Early Caffeine Therapy Reduces Risk of Moderate-to-Severe BPD in Preterm Infants

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Abstract

Objective: To assess the effectiveness of early caffeine (EC) administration within 24 h of birth in preventing bronchopulmonary dysplasia (BPD) in preterm infants.

Methods: This retrospective analysis included preterm infants (< 32 weeks or < 1,500 g) who received caffeine therapy at Wonju Severance Christian Hospital between 2017 and 2024. The infants were divided into two groups: the EC group (≤ 24 h after birth) and late caffeine (LC) group (> 24 h). Primary outcomes were overall and moderate-to-severe BPD. Secondary outcomes included the duration of respiratory support and other neonatal complications.

Results: Among 161 infants (EC: 65, LC: 96), the overall incidence of BPD did not differ between the groups (52.31% vs. 55.21%, p = 0.717). The incidence of moderate-to-severe BPD was significantly lower in the EC group (10.77%) than that in the LC group (27.08%), with an adjusted odds ratio of 0.26 (95% CI 0.09–0.77; p = 0.012). No significant differences were found in the duration of invasive or noninvasive respiratory support, and the incidence of other neonatal complications was comparable between the groups.

Conclusion: EC therapy, initiated within 24 h of birth, significantly lowered the risk of moderate-to-severe BPD in infants born at < 32 weeks of gestation or with a birth weight < 1500 g. EC therapy should be considered a preventive strategy for reducing BPD severity.

Introduction

BPD in Preterm Infants

BPD remains a major chronic lung disease in preterm infants.
It results from oxidative stress, oxygen toxicity, and ventilator-induced injury in immature lungs.

Why Caffeine?

Caffeine, widely used for apnea of prematurity, has been shown to reduce BPD and improve neurodevelopmental outcome when initiated within 3 days (CAP trial).

Our Approach

The optimal timing for caffeine initiation remains uncertain.
Our NICU implemented an early caffeine (≤ 24 h) protocol in May 2022.

Study Aim

To determine whether caffeine administration within 24 h after birth reduces the incidence and severity of BPD in preterm infants.

Methods

Study Design

- Retrospective cohort of preterm infants (< 32 weeks or < 1,500 g) admitted to Wonju Severance NICU, Korea (Sep 2017 – Apr 2024)
- IRB approved (CR322090)

Caffeine Protocol

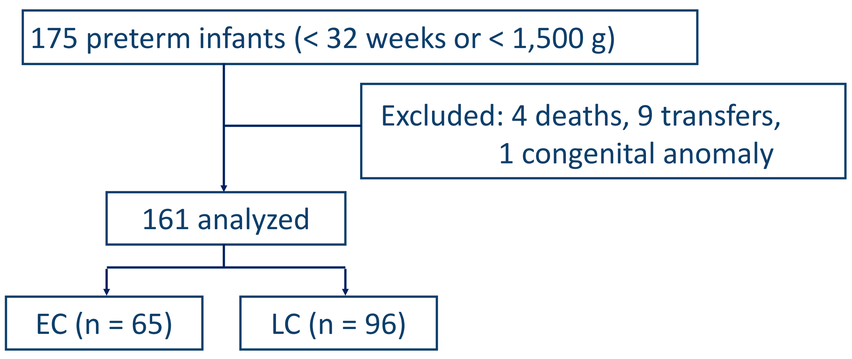
- Early: ≤ 24 h after birth
- Late: > 24 h after birth
- Loading 20 mg/kg → Maintenance 5–10 mg/kg/day
- Discontinued after 4–5 apnea-free days

Outcomes

- Primary – BPD & moderate-to-severe BPD (NIH 2001)
- Secondary – Invasive and noninvasive respiratory support duration & major morbidities (PDA, NEC, IVH, ROP)

Analysis

- Wilcoxon, χ^2, Fisher's exact tests; multivariable logistic regression
- Adjusted for GA, BW, sex, antenatal steroids, vent days
- Software: SAS 9.4; R 4.0.3



Results

Of 175 preterm infants identified, 161 were analyzed (EC = 65, LC = 96).
Baseline characteristics were comparable between groups. (Table)

Table. Comparison of Early and Late Caffeine Therapy

	EC (n = 65)	LC (n = 96)	*P*-value
Gestational age, weeks	29.43 [27.57–30.86]	29.14 [28.00–30.86]	0.357
Birth weight, g	1,250 [1,110–1,470]	1,310 [960–1,560]	0.878
PNA at caffeine initiation, days	0.0 [0.0–0.0]	5.0 [2.0–9.0]	< 0.001
Days of caffeine administration, days	38.0 [32.0–55.0]	31.0 [19.5–43.0]	< 0.001
BPD	34 (52.31)	53 (55.21)	0.717
Moderate-to-severe BPD	7 (10.77)	26 (27.08)	0.012

Data are presented as n (%) or median [Q1–Q3]. PNA, postnatal age.

EC significantly reduced moderate-to-severe BPD (10.8 % vs 27.1 %; aOR 0.26, 95% CI 0.09–0.77, p = 0.012), with similar overall BPD rates.
The duration of invasive (median 6 vs 8 days, p = 0.293) and noninvasive respiratory support (12 vs 14 days, p = 0.373) were similar between groups.
Major morbidities, including PDA, NEC, IVH, and ROP, were also comparable (all p > 0.05).
Early caffeine therapy remained independently associated with a lower risk of moderate-to-severe BPD after adjustment for gestational age, birth weight, sex, antenatal steroids, and ventilation days (Fig. A).
Model performance improved from AUC 0.621 to 0.833 after adjustment, demonstrating enhanced predictive accuracy for moderate-to-severe BPD (Fig. B).

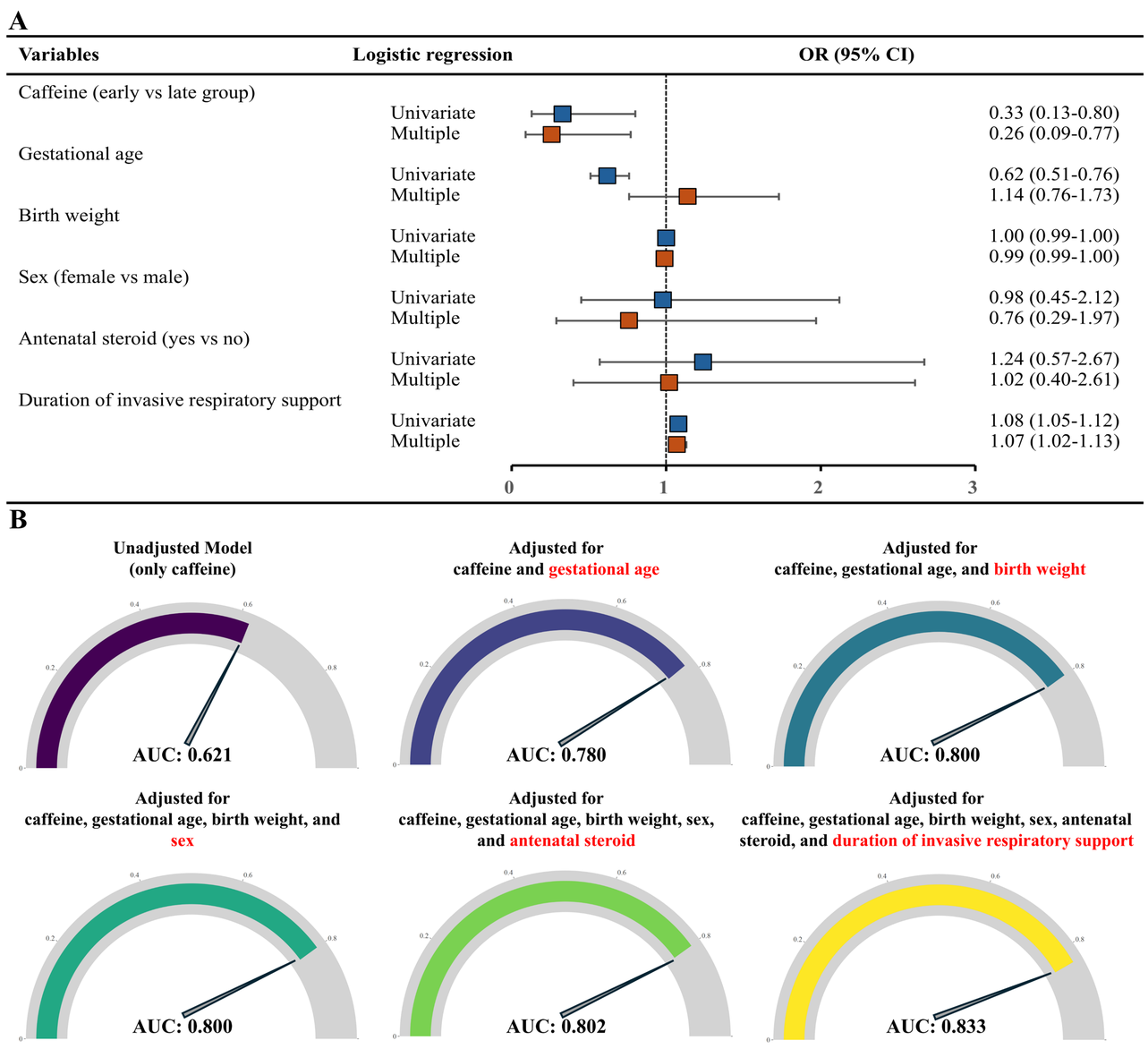


Fig. A. Forest plot of univariate and multivariable logistic regression analyses for moderate-to-severe BPD.
Fig. B. Gauge plots showing stepwise changes in AUC for predicting moderate-to-severe BPD.

Discussion

Impact of 24 h Initiation

From birth, preterm lungs are susceptible to oxygen toxicity and ventilator-induced stress, leading to inflammation and impaired alveolar development.
Starting caffeine within 24 h may protect immature lungs by reducing inflammation and oxidative stress.

Limitations

Although limited by a small single-center cohort, the study achieved consistent protocol application since May 2022 and high model accuracy (AUC 0.833).

Conclusion

Early caffeine initiation within 24 h after birth significantly reduced the incidence of moderate-to-severe BPD in preterm infants.

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