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Original Article

Comparison of Outcomes of High-Dose Versus Low-Dose Caffeine Citrate in the Treatment of Apnea of Prematurity: A Randomized Clinical Trial

Fatima Zahra[1*], Afsheen Asghar Khan[1], Awais Tariq[2], Marwah Asif Lodhi[3], Sana Asghar[3], Sidra Anjum[3] and Nusrat Hussain Buzdar[3]

[1]Department of Pediatrics, Nishtar Hospital, Multan, Pakistan
[2]Department of Pediatrics, Rahat Abdul Ghaffar Medical Complex, Gujranwala, Pakistan
[3]Department of Pediatric Medicine, Nishtar Hospital, Multan, Pakistan

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***Corresponding Author:**
Fatima Zahra
Department of Pediatrics, Nishtar Hospital, Multan, Pakistan
drfatimazahra1@gmail.com

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ABSTRACT

Apnea of prematurity (AOP) is common in preterm neonates, and the optimal caffeine citrate dose remains uncertain. **Objective:** To compare outcomes of high-dose versus low-dose caffeine citrate for AOP. **Methods:** This open-label randomized clinical trial (NCT06905496) was conducted at Nishtar Hospital, Multan, from January to October 2025 after approval (7028) and written consent. Preterm neonates 32 to less than 37 weeks' gestation with AOP were randomized 1:1. High-dose caffeine citrate comprised a 40 mg/kg loading dose followed by 20 mg/kg/day for 7 days; low-dose comprised 20 mg/kg then 10 mg/kg/day for 7 days. The primary outcome was extubation failure within 48 hours; secondary outcomes were apnea episode frequency, need and duration of mechanical ventilation, duration of oxygen therapy, and in-hospital mortality. Statistical Package for the Social Sciences version 26.0 was used with a probability value (p) < 0.05. **Results:** One hundred fourteen neonates were allocated (57 per group). Baseline characteristics were similar except for sex distribution (p=0.036). Apnea episodes were lower with high-dose therapy (10.74 ± 2.91 vs 12.89 ± 2.20), mean difference −2.16 (95% confidence interval −3.12 to −1.20; p<0.001). Mechanical ventilation requirement was similar (38.6% vs 43.9%; p=0.568). In ventilated neonates (47), extubation failure was reduced (27.3% vs 56.0%; p=0.047) and ventilation duration was shorter (median 2 vs 4 days; p=0.027). Oxygen therapy duration (median 10 vs 11 days; p=0.555) and mortality (5.3% vs 8.8%; p=0.463) did not differ. **Conclusion:** In conclusion, high-dose caffeine reduced apnea burden and improved extubation outcomes without differences in oxygen days or in-hospital mortality.

INTRODUCTION

Apnea of prematurity (AOP) is a disorder with an incidence inversely related to gestational age and birth weight, occurring in nearly all infants born before 29 weeks' gestation or weighing less than 1000 g, in about 50% at 30 to 32 weeks, and in approximately 7% at 34 to 35 weeks [1]. AOP is defined by recurrent respiratory pauses, typically 15 to 20 seconds or longer, with bradycardia and oxygen desaturation, and may be central, obstructive, or mixed, with mixed events predominating. Predisposition reflects immaturity of the respiratory centre and chemoreceptor responses, reduced airway patency, and autonomic instability, resulting in periodic breathing and cardio-respiratory events in more immature neonates [2]. Recurrent hypoxemia has been associated with adverse neurodevelopment and increased risk of death or disability, and persistent AOP has been linked with bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP), extubation failure, and prolonged

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respiratory support [3]. Management combines optimization of oxygenation, non-invasive respiratory support including continuous positive airway pressure (CPAP), and pharmacologic respiratory stimulants. Methylxanthines are commonly used; caffeine citrate is preferred over theophylline and aminophylline due to longer half-life, broader therapeutic range, and fewer adverse effects [4, 5]. The Caffeine for Apnea of Prematurity (CAP) trial established caffeine as an effective treatment for apnea of prematurity; however, uncertainty remains regarding the optimal dosing strategy, particularly for higher-dose regimen [6]. Uncertainty remains regarding the optimal maintenance ceiling and dosing strategy around extubation, and whether pharmacokinetic variability warrants individualised dosing, supporting evaluation of high-dose versus low-dose approaches [7, 8]. Although caffeine citrate is widely used in the management of apnea of prematurity, the most effective dosing regimen for improving apnea control and extubation outcomes remains uncertain. Previous studies have reported conflicting evidence which remain limited by differences in patient populations, dosing regimens, and reported outcomes. In addition, local data on this question is scarce. This leaves an important unanswered clinical question regarding dose selection in managing apnea in preterm neonates while maintaining safety. Therefore, the study aimed to conducted to compare high-dose versus low-dose caffeine citrate in preterm neonates with apnea of prematurity, with assessment of extubation failure, apnea episode frequency, need and duration of mechanical ventilation, duration of oxygen therapy, and in-hospital mortality.

METHODS

The open-label parallel randomized clinical trial (NCT06905496) was conducted in the Department of Pediatrics and Neonatology, Nishtar Hospital, a tertiary care center in Multan, Pakistan, from January 2025 to October 2025. Ethical approval was obtained from the hospital ethics body (approval no. 7028; dated 3rd June 2024). Written informed consent was obtained from the parents or legal guardians of all neonates before enrollment. Eligible participants were recruited using simple random sampling. The required sample size was estimated using a two-proportion comparison formula. The calculation assumed an extubation failure rate of 22% in the high-dose caffeine group and 47% in the low-dose caffeine group. With 95% confidence and 80% power, a total sample size of 114 neonates was determined, with 57 allocated to each treatment group [9]. It should be noted that this sample size was calculated for the full cohort based on anticipated rates of mechanical ventilation. The study was not specifically powered for subgroup analyses, including the primary outcome of extubation failure, which was applicable only to the subset of ventilated neonates (n=47). $n = [Z_{\alpha/2}\sqrt{2P(1-P)} + Z_{\beta}\sqrt{P_1(1-P_1) + P_2(1-P_2)}]^2 / (P_1 - P_2)^2$. Preterm neonates of either sex with a gestational age at birth of ≥32 weeks and <37 weeks were eligible if apnea of prematurity was diagnosed within the first 10 postnatal days. Apnea of prematurity was defined as at least two respiratory pauses lasting ≥20 seconds, or shorter pauses accompanied by bradycardia (heart rate <100 beats per minute), cyanosis, hypoxemia, or hypotonia. Exclusion criteria comprised hydrops fetalis; major congenital malformations or chromosomal disorders; culture-confirmed sepsis; and neurological conditions considered likely contributors to apnea, including intraventricular hemorrhage with post-hemorrhagic hydrocephalus or hypoxic-ischemic encephalopathy. Prior exposure to methylxanthines precluded enrollment. At enrollment, baseline demographic and clinical variables were recorded, including gestational age at birth, sex, birth weight, administration of exogenous surfactant, and mode of delivery. Caffeine citrate was administered according to the assigned protocol. All enrolled neonates were managed in the Neonatal Intensive Care Unit (NICU) and were monitored throughout the treatment period until hospital discharge. Apnea episodes were continuously observed and documented by the nursing staff on duty. After enrollment, neonates were randomly assigned in a 1:1 ratio to either a high-dose caffeine group (Group A) or a low-dose caffeine group (Group B). Simple randomization was performed using computer-generated random numbers. Group A received a caffeine citrate loading dose of 40 mg per kilogram followed by a maintenance dose of 20 mg per kilogram once per day for a total of seven days. Group B received a loading dose of 20 mg per kilogram followed by a maintenance dose of 10 mg per kilogram once per day for seven days. All doses of caffeine citrate were administered orally or via a nasogastric feeding tube. For ventilated neonates, caffeine was initiated intravenously immediately after intubation and transitioned to enteral administration once full enteral feeding was established. This variation in route of administration introduces potential differences in bioavailability, as intravenous administration results in immediate and complete absorption, whereas enteral administration may have variable absorption rates. Due to the nature of the intervention, this was an open-label trial, and blinding of treating physicians, nursing staff, and outcome assessors was not feasible. All outcome measures were, however, recorded prospectively using standardized data collection forms. For neonates who required endotracheal intubation and mechanical ventilation due to severe apnea, caffeine therapy was initiated immediately after intubation (via the intravenous route) and later transitioned to enteral administration once

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full enteral feeding was established. No enrolled neonate was lost to follow-up because all outcomes were assessed during the index hospitalization. The primary outcome was extubation failure, defined as the need for reintubation within 48 hours after a planned extubation. However, the absence of a formal, standardized extubation readiness score means that extubation decisions were made at the discretion of the treating physician, introducing potential variability in timing and decision-making. Secondary outcome measures included the frequency of apnea episodes (the number of documented apneic events per neonate during the hospital stay) and the need for mechanical ventilation (whether invasive ventilatory support was required at any point during hospitalization). To account for variable lengths of observation, apnea rates per neonate-day were additionally calculated. The total duration of mechanical ventilation (measured in days from initial intubation to successful extubation) and the duration of supplemental oxygen therapy (the number of days a neonate required oxygen via nasal cannula or face mask to maintain oxygen saturation above 92%) were also recorded. Weaning from mechanical ventilation was guided by standard NICU criteria, including sustained spontaneous breathing efforts, acceptable blood gas parameters, and stable oxygenation, at the discretion of the treating neonatologist. Discharge from the NICU was planned once a neonate exhibited full recovery from apnea of prematurity, evidenced by the absence of apnea episodes, stable spontaneous respiration, and the ability to maintain normal oxygen saturation without respiratory support. All study data, including outcome measures, were collected on a data collection proforma by a senior pediatric resident.

Data were analyzed using descriptive and inferential statistics on SPSS version 26.0. Numerical variables were summarized as mean with standard deviation or as median with range, according to distribution and variance assessment. Between-group comparisons for continuous outcomes used the independent-samples Student t test; when Levene's test indicated unequal variances, the Welch t test was applied, with mean differences and 95% confidence intervals reported. The duration of non-normally distributed was compared by the Mann-Whitney U test. The Shapiro-Wilk test was used to test normality. The Pearson chi-square test was used to compare the categorical variables; when the number of cells in the categories were small, the Fisher exact test (two sided) was interpreted. All analyses performed were set at p is equal to 0.05 or less.

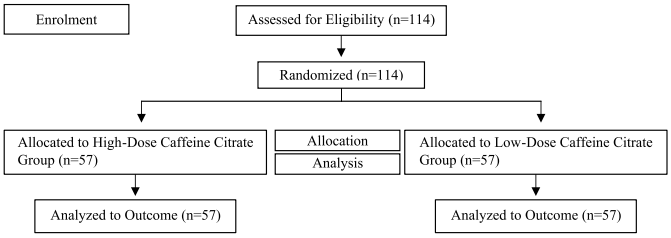


Figure 1: CONSORT Flow Diagram

RESULTS

Baseline continuous variables were similar between groups (postnatal age probability value (p=0.667; gestational age p=0.888; birth weight p=0.606). Gestational age category (p=0.691), birth weight category (p=0.432), and exogenous surfactant exposure (p=0.687) were comparable. Sex distribution differed (p=0.036) (Table 1).

Table 1: Baseline Characteristics by Treatment Group (High-dose vs Low-dose Caffeine Citrate) (n=114)

Broad Category	Subcategory	High-dose (n=57)	Low-dose (n=57)	Test Statistic	p-value
Demographic	—	2.02 ± 1.09	2.11 ± 1.08	t=-0.431	0.667
Gestational age (weeks)	—	34.00 ± 1.30	33.96 ± 1.36	t= 0.14	0.888
Anthropometry	Birth weight (g), mean ± SD	2438.60 ± 417.80	2398.25 ± 414.25	t= 0.518	0.606
Sex	Male, n (%)	39 (68.4)	28 (49.1)	χ^2= 4.380	0.036
	Female, n (%)	18 (31.6)	29 (50.9)	χ^2 = 4.380	
Gestational age category	32 to <34 weeks, n (%)	37 (64.9)	39 (68.4)	χ^2 = 0.158	0.691
	34 to <37 weeks, n (%)	20 (35.1)	18 (31.6)	χ^2 = 0.158	
Birth weight category	<2500-gram, n (%)	35 (61.4)	39 (68.4)	χ^2 = 0.616	0.432
	≥2500-gram, n (%)	22 (38.6)	18 (31.6)	χ^2 = 0.616	
Surfactant exposure	Yes, n (%)	17 (29.8)	19 (33.3)	χ^2= 0.162	0.687
	No, n (%)	40 (70.2)	38 (66.7)	χ^2= 0.162	
Mode of delivery	Normal vaginal delivery, n (%)	34 (59.6)	23 (40.4)	χ^2= 4.246	0.039
	Lower segment caesarean section, n (%)	23 (40.4)	34 (59.6)	χ^2= 4.246	

Apnea episodes were fewer with high-dose caffeine (10.74 ± 2.91) than low-dose (12.89 ± 2.20), with a mean difference of −2.16 episodes (95% confidence interval (CI) −3.12 to −1.20; p<0.001). Welch testing was applied because the variance homogeneity was not satisfied. Requirement for mechanical ventilation was similar (38.6% vs 43.9%; p=0.568). Among ventilated neonates, extubation failure was lower with high-dose therapy (27.3% vs 56.0%; p=0.047), and ventilation duration was

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shorter (median 2 vs 4 days; p=0.027). Oxygen therapy duration and in-hospital mortality did not differ (p=0.555 and p=0.463) (Table 2).

Table 2: Clinical Outcomes by Treatment Group (High-Dose Vs Low-Dose Caffeine Citrate)

Outcome Domain	High-dose	Low-dose	Effect Estimate / Test Statistic (95% CI)	p-value
Apnea episode (mean ± SD) (n = 114)	10.74 ± 2.91 (n = 57)	12.89 ± 2.20 (n = 57)	Mean difference −2.16; 95% CI (−3.12 to −1.20)	<0.001*
Need for mechanical ventilation (n = 114), n (%)	22/57 (38.6)	25/57 (43.9)	χ^2 = 0.326	0.568
Duration of mechanical ventilation, days (ventilated only; n = 47), median (range)	2.0 (7.0)	4.0 (7.0)	Mann–Whitney U = 174.5; Z = −2.210	0.027*
Extubation failure (ventilated only; n = 47), n (%)	6/22 (27.3)	14/25 (56.0)	χ^2 = 3.951	0.047*
Duration of oxygen therapy, days (n = 114), median (range)	10.0 (range 20), max 22 (n = 57)	11.0 (range 21), max 24 (n = 57)	Mann–Whitney U = 1520.5; Z = −0.590	0.555
In-hospital mortality (n = 114), n (%)	3/57 (5.3)	5/57 (8.8)	χ^2 = 0.538	0.463

On stratification by mode of delivery, apnea episode frequency remained lower in the high-dose group within both strata. Among neonates delivered vaginally, the high-dose group (n=34) had fewer apnea episodes than the low-dose group (n=23) (10.62 ± 3.02 vs 12.61 ± 2.55; mean difference −1.991; 95% CI −3.527 to −0.455; t=−2.597; p=0.012)

The extubation failure analysis was conducted in the ventilated subset (n=47) and should be interpreted with caution, as the study was not specifically powered for this subgroup.

Among neonates delivered by lower segment cesarean section, the high-dose group (n=23) similarly had fewer apnea episodes than the low-dose group (n=34) (10.91 ± 2.80 vs 13.09 ± 1.94; mean difference −2.175; 95% CI −3.432 to −0.919; t=−3.470; p=0.001) (Table 3).

Table 3: Stratified analysis of primary and secondary outcomes by baseline factors (mechanically ventilated subset for extubation failure; full sample for apnea frequency)

Outcome and Stratification Factor	Stratum	High-dose	Low-dose	Test Used (value)	p-value
Extubation Failure Among Mechanically Ventilated Patients Only					
Gender	Male	4/11 (36.4%)	7/14 (50.0%)	χ^2=0.465	0.689
	Female	2/11 (18.2%)	7/11 (63.6%)	χ^2=4.701	0.080
Gestational Age Category	32 to <34 Weeks	2/15 (13.3%)	11/18 (61.1%)	χ^2=7.823	0.011*
	34 to <37 Weeks	4/7 (57.1%)	3/7 (42.9%)	χ^2=0.286	1.000
Birth Weight Category	<2.0 kg	5/16 (31.2%)	12/21 (57.1%)	χ^2=2.451	0.185
	≥2.0 kg	1/6 (16.7%)	2/4 (50.0%)	χ^2=1.270	0.500
Mode of Delivery	Normal Vaginal Delivery	1/8 (12.5%)	8/11 (72.7%)	χ^2=6.739	0.020
	Lower-Segment Cesarean Section	5/14 (35.7%)	6/14 (42.9%)	χ^2=0.150	1.000
Exogenous Surfactant Administered	No	3/12 (25.0%)	11/19 (57.9%)	χ^2=3.213	0.138
	Yes	3/10 (30.0%)	3/6 (50.0%)	χ^2=0.640	0.607
Frequency of Apnea Episodes During the Monitoring Period					
Gender	Male	n=39, 11.00 ± 3.009	n=28, 12.79 ± 2.685	t=−2.504	0.015*
	Female	n=18, 10.17 ± 2.662	n=29, 13.00 ± 1.648	t=−4.519	<0.001*
Gestational Age Category	32 to <34 Weeks	n=37, 10.35 ± 2.700	n=39, 13.31 ± 2.002	t=−5.441	<0.001*
	34 to <37 Weeks	n=20, 11.45 ± 3.203	n=18, 12.00 ± 2.401	t=−0.593	0.557
Birth Weight Category	<2.0 kg	10.80 ± 2.898	13.18 ± 1.833	t=−4.265	<0.001*
	≥2.0 kg	10.64 ± 2.985	12.28 ± 2.803	t=−1.778	0.083
Exogenous Surfactant Administered	No	10.73 ± 2.944	12.66 ± 2.474	t=−3.131	0.002*
	Yes	10.76 ± 2.905	13.37 ± 1.461	t=−3.453	0.002*
Mode of Delivery	Normal Vaginal Delivery	10.62 ± 3.02	12.61 ± 2.55	−2.597	0.012*
	Lower Segment Cesarean Section	10.91 ± 2.80	13.09 ± 1.94	−3.470	<0.001*

DISCUSSION

In this randomized trial comparing high-dose versus low-dose caffeine citrate for apnea of prematurity, the high-dose regimen led to a significant reduction in apnea episodes, approximately two fewer events per neonate. Among mechanically ventilated neonates, high-dose caffeine was associated with lower extubation failure and shorter median ventilation duration. Oxygen therapy duration and in-hospital mortality did not differ between groups. In this trial, high-dose caffeine reduced apnea frequency by 2.16 episodes versus low-dose, with a probability value (p)<0.001 and a reduction overall.

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Comparable reductions were reported as median 9 vs 16 episodes in one study and 8.15% vs 13.22% with high-dose vs low-dose regimens [9, 10]. Lower early-event counts were observed with maintenance 10 vs 5 mg/kg/day (1.30 ± 1.41 vs 2.28 ± 1.98) [11]. Pooled analyses suggested fewer apnea events per day with high dosing [7]. Upper-range episode counts were reduced (0–14 vs 0–42) [12]. Null findings may reflect apnea definition differences and maturational profiles. Enhanced central adenosine receptor antagonism remains biologically plausible, as caffeine inhibits adenosine A1 and A2A receptors and thereby promotes respiratory drive [11]. In this trial, the requirement for invasive mechanical ventilation was similar between dose groups (38.6% vs 43.9%; probability value (p=0.568), consistent with studies showing no clear reduction in intubation frequency with high dosing [13, 14]. Among ventilated neonates, high-dose caffeine shortened ventilation duration (median 2 vs 4 days; p=0.027), aligning with trials reporting fewer ventilator days or earlier separation, although other trials and pooled analyses reported little difference [13-18]. Extubation failure was lower with high-dose therapy (27.3% vs 56.0%; p=0.047), concordant with randomized and observational evidence and meta-analytic estimates, but not with all dosing comparisons [13-16]. These data suggested improved extubation stability without reducing initial ventilation requirement. Duration of oxygen therapy was comparable between groups (median 10 vs 11 days; probability value (p)=0.555), consistent with trials reporting no difference in oxygen days across dosing strategies [12]. Some studies reported shorter oxygen exposure with high dosing or reduced post-ventilator oxygen duration, suggesting that benefits may be context dependent and influenced by baseline respiratory disease severity and outcome definitions [7, 9]. Longer-term follow-up of infants exposed to high versus standard caffeine loading doses has not demonstrated major differences in neurodevelopmental or socioemotional outcomes at five years [17]. In-hospital mortality remained low and similar between arms (5.3% vs 8.8%; p=0.463), consistent with previous clinical studies [18,19].Stratified analyses suggested larger apnea reductions in less mature and lower birth weight neonates, with non-significant effects in more mature strata, warranting cautious interpretation given multiplicity [13, 18]. Caffeine citrate antagonizes adenosine receptors, reducing respiratory inhibition and supporting ventilatory drive, which lowers apnea frequency and improves extubation stability. High dose is expected to sustain therapeutic plasma exposure between administrations [20]. Clinical trials have not shown excess feeding intolerance, necrotising enterocolitis, or intraventricular hemorrhage, and hemodynamic tolerance appears maintained [10, 19]. Bronchopulmonary dysplasia may further decline with high doses compared to low doses [20].

The study has several important limitations. Its open-label design may have introduced detection and performance bias, particularly in apnea documentation and extubation decisions, which were made by unblinded physicians without standardized extubation readiness criteria. The primary extubation outcome was assessed in only 47 ventilated neonates and the study was not powered for this subgroup; therefore, these findings should be considered hypothesis-generating. In addition, differences in intravenous versus enteral caffeine administration were not accounted for and may have affected plasma concentration profiles. Larger, adequately powered trials using standardized extubation criteria, pharmacokinetic monitoring, and longer-term follow-up are needed to confirm these findings and assess safety.

CONCLUSIONS

High-dose caffeine citrate was associated with fewer apnea episodes in preterm neonates with apnea of prematurity. A lower rate of extubation failure and shorter ventilation duration were observed among mechanically ventilated neonates; however, these findings should be interpreted cautiously because the subgroup was small and unpowered. No significant differences were observed in oxygen therapy duration or in-hospital mortality. Given the study limitations, these findings are hypothesis-generating and do not support routine use of high-dose caffeine.

Authors' Contribution

Conceptualization: AAK
Methodology: FZ, AAK, NUB
Formal analysis: AT, MAL, SA, SA, NUB
Writing and Drafting: SA, NUB
Review and Editing: FZ, AAK, AT, MAL, SA, SA, NUB

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflict of Interest

All the authors declare no conflict of interest.

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