Effect Of Early Caffeine Therapy On Weight Gain In Very Preterm Infants

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Abstract

Background: Premature infants were observed to have poor weight gain for the first 3 weeks after initiating caffeine therapy. The practical impact of this adverse effect in the era of prophylactic (early) caffeine therapy in very preterm infants have not been analyzed well.

Methods: A retrospective cohort study was conducted including preterm infants born at < 31 weeks gestation between June 2013 and June 2016. Infants were divided into 2 groups based on the timing of caffeine initiation: less than the 48 hours after birth (early) and 48 or more hours after birth (late). The outcome was weight in grams at the end of 3rd week of life. Independent t-test and repeated-measures analysis of covariance (ANCOVA) were used for analysis.

Results: Thirty-nine (84.6%) out of 46 infants born < 31 weeks gestation with a birth weight < 1250 grams were included in the study. Of the 39 infants, 22 received early caffeine therapy and 17 received late caffeine therapy. On comparing the weight at 3 weeks of age between the two groups, the early caffeine group had a significantly better weight gain with a mean weight at 3 weeks being 1140 grams vs 985 grams (p=0.03). Conclusion: In very preterm infants, early caffeine therapy was associated with better weight gain in the first 3 weeks of life.

Background

Caffeine citrate is a medication used for apnea of prematurity in neonates. (1,2) Caffeine therapy has been shown to reduce the rate of bronchopulmonary dysplasia in infants with very low birth weight in the Caffeine for Apnea of Prematurity (CAP) trial. Authors of the same trial did a long term follow up and showed improved survival without neurodevelopmental impairments at the corrected ages of 18 to 21 months and five years of age. (3, 4). They did a subgroup analysis and found that infants whose treatment with caffeine started at or before three days of age had a shorter duration of respiratory support than those started on treatment between 4 and ten days of age (5). These findings of the CAP trial led to the practice of prophylactic caffeine therapy (less than three days) in preterm infants less than 1250 grams in many NICUs in the US.

Several studies have reported the effects of early use of caffeine and neonatal outcomes correlating the findings of the post hoc analysis of the CAP trial. (6,7). Lodha et al. found reduction in the rates of death or bronchopulmonary dysplasia and reduced need for treatment of patent ductus arteriosus without increasing the risk of necrotizing enterocolitis (NEC) associated with early (prophylactic) caffeine (< 3 days) use in very preterm infants. (8). Caffeine prophylaxis increased the success of extubation (9) and reduced the mean duration of mechanical ventilation in very preterm infants (7, 10).

Caffeine therapy in neonates can cause adverse effects that include increased heart rate, jitteriness, irritability, and seizures. (11) Schmidt et al. reported that premature infant had
poor weight gain for the first three weeks after initiating caffeine therapy. However, similar studies that followed the CAP trial did not investigate the effect of prophylactic caffeine therapy on weight gain as an outcome. We have explored this effect in our patient population that has a unique ethnic/racial background.

**Objective**

The objective of our study was to compare the weight gain pattern in very preterm neonates who were initiated on prophylactic caffeine therapy less than 48 hours of birth, and those started after 48 hours of delivery in the first three weeks of life.

**Methods**

Design and Participants:

We conducted a retrospective cohort study in a level III NICU with a highly dense population of Afro-Americans in Brooklyn, New York.

Inclusion Criteria:

All infants born at a gestational age < 31 weeks and birth weight < 1250 grams admitted to the NICU and started on mechanical ventilation within 6 hours of birth from July 1, 2013, to June 30, 2016.

Exclusion Criteria:

1. Infants born with major congenital anomalies
2. Infants who died within 72 hours of birth

Ethical Approval and Informed Consent:

We obtained a waiver for an informed parent consent from the Institutional Review Board of Brookdale Hospital Medical Center as this was a retrospective study using routinely collected patient data. We kept the data with identifiers in an encrypted and computer password-protected datasheet. We de-identified the data before statistical analyses. Only the principal investigator and the senior investigator had access to the datasheet with identifiers.

Data Collection:

We collected the data from the Electronic medical record (EPIC). All preterm infants (<31 weeks) admitted to our NICU were included in the study, subject to the inclusion criteria. We identified eligible preterm infants who received caffeine from the EMR. We defined the day of birth as the day of life 1. We divided the patients into the following two groups based on the
timing of caffeine initiation: early (neonates who received caffeine < 48 hours after birth) and late (neonates who received caffeine starting ≥ 48 hours after delivery). The usual practice in our unit is to administer a loading dose of 20 mg/kg of caffeine, with a daily maintenance dose of 5 mg/kg initiated 24 hours after the loading dose.

We collected the data on duration of mechanical ventilation in days and weight in grams at the end of 1st, second and third weeks of life (7th day, 14th day and 21st day respectively) by chart review of each neonate from the Electronic medical records. Any change in the maintenance dose of caffeine in the intervening period was also collected.

Outcome Definition:

The outcome was defined as the weight change in grams at the end of the third week after birth compared to birth weight.

Statistical Analysis:

Data was collected using a password protected excel spreadsheet. We used descriptive statistics with frequencies and percentages for categorical variables and means and standard deviation for continuous variables. We analyzed the relationship between the day of initiation of caffeine therapy and weight gain in the first three weeks of life with SPSS statistical software. We used repeated measures of ANCOVA to analyze the outcome. A P value of less than 0.05 in the analysis was considered statistically significant.

Results

Forty-six preterm infants were born less than 31 weeks gestational age with a birth weight less than 1250 grams in the study period. Of those 46 infants, we excluded 7 (15.4%) because of death in less than three days. We included 39(84.6%) infants in the study. 22 out of 39 infants received the first dose of caffeine in less than 48 hours of birth (early caffeine group), and 17 infants received their first dose of caffeine more than 48 hours (late caffeine group) see figure 1. We compared the demographic characteristics of the infants included in the study between the groups (Table 1). There was no significant difference between the groups except gestational age, which we controlled during the outcome analysis.

We compared the weight change between the two groups at three time points (days 7, 14 and 21) by repeated-measures analysis of covariance with gestational age as the covariate (see figure 2). The weight gain was better in the early caffeine group at day 21 of life (p= 0.03). This statistically significant difference had a substantial effect size (eta^2 partial = 0.76) (Table 2).
We did a post hoc power analysis with various options. In all scenarios, the power was >0.99. Even though our sample size was quite small, our findings retained significance because the effect size (eta^2 partial) in our analysis was high.

**Discussion**

Reasonable amount of evidence exists in the current literature supporting the use of prophylactic caffeine therapy in very preterm infants to reduce the risks of critical short-term morbidities such as bronchopulmonary dysplasia (BPD), severe retinopathy of prematurity in addition to decreasing the incidence of cerebral palsy and cognitive delay at 18 months, and improving gross motor function at 5 years (1.3.4). However, caffeine had the potential to cause growth impairment in the first three weeks after the start of therapy (1). In the current era of prophylactic caffeine therapy, the impact of this effect needed investigation. The ideal study design for testing such a hypothesis would be to include extremely preterm infants without any caffeine therapy for the first three weeks of life as a control group. However, constructing such a study design will have practical/ethical challenges since prophylactic caffeine therapy in extremely preterm infants is a routine clinical practice in most NICUs in the United States including ours for bronchopulmonary dysplasia prevention.

In our NICU, the timing of initiation of caffeine therapy was dependent on the physician preference. The difference in the time of treatment initiation allowed us to compare the weight gain in two groups of very preterm infants differing in the introduction of caffeine therapy. We found that the weight gain was optimal in both (early and late caffeine) groups at three weeks of life. Our findings were contrary to the

**TABLE 1: CHARACTERISTICS OF INFANTS INCLUDED IN THE STUDY**

**TABLE 2: COMPARISON OF WEIGHT GAIN AT DAY 21 OF LIFE BETWEEN TWO STUDY GROUPS**

results observed in the CAP trial. The weight gain was significantly better with the early caffeine group. The association of early caffeine with better weight gain was strong enough to be ignored.

Nutritional management of very preterm infants has improved significantly in the last decade. Optimal use of total parenteral nutrition, fortified human milk, higher-calorie preterm formula, very early use of trophic feeds and aggressive enteral feed advancement have all contributed to
the success in preterm nutrition. The standard practice in our unit is to start the very preterm infants on trophic feeds on day 1, along with total parenteral nutrition. The calorie target averages 90 kcal/kg/day over the initial three weeks of life accompanied by enteral feed advancement as tolerated.

The diuretic effect and increase in metabolic rate caused by caffeine were considered as the reasons for poor weight gain associated with caffeine therapy. (12) However, there is growing knowledge on several pharmacological effects of caffeine on preterm neonatal physiology which could explain the results of our study.

Caffeine prevents apnea by increasing the sensitivity to carbon dioxide, increasing diaphragmatic contractility, decreasing muscle fatigability, and brings about diuresis via tubular adenosine A1 receptors. (11, 12). The benefit of reduction in bronchopulmonary dysplasia observed with early caffeine use has been hypothesized to be secondary to a decrease in the mean duration of mechanical ventilation by enhancing the success of extubation.

Mechanical ventilation in very preterm infants without paralysis is not an actual low metabolic state. The inflammatory cascade produced by invasive ventilation creates additional metabolic demands, which could be higher than the increased metabolic rate due to caffeine therapy. The success of early extubation could enhance feed tolerance and aid in faster feed advancement towards full enteral feeds. The advancements in the nutritional management of very preterm infant in the last decade could be a contributory factor for our findings. It may mask any slowing of weight gain caused by caffeine. We believe that the association between caffeine therapy and poor weight gain observed in the earlier studies (1) may not be relevant in the current NICU practice because we observed weight gain in both the groups irrespective of the timing of caffeine therapy. However early caffeine group had a better weight gain of the two groups.

Controversy surrounds the metabolic effects of caffeine in adult medicine. The literature on the results of caffeine on carbohydrate and lipid metabolism concerning preterm newborn physiology is very minimal. Caffeine causes hyperglycemia by decreasing insulin sensitivity. (13) Caffeine increases cortisol secretion and affects lipid metabolism. (14) These effects could lead to weight gain. Our study population was predominantly an African American population with a high incidence of childhood obesity. The literature in adult medicine had shown that the
effects of caffeine might vary with genetic variations. (15) Similarly, genetic factors could play a role in the weight gain observed in our study.

In the absence of any other proven therapy to prevent bronchopulmonary dysplasia, prophylactic caffeine therapy occupies a vital role in the management of very preterm infants. Prospective trials should relook at the weight loss and growth impairment considered to be associated with caffeine therapy which is the most important implication of this study.

The important limitations of our study are that we did not statistically compare the caloric intake of the infants in the two groups. A retrospective study with predominantly Afro-American population raises doubts about the generalizability of the study results.

We did not include the length and head circumference in the outcome variables, both of which are better predictors of growth. Study of the effect of prophylactic caffeine therapy on long term growth (at the time of discharge and beyond) will be helpful to expand our knowledge on long term caffeine therapy.

**Conclusions**

Early (prophylactic) caffeine therapy in very preterm infants was associated with better weight gain in the first three weeks of life.

**Abbreviations**

CAP – Caffeine for apnea of prematurity  
NICU – Neonatal Intensive Care Unit  
NEC – Necrotizing enterocolitis  
ANCOVA- Analysis of Covariance  
EMR- Electronic Medical Record

**Declarations**

Ethics approval and consent to participate:  
We obtained a waiver for an informed parent consent from the Institutional Review Board of Brookdale Hospital Medical Center (IRB reference number: Protocol 16-24) as this was a retrospective study using routinely collected patient data. We kept the data with identifiers in an encrypted and computer password-protected datasheet. We de-identified the data before statistical analyses. Only the principal investigator and the senior investigator had access to the datasheet with identifiers.

Consent to Publish : Not Applicable
Availability of data and materials:

The datasets used and analyzed during the study are available from the corresponding author on reasonable request.

Competing interests: None

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Authors' contributions:

1. SM: Conception of the study, analyses of the data, drafting of the manuscript.
2. FK: Critical review of the proposal, drafting of the manuscript, and critical review.
3. RK: Conception of the study, analyses of the data, drafting of the manuscript, and critical review.
4. All authors have read and approved the manuscript

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Tables
Due to technical limitations, tables are only available as a download in the supplemental files section

Figures
STUDY DESIGN
Figure 2

GRAPH COMPARING THE WEIGHT GAIN PATTERN IN THE FIRST 3 WEEKS OF LIFE BETWEEN THE TWO GROUPS

Supplementary Files

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