COMPARATIVE STUDY TO EVALUATE EFFICACY AND ADVERSE EFFECTS OF CAFFEINE AND AMINOPHYLLINE IN THE MANAGEMENT OF APNEA OF PREMATURITY

Pediatrics

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ABSTRACT

INTRODUCTION: An estimated 5.9 million children under 5 years of age died in 2015, with a global under-five mortality rate of 42.5 per 1000 live births.

AIMS: The aim of my study was to compare the beneficial effects and adverse effects of caffeine and aminophylline in the management of apnea of prematurity during hospital stay and 1 year follow up period after discharge.

MATERIAL AND METHODS: NICU (Neonatal Intensive Care Unit) in Department of Pediatric Medicine, R.G. Kar Medical College & Hospital, Kolkata, India. From 2015 to 2016. Intramural preterm neonates admitted to NICU diagnosed as having apnea of prematurity and satisfying the inclusion criteria mentioned below.

RESULT AND ANALYSIS: In our study showed that in GROUP A, 2 cells (50%) have expected count less than 5. In GROUP B, 4 cells (100%) have expected count less than 5. So, Pearson Chi-Square test is not applicable for this two groups. Instead Fisher's Exact Test (2 sided) is applied. In GROUP C, all babies who were put on CPAP/ventilator survived. So chi-square test could not be done.

SUMMARY AND CONCLUSION: Though Caffeine has some clear benefits over aminophylline like once a day treatment, no need of drug monitoring, and cost effectiveness. We prefer caffeine over aminophylline in the treatment of apnoea of prematurity in our institution.

KEYWORDS

INTRODUCTION

An estimated 5.9 million children under 5 years of age died in 2015, with a global under-five mortality rate of 42.5 per 1000 live births.¹ Of those deaths, 45% were newborns, with a neonatal mortality rate of 19 per 1000 live births.¹ In the year 2015 Under five mortality was 43 and 48² per 1000 live birth globally and in India respectively. Neonatal mortality rate in India was 27.7 per 1000 live births in 2015. New born deaths accounted for 44 % of under 5 mortality.³ The major causes of neonatal mortality in 2015 were prematurity, birth-related complications (birth asphyxia) and neonatal sepsis.¹ Prematurity accounts for around 1/6th cases of under-five mortality.

Apnea is very common in preterm neonate, termed Apnea of Prematurity (AOP) and is one of the leading cause of neonatal morbidity and mortality worldwide. AOP is one of the most common disorder in NICU. Recurrent episodes of apnea are common in preterm infants and the incidence and severity increases at lower gestational age.⁴ These episodes of loss of effective breathing can lead to hypoxemia and bradycardia, which may be severe enough to require resuscitation including use of positive pressure ventilation. There are clinical concerns that these episodes might be harmful to the developing brain or cause dysfunction of the gut or other organs.

Two forms of methylxanthine derivatives [aminophylline and caffeine] have been used to stimulate breathing in order to prevent apnea and its consequences. As aminophylline is known to have a narrow therapeutic window and significant adverse effects, there arises a need to consider alternative drug(s) for better control of apnea with adequate safety profile.

My study is intended to find out the comparative effects and side effects (during hospital stay and 1 year follow up period) of aminophylline and caffeine in AOP.

The aim of my study was to compare the beneficial effects and adverse effects of caffeine and aminophylline in the management of apnea of prematurity during hospital stay and 1 year follow up period after discharge.

MATERIAL AND METHODS

1. STUDY AREA:

NICU (Neonatal Intensive Care Unit) in Department of Pediatric Medicine, R.G. Kar Medical College & Hospital, Kolkata, India.

2. STUDY PERIOD: From 2015 to 2016.

3. STUDY POPULATION:

Intramural preterm neonates admitted to NICU diagnosed as having apnea of prematurity and satisfying the inclusion criteria mentioned below.

INCLUSION CRITERIA:

Premature newborns < 36 weeks of age, who had 2 or >2 episodes of apnea in last 24 hours, not explained by any other cause within day 7 of life.

EXCLUSION CRITERIA:

- Premature newborns with birth asphyxia,
- Premature newborns born to mothers on MgSO₄ therapy,
- Premature newborns with neonatal sepsis,
- Premature newborns with hypoglycemia, anemia, hypothermia,
- Premature newborns with major congenital anomalies.

4. SAMPLE SIZE :

Approximately 100 neonates having the inclusion criteria, divided in 2 groups.

CAFFEINE GROUP (C) – 50 preterm neonates.
AMINOPHYLLINE GROUP (A) – 50 preterm neonates.

5. ANALYSIS OF DATA :

Statistical analysis was carried out using SPSS statistical 17 software for Windows. Chi-square test was performed for data analysis of qualitative variables. The mean value of the two groups was compared mainly using independent t-test. P value <0.05 was considered significant.

RESULT AND ANALYSIS

Our study showed that bar diagram showing distribution of study population according to sex. Bar diagram showing distribution of study population according to religion. Pie diagram showing distribution of aminophylline group according to birth weight. Bar diagram showing distribution of total population according to birth

weight Histogram showing distribution of birth weight in caffeine group ($n = 50$). The distribution of birth weight among caffeine and aminophylline groups do not follow normal distribution pattern (as p value < 0.05). So t -test is not applicable in this situation. Instead Mann-Whitney U test is used.

We found that bar diagram showing distribution of study population according to gestational age. Histogram showing distribution of gestational age in caffeine group ($n = 50$). The distribution of gestational age among caffeine and aminophylline groups do not follow normal distribution pattern (as p value < 0.05). So t -test is not applicable in this situation. Instead Mann-Whitney U test is used. Bar diagram showing comparison of apnea response in GROUP A. Bar diagram showing comparison of apnea response in GROUP B. Bar diagram showing comparison of apnea response in GROUP C. In caffeine group, 35 babies achieved $>50\%$ reduction in apnea frequency (apnea response). The number was 32 in aminophylline group. There was no significant difference ($p=0.523$) in between caffeine and aminophylline groups.

In our study showed that in GROUP A, 2 cells (50%) have expected count less than 5. In GROUP B, 4 cells (100%) have expected count less than 5. So, Pearson Chi-Square test is not applicable for this two groups. Instead Fisher's Exact Test (2 sided) is applied. In GROUP C, all babies who were put on CPAP/ventilator survived. So chi-square test could not be done. Among 33 babies needing ventilatory support, 20 babies (caffeine group = 9, aminophylline group = 11) survived and rest 13 babies (caffeine group = 6, aminophylline group = 7) expired. Adverse effects were seen during hospital stay and follow up upto 1 year of age. Among all adverse effects, PDA and tachycardia were compared in between 50 babies of each caffeine (C) and aminophylline (A) groups. Those who were put on ventilator, 6 patients of C group and 7 patients of A group expired. So feeding intolerance, NEC, BPD were compared in between the rest of the patients, i.e. 44 patients in C group and 43 patients in A group.

DISCUSSION

Essentially, all infants less than 28 weeks of gestational age or less than 1,000 g of birth weight have AOP⁵. Persistent apnea may be harmful to the developing brain or organs. Methylxanthines (such as caffeine and aminophylline) are drugs that are believed to stimulate breathing and have been used to reduce AOP.

In the Cochrane review in 2010, Henderson-smart and Steer⁶, 5 trials involving a total of 108 infants were included. No difference in treatment failure rate was found between caffeine and theophylline after one to three days treatment or five to seven days treatment.

Side effect observed during therapy with these drug were tachycardia and signs of gastrointestinal dysfunction such as feeding intolerance, abdominal distension, vomiting, NEC. In Cochrane review in 2010,⁶ adverse effects were lower in caffeine group (summary relative risk 0.17, 95% CI 0.04 to 0.72). Aminophylline group was associated with higher rates of toxicity. Feeding intolerance was low in caffeine group (41%) compared to aminophylline group (58%) though not statistically significant. (p value = 0.108). Tachycardia was seen in comparatively less newborn in caffeine group (38%) than aminophylline group (46%) but statistically insignificant (p value = 0.418). PDA was diagnosed in 16% babies in caffeine group and 12% in aminophylline group (p value = 0.564). BPD developed in 9% caffeine treated babies and 14% in aminophylline group (p value = 0.521).

Erenberg et al⁷ revealed an increased rate of NEC in caffeine treated preterm neonates with AOP. Conversely, the larger Schmidt study identified no difference in rates of NEC between the caffeine and placebo groups. We did not observe any significant difference of signs and symptoms of NEC in between the two drug groups. NEC developed in 11% caffeine treated babies and 14% aminophylline treated patient (p value = 0.716).

Schmidt et al.⁸ conducted a randomized study in preterm infants during first 10 days of life and they received either caffeine or placebo; The authors evaluated the short-term outcomes before the preterm infants were discharged. In the caffeine group, the infants who remained alive at a post menstrual age of 36 weeks, the need for oxygen therapy was less in the caffeine group than the placebo group (36% v/s 47%, $P < 0.001$), frequency of NEC did not differ between two groups. Weight

gain was reduced temporarily in the caffeine group, and the difference was significant especially at two weeks after birth. Also, the frequency of PDA that required medical treatment (29.3% vs. 38.1%, $P < 0.001$), especially surgical treatment (4.5% vs. 12.6%, $P < 0.001$) was less in the caffeine group. Our study was not a placebo controlled study, but it was a comparative study between caffeine and aminophylline groups. There was no significant difference in incidence of PDA, NEC and BPD (p value = 0.564, 0.716, 0.521).

Also Schmidt et al.⁹ studied the long term effects of caffeine therapy on apnea of prematurity in infants with birth weights of 500 to 1250 gram at a corrected age of 18 to 21 months. The infants treated with caffeine showed reduced incidences of cerebral palsy (4.4% v/s 7.3%; $p=0.009$) and cognitive delay (33.8% v/s 38.3%; $p=0.04$) compared to placebo group. The rates of deafness and blindness and mean for height, weight, and head circumference did not differ significantly between two groups.

Babies who survived and discharged at home were followed up at 6 months and 1 year of age in terms of weight, length and head circumference and neurodevelopmental outcome like motor development, occurrence of blindness and hearing loss. No significant difference was seen in weight at 6 months of age (p value = 0.514); body weight in 1 year of age (p value = 0.346). Length at 6 month and 1 year of age were also not significantly different in caffeine and aminophylline groups, p value = 0.789 and 0.110 respectively. No significant difference in head circumference was seen in caffeine and aminophylline groups at 6 months and 1 year of age (p value = 0.383 and 0.789).

These observations were similar to those of Brouard et al¹⁰ at 2014, observed both aminophylline and caffeine to be equally efficacious in reducing apneic episodes by $> 50\%$ by day 5 of treatment of AOP in preterm neonates in a study conducted at NIMS medical college, Jaipur, India.

SUMMARY AND CONCLUSION

Both caffeine and aminophylline showed reduction in apnea frequency significantly. But no significant difference was noted in between aminophylline and caffeine group in all 3 age sub-groups (p value = 0.482 in group A; p value = 0.772 in group B; p value = 0.558 in group C).

The newborn babies who did not respond, were put on CPAP/mechanical ventilator. Response rate among the ventilated babies also showed no significant difference in both drugs in different gestational age group.

During the hospital stay babies were monitored for morbidities. In our study, less neonates (numerically) within caffeine group had feeding difficulty than aminophylline group, though statistically it was not significant (which may be due to relatively small sample size). Also tachycardia occurred in less number of neonates in the caffeine group compared to aminophylline group. Occurrences of BPD, PDA, and NEC were not significantly different in between caffeine and aminophylline groups.

In our study, no significant difference were seen in mean weight, length and head circumference at 6 month and 1 year of follow up nor in the occurrence of motor developmental delay, retinopathy of prematurity and hearing loss between caffeine and aminophylline groups were seen.

So, in conclusion Intravenous caffeine therapy is as efficacious as aminophylline in treatment of apnoea of prematurity among all the 3 gestational age groups. Tachycardia and feeding intolerance were relatively less in caffeine treated babies compared to aminophylline group though not significant statistically. No significant difference was found in other adverse effects like NEC, BPD, PDA in both groups. In case of long term neurodevelopmental outcomes, like reduction of motor developmental delay, caffeine was not proved to be superior over aminophylline. For clarifying the effect on long term neurodevelopmental morbidity a prospective, multi-center, randomized controlled study comparing each of the two methylxanthines (caffeine or aminophylline) with placebo or caffeine versus aminophylline is needed. Though Caffeine has some clear benefits over aminophylline like once a day treatment, no need of drug

monitoring, and cost effectiveness. We prefer caffeine over aminophylline in the treatment of apnoea of prematurity in our institution.

TABLE: Distribution of study population according to sex, Distribution of study population according to MOD

		CAFFEINE GROUP		AMINOPHYLLINE GROUP	
		NO.	%	NO.	%
SEX	BOY	36	72	32	64
	GIRL	14	28	18	36
	TOTAL	50	100	50	100
MOD	LUCS	19	38	17	34
	Normal Delivery	31	62	33	66
	TOTAL	50	100	50	100

REFERENCE

1. World Health Organisation: Monitoring health for the SDGs, Sustainable Development Goals. World Health Statistics 2016 : 48.
2. Levels & Trends in Child Mortality: UN Inter-agency Group for Child Mortality Estimation (UN IGME) 2015 : 20.
3. World Health Organisation. Causes of child mortality, 2000-2012. Global health Observatory (GHO).
4. Henderson-Smart, Peter A Steer. Caffeine versus theophylline for apnea in preterm infants. Cochrane Database of Systematic Reviews 2010; Issue 1. Art. No. CD000273.
5. Stokowski LA. A primer on apnea of prematurity. Adv Neonatal Care 2005;5:155– 170. quiz 71–4.
6. Henderson-Smart DJ, De Paoli AG. Methylxanthine treatment for apnea in preterm infants. Cochrane Database Syst Rev 2010.
7. Erenberg A, Leff RD, Haack DG, Mosdell KW, Hicks GM, Wynne BA. Caffeine citrate for the treatment of apnea of prematurity: a double-blind, placebo-controlled study. Pharmacotherapy 2000; 20: 644-52.
8. Schmidt B, Roberts RS, Davis P, Doyle LW, Barrington KJ, Ohlsson A et al. Caffeine therapy for apnea of prematurity. N Engl J Med 2006;354:2112–21. [RCT]
9. Schmidt B, Anderson PJ, Doyle LW, Dewey D, Grunau RE, Asztalos EV et al. Survival without disability to age 5 years after neonatal caffeine therapy for apnea of prematurity. JAMA 2012;307:275-82.
10. Brouard C, Moriette G, Murat I, et al. Comparative efficacy of theophylline and caffeine in the treatment of idiopathic apnea in premature infants. Am J Dis Child 1985; 139:698–700.