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The Influence of Dosage and Timing of Caffeine Administration on Neurodevelopmental Outcome of Very Preterm Infants

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Abstract

Objective: To analyze starting time (early versus late) and duration of caffeine treatment and its possible influence on neurodevelopmental (ND) outcome in very preterm infants.

Hypothesis: Early initiation of caffeine treatment with longer duration of treatment may significantly improve ND outcome in very preterm infants.

Design: Retrospective cohort study.

Setting: Level III Neonatal Intensive care Unit (NICU) and out-patient NICU follow-up clinic of an academic medical center in New York City.

Participants: A total of 146 inborn infants with gestational ages (GA) of 23-32 weeks who received caffeine treatment were included in this study with the following exclusion criteria: incomplete clinical data, insufficient ND follow-up and transfer of infants to other facilities.

Interventions: Information on the administration of Caffeine Citrate injection USP and Caffeine Citrate oral solution (20 mg/ml equivalent to 10 mg caffeine base) including duration of treatment were obtained from individual chart reviews.

Primary outcome measure: Normal and adverse (mild/moderate, severe) ND outcome.

Results: Duration and starting point (early versus late) of caffeine treatment were not associated with ND outcome; adjusted for GA, head ultrasound (HUS) results and gender. The only significant predictor of ND outcome was GA.

Conclusion: Gestational age (GA) seems to have more of an influence on ND outcome than caffeine citrate treatment regardless of duration (i.e., dose) and onset (early versus late) of such treatment.

Keywords: Caffeine treatment; Prematurity; Neurodevelopmental outcome

Strengths and Limitations of this Study

This is the first study analyzing the duration and timing of caffeine therapy in very preterm infants and its possible impact on neurodevelopmental (ND) outcome.

It is a single center study with homogenous patient population therefore the results may not be applicable for patients of different races.

It includes relatively small number of patients and does not include long term ND outcomes.

Introduction

Caffeine citrate is one of the most frequently prescribed medications in preterm infants for prevention and/or treatment of apnea of prematurity (AOP), which may affect more than 80% of infants with birth weight (BW) <1000 g and 26% of neonates with BW 1000 g -2500 g. [1,2] Methylxanthines (aminophylline, theophylline and caffeine) reduce the frequency of AOPs as respiratory stimulants and have been used for more than 30 years in the neonatal intensive care unit (NICU) [3].

Caffeine is a selective (on the A2A receptors) and non-selective (on the A1 receptors) adenosine antagonist [4,5]. Its effects include improved lung compliance, minute ventilation, respiratory muscle contractility, increased sensitivity to CO_2, enhanced catecholamine

activity and diuresis through tubular adenosine receptors, and decreased airway resistance [6,7]. Caffeine is also a central nervous system (CNS) stimulant. It influences the action of several neurotransmitters (i.e., dopamine, serotonin, glutamine, gamma-aminobutyric acid) [8]. By enhancing peripheral chemoreceptor activity, caffeine can terminate apnea. Other indications of caffeine use in neonatal intensive care include facilitation of weaning off of mechanical ventilation and use in patients with bronchopulmonary dysplasia (BPD) to improve pulmonary mechanics. Clinical outcome studies examining caffeine therapy in preterm infants have shown decreased incidence of BPD, death, and patent ductus arteriosus (PDA) requiring treatment, as well as reduced length of respiratory support [6,7,9-11].

Schmidt et al. reported improved neurodevelopmental (ND) outcome including decreased incidence of cerebral palsy (CP) and cognitive delay following caffeine treatment, but this effect does not seem to be associated with long term benefits [12]. As one of the main determinants of ND outcome, it is unclear how head ultrasound (HUS) results are distributed in the two groups of patients (caffeine treatment compared to no caffeine treatment) based on their severity in this report [13]. We sought in the present study to analyze timing and duration of caffeine treatment and its potential influence on ND outcome in infants with various morbidities of prematurity.

Patient population

This retrospective cohort study was performed at a single level III Neonatal Intensive Care Unit (NICU) at an inner city academic medical center. All infants were inborn between January 2008 and December 2011. Study entry criteria included gestational age (GA) ≤ 32 weeks, regardless of BW, caffeine treatment, and compliance with ND follow-up. BW ranged from 545 to 1,830 grams. Exclusion criteria included incomplete charts/medical data and permanent transfer to other institutions. Clinical data were obtained by individual chart reviews. All infants' mothers had prenatal care and received prenatal steroid treatment. All but 2 infants were African-American. The State University of New York Downstate Medical Center Institutional Review Board approved this study.

Methods

We reviewed the medical record of all patients including demographics, morbidities and caffeine treatment. We obtained information on the administration of Caffeine Citrate injection USP and Caffeine Citrate oral solution (20 mg/ml equivalent to 10 mg caffeine base), including duration and total dose of treatment. Caffeine citrate therapy was initiated based on GA at the discretion of the attending neonatologist, either using caffeine for prevention or treatment of AOP and/or facilitation of weaning off mechanical ventilation. Treatment was considered early onset if initiated from the first two days of life and late when it was started later on or after the third day of life. Caffeine citrate loading dose was given as 20 mg/kg weight; maintenance therapy was continued with 5 mg/kg weight per day. Termination of caffeine treatment (i.e., length of therapy) was also determined by the attending neonatologist either by discontinuing the drug or tapering the dose gradually. Caffeine level determinations were not done since previous research indicates that routine measurement of serum levels is not necessary since plasma level and its correlation with clinical efficacy is uncertain [13]. Rather, the effect of caffeine treatment was monitored according to its clinical impact. We

compared the duration and the onset (early versus late) caffeine administration with regard to ND outcome.

GA was determined by dating prenatal ultrasound and/or by the last menstrual period. Respiratory distress syndrome (RDS) was defined by presence of clinical symptoms, radiographic abnormalities, and need for respiratory support with or without intubation and/or surfactant replacement therapy. BPD was defined in this group of patients (G ≤ 32 weeks) as requiring supplemental O_2 therapy and/or respiratory support by 36 weeks of postmenstrual age. Prolonged mechanical ventilation (PMV) was defined as need of mechanical ventilation ≥ 7 days. PDA diagnosis was established with pediatric cardiologist's consultation and performing echocardiogram. All infants with PDA were treated either conservatively or surgically.

Infection was defined by clinical symptoms and/or presence of positive cultures and treatment with antibiotics for 7 or more days. Retinopathy of prematurity (ROP) was diagnosed by a pediatric ophthalmologist and included stages 1-3 in this cohort of patients. Serial HUS studies were routinely performed according to Papile [14] as part of standard of care and interpreted by a pediatric radiologist. All infants had their first HUS studies within the first seven days of life. HUS studies were repeated on a weekly basis, with the last HUS taking place just prior to discharge. This regimen was modified on an individual basis according to HUS findings. Necrotizing enterocolitis (NEC) was diagnosed by attending neonatologists and pediatric surgeons including all Bell's stages (stages I-III) [15] managed either conservatively or surgically.

Assessment of ND outcome was performed in all patients uniformly in an outpatient setting at 18-22 months of (corrected) age as published earlier [16,17] which included documenting anthropometric data (weight, height, head circumference and percentile values), physical exam and standard neurological exam and the Denver II Developmental Screening Test (DDST). Cognitive/visual -fine motor and speech and language evaluation were made using the Cognitive Adaptive test/Clinical Linguistic and Auditory Milestone Scale (CAT/CLAMS) [18]. Developmental quotients were calculated for both chronological and corrected age. Hearing tests were performed in each patient by otoacoustic emission (OE) and confirmed by audiometry with assessment by a pediatric otolaryngologist if necessary. Ophthalmologic assessments were done before discharge if indicated; further follow-up was determined by pediatric ophthalmologist.

Normal ND outcomes were defined as 1) normal development including normal neurologic examination; and 2) age appropriate developmental milestones. Adverse ND outcome included developmental delay in one or more domains of neurodevelopment, CP with or without sensorineural (i.e., visual/hearing) abnormalities. CP was defined as a group of non-progressive but often changing motor impairments resulting from lesions or anomalies of the brain during its early stages of development [19]. Hearing loss was defined as uni/bilateral hearing impairment requiring amplification. Severe visual impairment was defined as uni/bilateral blindness (i.e., corrected visual acuity less than 20/200) [12]. We operationally defined severe global ND delay as significant delay in more than two domains of neurodevelopment without CP. Severe ND outcome included CP with or without severe global ND delay.

Statistical analysis

Chi-square and t-tests were used to compare the two groups (early versus late caffeine treatment). Multiple logistic regression was used to

test the association between treatment and adverse ND outcome, adjusted for GA, duration of treatment and gender. P<0.05 was considered statistically significant. All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary NC).

Results

During the study period, 146 infants were included (78 males and 68 females). Table 1 includes patient data and clinical variables in the early and late caffeine treatment groups. No significant differences were found between the two groups with respect to all reported variables.

Characteristics	Early Caffeine Treatment (N = 100)	Late Caffeine Treatment (N = 46)	p
Birth weight (g)	545-1,725 (mean = 1,118)	565-1,830 (mean = 1,104)	0.8
Gestational age (weeks)	24-32 (mean = 28.02)	23-32 (mean = 28.17)	0.69
Male gender	56 (56%)	22 (48%)	0.37
Multiple birth	18 (18%)	5 (11%)	0.27
Respiratory distress syndrome/ surfactant therapy	99 (99%)	46 (100%)	1
Prolonged mechanical ventilation	48 (48%)	22 (48%)	0.86
Bronchopulmonary dysplasia	35 (35%)	13 (28%)	0.45
Patent ductus arteriosus	32 (32%)	16 (35%)	0.85
Sepsis	38 (38%)	18 (39%)	0.86
Retinopathy of prematurity	18 (18%)	10 (22%)	1
Necrotizing enterocolitis	5 (5%)	1 (2%)	0.67
Abnormal head ultrasound	13 (13%)	6 (13%)	0.86

Table 1: Patient data and morbidities.

Abnormal HUS results in the early treatment group included grade II-III intraventricular hemorrhage (IVH) (n = 1), grade III IVH (n = 7), grade III IVH with ventriculomegaly and periventricular leukomalacia (n = 1), grade IV IVH (n = 1), and ventriculomegaly without IVH (n = 3). In the late treatment group, one infant had grade II-III IVH and five had grade III IVH.

There were no other abnormalities seen (i.e., Grade I IVH, congenital brain anomalies). Adverse ND outcome was found in all infants with abnormal HUS results, and in 68 out of 127 (53%) infants with normal HUS.

In the early treatment group, 60 out of 100 (60%) infants had adverse ND outcome. This was comprised of 48 infants with mild/moderate impairment and 12 infants with severe disability, including four with cerebral palsy (CP), two with CP and severe global delay, and six with severe global delay without CP. In the late treatment group, 26 out of 46 (57%) of the infants were diagnosed with adverse ND outcomes. This included 19 patients with mild/moderate impairment, and seven with severe disability (one infant with CP and six with severe global delay without CP). All 19 infants with abnormal HUS

results had adverse ND outcome, while 68 out of 126 (53%) infants with negative HUS results had adverse ND outcome. There were no infants with hearing loss or severe visual impairments found in this study.

Mean duration of caffeine treatment for the early treatment group was 38 days (SD = 16.6 days). In the late treatment group, it was 33.7 days (SD = 15.7). The difference between the two groups was not statistically significant (p = 0.14).

Odds Ratio Estimates				
Effect	OR	95% Confidence Limits		p
Early vs late treatment	1.157	0.483	2.77	0.7436
GA	0.572	0.403	0.811	0.0017
Abnormal HUS	12.534	0.715	219.749	0.0836
Treatment duration	1.004	0.959	1.051	0.866
Gender	1.576	0.705	3.522	0.2674

Table 2: Odds Ratios (OR) for Onset of Caffeine Citrate Treatment Adjusted for Gestational Age (GA), Duration of Treatment, Abnormal Head Ultrasound (HUS) Results, and Gender.

Table 2 illustrates the odds ratio for onset and duration of caffeine citrate treatment, GA, abnormal HUS results, and gender as potential predictors of ND outcome. Onset of treatment was not significantly associated with ND outcome, after adjusting for GA, HUS results, duration and gender. The only significant predictor of ND outcome was the degree of prematurity (i.e., GA).

Discussion

Several authors published studies including animal data [20-27] and data from human adults [28] regarding the mechanism of possible neuroprotective effects and side effects of caffeine. The role of caffeine in CNS function and the likely mechanisms of neuroprotection by caffeine are mediated by the interaction between caffeine and the adenosine receptors [29]. Animal studies show that caffeine treatment decreases apoptosis [21], increases dendritic length in the limbic system [22], attenuates hippocampal injury [30], and blocks adenosine action on oligodendrocytes [27]. Furthermore, caffeine decreases hypomyelination in hypoxia-induced periventricular white matter injury which is the major cause of CP in preterm infants [26].

Studies in adults suggest that caffeine has a positive effect on vigilance, mood and arousal, increases cortical activity, and as a psychostimulant, appears to reduce cognitive decline [27]. It has also been shown that brain diffusion changes on MRI studies in preterm infants treated with caffeine are consistent with improved brain microstructural development [31].

The improved ND outcome of caffeine-treated preterm infants [9-12] was not seen when those infants were reassessed at five years of age [32].

When examining the desired effects of caffeine treatment, undesirable side effects or lack of benefits must also be considered [32-37]. Animal studies have shown that caffeine does not influence brain excitotoxicity [23]. Caffeine also causes adenosine receptor-related behavioral dysfunction [38] and may induce capillary leaks in

the CNS contributing to IVH [27]. In rabbits, caffeine alone does not show neuroprotective effects through its vascular effect [25].

Pharmacologic effects of caffeine are related to the degree of prematurity which influences its metabolism (liver function) and elimination (renal function). Nutritional factors including parenteral nutrition and breastfeeding also modify the effects of caffeine [34-37]. Since caffeine increases metabolic rate and O_2 consumption, it causes slower weight [38,39]. Other side effects of caffeine include tachycardia, increased urine output with increased calcium loss, agitation, irritability, tremor and seizure activity [38,40]. Agitation and irritability caused by caffeine may influence sleep states, especially active sleep or REM sleep. This in turn may adversely affect CNS developmental processes such as synaptogenesis, neurogenesis, and synaptic plasticity, which occur mainly during REM sleep [41-43].

There is a paucity of literature and little agreement among neonatologists regarding the duration of caffeine treatment and its clinical relevance in preterm infants. One study indicated that extended length of caffeine therapy may decrease intermittent hypoxia in preterm infants [44]. This may be beneficial regarding ND outcome.

We found that the duration of caffeine treatment did not seem to be associated with ND outcome. This may be explained by the fact that the degree of prematurity, with its concomitant and often multiple morbidities, has a stronger influence on ND outcome than the duration of caffeine treatment. Similarly, we did not find significant difference in ND outcome regarding the onset of treatment. Indeed, some authors suggest to start early caffeine treatment only in ventilator-dependent infants [45]. Inter-individual variability to caffeine response may be further explained by adenosine receptor gene polymorphism [46].

In summary, we did not find convincing evidence that the duration and timing of caffeine therapy would influence ND outcome in very preterm infants. The effect of caffeine may be offset by multiple morbidities related to prematurity, nutritional factors, as well as interaction from other pharmacological treatment. Since we previously reported data on patient compliance regarding ND follow-up, we believe that the data of this study are representative of our preterm infant patient population [47].

The strengths of this study are the analysis of the duration of caffeine treatment and its possible effect on ND outcome which have not been previously been reported. This single-center study includes a relatively small number of patients with homogenous (African-American) ethnicity.

The effects of caffeine in the developing preterm infant brain are still controversial [48].

Larger prospective studies and multi-center randomized controlled trials are necessary to clarify the side effects, safety issues, and the precise mechanism of action of caffeine treatment and its effect on the preterm developing brain and late ND outcome.

Authors' Contributions

All authors (Perenyi, Katz, Parris and Stefanov) were involved with all criteria recommended for authorship by the ICMJE: 1) substantial contributions to either the conception and design of the study or the acquisition, analysis or interpretation of the data; 2) drafting or revising the paper critically for important intellectual content; 3) final approval of the version to be published; and 4) agreement to be accountable for all aspects of the study in ensuring that questions related to the accuracy or integrity of the paper.

Additionally, specific contributions include the following:

Dr. Agnes Perenyi: involvement with in-patient (NICU) and out-patient ND follow-up clinic, data collection from chart reviews, and critical write-up of paper.

Dr. Joanne Katz: involvement with out-patient ND follow-up clinic, analysis of data, and critical write-up and submission of paper.

Dr. Rudolph Parris: involvement in research design, analysis of data and critical write-up of the paper.

Dr. Dimitre Stefanov: involvement in research design, analysis of data and critical write-up of the paper.

Ethics approval

This study was approved by the State University of New York Downstate Medical Center Institutional Review Board.

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