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To Evaluate and Compare Therapeutic Effect of High Dose versus Low Dose Caffeine Citrate for Treatment of Apnea in Preterm Infants

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Abstract
Background: *The infant mortality rate (IMR) is one of the indicators used to monitor achievements towards the Millennium Development Goals.*
Material and Methods: *A total of 54 preterm infants <35 weeks gestation, presented with AOP within the first 14 days of life were enrolled and randomized into two groups 28 in high dose group (loading 40 mg/kg/day and maintenance of 20 mg/kg/day) and 26 in conventional dose group (loading 20 mg/kg/day and maintenance of 10 mg/kg/day).*
Results: *Total 57.14% infants required CPAP in high dose group, compared to 53.85% in conventional dose group. High dose caffeine was associated with a significant reduction in the need for indigenous bubble CPAP.*
Conclusion: *To conclude the use of high dose caffeine as compared to than conventional dose may decrease the recurrence of apnea, duration of oxygen therapy, NICU stay and requirement of mechanical ventilation in preterm infants without significant side effects.*
Keywords: *Apnea of prematurity (AOP). Caffeine. Preterm infants.*

Introduction

Neonatal mortality is newborn death occurring within 28 days postpartum[1,2] . This accounts for 40–60% of infant mortality in developing countries. Low birth weight makes up 60–80% of the infant mortality rate in developing countries[3]. Along with birth weight, period of gestation makes up the two most important predictors of an infant's chances of survival and their overall health. Preterm infants are at greater risk for respiratory distress syndrome (RDS), necrotising enterocolitis (NEC), apnea of prematurity (AOP), retinopathy of prematurity (ROP) and brain white matter injury[4].

Apnea is defined as the cessation of breathing for more than 20 seconds or cessation of breathing for less than 20 seconds accompanied by bradycardia (less than 100 beats per minute) or oxygen desaturation (less than 90 %)[5]. Apnea in preterm infants is usually related to immaturity of the central nervous system and is called apnea of prematurity (AOP). Periods of apnea occur more often with decreases in gestational age.[6] Despite the fact that apnea can occur solely because of the

prematurity of the infant, certain situations, such as hypoxic periods, metabolic disorders, intracranial pathologies, and infections can also trigger it.[7] Methylxanthines stimulate breathing efforts and, therefore, several trials had been conducted to validate the use of methylxanthines for treatment of AOP[8-13]. Two commonly available forms of methylxanthines are theophylline and caffeine[14]. Caffeine is now used as a standard pharmacotherapy for AOP due to its higher therapeutic index, better enteral absorption, once daily administration, and longer half-life than other methylxanthines. Caffeine is effective in reducing numbers of apneic attacks and use of mechanical ventilation, duration of mechanical ventilation and used to facilitate extubation of preterm infants [15].

Materials and Methods

Source of Data

Present Study was conducted in neonatal intensive care units (NICUs) of Rajkiya Mahilla Chikitsalaya (intramural) as well as J.L.N. Hospital (extramural), attached to JLN Medical College, Ajmer. Study period extended from July 2015 onwards for 1 year. The study protocol was approved by the Institutional Ethics Committee of J.L.N. Medical College. The written informed consent was obtained from a parent of each infant.

Design of the Study

This is a parallel randomized controlled, pilot, prospective study, comparing two different dose regimens of caffeine citrate in preterm infants.

Sample Size

Total 54 inborn patients of apnea of prematurity (intramural 42 and extramural 12) fulfilling the case inclusion criteria were enrolled for the present study.

Inclusion Criteria

1. Preterm Infants born less than 35 weeks Gestational age.
2. Preterm Infants within first 14 days of life.
3. Apnea definition - cessation of breathing for longer than 20 sec or for any duration if accompanied by central cyanosis and bradycardia (heart rate <100).

Exclusion Criteria

1. Preterm Infants born more than 35 weeks Gestational age.
2. Preterm Infants after 14 days of life.
3. Cessation of breathing for less than 20 seconds and not accompanied by cyanosis and bradycardia.
4. Signed informed consent not given by parents.
5. Major congenital malformation.

Result

Table 1 Impact of caffeine on oxygen Requirement

O_2 Requirement (in hours)			
Group	High Dose	Conventional Dose	Total
<24 hours	2	0	2
	100.00%	0.00%	100.00%
24-48 hours	12	0	12
	100.00%	0.00%	100.00%
48-72hours	8	10	18
	44.40%	55.60%	100.00%
>72 hours	6	16	22
	27.30%	72.70%	100.00%
Total	28	26	54
	51.90%	48.10%	100.00%
Chi-Square=7.4390		P=0.05	

In current study 27.3% infants in high dose group and 72.7% infants in conventional dose group were required more than 72 hours oxygen therapy. High dose caffeine was associated with

statistically significant reduction in duration of oxygen therapy.

Table 2. Impact of caffeine on duration of NICU stay

Duration of NICU stay			
Group	High Dose	Conventional Dose	Total
1-2 weeks	14	2	16
	87.50%	12.50%	100.00%
3-4 weeks	12	16	28
	42.90%	57.10%	100.00%
> 4 weeks	2	8	10
	20.00%	80.00%	100.00%
Total	28	26	54
	51.90%	48.10%	100.00%
Chi-Square=26.23		P≤0.05	

In high dose group duration of hospital stay was 1-2 weeks in 87.50% infants, 3-4 weeks in 42.90% infants and >4weeks in 20.00% infants. In conventional dose group duration of hospital stay was >4weeks in 80.00% infants, 3-4 weeks in 57.10% and 1-2 weeks in 12.50% infants. High dose caffeine was associated with statistically significant reduction in duration of NICU stay.

Table 3. Impact of caffeine dose on CPAP requirement

Indigenous Bubble CPAP required			
Group	High dose	Conventional dose	Total
Yes	16	14	30
	57.14%	53.85%	55.56%
No	12	12	24
	42.86%	46.15%	44.44%
Total	28	26	54
	100.00%	100.00%	100.00%
Chi-Square=18.54		P=0.301	

Total 57.14% infants required CPAP in high dose group, compared to 53.85% in conventional dose group. High dose caffeine was associated with a significant reduction in the need for indigenous bubble CPAP.

Table 4. Impact of caffeine on neonatal mortality

Group Outcome	High dose	Conventional dose	Total
Survived	24	20	44
	85.70%	76.90%	81.50%
Expired	4	6	10
	14.30%	23.10%	18.50%
Total	28	26	54
	100.00%	100.00%	100.00%
Chi-Square=1.381		P=0.240	

In high dose group mortality was 4 (14.3%) infants compared to 6 (23.1%) in conventional dose group with no statistically significant difference.

DISCUSSION

In current study 27.3% newborns in high dose group and 72.7% newborns in conventional dose group required more than 72 hours oxygen therapy. High dose caffeine was associated with statistically significant reduction in duration of oxygen therapy. Corroborating with our findings Schmidt B et al in a study of 2006 neonates weighing 500 to 1250 g with AOP, revealed that caffeine therapy was associated with reduction of duration of oxygen therapy[16]. On contrary to our study recent trial by Mohammed S et al reported that the high-dose caffeine had no significant impact on supplemental oxygen requirement of infants after weaning off from mechanical ventilation[17]. So the variable result may be attributed to different set of study population.

Duration of caffeine therapy

In high dose group 18 neonates (64.3%) required caffeine for 7-10 days while in conventional dose group 18 neonates (69.2%) required caffeine for 10-14 days. High dose caffeine was associated with statistically significant reduction in duration of caffeine therapy. On the contrary Mohammed S et al found no significant difference between the high and low dose caffeine groups in term of duration of caffeine therapy[17]. These different results may be explained by different enrolment policy concerning the indication for starting caffeine therapy.

Darnall et al. concluded that caffeine therapy should be continued until preterm infants are 34 to 36 wk corrected gestational age and free of any apnea episodes for at least 8 days[18]. As per AIIMS protocol caffeine therapy should be continued till 34 weeks corrected gestational age or 7 days after last episode of apnea ,whichever is later.

Impact of caffeine on duration of hospital stay

In high dose group duration of hospital stay was 1-2 weeks in 87.50% neonates, 3-4 weeks in 42.90% neonates and >4weeks in 20.00% neonates. In conventional dose group duration of hospital stay was >4weeks in 80.00% neonates, 3-4 weeks in 57.10% and 1-2 weeks in 12.50% neonates. High dose caffeine was associated with statistically significant reduction in duration of NICU stay, whereas study by Mohammed S et al revealed no significant difference between the high and low dose caffeine groups in term of duration of hospital stay. This difference may be explained by inclusion of preterm infants with gestational age and higher birth weight in our study compared to above study (35 Vs 32 weeks).

Requirement of CPAP

Total infants 57.14% required CPAP in high dose group, compared to 53.85%in conventional dose group. High dose caffeine was associated with no significant reduction in the need for indigenous bubble CPAP (p value - 0.30). Similar results were seen in study by Mohammed S et al (p value - 0.47).

Miller MJ et al concluded that CPAP is also an effective treatment of AOP when clinically significant episodes persist despite optimal caffeine therapy. This reduction is primarily related to significant reduction in episodes of obstructive and mixed apneas and has been attributed to splinting open of the upper airways by the positive airway pressure[19].

Requirement of Mechanical Ventilation

Total 21.40% newborns required Ventilator support in high dose group, compared to 38.50% in conventional dose group. High dose caffeine was associated with a significant reduction in the need for mechanical ventilation. Similarly Steer et al. in a study of 234 preterm infants using a high-dose regimen of 20 mg/kg versus a low-dose regimen of 5 mg/kg; a significant difference in requirement of mechanical ventilation was shown for neonates of less than 28 weeks gestation receiving the high dose of caffeine (mean (SD) days 14.4 (11.1) v 22.1 (17.1); p = 0.01)[20]. Unlike our results Mohammed S et al noted that the high-dose caffeine had no significant impact on requirement of mechanical ventilation. This may be attributed to different guideline for initiation of mechanical ventilation[17].

A study on Effect of caffeine on control of breathing in infantile apnea by Aranda JV et al

concluded that Caffeine significant increases ventilation, tidal volume, and mean inspiratory flow, by increasing central inspiratory drive. The benefits of caffeine therapy on respiratory functions decrease requirement and duration of mechanical ventilation, also facilitate earlier weaning off from mechanical ventilation, and reduce ventilator-induced lung injury[21].

CONCLUSION

To conclude the use of high dose caffeine as compared to than conventional dose may decrease the recurrence of apnea, duration of oxygen therapy, NICU stay and requirement of mechanical ventilation in preterm infants without significant side effects.

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