

The effects of caffeine use in NICU on the neurodevelopmental outcome of premature infants: A prospective review

Lauren Phung¹, Rawad Obeid, MD²

¹Oakland University William Beaumont School of Medicine, ²Dept. Of Pediatric Neurology, Corewell Health East

Introduction

- Prematurity remains a major cause of neonatal morbidity as the developing brain is vulnerable to intermittent hypoxia and inflammation.
- Caffeine citrate (CC) is a cornerstone therapy in the NICU for apnea of prematurity, with neuroprotective effects through antioxidation and anti inflammation.^{1,2}

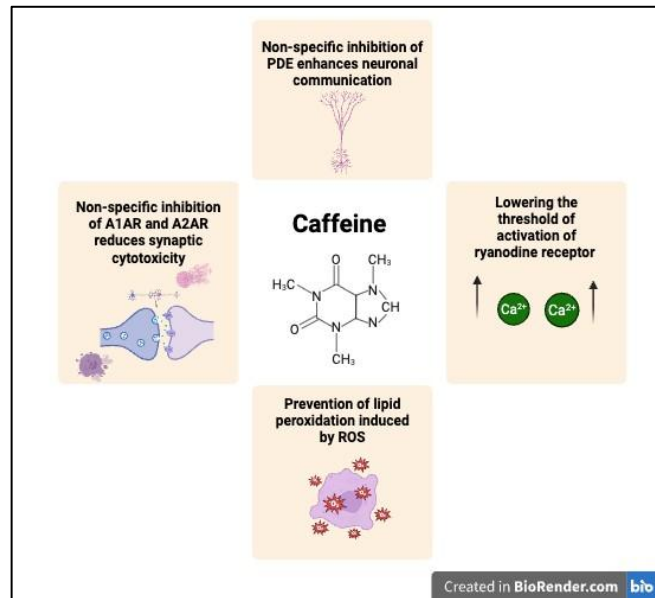


Figure 1: Molecular mechanisms of Caffeine (Created with BioRender.com)

- Early administration within 48 hours after birth appears to mitigate neurodevelopmental impairments in preclinical and clinical studies, though additional prospective studies of the long-term neuroprotective effects of CC are needed.³
- High daily average dose caffeine was associated with better motor, language, and cognitive performance than low-dose caffeine in multivariable analyses adjusted for gestational age and respiratory disease.⁴

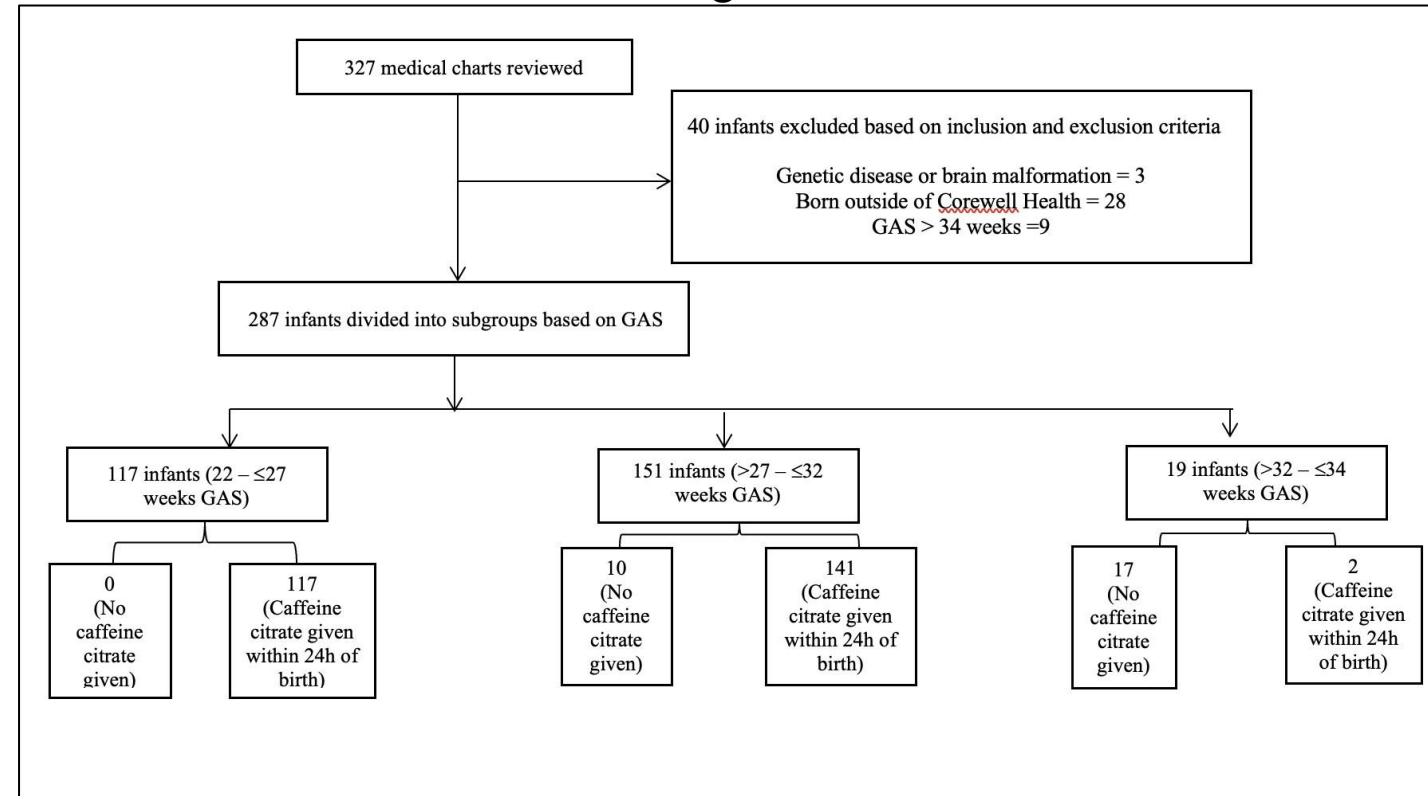
Aims and Objectives

- Evaluate the consistency the protocol of CC administration at NICU Corewell Health East NICU between the years of 2020 and 2024.
- Evaluate the cumulative dose of CC given in NICU on the neurodevelopmental outcomes of preterm infants measured at follow-up visits.

Results

- The following variables were collected: demographics, birth weight, neonatal comorbidities, Apgar scores, evidence of caffeine administration, and duration of mechanical ventilation.
 - The cumulative dose of caffeine is calculated as the sum of the initiation dose and the product of the maintenance dose and the number of days on maintenance.
- Alberta Infant Motor Score (AIMS), Peabody scores, and Bayley III scores are also collected at follow-up visits. Rating for the referenced scores is determined as follows:
 - AIMS score < 10th percentile is abnormal
 - Peabody Grasp and Visual: Δ Peabody score in months and corrected age in months is within 2 STDs (1 STD = 1 month), neurodevelopment is marked as consistent.
 - Bayley III score < 85 is abnormal

Method



Discussion

- Within the Corewell Health system, approximately 99.9% of preterm infants born at <32 weeks' gestational age receive caffeine citrate within the first 24 hours of life.
- Clinical comorbidities including PVL, SGA, PDA, BPD, and NEC, as well as low birth weight and low Apgar score are most significantly associated with a higher likelihood of reduced AIMS scores at short-term follow-up, consistent with current literature.
- Higher cumulative doses of caffeine citrate were not significantly associated with improvements in short- or long-term neurodevelopmental scores. This lack of significance may stem from unmeasured confounding factors or the extreme ranges of cumulative caffeine dosing observed within the current sample.
- Subsequent studies will evaluate the impact of average daily caffeine dosage using an expanded sample size and multivariate adjustments to minimize multicollinearity among clinical characteristics.

References

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Abbreviations

CC: Caffeine citrate
SGA: Small gestational age
PVL: periventricular leukomalacia
BPD: Bronchopulmonary dysplasia
NEC: necrotizing enterocolitis
DART: Dexamethasone: A Randomized Trial
OR: Odd ratio
NICU: Neonatal intensive care unit

	AIMS Score		Peabody grasping		Peabody VISUAL		Baley Cognitive	Bayley Language	Bayley Motor
	3 - 6.99 months (n = 201)	> 22.99 months (n=60)	3 - 6.99 months (n = 192)	> 22.99 months (n=57)	3 - 6.99 months (n = 181)	> 22.99 months (n=61)	> 22.99 months (n=57)	> 22.99 months (n=57)	> 22.99 months (n=57)
Characteristics	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Gender (Male = 1)	0.702 (0.258-1.913)	0.306 (0.068-1.365)	0.765 (0.279-2.099)	1.406 (0.424-4.665)	0.535 (0.192-1.497)	0.969 (0.336-2.798)	1.364 (0.377-4.927)	0.673 (0.215-2.106)	0.599 (0.181-1.986)
SGA (Yes = 1)	0.259 (0.087-0.773)*	2.250 (0.234-21.620)	0.541 (0.140-2.093)	0.603 (0.131-2.777)	0.383 (0.111-1.321)	0.396 (0.094-1.669)	0.756 (0.080-7.109)	0.709 (0.092-5.483)	1.263 (0.137-11.655)
Twin Gestation (Yes = 1)	1.352 (0.420-4.356)	1.800 (0.324-10.014)	1.215 (0.373-3.952)	1.243 (0.334-4.623)	1.312 (0.407-4.236)	1.583 (0.480-5.222)	2.137 (0.303-15.082)	2.600 (0.510-13.254)	1.755 (0.342-9.018)
PVL (Yes = 1)	0.331 (0.113-0.971)*	1.951 (0.201-18.979)	0.271 (0.094-0.779)*	1.296 (0.273-6.163)	0.228 (0.082-0.634)*	2.095 (0.470-9.333)	0.414 (0.061-2.795)	2.412 (0.293-19.854)	6.759 (0.268-170.65)
BPD (Yes = 1)	0.172 (0.038-0.783)*	1.435 (0.364-5.660)	0.368 (0.115-1.180)	1.200 (0.333-4.322)	0.893 (0.330-2.419)	2.816 (0.927-8.560)	0.502 (0.122-2.062)	0.513 (0.156-1.686)	0.592 (0.171-2.042)
NEC (Yes=1)	0.103 (0.031-0.344)*	0.426 (0.032-5.680)	0.593 (0.120-2.938)	0.500 (0.059-4.255)	0.247 (0.068-0.897)*	0.210 (0.019-2.340)	0.129 (0.021-0.809)*	0.158 (0.020-1.219)	0.475 (0.085-2.656)
Sepsis with positive blood culture (Yes=1)	0.718 (0.148-3.483)	small sample	0.816 (0.168-3.972)	small sample	0.873 (0.180-4.231)	2.182 (0.196-24.319)	0.548 (0.090-3.348)	0.353 (0.060-2.089)	0.946 (0.159-5.617)
DART protocol (Given = 1)	0.226 (0.082-0.624)*	2.613 (0.477-14.323)	0.269 (0.098-0.736)*	3.500 (0.901-13.591)	0.389 (0.146-1.035)	2.300 (0.741-7.136)	0.646 (0.141-2.955)	0.421 (0.102-1.730)	0.439 (0.107-1.798)
PDA requiring surgery (Yes = 1)	0.218 (0.080-0.597)*	1.459 (0.259-8.217)	0.449 (0.160-1.258)	1.083 (0.288-4.074)	0.382 (0.141-1.035)	1.760 (0.502-6.175)	1.547 (0.311-7.699)	3.001 (0.037-242.59)	3.001 (0.037-242.59)
Gestational Age (weeks)	1.185 (0.929-1.510)	0.822 (0.611-1.104)	1.208 (0.939-1.555)	0.791 (0.579-1.080)	1.038 (0.812-1.328)	0.798 (0.608-1.048)	1.050 (0.792-1.390)	0.984 (0.768-1.260)	1.064 (0.823-1.375)
Birth Weight in grams	1.003 (1.001-1.006)*	0.999 (0.998-1.001)	1.002 (1.000-1.004)	0.999 (0.998-1.001)	1.001 (0.999-1.003)	0.998 (0.996-1.000)*	1.000 (0.998-1.002)	1.000 (0.998-1.001)	1.000 (0.998-1.001)
Apgar Score at 5 minutes (1-10)	1.333 (1.060-1.676)*	0.837 (0.423-1.658)	1.570 (1.218-2.024)*	0.812 (0.458-1.441)	1.297 (0.997-1.686)	0.813 (0.504-1.311)	1.140 (0.824-1.578)	1.058 (0.785-1.426)	0.987 (0.722-1.350)
IVH Grade	1.369 (0.572-3.277)	0.838 (0.455-1.540)	0.858 (0.505-1.456)	0.918 (0.571-1.475)			0.897 (0.498-1.617)	0.900 (0.267-3.030)	0.900 (0.267-3.030)
Total doses of IV caffeine citrate	0.997 (0.994-1.000)	1.002 (0.999-1.006)	0.998 (0.995-1.000)	1.003 (0.998-1.008)	0.999 (0.996-1.002)	1.005 (1.000-1.009)*	0.999 (0.996-1.003)	1.000 (0.996-1.003)	0.998 (0.995-1.002)
Total days on ventilator							0.995 (0.984-1.005)	0.998 (0.988-1.008)	0.997 (0.987-1.007)
Length of stay in the NICU (wks)							0.954 (0.892-1.020)	0.963 (0.901-1.028)	0.969 (0.909-1.033)

Table 1: Univariate analysis of the effects of clinical characteristics of the cohort and cumulative dose of caffeine on the neurodevelopmental outcomes of <32 GAS weeks preterm infants.

(*p-value < 0.05; OR of impairment for categorical variables; OR of no impairment for continuous variable; Firth's correction with the logistic regression models was used to account for the smaller sample size of the Bayley III scores)