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Original Article

Prediction of Respiratory Morbidities in Late Preterm Neonates Using Cord Blood Arterial Lactate and Base Excess

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ABSTRACT

Background: Late preterm neonates may have the external appearance and behavior similar to their counterparts. However, they are susceptible to various neonatal morbidities , due to their physiological and metabolical immaturity. To assess the correlation between cord blood arterial lactate levels and base excess with the development of respiratory distress in late preterm neonates.

Methods: All inborn neonates born at Kasturba hospital Manipal, satisfying the criteria of late preterm infants (34-36 6/7 weeks) were included in this prospective observational study.The data recorded included gender, birth weight, multiple births, presence of major congenital anomalies, mode of delivery, APGAR score at minute 5, need for resuscitation, admission to the neonatal intensive care unit (NICU), and days of hospitalization. Lactate and base excess were estimated using blood obtained from umbilical artery sampling. The primary outcome assessed was the requirement of delivery room resuscitation. The secondary outcomes assessed were the development of respiratory distress, requirement of invasive/non- invasive ventilation, and respiratory support.

Results: Cord blood base excess levels were significantly higher in late preterm neonates requiring delivery room resuscitation compared to those who did not require resuscitation (median: -8 vs -4mEq/L, p-value: 0.002).In terms of respiratory morbidities, cord blood base excess levels were significantly higher in neonates with respiratory distress syndrome (RDS)(median: -8.5 vs -3.4 mEq/L, p-value 0.001), and transient tachypnea of newborn (TTNB) (median: -8 vs -3.4 mEq/L, p-value 0.004), compared to those without RDS and TTNB.However,there was no significant association between cord blood lactate levels and the outcomes assessed.

Conclusion: Estimation of arterial base excess levels obtained from umbilical cord blood sampling during delivery may serve as a sensitive marker for predicting respiratory morbidities in late preterm neonates.

Keywords: ----------

Introduction

Late preterm birth is defined as birth between 34 -36 6/7 weeks of gestation from the first day of the last menstrual cycle(1). Late preterm neonates are at a higher risk of respiratory distress immediately after birth, due to,TTNB, persistent pulmonary hypertension (PPHN), pneumonia, along with an increased need for surfactant therapy, continuous positive airway pressure (CPAP), and ventilator support when compared to term neonates(2).

This study aimed to assess the correlation between cord blood arterial lactate levels, base excess (BE) in late preterm neonates and the development of respiratory distress.The primary outcome assessed was the requirement of delivery room resuscitation. The secondary outcome assessed was the development of respiratory distress, requirement of invasive/non-invasive ventilation or other modalities of respiratory support and the time taken to establish breast-

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feeding.

Methods

All inborn neonates born at Kasturba hospital, Manipal, satisfying the criteria of late preterm neonates (34-36 6/7 weeks) were included in this prospective observational study. The study lasted from October 1st 2014 to June 30th 2016. Institutional ethical committee approval was obtained prior to the commencement of the study (IEC number: 655/2014).Late preterm neonates with congenital anomalies like congenital diaphragmatic hernia, complex congenital heart diseases, esophageal atresia, hydrocephalus, and neural tube defects were excluded from the study.

Gestational age was estimated by the assessment of ultrasound examination at first trimester of gestation. The data including, gender, birth weight, multiple births, presence of major congenital anomalies, mode of delivery, APGAR score at 5 minutes, need for resuscitation, admission to the neonatal intensive care unit (NICU), and days of hospitalization were recorded at the time of birth.

One ml of blood was collected from the umbilical artery after double clamping in a pre heparinized syringe immediately after delivery and the sample was sent for blood gas analysis and lactate level estimation.Blood samples were analyzed in GEM Premier 3000 blood gas analyzer in the neonatal intensive care unit. Hyperlactatemia was defined as an arterial blood lactate concentration greater than2.5 mmol/l or 25 mg/dL(3).The mean umbilical artery base excess was taken as -4.8meq/L(4).

Invasive ventilation was considered for those neonates with respiratory distress requiring intubation in the delivery room or neonates with Downe's score(5)>6 or requiring FiO_2> 40% on noninvasive ventilation. Extubated neonates were managed with non-invasive ventilation using nasal continuous positive airway pressure (N-CPAP)/, heated humidified high flow nasal cannula (HHHFNC), or humidified oxygen through headbox.The data on respiratory support such as oxygen therapy either invasive or non-invasive method was documented. The need for specific adjunctive therapies, such as surfactant administration, duration of respiratory support and highest level of respiratory support were analyzed. Blood glucose levels were monitored every 6 hours for a 72-hour period.

Statistical analysis was done using IBM SPSS statistics, version 23. Descriptive statistics was reported using mean ± standard deviation or median(range) for the continuous variables. Numbers and percentage were used for the categorical variables.

Results

There were 1558deliveries during the study that 156 late preterm neonates were included in the study. The demographic and clinical features of the study population are depicted in Table 1.

Nearly 50% of the late preterm neonates were born at 36 weeks of gestation and 82.7% were born AGA. The majority of them (75%) were delivered by emergency LSCS and the most common

Table 1. Demographic and clinical features of the study population

Variable	Late preterm neonates(156)-n (%)
Gestational age in weeks:34	44(28.2)
35	35(22.4)
36-6/7	77(49.4)
Gender:	
Male	75(48.1)
Female	81(51.9)
Weight for gestation:	
AGA	129(82.7)
SGA	24(15.4)
LGA	3(1.9)
Mode of delivery:	
Vaginal	16(10.2)
Elective LSCS	21(13.6)
Emergency LSCS	118(75.6)
Assisted vaginal delivery	1(0.6)
Pregnancy order:	
Singleton	123(78.9)
Twins	30(19.2)
Triplets	3(1.9)
APGAR score<7 at 5min	2(1.3)
Steroid prophylaxis:	
Received	53(34.0)
Not received	103(66.0)
Delivery room resuscitation:	
Requirement:	22 (14.1)
Type of resuscitation:	
Bag and mask	17(10.9)
Intubation and bag	4(2.6)
Intubation and mechanical ventilation	1(0.6)
Chest compressions	Nil
Respiratory morbidity:	
Present:	28(17.9)
Types:	
RDS	14 (9.0)
TTNB	9 (5.7)
Congenital pneumonia	2 (1.3)
MAS	3 (1.9)

AGA: appropriate for gestational age, SGA: small for gestational age, LGA: large for gestational age, LSCS: lower segment cesarean section. MAS: meconium aspiration syndrome.

indication was fetal distress. Resuscitation in the delivery room was required in 22 (14.1%) neonates and mostly by bag-mask ventilation. Subsequently, respiratory morbidities were observed in 28 (17.9%) neonates and the most common was RDS. Only 34% of mothers had received steroid prophylaxis prior to delivery. As depicted in table 2, the arterial base excess levels were significantly higher in neonates requiring resuscitation in the delivery room than those who did not require resuscitation.

The cord blood lactate and base excess levels in RDS and TTNB were elevated as depicted in table 3. Similarly, 2 neonates had congenital pneumonia with median lactate/base excess values of 4mmol/L /-6.5meq/L,and 3 neonates had MAS with median lactate/base excess of 7.6mmol/L /-12.1meq/L.

Neonates with RDS had significantly higher levels of base excess (-8.5), compared to those without respiratory morbidities (-3.4) as depicted in table 4.

Similarly neonates with TTNB had significantly higher levels of base excess (-8), compared to those without respiratory morbidities (-3.4) as depicted in table 5.

Of the total 156 late preterm neonates, 99(62.9%) newborns had cord blood lactate more than 2.5mmol/L, out of whom 19(19.2%) neonates had respiratory morbidities. Moreover, 57(36.3%) newborns had cord blood lactate less than 2.5mmol/L, out of whom 8(14%) neonates had respiratory morbidities. Similarly, 87(55.7%) neonates had base excess more than -4.8. Respiratory morbidities were observed in 27 (37.7%) neonates out of whom 69 newborns had cord blood base excess less than -4.8meq/L among whom none had respiratory morbidities.

The majority of the neonates requiring respiratory support, needed CPAP for a median duration of 36 hours as depicted in Table 6.

Among the late preterm neonates, those with 34 weeks gestational age required maximum duration of hospital stay for a mean duration of 8.7 days. The time taken to establish breastfeeding was maximum among late preterms of 34 weeks gestation, requiring a median duration of 7 days as depicted in table 7.

Table 2. Association of cord blood lactate and base excess with resuscitation requirement.

n = 156	Noresuscitation(134)	Resuscitation(22)	P value
Lactate (mmol/L) (Median, IQR 25th /75th)	2.8 (2.2, 3.6)	4.0 (2.0, 6.5)	0.35
Base excess (meq/L) (Median, IQR 25th/75th)	-4 (-6.6, -2.0)	-8 (-10.4, -2.0)	0.002

Table 3. Cord blood lactate and base excess in respiratory morbidities.

Variables	TTNB (n= 9)	RDS (n= 14)
Lactate (mmol/L) (median, IQR 25th /75th)	4.0 (2.5, 5.5)	3.0 (2, 6)
Base excess (meq/L) (median, IQR 25th /75th)	-8 (-10, -7.5)	-8.5 (-10, -7)

Table 4. Association between cord blood lactate /base excess in babies with RDS and without respiratory morbidities

Variable	RDS (n= 14)	No respiratory morbidity (n=128)	P-value
Lactate (mmol/L) median IQR 25th/75th	3.0 (2, 6)	2.7 (3.7, 2.2)	0.733
Base excess (meq/L) median IQR 25th/75th	-8.5 (-10, -7)	-3.4 (-6.3, -1.7)	0.001

Table 5. Association between cord blood lactate /base excess in babies with TTNB and without respiratory morbidities

Variable	TTNB (n=9)	No respiratory morbidity (n=128)	P-value
Lactate (mmol/L) median, IQR 25th/75th	4(2.5, 5.5)	2.7 (3.7, 2.2)	0.361
Base excess (meq/L) median, IQR 25th/75th	-8 (-10, -7.5)	-3.4 (-6.3, -1.7)	0.004

Table 6. Late preterm infants requiring respiratory support

Respiratory support	n= 28	Duration of O_2 requirement in Hours, Median (IQR 25th/75th)
Non-invasive ventilation	27	
CPAP	20 (9.2)	36 (24, 72)
Oxygen by nasal cannula	2 (1.2)	24
HHHFNC	5 (4.6)	72 (24,72)
Invasive ventilation	1	
<24 hours	1 (0.6)	24
24-48 hours	0	0
>48 hours	0	0

Table 7. Duration to establish breast-feeding and NICU stay

Gestational age in weeks	34 (n=44)	35 (n=35)	36-6/7 (n=77)
Duration of NICU stay –mean(SD)	8.7 (7.7)	6.9 (2.7)	2.7 (1.1)
Duration to establish breastfeeding in days, Median (IQR 25th/75th)	7 (4,12)	1	1

Discussion

Since the late 90s the preterm birth rate across the globe has increased by 33%,out of whom 72% constitutes late preterm neonates(6).Multiple factors have been attributed to the increasing incidence of late preterm (LPT) deliveries,such as the increase in the mean age of childbearing mothers,changes in infertility treatments, rising incidence of multiple gestation pregnancies, increasing use of labor induction, and cesarean delivery at 34-36 weeks of gestation(6). Due to the advances in reproductive technologies, there has been increasing surveillance of mother and fetus. Accordingly, fetuses who are considered at the risk of stillbirth, intrauterine growth retardation, and intrapartum asphyxia are identified earlier, resulting in more deliveries at 34-36 weeks gestation(7).Earlier studies on the outcomes of infants with respiratory distress have mainly focused on extremely premature infants, leading to a gap in knowledge and understanding of the physiology and mechanism of pulmonary diseases in late preterm neonates. A large study performed in USA(8) has reported respiratory morbidities in 9% of late preterm births and added that this risk decreased with each advancing week of gestation up to 38 weeks.

There is paucity of data on respiratory morbidities in late preterm neonates from India. In the present study, nearly 18% of late preterm neonates developed respiratory morbidities immediately after birth out of which 50% constituted RDS followed by TTNB. Additionally, our findings were consistent with the results of a study from USA which showed RDS as the most common respiratory morbidity among the late preterm deliveries(8). Studies have demonstrated that surfactant deficiency is the most common etiology of RDSin very preterm and moderately preterm neonates, while cesarean section and lung infection play major roles in RDS development in both late preterm and term neonates(9). It has been observed that neonates born at 34-36 weeks gestation are more likely to be delivered via cesarean than by labor induction, leading to increased rates of respiratory compromise(10). Neonates born by cesarean section have a larger residual volume of lung fluid and secrete less surfactant to the alveolar surface thereby increasing the risk of developing RFS(11). The detrimental effects of cesarean section without trial of labor on the development of RDS is more prominent in LPT and term infants(11). In our study 89% of LPT neonates were delivered by cesarean section.Studies have shown that administration of antenatal corticosteroids to mothers with the risk of imminent delivery between 34-36 weeks of gestation could significantly reduce the acute respiratory morbidity associated with LPT birth(12). In our study only 34% of late preterm neonates received steroid prophylaxis prior to delivery.Studies have shown that the efficacy of surfactant therapy in LPT neonates is not as good as it is for preterm neonates(9) and none of the neonates in our study received surfactant.

Cord blood lactate has been identified as a more specific factor than pH in the prediction of adverse neonatal outcomes(13). However, the present research indicated no significant correlation between cord blood arterial lactate and the outcomes assessed.Studies have demonstrated umbilical artery base excess (cut off value ≥ 12 mmol/l) as a reliable indicator of intrapartum asphyxia with best correlation to long term morbidities(14).A study performed by Victory et al.from Canada has shown a significant correlation between umbilical cord base excess values at birth (mean artery BE -5.6±3.0 mmol/l) and adverse neonatal outcomes, such as APGAR score less than 7 at 5 min, NICU admission and the need for assisted ventilation(15). In the current study, the umbilical artery BE increased significantly (median -8meq/L) in late preterms requiring resuscitation in the delivery room, compared to those who did need resuscitation. Moreover, this study demonstrated significantly increased BE values in late preterms with RDS (median -8.5meq/L) and TTNB (median -8meq/L), compared to those without any respiratory morbidities. The umbilical artery BE is directly related to fetal production of carbon dioxide and lactate which contributes to metabolic acidosis(15) and is significantly related to long term morbidities including death(16).

In this research,17.9% of late preterms required respiratory support predominantly in the form of CPAP, which is in line with the study conducted in the US(8)wherein the majority received oxygen via nasal cannula followed by

CPAP.The late preterm babies were reported to have significantly increased respiratory morbidities, increased use of intensive care, longer stay of hospitalization (17), increased rates of rehospitalization, and increased cost of health care(18), compared to term babies.

Conclusion

To the best of our knowledge,this study has been one of the first performed in literature that have assessed the prediction of respiratory morbidities in the late preterm neonates using cord blood lactate and arterial base excess levels. This research provided a significant insight into various respiratory morbidities, requirement of resuscitation, including respiratory support and the time taken to establish breastfeeding among LPT neonates. The estimation of umbilical arterial base excess levels at birth in late preterm neonates may serve as the most reliable parameter in assessing the severity of respiratory morbidities.

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Conflicts of interests

No conflict of interests is declared by the authors in this study.

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Original Article

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

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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.

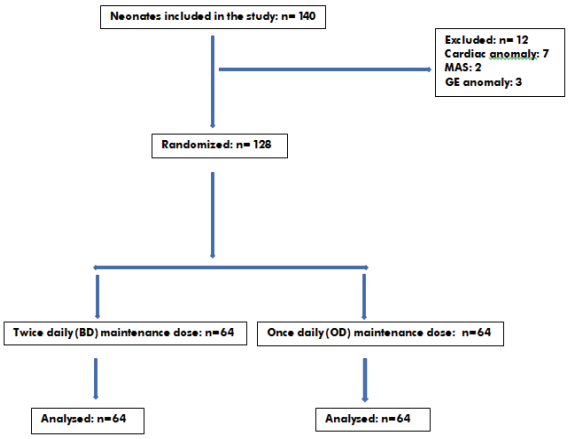
Both groups received a 20 mg / kg loading dose of caffeine citrate (or 10 mg / kg as caffeine base) which was administered intravenously over 30 minutes on day one of life followed by a maintenance dose of 2.5 mg / kg (1.25 mg / kg as caffeine base) every 12-hour-interval in group 1 and 5 mg / kg (or 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.

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