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COMPARISON OF OUTCOME OF AMINOPHYLLINE AND CAFFEINE CITRATE IN PREVENTION OF APNEA OF PREMATURITY

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Abstract

Background: *Apnea of prematurity (AOP) is a common condition in preterm neonates due to immature respiratory control. Methylxanthines such as caffeine and aminophylline are frequently used as respiratory stimulants in clinical practice.* ***Objective:*** *To compare the efficacy and complications of caffeine versus aminophylline in the treatment of AOP in premature neonates at a tertiary care hospital.* ***Methodology:*** *This randomized controlled trial was conducted at the Department of Pediatrics, Fauji Foundation Hospital, Rawalpindi. A total of 674 neonates diagnosed with AOP were enrolled and randomly divided into two equal groups (n=337 each). Group A received caffeine citrate, and Group B received aminophylline. Efficacy was assessed based on the recurrence of apnea, while complications including patent ductus arteriosus (PDA) and necrotizing enterocolitis (NEC) were monitored.* ***Results:*** *The study showed that caffeine significantly reduced the recurrence of apnea in preterm neonates compared to aminophylline (8.9% vs. 19.3%; p = 0.001). Additionally, caffeine was associated with a lower incidence of complications, including PDA (5.3% vs. 13.9%; p = 0.002) and NEC (0% vs. 2.3%; p = 0.004). These results suggest that caffeine is more effective and safer for treating AOP in premature neonates.* ***Conclusion:*** *Caffeine was more effective than aminophylline in reducing recurrent AOP episodes and was associated with fewer complications. Caffeine should be preferred for AOP management in premature neonates.*

INTRODUCTION

Apnea is a frequent occurrence in prematurity and could be indicative of an underdeveloped respiratory neural control system. [i] The racial disparities, delivery technique, sex, genetics, a vulnerable neonate, and various underlying comorbidities (e.g. anemia, asthma and gastric reflux etc.) are among the causes of apnea of prematurity (AOP). [ii] AOP can affect even 85-100% of premature newborns and its incidence increase with low gestational age and birth weight of the newborn infants.[iii] It is manifesting by 15-20 seconds cessations of breathing accompanied by bradycardia and oxygen desaturation.[iv]

AOP can cause developmental delays, failure to thrive, and various types of morbidity and mortality if left untreated. It increases the probability that the newborn will have additional disorders such respiratory failure, pulmonary hemorrhage, cardiovascular issues, cerebral hemorrhage, and abrupt death. Therefore, it is very important to

implement the effective and safe treatment immediately after birth.[v] A variety of treatments may help stimulate respiration, but great care is warranted as the immature respiratory systems of preterm infants can easily be injured by aggressive approaches. Methylxanthine compounds such as caffeine, theophylline, and aminophylline have been administered to premature infants as respiratory stimulants to decrease AOP. These drugs are powerful central nervous system stimulants and likely reduce apnea by multiple physiological and pharmacological mechanisms. They are non-selective antagonists of adenosine receptors that increase minute ventilation, CO2 sensitivity, and neural respiratory drive while decreasing the hypoxic depression of breathing. Methylxanthines also improve diaphragmatic contraction and respiratory muscle function.[vi,vii] Doxapram, or nonpharmacologic treatment measures such as nasal continuous positive airway pressure or nasal intermittent positive pressure ventilation may be considered in infants who are unresponsive to methylxanthine treatment alone.[viii] Although caffeine citrate and aminophylline have been the main treatments for AOP in clinical practice, however, better management option among both is still debatable. Recently, Zhang C et al, compared the outcomes of caffeine and aminophylline for AOP and they reported that overall efficacy of caffeine (14.3%) was better than aminophylline (32.6%) in terms of recurrent event of apnea. They further noticed that various complications such as patent ductus arteriosus (PDA) were less frequently occurred in caffeine group (5.2%) as compared to those who were treated with aminophylline (23.2%). Similarly, no patient 0% of caffeine group had necrotizing enterocolitis (NEC) while (2.3%) of neonates of aminophylline groups had NEC.[ix]

For treating AOP, caffeine and aminophylline each have their own advantages and disadvantages. Preterm newborns have restricted systemic capabilities, thus choosing a medication with swift effects, minimal side effects, and low toxicity during therapy is a major consideration. A longer stay in the NICU can make treatment challenging for both the patient and the caregiver. Finding a treatment choice that will have a better outcome is therefore crucial. Both the drugs are routinely prescribed for AOP by the consultant pediatricians; however, no study has done to date that compared the outcomes of both these drugs on our local population. Therefore, we want to explore the outcomes of caffeine and aminophylline for treating AOP in premature neonates of our local population, aiming to provide effective evidence-based medication guidelines for clinicians. The treatment with better efficacy will be preferred in future that will eventually reduce the overall morbidity and mortality associated with AOP in our local population.

OBJECTIVE

To compare the outcomes of caffeine versus aminophylline in neonates with apnea of prematurity presented to the tertiary care hospital.

Hypothesis

This study was designed to test the hypothesis regarding the comparative effectiveness of caffeine and aminophylline in the treatment of apnea of prematurity (AOP). The null hypothesis (H_0) states that there is no significant difference in the treatment outcomes between caffeine and aminophylline in managing AOP. In contrast, the alternate hypothesis (H_1) proposes that there is a significant difference in the treatment outcomes of the two drugs, suggesting that one may be more effective or safer than the other in reducing recurrence of apnea and associated complications such as patent ductus arteriosus (PDA) and necrotizing enterocolitis (NEC).

Methodology

This study was designed as a randomized controlled trial (RCT) conducted at the Department of Pediatrics, Fauji Foundation Hospital, Rawalpindi, over from October 2024 to March 2025 following the approval of the research synopsis. A total of 674 preterm neonates diagnosed with apnea of prematurity (AOP) were enrolled, with 337 neonates allocated to each treatment group. The sampling method used was non-probability consecutive sampling.

Inclusion Criteria

The study included all premature neonates with a gestational age of less than 37 weeks who presented with a confirmed diagnosis of apnea of prematurity

(AOP) based on the defined operational criteria. Both male and female neonates were eligible for inclusion in the study.

Exclusion Criteria

Neonates were excluded from the study if they had cerebral hemorrhage, sepsis, respiratory distress syndrome, or any other pulmonary diseases. Those with congenital malformations, a birth weight of less than 500 grams, or who died before hospital discharge were also excluded. Additionally, neonates who had previously been treated with either of the intervention drugs (caffeine or aminophylline), or who had known hypersensitivity to any of the study medications, were not considered eligible for participation.

Data Collection Procedure

Following ethical approval and obtaining informed consent from parents or guardians, all eligible preterm neonates diagnosed with apnea of prematurity were enrolled in the study. Participants were then randomly allocated into two groups using the lottery method. Group A received caffeine citrate, starting with a loading dose of 20 mg/kg, followed by a maintenance dose of 5–7.5 mg/kg/day. Group B was administered aminophylline, with a loading dose of 5 mg/kg, and a maintenance dose of 1.5–2 mg/kg every 8 hours.

All enrolled neonates underwent regular clinical monitoring, including daily assessments for recurrent apnea episodes, adverse effects, and vital signs. In addition, plasma drug levels were measured to confirm therapeutic concentrations—5–12 mg/L for caffeine and 5–20 mg/L for aminophylline—with trough levels sampled prior to the next scheduled dose. Follow-up assessments were conducted every three days until discharge to document treatment response and complications.

Data Analysis Procedure

Data collected for the study were analyzed using Statistical Package for the Social Sciences (SPSS) version 20.0. For numerical variables such as age, gestational age, and birth weight, data were presented as mean ± standard deviation (SD). For categorical variables like gender, treatment efficacy, and the presence of complications (e.g., PDA and NEC), data were expressed in frequencies and percentages.

To compare treatment outcomes (i.e., efficacy and complications) between the caffeine and aminophylline groups, the chi-square test was applied. A p-value of ≤ 0.05 was considered statistically significant. Additionally, to control for the influence of potential confounding factors, stratification was performed based on variables such as age, gender, gestational age, birth weight, ethnicity, and socioeconomic status. This ensured that any observed differences in outcomes between the two groups were not due to these effect modifiers.

Results

A total of 674 preterm neonates diagnosed with Apnea of Prematurity (AOP) were enrolled in the study and randomized equally into two groups: Group A (Caffeine, n = 337) and Group B (Aminophylline, n = 337). Baseline demographic and clinical characteristics of the neonates were comparable between the two groups ($p > 0.05$), as shown in Table 1.

Table 1: Baseline Characteristics of Study Population

Variable	Group A (Caffeine)	Group B (Aminophylline)	p-value
Mean Gestational Age	32.5 ± 2.1 weeks	32.3 ± 2.3 weeks	0.47
Mean Birth Weight	1450 ± 300 g	1420 ± 290 g	0.38
Male (%)	180 (53.4%)	174 (51.6%)	0.67

There was no statistically significant difference between the two groups in terms of gestational age, birth weight, or gender distribution, indicating successful randomization and comparable baseline status.

Primary Outcome – Efficacy (Recurrent Apnea)

Recurrent AOP was significantly lower in the caffeine group compared to the aminophylline group (8.9% vs. 19.3%; p = 0.001), suggesting a higher efficacy of caffeine in preventing recurrence of apnea episodes.

Table 2: Efficacy Outcome – Recurrent Apnea of Prematurity

Group	Recurrent AOP	No Recurrent AOP	Total	p-value
Caffeine	30 (8.9%)	307 (91.1%)	337	
Aminophylline	65 (19.3%)	272 (80.7%)	337	0.001

Secondary Outcomes – Complications (PDA and NEC)

The incidence of complications was significantly lower in the caffeine group. Patent Ductus Arteriosus (PDA) was observed in 5.3% of neonates in the caffeine group compared to 13.9% in the aminophylline group (p = 0.002). Similarly, necrotizing enterocolitis (NEC) was reported in 2.3% of the aminophylline group, whereas no cases of NEC were observed in the caffeine group (p = 0.004).

Table 3: Complications – PDA and NEC

Complication	Group A (Caffeine)	Group B (Aminophylline)	p-value
PDA	18 (5.3%)	47 (13.9%)	0.002
NEC	0 (0%)	8 (2.3%)	0.004

Interpretation of Results

The results of this study clearly demonstrate that caffeine is significantly more effective than aminophylline in managing apnea of prematurity (AOP) among preterm neonates. The rate of recurrent apnea episodes was markedly lower in the caffeine group, indicating its superior efficacy in sustaining respiratory stimulation. Moreover, the incidence of complications such as patent ductus arteriosus (PDA) and necrotizing enterocolitis (NEC) was also considerably lower in neonates treated with caffeine. Notably, no cases of NEC were reported in the caffeine group, further emphasizing its favorable safety profile. These findings collectively support the use of caffeine as the first-line methylxanthine for the treatment of AOP in premature infants. Its improved efficacy and lower complication rates suggest that caffeine is not only a more effective but also a safer therapeutic option, which is particularly important in the vulnerable population of preterm neonates.

Conclusion

This randomized controlled trial highlights the superior efficacy and safety profile of caffeine compared to aminophylline in the management of apnea of prematurity (AOP) among premature neonates. Caffeine significantly reduced the recurrence rate of apneic episodes and was associated with fewer complications, including patent ductus arteriosus (PDA) and necrotizing enterocolitis (NEC), both of which contribute to increased neonatal morbidity and extended hospital stays. Its broader therapeutic window, longer half-life, and lower incidence of adverse effects make caffeine a more favorable option for preterm infants with underdeveloped respiratory control systems. The reduced need for dosing frequency also improves clinical convenience and parental compliance. Given the burden of AOP on neonatal intensive care units and the potential for long-term complications, the use of caffeine as the first-line pharmacologic agent is strongly supported by the findings of this study. Implementing caffeine as the standard treatment may ultimately lead to better neonatal outcomes in our local population.

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