ORIGINAL RESEARCH ARTICLE

NATIONAL JOURNAL NJMR MEDICAL RESEARCH

High Vs Low Dose Caffeine in Management of Apnea of Prematurity: A Single-Center Observational Study

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DOI:
10.55489/njmr.150420251151

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Date of Submission: 18/06/2025
Date of Acceptance: 02/09/2025
Date of Publication: 01/10/2025

Funding Support:
None Declare

Conflict of Interest:
The authors have declared that no conflict of interests exists.

How to cite this article:
Shroff BN, Singh P, Surana AU, Chaudhari A. High Vs Low Dose Caffeine in Management of Apnea of Prematurity: A Single-Center Observational Study. Natl J Med Res 2025;15(04):280-285.
DOI: 10.55489/njmr.150420251151

ABSTRACT

Background: Apnoea of prematurity is one of the leading causes of apnoea in preterm infants leading to hypoxia and deleterious neurodevelopmental outcomes. Caffeine has been used for management for apnea but the optimum dose has not been well investigated and a wide variety of the dose are under trials. The study aimed to compare the efficacy and safety of high and low dose caffeine.

Methodology: All the preterm infants with gestational age <34weeks and fulfilling our inclusion criteria were included in study. Babies born between the dates August 2023 to January 2024 were studied prospectively (Group A) and those between July 2022 to December 2022 were studied retrospectively (Group B). The infants included in Group A were given high dose caffeine (loading 40mg/kg/day and maintenance 20mg/kg/day) vs low dose caffeine was given to the Group B infants (loading dose 20mg/kg/day and maintenance 10mg/kg/day) and they were followed up based on their oxygen requirements, frequency of apnoea episodes, duration of NICU stay, duration of ventilation and successful extubation.

Results: High dose caffeine was found to be effective in reducing duration of oxygenation (p value 0.003) and duration of NICU stay (p value 0.03). There was no statistical significance found in frequency of apnea episodes, side effects and successful extubation between both the groups.

Conclusion: High dose is preferred as the duration of oxygenation and the hospital stay is shortened with no increase in side effects.

Keyword: Prematurity Apnoea, Caffeine Dose, NICU Stay, Oxygenation, Extubation

INTRODUCTION

Apnea is defined as cessation of respiration for more than 20 seconds or cessation of breathing for less than 20 seconds which is accompanied with bradycardia or oxygen desaturation.[1] Apnea in preterm infants is usually related to immaturity of central nervous system and is called as apnea of prematurity (AOP). It is a developmental disorder that occurs as a result of immature respiratory control mechanisms and hence exhibits a widely variable incidence depending on gestational age and birth weight.

It is estimated to occur in almost all infants born at <29 weeks gestation or <1kg [2], 50% of infants born between 30 to 32 weeks, and in 7% of infants born at 34-35 weeks gestation [3].

Caffeine is effective in reducing the number of apneic attacks and use of mechanical ventilation, duration of mechanical ventilation and used to facilitate extubation of preterm infants.[4] Several studies using different loading and maintenance doses for caffeine have showed variable results like Mohammed et al. conducted in 2015 showed a reduction in extubation failure and

Publisher: Medsci Publications [www.medscipublications.com] ISSN: 2249 4995 Official website: www.njmr.in

reduced frequency of apnea episodes.[5] A Cochrane review with 7 studies in review on total 894 preterm newborns , concluded that high dose caffeine strategies reduce death prior to hospital discharge and unwanted side effects and high dose caffeine strategies probably reduce rates of chronic lung disease.[6]

This study was conducted to compare the efficacy of high dose caffeine v/s low dose for apnea of prematurity in our setup.

MATERIALS AND METHODS

The study was carried at NICU at tertiary care center over a duration of 12 months (prospective data collected between August 2023 to January 2024 and retrospective data collected from July 2022 to December 2022).

Study design: Cohort study

Group A: It includes babies admitted at our NICU between August 2023 to January 2024 and fulfilling our inclusion criteria who were given high dose caffeine i.e. loading dose 40mg/kg/day and maintenance dose 20 mg/kg/day.

Group B: It includes the neonates who were given low dose caffeine (i.e. loading dose 20mg/kg/day and maintenance dose 10mg/kg/day) and this treatment was given before the new guidelines for use of high dose caffeine [7] had been implemented, hence that data was collected from the case sheets submitted and were studied retrospectively.

Sample size: During the retrospective data collection period (July-December 2022), 44 eligible children who had received low-dose caffeine were identified and included in the study. For comparison, an equal number of gestational age-matched children (±1 week) who had received high-dose caffeine following the implementation of the new guideline (August 2023–January 2024) were selected. Thus, a total of 44 children were allocated to Group A (high-dose caffeine) and 44 children to Group B (low-dose caffeine).

Inclusion Criteria: The study includes preterm infants who meet specific gestational age and birth weight criteria. This includes infants born at or before 32 weeks of gestation and/or those with a birth weight of 1.2 kg or less, provided they receive prophylactic caffeine therapy in both Group A and Group B. Additionally, preterm infants born between 32 and 34 weeks of gestation who develop apnea within the first 14 days of life and are treated with caffeine therapeutically are also included in both groups.

Exclusion Criteria: Infants with major congenital malformations are excluded from the study, as well as those with a birth weight below 500 grams or a gestational age of less than 26 weeks. Newborns who die within the first 24 hours of life are also excluded. Furthermore, infants whose apnea is attributed to other identifiable causes such as hypoglycemia, hypothermia, hypocalcemia, birth asphyxia, intraventricular hemorrhage, or sepsis are not included in the study.

Duration of Caffeine therapy: These patients were given caffeine until 34 weeks postmenstrual age and stopped thereafter if no episode of apnea has occurred in last 7 days.[8]

Ethical Approval: The study was approved by Institutional Ethics Committee (Reference number -103 dated 02/11/2023). An informed consent from the parent/ guardian of these neonates who were included in group A was taken and as group B data was studied retrospectively consent could not be taken.

Study flow: We included all the preterm neonates born before gestational age 34 weeks admitted at our NICU as per inclusion criteria. Maternal and neonatal data was collected and entered and relevant investigations under strict aseptic precautions were sent to laboratory (Complete blood count for Hb and Hematocrit, CRP, Blood culture, Electrolytes, S. Calcium, arterial blood gas analysis). Other investigations like CXR, USG skull as per the protocol for the secondary causes of apnea were done and neonates having apnea due to prematurity were included in our study.

The Group A neonates {who were given high dose caffeine (loading dose: 40mg/kg/day and maintenance dose: 20 mg/kg/day)} were than studied prospectively and the preterm neonates were treated according to the routine NICU protocol for fluids, nutrition, thermal control and monitored for complications like apnoea. The infants were followed up based on their oxygen requirements, frequency of apnoea episodes, duration of NICU stay, duration of ventilation and successful extubation and all these was noted.

The neonates included in group B {who were given low dose caffeine (loading dose: 20mg/kg/day and maintenance dose: 10mg/kg/day)} were studied retrospectively by collecting all the data from the case sheets submitted in hospital records and all the relevant data was noted.

Some of the infants inspite of proper ventilation by CPAP may require mechanical ventilation were labelled as CPAP failure.[9] Certain infants after adequate mechanical ventilation when extubated required reintubation within 24 hours and were included under extubation failure.[10] Various known side effects of caffeine were noted as described below for comparing the incidence in both high and low dose caffeine groups.[11]

After collecting all these data both the groups were compared to find out its efficacy in both preventing and treating apnea of prematurity from the entry point till discharge.

The efficacy was then studied based on: Total Number of apnoea episodes during course of NICU stay, total Requirement of oxygenation, and duration of CPAP/ Mechanical ventilation.

Outcome was defined in terms of need for upgradation of respiratory support, incidence of CPAP failure, inci-

dence of extubation failure, and final outcome like discharge or death.

Development of side effects of caffeine like tachycardia, vomiting, abdominal distension, jitteriness, hyperglycemiawere noted and compared in both groups and all the standard definitions were followed.

Statistical Analysis: Data was entered into MS Excel database and then analyzed using OpenEpi software. The results obtained were then described by tables and statistical charts. The analysis of the patient demographics and baseline outcome variables was done by using descriptive statistics (frequencies and percentages for categorical variables) and analytical statistics were expressed as means (± standard deviation) for continuous variables. Categorical data was compared using chi-square test, t-test for independent samples. P value <0.05 was considered significant.

RESULTS

This study was done over a duration of 12 months (which includes the prospective and retrospective study duration) at a NICU of a tertiary care centre. During this period 720 neonates were admitted for prematurity (less than 37 weeks of gestational age) amongst which 170 babies were preterm and eligible for the study. Out of these, 82 babies were excluded (as 59 had apnoea due to secondary causes, 15 expired within 24 hours of admission, 5 had birth weight <500gm/<26 weeks,3 had major congenital malformations) hence the rest 88 babies were included in the study. Amongst these 44 babies were given high dose caffeine and they were followed up clinically based on their frequency of apnoea episodes, duration of NICU stays, duration of ventilation and side effects if any. And 44 babies who were given low dose caffeine were studied retrospectively by collecting the data from the case sheets.

The study population consisted of 88 participants, divided equally into high dose and low dose groups with 44 participants each. The mean birth weight for high dose group was 1.24 kg (±0.31) compared to 1.13 kg (±0.16) for the low dose group, and it was found to be statistically significant (p value 0.04). No statistical significance was found in any other parameter. Baseline maternal characteristics in both groups were almost similar (table 1).

No statistical significance was found between the dose and frequency of apnea episodes. Here we have considered the O2 requirements in all forms: only oxygen therapy, CPAP and mechanical ventilation all. A statistical significance was found between the dose of caffeine and duration of oxygenation (p value 0.003). No significance found between dose of caffeine and extubation failure (table 2).

The outcome was found to be better in terms of discharge rate. In neonates on high dose caffeine therapy discharge rate was 32(72%) whereas in those receiving low dose caffeine was 22 (50%). The percentage of death in those using high dose caffeine was 8(18%) whereas in those receiving low dose caffeine was 13(29%). Hence, we could say that high dose caffeine is beneficial and has better outcomes though not statistically significant (table 3).

Table 1: Baseline characteristics of the studied groups

Characteristics	Group A (n=44) (%) Mean (SD)	Group B (n=44) (%) Mean (SD)	Total (n=88) (%) Mean (SD)	P value
Neonatal data				
Gestational age(weeks)	31.07(±4.92)	31.06(±1.60)	31.42(1.76)	0.98
Birth weight(kg)	1.24(±0.31)	1.13 (±0.16)	1.19(0.25)	0.04
Gender				
Male	26(59)	21(47.7)	47(53)	0.28
Female	18(40)	23(52.2)	41(46)	
Weight for gestation				
SGA	20(45.5)	14(31.8)	34(38.6)	0.18
AGA	24(54.4)	30(68.1)	54(61)	
Duration of caffeine therapy given (days)	10.86(±4.64)	9.97(±6.19)	10.42(±5.46)	0.44
Day of life of starting caffeine therapy	1.38(±0.96)	1.55(±0.42)	1.27(±0.75)	0.28
Total number of doses of surfactant therapy (n= no. of babies)				
1 dose	10(22.7)	5(11.3)	15(17)	0.82
2 doses	4(9)	7(15.9)	11(12.5)	
Total	18	19	37	
Maternal Data				
Mode of delivery				
Vaginal	20(45.5)	22(50)	42(47.7)	0.66
Cesarean	24(54.4)	22(50)	46(52.4)	
Antenatal steroid therapy	29(65)	27(61.3)	56(63)	0.65
Gravida				
Primigravida	20(45.5)	23(52.2)	43(48.8)	0.52
Multigravida	24(54.5)	21(47.7)	45(21.1)	

Table 2: Caffeine and frequency of apnea episodes and mean duration of requirement of oxygenation

Variable	Group A (%)	Group B (%)	Total (%)	P value
No. of apnea episodes				
1 episode	10(22.2)	7(15.5)	17(37.7)	0.41
2 episodes	5(22.2)	9(40)	14(62.2)	0.24
Total number of apnea episodes	20(44.4)	25(55.5)	45	0.28
Mean duration of requirement of oxygenation Mean (SD)	2.88(1.13)	3.63 (1.61)	3.25 (1.93)	0.01
Extubation failure	1(50%)	1(50%)	2	>0.999
Duration of only oxygen therapy (days)	2.26(±1.01)	2.96(±2.95)	2.63(±2.25)	0.22
Duration of CPAP (days)	2.90(±1.91)	3.95(±3.05)	3.40(±2.30)	0.14
Duration of mechanical ventilation (days) Mean(±SD)	6.5(±3.47)	4.63(±4.58)	5.60(±4.06)	0.28

Table 3: Impact of caffeine on neonatal outcome

Duration (in days)	High dose (n=44) (%)	Low dose (n=44) (%)	Total (n=88) (%)	P value	Odd's Ratio (CI)
Outcome					
Discharge	32(72)	22(50)	54(61)		Ref
Death	8(18)	13(29)	21(23)	0.104	0.42 (0.15-1.19)
LAMA	4(9)	9(20)	13(14.7)	0.073	0.31 (0.08-1.12)
CPAP required					
Yes	22(50)	21(47.7)	43(48.8)	0.831	1.10 (0.47-2.53
No	22(50)	23(52.2)	45(51.1)		Ref
Mechanical Ventilation required					
Yes	12(27.2)	11(25)	23(26.1)	0.808	1.13 (0.43-2.91)
No	32(72.7)	33(75)	65(73.8)		Ref
Duration of NICU stay Median [IQR]	18[12,25]	16[7,29]		0.030	
Total patients having side effects	17(38.9)	13(29.5)		0.360	

(CI= Confidence interval)

There was no increase in the number of side effects with higher dose caffeine. Although a statistical significance was found in tachycardia which was noted in 8 neonates on high dose and 2 neonates on low dose caffeine (p value 0.04). No statistical significance found in other side effects like cyanosis, vomiting, abdominal intolerance and hyperglycemia. Mean of duration of NICU stay was longer in neonates receiving low dose caffeine (p value 0.03).

DISCUSSION

Our study is a cohort study done prospectively for infants receiving higher dose of caffeine and done retrospectively for infants who were on low dose caffeine therapy to evaluate for the efficacy, safety, overall hospital course up to hospital discharge of two different dosing regimens of caffeine citrate for apnea of prematurity.

In this study it was found that high dose was more effective in reducing duration of oxygenation (p value 0.003) and hospital stay (p value 0.03). There was decrease in the apnea episode though not significant. There was no difference in mechanical ventilation, CPAP and extubation failure.

Number of apnea episodes: In our study, in the babies receiving high dose therapy the total number of episodes of apnea were less than the number of apnea episodes in the neonates who had received low dose caffeine therapy. We did not find any statistical significance between the two groups. Mohammed et al (2015) showed decreased frequency of apnea episodes (p value <0.001) [5] and in another study Steer et al (2004) also showed similar results of decreased frequency of apnea episodes (p value <0.01) [12] with higher doses of caffeine. Also, Scanlon et al (1992) showed reduction in the number of apnea episodes by $1/3^{RD}$ within 24hours by standard dose vs reduction by >50% with the higher dose of caffeine.[13] Caffeine enhances the lung function improving the central respiratory drive [14] and also respiratory muscle strength [15]. In the current study, infants in high dose group had gained more respiratory benefit as evidenced by less documented number of apnea episodes and decreased requirements for duration of oxygenation.

Requirement of mechanical ventilation: Out of total 88 newborns studied in our study, infants on high dose required the mean duration of ventilation for 6.5 (± 3.47) days compared to 4.63 (±4.5) days in low dose group. Thus, in our study, there was no reduction on duration of mechanical ventilation in the neonates receiving high dose caffeine as compared to the low dose group. Similar results were obtained in the study by Mohammed S et al who also noted that the high-dose caffeine had no significant impact on requirement of mechanical ventilation.[5] Unlike our study, Steer et al. in a study of 234 preterm infants studied a high dose regimen of 20 mg/kg and low-dose regimen of 5 mg/kg showed that there is a significant difference in terms of duration of mechanical ventilation in both the groups of neonates <28 weeks (p value = 0.01).[12]

Impact of caffeine on duration of hospital stay: In our study, High dose caffeine was associated with statistically significant reduction in the duration of NICU stay (p

value 0.03), whereas a study by Mohammed S et al showed that there was no difference in both the groups in terms of duration of hospital stay.[5]

Impact of caffeine dose and associated side effects: In our study there was statistically significant incidence of tachycardia (p value 0.04) in those who were given high dose caffeine therapy than the neonates receiving low dose caffeine. Similarly, in a study by Mohammed et al he found out a significant increase in the incidence of tachycardia (p value 0.04).[5]

Extubation Failure: In our study 1 neonate of each group had extubation failure which was not statistically significant. This was different from other studies by Mohammed et al who had found a reduced incidence of extubation failure (p value 0.02) [5] and Steer et al in which loading dose of caffeine was given 24 hours of planned extubation or within 6 hours of an unplanned extubation and had found a statistically significant reduction in incidence the incidence of extubation failure (p value <0.01) [13]. In a study by Brattstrom (2019) had noted reduction in the cases of extubation failure (defined by author as RR 0.51, 95%CI 0.36-0.71).[16]

LIMITATIONS

The study has limitations, including the inability to assess long-term outcomes of caffeine therapy. Comparing retrospective and prospective data may have introduced bias, especially regarding modifiable risk factors. Additionally, although a statistically significant difference in birth weight was found between the two groups a factor linked to poor neonatal outcomes no statistical adjustment was made.

CONCLUSION

High dose caffeine was associated with lesser duration of oxygenation (p value 0.003) and lesser duration of NICU stay (p value 0.03). We also found decrease in the number of apnoea episodes but there was no statistical significance associated.

Acknowledgment: We would also like to express my sincere thanks to SMIMER Hospital for providing the necessary resources and support. Especially thankful to all the patients who participated in the study their cooperation and trust formed the foundation of this research.

Author's Contribution: BNS contributed to the study conception, study design, data collection, data analysis and interpretation, and manuscript preparation. **PS** was involved in the study conception, study design, data analysis and interpretation, and manuscript preparation. **AS** contributed to the study conception, study design, and data analysis and interpretation. **AC** contributed to the study design and data analysis and interpretation.

Availability of Data: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declaration of Non-use of generative AI Tools: This article was prepared without the use of generative AI tools for content creation, analysis, or data generation. All findings and interpretations are based solely on the authors' independent work and expertise.

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