Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/jptcp.v31i2.4776

THE ROLE OF CAFFEINE IN NONINVASIVE RESPIRATORY SUPPORT VERSUS AMINOPHYLLINE IN PREMATURITY APNEA

Muhammad Aslam Chandio[1*], Muhammad Tariq[2], Kanwal Shaikh[3], Kausar Keerio[4], Asma Bilal[5], Sirichand[6]

[1]*Assistant Professor Of Pediatrics, Department Of Pediatric Medicine, Shaheed Mohtarma Benazir Bhutto Medical College Lyari Karachi Pakistan. Email: Dr_Chandio79@Yahoo.Com
[2]Consultant Peadiatrician, Pakistan Institute Of Medical Sciences Islamabad Pakistan. Email: Muhammadtariq55494@Gmail.Com
[3]Paeds Emergency Incharge, National Medical Centre Karachi Pakistan. Email: Kanwalsh@Hotmail.Com
[4]Senior Registrar Pediatrics, Liaquat University Of Medical And Health Sciences Jamshoro Pakistan. Email: Kausarkeerio@Gmail.Com
[5]Registrar Pediatrics, Prime Hospital Dubai Garhoud UAE. Email: Drasmabilal111@Gmail.Com
[6] Assistant Professor Of Pediatrics, Hamdard University Of Medicine And Dentistry Karachi Pakistan. Email: Siritalreja@Hotmail.Com

***Corresponding Author:** Muhammad Aslam Chandio
*Assistant Professor Of Pediatrics, Department Of Pediatric Medicine, Shaheed Mohtarma Benazir Bhutto Medical College Lyari Karachi Pakistan. Email: Dr_Chandio79@Yahoo.Com

Abstract

Background: Since caffeine and aminophylline serve as both respiratory stimulants to raise minute ventilation and neurological stimulants to promote diaphragm contraction and respiratory muscle function, they are commonly administered as the first-line treatments for apnea in preterm newborns. A combination of two main therapies is used to treat preterm apnea: medication and oxygen supplementation, both of which are essential for healthy bodily functions. Even though aminophylline and caffeine citrate have historically been the main therapies for baby apnea in clinical settings, a comparison of the effectiveness and safety of these medications in the management of apnea has to be done.

Objective: To investigate the potential clinical benefits of giving caffeine and aminophylline to treat apnea of prematurity in varying oxygen (O2) delivery conditions.

Study design: A retrospective study

Place and Duration: This study was conducted in Pediatric Department, lyari General Hospital Shaheed Mohtarma Benazir Bhutto Medical College Lyari Karachi. from October 2022 to October 2023

Methodology: All of the participants in this research were preterm babies with apnea. All of the babies underwent aminophylline or caffeine treatment. The physician could choose either aminophylline or caffeine as a therapy. One group of newborns with apnea were given intravenous (IV) injections of caffeine, beginning with a 20 mg/kg dose and continuing with a regular maintenance

dose of 10 mg/kg until the babies reached the 34th week of gestation. Alternatively, other infants were given an IV dosage of aminophylline, commencing at 5 mg/kg, and then a maintenance dose of 2.5 mg/kg twice daily after delivery until the babies reached the 34th week of gestation.
Results: There were a total of 40 preterm babies involved in this research. Out of these 40 preterm babies, 21 were boys and 19 were girls. The birth weight of these babies ranged from 500 to 1250 grams. Our study found a significantly lower incidence of apnea with rates of 61.38% (≤ 29 weeks), 43.03% (30–31 weeks), 18.8% (32–33 weeks), and 2.99% (34–35 weeks). The neonates treated with both medications had comparable rates of ventilator replacement and recurrence of apnea.
Conclusion: Caffeine and aminophylline are both beneficial for reducing apnea episodes and assisting with ventilator weaning in extremely preterm newborns.

Keywords: Apnea of prematurity, caffeine, aminophylline, premature babies

INTRODUCTION

A respiratory pause lasting twenty seconds is referred to as apnea. Another type of apnea is periodic breathing, which is characterized by short breathing pauses after bouts of fast breathing (tachypnea) [1]. Central apnea, obstructive apnea, and mixed apnea are the three forms of apnea [2]. Breathing becomes difficult due to problems with the neurological system that cause central apnea. On the other hand, loose or extra tissue frequently causes obstructive apnea, which results from the upper airway closing [3].

Airway obstruction in premature newborns can result from the neck's posture, particularly when it is flexed [4]. Because chest wall motion is still recorded as breathing effort, standard cardiorespiratory monitoring is unable to diagnose obstructive apnea. With characteristics of both central and obstructive kinds, mixed apnea is the most prevalent type in premature newborns [5]. Mixed apnea episodes usually start with central apnea, which lowers the upper airway tone and leaves an obstruction that doesn't go away even when breathing is resumed. When breathing stops for at least 20 seconds or 10 seconds, together with bradycardia and hypoxemia, it is referred to as apnea of prematurity (AOP), and it usually occurs before 37 weeks of pregnancy [6].

The American Academy of Pediatrics recently published a clinical report on apnea of prematurity. AOP affects almost all newborns delivered before 28 weeks of pregnancy or who weigh less than 1000 grams at birth [7]. Lower birth weight and a decreasing gestational age are associated with an increased incidence of AOP. Unlike apnea, which can remain in newborns born at the youngest gestational ages, AOP is a developmental disorder that usually improves with the baby's growth. It's critical to understand that AOP in neonates differs from apnea [8]. Apnea in newborns is more commonly associated with a serious underlying illness, such as infection, neurological abnormalities, or metabolic disorders. Apnea in premature infants can also be a symptom of these conditions.

Hypoxia, hypercarbia, and acidosis can cause newborns' respiratory rates to rise [9]. Peripheral chemoreceptors sense a drop in blood oxygen saturation, which triggers this rise. Central chemoreceptors are more sensitive to hypercarbia than peripheral chemoreceptors, despite the fact that both types of chemoreceptors are involved in signalling an increase in respiratory rate. In acidosis, the central chemoreceptors are activated.

The number of repeated apneic episodes, the need for invasive ventilation instead of oxygen delivery devices, and changes in the amount and length of oxygen inhaled were all things that were looked at when comparing how well aminophylline and caffeine treated infant apnea [10]. The efficacy was evaluated based on the following requirements: "i) no alteration in the frequency of apneic episodes within 48 hours of drug administration; ii) no change in the frequency of apneic episodes within 48 hours of drug administration; iii) occurrence of apneic episodes twice a day accompanied by a normal breathing pattern; iv) recurrence of apnea with a three-day interval between the first and second episodes."

Medical issues were identified by means of diagnostic methods such as brain ultrasonography, echocardiography, radiography of the chest or abdomen, and evaluation of aberrant blood vessel formation in the retinal region [11]. Intraventricular haemorrhage (IVH), retinopathy of prematurity

(ROP), necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD), and patent ductus arteriosus (PDA) were the most common findings in the study [12]. The percentage of the populations treated with aminophylline and caffeine was used to calculate the occurrence of these problems. This study aims to investigate the potential clinical benefits of giving caffeine and aminophylline to treat apnea of prematurity in varying oxygen (O2) delivery conditions.

METHODOLOGY

All of the babies in this research underwent aminophylline or caffeine treatment. The physician could choose either aminophylline or caffeine as a therapy.

Infants included in this retrospective study met the following criteria: i) Apnea diagnosis in infants born after gestation of less than 34 weeks, with the mixed type constituting approximately 75% of all apnea types; ii) Absence of contraindications to both invasive and noninvasive ventilation; iii) Hospital stay of at least 24 hours; iv) Treatment exclusively involved caffeine or aminophylline for apnea of prematurity under varying oxygen (O2) delivery conditions; and v) No presence of complex congenital malformations affecting airways, chromosomal abnormalities, or inherited metabolic diseases.

Neonates having sepsis or other causes of apnea were excluded from the study.

One group of newborns with apnea were given intravenous (IV) injections of caffeine, beginning with a 20 mg/kg dose and continuing with a regular maintenance dose of 10 mg/kg until the baby reached the 34th week of gestation. Alternatively, other infants were given an IV dosage of aminophylline, commencing at 5 mg/kg, and then a maintenance dose of 2.5 mg/kg twice daily after delivery until the baby reached the 34th week of gestation.

SPSS version 26 was used to analyze the data. The t-test was used to compare variables between infants treated with caffeine and aminophylline. The chi-square test was used to compare population proportions for the two treatment modalities. A P-value of less than 0.05 indicated statistically significant differences.

RESULTS

There were a total of 40 preterm babies involved in this research. Out of these 40 preterm babies, 21 were boys and 19 were girls. The birth weight of these babies ranged from 500 to 1250 grams. Table 1 shows the characteristics of the preterm babies with O2 delivery, invasive mechanical ventilation, and non-invasive mechanical ventilation. The neonates treated with both medications had comparable rates of ventilator replacement and recurrence of apnea.

Table No. 1: characteristics of the preterm babies

Characteristics	**Group**	
	Caffeine	**Aminophylline**
Demographics of preterm babies with O2 delivery		
Gender		
● **Boy**	5	5
● **Girl**	7	3
Mean gestational age (weeks)	32.10	32.27
Mean birth weight (g)	1794.5	1880.6
Type of apnea		

● **Central**	3	13
● **Obstructive**	0	0
● **Mixed**	9	7
Demographics of preterm babies with invasive mechanical ventilation		
Gender		
● **Boy**	8	3
● **Girl**	5	4
Mean gestational age (weeks)	32.41	32.40
Mean birth weight (g)	1615.9	1645.7
Type of apnea		
● **Central**	2	2
● **Obstructive**	0	0
● **Mixed**	11	6
Demographics of preterm babies with non-invasive mechanical ventilation		
Gender		
● **Boy**	8	3
● **Girl**	6	3
Mean gestational age (weeks)	30.7	32.5
Mean birth weight (g)	1371.1	1723.2
Type of apnea		
● **Central**	3	2
● **Obstructive**	0	0
● **Mixed**	11	4

Table number 2 shows the complications in both groups of caffeine and aminophylline.

Table No. 2: complications in both groups of caffeine and aminophylline

Complications	**Caffeine (n=20)**	**Aminophylline (n=20)**
Intraventricular hemorrhage	6	3
Patent ductus arteriosus	2	5

Retinopathy of prematurity	1	1
Necrotizing enterocolitis	0	1
Recurrent event of apnea	6	7
Bronchopulmonary dysplasia	2	4

DISCUSSION

Approximately 70% of infants born before 34 weeks of gestation have clinically significant episodes of apnea, bradycardia, and desaturation while in the hospital [13]. Apnea is seen in 25% of infants born weighing less than 2,500 grams and in 84% of neonates weighing less than 1,000 grams during the postnatal period [14]. Carlo and Barrington found that apnea in neonates without respiratory distress syndrome (RDS) can begin as early as the first day after birth [15]. Furthermore, the incidence of apnea varies according to gestational stage.

According to Martin et al., 7% of neonates delivered at 34 to 35 weeks of gestation, 15% at 32 to 33 weeks, and 54% at 30 to 31 weeks had apnea of prematurity (AOP) [16]. Robertson et al. discovered that almost all newborns born at fewer than 29 weeks gestation or weighing less than 1,000 grams have AOP [17]. Our study found a significantly lower incidence of apnea than prior studies, with rates of 61.38% (≤ 29 weeks), 43.03% (30–31 weeks), 18.8% (32–33 weeks), and 2.99% (34–35 weeks) [18]. Additionally, premature infants with a gestational age of 35 weeks who required methylxanthines for apnea prevention, treatment, or extubation were included in the study.

The two methylxanthines have different dosing procedures. In the aminophylline group, the loading dose was given during extubation, followed by a maintenance dose until apnea was resolved. In the caffeine group, the loading dose was given in the first three days after birth, during extubation, as a treatment for apnea, or until apnea was resolved, resulting in a protracted dosage until caffeine administration at 34–36 weeks postconceptional age, as opposed to aminophylline. Neonates treated with caffeine had considerably fewer episodes of apnea on days 3 and 14 of therapy than those treated with aminophylline, but there was no statistically significant difference on days 7 and 14 [19]. This emphasizes the usefulness of methylxanthines in curing AOP and highlights caffeine's faster effects compared to aminophylline.

According to some experts, caffeine and aminophylline have similar short-term benefits in reducing bouts of apnea and bradycardia [20]. Weaning and extubation for preterm newborns on mechanical ventilation can be problematic due to their reduced respiratory drive and propensity to developing hypercarbia and apnea, especially in extremely premature cases. As a result, administering methylxanthines before extubation may help ventilated newborns cope with the cessation of respiratory assistance more easily. This is accomplished by increasing breathing efforts and reducing the incidence of post-extubation apnea.

CONCLUSION

Caffeine is very important for making the change from invasive to noninvasive respiratory support easier, cutting down on the time needed for positive airway pressure support, and lowering the risk of bronchopulmonary dysplasia (BPD). Caffeine and aminophylline are both beneficial for reducing apnea episodes and assisting with ventilator weaning in extremely preterm newborns. The neonates treated with both medications had comparable rates of ventilator replacement and recurrence of apnea.

Limitations of study:

This study was conducted in one center, more studies are needed with larger number of participants to support findings of this study.

Funding source
This research was conducted without receiving financial support from any external source.

Conflict in the interest
The authors had no conflict related to their interest in the execution of this study.

Permission
Prior to initiating this study, approval from the ethical committee was obtained to ensure adherence to ethical standards and guidelines.

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