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Original Article

Comparison of Aminophylline Alone and in Combination with Doxapram For Cessation of Apnea of Prematuriy

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ABSTRACT

Background: *Apnea of Prematurity remains exceedingly significant clinical problem of premature neonates, associated with significant morbidity and mortality in neonatal intensive care which may be treated with noninvasive respiratory therapy and methyl xanthenes. Aminophylline a freely available methyl xanthenes used alone in apnea of prematurity and given in conjunction with Doxapram in apnea not responding to tactile stimulus. The short term outcomes in term of their efficacy and safety were evaluated and compared in Neonatal intensive care.*

Methods: *We enrolled total 52 admitted newborns <32 weeks of gestational age with tactile stimulus refractory apnea of prematurity and divided into two equal groups by random blinded slips. One group was given aminophylline as a monotherapy and half received doxapram in a continuous intravenous infusion in combination with aminophylline. All the neonates in study were closely monitored for the recurrence of apnea up to 7 days and for the toxicity of the drug.*

Results: *Mean birth weight and gestational age of enrolled babies was 1.322+0.122Kg and mean gestational age of babies treated with Aminophylline was 31.11+0.03 weeks while 30.60+0.42 weeks in the combination group. The mean age of the base line apnea was 70.76 hrs in the aminophylline group whereas 68.32 hrs in the combination group. Out of the total 76.92% neonates in Aminophylline group and 80.80% in combination group neonates depicted complete cessation of apnea episodes and remained apnea free.*

Conclusions: *The combination of Doxapram & Aminophylline proved better then Aminophylline alone during initial hours of drug therapy in reducing the recurrence and need of intubation without any significant short term adverse effects. However until efficacy and safety are confirmed in more prospective trials, combination of Doxapram with Aminophylline should be used with caution.*

Keywords: *Aminophylline, Doxapram, Apnea of prematurity,Cessation of breath, Newborn.*

Introduction

Apnea is defined as cessation of respiration and time duration of cessation to classify as apnea has been decreasing since last few decades as to intervene early enough to avoid systemic consequences and latest definition of apnea is given by the American Academy of Pediatrics as "an unexplained episode of cessation of breathing for 20 seconds or longer, or a shorter respiratory pause associated with bradycardia, cyanosis, pallor, and/or marked hypotonia."[1] Apnea is more common in preterm infants. Apnea of prematurity is a sign of physiological immaturity and remains a common clinical problem of extreme premature babies. The apnea episode solitary or recurrent occurs in over 80% of infants less than 30 week and in 7% at 34-36 weeks of gestational age. Out of all these episodes 40% are central or diaphragmatic, 10 % are obstructive and 50% are of mixed variety. Recurrent episodes of apnea has significant impact on the blood flow to the vital organs including cerebral ischemia leading to undesired long term poor neuro developmental outcomes such as spastic diplagia.[2,3,4] The prolonged episode of apnea may sometimes require vigorous resuscitation due to fall of blood pressure during the episode and may lead to respiratory failure and death. The evidence is increasing that neonatal apnea is not only associated with brain damage but it may indeed reflect early disturbance of respiratory control system which may predispose infants to SIDS[5.]

Therefore aggressive approach in prevention and its management which includes specific therapy for the predisposing factors (such as hypoxia, hypothermia, hypoglycemia, infection and gastro-esophageal reflux), tactile stimulation and noninvasive respiratory therapy has become increasingly important to stimulate the respiration. Methylxanthines, such as caffeine, and aminophylline are the mainstay pharmacological treatment for apnea and have proven to reduce chronic lung disease and long-term outcome.[6,7] Doxapram was also used to treat neonates with persistent idiopathic apnea of prematurity unresponsive to methyl xanthenes therapy [8, 9.] It is a good respiratory stimulant and increases breathing by stimulating both central and peripheral chemoreceptors[10,11.] A number of observational trials have proved the efficacy of the individual drug in the successful reduction of the recurrent apnea and their short term and long term side effects. Here we have compared the efficacy, safety & short term outcomes of aminophylline mono therapy and in combination with doxapram in unresponsive neonatal apnea.

Methods

This study was conducted in NICU of a tertiary care teaching hospital of western Rajasthan for a period of one year. Written and informed consent was obtained from the parents prior to enrolment and the study was approved by the ethical committee of the institute. All those intramural newborns who were less than 32 weeks and had not any major congenital birth defect and any other severe central or pulmonary issues requiring mechanical ventilation soon after birth were included in the study which came out to be total of 52 neonates admitted in NICU. The general principles to start a treatment regimen were strictly followed in every case of apnea with tactile and proprioceptive stimulation being the first line measure to enhance the arousal state to forestall the progression of apnea followed by CPAP with pressure of 2-4 cm of H_2O to influence the respiratory reflexes and to splint and to ensure the patency of the upper airway. Drugs were started to enhance arousal state and respiratory reflexes after failure of tactile stimulation and CPAP, which is the main component of the treatment. All enrolled neonates were divided in to two equal groups of 26 each and babies were chosen by random blinded slips. Aminophylline group was given loading dose of 5-7mg/kg followed by a maintenance dose of 1.5-2 mg/kg every 6 hourly to achieve the therapeutic plasma concentration of 10 µg/ml. Aminophylline was discontinued in the neonates who attained the 36 week post conception age and no apnea spell

has noted over the period of one week.[4] Combination group was given doxapram in a continuous intravenous infusion initially in the dose of 1 to 1.5 mg/kg/hr to a maximum up to 2mg/kg/hr till the desired response was achieved in addition to aminophylline[12]. The recurrent apnea was labeled in the neonates who had the second episode of apnea after 48 hours of apnea free interval.

A detailed history regarding date, place, type of delivery, birth order, APGAR Scoring, day of life of apnea, birth weight, and gestational age were recorded in a pre-designed performa. Relevant laboratory and radiological investigations aimed to find out other co-morbidity and predisposing conditions of apnea were also done. The response to therapy was considered in the form of duration of apnea free interval in each study group. All the neonates in study were closely monitored for the recurrence of apnea up to 7 days after initiating the drugs and every episode of apnea was closely monitored for its duration, HR, CFT, Cyanosis and pallor and details were noted over apnea chart. Apnea attack rate per hour was determined in each study group after employing the drugs which was estimated by the numbers of episodes of apnea divided by postnatal age in hours.[13] All the neonates in study were also monitored closely for any side effects and for the toxicity of the drug like irritability, jitteriness, seizures, tachypnea, tachycardia, circulatory instability vomiting, GERD, shock and any other adverse effect related to drugs during entire course of therapy. The serious adverse effects of the drugs and incidence of NEC, IVH, PVL, ROP, persistent PDA, or worsening of pulmonary condition were closely monitored during drug therapy.

Results

A total of 52 premature Apneic neonates admitted in NICU were studied with mean birth weight of 1.322+0.122Kg however it was 1.32+0.59 kg in Aminophylline group and 1.318+0.66 Kg in the combination group. The mean gestational age of babies treated with Aminophylline was 31.11+0.03 weeks while 30.60+0.42 weeks in the combination group. In the present study the peak hours of onset of base line apneic episodes were 24-72 hours of the life and majority of the babies (54.75%) had the base line apnea during this period. The mean age of the base line apnea was 70.76 hrs in the aminophylline group whereas 68.32 hrs in the combination group. The overall range for onset of apnea was 3 hrs to 216 hrs of the life in the present study. Neonatal apnea was frequently associated with ongoing neonatal diseases and a variety of precipitating factors and in our study we observed perinatal asphyxia (14.28%), RDS(14.28%), NNS(14.28%), ICH (14.28%), CHD (14.28%), hyper viscosity (14.28%), hypoglycemia(14.28%) and hypocal-cemia (14.28%) were the frequent associated conditions. However hypoglycemia and hypocalcemia were the two most frequent metabolic derangements found to be associated with neonatal apnea.(Table No. I)

Out of the total 76.92% neonates in Aminophylline group and 80.80% in combination group neonates depicted complete cessation of apnea episodes and remained apnea free throughout the period of follow up and this difference was found significant statistically. (Table No. II) The Non responder to the drug therapy were mostly extreme premature ELBW neonates who needed intubation and mechanical ventilation despite of the drug therapy which was 23.08% in aminophylline group and 19.2% in the combination group and this difference again indicates that combination is superior than giving aminophylline alone in terms of improved survival and decrease the need of mechanical Ventilation. The drug toxicity was observed most commonly in combination group where the common side effects were vomiting and irritability but there was no increase in serious adverse effects like necrotizing enterocolitis, intraventricular hemorrhage, periventricular leukomalacia, retinopathy of prematurity, persistent ductus arteriosus, or worsening of pulmonary condition.

Table 1: Baseline characteristics of the Neonates Participated in the study

Base line characteristics	***Group (A) (Aminophylline) (N=26)***	***Group (B) (Combination) (N=26) (Aminophylline+Doxapram)***
Birth weight (g.),mean (SD)	1320±.59	1318±0.07
Gestational Age(Weeks)Mean(SD)	31.13±.03	30.60±.07
Gender Male/Female % (Ratio)	54/46	65/35
Maternal Morbidity (%)		
APH	11.53	23
PROM	34.6	15.38
PIH	11.53	11.53
Eclampsia	-	3.84
Mode of Delivery Normal/LSCS	24/2	24/2
5min APGAR <7	11.53%	19.23%
H/o Antenatal Steroids	24	23
Need of IPPVR (%)	22.7	19.2
Mean age of onset of Apnea (Hours)	78.76	68.02
Duration of baseline Apnea episode(Sec.)	43.84	34.80
Mean HR of baseline Apnea episode(b/min)	77.69	62.12
Common Co morbidity		
Hypocalcaemia, (%)	4.76	4.67
Hypoglycemia &	2.38	1.19
NNS	5.15	3.57

Table 2: Percentage of Apnea free Neonates after institution of drugs therapy

Duration of drug Therapy (Hours)	***Aminophylline Group[N=26]***	***Combination of drugs [N=26] (Aminophylline+Doxapram)***	***P value***
24	*16 (61.53%)*	*21(80.76%)*	*P<0.05*
48	*14 (53.84%)*	*18 (69.23%)*	*P<0.05*
72	*16 (61.53%)*	*17 (65.38%)*	*P>0.05*
96	*15 (60.5%)*	*19 (73.7%)*	*P>0.05*
120	*18 (69.23%)*	*20 (76.92%)*	*P>0.05*
144	*19 (73.70%)*	*21 (80.76%)*	*P>0.05*
168	*20 (76.92%)*	*21 (80.76%)*	*P>0.05*

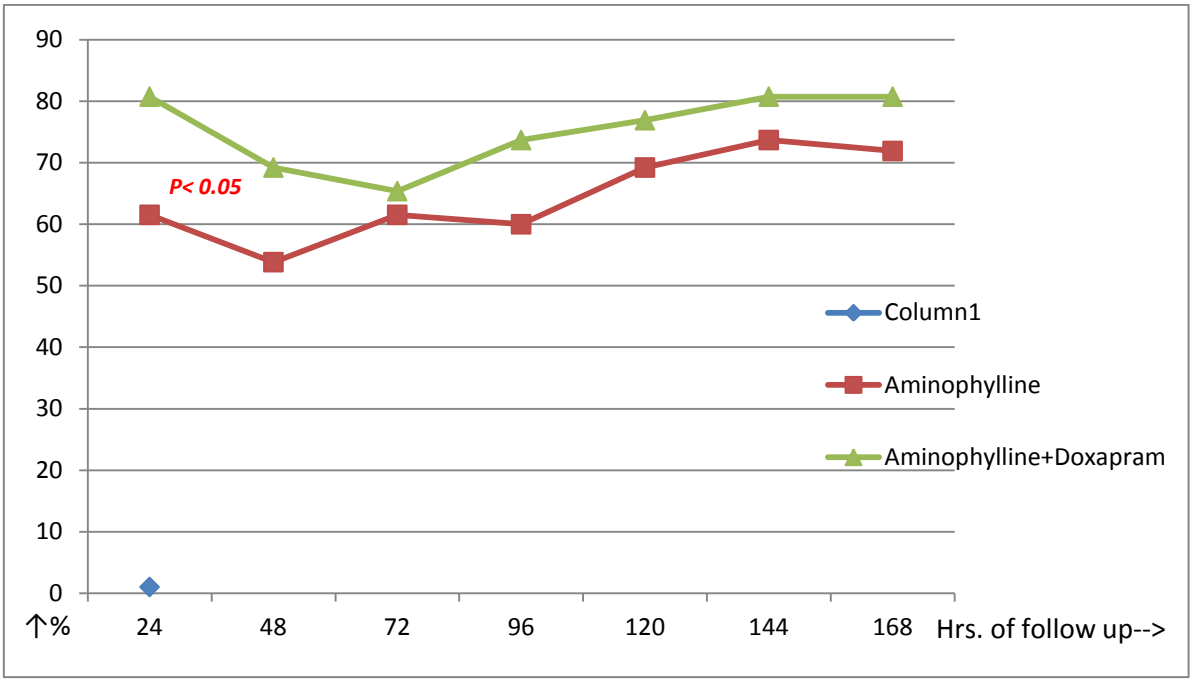

Fig 1: Percentage of. Apnea free Neonates after institution of drugs therapy in each study group

Discussion

In our study 76.92% neonates in aminophylline group and 80.76% in combination group responded and remained apnea free throughout the period of drug therapy, but this difference between the two groups was not statistically significant. Our results were comparable as reported in the study of Mayer T F et al[14]. (1980), Eyal et al[15] (1985) and Muttitt S C et al.[16] (1988). Although there was a large difference in percentage of responders in first 24 hrs in aminophylline vs combination group (61.53% vs 80.76%) and also at 48 hrs too (53.84% vs 69.23%) and both these results were statistically significant (p value<0.05). However after initial 48 hours of the combination drug therapy, Apnea attack rate was found almost identical in all the groups without any significant difference in doxapram combination versus aminophylline monotherapy (p value>0.05). Therefore we conclude that the combination therapy of aminophylline and doxapram in the therapeutic doses proves to be superior in the treatment and prevention of recurrence of apnea in the premature neonates (< 30 weeks) who have the maximum recurrence during initial few hours. The combination therapy is also effective in reducing the need of intubation and mechanical ventilation associated complications. Other studies done by Sagi E & Eyal. F et al [17] (1984), Barrington K.J. et al [18] (1987) and Pelivowski A[19] (1990) have also established the efficacy of doxapram in apnea of premature babies refractory to therapeutic level of aminophylline. Our study has also proved the superior efficacy *of doxapram* once given in combination with *aminophylline* during initial 48 hours of baseline apnea episode in therapeutic doses, and it is significantly associated with reduction of recurrence of apnea without any short term significant adverse drug effects in comparison to the use of *aminophylline* alone.(Fig-1) Since the response to the therapy in combination and with aminophylline alone after the period of maximum recurrence i.e. first 48 hours from the base line episode is almost identical so it is prudent to safely withdraw doxapram after 48 hrs from the combination to minimize their side effects.

There is a wide variation in responses of doxapram used by different authors for apnea of prematurity like Eyal F, et al[15].(1985) reported only 53.4% of all the neonates treated with doxapram were responded in term of complete cessation of apnea spells in their study, whereas ,

Peliowsky A et al[19] (1990) and Prins SA, et al[20] (2013) reported response to doxapram therapy was in 63.63% and 64.8 % respectively whereas Barrington KJ, et al[18]. has monitored therapeutic serum level of the drug and reported good response (82-89%) in apnea of prematurity and also noted better response with higher serum concentration of doxapram (i.e. 1.5µgm/ml).

Therefore in first 48 hours a combination of aminophylline and doxapram may be preferred over aminophylline alone, nevertheless, it is remarkable that essential evidence about the efficacy and safety from well-designed clinical trials is almost completely lacking. Therefore there is a need of more RCTs to evaluate the therapeutic benefits and long term outcomes related to the drugs toxicity of doxapram by monitoring of therapeutic serum concentration and its possible impact on the survival and safety in extreme premature neonates.

Conclusion

Considering the maximum therapeutic benefits in Extreme Premature neonates with Apnea of prematurity, it is to conclude that using doxapram in combination with aminophylline in unresponsive apnea during the initial hours of the management results in reducing the need of intubation and mechanical ventilation and its associated morbidity and mortality. However therapeutic benefits and long term outcomes related to the drugs toxicity of doxapram, either use alone or together with Methyl xanthenes need to confirm with more RCTs and until efficacy and safety are confirmed in more prospective trials, combination of doxapram with aminophylline should be used with caution.

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Competing Interest: None stated

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