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Role of Methylxanthines in The Treatment of Apnea in Neonates

KEYWORDS

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ABSTRACT *Apneic episodes occur frequently in premature infants and is a major contributor to the morbidity and mortality in the low birth weight infants. For such episode, tactile stimulation and positive pressure ventilation are tried first. Respiratory stimulant drugs like caffeine, methylxanthines, doxapram are also tried. Therefore this study was planned to evaluate role of different methylxanthines in the treatment of apnea.*

40 neonates with neonatal apnea admitted in (NICU) were evaluated. The recording of the apnea was done with apnea monitors and observation by the nursing staff/doctors. Study group was randomised in to caffeine group or aminophylline group.Appropriate dosage regimen was followed. The blood samples were collected 24 hours after the loading dose for monitoring the drug levels. The possible adverse effects were recorded. Survival outcome was monitored with both modes of treatment.

40 infants with apneic episodes were included in the study. There were 26 males(65%) and 14 females(35%). Caffeine was given to 24 babies (60%) and aminophylline to 16 babies (40%). There was no significant difference in the drug levels achieved by both the drugs. The overall survival of the infants in the study group was 40%. 15 babies survived while 25 babies died. There was no correlation between the methylxanthines and survival.

Introduction

Apnea is cessation of breathing with hypoxia, bradycardia and/or cyanosis. Apneic episodes occur frequently in premature infants. Incidence of apnea is inversely related to the gestational age of the neonate. [1] 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 needs an immediate treatment as there will be cerebral hypoxia and hypoperfusion which can affect the survival and subsequent neurodevelopment.[2]

Considerable progress has been made in the understanding of neonatal apnea in last few years. In late 1950's Illingworth and Miller recognised that cyanotic episodes and apnea were more common in preterm infants and signified a poor prognosis.[3]Since then, many of the controversial issues related to the neonatal apneas, have been extensively studied.

Apnea is a major contributor to the morbidity and mortality in the low birth weight infants, and that's why it should be treated aggressively. Identifiable and treatable causes such as infection, hypoxia, hypoglycaemia, hypothermia and others should be corrected immediately. For each episode, tactile stimulation, positive pressure ventilation(bag and mask)and mechanical ventilation should be provided.[4] The pharmacological approach is to administer drugs that stimulate respiration in the neonate. Several drugs such as theophylline, caffeine, doxapram and nikethamide have been used.[5]

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 followed by caffeine, which proved to be more safe, easier to administer, better stimulant of central nervous system, lesser side effects compared to theophylline. However, the choice between caffeine and theophylline in the treatment of neonatal apnea remains a debatable issue.[6,7]

Therefore this study was planned to evaluate role of methylxanthines in the treatment of apnea.

AIMS AND OBJECTIVES

To study efficacy of methylxanthines like caffine and aminophylline in the treatment of apnea by measuring the blood levels of the drug and comparing survival outcome in both the drugs.

MATERIALS AND METHODS

In this prospective study 40 neonates with neonatal apnea admitted in level II/III Neonatal Intensive Care Unit (NICU) attached to post graduate teaching hospital were evaluated . The duration of study was one year.

Any neonate admitted in NICU was selected to the study on first episode of apnea. The babies that were monitored for the selection were:-(i) All babies less than 34 weeks post conceptional age.(ii)Term or preterm babies with sepsis.(iii)Babies with intracranial bleeds, birth asphyxia.
All babies discharged against medical advice before the completion of study period were excluded from the study.

A pilot study was conducted on 9 neonates with apnea 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.

At the first episode, the babies received caffeine or aminophylline . Study group was randomised in to caffeine group or aminophylline group. The babies received a loading dose of aminophylline or caffeine in the following dosage regimen.[8,9]

Caffeine was given 10 mg/kg(base) orally, with nasogastric

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tube. Aminophyllinewas given 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.

Caffeinewas given 2.5mg/kg/day. Orally,once daily & Aminophylline was given 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. 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 eg. Tachycardia, feeding intolerance increased irritability, rash, NEC. Survival outcome was monitored with both modes of treatment. All findings were recorded in the computerized data base.

RESULTS

40 infants with apneic episodes satisfying the inclusion criteria were included in the study. There were 26 males(65%) and 14 females(35%).The gestational age was ranging from 28 to37 weeks. The mean gestational age was 31.38 +/- 2.72 weeks. The birth weight of babies was ranging from 740gms to 1980gms, with mean of 1271.5+/-287.69gms. Full term babies and babies above 2500gms were not excluded from the study. Still, the maximum gestational age in our study was 37 weeks and the maximum birth weight was 1900gms. Apnea was more commonly observed in babies less than 34 weeks, and 85% of the babies were less than 34 weeks. The mean gestational age was around 31.38 +- 2.72 weeks. Similarly, babies between 1000–1500gms constituted 62.5% of infants under the study group. We had more SGAs (55%) than AGAs (45%).

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.3 patients with caffeine and 6 patients with aminophylline had drug levels less than 10 mgs/L.Only 2 patients had tachycardia while receiving aminophylline. One of them had serum theophylline levels of 16.0 mg/L and the other had 16.5 mg/L.

The overall survival of the infants in the study group was 40%. 15 babies survived while 25 babies died. The outcome of the neonatal apneas in terms of mortality was analysed.The results of the study were as follows:-

Table Correlation between methylxanthines and survival

Drug	Living	Dead
Caffeine	9	15
Aminophylline	6	10
p >1.000		

There was no correlation between the methylxanthines and survival.

DISCUSSION

Neonatal apnea remains one of the most common respiratory problem in neonates. Apnea is common in preterm and very low birth infants. The magnitude of the problem is increasing since many preterm and low birth weight babies are surviving.

Our study group consisted of more male infants 26 (65%) than female infants 14 (35%).There is insufficient information regarding the prediction of apnea to either of the sex.

It has been widely accepted that apnea is more common in preterms and low birth weight infants. [10]Our study also showed exclusive occurrence of apnea in preterm and low birth weight group. However there are no studies comparing the incidence of apnea in AGAs and SGAs so far,though our series showed more number of SGAs than AGAs.

We studied a total of 207 apneic episodes in 40 neonates. Apneic spells generally occur in first week of life. In our study, number of apneas per infant was ranging from a minimum of 1 to maximum of 22 per infant with a mean of 5.17 +- 4.92. Ann Stark has mentioned that if the apneic spells do not occur in the first week, they are unlikely to occur later.[11]But,4 infants in our study had their apneic spells after 7 days of life. However, these apneic spells were severe and related to sepsis.

Cessation of airflow in an adult and mature infant results in compensatory mechanisms which attempt to overcome ventilatory embarrassment and also stimulate cardiovascular responses e.g. tachycardia. This ability to respond reflexly is a measure of maturity of respiratory control system.A newborn with immature respiratory control system reacts to the lack of airflow with bradycardia and diminished gas exchange .[12]The concomitant reduction in the cardiac output is reminiscent of the diving reflex. This sequence of events has an impact on cerebral blood flow and other organ blood flow. Effect of hypoxemia with decreased blood flow to various organ systems, followed by reperfusion causes injury to the developing extrauterine organs. In our study,in all 207 apnea episodes there was bradycardia. Usually,apneas of duration longer than 20 seconds are associated with bradycardia.Cyanosis was seen in 33 babies(82.7%).We could prove that there is correlation between cyanosis and bradycardia. However,there was no statistical correlation between duration of apnea and cyanosis in our study.

Apnea and Treatment

The pharmacological approach to the management of neonatal apnea has gained universal acceptance over the past 25 years. Caffeine is more reliably absorbed when administered orally and has longer half life. Caffeine can be given once a day while theophylline has to be given three times a day. For our study, the preparation used was caffeine citrate dropsmade 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 differ-

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ence in the number of apneas between the two groups.

The drug levels achieved by the xanthines were analysed. The caffeine and theophylline both achieved therapeutic levels with the dosage regimen we followed. Caffeine showed drug levels ranging from 5.0 mg/L to18.5 mg/L with a mean of 13.7 +- 3.79mg/L and aminophylline, showed drug levels ranging from 3.5mg/L to 24.0mg/L with a mean of 11.31 +-4.919mg/L. There was no significant difference in the drug levels achieved by both the drugs.

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 .[13]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.[14]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.

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 =0.001).There was no difference in the survival between the caffeine group and aminophylline group. When the survival was correlated with lower drug levels(< 10mg/L) with either of the methylxanthines there was no significant correlation.However,there was no significant predictors of number of apneas in our study when analysed by logistic regression analysis.

SUMMARY AND CONCLUSIONS

Neonatal apnea remains a major diagnostic and therapeutic challenge today as the survival of very low birth weight babies and preterms are increasing with better neonatal care. Immaturity of the respiratory system with an associated postnatal stress makes the newborns susceptible to hypoxemic episodes.

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 are increasing, caffeine preparations should be made readily available.

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