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Five-year outcomes of premature infants randomized to high or standard loading dose caffeine

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Abstract

Objective: To examine five-year outcomes in children enrolled in a pilot randomized controlled trial of a high loading dose of caffeine after preterm birth

Study design: Seventy-four very low birth weight neonates were randomized within the first 24 hours of life to receive a high (80 mg/kg) or standard (20 mg/kg) loading dose of caffeine citrate. At five years of age, we conducted standardized neurodevelopmental tests and collected parent reports of child socioemotional problems.

Result: Seventy-four percent of survivors returned for follow up. Children obtained similar scores on neurodevelopmental and socioemotional evaluations. There was no difference in the incidence of any neurodevelopmental delay after controlling for confounding factors.

Conclusion: Five year follow up of a pilot trial of high loading dose caffeine citrate documented no profound impacts on childhood neurodevelopment or socioemotional outcome.

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Author Contributions

CCM and TEI contributed to the design and execution of the original pilot randomized controlled trial. TEI, CER, and CDS designed the follow up study. CER, CDS, REL, and PEPC executed the follow up study. CCM and REL completed data analysis. CCM wrote the first draft of the manuscript, with all authors revising it critically for important intellectual content. All authors approved the final version to be published.

Supplementary information is available at JPER's website.

Conflict of interest

The authors declare no competing financial interests in relation to the work described.

Introduction

At standard doses, caffeine citrate improves survival and lowers the risk of subsequent cerebral palsy, motor impairment, cognitive delays, and visual perceptual problems in very low birth weight (<1500 grams) and/or very preterm infants (VPT, ≤30 weeks' gestational age) compared to placebo.[1, 2, 3, 4] In this pilot trial, it was hypothesized that administration of caffeine at a higher dose (loading dose of 80 mg/kg caffeine citrate) may have greater neurologic benefit than standard doses, and we examined this hypothesis through comparing measures of white matter maturation seen on term-equivalent magnetic resonsance imaging in a pilot randomized controlled trial.[5, 6] We found a higher rate of cerebellar hemorrhage in infants randomized to high-dose caffeine compared to standard-dose (36% vs. 10%, p=.03), with more hypertonicity and more deviant neurologic signs on term-equivalent NICU Network Neurobehavioral Scale and Dubowitz neurologic examinations, respectively.[7] Developmental outcomes at age two years were similar between high-dose and standard-dose groups. However, VPT children are a heterogeneous population, with longer-term outcome studies showing developmental "catch-up" in some children and worsening delay in others.[8] Additionally, learning disabilities and socioemotional impairments may not be readily identifiable until school age when the cognitive and behavioral demands placed on children increase. The objective of this follow-up study was to examine the neurodevelopmental and socioemotional outcomes of VPT children at five years of age who were enrolled in a randomized controlled trial of high versus standard loading dose caffeine citrate during their first 24 hours of life in the neonatal intensive care unit (NICU).

Methods

This pilot, randomized, double-blind trial enrolled 74 VPT infants (≤30 weeks' gestational age) admitted to the level IV NICU at St. Louis Children's Hospital between November 2008 and June 2010 (Supplementary Figure 1). Thirty-seven infants were randomized to high-dose caffeine citrate (80 mg/kg, Cafcit®, Bedford Laboratories) and 37 infants to standard-dose caffeine citrate (20 mg/kg) within the first 24 hours of life. Seven pairs of twins were enrolled in the study and randomized independently. For five twin pairs, one sibling was randomized to the high-dose group and one sibling was randomized to the standard-dose group; for one twin pair, both siblings were randomized to the high-dose group; for one twin pair, both siblings were randomized to the low-dose group. All infants received caffeine citrate 10 mg/kg every 24 hours after the initial caffeine citrate dose, adjusted weekly for growth, and continuing until resolution of apnea of prematurity per the attending physician (postmenstrual age in high-dose 34.9±2.1 weeks vs. standard-dose 34.4±1.6 weeks, p=0.45). Complete details of the trial along with term equivalent age outcomes and two year follow up are available elsewhere.[7] The study was approved by the Human Research Protection Office at Washington University in St. Louis. All parents provided written informed consent. The trial was registered on www.clinicaltrials.gov (NCT00809055).

Social and Family Background

Social risk was quantified using the social risk index score, the composite in which one point was given for each of: maternal age at delivery ≤ 18-years, African-American race (as a proxy for systemic and individual experiences of racial discrimination), mother with no high school degree, public health insurance, and single-parent household.[9] Socioeconomic status was estimated using the income-to-needs ratio, representing the total family income divided by the poverty threshold for the size of the family household. Family dysfunction was assessed using the General Dysfunction subscale of the McMaster Family Assessment Device.[10]

Follow-up Assessment at Age Five Years

Between August 2012 and March 2016, children returned for a follow-up assessment involving standardized neurodevelopmental tests and parent report of child socioemotional problems at age five years (Supplementary Figure 1). The researchers attempted to contact the families of all surviving children, regardless of participation in two-year follow up. General cognitive, verbal, and non-verbal abilities were assessed with the Wechsler Preschool and Primary Scale of Intelligence – Third Edition (WPPSI-III).[11] Two children were assessed with the Differential Abilities Scales due to severe cognitive delay.[12] The Clinical Evaluation of Language Fundamentals-Preschool 2 (CELF-P2) Core Language Score provided a measure of overall expressive and receptive language ability.[13] For cognitive and language domains, delay and impairment were defined as composite scores <85 and <70, respectively. To assess general motor ability, children were assessed with the Movement Assessment Battery for Children, Second Edition (MABC-2).[14]. Motor delay and impairment were defined as a MABC-2 Total Motor standardized score ≤15th percentile and ≤5th percentile or unable to complete MABC-2 assessment, respectively. The Shape School Task was used to assess executive control skills.[15] Efficiency scores (correct-errors/time) and the rates of children unable to complete the inhibition, set shifting, and inhibition-shifting switch conditions are reported. Neurodevelopmental assessments were performed by examiners blind to children's clinical status. To assess socioemotional outcomes, the primary caregiver of the child completed the Child Behavior Checklist/1.5–5 (CBCL/1.5–5) and the Social Responsiveness Scale-2.[16, 17] The Internalizing scale of the CBCL/1.5–5 assesses mood/affective problems, somatic complaints, and social withdrawal, whereas the Externalizing scale captures inattention/hyperactivity symptoms and aggressive behavior. The SRS-2 provides a measure of quantitatively distributed autistic traits, across two subscales Social Communication and Interaction and Restricted Interests and Repetitive Behavior. CBCL/1.5–5 and SRS-2 *t*-scores >60 suggest socioemotional problems above the typical range.

Statistical Analysis

Statistical analyses were performed using SPSS 25 (SPSS, Inc., Chicago, Illinois). Between-groups differences were examined using Student's t-tests and chi-squared analyses. Odds ratios (OR) with 95% confidence intervals (CI) were generated for any neurodevelopmental delay (the composite of cognitive, language, and/or motor delay and/or mild-to-moderate autistic traits) and any neurodevelopmental impairment (the composite of cognitive,

language, and/or motor impairment, behavioral problems, severe autistic traits, blindness, and/or deafness) utilizing logistic regression. *P* values were two-sided and deemed statistically significant if <.05. Results were not adjusted for multiple comparisons due to the exploratory nature of this report. Although the pilot trial was powered to detect between-groups differences at term-equivalent age, the trial was not powered for long-term follow-up after accounting for sample attrition over time.

Results

Clinical and Social Background Characteristics.

Seventy four percent of survivors returned for a follow-up assessment at age five years (21 high-dose, 25 standard-dose). Children who were lost to follow-up were more likley to be African American and mothers had a lower age at delivery and were less likely to have private insurance, more likely to use marijuana prenatally, and less likely to receive antenatal steroids. Among children who did not participate in follow-up, only maternal age was unequally distrubted between the high-dose and standard-dose caffeine groups (26.6 ± 7.0 vs. 21.7 ± 4.3 years, p=0.04), a difference consistent with the original overall cohort.[7] Among children who participated in follow up, those in the high-dose group had a lower Social Risk Index score, lower birth weight, and greater neonatal growth restriction of the head than the standard-dose group (Table 1). Clinical outcomes, drug exposures, the incidence of brain injury across types, and developmental outcomes at age two years were similar between the high- and standard-dose groups (Tables 2, 3, and 4).

Neurodevelopmenal Outcomes.

Cognitive and language assessments were completed for all 46 children (Table 5). Children in the high- and standard-dose groups obtained similar general, verbal, or non-verbal cognitive scores on average (p>.05), with only a modest 3–4 point difference favoring the high-dose group. CELF-P2 core language scores were similar between the groups (p=.79). Approximately 33–44% of VPT children in the high- or standard-dose groups demonstrated a cognitive or language delay, with fewer children falling into the impaired range (4–19%) (p>.05). Executive control data were obtained for 37 children (four children in the high-dose group and five children in the standard-dose group did not know shapes or colors, did not understand task instructions, or demonstrated behavioral problems preventing task administration). Efficiency scores for the cognitive inhibition, shifting, and inhibition-shifting switch conditions, as well as proportions of children failing task conditions, were similar between groups (p>.05).

For motor outcomes (Table 5), 89% of children completed motor testing (19 high-dose, 22 standard-dose; high-dose: one unable due to severe delay and one was unwilling; standard-dose: two unable due to severe delay and one was unwilling). Children in the high- and standard-dose groups demonstrated similarly poor motor outcomes (p=.53), with both groups obtaining MABC-2 Total scores more than 1 SD below the standardized mean. Inclusive of children unable to complete motor testing due to severe impairment, rates of motor delay and impariment were similar between high- and standard-dose groups (p>.05).

Socioemotional Outcomes.

Socioemotional outcome data were obtained for 42 children (one was accompanied by a parent with limited English proficiency, three parents did not complete questionnaires). There were no differences between-groups in Internalizing symptoms, Externalizing symptoms, or autistic traits, with mean *t*-scores in the typical range across measures ($p>.05$, Table 5). Although there was nearly twice the rate of Internalizing problems (21% vs. 11%) and Externalizing problems (21% vs. 11%) in the standard-dose group compared to the high-dose group, this difference was not significant ($p=.45$). Rates of autistic traits above the typical range were highly comparable (24% vs. 28%, $p=.68$).

Any Neurodevelopmental Delay.

There was no difference in the risk of any delay (71% vs. 96%, $p=0.12$; unadjusted OR 0.22, 95% CI 0.04 – 1.22) or any impairment (57% vs. 72%, $p=0.29$; unadjusted OR 0.52, 95% CI 0.15 – 1.77) between children who received high-dose caffeine compared to controls on univariate analysis. Adjustment for social risk, birth weight, and growth restriction of the head at birth produced similar odds ratios for delay (OR 0.36, 95% CI 0.03 – 4.46, p=0.43) and impairment (OR 0.74, 95% CI 0.14 – 3.95, p=0.72) in children who received high-dose caffeine.

Discussion

This study reports the five-year neurodevelopmental and socioemotional outcomes of two groups of VPT children who were enrolled in a randomized trial of high versus standard loading dose of caffeine citrate during the first 24 hours of life in the NICU.[7] Despite the increased prevalence of cerebellar hemorrhage in infants randomized to the high-dose caffeine group, there was no clear association between high-dose caffeine administration in the neonatal period and subsequent neurodevelopmental and socioemotional outcomes at age five years. Importantly, both the high- and standard-dose caffeine groups performed poorly on measures of cognitive, language, and motor function, with standardized scores around 0.5 to 1.5 SD below the normative mean. This finding is consistent with prior reports of neurodevelopmental outcomes in VPT children.[18, 19] Also consistent with existing studies, 11–28% of children in this cohort had socioemotional impairments.[20]

Follow-up of this cohort to early school age was vital due to the disproportionate rate of cerebellar hemorrhage in infants randomized to early, high-dose caffeine in the initial trial and ongoing research regarding the optimal dose and timing of caffeine.[21, 22] Existing studies have shown that children born prematurely with severe cerebellar hemorrhage before term-equivalent age have a higher likelihood of longer-term neurologic abnormalities, including hypertonia and hyerreflexia, and that cerebellar hemorrhage is associated with adverse neurodevelopmental outcomes.[23, 24] Previous work in this cohort has shown that infants who received high-dose caffeine exhibited increased tone and more deviant neurologic signs on standardized neurobehavioral assessment at term-equivalent age,[7] a finding that we attributed to the increased incidence of cerebellar hemorrhage in the high-dose group.[24] We did not detect differences in neurodevelopmental and socioemotional outcomes at five years of age. Notably, while others have shown that the presence of *severe*

cerebellar injury is linked with neurodevelopmental impairment, the majority of cerebellar lesions in this cohort were focal punctate lesions.[24]

Although we did not find clear evidence of neuroprotection or neurotoxicity from early neonatal high-dose caffeine citrate administration on early school-age developmental outcomes, the findings of this study should be interpreted with caution. Given the size of the pilot trial in combination with sample attrition to follow-up, it is likely that the follow-up phase of this study was underpowered to detect small-medium effect sizes in outcome measures. This study was designed to be a pilot randomized trial focused on term-equivalent age magnetic resonance imaging and was not designed to account for sample attrition over time (rate: 24%), an inherent difficulty in conducting longitudinal research. Considering this limitation, we must continue to caution against the utilization of early, high loading doses of caffeine citrate given the higher rate of cerebellar hemorrhage detected on term-equivalent magnetic resonance imaging in this cohort and outstanding questions regarding the safety of prophylactic, standard-dose caffeine.[7,25]

Given the limited power of this follow-up study, we cannot exclude that neonatal caffeine dosage may be related to individual trajectories of development rather than cross-sectional outcomes. An additional limitation of the current study is enrollment of infants from a single NICU with unit-specific practices that may limit the generalizability of our five-year outcome findings. Importantly, randomization occurred over a decade ago, prior to many practice changes in neonatology including more conservative utilization of invasive mechanical ventilation and surfactant, pharmacotherapy for patent ductus arteriosus, and corticosteroids for the prevention and treatment of bronchopulmonary dysplasia. Despite these limitations, this study highlights the feasibility of long-term follow-up for VPT infants enrolled in pilot clinical trials early in life, as well as the importance of early and continued developmental surveillance to identify VPT infants at risk for neurodevelopmental and socioemotional problems that persist into school age.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1 –

Perinatal Factors and Demographics

	High-dose N=21	Standard-dose N=25	P value
Maternal variables			
Race			0.50
African American, n (%)	7 (33)	12 (48)	
White, n (%)	12 (57)	11 (44)	
Asian, n (%)	1 (5)	2 (10)	
Hispanic, n (%)	1 (5)	0	
Maternal age, years	30.8 ± 7.6	27.2 ± 6.8	0.10
High school graduate, n (%)	20 (95)	23 (92)	1
Private insurance, n (%)	14 (67)	5 (20)	0.01
Single parent household, n (%)	2 (10)	6 (24)	0.25
Social Risk Index Score	1.0 ± 1.3	1.8 ± 1.4	0.04
Income-to-needs ratio	2.7 ± 2.3	1.7 ± 1.6	0.08
Family dysfunction score	1.4 ± 0.5	1.5 ± 0.4	0.45
Alcohol use, n (%)	0	4 (16)	0.11
Illicit drug use, n (%)	0	1 (4)	1
Antenatal steroids, n (%)	18 (86)	18 (72)	0.31
Chorioamnionitis, n (%)	8 (38)	12 (48)	0.56
Vaginal delivery, n (%)	7 (33)	7 (28)	0.76
Infant variables			
Gestational age at birth, weeks	26.1 ± 2.1	27.1 ± 1.9	0.11
Birth weight, grams	817 ± 230	995 ± 250	0.02
Growth restriction (weight z-score < −2 SD), n (%)	3 (14)	1 (4)	0.32
Growth restriction (OFC z-score < −2 SD), n (%)	4 (19)	0	0.04
Male sex, n (%)	10 (48)	11 (44)	1
CRIB score	5.0 ± 4.4	3.4 ± 3.3	0.17

OFC, occipitofrontal circumference

Values represent mean ± standard deviation unless otherwise indicated

Table 2 –

Clinical characteristics

	High-dose N=21	Standard-dose N=25	P value
Exogenous surfactant therapy, n (%)	21 (100)	25 (100)	1
Inotrope, n (%)	2 (10)	7 (28)	0.15
Ventilator days, median (interquartile range)	5 (1–36)	3 (1–24)	0.40
Dexamethasone, n (%)	2 (10)	4 (16)	0.67
Hydrocortisone, n (%)	7 (33)	5 (20)	0.34
Oxygen requirement at 36 weeks postmenstrual age, n (%)	14 (67)	14 (56)	0.55
Patent ductus arteriosus requiring treatment, n (%)	10 (48)	12 (48)	1
Necrotizing enterocolitis, n (%)	2 (10)	3 (12)	1
Retinopathy of prematurity ≥ grade 3, n (%)	2 (10)	3 (12)	1

Table 3 –

Brain Injury

	High-dose N=21	Standard-dose N=25	P value
Any brain injury, n (%)	9 (43)	10 (40)	0.85
Any intraventricular hemorrhage, n (%)	5 (24)	10 (40)	0.35
Grade III/IV intraventricular hemorrhage, n (%)	0	4 (16)	0.11
Cystic periventricular leukomalacia, n (%)	1 (5)	2 (8)	1
White matter injury, n (%)[1]	3 (14)	2 (8)	0.77
Cortical gray matter injury, n (%)[1]	0	0	1
Deep gray matter injury, n (%)[1]	0	2 (8)	0.49
Cerebellar hemorrhage, n (%)[1]	7 (33)	2 (8)	0.06
Focal unilateral	1 (5)	0	
Focal bilateral	3 (14)	1 (4)	
Extensive unilateral	2 (10)	0	
Extensive bilateral	1 (5)	1 (4)	

[1]Diagnoses based on magnetic resonance images at term-equivalent age

Table 4 –

Developmental Outcomes at Two Years of Age

	High-dose N=19	Standard-dose N=23	P value
Bayley-III Cognitive score	86.1 ± 12.8	88.0 ± 8.4	0.55
Cognitive delay (Mental Development Index < 85), n (%)	6 (32)	5 (22)	0.50
Cognitive impairment (Mental Development Index < 70), n (%)	2 (11)	0	0.20
Bayley-III Composite Language score	92.6 ± 13.7	88.9 ± 11.7	0.36
Language delay (Language Scale score < 85), n (%)	4 (21)	8 (35)	0.49
Language impairment (Language Scale score < 70), n (%)	1	1	1
Bayley-III Composite Motor score	85.7 ± 10.4	85.9 ± 10.4	0.96
Motor delay (Psychomotor Development Index < 85), n (%)	7 (37)	6 (26)	0.38
Motor impairment (Psychomotor Development Index < 70), n (%)	2 (11)	2 (9)	1
Cerebral palsy, n (%)	3 (16)	2 (9)	0.32
Blindness	0	0	N/A
Deafness	0	0	N/A

Table 5 –

Five-Year Developmental Outcomes

	High-dose	Standard-dose	P value
WPPSI-III, m ± SD	**N=21**	**N=25**	
General cognition score	90.4 ± 15.4	87.0 ± 11.2	0.39
Verbal cognition score	89.4 ± 16.3	86.7 ± 12.4	0.54
Non-verbal cognition score	96.0 ± 16.8	91.7 ± 16.1	0.39
General cognitive delay[1], n (%)	7 (33)	11 (44)	0.55
General cognitive impairment[2], n (%)	2 (10)	1 (4)	0.59
CELF-P2, m ± SD	**N=21**	**N=25**	
Language score	89.0 ± 19.4	87.6 ± 14.6	0.79
Language delay[1], n (%)	8 (38)	9 (36)	1
Language impairment[2], n (%)	4 (19)	3 (12)	0.69
MABC-2, m ± SD	**N=20**	**N=24**	
Total Motor score	5.4 ± 3.7	4.8 ± 2.8	0.53
Motor delay[3], n (%)	13 (65)	20 (83)	0.16
Motor impairment[4], n (%)	12 (60)	15 (63)	1
Shape School, m ± SD	**N=17**	**N=20**	
Cognitive inhibition efficiency	0.72 ± 0.49	0.54 ± 0.30	0.18
Failed cognitive inhibition condition, n (%)	1 (6)	2 (10)	1
Set shifting efficiency	0.13 ± 0.29	0.13 ± 0.22	0.97
Failed set shifting condition, n (%)	4 (24)	4 (20)	1
Inhibition-shifting switch efficiency	0.25 ± 0.31	0.22 ± 0.29	0.75
Failed inhibition-shifting switch condition, n (%)	4 (24)	5 (25)	1
CBCL/1.5–5, m ± SD	**N=18**	**N=24**	
Internalizing *t*-score	45.8 ± 13.5	50.5 ± 16.7	0.33
Internalizing problems[5], n (%)	2 (11)	5 (21)	0.45
Externalizing *t*-score	45.0 ± 13.7	49.9 ± 17.2	0.33
Externalizing problems[5], n (%)	2 (11)	5 (21)	0.45
SRS-2, m ± SD	**N=21**	**N=25**	
Social Communication and Interaction *t*-score	53.2 ± 11.4	56.2 ± 11.6	0.39
Restricted Interests and Repetitive Behavior *t*-score	54.9 ± 15.3	57.1 ± 13.5	0.60
High levels of autistic traits[5], n (%)	5 (24)	7 (28)	0.68

[1] Delay defined as a standardized score < 85

[2] Impairment defined as a standardized score < 70

[3] Delay defined as a standardized score ≤ 15th percentile or unable to complete

[4] Impairment defined as a standardized score ≤ 5th percentile or unable to complete

[5] Defined as composite *t*-score > 60