

ORIGINAL RESEARCH

CLINICAL OUTCOMES FOLLOWING EARLY AND LATE CAFFEINE ADMINISTRATION IN VERY PRETERM NEONATES**Ashfaq Masood¹, Syed Basharat Ahmed¹, Mushtaq Ahmad Bhat^{1*}, Sheikh Sabat¹, Inaamul Haq², Masood ul Hassan¹**¹ Department of Neonatology, Sher I Kashmir Institute of Medical Sciences J & K, India² Department of Community Medicine, Government Medical College Srinagar J & K, India

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ABSTRACT

To compare early and late caffeine therapy in very preterm low birth weights newborns for apnoea of prematurity and its effects on various clinical parameters and mortality. Prospective observational study performed on 62 preterm (GA<32weeks and weight<1200g) newborns who randomly received either early caffeine (EC) initiation (<72 hours) or late caffeine (LC) initiation (≥72 hours). The patients were further categorized as 'survival' or 'mortality' groups. Of 62 patients 38 (61.3%) received EC therapy and 24 (38.7%) received LC therapy. There was 57.8% mortality in the EC and 4.1% in LC group (p value<0.01). EC group had higher incidence of intraventricular hemorrhage (IVH) and shock (p-value<0.01). EC showed better outcome in FiO₂ requirement and ICU stay (p-value<0.01). EC was observed to be an independent risk factor for mortality (unadjusted logistic regression OR=31.6, 95% CI=3.9-259, p-value=0.001; adjusted logistic regression OR=69.6, 95% CI=4.6-1059.3, p-value=0.002). EC therapy causes IVH and increased mortality in preterm.

Keywords: Preterm newborns, caffeine therapy, apnea, intraventricular hemorrhage.**INTRODUCTION**

An estimated 13.4 million babies are born preterm low birth weight (LBW) (1 in 10 babies born/year) [1]. Almost 50% of premature newborns are contributed by south Asian regions with India being the major contributor [2]. Considerable progress has been made in improving the survival of ELBW/ preterm newborns however morbidities and mortality remains high [3]. Methylxanthine (caffeine) has proved its efficacy in apnea of prematurity with reduction in morbidity and mortality [4]. Studies on the use of caffeine in preterm babies has also revealed its beneficial effect on the acute respiratory problem, promising effect on reduction of bronchopulmonary dysplasia (BPD) and mortality and its role in decreasing dependence of assisted ventilation and higher FiO₂ (fraction of inspired oxygen) requirement [5]. Despite these beneficial effects of caffeine use in preterm babies, there doesn't seem to be any significant difference in mortality between early and late caffeine use in preterm neonates [6]. Moreover higher mortality rates have been observed by many researchers in early caffeine initiation compared to late caffeine initiation [7,8].

We undertook a prospective, analytical study of very preterm /LBW babies to determine the timing of caffeine induction and its effects on prognostic/ comorbid features affecting the premature newborns and their outcome. This study also evaluated all the comorbid/prognostic features of very preterm low birth weight babies during the course of stay in ICU and the outcome (mortality/survival) in relation to the time of initiation of caffeine therapy (early/late) to draw any inference of probable factors responsible for outcome.

METHODOLOGY

This was a prospective, analytical/randomised study on very preterm, very low birth weight newborns which was undertaken at a tertiary Care centre, Department of Neonatology Sher I Kashmir Institute of Medical Sciences J&K, India

from year 2019 to 2022 after seeking approval from institutional ethical committee. Written informed consent was taken from the parents/caregivers of the newborns before including them in study.

Eligibility criteria for the study:

1. Gestational age <32 weeks
2. Birth weight < 1200 grams
3. No congenital/metabolic abnormality
4. No cyanotic heart disease
5. Referred cases after 24 hours of post-natal life at admission to neonatal ICU.

Overall, 142 babies were referred to Neonatal ICU between August 2019 and July 2022, of which only 62 fulfilled eligibility criteria.

Initiation of caffeine therapy was randomly done in eligible newborn babies with alternately allotting the baby either for early caffeine (caffeine initiation <72 hours of life) or late caffeine (caffeine initiation \geq 72 hours of life) treatment modalities. The selected newborn babies received a 20mg/kg intravenous dose of caffeine citrate followed by a maintenance dose of 5mg/kg/day in two divided doses 24 hours after first bolus dose in both the groups. For ethical consideration, in case of clinical worsening like apnea, delayed perfusion, respiratory failure patients randomly selected for late caffeine therapy received an immediate bolus dose of caffeine citrate intravenously followed by daily maintenance and therefore dropped for the purpose of analysis from late caffeine group. The final numbers in Early caffeine group were 38 and for late caffeine group as 24.

Patient analysis and data collection

At admission patients (very preterm and very low birth weight newborns) were evaluated for base line characteristic viz mode of delivery, birth order, gestational age, birth weight, gender, antenatal steroids to the mother, respiratory distress, surfactant administration. For the clinical characteristics an increased FiO₂ requirement, assisted ventilation and days of assisted ventilation, stay in ICU and hospital were assessed. Similarly for co-morbid factors in preterm babies - neonatal sepsis, necrotising enterocolitis (NEC), coagulation derangements, PDA, germinal matrix (GM) bleed/intraventricular hemorrhage (IVH), shock, BPD were monitored.

Bronchopulmonary dysplasia in neonates with prematurity was assessed by X ray and FiO₂ requirement beyond 36 weeks gestation and grading of BPD was done as follows:

Mild BPD: FiO₂ >21% for 28 days of post-natal life

Moderate BPD: FiO₂ >30% at 36 weeks post-natal life

Severe BPD: FiO₂ >30% with positive pressure ventilation at 36 weeks post-natal life [9,10].

Germinal matrix bleed/ intraventricular haemorrhage was evaluated by routine bed side high resolution ultrasonography by radiologist [11,12].

Outcomes were compared by the timing of initiation of caffeine therapy. All the baseline characteristics were compared during the course of caffeine induction and were analyzed to draw inference about effects of early and late caffeine therapy in preterm neonates.

For comparison of the various baseline characteristics, caffeine exposure and its effect on clinical characteristics and mortality the early caffeine and late caffeine groups were further sub classified as 'survival' and 'mortality' groups.

Statistical analysis

The data was entered in Microsoft excel sheets. Continuous variables were represented as means and standard deviations. Categorical variables were represented as numbers. Statistical tests were applied to calculate the p-value. Continuous

variables were evaluated using paired and unpaired t-test using 2×2 contingency tables. Categorical variables were evaluated using Fisher exact test. Multiple logistic regression was applied to see the relationship between various independent variables and outcome. A p-value of <0.05 was taken as significant.

RESULTS

Of the total 142 (very preterm gestation) newborns referred to Neonatal Intensive Care Unit of a tertiary care hospital from August 2019 to December 2022, while 80 preterm newborns had not fulfilled the inclusion criteria- i.e gestation < 32 weeks and birth weight<1200 gms (and or other criteria's as specified in methodology); Only 62 preterm neonates fulfilling the inclusion criteria and who underwent early or late caffeine therapy modalities are presented.

Baseline characteristics, respiratory parameters, and prematurity-associated comorbidities showed minimal variation between the early and late caffeine groups (Table 1). The comparative analysis of clinical characteristics is summarized in Table 1.

Table 1. Baseline, Respiratory, and Clinical Characteristics in Early and Late Caffeine Therapy Groups (n=62)

Characteristic	Early Caffeine (n=38)	Late Caffeine (n=24)	P value
Mode of Delivery			
Vaginal	36 (94.9%)	21 (87.5%)	0.31
LSCS	2 (5.1%)	3 (12.5%)	
Gender			
Male	17 (44%)	12 (50%)	0.68
Female	21 (55%)	12 (50%)	
Mean Gestational Age (weeks, SD)	29.5 (0.6)	30.6 (0.5)	0.36
Birth Weight (kg, SD)	1.014 (0.09)	1.022 (0.08)	0.41
Birth Order			
1st	27 (71%)	16 (66.7%)	
2nd	7 (18.4%)	8 (33.3%)	
3rd	3 (7.9%)	0	
4th	1 (2.7%)	0	
Ballard Score (SD)	12.5 (2.12)	14 (2.01)	0.8
Antenatal Steroids Received	35 (92.1%)	22 (91.7%)	0.95
Surfactant Administration	35 (92.1%)	19 (70.9%)	0.138
Acute Respiratory Distress	35 (90.2%)	22 (91.6%)	0.95
Sepsis	5 (13.9%)	5 (20.9%)	0.48
NEC	2 (5.3%)	2 (8.3%)	0.63
Coagulation Derangement	5 (13.2%)	5 (20.9%)	0.48
IVH	24 (60.4%)	6 (25%)	0.0034
Shock	24 (60.4%)	3 (12.5%)	0.000089
PDA	33 (80.7%)	24 (100%)	0.1465
BPD	2 (5.3%)	3 (12.5%)	0.36
Duration of ICU Stay (days, SD)	10.35 (3.13)	16.17 (6.76)	0.000034
Duration of Increased FiO ₂ Requirement (days, SD)	9.43 (3.37)	15.16 (6.1)	0.0013
Mortality	22 (57.9%)	1 (4.2%)	0.000004

PDA-Patent ductus arteriosus; BPD-Bronchopulmonary dysplasia; FiO₂-Fraction of inspired oxygen

Primary outcome:

1. Higher mortality in early caffeine therapy compared to late caffeine therapy with a p-value of **0.000003984**.
2. Statistically significant increased incidence of intraventricular hemorrhage/GM bleed was seen in early caffeine group compared to late caffeine group (p value=**0.034**)
3. Cardiovascular compromise (shock) was also higher in early caffeine therapy compared to late caffeine therapy which was also statistically significant. (p value =**0.000089**)

Secondary outcome:

1. Statistically significant improvement in high FiO2 requirement in days in early caffeine therapy [9.43 (SD=3.37)] compared to late caffeine therapy [15.16 (Sd=6.1)] (**p value =0.0012**)
2. Statistically significant shorter ICU stay in early caffeine group compared to late caffeine group[10.35 (sd =3.13) vs 16.17 (sd =6.76) **p-value =0.00003**].
3. Bronchopulmonary dysplasia was low in both the groups of caffeine therapy.
4. Other baseline characteristics, respiratory characteristics and clinical characteristics were comparable in both groups.

In view of high mortality and increased incidence of intraventricular hemorrhage in the early caffeine group we further categorized both early and late caffeine group into survival and mortality groups and compared the early caffeine mortality/survival with late caffeine mortality/survival group to evaluate the factors which could be responsible for increased propensity of intraventricular hemorrhage and the outcome.

The comparison of EC induction (mortality group 22/38 (57%)) vs LC induction (survival group 23/24 (95%)) to evaluate factors which could increase the risk of IVH and mortality are given in Table 2.

Table 2. Comparison of risk factors between early caffeine mortality group and late caffeine survival group

	EC mortality	LC survival	p value	
	n=22	n=23		
Prenatal steroids	22 (100%)	22 (95.6%)	1	
Acute Respiratory distress	22 (100%)	20 (87%)	0.23	
Surfactant given	22 (100%)	18 (78.2%)	0.049	
Increased FiO2 requirement	22 (100%)	20 (87%)	0.23	
Mechanical ventilation	22 (100%)	20 (87%)	0.23	
Sepsis	4 (18.2%)	5 (21.9%)	1	
NEC	1 (4.6%)	2 (8.7%)	1	
Coagulation derangement	3 (13.9%)	4 (17.9%)	1	
PDA	17 (77.29%)	23 (100%)	0.021	
IVH	Before caffeine	3 (13.7%)	2 (8.79%)	0.66
	After caffeine	22 (100%)	6 (26.08%)	<0.00001
Shock	Before caffeine	5 (22.7%)	2 (8.79%)	0.24
	After caffeine	22 (100%)	3 (13.04%)	<0.00001

Primary outcome:

1. All the prognostic factors of respiratory support characteristics except surfactant administration were comparable in early caffeine mortality vs late caffeine survival group.
2. IVH in early caffeine mortality group showed significant increase after initiation of caffeine therapy (**p value<0.00001**).

3. Shock was also seen to be significantly associated with initiation of caffeine therapy (**p-value<0.00001**). All cases were associated with IVH.

4. The probable factors for increased propensity of IVH and mortality were comparable in both the groups.

Subjecting the observations to multiple logistic regression of, we found a direct relationship with early initiation of caffeine therapy and mortality (unadjusted logistic regression OR=31.6, 95% CI=3.9-259, p-value=0.001; adjusted logistic regression OR=69.6, 95% CI=4.6-1059.3, p-value=0.002) (Table 3)

Table 3. Multiple logistic regression of various variables in early caffeine group associated with mortality

	Unadjusted logistic regression			Adjusted logistic regression		
	OR	95% CI	P value	OR	95% CI	P value
Caffeine	31.6	3.9 to 259	0.001	69.6	4.6 to 1059.3	0.002
Gestation	0.5	0.3 to 0.84	0.01	1.15	0.42 to 3.11	0.78
Birth wt<1000g	0.17	0.056 to 0.55	0.003	0.19	0.023 to 1.5	0.12
Gender	1.41	0.5 to 3.9	0.5	2.3	0.39 to 14.14	0.34
Apgar<5	0.4	0.26 to 0.6	0	0.39	0.21 to 0.7	0.002

On comparison of early caffeine survival group of 16 (42.47%) vs late caffeine survival group of 23 (95.83%) to analyse differences in baseline, respiratory characteristics and co morbid factors we found the observations given in Table 4.

Table 4. Comparison of survival group

		Early caffeine n=16	Late caffeine n=23	P value
Respiratory characteristics	Antenatal steroids	15 (95.6%)	22 (95.5%)	1
	Acute respiratory distress	16 (100%)	20 (86.9%)	0.25
	Surfactant administration	13 (81.25%)	18 (78.29%)	1
	Mechanical ventilation	16 (100%)	20 (86.9%)	0.25
	High FiO2 requirement	16 (100%)	20 (86.9%)	0.25
PDA	DHS	16 (100%)	23 (100%)	1
	Improved	16 (100%)	20 (80.69%)	0.25
NEC	DHS	1 (6.2%)	2 (8.69%)	1
	Improved	1 (100%)	2 (100%)	1
Sepsis	DHS	1 (6.2%)	5 (21.9%)	0.37
	Improved	1 (100%)	5 (100%)	1
Coagulation deranged	DHS	2 (12.4%)	3 (18.79%)	1
	Improved	2 (100%)	3 (100%)	1
IVH	DHS	2 (12.4%)	6 (26%)	0.43
	Improved	2 (100%)	6 (100%)	1
Shock	DHS	2 (12.4%)	2 (8.69%)	1
	Improved	2 (100%)	2 (100%)	1
BPD	DHS	2 (12.4%)	3 (13%)	1
	Improved	2 (100%)	2 (66.6%)	1
Increased FiO2 requirement in Patients		6	12	0.37
Duration of Mechanical ventilation (Days)		3.5 (sd=3.5)	3.56 (sd=3.68)	0.91

DHS-During hospital stay; NEC-Necrotising enterocolitis

Primary outcome in early caffeine survival vs late caffeine survival:

1. The difference in mean duration of mechanical ventilation in both the groups was statistically insignificant (p-value=0.91).
2. The mean duration of respiratory support in both the survival groups was comparable (p value=0.64)
3. Incidence of BPD lower in both the groups and comparable in both the groups (p value=1).
4. Comorbid factors like IVH, sepsis, NEC, coagulation derangement were comparable with low incidence in both the early and late caffeine survival groups with complete improvement at discharge.

The salient inferences which could be drawn from our study reveal that there was an increased incidence of IVH in the early caffeine group and more so in the post-caffeine initiation period. Similarly, there was an overall increased incidence of cardiovascular compromise (shock) in the early caffeine group and that too after giving caffeine therapy. There was also significant mortality in the early caffeine group.

With regards to baseline characteristics and other propensity factors which could cause IVH, we did not find any statistically significant difference between the groups.

However, our observations indicated an overall better outcome in early caffeine group with regards to respiratory characteristics (decreased FiO₂ requirement) and lesser duration of ICU stay, and decreased incidence of BPD, NEC, IVH and significant closure of PDA in the 'survival' groups of both early and late caffeine therapy.

DISCUSSION

Prevention of mortality and morbidity of extreme premature newborns is considered to be a central health priority [3]. International strategies favour non invasive respiratory support in extreme preterm birth care to reduce the morbidity and mortality [8,13]. Pharmacological drug caffeine has been extensively researched for apnea of prematurity, oxygen requirement, ventilatory support, extubation success, intensive care unit stay and its role in bronchopulmonary dysplasia, patent ductus arteriosus and intraventricular haemorrhage [4]. However till now there is no agreed standard protocol in optimising the dose and time of caffeine administration in very preterm infants [14].

Review of literature regarding effect of caffeine therapy on clinical and respiratory outcome reveals beneficial results in premature babies. Our results of better outcome in caffeine administration in both 'survival' groups (early caffeine survival vs late caffeine survival) with slightly better outcome in early caffeine survival group vis a vis clinical, respiratory and co morbid factors is consistent with the published literature regarding caffeine and preterm babies [4,7,15,16].

Higher mortality (57.89%) in early caffeine vs lower mortality (4.16%) and better survival (95.84%) in late caffeine was a highly significant finding in our study. Review of literature of early caffeine vs late caffeine administration in preterm infants showed an increased mortality in early induction of caffeine (before 3 days of postnatal life) [17]. Earlier reviews and updates regarding the subject also demonstrate an increased odds of mortality in early caffeine group compared to late caffeine group [7,8,18,19,20]. Till date no conclusive factors have been determined for increased odds of mortality in early caffeine therapy in preterm babies [21] and the increased mortality in early caffeine therapy has been attributed to the survival bias favouring late caffeine therapy [22].

While the study gives us an impression that intraventricular haemorrhage and its progression after initiation of early caffeine therapy is the probable factor for mortality in our patients.

Various studies and literature regarding IVH in preterm and the factors which could increase its risk and progression have been observed as respiratory distress, surfactant administration, sepsis, necrotising enterocolitis, coagulation derangements, bronchopulmonary dysplasia, patent ductus arteriosus [23,24,25].

We evaluated all the factors responsible for increased risk of intraventricular haemorrhage in early caffeine mortality group (57%) vs late caffeine survival (95%). We found that all the propensity factors for IVH like respiratory distress, sepsis, NEC, coagulation derangements, PDA and BPD were comparable in both the groups. This gives us an indication that these factors are not the sole factors which can predispose development of IVH in preterm newborns.

The question arises, if the risk factors for the development of IVH in preterm newborns are comparable, still there is progression of IVH more in the early caffeine mortality group vs the late caffeine survival group. Could it be that the early initiation of caffeine in preterm newborns predisposes them to the development and progression of IVH and ultimately mortality.

Caffeine in preterm newborns is known to be neuroprotective especially in GM bleed/IVH by blocking the inflammatory cascade by blocking Adenosine receptors. Nevertheless studies focusing on direct effect of caffeine on GM bleed/IVH are limited and till date the role of caffeine in preterm babies addresses other complications of prematurity, whereas the role of caffeine in GM bleed/IVH are largely secondary outcomes [26,27]. Borszewska Kornacka et al [6] in their multi-centric study found that early caffeine therapy had better IVH outcomes compared to late caffeine therapy as against our observations. However in their study they had defined early caffeine as caffeine administration within first 24 hours of life only, compared to our study where we included newborns who received caffeine within first 72 hours of life in the early caffeine group.

Review of pathogenesis of GM bleed/IVH in prematurity reveals that GM bleed/IVH occurs in 3 days of post-natal life in extreme premature babies. After 3 days of post-natal life the tendency of GM to bleed is markedly reduced, despite fluctuations in cerebral blood flow, irrespective of gestational age [26].

Caffeine acts on cerebral vessels especially GM by vasoconstriction [28,29]. Hypoxemic insult to GM triggers up regulation of VEGF, increased expression of angiopoietin and reduced expression of GFAP leading to increased propensity of GM bleed/IVH bleed [30,31].

The results of our study in the analysis of early vs late caffeine therapy in preterm babies reveals significant mortality and progression of GM bleed /IVH in early caffeine group compared to significant survival and non-progression of IVH in late caffeine group, which makes us to presume that early caffeine initiation in preterm babies could be factor in the development of IVH with an outcome of increased mortality.

CONCLUSION

We, therefore, conclude that early caffeine initiation (<72 hours of post-natal life) in preterm babies could be a risk factor in development of GM bleed/ IVH leading to mortality, either alone or along with other risk factors of prematurity. It therefore demands more controlled studies on large samples at various centers (A Multicentric study) to establish probable risk of IVH in early caffeine initiation therapy among preterm babies to confirm the hypothesis.

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Conflicts of Interest

The authors declare no conflicts of interest.

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