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Original Research Article

A Study of Modalities of Treatment of Apnea in Neonates – Focus on Role of Methylxanthines

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Abstract:

Introduction: Methylxanthine drugs such as caffeine or theophylline are used for treating neonatal apnea. However, choice between caffeine and theophylline in the treatment of neonatal apnea remains a debatable issue.

Material & Methods: This randomised study of 40 neonates with neonatal apnea was carried out in a tertiary care hospital in maharashtra. Treatments compared were caffeine and theophylline in terms of prognosis.

Results: overall survival was 40%. The average number of apneas in caffeine treated group was 5.62 $\pm$ 4.67 per infant and in aminophylline treated group 4.50 $\pm$ 5.36 per infant. There was no significant difference in the drug levels achieved by both the drugs. Association between survival with methylxanthines and its levels was not significant. When the survival was analysed with modes of treatment required, only in babies requiring physical stimulation and not requiring bag and mask, IPPR, ventilators, the survival was good (p=0.0003).

Conclusion: The efficacy of caffeine and aminophylline was similar in our study. Number of apneas, drug levels and the survival no significant difference. However, caffeine has distinct advantage of ease of administration, and fewer peripheral effects. Of the variables studied bradycardia during the episode and prematurity were strong predictors of poor survival.

Keywords: Apnea, neonate, methylxanthines. Caffeine, Aminophylline.

Introduction

About 25% of all newborns weighing less than 1800gms (gestation ≤ 34 weeks) will have at least one apneic episode. These spells generally occur in the first week of life, more commonly in the first 1 or 2 days. Postnatally, most of the episodes disappear by 37 weeks postconceptional age.

The apneic episode in a neonate warrants an immediate treatment as there will be cerebral hypoxia and hypoperfusion that is expected to adversely affect the survival and subsequent neurodevelopment. Due to its significant contribution to the morbidity and mortality in the low-birth-weight infants, various aggressive approaches in the prevention and therapy of apnea have come up. [1] In general, identifiable, and treatable causes such as infection, hypoxia, hypoglycaemia, hypothermia, and others should be corrected. For each episode, tactile stimulation, positive pressure ventilation (bag and mask) and mechanical ventilation should be provided as may be required. [2] The pharmacological approach to the management of this problem is to administer drugs that stimulate respiration in the neonate. Several drugs such as theophylline, caffeine, doxapram and nikethamide have been used.

Among the methylxanthines used in neonatal apnea, theophylline and caffeine are widely used. Although these drugs were known since a long time, their use in neonatal apneas started since mid-1970's. Initially theophylline was widely used. This was soon followed by caffeine, which proved by various studies to be safer, easier to administer, better stimulant of central nervous system, lesser side effects compared to theophylline. [3-4] As more studies were conducted, better information regarding these drugs became available. However, the choice between caffeine and theophylline in the treatment of neonatal apnea remains a debatable issue. The newborns in this study were treated for hypoxemic episodes with physical stimulation or

positive pressure ventilation. These babies received caffeine or aminophylline on the first apneic episode and thereafter till they were completely treated. These babies were looked for any of the adverse effects due to methylxanthines given. Various modalities of treatment on apnea in neonates and the role of methylxanthines in neonatal apnea was studied.

Materials and Methods

This randomised trial of 40 neonates with neonatal apnea was carried out in a level II/III Neonatal Intensive Care Unit (NICU) in Niramay hospital and research centre, in Satara, maharashtra, after obtaining IEC clearance. The duration of study was one year from April 2011 to April 2012. On admission to NICU, all babies receive the routine neonatal care consisting of cord care, eyecare, administration of Vit.K and stabilization of temperature. Oxygen and parenteral fluids are supplemented as per indications. The babies are footprinted for identification and New Ballard score was done for maturity. Weight recording of all babies done once daily as a routine. A detailed antenatal history including all maternal factors, birth history including need for resuscitation, the type of resuscitation was recorded. A written consent was taken from parents on admission for all the procedure done in NICU. Gestational assessment (post conceptional age) was done by modified Dubowitz method. A routine clinical examination including cardiovascular, respiratory, abdominal, and neurological assessment is done on admission and every day thereafter. Monitoring of temperature is done 12hourly, or more frequently if indicated. A recording of BSL, BP, SaO2 is done on all babies on admission. Minimum handling of neonate is done.

Selection Criteria: Any neonate admitted in NICU was selected to the study on first episode of apnea. The babies that were monitored for the selection were: 1. All babies less than 34 weeks post conceptional age. 2. Term or preterm babies with sepsis. 3. Babies with intracranial bleeds, birth asphyxia. Neonatal apnea was defined as the cessation of breathing for more than 20 seconds or if less than 20 seconds, accompanied by bradycardia (with heart rate less than 100/min) and /or cyanosis. Exclusion Criteria: All babies discharged against medical advice before the completion of study period were excluded from the study.

As soon as the apneic episode occurred, the following modes of treatment were offered to the babies in that order in addition to caffeine or aminophylline. 1. Physical stimulation: Gentle stroking, slapping of the baby was done by staff nurse or doctors. 2. Bag and mask ventilation: When apnea was severe or not responding to physical stimulation bag and mask ventilation was given. 3. Endotracheal intubation and intermittent positive pressure ventilation: If apnea was prolonged and frequently repeated for more than one to two minutes and there was no improvement with bag and mask ventilation, endotracheal intubation was done, and intermittent positive ventilation was started. 4. Ventilatory support with mechanical ventilators: Babies were taken on ventilator when there were repeated apneas and the underlying cause needed ventilator support e.g. respiratory distress syndrome.

At the first episode, the babies received caffeine or aminophylline. Study subjects were randomised into caffeine group or aminophylline group. The babies received a loading dose of aminophylline or caffeine in the following dosage regimen. Caffeine: 10 mg/kg(base) orally, with nasogastric tube. Aminophylline: 5 mg/kg intravenously, slowly over 20 min. This was followed by a maintenance dose 24 hours after the loading dose, in the following regimen. Caffeine: 2.5mg/kg/day, Orally, once daily. Aminophylline: 2mg/kg/dose, intravenously, 8 hourly. The blood samples were collected 24 hours after the loading dose for monitoring the drug levels. The drug levels were done with the help of standard HPLC method. The babies were examined daily with regular Weight recording, routine clinical examination and for the abovementioned parameters like heart rate, BP, SAO2, ABG, Hb and rectal temperature. Continuous monitoring of the babies was done with apnea monitors. The babies were also looked for possible adverse effects due to these drugs and these were recorded whenever observed e.g., Tachycardia, feeding intolerance increased irritability, rash, NEC. All findings were recorded in the computerized data base.

Period of follow up: Up to 37 weeks post conceptional age, or up to a period of at least two weeks from the last apnea. A pilot study consisting of 9 neonates with apnea was conducted to look for the feasibility of the study and to prepare a complete protocol for the proper conduct of the study. The recording of the apnea was done with apnea monitors and observation by the nursing staff/doctors.

Every day the total number of apneas, time of occurrence of the apnea was noted in addition to the following detail. Heart rate, Duration of apnea, Day of 1stapneic episode, Presence of cyanosis, Relation of apnea to feeds, Posture of the baby during episode (particularly position of neck: flexion or extension), Blood pressure, Temperature (rectal), Pulse oximetry, Arterial blood gases, Routine hemogram for Hb, Total counts. Septic work up: blood culture. Chest radiograph and sonography of brain. Routine clinical examination for a possible cause. Data analysis was done in MS Excel software and results presented in percentages and statistical significance as p value of less than 0.05.

Results

Table 1 shows the Distribution of risk factors and patterns of findings on investigations in apneic patients (n=40). Table 2 shows the clinical parameters in the study. At the onset of the apnea, the modalities of treatment offered were analysed. 14 babies (35%) had apnea requiring physical stimulation,13 babies (32.5%) required bag and mask ventilation, 10 babies (28%) required endotracheal intubation and IPPR. 3 babies (7.5%) had to be taken on ventilator. Caffeine was given to 24 babies (60%) and aminophylline to 16 babies (40%). No patient had to be switched over from one drug to the other. The average number of apneas in caffeine treated group was 5.62 +- 4.67 per infant and in aminophylline treated group 4.50 +- 5.36 per infant. There was no significance difference in the number of apneas between the two groups. The drug levels done by HPLC method were analysed. For caffeine, the levels were ranging from a minimum of 5.0mg/L to a maximum of 18.5mg/L with a mean level of 13.7 +- 3.79 mg/L. For aminophylline, the levels were ranging from a minimum of 3.5 mg/L to maximum of 24.0 mg/L with a mean of 11.31 +- 4.91 mg/L. There was no significant difference in the drug levels achieved by both the drugs. Table 3 shows association between survival and mode of treatments, and with methylxanthines. The overall survival of the infants in the study group was 40%. 15 babies survived while 25 babies died.

Table 4 shows the logistic regression of survival. When the affecting the survival were to be analysed, we did logistic regression analysis of survival with other variables like sex, birth weight ,gestational age, weight for gestation, birth asphyxia, position of neck, feeds, RDS, pneumonia, pneumothorax, sepsis, intracranial bleed, BP, SaO2, number of apnea, day of first apnea, duration of apnea, heart rate, cyanosis, Hb, temperature and acidosis, the following results were found. The heart rate during the episode and prematurity were strong predictors of poor survival.

Table 1: Distribution of risk factors and patterns of findings on investigations in apneic patients (n=40).

Parameter			**Parameter**		
Factor	**n**	**%**	**Radiological Findings**	**n**	**%**
Flexion of neck	25	62.5	Normal	25	62.5
Post feed	12	30.0	RDS	10	25.0
Respiratory distress syndrome	10	25.0	Pneumonia	4	10.0
Intracranial bleed	10	25.0	Pneumothorax	1	2.5
Culture proved sepsis	7	17.5	Findings in USG Brain	n	%
Birth asphyxia	5	12.5	Normal	30	75
Pneumonia	4	10.0	Intracranial bleed	10	25
Pneumothorax	1	2.5	Lab parameter	n	%
Type of Acid base distribution	n	%	Haemoglobin (< 10gms %)	4	10
Normal ABG	24	60	Hypoglycemia (BSL≤ 40 mgs %)	20	50
Respiratory acidosis	5	12.5	Acidosis	16	40
Metabolic acidosis	5	12.5			
Respiratory air + metabolic acidosis	6	15.0			

Table 2: Clinical parameters in apnea in the study

Clinical Parameters	**Min Value**	**Max Value**	**Mean**	**SD**
No. of apneas per infant	1	22	5.17	4.92
Day of first apnea	1	17	3.87	3.61
Duration of apnea in secs	20	240	41.99	33.99
Heart rate per min	10	96	76.31	26.15
Systolic BP	33	76	56.40	10.203
Diastolic BP	15	50	33.65	6.705
SaO2 (%)	75	95	88.075	4.703

Table 3: Association of survival with mode of treatments and methylxanthines

Mode of treatments with survival					
Mode of Treatments	**Living**	**Dead**	**Chi square**	**P value**	**Sig.**
Physical stimulation	11	3	15.9571	0.0003	HS
Bag and Mask	2	11			
ET and IPPR	1	9			
Methylxanthines with survival					
Caffeine	9	15	0	1	NS
Aminophylline	6	10			
Methylxanthine levels and survival					
<10	4	5	0.2389	0.6249	NS

≥10	11	20			

Table 4: Logistic regression analysis of survival

Variables	B	S.E.	Sig.	R	Odds ratio
Gest	-0.3083	0.1567	0.0491	-0.1880	0.7347
HR	-0.0436	0.0202	0.0305	-0.2250	0.9573
Constant	12.8449	5.2127	0.0137	--	--

Discussion:

Whether an underlying illness is present or not, recurrent episodes of abnormal and severe hypoxemia may warrant treatment. Some of the episodes are self-resolving and responsive to stimulation. Any episode which is neither self-resolving, nor responsive to stimulation, may also result in a used for additional inspired oxygen, bag, and mask ventilation and IPPR. It is the severity, duration and frequency of hypoxemia that is likely to reflex most serious disturbance.

In our study, 14 babies (35%) had apneas requiring physical stimulation, 13 babies (32.5%) required bag and mask ventilation, 10 babies (25%) required endotracheal intubation and IPPR. 3 babies (7.5%) were taken on ventilators. Stimulation was given by gentle stroke /slap to the sole back etc. No oscillating water beds used. Jones et al., and Saigal et al., in their separate trials have confirmed no significant benefit from oscillating water beds. [5-6] The pharmacological approach to the management of neonatal apnea has gained universal acceptance over the past 25 years. Although the drugs caffeine and aminophylline were known since a long time, it was only in 1973. Kuzemko confirmed the efficacy of xanthines in neonatal apneas. Since then, several trials have done comparing the efficacy of theophylline and caffeine. On the basis that caffeine has potent was stimulant properties with fewer peripheral effects, achieves good therapeutic levels and safer than theophylline. [7]

Caffeine is more reliably absorbed when administered orally and has longer half-life. Caffeine can be given once a day while theophylline must be given three times a day. A readily available commercial preparation of caffeine is lacking. For our study, the preparation used was caffeine citrate drops made available from one of the reputed pharmaceutical companies. We had a total of 24 newborns (60%) on caffeine and 16 newborns (40%) on aminophylline. No neonate had to be switched over from one done to the other. The average number of apneas in caffeine treated group was 5.62 +- 4.67 and in theophylline treat group, 4.5 +- 5.36 per infant. However, there was no statistically significant difference in the number of apneas between the two groups. One Cochrane review pointed that there was no significant difference between these 2 drugs when apnea rate was studied. [8]

The therapeutic plasma concentrations desired for theophylline and caffeine are about 5-15 and 5-20mg/L respectively. The anti-apneic effects are the better when the serum levels are more than 10mg/L. [9] 3 patients with caffeine and 3 patients with aminophylline had drug levels less than 10mg/L. The maximum caffeine level in our study was 18mg/L and plasma concentrations of upto50mg/L may occur with no adverse effects. [10] The highest theophylline concentration in our study was 24mg/L.

Plasma concentrations greater than 15mg/L may be associated with tachycardia. The two patients in the study had tachycardia on theophylline. Both patients had theophylline levels 16.0 and 16.5mg/L. It should be, however, noted that the underlying risk factors like sepsis, pneumonia, anaemia, etc., were treated when the study was carried out. Side effects of caffeine group are reported to be lower than theophylline. theophylline is also noted to cause high toxicity.8 Cost of caffeine is higher than theophylline, however, it is usually prescribed once a day and covers wide treatment range. [11-12] A randomised trial of preterms with birthweight between 500grams to 1250 grams notes that preterms on caffeine were removed from positive airway pressure 1 week before placebo group. [13]

Cerebral hypoxia and hypoperfusion that occurs during apneic episodes will adversely affect the survival and subsequent neurodevelopment in the infants. With improved neonatal care, and availability of infant ventilators, the neonatal mortality is decreasing.10 (56). The survival of neonates with the age group of 28 to 37 weeks in the study period was 33.2%. In our study the overall survival was 40%. 25 babies (62.5%) died. The logistic regression analysis of survival with other variables like sex, birthweight, gestational age, weight for gestation, birth asphyxia, position of neck, feeds, RDS, pneumonia, pneumothorax, sepsis, intracranial bleed, BP, SaO2, number of apneas, day of first apnea, duration of apnea, heart rate, cyanosis, Hb, temperature and acidosis, gestational age and heart rate turned out to be a good predictor of survival. Of the variables studied bradycardia during the episode and prematurity were strong predictors of poor survival. In Infants surviving post menstrual period of 36 weeks the need for oxygen therapy is less in caffeine group. [13] In one study, aminophylline treated babies

noted that aminophylline treated infants had less risk of apnea compared to caffeine. [14]

Tachycardia is reported to be the important acute side effect in infants on aminophylline. [15-16] When the survival was analysed with modes of treatment required, only in babies requiring physical stimulation and not requiring bag and mask, IPPR, ventilators, the survival was good (p =0.0003). There was no difference in the survival between the caffeine group and aminophylline group. When the survival was checked with lower drug levels (< 10mg/L) with either of the methylxanthines there was no significant association. However, there was no significant predictor of number of apneas in our study when analysed by logistic regression analysis.

Conclusion:

The efficacy of caffeine and aminophylline was similar in our study. Number of apneas, drug levels and the survival no significant difference. However, caffeine has distinct advantage of ease of administration, and fewer peripheral effects. In India, caffeine preparation is not readily available.

As the number of NICUs is increasing, caffeine preparations should be made readily available. Of the variables studied, bradycardia during the episode and prematurity were strong predictors of poor survival.

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