Is Early High-Dose Caffeine citrate Improves Outcomes in Preterm Infants?

By

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ABSTRACT

Background: There has been a shift towards early initiation of caffeine citrate, while the efficacy and safety of prophylactic use and higher dosing of caffeine is still not well established.

Objectives: The aim of this study is to find the efficacy of early high-dose caffeine (HD) therapy on significant apnea, duration of invasive or non-invasive ventilation and short outcomes in preterm infants admitted in Intensive Care Unit (NICU) at Al-Hussein University Hospital.

Patients & Methods: This prospective observational study was conducted during the period from January 2023 to December 2023 on 50 preterm admitted to NICU. They were divided into two groups: **Group 1** included 25 preterm who received high maintenance dose of caffeine citrate 10 mg/kg/day intravenous with loading dose 20 mg/kg/day given less than 24h of life, and **Group 2** include 25 preterm who received low maintenance dose of caffeine citrate 6 mg/kg/day intravenous with variable timing of loading dose 20 mg/kg/day. The Caffeine treatment lasted up to 34–35 wk of Postmenstrual age. Complete clinical examination, history taking and laboratory investigation was done at time of admition.

Results: The Results showed that the Mean ± SD of Gestational age (weeks) was 28.72 ± 1.02 in group 1 and 29.80 ± 0.71 in group 2 ;(52.0%) Female and (48.0%) male in group 1 where (48.0%) Female and (52.0%) Male in group 2. Also, There was statistically significant difference between studied groups as regard duration of MV with significant increase in duration of oxygen therapy in group2 than group1. Duration of hospital stay was significant long in group2 than group1. As regard developing of bronchopulmonary dysplasia (BPD) there was significant increase in group2 (15 cases = 60%) than group1 (7 cases = 28%).

Conclusion: The study revealed that the initiating caffeine citrate therapy within the first day of life in heigh dose (≥10 mg/kg/day) was associated with marked decreased duration of MV and apnea recurrence than that observed in infants with low dose (≤ 6 mg/kg/day) initiation with a statistically significant reduction in the rates of morbidity. Further studies should be done to determine optimal dose and duration of caffeine therapy and the long-term outcomes in preterm infants.

Key words: Caffeine, Outcomes, Preterm, Infants, Intensive Care Units, neonatal

INTRODUCTION

Caffeine citrate is one of the most widely used drugs in the neonatal intensive care unit (NICU). It is a methylxanthine class agent which has been well validated as a treatment for apnea of prematurity ***(Lamba et al., 2021).***

It has also been shown to increase the chances of successful extubation. Proposed mechanisms include enhancement of respiratory control and improvement in diaphragmatic contractility and airway function ***(Rodak et al., 2021).***

A significant number of extremely low birth weight (ELBW) infants require prolonged mechanical ventilation which is associated with poor neurodevelopmental outcomes and bronchopulmonary dysplasia (BPD) ***(Lee et al., 2022).***

The Caffeine for Apnea of Prematurity (CAP) trial showed that caffeine administration within the first 10 days of life for apnea of prematurity prevention resulted in a reduction in time on positive pressure ventilation by one week, as well as lowering the incidence of BPD ***(Lamba et al., 2021).***

Higher doses of caffeine than historically used as standard in NICUs has sparked interest. A recent systematic review suggested that a higher dose of caffeine (10 to 30 mg/kg/day of caffeine citrate) may enhance its beneficial effect on BPD, However, there was a significant variability in the indication for caffeine use and its time of initiation ***(Dekker et al., 2021).***

Caffeine has a neuroprotective effect, where infants who receive it had a lower incidence of bronchopulmonary (BPD) and severe retinopathy of prematurity (ROP) and on follow-up at 18 months of age, they had a lower incidence of cerebral palsy and cognitive delay, besides, improved respiratory morbidity, including an approximate 1-week reduction in the duration of MV ***(Lamba et al., 2021).***

AIM OF THE STUDY

The aim of this study is to find the efficacy of early high-dose caffeine therapy on significant apnea, duration of invasive or non-invasive ventilation and short outcomes in preterm infants admitted in Intensive Care Unit (NICU) at Al-Hussein University Hospital.

Ethical consideration:

1. written consent was taken from parents of each participant before the study.
2. Approval of ethical committee in the pediatric department, collage and university was obtained before the study.
3. The parents has the right to withdraw his or her newborn from the study at any time.
4. The author received no financial support for the research, authorship, and or publication of the article.
5. The author declared that there is no conflict of interest regarding the study.
6. Privacy of all data will be assured

sample size equation

The sample size and power analysis was calculated using Epi-Info software statistical package created by World Health organization and center for Disease Control and Prevention, Atlanta, Georgia, USA version 2002. The criteria used for sample size calculation were as follows:

- Confidence limit 95%
- Accepted error 5%
- Power of the study 86 %

The sample size was found at N = 46 cases at least

Inclusion criteria

- Gestational age (GA) less than 32 weeks from last menstrual period (LMP) and by New Ballard score ***(Ballard et al., 1991)***
- Admission to the NICU within 7 days postnatal.
- Both sex.
- All preterm with respiratory distress

Exclusion criteria

- Congenital or chromosomal anomalies.
- Birth weight (BW) > 2200 gram (90th percentile for 32 weeks).
- Hypersensitivity to caffeine citrate.

The Caffeine treatment lasted up to 34–35 wk. Postmenstrual Age (PMA), or until infants no longer had apneic events off non – invasive ventilation or high - flow respiratory support for five days. Analysis and short outcomes were compared between the early high dose (10mg/kg/day) group and low dose (6 mg/kg/day) group.

PATIENTS AND METHODS

This prospective observational study that was conducted on 50 preterm admitted to neonatal intensive care unit in Al-Hussein University Hospital during the period from January 2023 to December 2023 on 50 patients, 25 of them with early high maintenance dose of caffeine citrate 10 mg/kg/day intravenous with loading dose 20 mg/kg/day given less than 24h of life, respectively, and another 25 with low maintenance dose of caffeine citrate 6 mg/kg/day intravenous with variable timing of loading dose 20 mg/kg/day, respectively. The patients were selected by simple random method

All neonates included in the study were subsequently subjected to:

Full medical history talking including: prenatal history: (for preexisting maternal or fetal problems), natal history: (perinatal asphyxia), and postnatal history: (for pulmonary, cardiovascular or neurological abnormalities).

I. Complete clinical examination including:

General examination as:

- Apgar score, to predict neonatal mortality and morbidity in term infants, at 1, 5 and 10 minutes (Cnattingius et al., 2020).
- Gestational age determination using Ballard score (Ballard et al., 1991).
- Determination of birth weight, length, HC and AC. With their position on percentile
- Measuring vital signs (HR, RR, temperature and BP). With their position on percentile

Local examination as:

- Chest examination: (Signs of respiratory distress, and degree of respiratory distress detected by Downes' Score and Silverman Anderson retraction score (Shashidhar et al., 2016).
- Cardiovascular examination: included assessment of perfusion state as by measuring HR, BP, capillary refill time (CRT) and auscultation of heart sounds and murmurs.
- Abdominal examination: included the presence of feeding intolerance, gastric residual, vomiting or abdominal distention.
- Neurological examination and extremities and genitalia were also performed.
- Development of any complications: included pulmonary hemorrhage, circulatory failure, necrotizing entero-colitis, APNEA, Heart rate, and blood pressure.

Laboratory evaluations included:

II. complete blood Count (CBC) (Gothwal et al., 2021). and C-reactive protein (CRP) (Elsayed et al., 2021) on admission, Arterial blood gases (ABG) or venous blood gases (VBG) (Chong et al., 2021) and chemistry on admission (Jang et al., 2011).

III. Imaging procedures: included chest or abdominal x-ray (Berna and Çiğdem, 2021) cranial or abdominal ultrasound (US) (Latteri et al., 2017) and echocardiography (Alsharqi et al., 2018).

IV. Follow up of cases during the study period till discharge from NICU: After the first- and second-weeks comparison was made between both groups for different modes of oxygen support needed by each group. Complications in terms of death, BPD, PDA, sepsis and NEC were recorded during the period of stay in NICU.

Statistical analysis

Data were collected, coded, revised and entered to the Statistical Package for Social Science (IBM SPSS) version 20 (Kirkpatrick and Feeney,2013).

Chi-square test was used in the comparison between the two groups with qualitative data and Fisher exact test was used instead of the Chi-square test when the expected count in any cell found less than 5. Independent t-test was used in the comparison between the two groups with quantitative data and parametric distribution and Mann-Whitney test was used in the comparison between the two groups with quantitative data and non-parametric distribution. The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the P-value >0.05 was considered non-significant (NS), and P-value <0.01 was considered highly significant (HS) in all analyses

RESULTS

The result of our study will be demonstrated in the following tables:

Table (1): Demographic and some clinical parameters in studied groups.

Neonatal data		High dose group(1)	Low dose group(2)	Test value	P-value	Sig.
		No. = 25	No. = 25			
Sex	Female	13 (52.0%)	12 (48.0%)	0.080*	0.777	NS
	Male	12 (48.0%)	13 (52.0%)			
Gestational age (weeks)	Mean ± SD	28.72 ± 1.02	29.80 ± 0.71	-0.322•	0.749	NS
Birth weight (grams)	Mean ± SD	1298.48 ± 114.55	1345.40 ± 81.80	-1.667•	0.102	NS
Birth weight z-score	Median (IQR)	0.12 (-1.29 – 0.5)	0.28 (0.02 – 0.64)	-1.657≠	0.113	NS
Length (cm)	Mean ± SD	41.48 ± 3.62	40.92 ± 3.68	0.542•	0.590	NS
Length z-score	Median (IQR)	-0.06 (-0.61 – 0.5)	0.22 (-0.88 – 0.5)	-0.195≠	0.845	NS
Head circumference (cm)	Mean ± SD	29.80 ± 2.84	29.28 ± 2.72	0.661•	0.512	NS
Head circumference (centile)	< 3rd	1 (4.0%)	0 (0.0%)	1.021	0.312	NS
	(3rd - 25th)	2 (8.0%)	7 (28.0%)	3.389	0.066	NS
	On 50th	5 (20.0%)	1 (4.0%)	3.028	0.082	NS
	>50th	3 (12.0%)	5 (20.0%)	0.221	0.637	NS
	(90 – 97th)	6 (24.0%)	6 (24.0%)	0.0	1.0	NS
	>97th	8 (32.0%)	6 (24.0%)	0.402	0.529	NS
APGAR score 1 min	Median (IQR)	4 (4 – 4)	3 (0 – 4)	-1.849≠	0.064	NS
APGAR score 5 min	Median (IQR)	7 (7 – 7)	7 (3 – 7)	-1.706≠	0.088	NS

This table show that: There was non-significant difference between studied groups as regard sex, gestational age, weight, Length, Head circumference and Apgar score at 1 and 5 min

Table (2): Mode of O2 supplementation in studied groups during the first week.

Oxygen therapy	High dose group(1)	Low dose group(2)	Test value	P-value	Sig.
	No. = 25	No. = 25			

Day 1	**MV**	12 (48.0%)	13 (52.0%)	0.082	0.777	NS
	CPAP	6 (24.0%)	4 (16.0%)	0.502	0.480	NS
	nasal cannula	7 (28.0%)	8 (32.0%)	0.102	0.758	NS
Day 2	**MV**	**11 (44.0%)**	20 (80.0%)	16.258	<0.001**	S
	CPAP	**10 (40.0%)**	3 (12.0%)	5.094	0.024*	S
	Nasal cannula	**4 (16.0%)**	2 (8.0%)	0.758	0.384	NS
Day 7	**MV**	**7 (28%)**	16 (64%)	6.523	0.011*	S
	CPAP	**11 (44%)**	4 (16%)	4.668	0.031*	S
	Nasal cannula	**4 (16%)**	5 (20%)	0.142	0.713	NS

This table show that: There was statistically non-significant difference between studied groups as regard mode of O2 supply after birth. And there was statistically significant difference between studied groups as regard (MV and CPAP) and no statistically significant difference as regard (Nasal cannula). And there was statistically significant difference between studied groups as regard (MV and CPAP) and no statistically significant difference as regard (Nasal cannula).

Table (3): Mode of O2 supply in studied groups after two weeks of caffeine administration.

Oxygen therapy		**High dose group(1)**	**Low dose group(2)**	**Test value**	**P-value**	**Sig.**
		No. = 25	**No. = 25**			
Complete two weeks of caffeine	**MV**	3 (12%)	11 (44%)	6.349	0.012*	S
	CPAP	7 (28%)	3 (12%)	2.001	0.157	NS
	Nasal cannula	1 (4%)	5 (20%)	3.031	0.082	NS
	Off oxygen	11 (44%)	4 (16%)	4.668	0.031*	S
	Head box	1 (4%)	0 (0.0%)	1.021	0.312	NS
	Death	2 (8%)	2 (8%)	0.0	1.0	NS

This table show that: There was statistically significant difference between studied groups as regard (MV and Off Oxygen) and no statistically significant difference as regard (CPAP, Nasal Cannula, Head box and Death).

Table (4): Mode of O_2 supply at 36 weeks postmenstrual age (PMA).

Oxygen therapy		High dose group(1)	Low dose group(2)	Test value	P-value	Sig.
		No. = 25	No. = 25			
At complete 36 wks. PMA	MV	0 (0.0%)	2 (8%)	2.079	0.149	NS
	CPAP	0 (0.0%)	0 (0.0%)	-	-	NS
	Nasal cannula	3 (12%)	10 (40%)	5.088	0.024*	S
	Off oxygen	16 (64%)	9 (36.0%)	3.917	0.048*	S
	Head box	3 (12%)	0 (0.0%)	3.192	0.074	NS
	Death	3 (12%)	4 (16%)	0.172	0.684	NS

This table show that: There was statistically significant difference between studied groups as regard (Nasal Cannula and Off Oxygen) and no statistically significant difference as regard (MV,CPAP, Head box and Death).

Table (5): Duration of caffeine therapy till 34-36 weeks PMA, O2 supply and length of stay in studied groups.

Oxygen therapy		High dose group(1)	Low dose group(1)	Test value	P-value	Sig.
		No. = 25	No. = 25			
Duration of CPAP after birth (day)	Mean ± SD	4.72 ± 2.26	3.63 ± 1.30	-2.090	0.041*	S
Duration of MV after birth (day)	Mean ± SD	6.67 ± 2.87	12.23 ± 4.82	4.956	<0.001**	HS
Duration of oxygen therapy (day)	Mean ± SD	18.72 ± 12.99	26.76 ± 14.48	-2.067	0.044*	S
Duration of hospital stay (day)	Mean ± SD	39.04 ± 20.57	54.04 ± 29.72	2.075	0.043*	S
Duration of caffeine therapy (day)	Mean ± SD	24.58 ± 11.62	17.24 ± 10.67	-2.326	0.024*	S

This table show that: Regarding duration of MV there was significant increase in group 2 than group1 while there was significant increase in group1 than group2 as regard duration of CPAP. Regarding duration of oxygen therapy there was significant increase in group2 than group1. And regarding duration of hospital stay there was significant increase in group2 than group1. And duration of caffeine therapy was significantly higher in group1 than group 2.

Table (6): Comparison between studied groups regarding complications.

Complication		High dose group(1)	Low dose group(2)	Test value	P-value	Sig.
		No. = 25	No. = 25			
BPD at 36 wks.	**No**	18 (72.0%)	10 (40.0%)	5.195*	0.023	S
	Yes	7 (28.0%)	15 (60.0%)			
Air leak	**No**	23 (92.0%)	17 (68.0%)	4.500*	0.034	S
	Yes	2 (8.0%)	8 (32.0%)			
Sepsis	**No**	21 (84.0%)	13 (52.0%)	5.882*	0.015	S
	Yes	4 (16.0%)	12 (48.0%)			
NEC	**No**	20 (80.0%)	19 (76.0%)	0.117*	0.733	NS
	Yes	5 (20.0%)	6 (24.0%)			
PDA	**No**	13 (52.0%)	11 (44.0%)	0.321*	0.571	NS
	Yes	12 (48.0%)	14 (56.0%)			
Death	**No**	22 (88.0%)	21 (84.0%)	0.166*	0.684	NS
	Yes	3 (12.0%)	4 (16.0%)			

This table show that: There was significant increase in group2 than group1 as regard BPD at 36 wks., air leak and sepsis. However, there was non-significant difference between both groups as regard death and NEC.

Table (7): Comparison between studied groups regarding apnea.

		High dose group(1)	Low dose group(2)	Test value	P-value	Sig.
		No. = 25	No. = 25			
Apnea on first day	**No**	22 (88.0%)	23 (92.0%)	0.222*	0.637	NS
	Yes	3 (12.0%)	2 (8.0%)			
Apnea relapse	**No**	23 (92.0%)	17 (68.0%)	4.500*	0.034	S
	Yes	2 (8.0%)	8 (32.0%)			

This table show that: There was non-significant difference between group1 (12%) and group2 (8%) as regard apnea on day one of life (DOL) after birth. while regarding apnea relapse, there was statistically significant increase in group2 (32%) than group1 (8%).

DISCUSSION

This prospective observational study that was conducted on 50 preterm admitted to neonatal intensive care unit in Al-Hussein University Hospital during the period from January 2023 to December 2023 on 50 patients, 25 of them received high maintenance dose of caffeine citrate 10 mg/kg/day intravenous with loading dose 20 mg/kg/day given less than 24h of life, respectively and another 25 received low maintenance dose of caffeine citrate 6 mg/kg/day intravenous with variable timing of loading dose 20 mg/kg/day, respectively.

In our study, there was non-significant difference between studied groups as regard demographic data: sex, mode of delivery, GA, weight, Apgar score at 1 and 5 min, maternal risk factors and multiple birth.

In our study, all cases in studied groups with respiratory distressed after birth (100%) and mode of O2 supply was recorded. In group(1) 48.0% were on MV, 24.0% on CPAP and 28.0% on Nasal cannula. However, in group(2) 52.0% were on MV, 16.0% on CPAP and 32.0% on Nasal cannula. There was non-significant difference between both groups.

While ***Patel et al., 2013*** found similar proportion of infants in both studied groups required mechanical ventilation on day of life 1 Early Caffeine: 71%, Late Caffeine: 79% (P=0.30) on mechanical ventilation.

On the other hand, in the study of ***Lodha et al., 2015*** there was increase in rate of intubation after birth in early (38.3%) than late group (34.8%) with significant difference (P= 0.03). This may be explained by large early studied group (n = 3806) when compared to late studied group (n = 1295).

On the 2nd day of caffeine administration, percentage of neonates on MV had decreased to 44.0% in group1 and increased to 80.0% in group2 with highly significant difference (P<0.001), however, percentage of neonates on CPAP had increased to 40.0% in group1 and decreased to12.0% in group2 with significant difference (P=0.024).

The same results were observed in the study of ***Lodha et al., 2015*** in which preterm neonates in the early group required more significant CPAP support on day 2 after birth (38% vs. 27%, P<0.01) in contrast to neonates in the late group, who needed more significant MV (45.5% vs. 57.7%, P<0.01).

After one week of caffeine administration, as regard in group1 28% stayed on MV, 44% on CPAP, 16 % on Nasal cannula and 4% on head box. On the other hand, in group2, 64.0 % stayed on MV, 16.0 % on CPAP and 20.0% on Nasal cannula, there was statistically significant difference between studied groups as regard MV and CPAP (P=0.011 and 0.031).

After the 2nd week of caffeine administration, in group1, 12% stayed on MV, 28% on CPAP, 4% on Nasal cannula, 4% on head box and 44% Off oxygen. On the other hand, in group2, 44% stayed on MV, 12% on CPAP, 20% on Nasal cannula and 16% Off oxygen. Again, there was statistically significant difference between studied groups as regard MV and Off oxygen (P=0.012 and 0.031).

At 36 weeks PMA, in group(1) 12 % were on Nasal cannula and 12 % on head box and 64 % off oxygen. On the other hand, in group2, 8 % stayed on MV and 40 % on Nasal cannula and 36 % off oxygen. there was statistically significant difference between studied groups as regard Nasal cannula and Off oxygen (P=0.024 and 0.048).

This was in accordance with the studies done by ***Patel et al., 2013*** and ***Dobson, 2014*** who found that infants receiving early caffeine had lower levels of respiratory support at 36 weeks post menstrual age (PMA) with significant difference.

In our study the duration of MV was significantly higher in group2 than group1. (P <0.001) with significant increase in the total oxygen duration in group2 than group1. (P = 0.044).

Maria et al., 2017 noted that early caffeine admenstration was associated with significantly shorter total duration of mechanical ventilation relative to late caffeine (mean 5 ±11.1 days vs 10.8 ±14.6 days; P = 0.0000).

In our study, the median duration of caffeine therapy was significantly higher in group1 than group2 as infants in the low dose (LD) group were of slightly older GA.

Moreover ***Maria et al., 2017*** noted that median duration of caffeine therapy was higher in early than late group with significant difference early caffeine: 31days, late caffeine : 21days, (P=0.00).

In contrast, ***Patel et al., 2013*** found that the median duration of caffeine therapy was similar between early caffeine and late caffeine groups, early caffeine: 40 days, late caffeine: 39.5 days (P=0.60) as infants in the EC group were of slightly older GA EC: 27.3 weeks, LC: 26.6 weeks, (P=0.03).

In 0ur study, we observed significant decrease in length of stay in NICU in infants receiving caffeine early.

However, ***Hand et al., 2016*** observed non-significant difference between studied groups as regard duration of stay in NICU (79.79 ± 30.51vs. 75.72 ± 27.64,

P=0.47). The difference in the results of our study may be related to different environmental factors between populations.

In our study, it was found that infants with early caffeine had a significant decrease in incidence of BPD when compared with infants in the late group.

The same results were observed in the study of ***Patel et al., 2013*** who observed that infants who received early caffeine initiation had a significantly decreased incidence of BPD when compared with those infants with later initiation (EC: 23.6%, LC: 50.9%, P=0.04) and this difference remained significant after adjustment for important predictors of BPD (adjusted odds ratio 0.26, 95% confidence interval 0.09 to 0.70).

On the other hand, ***Hand et al., 2016*** did not observe any statistical difference in BPD between studied groups, as they approved that the timing of caffeine treatment did not influence the risk of BPD.

In our studied When looking for mortality, we found that at complete 36 weeks of caffeine administration, 3 preterm babies in group(1) were died leaving a total of 22 preterm babies, while 4 were died in group2 leaving a total of 21 preterm babies. There was non-statistically significant difference between the two groups regarding mortality but early caffeine use was associated with a reduced risk of death compared to late caffeine use.

This result was similar to ***Park et al., 2015*** study, who found that the early use of caffeine was associated with a reduced risk of death (OR, 0.902; 95% CI, 0.828 to 0.983; P=0.019).

In contrast, ***Dobson, 2014*** found that the odds of death were higher among infants receiving early caffeine (OR=1.23; 1.05–1.43), with a risk difference of 0.8% between the 2 groups (P<0.01). Possible explanation was increased odds of death in infants who were <24 weeks 'gestation in the early caffeine group, which was not seen in any of the other GA strata.

In our study there was significant reduction in apnea relapse and re-intubation in early group.

This comes in agreement with the study by ***Mohammed et al., 2015***, where they reported that the efficacy for the use of high caffeine dose in apnea of prematurity, in comparison to low dose caffeine, as it was associated with a significant reduction of incidence of apneic episodes, and less days of documented apnea

Finally, early caffeine administration within the first day of life is better than late administration as it has beneficial effects on neonatal outcome.

CONCLUSION

Initiating caffeine citrate therapy within the first day of life in heigh dose was associated with marked decreased duration of MV than that observed in infants with low dose therapy initiation. In addition to significant reduction in apnea recurrence in infants received caffeine early and with heigh dose, It also was associated with a statistically significant reduction in the rates of morbidity.

RECOMMENDATIONS

Caffeine should be used early with heigh dose within the first day of life in preterm babies aged < 32 gestational weeks who required surfactant treatment. Further studies should be done to determine optimal dose and duration of caffeine therapy and the long-term outcomes in preterm infants. Randomized controlled trials of caffeine prophylaxis to prevent neonatal morbidities, such as BPD, PDA and NEC are necessary to conclusively support the routine use of caffeine in NICUS as a preventative therapy and to ensure the safety of early initiation of caffeine in extremely preterm infants.

Limitation of the study

One of our research limitation was difficulty in caregiver to preterm because data collection and sampling methods became stop if they didn't participated.

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