

# Comparison of Caffeine Versus Aminophylline for Apnea of Prematurity

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## Authors Contribution:

AA – Conceived Idea, Designed Study, Data Analysis

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## Abstract

**Objective:** To make a comparison between the efficacy and safety of Caffeine and Aminophylline for Apnea of prematurity at standard doses. **Methodology:** The participants (neonates) were allocated randomly into 2 groups. Caffeine was given in loading dose of caffeine citrate (20 mg/kg) followed by 5 mg/kg/day maintenance dose every 24 hour to one group. The Aminopylline group was given (loading dose 5mg/kg and maintenance dose of 1.5 mg/kg) every 8 hour. The assesment for variations in the episodes of apnea, corresponding respiratory disorders, along with acute detrimental effects was done. The therapeutic drug levels related to the efficacy were also determined. **Results:** The mean apnea events/day in neonates administrated by caffeine was  $0.8\pm 0.3$ ,  $1.9\pm 0.18$ ,  $1.4\pm 1.8$ ,  $0.9\pm 0.11$  and  $0.98\pm 0.15$  for 0, 1-3, 4-7, 8-14 and 15-21 days respectively. While, The mean apnea events/day in neonates administrated by Aminophylline was  $0.6\pm 0.4$ ,  $0.4\pm 0.24$ ,  $0.3\pm 1.6$ ,  $0.8\pm 0.14$  and  $0.69\pm 0.15$  for 0, 1-3, 4-7, 8-14 and 15-21 days respectively. The difference was statistically significant for one to three days ( $p=0.000$ ) and four to seven days ( $p=0.000$ ), 15-21 days ( $p=0.004$ ) While the difference was statistically insignificant at 0 day ( $p=0.845$ ), 8-14 days ( $p=0.741$ ). **Conclusion:** Results of our study revealed that caffeine is more effective than Aminophylline in treatment of apnea of prematurity.

**Keywords:** Apneic spells, Methylxanthines, Preterm neonates.

## Introduction

The persistently repeated incident of aop associated with hypoxemia and bradycardia is more life threatening to the child than the mere occurrence of the disease of aop as the former is related to high contingency of brain damage in preterm infants [1,2,3]. It has been shown by Cochrane meta-analysis that administration of methylxanthines in infants with aop significantly reduces the episodes of apnea and enhances the process of mechanical ventilation[4,5].

Only a narrow range of investigation and research have been carried out to establish the effectiveness and safeness of caffeine versus aminophylline among the third world nation [6,7,8]. Other than that, small for gestational age (SGA) growth retarded babies are increasing in number day by day in these countries and the effect of methylxanthine is still partially unclear [9,10]. Thus, the following study has been performed in to arbitrate the effects of caffeine on SGA and other preterm babies.

## Methodology

A randomized controlled trial study was organized from December 2016 to December 2017 in one year duration. Approval from ethics committee was obtained and an informed consent in written form was taken from parent of each participating individual.

6 or more episodes of apnea in 24 hours experienced preterm infants having gestational age less than 34, or the need for mask ventilation to abate the apnea were considered as the study group. Various investigations were performed such as Sepsis workup, echocardiography, relevant blood, and radiology to assess and eliminate the neonates having other minor causes of apnea. Further exploration was established on the clinical signs and symptoms. Other elimination criteria comprised of primary congenital abnormalities, respiratory distress due to medicines and Patent ductus arteriosus (PDA) as origin of apnea. Randomization was done with the help of computer-generated program using a block size of 10. Allotment was performed with the help of sequential numbered, sealed and opaque envelopes. A research officer, unconcerned with the ongoing study or the management of candidate infants; performed the allocation sequencing and concealment. The attending clinician in the neonatology unit was assigned the treatment of participating infants. Infants belonging to Caffeine group were given a loading dose of 20 mg/kg of caffeine citrate (10 mg/kg caffeine base) diluted in 5% dextrose administered for 30 min and a maintenance dose of 5 mg/kg (2.5 mg caffeine base) 24 hourly (iv or oral preparation of caffeine citrate solution 20 mg/mL). the dose was optimized to 7.5 mg/kg if sufficient response was not observed. Neonates assigned to aminophylline group received a loading dose of 5 mg/kg of aminophylline, diluted in 5 % dextrose followed with a maintenance dose of 1.5 mg/kg 8 hourly (Inj.

aminophylline 250 mg/10 mL). Dose was increased up to 2mg/kg if appropriate response was not recorded.

All the vitals and standard specifications were determined for all the participants. Then the gestational age of infant was estimated from the menstrual history of mother or through the ultrasound scan if present. A new Ballard's system of evaluation was done for the patients who could not provide either of these and was considered as final. Lubchenco growth chart was used to categorize the intrauterine growth. The recordings for birth weight, surfactant, gender, antenatal steroids, APGAR were noted. There was a continuous observation of vitals and oxygen saturation by neonatal monitors with alarms set to alert at SpO<sub>2</sub> <85% saturation and heart rate (HR) <100 bpm; SpO<sub>2</sub> of 90-95% was focused. After initiating the treatment with methylxanthines, clinical evaluation was performed after every 24 hours. All the records for isolated desaturations, the intervention used, Daily apneic episodes, adverse effects and mean of 24 hours heart rate were noted. The discharge criteria for neonates was self-feeding, weight 1800g, euthermia and free of apnea 7 days after withdrawal of methylxanthines. High-risk neonates were followed up. A blood sample (0.25mL) was withdrawn following plasma concentration 4-5 t1/2 after initialising therapy in order to calculate the plasma levels of theophylline and caffeine, targeting to reach a therapeutic concentration (5 to 12 mg/L theophylline and 5 to 20 mg/L caffeine). Trough levels were taken for the purpose of sampling before the need for next dose. In order to avoid unnecessary sampling pricking, sampling was performed while IV line was being changed or with other blood samples. The concentrations of plasma caffeine and theophylline were calculated with LCMS assay. The episodes of apnea (per 24 hours) at an interval of one to three day, four to seven day and eight to fourteen day of therapy were considered as primary outcome while Mean apnea rate (MAR) was taken as a secondary outcome. The Mean apnea rate is defined as "average number of desaturations with bradycardia per neonate over 24 hours period), frequency of desaturations (Number of isolated desaturation per 24 hour) calculated in set interval of 1 to 3 day, 4 to 7 day and 8 to 14 day of therapy, time required for resolution of apnea, duration of hospital stay, HR variability on 1st, 2nd, 3rd, 7th and 14th day of methylxanthine therapy, and safety profile in regards to some known reported adverse events of methylxanthines (tachycardia, jitteriness, feed intolerance and abnormal blood sugar)."

Data was analyzed by using SPSS version 24, mean and SD was calculated for quantitative data like gestational age and mean concentration of caffeine and aminophylline. Numbers and frequencies were calculated for qualitative data like nasal CPAP no. and apnea events. Students t test and  $\chi^2$  was applied see association among variables. P value less than 0.05 was considered as significant.

## Results

100 infants were included in this study (n=100). This study was further divided into two equal groups i.e. 50% (n=50) in each, treated with Caffeine and Aminophylline respectively. The mean gestational age of caffeine group was 30.40±1.57 weeks. The mean gestational age of Aminophylline group was 31.36±1.68 weeks. Supplemental O<sub>2</sub> – no. was observed as 30% (n=15) and 28% (n=14) for caffeine group and Aminophylline group respectively. Nasal CPAP – no. was noted in 20% (n=10) and 12% (n=6) infants, for caffeine group and Aminophylline group respectively. While, IVH grade I was observed in 8% (n=4) and 14% (n=7) infants, for caffeine group and Aminophylline group respectively. The difference was statistically insignificant, except gestational age (p=0.000). (Table. 1).

The mean concentration at day 3, 7, 14 and 21 of caffeine group was 13.27±2.45, 11.62±2.36, 12.07±2.76 and 11.32±2.0 respectively. The mean concentration at day 3, 7, 14 and 21 of Aminophylline group was 1.79±1.36, 2.44±1.13, 4.0±2.22 and 3.29±1.05 respectively. The differences was statistically significant (p<0.005), according to student t test. (Table. 2).

The mean apnea events/day in neonates administrated by caffeine was 0.8±0.3, 1.9±0.18, 1.4±1.8, 0.9±0.11 and 0.98±0.15 for 0, 1-3, 4-7, 8-14 and 15-21 days respectively. While, The mean apnea events/day in neonates administrated by Aminophylline was 0.6±0.4, 0.4±0.24, 0.3±1.6, 0.8±0.14 and 0.69±0.15 for 0, 1-3, 4-7, 8-14 and 15-21 days respectively. The difference was statistically significant for 1-3 days (p=0.000) and 4-7 days (p=0.000), 15-21 days (p=0.004) While the difference was statistically insignificant at 0 day (p=0.845), 8-14 days (p=0.741). (Figure. 1).

**Table. 1**

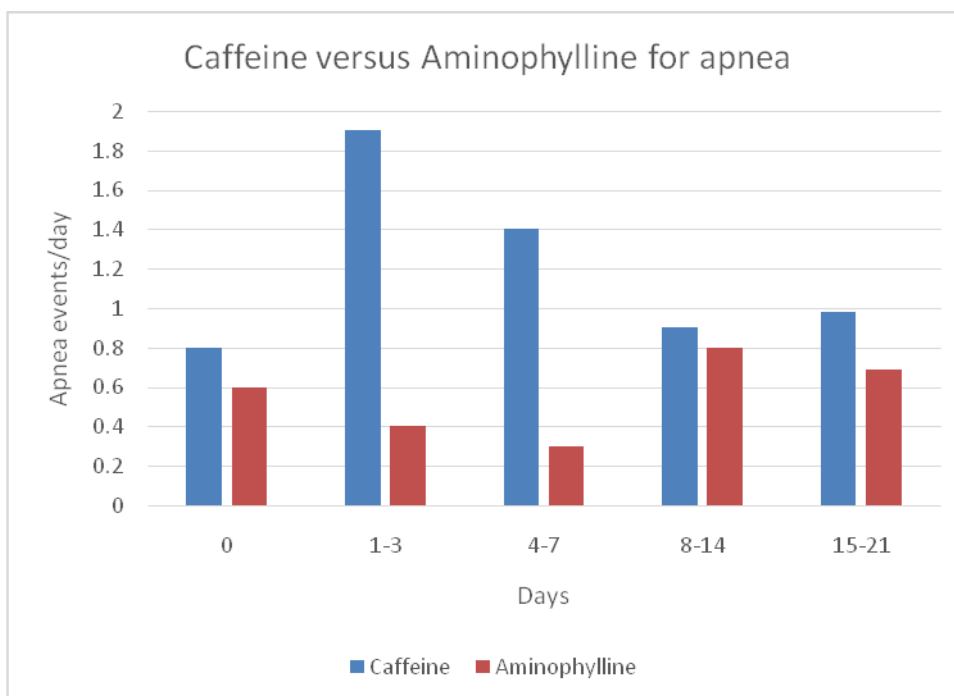
**Demographic Characteristics among the study groups**

Characteristics	Caffeine (n=50)	Aminophylline (n=50)	P Value
Gestational Age (weeks)	30.40±1.57	31.36±1.68	<b>0.004</b>
Supplemental O <sub>2</sub> – no.	30% (n=15)	28% (n=14)	<b>0.826</b>
Nasal CPAP – no.	20% (n=10)	12% (n=6)	<b>0.275</b>
IVH grade I	8% (n=4)	14% (n=7)	<b>0.338</b>

**Table-2**  
**Serum concentrations in infants receiving methylxanthines for apnea of prematurity**

Characteristics	Caffeine (n=50)	Aminophylline (n=50)	P Value
<b>Mean concentration</b>			
<b>Day 3</b>	13.27±2.45	1.79±1.36	<b>0.000</b>
<b>Day 7</b>	11.62±2.36	2.44±1.13	<b>0.000</b>
<b>Day 14</b>	12.07±2.76	4.0±2.22	<b>0.000</b>
<b>Day 21</b>	11.32±2.0	3.29±1.05	<b>0.000</b>

**Figure. 1**



### Discussion

There have been various options for the treatment of AOP. It is reported by a study [11] that the modern day management of AOP does not vary greatly from the one that was done two decades ago. The mainstay of the therapy is the pharmacologic and non-pharmacologic treatment options. The study claimed that methylxanthines are the most widely used drugs these days for this purpose. But the study also insisted upon the use of caffeine as it has a wider therapeutic index and is easy to administer. While the infants unresponsive to the methylxanthines, must be treated with doxapram. The aforementioned study suggested providing a home apnea monitor for each patient to have better outcomes.

AOP results in the immature development of the neurologic and respiratory system. For the encounter of such grave condition, another study [12] describes the current options for the treatment of AOP. Close monitoring of infant along with supportive care such as "tactile stimulation, continuous positive airway pressure, or mechanical ventilation" is stated as fundamental principles in this study. The pharmacologic therapy included methylxanthines as first-line drugs, while for second-line drugs, a different class of agent like respiratory stimulants as doxapram are suggested. Caffeine is also recommended as the drug of choice. The clinical trials depicted that "caffeine is at least as effective as theophylline, has a longer half-life, is associated with fewer adverse events, and, in addition, has a greater ease of administration". The study demonstrates that caffeine has a wider application due its fewer side effects, greater therapeutic margin and increasing ability to stimulate the respiratory and central nervous system. Theophylline requires constant and crucial monitoring.

A study by Khurana S. et al [13] was conducted to determine the neurodevelopmental outcome of caffeine versus aminophylline therapy for apnea of prematurity. It was claimed that methylxanthines are prescribed the most for treating the AOP. 240 infants were assessed for the comparison of caffeine and aminophylline as treatment of AOP. 83% decreased the risk of cognitive impairment was calculated for the infants being treated with caffeine, 50% less risk of developing motor deficits (RR 0.50; CI 95% range 0.12 to 1.95) and 24% less risk of developing language problems (RR 0.76; CI 95% range 0.36 to 1.58). The difference among the study groups

regarding all the neurodevelopmental domains, physical growth, abnormality in vision and hearing were not found to be statistically significant. Risk of mortality in caffeine group was 9% less than aminophylline group which was also statistically non-significant. The study concluded that caffeine and aminophylline groups demonstrated similar results in reducing mortality rates in infants with AOP although the "clinical significance of caffeine over aminophylline cannot be undermined".

Caffeine has wide applications in the field of neonatology. As stated by Abdel Hady H. et al [14] caffeine fairly decreases the likelihood of intermittent hypoxemia and frequency of apnea, reduces the incidence of bronchopulmonary and patent ductus arteriosus and facilitates extubation from mechanical ventilation in preterm infants. The study stresses upon the controversies with respect to duration and initiation of therapy, safety and efficacy of high doses, and the need for monitoring of therapeutic levels of drug, so care must be taken in order to get safer outcomes. Caffeine is not only the most commonly prescribed medicine for AOP, but it has its proven role in other disorders such as "intermittent hypoxemia and extubation failure in mechanically ventilated preterm infants". It has been compared to other methylxanthines in terms of the dosage regimens, initiation and duration of therapy, therapeutic index and drug safety and monitoring. It must be noted here that concentrations and timing of initiation of caffeine therapy play a vital role in the outcome of treatment. As stated by Kua K. et al [15] "early initiation of caffeine may have incremental benefits on neonatal outcomes". They further add their results as early caffeine therapy (initiated <3 days of life) demonstrated a marked decrease in the rate of occurrence of bronchopulmonary dysplasia as compared late caffeine therapy. Another study done by Dobson N. et al [16] focuses on the similar issue and predicts that prior induction of caffeine therapy is affiliated with a lesser risk of Bronchopulmonary Dysplasia. Further Randomized trials are required to establish the efficacy and safety of early caffeine prophylaxis in Very Low birth infants.

Caffeine citrate has proved to be quite effective for the treatment of AOP. It has been called as "silver bullet in neonatology" by Shreshta B. et al [17]. The authors further claim that owing to its broad therapeutic index, its increasing efficacy, and safety margin, caffeine is a drug of choice among the other methylxanthines. When caffeine citrate is used in greater doses, it causes improvement in acute neonatal outcomes when administered properly as stated by Lista G. et al [18]. The author further suggests that caffeine and theophylline are a mainstay in treating the AOP. Although a series of clinical trials must be carried out in order to determine the long-term neurological effects of a large loading dose of caffeine.

A study conducted by Skouroliaou M. et al [19] compared the relative efficacy of caffeine with theophylline for treating AOP. It concluded that there is the relative "advantage of caffeine over theophylline for infants <33 weeks gestation during the first week of therapy", as it did not require any routine monitoring of concentration unless indicated by clinical effects during the first three months of treatment. There was an increase in survival incidence among the infants being treated with caffeine for AOP; of course, further trials are needed to confirm the findings.

A similar study comparing the use of caffeine citrate and aminophylline for treating primary apnea in premature infants was carried out by Xu JL et al [20] a clinical trial upon 125 patients was performed and it was observed that the overall response rate in the caffeine citrate group was 86% (56 cases), which was significantly higher than that in the aminophylline group (72%, 43 cases). The adverse reactions in the caffeine citrate group included tachycardia (1 case), restlessness (5 cases), feeding intolerance (7 cases), electrolyte disturbance (2 cases), and high blood glucose (5 cases), the incidence of which was significantly lower than that in the aminophylline group. It was concluded that caffeine citrate is more efficacious and less likely to cause an adverse reaction as compared to aminophylline in the treatment of apnea of prematurity in preterm infants.

## Conclusion

Results of our study revealed that caffeine is more effective than Aminophylline in treatment of apnea of prematurity.

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