İSTANBUL UNIVERSITY PRESS

Çocuk Dergisi–Journal of Child,
JCHILD 2025, 25 (4): 258–262

https://doi.org/10.26650/jchild.2025.1748075

Submitted: 23.07.2025
Revision Requested: 11.08.2025
Last Revision Received: 14.08.2025
Accepted: 23.09.2025

Çocuk Dergisi
Journal of Child

Research Article

Open Access

Dose-Dependent Effects of Caffeine Citrate in Preterm Infants: A Retrospective Analysis of Weight Gain and Cardiac Outcomes

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Abstract

Objective: A xanthine, caffeine citrate (CC), increases the metabolic rate with the release of catecholamine and affects weight gain in these patients in the first days. The cardiovascular system increases cardiac output and average arterial blood pressure by increasing heart rate, cardiac contractility, and stroke volume. This study investigated the effects of 5 and 10 mg/kg/day doses of CC on early postnatal weight gain velocity, discharge weight percentile, and cardiac function parameters in preterm infants.

Methods: Neonates who underwent CC-therapy between January 2020 and April 2023 and were ≤34 weeks gestation were included in this retrospective analysis. Twenty-three patients were given 5 mg/kg maintenance CC (group 1). Twenty-three patients were given 10 mg/kg maintenance CC (group 2). The groups were compared in terms of demographic data, complications of prematurity (RDS, BPD, NEC, IVH, ROP, PDA), type and duration of respiratory support, time to birth weight, time to total enteral nutrition, discharge weight percentile, and echocardiography (Echo) findings. Data for groups 1 and 2 were examined independently.

Results: The study included 46 neonates. Patients in group-1 (11± 6.1 day) achieved their birth weight for a statistically significant shorter period compared to group-2 (15± 5 day) ($p < .05$). The groups did not differ in any way regarding time to transition to full enteral nutrition, discharge weight percentile, discharge time, echocardiographic results, premature complication, type and duration of respiratory support.

Conclusion: Babies receiving CC at a dose of 5 mg/kg/day achieved their birth weight in a shorter time than those receiving 10 mg/kg/day. Both dosage regimens have similar safety in terms of side effects, weight gain after the first week, and cardiological aspects.

Keywords Caffeine citrate · neonates · gain weight · cardiologic side effects · neonatal nutrition

Citation: Yılmaz FH, Ceylan C, Yılmaz H, Yümlü K, Silahlı M. Dose-dependent effects of caffeine citrate in preterm infants: A retrospective analysis of weight gain and cardiac outcomes. Çocuk Dergisi–Journal of Child 2025;25(4):258-262. https://doi.org/10.26650/jchild.2025.1748075

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INTRODUCTION

Apnea of prematurity (AOP) represents a significant clinical challenge in preterm infants, particularly affecting 85% of those born before 34 weeks of pregnancy and 100% of babies born before 30 weeks (1). AOP that is not well controlled raises the risk of retinopathy of prematurity (ROP), bronchopulmonary dysplasia (BPD), neurological impairment, and preterm death from bradycardia and hypoxemia episodes (2). For this reason, it is critically important to treat AOP. Caffeine citrate (CC) is a derivative of methylxanthine that has become the first choice in the pharmacological treatment of AOP for reasons such as its therapeutic index is better, its half-life is longer, the advantage of using a single dose per day and requiring less drug level control (3). However, CC increases the metabolic rate with the release of catecholamine. Caffeine citrate can affect weight gain in these patients in the first days with a catabolic effect (4). In the cardiovascular system, it increases the cardiac output and average arterial blood pressure by increasing the heart rate (HR), cardiac contractility and stroke volüme (5). While CC therapy has demonstrated established efficacy in AOP management, the effects of different dosing regimens on early growth parameters and cardiac function remain insufficiently elucidated. This study aimed to compare the effects of 5 mg/kg versus 10 mg/kg CC doses on weight gain velocity during the first week of life, discharge weight percentile, and cardiac function parameters in preterm neonates.

METHODS

Design, Setting, and Population

The records of patients treated in Ministry of Health Dr. Ali Kemal Belviranlı Obstetrics and Child Health Hospital's tertiary NICU from January 2020 to April 2023 were examined for this retrospective analysis. The trial comprised patients with gestational ages ranging from 22 to 34 weeks who were treated with prophylactic CC to avoid AOP, lessen BPD, and provide cognitive advantages.

Power analyses using G*Power version 3.1.9.4 (test family: t tests, statistical test: Means: Difference between two independent means, two groups, one-tailed), with $\alpha = 0.05$, effect size $d = 0.75$and a desired power of 0.80, the required sample size was calculated as $n = 23$ infants per group (total $N = 46$). This matched the actual sample size of the study, yielding an actual power of 0.8049.

Infants whose feeding was discontinued because of NEC, who were small for gestational age (SGA), who had chromosomal anomalies, and who had congenital anomalies were excluded. Twenty-three patients received a 20 mg/kg CC load followed by 5 mg/kg maintenance (group 1). Twenty-three patients received a 20 mg/kg CC load followed by 10 mg/kg maintenance (group 2). Demographic information, prematurity complications [respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH), necrotizing enteroclitis (NEC), retinopathy of prematurity (ROP), bronchopulmonary dysplasia (BPD), patent ductus arteriosus (PDA), time to birth weight, time to full enteral nutrition, discharge weight percentile, and echocardiographic results were compared between the groups.

Patients received parenteral nutrition according to their clinical needs. Enterally fed patients were fed breast milk and fortified breast milk as the first choice and preterm formula when this was not sufficient. From the time of delivery until discharge, skilled neonatal nurses took a daily weight reading and recorded any changes following the unit procedure.

Echocardiography Procedure

Echocardiographic was examined using Philips Affiniti 50 (2017 USA) Echo device and S12 probe by an experienced pediatric cardiologist. Echocardiographic was examined using the standard imaging techniques recommended by the American Society of Echocardiography (6).

Unit Procedure for Caffeine Usage

Licensed newborn products (Kafsiton, 60 mg/3 ml solution by Onfarma Ltd.) were administered intravenously (IV) and orally to neonates during the trial period. According to the unit protocol, an IV loading dosage of 20 mg/kg was given, and 24 h later, 5–10 mg/kg CC (or 2.5–5 mg/kg caffeine base) was administered as a once-daily maintenance dose. After achieving sufficient enteral nutrition (>100 mL/kg/day), intravenous-CC was shifted to an oral route.

Statistical Analysis

Statistical analyses were performed using SPSS version 22.0 (IBM Corp., Armonk, NY, USA). Ordinal and nominal variables are presented as frequencies and percentages, while continuous variables are expressed as mean ± standard deviation (SD) as appropriate. The distribution of continuous variables was tested for normality using the Shapiro-Wilk test. For variables that did not meet the assumption of normality, the Mann–Whitney U test was applied to compare the groups. A 95% confidence interval was adopted, and p-values of <0.05 were considered statistically significant.

Ethical approval and consent to participate

Approval for the study was received by the Selcuk University local ethics committee (Date: 2024, Decision No: 19). The parents/legal guardians of the children provided informed consent.

RESULTS

During January 2020 to April 2023, 350 patients were admitted to the unit that were <34 gestational weeks and under 1500 g. The exclusion criteria consisted of patients with feeding discontinuation due to NEC, SGA infants, and those with chromosomal or congenital anomalies. After applying these exclusions, 60 patients (30 per

group) were screened. Due to the family's refusal to work later, the transfer of the patient to another unit and the death of the patient, the study was completed with 23 patients in both groups. Details are given in Figure 1.

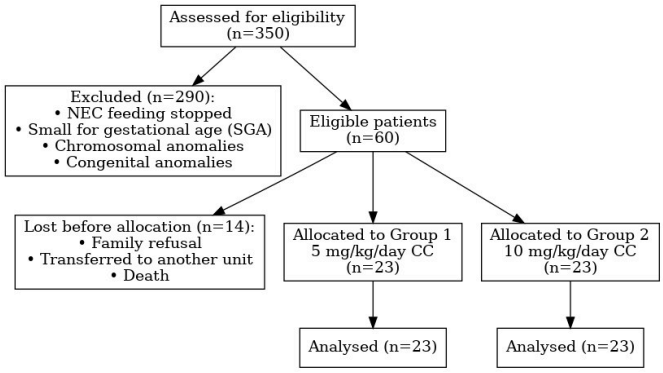


Figure 1. consort diagram

The groups were similar in terms of demographic characteristics. Details are given in Table 1. Patients in group-1 (11± 6.1 day) achieved their birth weight for a statistically significant shorter period compared to group-2 (15± 5 day) (p <.05). There was no difference between the groups in terms of time to transition to full enteral nutrition, discharge weight percentile, discharge time, premature complication, type and duration of respiratory support. Details are given Table 2.

Table 1. Patient demographic status

	Group 1	Group 2	p
Birth week (n, %)			
<27	1, %4.35	2, %8.70	
27-31	19, %82.61	16, %69.57	*p*>0.05
>31	3, %13.04	5, %21.74	
Mean Birth Weight, (g) (mean ± SD)	1341.30 ± 206.43	1271.96 ± 259.54	*p*>0.05
Gender (n, %)			
Male	11, %47.8	12, %52.2	*p*>0.05
Female	12, %52.2	11, %47.8	

SD: Standard deviation

Table 2. Patient clinical features

	Group 1 (Mean ± SD)	Group 2 (Mean ± SD)	p
Duration of non-invasive ventilation, days	8.69 ± 9.04	14.82 ± 13.26	*p*>0.05
Duration of invasive ventilation, days	7.34 ± 11.76	9.82 ± 12.04	*p*>0.05
Duration of free oxygen intake, days	9.36 ± 12.89	10.69 ± 13.34	*p*>0.05
Duration of transition to total enteral nutrition, days	9.91 ± 7.64	12.65 ± 16.10	*p*>0.05
Duration of achieving birth weight, days	11.04 ± 6.11	15.04 ± 5.08	***p*=0.004**
Duration of discharge, days	50.65 ± 23.00	59.47 ± 26.65	*p*>0.05
Discharge weight percentile, %	22.00 ± 19.60	20.43 ± 21.34	*p*>0.05
RDS, (n)			
None	13	7	*p*>0.05
Positive	10	16	
PDA, (n)			
None	22	17	
Surgery	0	1	*p*>0.05
Medical treatment	1	5	
IVH, (n)			
Negative	19	20	
Grade 1-2	1	3	*p*>0.05
Grade 3-4	3	0	
NEC, (n)			
None	22	22	
Surgery	1	0	*p*>0.05
Medical treatment	0	1	
ROP, (n)			
None	16	13	*p*>0.05
Positive, regressed	7	19	
BPD, (n)			
None	19	18	
Mild	4	4	*p*>0.05
Severe	0	1	

SD: Standard deviation, RDS: Respiratory distress syndrome, PDA: Patent ductus arteriosus, IVH: intraventricular hemorrhage, NEC: necrotizing enterocolitis, ROP: Retinopathy of prematurity, BPD: bronchopulmonary dysplasia

Comparative analysis of echocardiographic measurements showed no statistically significant variations between the groups. Details are given in Table 3.

Table 3. Patient cardiac outcomes

	Group 1 (mean ± SD)	Group 2 (mean ± SD)	*p*
Septum thickness, (mm)	2.73 ± 0.48	2.78 ± 0.58	*p*>0.05
Posterior wall thickness (mm)	2.91 ± 3.08	2.93 ± 2.08	*p*>0.05
Left Ventricular End-Diastolic Diameter (mm)	13.29 ± 1.43	13.74 ± 1.15	*p*>0.05
Left ventricular end-systolic diameter (mm)	8.53 ± 1.43	8.27 ± 1.15	*p*>0.05
EF, (%)	73.86 ± 3.50	74.82 ± 2.62	*p*>0.05
FS, (%)	40.30 ± 2.73	40.39 ± 2.49	*p*>0.05
LA, (mm)	0.93 ± 0.11	1.01 ± 0.16	*p*>0.05
Ao, (mm)	1.08 ± 1.46	1.64 ± 2.19	*p*>0.05
LA/Ao	1.19 ± 0.11	1.25 ± 0.10	*p*>0.05

SD: standard deviation, EF: ejection fraction, FS: fractional shortening, LA: left atrial diameter,

Ao: aortic root diameter

No adverse drug-related effects were observed in either group.

DISCUSSION

Our study shows that preterm infants treated with lower daily and cumulative doses of CC reached birth weight in a clinically and statistically significantly shorter time. However, this initial difference disappeared over time, and no difference was observed in the discharge percentiles between the 5 mg/kg and 10 mg/kg daily caffeine groups. These findings align with those of Philip et al., who reported higher daily weight gain in infants receiving 5 mg/kg/day compared to 10 mg/kg/day (5), and Hussein et al., who found minimal weight gain in neonates exposed to doses >5 mg/kg/day until the sixth postnatal week (7). Schmidt et al. also reported greater early postnatal weight loss followed by stabilization in infants receiving CC (8, 9).

No significant differences were found between the two dosage groups regarding invasive or non-invasive respiratory support, oxygen supplementation duration, or BPD rates. Although doses higher than 5–10 mg/kg/day are sometimes preferred in clinical practice, evidence suggests that single high doses may reduce extubation success compared with divided doses throughout the day (10,11). Meta-analyses also report that high-dose caffeine reduces apnea frequency, increases extubation success, and shortens the duration of mechanical ventilation (12–15). However, concerns remain regarding the long-term safety and adverse effects such as increased tachycardia and cerebellar hemorrhage. Our results indicate that within the standard dosing range, respiratory outcomes are comparable, supporting individualized dosing decisions.

Previous reports have identified side effects such as feeding intolerance, hepatic and renal dysfunction, seizures, and tachycardia, especially at higher doses (16,17). In our study, only two cases of transient tachycardia were observed, which resolved with calming measures. No significant differences in cardiological rhythm disturbances or other adverse effects were detected between the groups, supporting the short-term safety of both dose regimens.

Cardiological evaluations, including Echo and ECG, revealed no significant differences in rhythm or function between the groups. Prior studies using near-infrared spectroscopy and electrical velocimetry found that CC administration increased systemic vascular resistance and left ventricular output, reflecting mild pressor and inotropic effects (18,19). Our findings indicate that these effects are clinically insignificant at standard doses and confirm the cardiac safety of CC within this range.

Potential confounders such as nutritional variability, types of respiratory support, and clinical care differences were not fully controlled. These factors may influence the observed outcomes and should be considered when interpreting the results.

Limitations

The lack of serum caffeine level measurements constrained the interpretation of the pharmacodynamic data. The single-center design and small sample size significantly limit the generalizability of our findings.

CONCLUSION

This study demonstrated that preterm infants receiving 5 mg/kg/day of CC regained birth weight faster than those on 10 mg/kg/day, although this early advantage did not persist. Both regimens showed comparable safety regarding adverse effects, postnatal growth, and cardiac outcomes. These results suggest that lower CC doses may offer equivalent efficacy with improved tolerability, highlighting the need for individualized dosing and timely discontinuation. Such evidence can inform optimized, safety-conscious CC strategies in NICU settings.

Ethics Committee Approval	This study was approved by the ethics committee of Selcuk University local ethics committee (Date: 2024, Decision No: 19).
Informed Consent	Written consent was obtained from the participants
Peer Review	Externally peer-reviewed.
Author Contributions	Conception/Design of Study- F.H.Y., C.C. Data Acquisition- Data Analysis/Interpretation- F.H.Y Drafting Manuscript- H.Y.. ; Critical Revision of Manuscript- C.C. ..; Final Approval and Accountability- F.H.Y., C.C., H.Y., K.Y., M.S.
Conflict of Interest	The authors have no conflict of interest to declare.
Financial Disclosure	The authors declared that this study has received no financial support.

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