blood

pressure, respiratory rate, oxygen saturation before and after ventilation, duration of hospitalization, need for re-intubation, blood sugar and feeding tolerance were recorded in a pre-designed checklist. Also, complications such as necrotizing enterocolitis (NEC), pneumothorax, intraventricular hemorrhage (IVH), need for NCPAP, pneumonia and bronchopulmonary dysplasia (BPD) as well as adverse effects of medications were recorded.

After explanation of study protocol for parents and signing an informed consent form infants were randomly allocated to two groups using random number table; infants in group A received 5mg/kg of Aminophylline as bullous dose and 1.5 mg/kg TDS; while, Group B infants underwent treatment with 20mg/kg of Caffeine as bullous dose and 5mg/kg daily. We had no lost to follow-ups and all the patients completed the trial.

Data were analyzed using SPSS software version 21 (SPSS Inc., Chicago, IL) for Microsoft Windows. Normal distributed variables (approved by -1sample Kolmogorov-Smirnov test) were compared using independent sample *t* test between the groups. The chi square test was used to compare categorical variables in the 2 groups. Mean and standard deviation (SD) were used for describing categorical variables. A *p* value of less than 0.05 was considered as statistically significant.

### Results

Eventually 21) 64 female and 43 male) premature infants were investigated (*p*=0.185). Mean of gestational age in infants who received caffeine (group A) was 31.27 weeks and in infants who received aminophylline (group B) was 31.07 weeks (*p*=0.806). Also mean birthweight in group A was 1481.25 gr and 1476 gr in group B (*p*=0.949). Mean Apgar score was 7.23 in group A and 7.73 in group B (*p*=0.061).

We investigated some variables that have effects on the condition of the newborns under study. One of the mothers in group A had gestational diabetes and two mothers had this problem in group B ( $p=0.595$ ). Gestational blood pressure was observed in 7 mothers of group A and 5 mothers of group B ( $p=0.756$ ). Prevalence of placental abruption was 8% in group B mothers

while there were no cases of placental abruption in group A ( $p=0.210$ ). Received doses of each drug (except studied drugs) by two groups have been summarized in table 1.

Medications	Group A N(%)		Group B N(%)		p value
NAC	0	%0	0	%0	NC
Surfactant	33	%97.1	24	%80	0.044
Budesonide	24	%70.6	20	%66.7	0.791
Albuterol	22	%64.7	16	%53.3	0.447
Cefotaxime	22	%64.7	22	%73.3	0.591
Amikacine	18	%52.9	20	%66.7	0.314
Ampicillin	5	%14.7	6	%20	0.742
Meropenem	1	%2.9	1	%3.3	>0.999
Tasubactam	0	%0	0	%0	NC
Imipenem	1	%2.9	0	%0	>0.999
Ceftazidime	1	%2.9	2	%6.7	0.596
Vancomycin	7	%20.6	6	%20	>0.999

Table 1. Received doses of each medication by each group

None of the infants in two groups had necrotizing enterocolitis, sepsis or pneumonia. Among group A infants 17.60% had patent ductus arteriosus (PDA) and it was 6.9% in group B infants ( $p=0.270$ ). Three infants in group A and two infants in group B had intra ventricular hemorrhage (IVH) ( $p>0.999$ ). One infant in group B had pneumothorax ( $p=0.46$ ). Prevalence of oxygen dependence in infants with 35 gestational week age was 18.2% in group A and 0% in group B. There was a significant difference between two groups ( $p=0.045$ ).

The mean duration of mechanical ventilation was 57.2 days in group A infants, and this was 78.2 days in group B infants ( $p=0.582$ ). Mean duration of hospitalization was 18.4 days in group A and 14.5 days in group B ( $p=0.939$ ).

Table 2 summarizes the occurrence of apnea and Table 3 shows main outcome measures of study. According to our study

the mean respiratory rate was decreased in both groups after the test. The mean heart rate in group A decreased, but in group B, the incidence of coronary heart disease was increased. The mean oxygen concentration raised in all newborns after receiving caffeine and aminophylline. After starting treatment and using caffeine and aminophylline, the number of infants who needed mechanical ventilation and oxygen dependence was decreased.

We expected side effects such as seizure, restlessness, tachycardia, hyperglycemia, and feeding intolerance. One of the infants receiving caffeine (2.9%) and two infants from the aminophylline group (6.7%) had seizures ( $p=0.596$ ). Restlessness and tachycardia were seen in only one of the infants (group A 2.9%, group B 3.4%) of each group ( $p>0.999$ ). Six infants from the caffeine group (17.6%) and four

Intervention Day	Caffeine Group N(%)	Aminophylline Group N(%)	p value
First day	5(14.7%)	15(50%)	0.003
Second day	3(8.8%)	9(30%)	0.052
Third day	2(5.9%)	5(16.7%)	0.238
Fourth day	1(2.9%)	2(6.7%)	0.596
Fifth day	1(2.9%)	1(3.3%)	0.999
p value	0.183	0.001	

Table 2. Frequency of apnea occurrence during the first five days of study

Caffeine Number of breaths Aminophylline	66.06	7.88	53.94	8.27	<0.001	-12.12	0.510
	65.17	6.75	54.31	7.53	<0.001	-10.86	
Caffeine Heart rate Aminophylline	146.06	9.33	142.06	24.88	0.382	-4	0.003
	141.43	7.92	149.68	14.00	0.001	8.25	
Caffeine Oxygen saturation Aminophylline	93.52	1.82	94.30	1.13	<0.00	0.78	0.153
	93.62	1.61	93.79	1.76	0.493	0.17	
	Number	percent	Number	percent	p-value	Difference	p-value
Caffeine mechanical ventilation Aminophylline	33	100%	13	39.4%	<0.001	-61%	0.444
	28	96.6%	14	48.3%	<0.001	-48%	
Caffeine Dependence on oxygen Aminophylline	33	100%	20	69%	<0.001	-31%	0.423
	28	96.6%	20	60.6%	0.008	-36%	

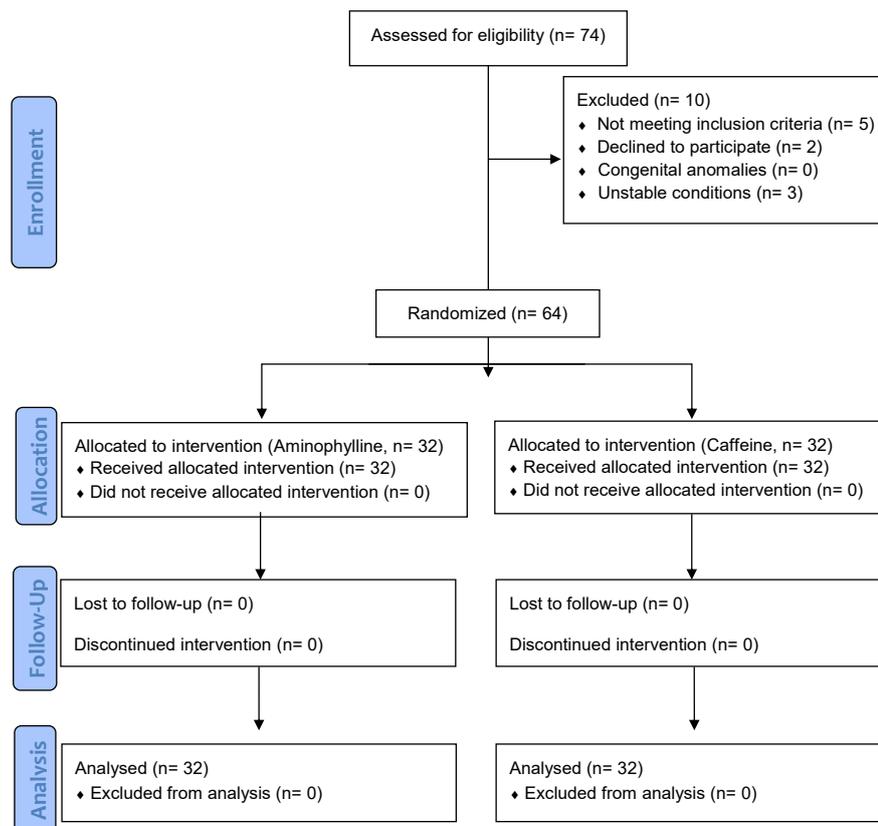
Table 3. Main outcome measures of study

neonates from the aminophylline group (%13.8) showed hyperglycemia ( $p=0.741$ ). The percentage of newborns in the aminophylline group was affected by a lack of %27.6 of infants in the caffeine group and %5.9 were ultimately fed with the tolerance ( $p=0.035$ ). Using both drugs in a small number of infants, side effects were observed. The incidence of nutritional intolerance was more pronounced in the newborns treated with aminophylline.

## Discussion

In the present study we found that there is no statistically significant difference for mean duration of hospitalization

and also mean duration of mechanical ventilation between two Aminophylline and Caffeine groups. Also results showed that patients in Aminophylline group had a significantly less oxygen dependency in 35<sup>th</sup> week of gestational age in comparison with Caffeine group. We assessed patients'



response to Caffeine and Aminophylline by respiratory rate, heart rate, oxygen saturation, need for mechanical ventilation and oxygen dependency.

Both Aminophylline and Caffeine groups showed a significant improvement in respiratory rate, need for mechanical ventilation and oxygen dependency. On the other hand, oxygen saturation was not significantly improved in Aminophylline receiving patients. Heart rate was decreased in Caffeine group; this decrease was not significant though.

We also found that frequency of apnea occurrence was decreased in both groups during the first 5 days of intervention; however, caffeine was more effective in the first day in comparison with Aminophylline.

A similar study was conducted by Steer et al. comparing the effects of Aminophylline and Theophylline on treatment of apnea and mechanical ventilation dependency

in premature infants. They reported no significant difference between two groups for rate of apnea after intervention; however, side effects such as tachycardia or feeding intolerance were lower in Caffeine group (11).

Korvadiya et al. compared the effect of Aminophylline and Theophylline on 40 Indian premature infants with apnea of prematurity. Infants were between 28 and 36 weeks of gestational age and had 2 or more episodes of apnea in the recent 24 hours. They reported no significant difference between these two groups in terms of response to treatment and adverse effects (12). In 2016 Dobson et al. assessed the effect of Caffeine on non-invasive respiratory support and reported beneficial effects such as decrease in duration of positive pressure respiratory support as well as development risk of bronchopulmonary diseases (BPD) (13).

## Conclusion

In conclusion the finding of the present study suggest that there is no significant difference in decreasing apnea attacks, length of hospitalization and duration of mechanical ventilation between the two Aminophylline and Caffeine groups. Future studies are suggested to be conducted with a higher sample size and to compare the therapeutic effects of Aminophylline and Caffeine in different weight and gestational age groups.

## Authors' Contributions

BN and MS designed the study and drafted the manuscript. BN and FA helped in manuscript drafting and analysis as well as acquisition of data. All authors have approved the final version of manuscript.

## Conflict of Interest Disclosures

There are no conflicts of interest in terms of the present manuscript.

## Ethical approval/Consideration:

This study was registered at ethics committee of Baqiyatallah University of Medical Sciences, Tehran, Iran. A written informed consent was taken from patients' guardians for participating in this study. All the personal information remained anonymous.

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