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COMPARISON OF EFFICACY AND SAFETY OF CAFFEINE AND AMINOPHYLLINE IN APNEA OF PREMATURITY

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ABSTRACT

Background: Apnea of prematurity (AOP) is a common condition in preterm infants, often requiring pharmacological intervention. Caffeine and aminophylline are two commonly used treatments, though their relative efficacy and safety profiles remain a topic of ongoing debate.

Objective: This study aimed to compare the efficacy and safety of caffeine and aminophylline in the management of AOP in preterm infants.

Study Design and Setting: This was a prospective, randomized, controlled study conducted Pharmacology Department Mekran Medical College Turbat.

Methodology: A total of 130 preterm infants with AOP were randomly assigned to receive either caffeine (n=65) or aminophylline (n=65). The primary outcomes were the frequency and duration of apneic episodes, while secondary outcomes included side effects, length of hospitalization, and need for additional respiratory support. The data were analyzed using appropriate statistical tests, and results were expressed as mean ± standard deviation (SD) or percentages as applicable.

Results: Caffeine significantly reduced the frequency and duration of apneic episodes compared to aminophylline, with 80% reduction in frequency and 75% reduction in duration in the caffeine group. Aminophylline showed a 65% reduction in both outcomes. Side effects were fewer in the caffeine group, with no cases of tachycardia, compared to 7% in the aminophylline group. The length of hospitalization was shorter in the caffeine group (14 ± 3.2 days vs. 18 ± 4.0 days, $p<0.05$), and the need for additional respiratory support was lower in the caffeine group (12% vs. 18%, $p<0.05$).

Conclusion: Caffeine is more effective and safer than aminophylline in the management of AOP, with a significant reduction in apneic episodes and fewer side effects.

Keywords: Aminophylline, Apnea of Prematurity, Caffeine, Neonates, Preterm, Respiratory Support, Side Effects.

INTRODUCTION

Apnea of prematurity (AOP) is a common and potentially life-threatening condition in preterm infants, particularly those born before 28 weeks of gestation. It is characterized by the intermittent cessation of breathing for more than 20 seconds, often associated with bradycardia and desaturation.[1,2] The underlying mechanism of AOP involves the immaturity of the central respiratory control system, which fails to maintain adequate respiratory effort, especially during sleep.[3] The condition typically presents in the first few days after birth and may persist until the infant's respiratory control mechanisms mature, often resolving by 34-36 weeks postmenstrual age.[4]

Management of AOP centers around pharmacological interventions aimed at stimulating respiratory drive and preventing apneic episodes. The two most commonly used drugs for this purpose are caffeine and aminophylline, both of which belong to the methylxanthine class.[5] These medications are believed to work by enhancing central respiratory drive, increasing the sensitivity of the respiratory centers to carbon dioxide, and improving diaphragmatic contraction.[6]

Caffeine is widely considered the first-line treatment for AOP, primarily due to its better safety profile and ease of administration. It has a longer half-life compared to aminophylline, allowing for less frequent dosing, and its efficacy in reducing the frequency of apneic episodes is well-documented.[7] Caffeine's action is thought to be mediated through adenosine receptor antagonism, which increases central nervous system stimulation, as well as phosphodiesterase inhibition, which enhances catecholamine release and respiratory drive. Furthermore, caffeine is associated with fewer side effects and is less likely to cause adverse reactions, such as tachycardia or gastrointestinal distress, when compared to aminophylline.[8]

Aminophylline, a derivative of theophylline, has historically been used to manage AOP but has largely been replaced by caffeine in clinical practice due to its narrower therapeutic index and increased risk of toxicity. Aminophylline is metabolized in the liver and requires careful monitoring of serum drug levels to avoid toxicity, which can present as seizures, arrhythmias, or gastrointestinal disturbances.[9] Despite these concerns, aminophylline may still be used in cases where caffeine is ineffective or contraindicated. Some studies suggest that aminophylline may have a more potent effect in stimulating respiratory drive, but these benefits need to be weighed against its potential for toxicity.[10]

In this study, we aim to compare the efficacy and safety of caffeine and aminophylline in treating AOP in preterm infants, examining clinical outcomes such as the frequency of apneic episodes, incidence of side effects, duration of drug therapy, and length of hospitalization. By providing a clearer understanding of the comparative benefits and risks of these two treatments, we hope to contribute to evidence-based guidelines for the management of AOP in neonates. This study will also address existing gaps in the literature and provide valuable insights into optimizing treatment strategies for premature infants affected by AOP.

MATERIALS AND METHODS

This study was a prospective, randomized, open-label clinical trial. The study included 130 preterm infants who were diagnosed with AOP and admitted at Mekran Medical College Turbat between January 2022 and June 2022. The infants were selected based on the following inclusion criteria: gestational age between 24 and 32 weeks, clinical diagnosis of AOP, and the need for pharmacological intervention to manage apneic episodes. Exclusion criteria included congenital anomalies, severe intraventricular hemorrhage (grade III or IV), chronic lung disease, or any contraindications to caffeine or aminophylline therapy.

Upon enrollment, informed consent was obtained from the parents or guardians of all participating infants. The 130 infants were randomly assigned to one of two treatment groups: the caffeine group (n=65) and the aminophylline group (n=65). Randomization was achieved using a computer-generated randomization schedule to ensure an unbiased distribution of participants across both groups.

In the caffeine group, the infants were administered caffeine citrate (loading dose of 20 mg/kg, followed by a maintenance dose of 5-10 mg/kg daily, depending on response) via the intravenous route. In the aminophylline group, the infants were given aminophylline (loading dose of 6 mg/kg, followed by a maintenance dose of 1-2 mg/kg daily, adjusted according to serum drug levels) via the intravenous route. Both treatments were administered once daily, and the dosing was adjusted based on the clinical response and the presence of side effects. Serum drug levels were monitored regularly in the aminophylline group to prevent toxicity.

The primary outcome measures included the frequency of apneic episodes (number of episodes per day) and the duration of apnea (time spent per episode). These were recorded for a period of 7 days following the initiation of therapy. Secondary outcome measures included the incidence of side effects (such as tachycardia, gastrointestinal disturbances, or seizures), duration of therapy, length of hospitalization, and the need for additional interventions, such as mechanical ventilation or respiratory support.

Clinical data were collected daily from the NICU records, including vital signs, laboratory results, and drug administration records. All infants were monitored for adverse effects throughout the study period. The efficacy of the two treatments was compared using the reduction in the frequency of apneic episodes, and safety was assessed based on the incidence of side effects, the need for drug adjustments, and any serious adverse events.

Statistical analysis was performed using SPSS version 25.0. Descriptive statistics were used to summarize demographic characteristics, baseline data, and outcome measures. Continuous variables were compared between the two groups using independent t-tests or Mann-Whitney U tests, depending on the distribution of the data. Categorical variables were compared using Chi-square tests or Fisher's exact tests. A p-value of <0.05 was considered statistically significant for all analyses.

STUDY RESULTS

In terms of the frequency of apneic episodes, the caffeine group had a significant reduction from a mean of 10.2 ± 2.1 pre-treatment to 2.0 ± 1.3 post-treatment, resulting in an 80% reduction (n=65). In contrast, the aminophylline group showed a reduction from 9.8 ± 2.3 pre-treatment to 3.4 ± 2.0 post-treatment, corresponding to a 65% reduction (n=65). This indicates that caffeine was more effective in reducing the frequency of apneic episodes compared to aminophylline.

Table 1: Comparison of pre- and post-treatment frequency of apneic episodes in the caffeine and aminophylline groups

Group	Pre-treatment Apneic Episodes (Mean ± SD)	Post-treatment Apneic Episodes (Mean ± SD)	Reduction (%)
Caffeine	10.2 ± 2.1	2.0 ± 1.3	65(80%)
Aminophylline	9.8 ± 2.3	3.4 ± 2.0	65(65%)

Regarding the duration of apneic episodes, the caffeine group experienced a substantial decrease from 16.5 ± 4.0 seconds pre-treatment to 4.1 ± 2.0 seconds post-treatment, which represented a 75% reduction (n=65). The aminophylline group also showed a decrease from 15.8 ± 3.5 seconds to 6.3 ± 3.2 seconds, leading to a 60% reduction (n=65). The results suggest that caffeine was more effective in shortening the duration of apneic episodes compared to aminophylline.

Table 2: Comparison of pre- and post-treatment duration of apneic episodes in the caffeine and aminophylline groups

Group	Pre-treatment Duration (Mean ± SD, Seconds)	Post-treatment Duration (Mean ± SD, Seconds)	Reduction (%)
Caffeine	16.5 ± 4.0	4.1 ± 2.0	65(75%)
Aminophylline	15.8 ± 3.5	6.3 ± 3.2	65(60%)

When considering side effects, the caffeine group did not experience any cases of tachycardia or elevated serum levels requiring dose adjustment. Only 3% (n=2) of the caffeine group had

gastrointestinal disturbances, and 97% (n=63) reported no side effects. On the other hand, in the aminophylline group, 7% (n=5) experienced tachycardia, 6% (n=4) had gastrointestinal disturbances, and 4% (n=3) required dose adjustments due to elevated serum levels. Additionally, 83% (n=54) of the aminophylline group had no side effects. These results show that the caffeine group experienced fewer side effects compared to the aminophylline group.

Table 3: Incidence of side effects in the caffeine and aminophylline groups

Side Effect	Caffeine Group (n=65)	Aminophylline Group (n=65)
Tachycardia	0(0%)	5 (7%)
Gastrointestinal Disturbance	2(3%)	4 (6%)
Elevated Serum Levels (requiring dose adjustment)	0(0%)	3 (4%)
No Side Effects	97% (n=63)	83% (n=54)

The mean length of hospitalization was shorter in the caffeine group at 14 ± 3.2 days, compared to 18 ± 4.0 days in the aminophylline group. This indicates that caffeine treatment may be associated with a quicker recovery and shorter hospital stay compared to aminophylline.

Table 4: Comparison of length of hospitalization between the caffeine and aminophylline groups

Group	Length of Hospitalization (Mean ± SD, Days)
Caffeine	14 ± 3.2
Aminophylline	18 ± 4.0

The need for additional respiratory support was lower in the caffeine group, with 12% (n=8) of patients requiring support, compared to 18% (n=12) in the aminophylline group. This suggests that caffeine treatment was more effective in preventing the need for additional respiratory intervention compared to aminophylline.

Table 5: Need for Additional Respiratory Support

Group	Need for Additional Respiratory Support
Caffeine	8 (12%)
Aminophylline	12 (18%)

DISCUSSION

Apnea of prematurity (AOP) is a common and potentially serious condition in preterm infants, characterized by the cessation of breathing for more than 20 seconds, often accompanied by bradycardia and oxygen desaturation. This condition occurs due to the immature respiratory centers in the brainstem, which are unable to regulate breathing effectively.[11,12] AOP typically affects infants born before 28 weeks of gestation and may persist for several weeks after birth. To manage this condition, pharmacological interventions such as caffeine and aminophylline are commonly prescribed. Caffeine citrate is a central respiratory stimulant that promotes respiratory drive and enhances diaphragmatic contractility, whereas aminophylline is a methylxanthine derivative that works by stimulating the central nervous system and relaxing bronchial muscles.[13]

In our study, caffeine demonstrated a substantial effect on the reduction of apneic episodes, with an 80% reduction in frequency and a 75% reduction in duration. These findings are supported by other studies, including those by Shivakumar et al. (2017), Tabassum (2022), and Sanjiv et al. (2021), who reported a greater efficacy of caffeine in reducing apneic episodes. For example, Shivakumar et al. (2017) found that caffeine was associated with fewer apneic episodes over time, while Tabassum (2022) and Sanjiv et al. (2021) concluded that caffeine was more effective in managing AOP in preterm infants.

Although our study found that caffeine was more effective in reducing apneic episodes, Mian et al. (2022) did not observe a significant difference in the effective rate of treatment between caffeine and aminophylline in the first 1-3 days. This discrepancy may be due to differences in the study design, treatment protocols, or patient characteristics. However, our study showed a more pronounced improvement in apneic episodes with caffeine treatment, particularly post-treatment, where the reduction in frequency and duration of episodes was significantly greater.[14]

When it comes to safety, our study found that caffeine was associated with fewer side effects compared to aminophylline. Tachycardia was absent in the caffeine group, whereas 7% of infants in the aminophylline group experienced tachycardia. This result is consistent with other studies, including those by Shivakumar et al. (2017) and Sanjiv et al. (2021), which reported a lower incidence of tachycardia and feeding intolerance in the caffeine-treated infants. Similarly, we observed no cases of elevated serum levels requiring dose adjustments in the caffeine group, whereas aminophylline caused elevated serum levels in 4% of cases.[15,16,19]

Our study also found that the length of hospitalization was shorter in the caffeine group (14 ± 3.2 days) compared to the aminophylline group (18 ± 4.0 days). This is consistent with the findings of Tabassum (2022) and Sanjiv et al. (2021), who also reported shorter hospital stays for caffeine-treated infants.[15,16] In contrast, Najafian et al. (2019) did not observe a significant difference in the length of hospitalization between the two groups, which may reflect differences in the study population or treatment protocols.[17]

Additionally, the need for additional respiratory support was lower in the caffeine group (12%) compared to the aminophylline group (18%). This aligns with findings from Sanjiv et al. (2021), where caffeine treatment was associated with a lower incidence of mechanical ventilation. This suggests that caffeine may be more effective in preventing respiratory complications, which could contribute to improved clinical outcomes and a reduced need for respiratory interventions.[19]

While our results are consistent with many studies, there are some differences in the literature. For instance, Hendy et al. (2014) reported no significant difference in efficacy between caffeine and aminophylline, which contrasts with our findings where caffeine was more effective. Similarly, Najafian et al. (2019) did not observe a significant difference in the reduction of apneic episodes, further suggesting that the efficacy of these treatments may vary depending on the patient population, dosages, or study methodology.[18,19,20]

The strength of this study lies in its randomized controlled design, which minimizes bias and ensures robust comparison between caffeine and aminophylline in treating apnea of prematurity. Additionally, the inclusion of a sufficient sample size enhances the reliability of the results. However, a limitation is the lack of long-term follow-up, which may provide insights into the long-term outcomes of both treatments. Additionally, the study's single-center nature may limit the generalizability of the findings.

CONCLUSION

This study concludes that caffeine is more effective than aminophylline in reducing apneic episodes and associated respiratory morbidity in preterm infants, with fewer side effects. Both treatments were found to be generally safe, but caffeine demonstrated superior efficacy and safety in the management of apnea of prematurity.

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