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Original Article

Very Early (<2 h) Versus Early (12 h) Administration of Caffeine Citrate for Reducing Need for Mechanical Ventilation within 24 h of Life in Preterm Infants on Continuous Positive Airway Pressure

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Abstract

Background and Objective: In the caffeine for apnea of prematurity (CAP) trial, post hoc analyses have discovered reductions in respiratory and neurologic morbidities associated with earlier caffeine initiation (within 3 days). This study aims to compare the effects of early (<2 h) and late (12 h) initiation of caffeine in preterm neonates on continuous positive airway pressure (CPAP).

Study Design: A total of 36 neonates <32 weeks gestational age were randomized to receive intravenous caffeine citrate (20 mg/kg) before 2 h (early n = 19) or at 12 h of age (late n = 17). This was a pilot randomized controlled trial to determine the power needed to reduce the need for endotracheal intubation by 24 h of age. Other outcomes included the duration of respiratory support, duration of oxygen therapy, need for vasopressors, incidence of intraventricular hemorrhage, patent ductus arteriosus needing treatment, necrotizing enterocolitis, bronchopulmonary dysplasia, retinopathy of prematurity, sepsis, and mortality.

Results: There was no difference in the need for intubation ($P = 0.615$) or vasopressors ($P = 0.455$) by 24 h of age. Statistically significant reduction was noted in the total duration of CPAP support ($P = 0.003$). However, total duration of respiratory support ($P = 0.425$), total duration of mechanical ventilation days ($P = 0.237$), and oxygen days ($P = 0.145$) were favoring early caffeine group, which were not statistically significant. None of the babies in both the groups had apnea of prematurity. There was no difference in other outcomes.

Conclusion: This pilot study demonstrated the feasibility of conducting such a trial in very preterm neonates. We found that early caffeine administration was associated with statistically significant reduction in the duration of non-inWvasive respiratory support. Larger studies are needed to determine whether early caffeine reduces intubation, intraventricular hemorrhage, duration of respiratory support, and related long-term outcomes.

Key words: Airway pressure, Infants, Ventilation

INTRODUCTION

Respiratory distress syndrome can be successfully treated in very preterm infants with nasal continuous positive airway pressure (CPAP) beginning at birth.[1] However, many of these infants will fail CPAP and require endotracheal intubation and surfactant administration to achieve adequate gas exchange.[2,3] Early use of caffeine as a respiratory stimulant represents a potential adjunctive therapy with CPAP to prevent intubation.

In the caffeine for apnea of prematurity (CAP) trial, infants in the caffeine group were able to discontinue positive pressure ventilation approximately 1 week earlier than the placebo group and had a significant reduction in their incidence of bronchopulmonary dysplasia (BPD).[4] The average postnatal age of caffeine initiation in the CAP trial was 3 days. *Post hoc* analyses of the CAP trial,

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and retrospective studies performed by other groups, have discovered reductions in respiratory and neurologic morbidities associated with earlier caffeine initiation.[5]

Few, small, observational studies have investigated the cardiovascular effects of caffeine in the neonate. Some have demonstrated transient decreases in cerebral and intestinal blood flow after a caffeine dose with no change in cardiac output.[6] Others have shown increased blood pressure after a dose of intravenous caffeine.[7,8] It is possible that these cardiovascular effects could be beneficial for early transitional circulation, especially in the premature infant who is prone to hypotension and cardiac dysfunction.

European centers have adopted a technique to administer surfactant during spontaneous breathing while receiving nasal CPAP (minimally invasive surfactant therapy).[9] As part of this protocol, infants are given intravenous caffeine in the 1st h of age.[10] Many centers have adopted the use of early caffeine as soon as infants have intravenous access along with antibiotics and fluids. However, this practice has never been demonstrated to be beneficial in a randomized controlled trial.

Recently, a pilot randomized controlled trial conducted at California comparing caffeine administration at 2 versus 12 h did not find any difference in need for intubation or vasopressors at 12 h of life.[11]

Our center has a range of caffeine initiation from 1 to 24 h of age. We hypothesized that very early caffeine given in the first 2 h after birth to non-intubated preterm infants on nasal CPAP will be associated with a reduction in risk of intubation and inotrope support within the first 24 h of age, compared with caffeine administration at 12 h of age. Given the lack of previously published studies, our objective was to perform a pilot trial to determine the appropriate power for a larger study.

Study Design

This blinded, randomized pilot study was conducted in the Level III neonatal intensive care unit (NICU) at the Lokmanya Tilak Municipal General Hospital in Sion, Mumbai, between February 2018 and July 2018. Consent was obtained for infants within 1 h of birth after the baby was stabilized on CPAP. Any newborn delivered between 26 and $31^{6/7}$ weeks gestational age (GA) by the best obstetric estimates was eligible for inclusion. Exclusion criteria were one or more of the following: (1) Major congenital anomaly including airway anomalies, congenital diaphragmatic hernia, or hydrops, (2) known or a discovered major cardiac defect other than a patent ductus arteriosus (PDA), patent foramen ovale, or small ventricular septal defect, and (3) severe apnea or bradycardia in the first 10 min of age requiring emergent endotracheal intubation.

Eligible neonates were randomly assigned to receive intravenous caffeine citrate 20 mg/kg infused over 15 min within the first 2 h of age (early caffeine group) and at 12 h of age (late caffeine group). Subjects were randomized by stratification in blocks of 10 using a computer-generated block randomization schedule. Infants were intubated if they had PCO2 >60 mmHg and pH <7.20 or FIO2 >0.5 on CPAP or hemodynamic instability (mean arterial blood pressure <GA requiring two inotrope support).

A single-blinded echocardiogram was performed in the first 12 h of age using the Sonosite echocardiography machine. Measures of diameters of the PDA, shunt direction, left pulmonary artery end-diastolic velocity, and left atrial to aortic root ratio were collected on each examination done 12 h apart. Ultrasound head was performed on day of life 1, 3, and 7 for intraventricular hemorrhage diagnosis and assessment of the grade.

Relevant maternal and neonatal medical information was collected. Serial measurements of heart rate, mean arterial pressure, respiratory rate, and Silverman-Anderson score were done each hour. Normally distributed variables were analyzed with the independent samples *t*-test and non-parametric continuous outcome variables were analyzed with the Mann–Whitney *U*-test. Demographic data are presented as numbers and proportions for categorical variables or means with standard deviation for normally distributed continuous variables and medians for skewed distribution. Fisher's exact test and Chi-square test were used to analyze categorical outcome variables. Significance was set at $P < 0.05$. For statistics, IBM SPSS Statistics 21.0 (SPSS, Inc., Chicago, IL) functions were utilized.

RESULTS

A total of 36 subjects were enrolled. Nineteen subjects received early caffeine and 17 subjects received late caffeine. Figure 1 represents a flow diagram that quantifies participant progress through the trial. No parents who were approached for informed consent declined to participate, and no enrolled subjects were lost to follow-up.

There were no significant differences in maternal characteristics or delivery complications between the two groups [Table 1]. There was no statistically significant difference in need for ventilation within 24 and 72 h. No difference in need for inotrope support by 24 hours of life. Neonates who received early caffeine had a significant reduction in duration of CPAP ($P = 0.003$), but statistically non-significant reduction in duration of respiratory support ($P = 0.425$) and oxygen therapy ($P = 0.145$). Other morbidities were similar between the two groups [Table 2].

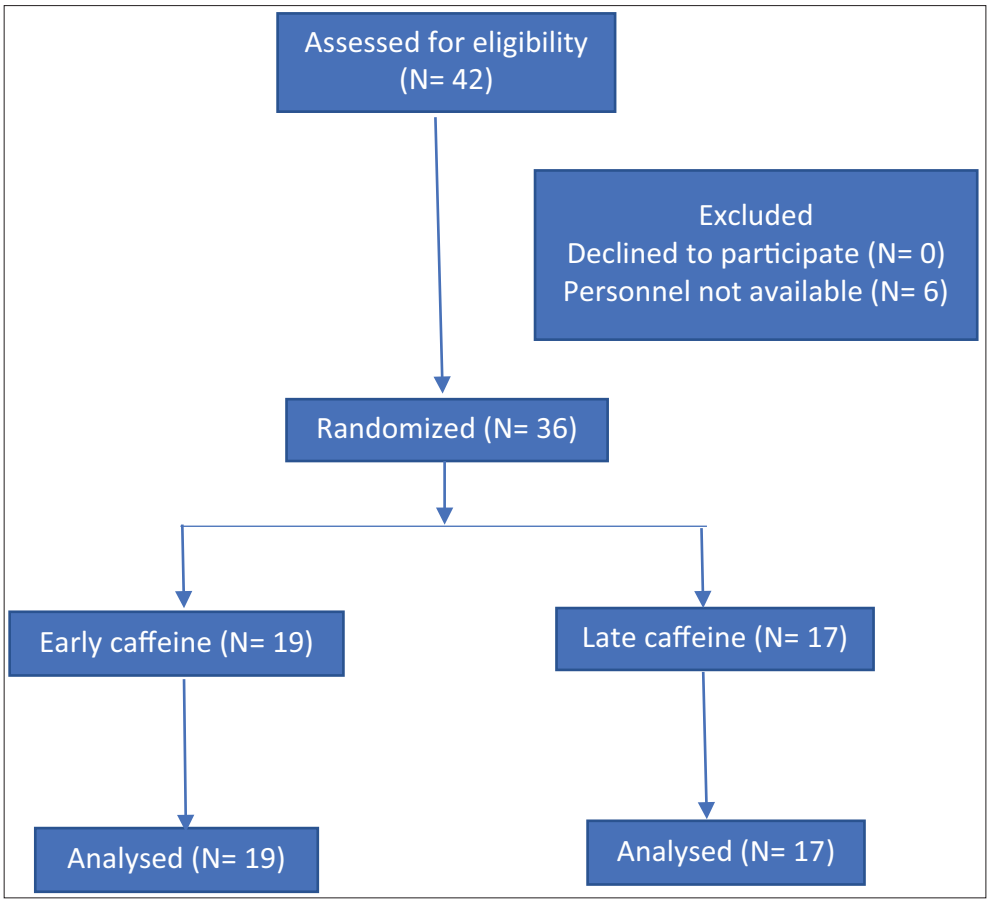

Figure 1: Tabular description

Table 1: Maternal characteristics

Characteristics	Early (*n*=19)	Late (*n*=17)	*P*-value
Maternal age (years)	28±2	29±2	0.802
Gravida/para (med)	2	3	0.516
Gestational age (weeks)	29.58±2	29.17±2	0.901
Birth weight (grams)	1198±374	1224±288	0.301
Male *n* (%)	11 (57.89)	9 (52.94)	0.765
Some antenatal steroids (%)	11 (57.89)	11 (64.70)	0.676
C-section deliver (%)	12 (63.15)	8 (47.05)	0.332
Premature rupture of membranes (%)	3 (15.78)	7 (41.17)	0.090
Pre-eclampsia (%)	6 (31.57)	2 (11.76)	0.153
Placental abruption (%)	1 (5.26)	2 (11.76)	0.481
GDM (%)	0 (0)	1 (5.26)	0.284
First surfactant administration	6 (31.57)	9 (52.94)	0.194
BMV (%)	4 (21.05)	4 (23.52)	0.858
Second surfactant administration	2 (10.52)	0 (0)	0.168

DISCUSSION

Caffeine's favorable efficacy and safety record in the NICU for the treatment of apnea of prematurity, and for preventing failed extubation, is well known.[4,12-14] A potential new direction for caffeine therapy targets early administration for preterm neonates at risk for respiratory failure and cardiovascular insufficiency. Such an intervention should be feasible in most settings as intravenous access is routinely achieved in these patients for provision of intravenous fluid and antibiotics. Infants managed initially on CPAP alone may take time to develop respiratory insufficiency and apnea. Waiting to give caffeine when these symptoms develop may not prevent the need for intubation.

This is the first randomized controlled trial of caffeine to compare timing of initiation of intravenous caffeine therapy in very preterm neonates. While our study did not demonstrate a difference in the need for endotracheal intubation at 24 h of age, we did see a trend for decreased duration of respiratory support, mechanical ventilation, and oxygen therapy. To detect 50% difference (from 30 to 15%), we would need at least 20 infants in each arm to adequately power for this outcome. Our primary hypothesis was based on the assumption that most intubation would occur in the first 24 h of age. Statistically non-significant reduction in the duration of respiratory support infants receiving early caffeine versus late caffeine group [Table 2], but need further study in a larger trial.

It is known that caffeine is a potent inhibitor of the vasodilator adenosine.[15] This action may result in vasoconstriction of cerebral vessels or attenuation of

Table 2: Neonatal outcomes

Outcomes	Early (*n*=19)	Late (*n*=17)	*P*-value
Median Apgar score 1 min (IQR)	8 (7.8)	7 (6.8)	0.791
Median Apgar score 5 min (IQR)	9 (9.9)	9 (8.9)	0.438
Worst pH in 24 h	7.30±0.07	7.29±0.1	0.267
Worst base deficit in 24 h	−7.05±−2.7	−7.21±−2.6	0.879
Time of caffeine administration after birth	2	12	-
Peak PaCO2 in the first 24 h, mmHg	40.52±10.38	42.04±10.46	0.853
Required intubation by 24 h – *n* (%)	2 (10.52)	1 (5.88)	0.615
Required intubation by 72 h – *n* (%)	3 (15.78)	2 (11.76)	0.727
Required inotrope by 24 h – *n* (%)	4 (21.05)	2 (11.76)	0.455
CPAP duration (h)	24±16	60±58	0.003
Days of mechanical ventilation (h)	12.6±30.5	21.1±58.14	0.237
Days of total respiratory support (h)	52.5±65	81±111	0.425
Days of oxygen (h)	24±34	34.4±55	0.145
IVH (>3) – *n* (%)	0 (0)	2 (11.76)	0.124
HsPDA – *n* (%)	4 (21.05)	6 (35.29)	0.196
PDA requiring treatment – *n* (%)	4 (21.05)	5 (29.41)	0.563
NEC (Stage 2 or 3) – *n* (%)	1 (5.26)	0 (0)	0.337
Apnea of prematurity – *n* (%)	0 (0)	0 (0)	-
Apnea – *n* (%)	7 (36.84)	9 (52.94)	0.332
IVH any grade – *n* (%)	4 (21.05)	2 (11.76)	
Oxygen at 36 weeks corrected age – *n* (%)	1 (5.26)	1 (5.88)	0.935
ROP requiring treatment – *n* (%)	0 (0)	0 (0)	-
CRP-positive EOS – *n* (%)	3 (15.78)	1 (5.88)	0.345
CRP-positive LOS – *n* (%)	0 (0)	1 (5.88)	0.284
Blood culture-proven EOS – *n* (%)	0 (0)	0 (0)	-
Blood culture-proven LOS – *n* (%)	2 (10.52)	3 (17.64)	0.906
Time to reach full feeds (days)	8.89±3.52	7.29±3.91	0.409
Survival (%)	18 (94.73)	15 (88.23)	0.766

CRP: C-reactive protein, LOS: Late-onset sepsis, EOS: Early-onset sepsis, IVH: Intraventricular hemorrhage, IQR: Interquartile range, ROP: Retinopathy of prematurity, CPAP: Continuous positive airway pressure, NEC: Necrotizing enterocolitis

adenosine-induced vasodilation that may occur during hypoxia or hypercarbia. Caffeine may, therefore, act in a similar mechanism to indomethacin, by decreasing the risk of reperfusion injury by limiting cerebral blood flow. Indomethacin has also demonstrated a transient decrease in cerebral saturations, but within 2 h of administration was shown to improve both blood pressure and superior vena cava flow.[16] The protective effects for intraventricular hemorrhage (IVH) have only been demonstrated when given shortly after birth.[16] Avoiding early fluctuations in cerebral blood flow may reduce morbidities, such as IVH, but this needs further study.

Interestingly, centers conducting similar retrospective studies of early (<3 days) versus late (>3 days) caffeine are reporting lower rates of IVH in the early caffeine-treated babies.[17]

Patel *et al.* recently described their single center's experience with caffeine given before or after 3 days of age to preterm neonates 1250 g birth weight.[18] In their retrospective study (*n* = 140), infants receiving early caffeine were significantly less likely to develop death or BPD (25 vs. 53%), BPD (24 vs. 51%), or a PDA requiring medical or surgical treatment (10 vs. 36%). These differences remained statistically significant even after adjustments for confounding variables. In addition, the median duration of endotracheal intubation and mechanical ventilation was more than 2 weeks longer in the late caffeine group (6 vs. 22 days).[18] A subsequent multicenter retrospective study of preterm infants with birth weights <1500 g (*n* = 29,070) also demonstrated significant associations between early caffeine initiation before 3 days of age and a reduced incidence of BPD, PDA treatment, and duration of mechanical ventilation.[5] Meanwhile, those in the GA <24 weeks strata who received early caffeine and who survived had significantly lower BPD rates (43.7 vs. 67.1%) compared with late caffeine recipients. The incidence of late onset sepsis (21.2 vs. 24.5%) and inotropic support (21.6 vs. 31.6%) was also significantly less in the early caffeine group.[5]

Lodha *et al.* with the Canadian Neonatal Network recently reported results from their multicenter retrospective study of caffeine initiation before or after 2 completed days of age in preterm infants GA <31 weeks (n ¼ 5517). Positive outcomes associated with early caffeine in this study included fewer days of mechanical ventilation (2 vs. 4 days), a lower incidence of requiring high-frequency ventilation on day 2 (6.2 vs. 19.4%), a lower odds of having BPD at 36 weeks postmenstrual age (odds ratio [OR] 0.79, 95% confidence interval [CI] 0.64–0.96), and of surgically treated PDA (OR 0.58, 95% CI 0.42–0.8). Other outcomes

such as mortality, necrotizing enterocolitis, retinopathy of prematurity, neurological injury, and total length of hospital stay were not different. The median time of caffeine initiation in this study was 1 day of age in the early group and 4 days of age in the late group.[19] These studies suggest that early caffeine, more so than caffeine *per se*, is associated with a reduction in time exposed to endotracheal intubation and positive pressure or mechanical ventilation, which, in turn, reduces the risk of developing BPD and possibly other associated complications.

While it is natural to assume that the respiratory and cardiovascular stimulant and vasoconstrictive effects of caffeine provide the pharmacologically plausible basis for these observed outcomes, recent animal studies indicate that caffeine can also ameliorate the inflammatory response and lung injury due caused by acute hyperoxia or intrauterine infection.[20,21]

Our study has several limitations. First, since this was a pilot study, we were underpowered to achieve any differences in the outcome of reducing intubation. Second, given that our study included only non-intubated infants at birth, it is unclear whether early caffeine would have the same hemodynamic effects on potentially sicker intubated infants.

CONCLUSION

This pilot study demonstrated that conducting a prospective, randomized, placebo-controlled trial comparing early to late caffeine administration in very preterm neonates is feasible. We found that giving early intravenous caffeine administration to non-intubated, very preterm neonates resulted in reduction in total duration of respiratory support.

Larger prospective studies are needed to determine the effects of early caffeine on the need for intubation, IVH, and related long-term outcomes such as chronic lung disease and neurodevelopmental impairment.

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