Original Article

DOI: 103126/JNPS.V4113

The Efficacy and Safety of Once Daily versus Twice Daily Dosing of Caffeine Citrate in Apnea of prematurity: a Randomised Control Trial

Farooq Syed,[1] Sandesh Kini,[2] Abdul Majeed[3]

[1]Department of Paediatrics, Mount Zion Medical College, Chayalode Post, Enadimangalam, Kerala 691556, India.
[2]Department of Paediatrics, Kasturba Medical College, Manipal, Manipal Academy of Higher Education, Manipal, Karnataka, India
[3]Department of Paediatrics, CRAFT Hospital NICU, CRAFT Hospital and Research Centre, Kodungallur, Thrissur, Kerala, India.

Article History
Received On: May 18, 2021
Accepted On: Apr 05, 2022

Funding sources: None

Conflict of Interest: None

Keywords: Randomised control trial; caffeine citrate, apnea of prematurity, efficacy and safety

Online Access

DOI: https://doi.org/10.3126/jnps.v42i1.37173

***Corresponding author**

Sandesh Kini
Associate Professor,
Department of Paediatrics,
Kasturba Medical College, Manipal,
Manipal Academy of Higher Education,
Manipal, Karnataka, India
Email: sandesh.kini@manipal.edu

Abstract

Introduction: Caffeine citrate is widely used for prevention of apnea of prematurity and helps in successful extubation from mechanical ventilation. The optimum caffeine dose in preterm infants with apnea of prematurity has been extensively investigated with varied results. The objective of our study was to compare the efficacy and safety of once versus twice daily maintenance dose of caffeine citrate in premature infants with apnea.

Methods: In this study, preterm neonates with gestational age of 28 to 34 weeks, with evidence of apnea of prematurity were included. Both groups received a 20 mg / kg loading dose of caffeine citrate followed by a maintenance dose of 2.5 mg / kg every 12-hour-interval in group 1 and 5 mg / kg every 24-hour-interval in group 2, either orally or by intravenous infusion. Response to treatment, duration to achieve full feeds, possible adverse reactions were evaluated and compared among the two groups.

Results: Among two groups, group 1 had early reduction in number of apneic episodes on five consecutive days after loading dose, which was statistically significant. Time taken to establish full feeds following treatment initiation was lower in group 1 compared to group 2 (median: Two vs four days) which was statistically significant.

Conclusions: In this study, neonates who received twice daily maintenance dose of caffeine citrate had better outcomes in terms of early reduction in number of apneic episodes and early feed establishment when compared to those receiving once daily maintenance dose of caffeine citrate.

Introduction

The incidence of apnea of prematurity (AOP) increases as gestational age decreases, from 7% of neonates born at 34 to 35 weeks to nearly 100% of those born before 29 weeks.[1] Severe apnea (Lasting longer than 20 seconds) is usually associated with bradycardia or desaturation, which may in turn lead to disturbances of cerebral hemodynamics, subsequently impacting neurodevelopment.[2] Methylxanthine therapy is the mainstay of pharmacologic therapy for AOP.[3] Compared with theophylline, caæine citrate has a longer half- life and does not require drug- level monitoring, and is therefore described in guidelines as generally preferred.[4] The current standard dosing regimen for caffeine citrate which has been widely used is 20 mg / kg (or 10 mg / kg as caffeine base) loading dose as intravenous (IV) infusion followed by 5 mg / kg / day (or 2.5 mg / kg as caffeine base) as maintenance dose.[5] We hypothesized that the 12-hour-interval of caffeine leads to more stable plasma drug

concentrations and improves neonatal outcome compared to once-daily dosing regimen. The primary objective of this study was to compare the efficacy of two different maintenance dosing regimen of caffeine citrate in decreasing the number of apneic episodes and comparing feed tolerance among preterm neonates between 28 to 34 weeks of gestation. The secondary objective of this study was to compare heart rate, daily weight monitoring and adverse effects of two different maintenance dosing regimen of caffeine citrate among preterm neonates between 28 to 34 weeks of gestation.

Methods

This study was a randomized clinical trial conducted between June 2018 to June 2019 at a level IIIa neonatal intensive care unit (NICU) in CRAFT Hospital and Research Centre, Thrissur, India. Study protocol was approved by the institutional ethics committee. Informed signed consent was obtained from the parents of newborns who were recruited into the study. All preterm neonates between 28 to 34 weeks of gestation with AOP defined as a pause of breathing for more than 15 to 20 seconds, or accompanied by oxygen desaturation (SpO2≥ 80% for ≥ four seconds) and bradycardia (Heart rate < 2 / 3 of baseline for ≥four seconds) were included in the study.[6] Neonates with birth asphyxia, meconium aspiration syndrome (MAS), hypoglycemia, intracranial ventricular haemorrhage (IVH), sepsis, haemodynamically significant cardiac anomaly, other major congenital anomalies and previous exposure to methylxanthine therapy were excluded. If the neonate met the inclusion criteria, he / she was enrolled and randomly assigned to one of the two study groups with a 1:1 allocation as per a computer-generated randomisation schedule. Demographic characteristics (Gestational age, gender, birth weight, type of delivery and APGAR score at 1 and 5 minutes after birth, antenatal steroids, surfactant therapy) were recorded. In addition, heart rate, daily weight monitoring, oxygen saturation (SpO2), apneic events based on the values registered in the daily sheets were recorded for all neonates.

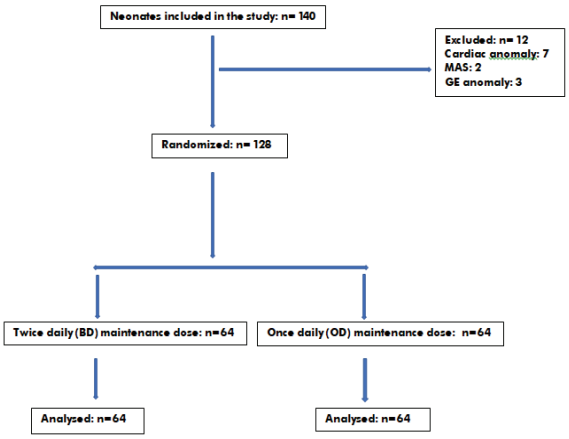
Both groups received a 20 mg / kg loading dose of caffeine citrate (or 10 mg / kg as caffeine base) which was administered intravenously over 30 minutes on day one of life followed by a maintenance dose of 2.5 mg / kg (1.25 mg / kg as caffeine base) every 12-hour-interval in group 1 and 5 mg / kg (or 2.5 mg / kg as caffeine base) every 24 hours in group 2, orally or by IV infusion over 20 minutes. Neonates receiving maintenance dose of caffeine citrate, were continued on treatment until they reached an age of 37 weeks or had five to seven days without significant apnea events. Significant apnea events were defined as those accompanied by desaturation < 80% SpO2 and / or bradycardia with heart rate < 100 beats per minute. The possible adverse drug reaction of caffeine including tachycardia, feed intolerance, hyperglycemia or hypertension were investigated. Feed intolerance was defined as the presence of one or more signs leading to the interruption of enteral feeding regime of the preterm as increased gastric residuals > 50% of the previous feeding, emesis, abdominal distention with increase in abdominal girth by 2 cm or more in between feedings, bloody stool, diarrhea and visible bowel loops.[7] Side effects and clinical worsening were used to assess tolerability. The above mentioned parameters were assessed since the time of caffeine therapy initiation until the completion of treatment.

All statistical analyses were done using statistical package for the social sciences (SPSS) version 25 (IBM® SPSS® Statistics) and a p-value of 0.05 was considered statistically significant. Number and percentage were used to represent the qualitative variables and mean ± standard deviation (SD) were used for the quantitative variables. Since data was not supporting normal distribution, nonparametric technique was adopted. Continuous variables of two groups were compared using Mann– Whitney U test. The number of apnea events and bodyweight were compared to baseline among two groups by means of Mann- Whitney U test.

Results

In this randomised clinical trial, a total of 140 neonates were included with gestational age between 28 to 34 weeks. Of those who were excluded, seven neonates had haemodynamically significant cardiac anomalies, two neonates had MAS and three neonates had gastro-esophageal (GE) anomalies. Hence a total of 128 neonates were randomised into two groups of 64 each as per a computer-generated randomisation schedule.

Figure 1. Participant CONSORT flow diagram



The demographic and clinical characteristics were comparable among the two groups as depicted in table 1. The mean birth weight among group 1 and 2 were 2043.50 ± 181.13 grams and 1982.25 ± 181.13 grams respectively. Majority of the neonates were born by emergency LSCS (82.8% vs 84.3%) and did not require resuscitation. Antenatal steroids were received by 95% of the mothers in both groups and hence 90% of the neonates did not require surfactant.

Table 1. Demographic data and clinical characteristics

Variables		Group 1 (BD): n = 64	Group 2 (OD): n = 64
Gender	Male	35 (56.7%)	38 (57.4%)
	Female	29 (45.3%)	26 (42.6%)
Gestational age in weeks	28 to 28 6/7	2 (3.1%)	0 (0%)
	29 to 29 6/7	9 (14.0%)	7 (10.9%)
	30 to 30 6/7	8 (12.5%)	14 (21.8%)
	31 to 31 6/7	24 (37.5%)	17 (26.5%)
	32 to 32 6/7	14 (21.8%)	15 (23.4%)
	33 to 33 6/7	7 (10.9%)	11 (17.1%)
Birth weight in grams: (Mean, SD)		2043.50 ± 181.13	1982.25 ± 181.13
Mode of delivery	NVD	4 (6.1%)	3 (4.6%)
	AVD	2 (3.1%)	4 (6.2%)
	El LSCS	5 (7.8%)	3 (4.6%)
	Em LSCS	53 (82.8%)	54 (84.3%)
Mode of resuscitation	No resuscitation	52 (81.2%)	50 (78.1%)
	B & M V	10 (15.6%)	13 (20.3%)
	B & T V	2 (3.1%)	1 (1.5%)
APGAR score @ 1 min	6	0 (0.0%)	2 (3.1%)
	8	28 (43.7%)	30 (46.8%)
	9	36 (56.2%)	32 (52.4%)
APGAR @ 5min	8	5 (7.8%)	5 (7.8%)
	9	59 (92.1%)	59 (92.1%)
Antenatal steroids	Received	61 (95.3%)	61 (95.3%)
	Not received	3 (4.6%)	3 (4.6%)
Surfactant (INSURE/LISA)	Received	6 (9.3%)	4 (6.2%)
	Not received	58 (90.6%)	60 (93.7%)

NVD: Normal vaginal delivery, AVD: Assisted vaginal delivery, El LSCS: Elective lower segment caesarean section, Em LSCS: Emergency LSCS, B & MV: Bag and mask ventilation, B & TV: Bag and tube ventilation, APGAR: Appearance Pulse Grimace Activity Respiration, INSURE: intubate surfactant extubate, LISA: less invasive surfactant administration.

In this study the time taken to establish full feeds following the administration of loading dose of caffeine was significantly lower in group 1 receiving twice daily maintenance dose of caffeine (Median: Two days) compared to group 2 receiving once daily maintenance dose of caffeine (Median: Four days). The time taken to achieve 50% reduction in the number of apneic spells from baseline following loading dose of caffeine was significantly lower in group 1 (Median: Two days) compared to group 2 (Median 3.5 days) as depicted in table 2.

Table 2. Time taken to establish full feeds and to reduce apneic episodes among two groups

Variables	Group 1 (BD): n = 64	Group 2 (OD): n = 64	p value
Time taken to establish full feeds following treatment initiation: in days (Median, IQR) / (Mean ± SD)	2.00 (3 - 2) 2.43 ± 0.74	4.00 (5 - 4) 4.40 ± 1.30	< 0.001
Time taken to achieve 50% reduction in apneic spells from baseline following treatment initiation: in days (Median, IQR) / (Mean ± SD)	2.00 (2 - 1) 1.73 ± 0.75	3.55 (4 - 3) 3.52 ± 1.20	< 0.001

IQR: inter-quartile range, SD: standard deviation

The median number of apneic episodes on consecutive days following loading dose of caffeine was significantly lower in group 1 compared to group 2 as depicted in table 3.

Table 3. Number of apneic episodes on consecutive days among two groups

Number of apneic episodes	Group 1 (BD): n = 64	Group 2 (OD): n = 64	p value
Day 2 (Median, IQR) (Mean ± SD)	3 (4 - 2) 3.14 ± 1.06	4 (4 - 3) 3.71 ± 0.93	0.002
Day 3 (Median, IQR) (Mean ± SD)	2 (3 - 1) 1.93 ± 1.35	3 (4 - 2) 2.78 ± 1.25	0.001
Day 4 (Median, IQR) (Mean ± SD)	1 (2 - 0) 1.10 ± 1.20	2 (3 - 1) 2.24 ± 1.15	< 0.001
Day 5 (Median, IQR)(Mean ± SD)	0 (1 - 0) 0.71 ± 0.94	1 (2 - 0) 1.29 ± 1.22	0.008
Day 6 (Median, IQR) (Mean ± SD)	0 (1 - 0) 0.40 ± 0.65	1 (2 - 0) 0.89 ± 0.92	0.001

The mean heart rate on consecutive days following loading dose of caffeine was significantly lower in group 1 compared to group 2 as depicted in table 4. The mean weight on consecutive days was significantly higher in group 1 compared to group 2 as depicted in table 4.

Table 4. Variation of heart rate and weight on consecutive days

Variable	Day	Group1 (BD): n = 64	Group 2 (OD): n = 64	P value
Heart rate in beats per minute (Mean, SD)	2	137 ± 5.33	151 ± 5.29	< 0.001
	3	137 ± 4.41	152 ± 4.88	< 0.001
	4	136 ± 4.90	152 ± 5.32	< 0.001
	5	135 ± 4.09	150 ± 4.99	< 0.001
	6	133 ± 3.57	150 ± 5.04	< 0.001
Weight in grams (Mean, SD)	2	2043.50 ± 181.13	1982.25 ± 181.13	0.048
	3	2033.00 ± 179.71	1963.41 ± 168.93	0.013
	4	2023.00 ± 177.75	1952.00 ± 170.97	0.011
	5	2016.00 ± 178.16	1841.63 ± 170.85	0.009
	6	2009.42 ± 176.85	1927.00 ± 166.17	0.003

Adverse effects among both the groups could not be assessed due to less numbers. However, two neonates had hyperglycemia and three neonates had feed intolerance in group 2. None of the neonates in group 1 had adverse reactions following treatment.

Discussion

In this study, we compared two different dosing regimen of caffeine citrate (Once daily vs twice daily divided doses) in terms of its efficacy, safety and short-term effects in the treatment of AOP. We used the current standard dose of caffeine citrate ie 20 mg / kg as caffeine base for loading followed by 2.5 mg / kg as caffeine base for maintenance therapy.[5] However, caffeine loading doses (10 to 40 mg / kg caffeine base) and maintenance doses (2.5 to 10 mg / kg / d caffeine base) have been used by various studies.[8] Nevertheless, the optimum caffeine dose in preterm infants with AOP has not been well studied. There are heterogeneous reports on the optimal loading and maintenance dose of caffeine in several studies in terms of benefits and risks.[9-11]

Our study showed that those babies receiving twice daily divided dose of caffeine had 50% reduction in apneic episodes from baseline within two median days compared to 3.5 median days in babies receiving single daily dose and the results were statistically significant. In our study the median number of apneic episodes on consecutive days was significantly lower in group 1 (BD) achieving a median of zero episodes by day five compared to group 2 (OD) and the results were statistically significant. A randomized double - blind clinical trial conducted by Steer et al comparing three dosing regimens of caffeine (3, 15 or 30 mg / kg) for periextubation control of premature infants revealed that the infants in higher dose group had lower apnea events through the week after extubation.[12] A study done by Mohammed S et al comparing high-dose (Loading 40 mg / kg / day and maintenance of 20 mg / kg / day) versus low-dose (Loading 20 mg / kg / day and maintenance of 10 mg / kg / day) caffeine citrate in preterm infants < 32 weeks with AOP showed that high-dose caffeine was associated with a significant reduction in extubation failure in mechanically ventilated preterm infants ($P < 0.05$), the frequency of apnea ($p < 0.001$), and days of documented apnea ($p < 0.001$).[10] A study by Zhao et al comparing two different maintenance doses of caffeine (5 mg / kg / day vs 15 mg / kg / day) in preterm infants with apnea found that the number of apneas in the high - dose group was significantly lower than that of the low-dose group [Median / IQR: 10 (8, 15) vs 18 (13, 22) times, $Z = -2.610$, $p = 0.009$].[11] However the study done by Rebentisch A et al in neonates less than 32 weeks of gestation with AOP comparing once daily versus twice daily dosing regimen of caffeine (maintenance dose-10 mg / kg / day), found no significant difference in the five-day average incidence of apnea and bradycardia events (Median : 6.2 vs 6.4, $p = 0.09$).[13]

In this study, the neonates receiving twice daily dose of caffeine achieved full feeds significantly earlier (Median days: 2 vs 4) than those receiving once a day caffeine. Caffeine is generally well tolerated with lower rate of adverse effects.[14] In our study five neonates in group 2 (OD) had adverse reactions in the form of hyperglycemia and feed intolerance compared to none in group 1 (BD). In the study by Steer et al the total mean days of feed intolerance was higher in the group receiving 30 mg / kg caffeine than the 3 mg / kg group.[12] In our study the mean heart rate among group 1 (BD) on consecutive days was significantly lower than that in group 2 (OD). In the study by Faramarzi et al comparing single versus twice daily divided dose of caffeine, none had tachycardia.[9] However hyperglycemia and hypertension episodes were lower in preterm infants that received caffeine twice a day compared to those with once-daily-dose.[9] The lower frequency of short- term adverse effects of caffeine in twice-daily-dose group was attributed to the stable concentrations and lower plasma peak levels of caffeine following the twice-daily-dose administration.[9] In the study by Steer et al there was no statistically significant difference in the number of infants experiencing tachycardia while receiving three different doses of caffeine (3, 15, 30 mg / kg).[12] However in the study by Mohammed S et al more patients in high-dose caffeine group (23%) experienced tachycardia compared to the low- dose group (23 vs 8 %, $p < 0.05$) with no significant difference in the incidence of hypertension or time to reach full enteral feeding.[10]

Through this study we have highlighted the beneficial effects of twice daily divided dose of caffeine citrate, using the standard dose regimen in the treatment of AOP. The limitations of our study is that the sample size was not calculated statistically. A pilot study was not done to assess / calculate the sample size. We did not measure the serum levels of caffeine among both the groups. However, it does show some light upon the advantages of twice daily dosing of maintenance caffeine therapy than single daily dose. We recommend that our study results need to be verified in larger, multi centric trials in the future.

Conclusions

In this randomised clinical trial, preterm neonates between 28 to 34 weeks of gestation with apnea of prematurity who received twice daily maintenance dose of caffeine citrate had better outcomes in terms of early reduction in number of apneic episodes and early feed establishment when compared to once daily maintenance dose of caffeine citrate. These beneficial effects may be attributed to a more steady-state plasma level of caffeine in infants receiving twice daily divided dose.

References

1. Zhao J, Gonzalez F, Mu D. Apnea of prematurity: from cause to treatment. Eur J Pediatr. 2011 Sep;170(9):1097-105. PMID: 21301866.
DOI: 10.1007/s00431-011-1409-6.

2. Poets CF, Roberts RS, Schmidt B, Whyte RK, Asztalos EV, Bader D, et al. Canadian Oxygen Trial Investigators. Association Between Intermittent Hypoxemia or Bradycardia and Late Death or Disability in Extremely Preterm Infants. JAMA. 2015 Aug 11;314(6):595-603.
DOI: 10.1001/jama.2015.8841.

3. Henderson-Smart DJ, De Paoli AG. Methylxanthine treatment for apnoea in preterm infants. Cochrane Database Syst Rev. 2010 Dec 8;(12):CD000140. PMID: 21154343
DOI: 10.1002/14651858.CD000140.pub2.

4. Henderson-Smart DJ, Steer PA. Caffeine versus theophylline for apnea in preterm infants. Cochrane Database Syst Rev. 2010 Jan 20;(1):CD000273.
DOI: 10.1002/14651858.CD000273.pub2.

5. Garg S, Lal M, Tin W. Apnoea in premature infants and caffeine therapy. Infant. 2013; 9(1): 9-12

6. Eichenwald EC and AAP committee on fetus and newborn. Apnea of Prematurity. Pediatrics. 2016;137(1):e20153757. DOI: 10.1542/peds.2015-3757.

7. Moore TA, Wilson ME. Feeding intolerance: a concept analysis. Adv Neonatal Care. 2011 Jun;11(3):149-54. PMID: 21730906. DOI: 10.1097/ANC.0b013e31821ba28e.

8. Leon AE, Michienzi K, Ma CX, Hutchison AA. Serum caffeine concentrations in preterm neonates. Am J Perinatol. 2007 Jan;24(1):39-47. DOI: 10.1055/s-2006-958163.

9. Faramarzi F, Shiran M, Rafati M, Farhadi R, Salehifar E, Nakhshab M. The efficacy and safety of two different doses of caffeine in respiratory function of preterm infants. Caspian J Intern Med. 2018; 9(1):46-53. DOI: 10.22088/cjim.9.1.46.

10. Mohammed S, Nour I, Shabaan AE, Shouman B, Abdel-Hady H, Nasef N. High versus low-dose caffeine for apnea of prematurity: a randomized controlled trial. Eur J Pediatr. 2015 Jul;174(7):949-56. DOI: 10.1007/s00431-015-2494-8.

11. Zhao Y, Tian X, Liu G. Clinical effectiveness of different doses of caffeine for primary apnea in preterm infants. Chin J Pediatr. 2016 Jan;54(1):33-6. DOI: 10.3760/cma.j.issn.0578-1310.2016.01.008.

12. Steer PA, Flenady VJ, Shearman A, Lee TC, Tudehope DI, Charles BG. Periextubation caffeine in preterm neonates: a randomized dose response trial. J Paediatr Child Health. 2003 Sep-Oct;39(7):511-5. DOI: 10.1046/j.1440-1754.2003.00207.x.

13. Rebentisch A, Kovey K, Denslow S. An evaluation of twice-daily dosing of caffeine for apnea of prematurity. J Pediatr Pharmacol Ther. 2021;26(3):253-257. DOI:10.5863/1551-6776-26.3.253.

14. Johnson PJ. Caffeine citrate therapy for apnea of prematurity. Neonatal Network: J Neonatal Nurs. 2011 Nov-Dec; 30(6), 408–412. DOI:10.1891/0730-0832.30.6.408.