Section: Pediatrics

Original Research Article

RANDOMIZED CONTROL TRIAL COMPARING EFFECTIVENESS OF ROUTINE AND RESCUE DOSE OF CAFFEINE IN APNEA OF PREMATURITY IN PRETERM BABIES BETWEEN 26 TO 36 WEEKS OF GESTATION IN A TERTIARY CARE CENTRE IN COIMBATORE MEDICAL COLLEGE HOSPITAL

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Received *: 04/12/2025*
Received in revised form *: 12/01/2026*
Accepted *: 01/02/2026*

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DOI: 10.70034/ijmedph.2026.1.271

Source of Support: Nil,
Conflict of Interest: None declared

Int J Med Pub Health
2026; 16 (1); 1551-1559

ABSTRACT

Background: Apnea of prematurity (AOP) is a common and clinically significant problem in preterm neonates due to immaturity of respiratory control mechanisms. Recurrent apneic episodes are associated with hypoxemia, bradycardia, increased need for respiratory support, prolonged neonatal intensive care unit (NICU) stay, and higher morbidity. Caffeine citrate is the drug of choice for the management of AOP because of its efficacy, safety, and wide therapeutic window. While routine-dose caffeine is commonly used, evidence regarding the benefit of higher or rescue-dose caffeine in symptomatic apnea remains limited, particularly in low- and middle-income settings. **Aim:** To compare the effectiveness and safety of routine-dose versus rescue-dose caffeine citrate in the management of apnea of prematurity in preterm neonates between 26 and 36 weeks of gestation.

Materials and Methods: This open-labelled randomized controlled trial was conducted in the Neonatology Unit of Coimbatore Medical College Hospital from December 2019 to December 2020. A total of 56 preterm neonates with apnea of prematurity were enrolled and randomly allocated into two equal groups: Group A (routine-dose caffeine) and Group B (rescue-dose caffeine). Group A received a loading dose of 20 mg/kg followed by a maintenance dose of 10 mg/kg/day, while Group B received a loading dose of 40 mg/kg followed by a maintenance dose of 20 mg/kg/day of caffeine citrate. Neonates were monitored for frequency and duration of apnea, need for respiratory support, duration of ventilation, neonatal morbidities, length of hospital stay, and adverse effects.

Results: The rescue-dose group showed a significant reduction in the severity and frequency of apneic episodes, with 82.1% having fewer than three episodes compared to 14.3% in the routine-dose group ($p<0.001$). The need for mechanical ventilation was significantly lower in Group B (14.3%) compared to Group A (60.7%) ($p<0.001$). Duration of level 3 NICU stay was also significantly shorter in the rescue-dose group. There were no statistically significant differences between the groups in chronic lung disease, necrotizing enterocolitis, intraventricular hemorrhage, retinopathy of prematurity, or mortality. Rescue-dose caffeine was well tolerated with no increase in clinically significant adverse effects.

Conclusion: Rescue-dose caffeine citrate is more effective than routine-dose caffeine in reducing apneic episodes and the need for mechanical ventilation in

preterm neonates with apnea of prematurity, without added safety concerns. Larger, well-powered trials are needed to further validate these findings and refine optimal caffeine dosing strategies.
Keywords: Apnea of prematurity; Caffeine citrate; Preterm neonates; Mechanical ventilation; Rescue dose.

INTRODUCTION

Apnea of prematurity (AOP) is a developmental disorder of respiratory control that predominantly affects infants born preterm and typically resolves with advancing postmenstrual age. The frequency and persistence of recurrent apneic events are strongly related to gestational immaturity; classic epidemiologic data demonstrate that the incidence rises as gestational age decreases, with recurrent apnea being most common around 30–31 weeks and becoming much less frequent by 34–35 weeks.[1] In clinical practice, AOP is not merely a transient bedside nuisance; repeated episodes can cause intermittent hypoxemia and bradycardia, destabilize cardiorespiratory homeostasis, increase the need for respiratory support, and prolong hospital stay—effects that may compound other morbidities of prematurity. The pathophysiology of AOP is multifactorial and reflects immaturity at multiple levels of the respiratory network, including central rhythm generation, chemoreceptor responsiveness, arousal mechanisms, and upper airway control. Preterm infants exhibit unstable breathing characterized by central apnea and periodic breathing, and this instability can be amplified by factors such as sleep state, infection/inflammation, temperature instability, gastroesophageal reflux, anemia, and evolving lung disease. The concept of AOP as a "perfect storm" underscores how immature control systems, coupled with intermittent hypoxemia, can interact to perpetuate respiratory instability and contribute to downstream morbidity.[2] From a physiologic standpoint, neonatal apnea is heterogeneous and includes central, obstructive, and mixed forms, each with differing cardiopulmonary correlates and bedside manifestations. Detailed physiologic studies show that heart rate and oxygen saturation responses vary by apnea type and duration, and that responses may be influenced by concurrent therapies and infant maturity.[3] Standard management of AOP begins with careful evaluation for secondary causes and optimization of supportive care (thermoregulation, anemia management, infection evaluation when indicated, positioning, and appropriate respiratory support such as CPAP/HFNC for airway splinting and work-of-breathing reduction). Pharmacotherapy remains a cornerstone when recurrent clinically significant apnea persists, and methylxanthines—particularly caffeine—are widely used due to their respiratory stimulant effects and practical advantages. The American Academy of Pediatrics clinical report highlights the variability in definitions and monitoring practices, but also reinforces that caffeine is a key evidence-based therapy for AOP and provides a structured approach to assessment, treatment, and discharge planning for infants with recurrent events.[4] Caffeine citrate acts primarily through adenosine receptor antagonism, enhancing respiratory drive, improving diaphragmatic contractility, and reducing hypoxic depression of breathing. Randomized placebo-controlled evidence demonstrates that caffeine citrate improves short-term apnea control, with clinically meaningful reductions in apnea burden within days of therapy initiation and higher rates of treatment "success" (defined by substantial reduction or elimination of apnea).[5] Despite broad agreement that caffeine is effective, uncertainty persists regarding the optimal timing and intensity of dosing across different clinical contexts. Practice variation is well documented, including differences in early initiation, maintenance dosing, and the use of additional ("rescue") dosing when apnea persists or escalates. Large multicenter observational data describing contemporary practice patterns indicate that timing of caffeine exposure is associated with clinically important outcomes, including bronchopulmonary dysplasia and composite morbidity measures, suggesting that not only the drug but also when and how it is delivered may influence the trajectory of respiratory disease in very low birth weight infants.[6]

MATERIALS AND METHODS

An open-labelled randomized controlled trial was conducted in the Neonatology Unit, Department of Paediatrics, Coimbatore Medical College Hospital, Coimbatore, Tamil Nadu, India, over a 12-month period from December 2019 to December 2020. The trial compared the efficacy of a routine-dose versus a rescue-dose caffeine citrate regimen in preterm newborns diagnosed with apnea of prematurity (AOP) between 26 and 36 weeks of gestation.

The study population consisted of preterm neonates (<36 weeks' gestation) diagnosed with AOP. Newborns more than 36 weeks of gestation were excluded. Additional exclusions included congenital malformations and chromosomal anomalies, respiratory distress syndrome, requirement of inotrope support, necrotising enterocolitis diagnosed before the onset of AOP, sepsis, and neonates already receiving antibiotics. Parents or caregivers were counselled regarding the purpose of the study, potential benefits, intervention details, and possible adverse effects; written informed consent was obtained in the caregiver's preferred language prior to enrolment. Recruited neonates underwent thorough clinical examination to exclude congenital anomalies and other neonatal illnesses, baseline vital

parameters were recorded, and Downes score was documented. A sepsis score was applied as part of screening; neonates with a sepsis score ≥3 were excluded. If the score was 2, sepsis screening was performed as per unit protocol, and neonates with a positive screen were excluded and managed appropriately; those with a negative screen continued in the allocated study group with close monitoring.

Methodology

A total of 56 neonates were allocated equally to two arms with an allocation ratio of 1:1 (28 in Arm A and 28 in Arm B). Randomisation was implemented using a sealed-envelope method. After consent and eligibility confirmation, each neonate was assigned to either the routine-dose caffeine group (Group A) or the rescue-dose caffeine group (Group B) according to the randomisation sequence obtained by opening the sealed envelope, which contained a paper indicating group allocation; the investigator opening the envelope was blinded to the allocation until the envelope was opened. Baseline maternal and neonatal data were entered in a predesigned proforma, including antenatal risk factors and therapies, labour and delivery details, neonatal condition at birth, respiratory support requirements, apnea characteristics, and relevant comorbidities and outcomes.

Infants in Arm A received intravenous caffeine citrate as a routine-dose regimen with a loading dose of 20 mg/kg/day (equivalent to 10 mg/kg/day caffeine base) followed by a maintenance dose of 10 mg/kg/day (equivalent to 5 mg/kg/day caffeine base). Infants in Arm B received a rescue-dose regimen with a loading dose of 40 mg/kg/day (equivalent to 20 mg/kg/day caffeine base) followed by a maintenance dose of 20 mg/kg/day (equivalent to 10 mg/kg/day caffeine base). Caffeine was administered by intravenous infusion over 30 minutes, diluted with an equivalent volume of normal saline. Caffeine therapy was initiated once the preterm infant exhibited AOP; in infants with significant AOP requiring mechanical ventilation, caffeine was initiated immediately after intubation. Once full enteral feeding was established, caffeine was switched from intravenous to enteral/oral administration. Apnea was defined as cessation of breathing for more than 20 seconds, or cessation of breathing for less than 20 seconds accompanied by bradycardia (heart rate <100 beats/min) or oxygen desaturation (SpO_2 <90%). Frequency of apnea and bradycardia episodes was captured from monitors and validated by qualified nursing staff.

Continuous preductal monitoring of oxygen saturation, heart rate, and respiratory rate was performed using a Masimo pulse oximeter, with a targeted oxygen saturation range of 91–95%. Blood pressure was measured twice daily. Tachycardia was defined as an increase in heart rate greater than 15 beats per minute from baseline without an alternative explanation. Clinical monitoring for suspected caffeine-related adverse effects included tachycardia, tachypnea, jitteriness, tremors, vomiting episodes, abdominal distension, and any unexplained seizures, alongside routine assessment for evolving comorbidities such as intraventricular hemorrhage, necrotizing enterocolitis, bronchopulmonary dysplasia/chronic lung disease, pneumonia, and retinopathy of prematurity. Standard unit-based weaning criteria were applied for respiratory supports. Mechanical ventilation weaning required spontaneous respiratory effort, protective airway reflexes with suctioning, acceptable blood gases (pH >7.25, pCO_2 <60 mmHg, base deficit <8 mEq/L) on mean airway pressure <8 cm H_2O, ventilator rate <30 breaths/min, and oxygenation stability (saturation >88% on FiO_2 <30% in the preceding 24 hours), with attending physician approval. CPAP weaning required stable pressure (3–6 cm H_2O) for 24–48 hours, FiO_2 <30% to maintain targets, respiratory rate <60 breaths/min, no apnea requiring bagging in the preceding 24 hours, no more than six apneas requiring stimulation in the preceding 24 hours, satisfactory blood gases (pH >7.25, pCO_2 <60 mmHg, base deficit <8 mEq/L), tolerance of time off CPAP during nursing care, and attending physician approval. Among survivors, duration of CPAP, duration of mechanical ventilation, duration of oxygen therapy, and length of hospital stay were calculated.

Statistical Analysis

Statistical analysis used descriptive statistics with frequency and proportion for categorical variables, and data presentation included appropriate diagrams (pie and bar charts). Categorical outcomes were compared between study groups using the Chi-square test or Fisher's exact test; Fisher's exact test was applied when overall sample size was <20 or when expected cell counts were <5. A p value <0.05 was considered statistically significant.

RESULTS

Table 1: Descriptive statistics of maternal variables in the study population (N=56)

This table describes the baseline maternal profile of the 56 mothers included in the analysis. Most pregnancies were in the 28–32 weeks gestational age bracket, with 46 women (82.14%), while only 10 (17.86%) were beyond 32 weeks. Gravidity was almost evenly split, with 29 primigravida mothers (51.79%) and 27 mothers who were >2nd gravida (48.21%), suggesting the cohort included both first-time and multiparous pregnancies in nearly equal proportions. Maternal comorbidities were generally uncommon except for pregnancy induced hypertension. Maternal anaemia was rare, with 55 mothers (98.21%) not anaemic and only 1 (1.79%) anaemic. Pregnancy induced hypertension was the most frequent maternal condition, present in 31 mothers (55.36%), while 25 (44.64%) did not have it. Regarding antenatal interventions and obstetric risk markers, 44 mothers (78.57%) received a full course of antenatal steroids and 12 (21.43%) received a

partial course, showing that the majority achieved complete steroid coverage. Abnormal Doppler findings were uncommon (2 mothers, 3.57%) and most had normal Doppler studies (54, 96.43%). PROM and oligohydramnios were also relatively uncommon, each reported in 3 mothers (5.36%), while 53 (94.64%) had no PROM and 53 (94.64%) had no oligohydramnios.

Table 2: Descriptive statistics of secondary outcome variables in the study population (N=56)

This table summarizes neonatal characteristics and clinical outcomes across the full cohort. Sex distribution showed a slight female predominance, with 31 girls (55.36%) and 25 boys (44.64%). Birth weight was heavily skewed toward extremely low birth weight, with 43 neonates weighing <1 kg (76.79%) and 13 weighing 1–2 kg (23.21%). Several major neonatal morbidities were absent or rare in this dataset. Respiratory distress syndrome was not recorded in any neonate (56, 100% "No"), and chromosomal anomalies were also absent (56, 100% "No"). NEC occurred in 4 neonates (7.10%), while 52 (92.90%) had no NEC. Apnoea-related outcomes show a substantial burden of events in the cohort. Documented days of apnoea were most commonly 2–4 days (35, 62.50%), followed by <2 days (18, 32.14%), and >4 days (3, 5.36%). Episodes of apnoea were distributed across severity bands, with 27 neonates (48.21%) having <3 episodes, 17 (30.36%) having 3–5 episodes, and 12 (21.43%) having >5 episodes, indicating that about one-fifth experienced frequent episodes.

Table 3: Comparison of baseline maternal variables between the Study groups (N=56)

This table compares baseline maternal characteristics between Group A (Routine Dose, n=28) and Group B (Rescue Dose, n=28) to assess comparability at baseline. Gestational age distribution differed numerically, with Group B having a higher proportion of 28–32 week pregnancies (26, 92.90%) compared with Group A (20, 71.40%), while >32 weeks was more common in Group A (8, 28.60%) than Group B (2, 7.10%). However, the p value of 0.078 indicates this difference was not statistically significant at the conventional 0.05 threshold, though it may suggest a trend toward slightly lower gestational ages in Group B.

Gravida distribution also differed numerically: primigravida mothers were more frequent in Group A (18, 64.30%) than Group B (11, 39.30%), whereas >2nd gravida mothers were more frequent in Group B (17, 60.70%) than Group A (10, 35.70%). The p value (0.108) indicates no statistically significant difference. Mode of delivery was very similar between groups for normal vaginal delivery (8, 28.60% in both groups), and LSCS was high in both (20, 71.40% in Group A vs 19, 67.90% in Group B). Assisted vaginal delivery occurred only in Group B (1, 3.60%), and the mode of delivery comparison overall was marked NA.

Table 4: Comparison primary outcome between the Study groups (N=56)

This table focuses on the primary respiratory outcome: the need for mechanical ventilation, and the duration of ventilation. A clear between-group difference is seen in ventilation requirement. In Group A, 17 neonates (60.70%) required mechanical ventilation and 11 (39.30%) did not. In Group B, only 4 neonates (14.30%) required mechanical ventilation while 24 (85.70%) did not. The reported significance is <0.001, indicating a statistically significant and clinically large reduction in mechanical ventilation requirement in Group B compared with Group A.

Table 5: Comparison secondary outcome between the Study groups (N=56)

This table compares multiple secondary outcomes and provides the most granular view of how the groups differed clinically. Apnoea severity differed markedly. In Group A, only 4 neonates (14.30%) had <3 apnoea episodes, while 12 (42.90%) had 3–5 episodes and another 12 (42.90%) had >5 episodes. In Group B, most neonates were in the mild category, with 23 (82.10%) having <3 episodes, 5 (17.90%) having 3–5 episodes, and none having >5 episodes. The p value is <0.001, indicating a statistically significant reduction in apnoea episode frequency/severity in Group B.

Documented days of apnoea also favored Group B numerically. In Group A, 5 (17.90%) had <2 days, 21 (75.00%) had 2–4 days, and 2 (7.10%) had >4 days. In Group B, 13 (46.40%) had <2 days, 14 (50.00%) had 2–4 days, and 1 (3.60%) had >4 days. The p value of 0.051 is borderline and does not meet the conventional threshold, but it suggests a near-significant trend toward fewer apnoea days in Group B.

Hospital course variables show important differences in higher-acuity stay. Total duration of stay categories were broadly similar and largely concentrated in 10–20 days for both groups (27, 96.40% in Group A; 25, 89.3% in Group B), with the longest stay category (>20 days) occurring only in Group A (1, 3.60%) and shorter stays (<10 days) occurring only in Group B (3, 10.7%); the table marks NA for the p value here. However, the length of hospital stay in level 3 (higher level care) showed a strong group difference: <3 days occurred in 7 (25.00%) in Group A and 21 (75.00%) in Group B, while >3 days occurred in 21 (75.00%) in Group A and 7 (25.00%) in Group B, with p <0.001.

Table 6: Comparison of mortality between the Study groups (N=56)

This table shows that mortality was zero in both groups. All neonates survived to discharge in Group A (28, 100%) and Group B (28, 100%), with no deaths recorded (0% in both). Because there were no events, a statistical comparison is not applicable (NA).

Table 1: Descriptive statistics of maternal variables in the study population (N=56)

Variables	Summary statistics (n)	(%)
Gestational Age		
28-32 Weeks	46	82.14
>32 Weeks	10	17.86
Gravida		
PRIMI	29	51.79
>2nd GRAVIDA	27	48.21
Maternal Anaemia		
No	55	98.21
Yes	1	1.79
Pregnancy Induced Hypertension		
No	25	44.64
Yes	31	55.36
Gestational diabetes mellitus		
No	54	96.43
Yes	2	3.57
Hypothyroid		
No	55	98.21
Yes	1	1.79
Antenatal Steroid		
Full Course Complete	44	78.57
Partial Course Complete	12	21.43
Abnormal Doppler		
No	54	96.43
Yes	2	3.57
PROM		
No	53	94.64
Yes	3	5.36
Oligohydramnios		
No	53	94.64
Yes	3	5.36
Mode of Delivery		
Normal Vaginal Delivery	16	28.57
Assisted Vaginal Delivery	1	1.79
LSCS	39	69.64

Table 2: Descriptive statistics of secondary outcome variables in the study population (N=56)

Variables	Summary statistics (n)	(%)
Sex		
Boy	25	44.64
Girl	31	55.36
Birth Weight		
<1 Kg	43	76.79
1-2 Kg	13	23.21
APGAR		
>7 AT 5TH minute	54	96.43
<7 AT 5TH minute	2	3.57
Respiratory Distress Syndrome		
No	56	100.00
Chromosomal Anomaly		
No	56	100.00
NEC		
No	52	92.90
Yes	4	7.10
Feed intolerance		
No	46	82.10
Yes	10	17.90
Sepsis		
No	56	100.00
Documented Days Apnoea of		
<2 Days	18	32.14
2 - 4 Days	35	62.50
>4 Days	3	5.36
Episodes of Apnoea		
<3	27	48.21
3 – 5	17	30.36
>5	12	21.43
Weight gain		
Not adequate	40	71.40
Adequate	16	28.60
Number of days in level 3		

<3 days	28	50.00
>3 days	28	50.00
Needs for O2 Support (CPAP, HFNC)		
No	28	50.00
Yes	28	50.00
Need for Mechanical Ventilation		
No	35	62.50
Yes	21	37.50
Days on Ventilation Mechanical		
<3 Days	47	83.93
3-5 Days	9	16.07
Recurrence of Apnoea (After Rescue Dose)		
NA	28	50.00
Nil	23	41.07
<3 episodes	5	8.93
Chronic Lung Disease		
No	53	94.64
Yes	3	5.36
Duration of Stay		
<10 days	3	5.36
10 - 20 days	52	92.86
>20 days	1	1.79
Intraventricular haemorrhage		
No	55	98.21
Yes	1	1.79
Retinopathy prematurity		
No	51	91.07
Yes	5	8.93
Discharge Weight		
<1.5 Kg	56	100.00
Death		
No	56	100.00

Table 3: Comparison of Baseline maternal variables between the Study groups in the study population (N=56)

VARIABLES	GROUP A (n=28)	GROUP A (%)	GROUP B (n=28)	GROUP B (%)	P value
Gestational Age					
28-32 Weeks	20	71.40%	26	92.90%	
>32 Weeks	8	28.60%	2	7.10%	0.078*
Gravida					
Primi	18	64.30%	11	39.30%	
>2nd Gravida	10	35.70%	17	60.70%	0.108**
Mode of Delivery					
Normal Vaginal Delivery	8	28.60%	8	28.60%	
Assisted Vaginal Delivery	0	0%	1	3.60%	
LSCS	20	71.40%	19	67.90%	NA
Maternal Anaemia					
No	16	56..20%	10	37.10%	
Yes	12	42.90%	18	66.60%	0.062*
Pregnancy Induced Hypertension					
No	16	57.10%	9	32.10%	
Yes	12	42.90%	19	67.90%	0.060**
Gestational diabetes mellites					
No	27	96.40%	27	96.40%	
Yes	1	3.60%	1	3.60%	0.755*
Hypothyroid					
No	27	96.40%	28	100%	
Yes	1	3.60%	0	0%	0.500*
Antenatal Steroid					
Full Complete Course	25	89.30%	19	67.90%	
Partial Complete Course	3	10.70%	9	32.10%	0.101*
Abnormal Doppler					
No	27	96.40%	27	96.40%	
Yes	1	3.60%	1	3.60%	0.755*
PROM					
No	18	64.30%	11	39.30%	
Yes	10	35.70%	17	60.70%	0.108*
Oligohydramnios					
No	26	92.90%	27	96.40%	
Yes	2	7.10%	1	3.60%	0.446*

Fishers exact test, **Pearson chi-square, NA- Not Applicable

Table 4: Comparison primary outcome between the Study groups in the study population (N=56)

Primary outcome		GROUP A (n=28)	GROUP A (%)	GROUP B (n=28)	GROUP B (%)	Sig
Need for Mechanical Ventilation	No	11	39.30%	24	85.70%	
	Yes	17	60.70%	4	14.30%	<0.001*
Duration Mechanical Ventilation on	<3 Days	21	75.00%	26	92.90%	
	3-5 Days	7	25.00%	2	7.10%	0.143*

Table 5: Comparison secondary outcome between the Study groups in the study population (N=56)

Secondary outcome variables		GROUP A (n=28)	GROUP A (%)	GROUP B (n=28)	GROUP B (%)	P value
Episodes Apnoea of	<3	4	14.30%	23	82.10%	
	3 - 5	12	42.90%	5	17.90%	
	>5	12	42.90%	0	0%	<0.001*
Documented Days of Apnoea	<2Days	5	17.90%	13	46.40%	
	2-4 Days	21	75.00%	14	50.00%	
	>4 Days	2	7.10%	1	3.60%	0.051*
Duration of Stay	<10 days	0	0%	3	10.7%	
	10 - 20 days	27	96.40%	25	89.3%	
	>20 days	1	3.60%	0	0%	NA
Length hospital stay level 3 of in	<3 days	7	25.00%	21	75.00%	
	>3 days	21	75.00%	7	25.00%	<0.001**
Need for oxygen support	Yes	16	57.10%	12	42.90%	
	no	12	42.90%	16	57.10%	0.212%
Chronic lung disease	No	27	96.40%	26	92.90%	
	Yes	1	3.60%	2	7.10%	0.500*
NEC	No	25	89.30%	27	96.40%	0.611*
	Yes	3	10.70%	1	3.60%	
Intraventricular haemorrhage	No	28	100%	27	96.40%	
	Yes	0	0%	1	3.60%	0.500*
Retinopathy prematurity	No	25	89.30%	26	92.90%	
	Yes	3	10.70%	2	7.10%	0.569*
Weight gain	Not adequate	17	60.70%	23	82.10%	0.138**
	Adequate	11	39.3%	5	17.90%	
Other relevant variables						
Sex	Boy	11	39.30%	14	50%	
	Girl	17	60.70%	14	50%	0.420**
Birth Weight	<1 Kg	22	78.60%	21	75.00%	
	1-2 Kg	6	21.40%	7	25.00%	0.752**
APGAR score	>7 AT 5TH minute	28	100%	26	92.90%	
	<7 AT 5TH minute	0	0%	2	7.10%	0.245*
RDS	No	28	100%	28	100%	NA
Sepsis	No	28	100%	28	100%	NA
Feed intolerance	No	18	64.30%	28	100%	<0.001
	Yes	10	35.70%	0	0%	
Chromosomal anomaly	No	28	100%	28	100%	NA

Table 6: Comparison of mortality between the Study groups in the study population (N=56)

VARIABLES		GROUP A (n=28)	GROUP A (%)	GROUP B (n=28)	GROUP B (%)	Sig
Mortality	No	28	100%	28	100%	
	Yes	0	0%	0	0%	NA

NA- Not Applicable

DISCUSSION

In this randomized controlled trial (N=56; 28 per arm) conducted in a tertiary care NICU in Coimbatore, the cohort was predominantly very preterm and very low birth weight, which is the population in whom apnea of prematurity is most expected to be clinically relevant: 46/56 (82.14%) were 28–32 weeks' gestation and 43/56 (76.79%) weighed <1 kg. Clinically, the routine-dose group (Group A) showed a much heavier apnea burden than the rescue-dose group (Group B): only 4/28 (14.30%) in Group A had <3 apnea episodes compared with 23/28 (82.10%) in Group B, while 12/28 (42.90%) in Group A had >5 episodes versus 0/28 in Group B ($p<0.001$). This direction is consistent with the prophylaxis concept described by Armanian et al. (2016), where prophylactic caffeine markedly reduced apnea occurrence (15.4% in the caffeine group vs 61.5% in controls), supporting that

earlier/augmented caffeine exposure can shift infants from frequent to infrequent apnea events.[7]

The primary outcome in this study was strongly in favor of the rescue-dose strategy: mechanical ventilation was required in 17/28 (60.70%) in Group A versus 4/28 (14.30%) in Group B (p<0.001). This large absolute difference mirrors the established extubation-facilitating effect of higher caffeine exposure seen in Steer et al. (2004), where a higher periextubation caffeine citrate regimen reduced extubation failure from 29.8% to 15.0% (RR 0.51) and, among infants <28 weeks, shortened mean ventilation duration (14.4 vs 22.1 days). In this dataset, ventilation duration also numerically favored Group B (<3 days: 92.9% vs 75.0%), although it did not reach statistical significance (p=0.143), which may reflect limited sample size despite a consistent trend.[8]

Beyond whether ventilation was needed, secondary apnea control outcomes also show a clear separation between arms: documented apnea days shifted toward shorter duration in Group B (<2 days: 46.40% vs 17.90% in Group A; p=0.051 borderline), and severe recurrence patterns (>5 episodes) disappeared entirely in Group B (0%) while remaining high in Group A (42.90%). These magnitudes are directionally aligned with Wan et al. (2020), where a higher maintenance dose (10 mg/kg/day vs 5 mg/kg/day after standard loading) reduced extubation failure (16.7% vs 36.8%) and reduced apnea burden (days of apnea 1.8±1.3 vs 3.2±1.1). This trial similarly suggests that a "more intensified" caffeine approach (here operationalized as rescue dosing strategy) can translate into fewer apnea events and less escalation to invasive ventilation.[9]

Regarding broader respiratory morbidity, this study observed low chronic lung disease (CLD) overall (3/56, 5.36%) with no statistically significant between-group difference (Group A 3.60% vs Group B 7.10%; p=0.500), and oxygen support need was also not significantly different (57.10% vs 42.90%; p=0.212). This is compatible with the larger evidence base where caffeine reduces major pulmonary morbidity, but small single-center samples may not detect differences in CLD/BPD reliably. In the CAP Trial by Schmidt et al. (2006), caffeine reduced bronchopulmonary dysplasia (oxygen at 36 weeks: 36% vs 47%, OR 0.63) and also shortened respiratory support milestones (earlier discontinuation of positive pressure and oxygen). This trial's strongest signal was earlier in the pathway (apnea control and avoidance of ventilation), while downstream outcomes like CLD may require larger numbers and longer follow-up to show separation.[10]

For other key neonatal morbidities and resource utilization, the groups were broadly similar in NEC, IVH, and ROP (all p>0.05), while the need for prolonged high-acuity care was clearly reduced in Group B: level-3 stay <3 days occurred in 21/28 (75.00%) in Group B versus 7/28 (25.00%) in Group A (p<0.001). This type of "resource-use" improvement parallels the population-level experience in Lodha et al. (2015), where early caffeine (≤2 days) was associated with reduced odds of the composite death or BPD (AOR 0.81) and reduced PDA (AOR 0.74) without increasing NEC (AOR 0.88), severe neurologic injury, or severe ROP. In this trial, mortality was 0% and NEC was low overall (7.10%), and the marked reduction in level-3 days in the rescue group is consistent with caffeine's capacity to stabilize breathing and reduce escalation/ongoing intensive support even when longer-term morbidities remain statistically similar in small samples.[11]

Survival and major neurologic outcomes were excellent in this dataset (mortality 0/56; IVH 1/56, 1.79%), and between-group mortality was necessarily "not applicable" due to zero events. These findings can be contextualized against the longer-term safety/benefit profile of caffeine shown in Schmidt et al. (2007), where caffeine therapy reduced the composite of death or survival with neurodevelopmental disability at 18–21 months (40.2% vs 46.2%; adjusted OR 0.77) and reduced cerebral palsy (4.4% vs 7.3%; adjusted OR 0.58). While this trial did not measure longer-term neurodevelopment, the absence of mortality and the very low incidence of IVH/major injury are at least compatible with the broader literature that caffeine is not only effective but also not associated with worsened neurodevelopmental outcomes, and may be protective at scale.[12]

A notable discordant finding in this trial is feeding intolerance: it occurred in 10/28 (35.70%) in Group A and 0/28 (0%) in Group B (p<0.001), suggesting substantially better feed tolerance with the rescue-dose strategy in this setting. This contrasts with physiologic concerns raised by Gounaris et al. (2020), who reported delayed gastric emptying during caffeine exposure and higher gastrointestinal complications with caffeine compared with no caffeine (6/22, 27.7% vs 1/22, 4.6%; p=0.039). A plausible interpretation is that in this trial the overall clinical trajectory (less apnea, less ventilation, shorter high-acuity stay) in Group B may have indirectly improved feeding tolerance despite caffeine's potential GI motility effects, whereas Group A's higher respiratory instability and ventilation exposure may have contributed to feed intolerance (through hypoxia, stress responses, or feeding interruptions).[13]

Adverse effects in the side-effect table show more tachycardia in Group A (7/28, 25%) than Group B (2/28, 7%) with no statistically significant difference reported (p=0.143), and hypertension was rare (2 vs 1). This pattern is clinically reassuring because intensified caffeine strategies often raise concern about cardiovascular stimulation. Comparative safety data can be framed using Shivakumar et al. (2017), where caffeine (vs aminophylline) was associated with fewer tachycardia events (RR 0.30; 95% CI 0.17–0.51) while showing similar efficacy on apnea outcomes. In this study, the rescue-dose approach did not appear to increase cardiovascular adverse effects;

if anything, tachycardia was numerically lower in Group B, which may reflect less overall physiologic stress from apnea/ventilation rather than a direct pharmacologic difference alone.[14]

Taken together, the pattern across the tables—marked reduction in apnea severity ($p<0.001$), marked reduction in mechanical ventilation requirement ($p<0.001$), and reduced prolonged level-3 stay ($p<0.001$) without worsening NEC, IVH, ROP, CLD, or mortality—fits well within the established evidence that methylxanthines reduce apnea and reduce the need for ventilatory support soon after initiation. Henderson-Smart et al. (2010) synthesized randomized trials (total 192 infants across short-term studies) and concluded that methylxanthine therapy reduces apnea and reduces use of intermittent positive pressure ventilation in the first 2–7 days after starting treatment, with caffeine preferred due to lower toxicity and better longer-term outcomes. This RCT extends this general evidence into a "routine vs rescue strategy" comparison in this local setting, with results suggesting that the rescue-dose strategy produced clinically important reductions in respiratory escalation and apnea burden in this preterm population.[15]

CONCLUSION

This randomized controlled trial demonstrates that the use of a rescue dose of caffeine in preterm neonates with symptomatic apnea of prematurity significantly reduces the frequency of apneic episodes and the need for mechanical ventilation, without increasing clinically significant adverse effects. The rescue-dose strategy was also associated with a shorter duration of higher-level neonatal care, suggesting a potential reduction in morbidity and resource utilization. These findings support the clinical usefulness and safety of rescue-dose caffeine in preterm infants, particularly in those of lower gestational age.

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