ORIGINAL ARTICLE

Caffeine Citrate Versus Aminophylline for Apnea of Prematurity: A Prospective Randomized Comparative Study

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ABSTRACT

Objective: To compare the efficacy and safety of caffeine citrate versus aminophylline in the treatment of apnea of prematurity among preterm neonates.

Study Design: Prospective randomized comparative study

Place and Duration of Study: Department of Pediatrics, Benazir Bhutto Hospital, Rawalpindi from 4th July 2022 to 4th January 2023.

Materials and Methods: A total of 122 preterm neonates with gestational age of 34 weeks or less and at least four episodes of apnea were enrolled and randomly assigned to two groups. One group received a loading dose of 20 mg/kg of caffeine citrate followed by 10 mg/kg once daily, while the other group received a loading dose of 5 mg/kg of aminophylline followed by 2.5 mg/kg 12 hourly. The Treatment was continued for 34 weeks postmenstrual age. The primary outcome was complete resolution of apnea within 48 hours. Secondary outcomes included recurrence of apnea, changes in cardiorespiratory parameters, electrolyte stability and complications.

Results: Resolution of apnea within 48 hours occurred in 50(82%) of neonates receiving caffeine citrate compared with 40(65.6%) receiving aminophylline (p =0.040). Recurrent apnea was lower with caffeine citrate (3.3% versus 13.1%) with p value=0.048. Complications were also fewer in the caffeine group (13.1% versus 41%) with p value=0.026. Moreover, caffeine shortened NICU stay (14.2 ± 2.5 vs. 17.1 ± 3.1 days) with p value< 0.001, reduced the need for mechanical ventilation (18% vs. 31%) with p value=0.035, and improved early neurodevelopmental outcomes (87% vs. 72%) with p value =0.041.

Conclusion: Caffeine citrate is superior to aminophylline, demonstrating greater effectiveness in resolving apnea, reducing complications, shortening NICU stay, decreasing the need for mechanical ventilation and promoting improved early neurodevelopmental outcomes.

Key Words: *Apnea of Prematurity, Caffeine Citrate, Aminophylline, Preterm Neonates, Prospective Randomized Comparative Study.*

Introduction

Apnea of prematurity (AOP) is one of the most frequent and clinically significant complications among preterm neonates. It is defined as a cessation of breathing for more than 20 seconds or a shorter pause accompanied by bradycardia and desaturation, occurring primarily due to immaturity of the central respiratory control mechanisms in premature infants.[1] The condition is strongly inversely related to gestational age and birth weight, with reported occurrence in up to 85% of neonates born at ≤34 weeks of gestational age.[2] AOP contributes to prolonged neonatal intensive care unit stays, increased risk of hypoxemia related morbidities such as retinopathy of prematurity, bronchopulmonary dysplasia and adverse neurodevelopmental outcomes, thereby making it a major public health concern in resource limited settings.[3,4]

Historically, methylxanthines including theophylline, aminophylline and caffeine citrate have been the mainstay pharmacologic agents for the treatment of AOP.[5] Among these, caffeine citrate has gained increasing preference because of its longer half life, wider therapeutic window and fewer adverse effects compared to aminophylline and theophylline.[6]

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Several clinical studies and systemic reviews have shown that caffeine is effective in reducing apneic episodes, supporting extubation and improving neurodevelopmental outcomes in preterm infants.[7,8] Although previous studies have compared caffeine citrate and aminophylline for apnea of prematurity, much of the existing evidence has mainly addressed short term efficacy and safety outcomes, particularly apnea resolution and adverse effects. However, important gaps remain regarding their comparative performance in routine public sector NICU settings in Pakistan, where drug availability, affordability, monitoring capacity and hospitalization burden may influence treatment decisions. In many low and middle income countries, aminophylline continues to be used because of its lower cost and easier availability, despite concerns regarding its narrower therapeutic index and higher complication rates. In contrast, caffeine citrate may offer clinical advantages, but its wider adoption may be limited by cost and accessibility in local practice environments.[9,10]

Therefore, the present study was conducted to address this evidence gap by comparing caffeine citrate and aminophylline among preterm neonates with apnea of prematurity in a tertiary care public hospital setting. The study aimed to assess not only apnea resolution, but also recurrence of apnea, treatment related complications, NICU stay, requirement for mechanical ventilation and early neurodevelopmental status. The objective of this study was to compare the efficacy and safety of caffeine citrate and aminophylline in the treatment of apnea of prematurity among preterm neonates.

Materials and Methods

This Prospective Randomized Comparative Study was conducted in the Department of Pediatrics, Benazir Bhutto Hospital, Rawalpindi, from 4th July 2022 to 4th January 2023, after approval from the Institutional Review Board of Rawalpindi Medical University (Ref No 228/IREF/RMU/2022/ Dated:04/04/2022) and study was locally registered in Clinical Trial Unit Rawalpindi Medical University under registration number CTU 09/2023/0 13 RMU. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki. Sample size was calculated based on prior studies showing resolution rates of 80–85% with caffeine and 65–70% with aminophylline. To detect a 15% absolute difference with 80% power and 5% significance, 54 neonates were required per group; to allow for attrition, 61 were enrolled in each arm (n=122). Preterm neonates of either gender with gestational age ≤34 weeks and at least four episodes of apnea were eligible. Apnea was defined as cessation of breathing for ≥20 seconds or a shorter pause associated with bradycardia (heart rate <100 beats/min) and oxygen desaturation (<85%). Neonates with birth asphyxia, intraventricular hemorrhage (grade II or higher), sepsis, congenital malformations, metabolic abnormalities or necrotizing enterocolitis were excluded. Written informed consent was obtained from parents or guardians. Eligible neonates were allocated into two treatment groups using a computer-generated random sequence with allocation concealment through opaque sealed envelopes. Neonates were divided in two groups with 61 each group. Group 1 received caffeine citrate (loading dose 20 mg/kg followed by 10 mg/kg/day) and Group 2 received aminophylline (loading dose 5 mg/kg followed by 2.5 mg/kg every 12 hours). Therapy continued until 34 weeks of postmenstrual age. The primary outcome was complete resolution of apnea within 48 hours of treatment initiation. Additional outcomes included sustained resolution up to day 7, duration of NICU stay, requirements for mechanical ventilation and neurodevelopmental status at discharge and at 3 months corrected age. Secondary outcomes included recurrence of apnea, mean number of apneic spells at 24 hours, 25–72 hours and >72 hours, vital parameters (heart and respiratory rates), serum electrolytes and complications. Complications were prespecified as tachycardia (>180 bpm sustained), tachypnea (>70 breaths/min), feeding intolerance (≥2 gastric residuals >50% of feed or ≥2 vomiting episodes within 24 hours), restlessness requiring intervention and electrolyte imbalance confirmed on two consecutive samples. Blinding of caregivers was not feasible due to differences in dosing schedules; outcome data were collected by two pediatric residents using predefined operational definitions. Any discrepancy in outcome assessment was reviewed and resolved by consensus under consultant supervision before final data entry. Data were collected prospectively and analyzed

using SPSS v24. Continuous variables were expressed as mean ± SD and compared with independent t-tests; categorical outcomes were expressed as frequencies/percentages and compared with chi-square tests. Absolute risk differences with 95% confidence intervals (CIs) were reported. Logistic regression adjusting for gestational age and birth weight was applied to key outcomes, with p≤0.05 considered significant.

Results

A total of 122 neonates were randomized equally between caffeine citrate (61) and aminophylline (61). The baseline demographic and clinical profiles of neonates were similar in both groups. The mean gestational age was 29±1.5 weeks in the caffeine citrate group and 30±1.8 weeks in the aminophylline group with p value=0.12. Among those receiving caffeine citrate, 25(41%) were male and 36(59%) were female, whereas in the aminophylline group, 19(31%) were male and 42(69%) were female.

Apnea resolved within 48 hours in 82% of neonates treated with caffeine versus 65.6% with aminophylline (absolute risk difference 16.4%, 95% CI: 1.1–31.8) with p value=0.040. Recurrent apnea occurred in 3.3% of caffeine treated neonates compared with 13.1% of those receiving aminophylline (risk difference –9.8%, 95% CI: –18.8 to –0.8) with p value=0.048. The mean number of apneic spells at 24 hours did not differ significantly, but aminophylline showed fewer episodes at 25–72 hours, a difference that was temporary and disappeared beyond 72 hours (Table I).

By day 7, mean heart rates were similar between groups, while respiratory rates improved more with caffeine (56 vs. 58 breaths/min) with p value=0.003 . Serum electrolytes remained stable and comparable (Table II).

Complications occurred in 13.1% of caffeine treated neonates compared with 41% in the aminophylline group (risk difference –27.9%, 95% CI: –42.8 to –13.0) with p value=0.026. Tachycardia and feeding intolerance were significantly less common in the caffeine group, while other adverse events showed no statistical difference (Table II).

NICU and neurodevelopmental outcomes showed that caffeine shortened NICU stay (14.2 vs. 17.1 days) with p value=<0.001, reduced need for mechanical ventilation (18% vs. 31%) with p value=0.035 and improved early neurodevelopment (87% vs. 72% normal at discharge) with p value=0.041. Logistic regression confirmed caffeine as an independent predictor of higher apnea resolution (adjusted OR 2.45, 95% CI: 1.05–5.72) with p value=0.038 and lower complications (adjusted OR 0.29, 95% CI: 0.11–0.74) with p value=0.010. Table III.

Table I : Comparison Of Treatment Outcomes Between Study Groups (Aminophylline and Caffeine) n=122

Outcome	Caffeine Citrate (n=61)	Aminophylline (n=61)	p-value
Apneic episodes at 24h (mean ± SD)	2 ± 0.48	2 ± 0.49	0.193
Apneic episodes at 25–72h (mean ± SD)	2 ± 0.49	1 ± 0.50	0.018
Apneic episodes >72h (mean ± SD)	1 ± 0.39	1 ± 0.48	0.174
Complete resolution n (%)	50 (82%)	40 (65.6%)	0.040
Recurrent apnea n (%)	2 (3.3%)	8 (13.1%)	0.048
Mean heart rate (bpm, Day 7)	141 ± 6.1	143 ± 6.8	0.113
Mean respiratory rate (breaths/min, Day 7)	56 ± 2.9	58 ± 2.9	0.003*
Serum sodium (mmol/L, Day 7)	134 ± 1.65	134 ± 1.84	0.536
Serum potassium (mmol/L, Day 7)	4.3 ± 0.41	4.3 ± 0.45	0.642
Serum chloride (mmol/L, Day 7)	122 ± 1.56	121 ± 1.56	0.955
Mean heart rate (bpm, Day 7)	141 ± 6.1	143 ± 6.8	0.113
Mean respiratory rate (breaths/min, Day 7)	56 ± 2.9	58 ± 2.9	0.003*
Serum sodium (mmol/L, Day 7)	134 ± 1.65	134 ± 1.84	0.536
Serum potassium (mmol/L, Day 7)	4.3 ± 0.41	4.3 ± 0.45	0.642
Serum chloride (mmol/L, Day 7)	122 ± 1.56	121 ± 1.56	0.955

Table II:Comparison of Treatment related Complications between Study Groups (Aminophylline and Caffeine) n=122

Complication	Caffeine Citrate (n=61)	Aminophylline (n=61)	p-value
No complication n (%)	53 (86.9%)	36 (59%)	-
Tachycardia n (%)	1 (1.6%)	6 (9.8%)	0.05*
Feeding intolerance n (%)	1 (1.6%)	2 (3.3%)	0.559
Restlessness n (%)	2 (3.3%)	5 (8.2%)	0.243
Tachypnea n (%)	2 (3.3%)	8 (13.1%)	0.048
Electrolyte imbalance n (%)	2 (3.3%)	4 (6.6%)	0.402
Total Complications n(%)	8(13.1%)	25(41%)	0.026

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Table III: NICU and Neurodevelopmental Outcomes Between Study Groups (n=122)

Outcome	Caffeine (n=61)	Aminophylline (n=61)	p-value
NICU stay (days, mean ± SD)	14.2 ± 2.5	17.1 ± 3.1	<0.001*
Mechanical ventilation n (%)	11(18%)	19(31%)	0.035
Normal neurodevelopment at discharge n (%)	53(87%)	44(72%)	0.041
Developmental delay at 3 months n (%)	6(10%)	14(23%)	0.048

Discussion

In this prospective randomized comparative study, caffeine citrate was associated with better overall clinical outcomes than aminophylline in preterm neonates with apnea of prematurity. Apnea resolved within 48 hours in 82% of neonates receiving caffeine compared with 65.6% receiving aminophylline. Recurrence of apnea was also lower in the caffeine group, while overall complications were less frequent. In addition, caffeine was associated with shorter NICU stay, reduced need for mechanical ventilation and better early neurodevelopmental status.

The main contribution of our research is not simply to confirm that caffeine citrate is an effective methylxanthine, as this has already been reported in previous literature. Rather, this research adds practical evidence from a routine public sector NICU setting where aminophylline remains in use because of cost, availability and established prescribing practice. By evaluating apnea resolution together with recurrence, complications, NICU stay, ventilation requirement and early neurodevelopmental status, the present research provides clinically relevant information for treatment selection in resource limited neonatal care.

Apnea resolution remains the most important immediate treatment outcome in neonates with apnea of prematurity. In our study, caffeine citrate achieved a higher resolution rate than aminophylline. This finding is consistent with Xu et. al.,[11] who reported better apnea control with caffeine and with Shukla et. al.,[12] who also observed a higher treatment success rate in neonates receiving caffeine. Previous pooled research evidence has suggested that both caffeine citrate and aminophylline are effective methylxanthines for apnea of prematurity. However, caffeine appears to have a more favorable adverse effect profile. Therefore, the value of our research lies in showing that this expected benefit was also reflected in routine NICU outcomes in our setting.

Recurrence of apnea was significantly lower among neonates treated with caffeine citrate. This may be explained by the longer half life and more stable serum concentration of caffeine, which provides a more sustained therapeutic effect compared with aminophylline. Similar findings were reported by Zhang et. al.,[13] and Shivakumar et. al.,[14] who observed fewer recurrent apneic episodes in neonates treated with caffeine. Although aminophylline showed a temporary reduction in apneic spells during the early 25–72 hour period in our results, this effect did not persist beyond 72 hours. Clinically, this suggests that aminophylline may provide short term improvement, whereas caffeine offers more sustained control.

The safety profile also favored caffeine citrate. Overall complications were markedly lower in the caffeine group compared with the aminophylline group. Tachycardia, tachypnea, feeding intolerance, restlessness and electrolyte imbalance were all numerically less frequent among neonates receiving caffeine. These findings are in agreement with Schellack et. al.,[15] and Shivakumar et. al.,[14] who reported greater cardiovascular and systemic adverse effects with aminophylline. The narrower therapeutic index of aminophylline may explain its higher complication rate, whereas caffeine has more predictable pharmacokinetics and a wider therapeutic margin.

The present study also assessed outcomes beyond immediate apnea control. Neonates receiving caffeine had a shorter duration of nursery admission and a lower requirement for mechanical ventilation. These findings are clinically important in resource limited settings, where prolonged NICU stay increases treatment cost, bed occupancy and burden on families and healthcare systems. The CAP trial by Schmidt et al.[16] demonstrated important benefits of caffeine therapy in preterm infants, including improved longer-term outcomes. Similarly, Bruschettini et. al., [17] supported the role of caffeine in

improving clinically relevant neonatal outcomes. Our findings are consistent with this broader evidence, while adding local data from a public sector neonatal unit.

Early neurodevelopmental status was also more favorable in the caffeine group. A higher proportion of neonates having normal neurodevelopment at discharge and fewer showing developmental delay at three months. Although this follow up period was short and cannot establish long term neurodevelopmental benefit, the finding is clinically relevant and supports the need for extended follow up in future studies. Previous evidence, including the CAP trial, has suggested potential neurodevelopmental advantages of caffeine therapy in preterm neonates.[16]

Serum electrolyte levels remained comparable between the two groups, suggesting that neither drug produced clinically meaningful electrolyte disturbance in this cohort. This finding is consistent with Du et al.[18], who reported stable electrolyte parameters during caffeine therapy. Although routine monitoring remains important in critically ill preterm neonates, our result findings do not suggest a major difference between the two drugs in relation to sodium, potassium or chloride levels.

Recent researches from Pakistan and other low and middle income regions supports the practical relevance of our results. Umbreen et. al., and Afzal et. al., also found better outcomes with caffeine than aminophylline in apnea of prematurity, while Amponsah et. al., emphasized that the major challenge in low resource settings is improving access, affordability and routine use of caffeine. Therefore, the present research adds context by showing that caffeine's benefit is reflected not only in apnea resolution, but also in recurrence, complications, NICU stay, ventilation requirement and early neurodevelopmental outcomes in a public sector NICU setting.[19,20,10]

Overall, the findings support caffeine citrate as the preferred treatment option for apnea of prematurity because it was associated with better apnea resolution, fewer recurrences, lower complication rates, shorter NICU stay, reduced mechanical ventilation requirement and better early neurodevelopmental status. Aminophylline may still be used where caffeine is unavailable or unaffordable, but its higher adverse effect burden should be considered, especially in neonatal units with limited monitoring capacity.

This study has some limitations. It was conducted at a single tertiary care public hospital, which may limit generalizability to other settings. Blinding was not feasible because caffeine citrate and aminophylline have different dosing schedules; however, predefined operational definitions and consultant supervised verification were used to reduce observer bias. Long term neurodevelopmental outcomes beyond three months corrected age were also not assessed. Despite these limitations, the study provides useful real-world evidence from a setting where treatment choice is influenced by cost, availability, monitoring capacity and NICU resource burden.

Future multicenter studies with larger sample sizes and longer follow up are needed to confirm these findings and assess sustained neurodevelopmental outcomes. Cost effectiveness and implementation studies are also required in low resource settings, as caffeine citrate may offer clinical advantages, but wider adoption depends on affordability, availability and health system capacity.

Conclusion

Caffeine citrate is superior to aminophylline, demonstrating greater effectiveness in resolving apnea, reducing complications, shortening NICU stay, decreasing the need for mechanical ventilation and promoting improved early neurodevelopmental outcomes.

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CONFLICT OF INTEREST

Authors declared no conflicts of Interest.

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DATA SHARING STATEMENT

The data that support the findings of this study are available from the corresponding author upon request.