

Comparison of Efficacy and Safety of Caffeine and Aminophylline in Apnea of Prematurity

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ABSTRACT

Background: Apnea of prematurity usually occurs in neonates having gestational age of less than 36 weeks. Caffeine and aminophylline both drugs are available as a treatment option for apnea of prematurity. **Objective:** Our objective is to compare the efficacy and safety of standard recommended doses of caffeine and aminophylline in the treatment of apnea of prematurity. **Study Design:** Randomized controlled trial. **Settings:** Department of Pediatrics, Central Park Teaching Hospital, Lahore Pakistan. **Duration:** 12 months from May 5th, 2022 to May 4th, 2023. **Methods:** A randomized controlled trial was conducted in the NICU Department of Central Park Teaching Hospital, Lahore which included 160 preterm neonates and efficacy and adverse effects of both drugs were compared. **Results:** There was a significant difference in the means of the rate of apnea of both the groups over the span of 7 days with caffeine being more effective. There was a decrease in duration of hospital stay and duration of oxygen inhalation along with reduced patients with tachycardia and tachypnea in caffeine group with significant p- value. Caffeine proved to be safer in terms of lesser side effects as compared to aminophylline. **Conclusion:** This study concludes that caffeine has a greater efficacy and a better safety in comparison with aminophylline, while treating apnea of prematurity.

Keywords: Apnea, Prematurity, Aminophylline, Caffeine.

INTRODUCTION

Apnea of prematurity (AOP) is one of the most common and frequently occurring problem in very low birth weight infants and is defined as cessation of breathing lasting for >20 seconds or for >10 seconds if accompanied by bradycardia (< 80 beats per minute) or oxygen desaturation (O₂ saturation of < 80 – 85%).¹ The incidence of AOP is 7% percent of neonates born at 34 to 35 weeks gestation, 15% at 32 to 33 weeks, 54% at 30 to 31 weeks and nearly all infants born at <29 weeks gestation or <1000g weight. It has been noted to be inversely related to birth weight and gestational age.²

Apnea in preterm infants is classified as central, obstructive and mixed. Central apnea is due to absent inspiratory efforts, obstructive type is due to airway obstruction with present inspiratory efforts and mixed

type is the combination of both, with the latter being the most common.³ Other common causes of neonatal apnea are brain tissue damage, respiratory disease, infection, GERD, cardiac issues, and metabolic disorders.⁴ Recurrent apnea can lead to serious adverse effects like respiratory failure, pulmonary hemorrhage, intracranial bleeding, abnormal nervous system development, and even sudden death, therefore early intervention is key in order to prevent such complications.⁵ Various other complications include respiratory distress syndrome, intraventricular hemorrhage, bronchopulmonary dysplasia and retinopathy of prematurity.⁶

Methylxanthines (aminophylline, theophylline, and caffeine) are the backbone of pharmacological therapy for the last 25 years and they not only reduce the frequency of apnea but also decrease the need for mechanical

ventilation during the first seven days of starting therapy.⁷ However, there are few adverse effects of methylxanthines such as tachycardia, hypertension, tremors, vomiting, hyperglycemia, electrolyte disturbance, jitteriness, seizures and hypertonemia.⁸ One study in South Africa has reported that caffeine group has fewer cardiovascular and respiratory side effects and lesser incidence of apneic spells as compared to the aminophylline group.⁹

Another study of India shows that aminophylline is equally effective as caffeine for the prevention of apneic attacks in preterm neonates however has higher side effects on the cardiovascular system which includes tachycardia.¹⁰ Another study of China shows that apneic spells were lower in the caffeine group as compared to aminophylline group showing 14.3% and 32.6% recurrent incidents, respectively.¹¹ A study in Pakistan shows that caffeine is more effective than theophylline for treating apnea of prematurity.¹²

There is limited data and no previous study is done at institutional level regarding the efficacy and safety of aminophylline and caffeine.

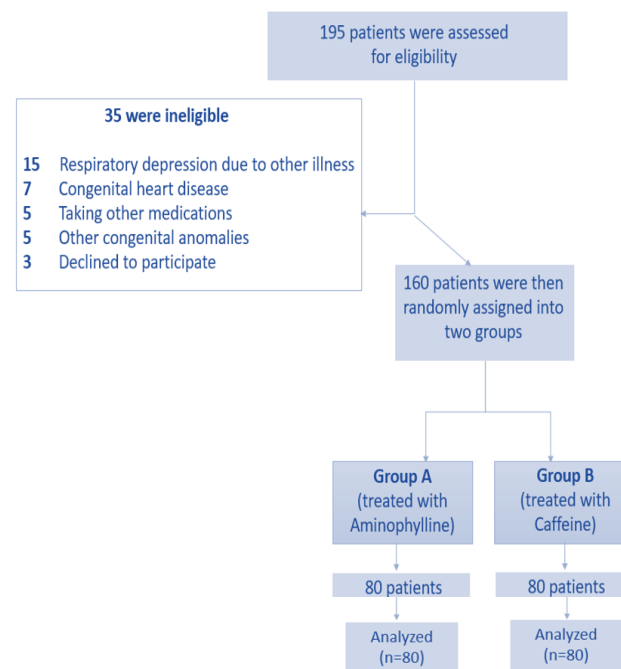
Our objective is to study the efficacy and safety of aminophylline and caffeine in the premature infants presenting in NICU of Central Park Teaching Hospital having apnea of prematurity.

METHODS

The study is a prospective randomized control trial that was conducted in the NICU Department of Central Park Teaching Hospital, Lahore, for a duration of 12 months from May 5th, 2022 to May 4th, 2023. A sample of 160 neonates of first 28 days of life with gestational age of less than 37 weeks having apnea of prematurity were selected randomly through the opaque envelope technique. A strict inclusion criterion was followed which included infants born at <36 weeks of gestation, having birth weight of equal to or less than 2.5kg and who had one or more apneic spells in 24 hours, or requiring bag and mask ventilation for termination of apnea or having hospital stay of >24 hours. Newborns having congenital anomalies, respiratory depression from any other illness or any medication and those having any inherited metabolic diseases were all excluded from the study. A detailed questionnaire was developed that included demographic details, type of delivery, drug used, etiology and frequency of apnea and measurement of vitals at day 1, 2, 3, 5 and 7, type and duration of oxygen inhalation, common side effects and duration of hospital stay. Ethical approval was obtained from the institution review board of Central Park Teaching Hospital. Consent was taken on the admission file after informing parents about detailed procedure of

drug administration and follow up. Neonates were then randomly divided into two groups, each comprising of 80 neonates. One group was given aminophylline (Group A) while the other one (Group B) was given caffeine as the first-line treatment of apnea of prematurity. The loading dose of caffeine was 20mg/kg and maintenance dose was 5mg/kg OD, whereas the loading dose of aminophylline was 6mg/kg and maintenance dose was 2mg/kg TDS. All the relevant information was documented on the predesigned Performa. Data that was collected was then duly entered in SPSS version 25.0 twice and checked for any errors. It was then analyzed using SPSS version 25.0 and T-test was performed to compare the efficacy of caffeine and aminophylline in the treatment of apnea of prematurity. A p-value of <0.05 was taken as significant. Cronbach's Alpha was 0.902.

Figure 1: The Consolidated standards of reporting trials (CONSORT) flow diagram



RESULTS

Out of the 160 neonates included in the study, 56 (35%) were females whereas 104 (65%) were males. Group A included 25 (31.25%) males and 55 (68.75%) females, whereas Group B included a total of 31 (38.75%) males and 49 (61.25%) females. There was no significant effect of gender on the efficacy of the drugs as evident by a p-value of 0.323.

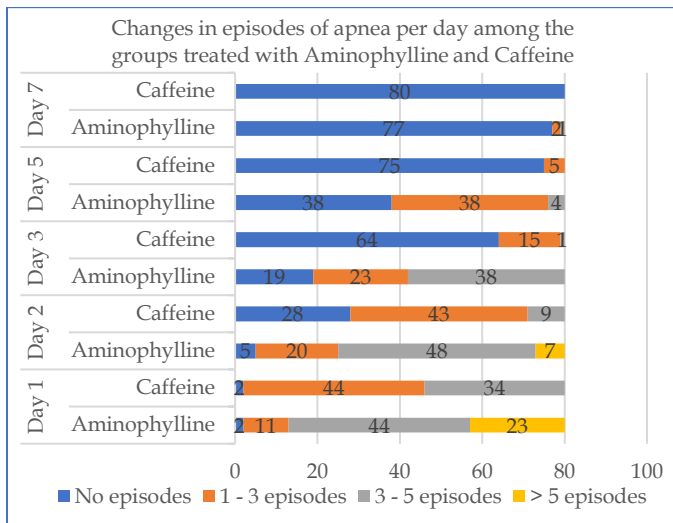
According to these results, there was a significant difference in the means of the rate of apnea of both the groups over the span of 7 days, with a much more significant difference after the third day of treatment.

This is evident by the p-values listed in Table 1 below:

Table 1: Demonstration of the total number of episodes of apnea that occurred in each group on the respective day of treatment. T-test results showing degree of apnea treated by both the drug groups at different days after administration

Day	Total number of episodes of apnea in Group A (Aminophylline)	Total number of episodes of apnea in Group B (Caffeine)	P-value
1	336	224	0.838
2	274	122	0.554
3	198	34	0.001
5	92	10	0.001
7	8	0	0.001

Figure 2: A stacked bar chart showing the changes in episodes of apnea per day, in both the groups, one treated with Aminophylline and the other by Caffeine



As the bar chart in Figure 2 clearly shows, there was a lot of improvement in episodes of apnea among neonates that were given Caffeine as compared to Aminophylline. Neonates of Group B not only recovered earlier but also had a fewer number of neonates with apnea of more than 3 episodes.

The vitals recorded on each of these days also showed a significant difference in the means of both groups suggesting a greater efficacy of caffeine. The average respiratory rate in group A was 61 – 70 breaths/min as compared to group B which was 40 – 50 breaths/min with a significant p- value of 0.001 at day 3, day 5 and day 7 which showed that there was significant improvement in respiratory rates in group B.

Similarly, the average heart rate in group A was 161 – 180/min as compared to group B which was 120-139/min with a significant p- value of 0.001 at day 3, day 5 and day 7 which showed that there was significant improvement in respiratory rates in group B.

The improvement in respiratory rate and heart rate of neonates is evident in Figure 3 and Figure 4, below. Caffeine seems to be more effective as there are lesser number of patients with respiratory rates of >70 breaths/min and heart rate of 181 to 200 bpm, as compared to those treated with aminophylline.

Figure 3: A stacked column chart showing changes in respiratory rate of the neonates over the span of 7 days after initiating treatment with both the drugs.

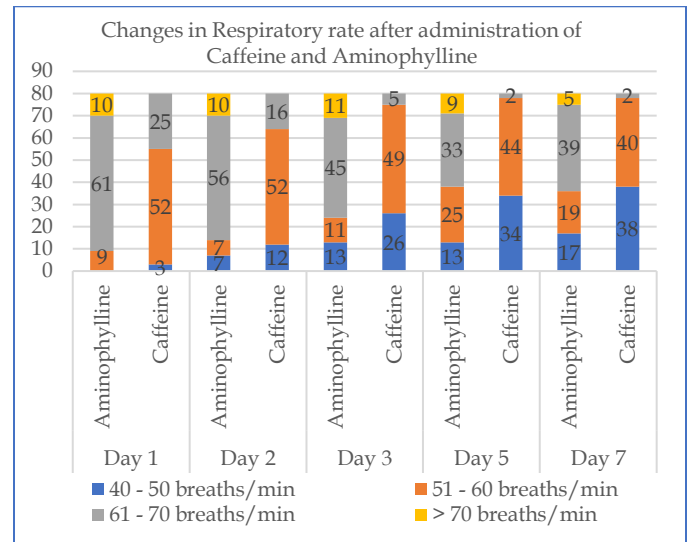
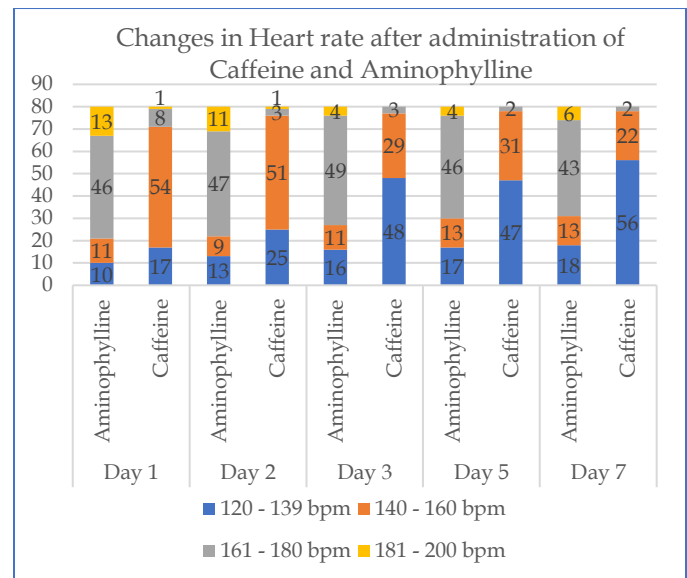


Figure 4: A stacked column chart showing changes in heart rate of the neonates over the span of 7 days after initiating treatment with both the drugs.

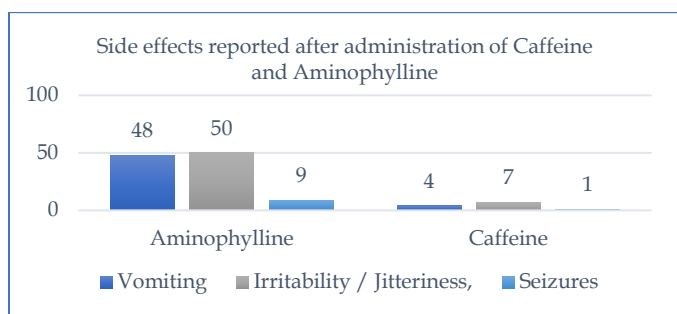


Moreover, there has been a decrease in duration of hospital stay as well, which is more significant with administration of caffeine (p-value = 0.001). The duration of Oxygen inhalation also decreased with an average of <3 days of oxygen required for caffeine-treated neonates, as compared to an average of 4-7 days of Oxygen inhalation required in aminophylline-treated neonates.

According to results of the t-test, this decrease is significant with a p-value of 0.007.

Not only this, but the neonates who were given caffeine were also observed to have shown lesser side effects, compared to those treated with aminophylline. This can be demonstrated in Figure 5 below. Only 10 (12.5%) neonates showed one or more side effects among the group treated with caffeine, whereas 52 (65%) neonates treated with aminophylline experienced one or more side effects. T-test results show a p-value of 0.001.

Figure 5: A bar chart showing the incidence of side effects, mainly vomiting, irritability/jitteriness and seizures, caused by caffeine and aminophylline.



16% of the neonates treated with caffeine were also given surfactant, while 21% of the neonates treated with aminophylline required surfactant administration. However, there is no significant difference among the means of the two groups (p-value = 0.107). Similarly, 81% of the neonates of each group were given antenatal steroids and that also was not significant (p-value = 1.000).

The type of delivery (p-value = 0.739) did not have any significant effect on the degree of apnea and neither did the birth weight (p-value = 0.751). Their distribution among the two drug groups is summarized in Table 2 and 3, respectively.

Table 2: Distribution of neonates according to type of delivery

Type of Delivery	Group A (Aminophylline)	Group B (Caffeine)
Spontaneous Vaginal Delivery	26 (32.5%)	27 (33.75%)
Caesarean section	54 (67.5%)	53 (66.25%)

Table 3: Distribution of neonates according to birth weight

Birth weight	Group A (Aminophylline)	Group B (Caffeine)
600 g to 1 kg	6 (7.5%)	6 (7.5%)
1.1 kg to 1.5 kg	36 (45%)	31 (38.75%)
1.6 kg to 2 kg	31 (38.75%)	38 (47.5%)
2.1 kg to 2.5 kg	7 (8.75%)	5 (6.25%)

DISCUSSION

The overall results indicate that caffeine has a greater efficacy as compared to aminophylline as it is able to treat the patients earlier. However, results demonstrate there was no significant difference in efficacy of both the drugs during the first two days. This finding is in line with the results of a meta-analysis conducted in 2022 which stated that there was no significant difference in efficacy observed between both the drugs during the first three days of treatment.¹³ Another study has also shown that these drugs are more effective following the second day of treatment.¹⁴

The view of the existing literature on this subject matter is mixed. There are studies that suggest that caffeine has a greater efficacy when used for treatment and prevention of apnea of prematurity, owing to lesser use of oxygen and improved pulmonary function tests.^{15, 16} Our results build on these studies and show that caffeine more effective in treating apnea which is evident as it minimizes the duration of oxygen inhalation and hospital stay. Caffeine has also proven to restore vitals faster and does not result in very high heart rates. This finding is in line with another study that was performed to compare hemodynamic effects of both the drugs and has shown that neonates treated with aminophylline had higher heart rates.¹⁷

There also is some of the existing literature which suggests that caffeine and aminophylline are equally effective.¹⁸⁻²⁰ Some say that both the drug treatments demand an equal need of oxygen and respiratory therapy.²¹ However, our results are in contrary to these.

Even though there are mixed views regarding which drug is more effective, it is unanimously agreed that both caffeine and aminophylline are at some degree, quite effective in treating apnea of prematurity and can be used alternatively.²²

The data also suggests that caffeine has a greater safety compared to aminophylline as it reported lesser side effects. These results are in line with existing literature that have previously shown aminophylline to have caused a great deal of adverse effects including seizures, vomiting and hyperglycemia.^{8,9,13} Caffeine, in contrast, has proven to be a safer drug with very low incidence of side effects including restlessness and tachycardia.^{14,23-25} Another study that was exclusively done to compare irritability among the neonates treated with caffeine and aminophylline also showed that caffeine was not associated with causing irritability.²⁶

It is beyond the scope of this study to comment on long term side effects of caffeine and aminophylline. Additional research is required to establish the safety of these drugs in the long term as well.

CONCLUSION

This study concludes that caffeine has a greater efficacy and a better safety in comparison with aminophylline, for the treatment of apnea of prematurity. These results should be taken into account when deciding which drug regimen to start the treatment with. It is recommended that treatment for apnea of prematurity in neonates be initiated with caffeine.

LIMITATIONS

Limitations of this study are that this was conducted in only one hospital and the findings may not be able to be generalized. Studies from other hospitals across the country are needed to make generalizations. Moreover, the drugs levels of both drugs were not checked in the patients as it was expensive and unavailable in many settings. Severe apnea has a negative impact on the neurodevelopmental outcome and caffeine improves it, therefore, another study is required to evaluate the efficacy of caffeine in protecting cerebrum from any kind of neurodevelopmental impairment in the long term.

SUGGESTIONS / RECOMMENDATIONS

It is recommended that further research be carried out using greater sample.

CONFLICT OF INTEREST / DISCLOSURE

The authors have declared no conflicts of interest.

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