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

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ABSTRACT

Caffeine plays a key role in noninvasive respiratory support, easing the transition from invasive to noninvasive support, shortening the length of positive airway pressure support, and lowering BPD risk. Caffeine and aminophylline are effective in decreasing apnoea and facilitating and ventilator weaning in extremely preterm newborns. This study aims to investigate the clinical significance of caffeine and aminophylline in treating premature infants with apnea under varying conditions of oxygen (O2) delivery. The current study included 38 preterm babies with apnea who underwent caffeine or aminophylline treatment at the Al-Mahaweel General Hospital between January and December 2020; the infants were 20 boys and 18 girls, with birth weights ranging from 500 to 1,250 grams. The study came out to the result that caffeine plays a key role in noninvasive respiratory support, easing the transition from invasive to noninvasive support, shortening the length of positive airway pressure support, and lowering BPD risk. Caffeine and aminophylline both are effective in decreasing apnoea and facilitating and ventilator weaning in extremely preterm newborns. Caffeine has therapeutic advantages over aminophylline, such as better enteral absorption, a longer half-life that allows for a single daily dose, reduced side effects, and a good long-term cost/benefit ratio, making it the first choice drug for the cure of apnoea in premature neonates.

Keyword: Caffeine, Noninvasive Respiratory Support, Aminophylline, Apnea

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INTRODUCTION

A 20-second pause in breathing is referred to as apnoea. A short pause in breathing preceded by bouts of tachypnoea is referred to as periodic breathing. These are the three forms of apnoea; central apnoea, obstructive apnoea, (1) and mixed apnoea. The nervous system is the source of central apnoea, which is described as a lack of breathing ability. This closure of the upper airway, which is commonly caused by superfluous or floppy tissue, causes obstructive apnoea. In preterm newborns, neck posture, particularly flexion, can induce airway blockage. Routine cardiorespiratory monitoring does not detect obstructive apnoea since breathing effort is still recorded as chest wall motion. However, the most prevalent kind of apnoea in preterm newborns is mixed apnoea, which combines elements of the other two types. Mixed apnoeic episodes commonly begin with central apnoea, leading to reduced upper airway tone,

resulting in a blockage that remains even after breathing is resumed; starting at 37 weeks gestation, apnoea of prematurity (AOP) is described as a stoppage of breathing lasting at least 20 seconds or 10 seconds, preceded by bradycardia and hypoxemia.

The American Academy of Pediatrics has just released a clinical study on AOP. AOP affects virtually all infants born before 28 weeks of pregnancy or weighing less than 1000 grams at birth. The frequency rises with a shorter gestational period and less birth weight. AOP is a developmental illness that usually improves with maturity, while apnoea often lingers through the term in infants born at the earliest gestational ages. AOP is not the same as apnoea in newborns (2, 3) A significant underlying illness such as infection, neurological abnormality, or metabolic disorder is more probable in newborns with apnoea, while these disorders can also appear as apnoea in premature newborns.

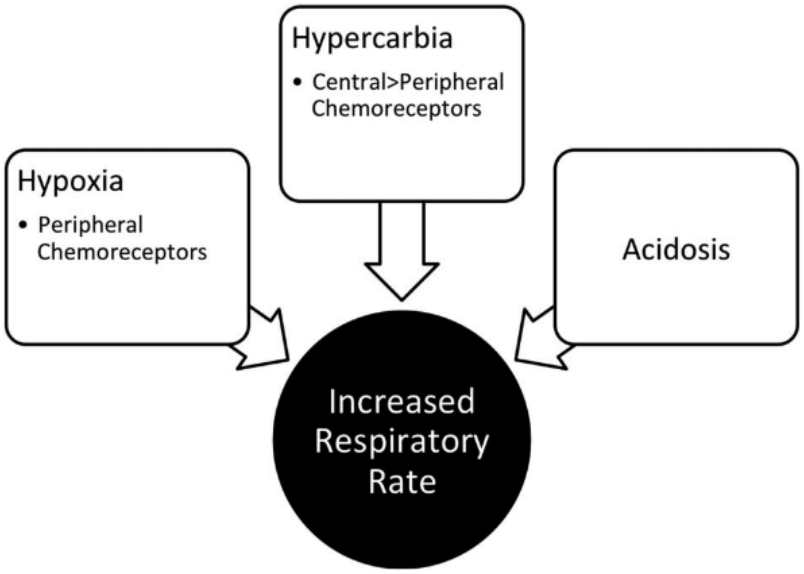

Figure 1: Respiratory drive modifier in term neonates

In newborns, all of these conditions raise respiratory rates: hypoxia, hypercarbia, and acidosis. This rise is triggered by a reduction in blood oxygen saturation via peripheral chemoreceptors. Although both central and peripheral chemoreceptors are active in signalling to increase respiratory rate, central chemoreceptors are more susceptible to hypercarbia than peripheral chemoreceptors (5–7). Central chemoreceptors are activated by acidosis.

Aminophylline and caffeine efficacy criteria in apnea treatment

The effectiveness of Aminophylline and caffeine in treating the babies with apnea was measured using the frequency of repeated apneic episodes, the use of invasive ventilation to replace O2 delivery devices, and the change in the time and concentration of breathed O2. The following criteria were used to assess efficacy: "I No change in the frequency of apnea episodes within 48 hours of administering the drugs; ii) apnea episodes of 2 times per day associated with a normal breathing rhythm; iii) no change in the frequency of apnea episodes within 48 hours of administering the drugs; iv) apnea recurrence (a time interval of 3 days between the first and second apnea episode) (2, 4),."

Complications in premature babies treated with caffeine and aminophylline

Clinical and laboratory exams, such as chest or abdomen radiography, echocardiography, development of aberrant blood vessels in the region of the retina, and brain ultrasonography, were used to diagnose the issues (16-20). "Patent ductus arteriosus (PDA), bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), retinopathy of prematurity (ROP), and intraventricular hemorrhage were the most common sequelae reported in the current research (IVH)." The rate of such issues was calculated as a percentage of the population proportion in aminophylline-treated and caffeine (8).

Criteria for drug therapy and withdrawal

The following were the indications for caffeine and aminophylline treatment: I apnea in preterm newborns or infants still at high risk of apnea; and ii) regardless of the kind of mechanical ventilation utilized, pharmacological therapy would begin within 24 hours of the ventilator being disconnected. In addition, the following were the criteria for drug withdrawal: I newborns who had been apnea-free for at least 7 days or had reached 34 weeks gestational age ii) For seven days, no mechanical ventilation was necessary; and iii) Serious side effects from the usage of the medications in combination with mechanical breathing, such as slowed nerve, brain, as well as other organ developments (8, 9,10).

MATERIALS AND METHODS

Inclusion criteria for premature neonates

The current study included 38 preterm babies with apnea who underwent caffeine or aminophylline treatment at the Al-Mahaweel General Hospital between January and December 2020. The physician had the option of using caffeine or aminophylline as a therapy. There were 20 boys and 18 girls among the hospitalized babies, with birth weights ranging from 500 to 1,250 grams. Tables I through III show the demographic features of the babies.

"The infants selected for the current retrospective study fulfilled the following criteria: i) All infants born after <34 weeks of gestation were diagnosed with apnea (the mixed type accounted for ~75% of all the types of apnea); ii) a stay of ≥24 h in hospital occurred; iii) the apnea of prematurity was solely treated with either caffeine or aminophylline under varying conditions of oxygen (O2) delivery; iv) there were no contraindications to either invasive or noninvasive ventilation; and v) there were no complex congenital malformations occurring in airways, chromosomal abnormalities or inherited metabolic diseases".

Medications and supplementary O2 delivery.

Aminophylline and caffeine were given to newborns of apnea by an intravenous (IV) injection at a starting dose of 20 mg/kg, followed by regular maintenance of 10 mg/kg till the mother's 34th week of pregnancy. The other newborns were given an IV dosage of aminophylline at a starting dose of 5 mg/kg, followed by a maintenance dose of 2.5 mg/kg twice daily after delivery till the mothers were 34th weeks of pregnancy.

Ventilator settings.

"The tidal volume (4-6 ml/kg) and respiratory rate (30-40 times/min) were used to calculate the minute ventilation. The sensitivity setting was used to adjust the level of negative pressure required to trigger the SLE5000 infant ventilator (SLE Ltd.). The

peak inspiratory (PIP) and end-expiratory pressure settings for all premature infants were adjusted to 16-28 and 5-6 cmH2O, respectively, according to previous reports (13,14). The pressure settings were adjusted according to the result of the arterial blood gas analysis performed by the i-STAT®1 analyzer (LumiraDx, Ltd.). The results are presented as the mean ± standard deviation or a percentage (%) of the population, as appropriate. The statistical analysis was performed using SPSS software version 17.0 (SPSS, Inc). The comparisons between the variables of the infants treated with caffeine and aminophylline were made using the unpaired Student's t-test. The $\chi 2$ test was used to analyze the differences between the population proportions observed in these two treatment approaches. $P<0.05$ was considered to indicate a statistically significant difference".

RESULTS

Table I. Characteristics of premature infants with O2 delivery devices.

Group	Sex, M/F	Gestational age,	weeks Birth weight, g	Type of apnea, C/O/M
Caffeine	5/7	32.10±0.76	1,794.58±210.51	3/0/9
Aminophylline	5/3	32.27±0.70	1,880.63±238.56	13/0/7
P-value	0.15	0.73	0.38	0.64

Data are presented as the mean ± standard deviation. M, male; F, female; C, central apnea; O, obstructive apnea; M, mixed apnea.

Table II. Characteristics of premature infants with noninvasive mechanical ventilation.

Group	Sex, M/F	Gestational age	weeks Birth weight, g	Type of apnea, C/O/M
Caffeine	8/5	32.41±1.26	1,615.80±221.17	2/0/11
Aminophylline	3/4	32.40±1.11	1,645.67±227.11	2/0/6
P-value	0.22	0.51	0.59	0.74

Table III. Characteristics of premature infants with invasive mechanical ventilation.

Group	Sex, M/F	Gestational age at admission	weeks Birth weight, g	Type of apnea, C/O/M
Caffeine	8/6	30.78±1.42	1,371.07±326.40	3/0/11
Aminophylline	3/3	32.44±1.20	1,723.33±317.70	2/0/4
P-value	0.84	0.76	0.98	0.80

Table IV. Comparison of efficacy and safety between caffeine and aminophylline.

Complication,	Caffeine n=17	Aminophylline, n=21	P-value
Intraventricular hemorrhage (%)	6 (14.3)	3 (16.3)	0.794
Recurrent event of apnea (%)	6 (14.3)	7 (32.6)	0.033
Patent ductus arteriosus (%)	2 (5.2)	5 (23.2)	0.006
Bronchopulmonary dysplasia (%)	2 (3.9)	4 (18.6)	0.016
Necrotizing enterocolitis (%)	0 (0)	1 (2.3)	0.358
Retinopathy of prematurity (%)	1 (2.6)	1 (2.3)	1.000

Table V. Main outcome measures of the study

	Number	percent	Number	percent	p-value	Difference	p-value
Caffeine	66.06	7.88	53.94	8.27	<0.001	12.12	
Number of breaths							0.51
Aminophylline	65.17	6.75	54.31	7.53	<0.001	-10.86	
Caffeine	146.06	9.33	142.06	24.88	0.382	-4	
Heart rate							0.003
Aminophyline	141.43	7.92	149. 68	14	0.001	8.25	
Caffeine	93.52	1.82	94.3	1.13	<0.00	0.78	
Oxygen saturation							0.153
Aminophyline	93.62	1.61	93.79	1.76	0.493	0.17	
Caffeine	33	100%	13	39.40%	<0.001	61%	
mchanical ventilation							0.444
Aminophyline	28	96.60%	14	48.30%	<0.001	-48%	
Caffeine	33	100%	20	69	<0.001	-31%	
Dependence on oxygen							0.423
Aminophyline	28	96.60%	20	60.60%	. 0.008	-36%	

DISCUSSION

Around 70% of newborns delivered before thirty-four weeks of pregnancy have clinically severe apnoea, bradycardia, and desaturation during their hospital stay. Apnoea can occur in 25% of newborns weighing at birth, less than 2,500 grams, and 84 percent of neonates weighing less than 1,000 g at birth throughout the postnatal period (10). Carlo and Barrington demonstrated that apnoea could start as early as the first day of delivery in newborns who do not have RDS (11,12). In addition, apnoea occurs at different rates depending on the stage of pregnancy. According to Martin et al., "7% of neonates born at 34 to 35 weeks gestation, 15% at 32 to 33 weeks, and 54% at 30 to 31 weeks gestation" (13), "while Robertson et al. established that nearly all infants born at <29 weeks gestation or <1,000 g exhibit AOP" (14). It is critical to remember that apnoea of prematurity is mostly diagnosed as apnoea can be caused by a variety of things, "including intrapartum magnesium exposure, systemic infections or the fetal inflammatory response syndrome, pneumonia, intracranial pathology, seizures, hypoglycemia, and other metabolic disturbances, the incidence of apnoea reported by our study, respectively 61.38% (≤ 29 wks.), 43.03% (30-31 wks.), 18.8% (32-33 wks.), and 2.99% (34-35 wks.)." (10), significantly lower than the figures reported in the previous research. In addition, premature babies with GA thirty-five weeks who needed methylxanthines for apnoea prevention, therapy, or extubation were included in the study.

The two methylxanthines have distinct administration procedures. The loading dosage of aminophylline was given during extubation, then by the maintenance dose until the apnoea was resolved in the aminophylline group. Within the caffeine group, the loading dose was given in the first 3 days after birth, at extubation, and as a cure for apnoea or until the apnoea resolves, leading to a long dose until 34-36 weeks postconceptional age administration of caffeine, compared to aminophylline. Caffeine-treated neonates had significantly less apnoea on days 3 and 14 of therapy than aminophylline-treated neonates without any statistically significant difference on days 7 and 14 of treatment; this demonstrates the efficacy of methylxanthines in the treatment of AOP, as well as the fact that caffeine has a faster impact than aminophylline.

According to some writers, caffeine and aminophylline appear to have similar short-term benefits in decreasing apnoea/bradycardia. (8). Because of their low respiratory drive and proclivity for developing hypercarbia and apnea, weaning and extubating preterm newborns on mechanical ventilation can be challenging, especially in extremely preterm infants. Therefore, pre-extubation methylxanthine therapy may be useful in facilitating the removal of respiratory support in ventilated infants by promoting breathing and minimizing post-extubation apnoea. (15).

In comparison to aminophylline, caffeine administration was related to a modest reduction in CPAP and mechanical breathing requirement, but the differences were not statistically significant. In the long run, our research found that the incidence of respiratory illness was much lower in the caffeine group than in the aminophylline group, which is consistent with earlier studies (15). Anemia, intraventricular hemorrhage, "chronic ductus arteriosus, and chronic lung disease," are statistically linked to a protracted treatment period for apnoea of prematurity.

The coffee group experienced more bouts of agitation, tachycardia, and feed intolerance, although aminophylline therapy was linked to a greater incidence of NEC, hypertension, and weight loss. Henderson-Smart and Steer conducted a meta-analysis of five trials that involved preterm babies who took methylxanthines for AOP and had a mean GA of 30 weeks. (8). The scientists concluded that theophylline was linked to a greater risk of toxicity. Our findings differed from previous studies, although this might be explained because the aminophylline group had a substantially smaller number of newborns than the caffeine group. Nevertheless, the shorter hospital stay of caffeine-treated infants than aminophylline-treated infants and the reduced need for invasive and non-invasive respiratory support suggest that caffeine has a better cost-benefit ratio, making it the drug available for the apnoea premature infants treatment.

CONCLUSION

Caffeine plays a key role in noninvasive respiratory support, easing the transition from invasive to noninvasive support, shortening the length of positive airway pressure support, and lowering BPD risk. Caffeine and aminophylline both are effective in decreasing apnoea and facilitating and ventilator weaning in extremely preterm newborns. Caffeine use was also linked to a "decreased risk of bronchopulmonary dysplasia." Caffeine has therapeutic advantages over aminophylline, such as better enteral absorption, a longer half-life that allows for a single daily dose, reduced side effects, and a good long-term cost/benefit ratio, making it the first choice drug for the cure of apnoea in premature neonates**.** Given the benefits of caffeine treatments the higher cost of aminophylline, it could be very beneficial to develop a set of national guidelines for the prevention and treatment of apnoea in premature infants and a larger multicenter study on a larger number of neonates, to determine the efficacy and safety of caffeine administration on long-term neurodevelopment and growth.

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