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Compare the efficacy and the safety of caffeine versus aminophylline for prophylaxis and treatment of apnea of prematurity in preterm neonates (≤34 weeks)

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Abstract
Background: Prematurity apnea is described as inability to breathe for 20 seconds or less, accompanied by bradycardia (heart rate <100/minute) or cyanosis, in neonates under 37 weeks gestational age. Since the 1970s, methylxanthines have been used to treat apnea by stimulating breathing. Few developing country trials compare caffeine with aminophylline for efficacy and safety.
The aim of the study: To compare the efficacy and the safety of the Caffeine versus the Aminophylline in prophylaxis and treatment of apnea of prematurity in Preterm Neonates (<34 weeks).
Methods: A prospective, open-label, randomized controlled trial was conducted from October 2017 to January 2018 in Al-Yarmouk Teaching Hospital's tertiary NICU. Patients were followed up at Child's Central Teaching Hospital if they were referred for weight gain until 35 weeks of gestational age, infants were randomly assigned to two therapy groups (aminophylline and caffeine) based on their birth date (odd or binary), given loading and maintenance doses, and documented for apnea, bradycardia, cyanosis, tachycardia, CPAP, mechanical ventilator, seizure, NEC, and ICH.
Results: There were no significant statistical differences in the mean of (sex, gestational age, twin or single, mother age, methods of delivery, apnea occurrence, NEC, ICH, length of treatment, and mortality) between the two therapy groups for the 55 preterm neonates. Compared to the Caffeine group, the Aminophylline group had a significant association with CPAP and mechanical ventilator use, but not duration.
Conclusion: Caffeine decreases the need for CPAP and mechanical ventilation, Caffeine is considered as having the efficacy and the safety outcome in comparison with the Aminophylline.

Keywords: Compare, efficacy, safety, caffeine, aminophylline, prophylaxis, treatment, apnea, prematurity, preterm, neonates

Introduction
Preterm birth (PTB), defined as the delivery of a baby before 37 completed weeks of gestation, is a significant health concern globally, categorized based on the gestational age into extremely preterm (before 28 weeks), very preterm (between 28 and 31 weeks), and moderate-to-late preterm (between 32 and 36 weeks) [1, 2]. PTB is distinguished from low birth weight (LBW), which is defined as infants born weighing less than 2,500 grams and further categorized into very low birth weight (less than 1,500 grams) and extremely low birth weight (less than 1,000 grams) [1]. Although prematurity and LBW are related, they are not identical; about two-thirds of LBW infants are preterm, and others may be term but small for gestational age due to factors like fetal growth restriction or genetic syndromes [1]. Preterm birth is the leading cause of neonatal morbidity and mortality, accounting for over 10% of births worldwide in 2010, with an estimated 15 million babies born preterm annually, and this number is increasing [2, 3]. Infants born preterm face higher risks of long-term health issues, including neurodevelopmental disorders, chronic lung disease, infection risks, visual and gastrointestinal impairments, and challenges in weight gain and development [3, 4]. Assessment of gestational age is vital for newborn care, utilizing physical and neuromuscular maturity signs to accurately estimate fetal age [5]. This assessment, along with the Apgar score, which measures newborns' vital signs and response to resuscitation, forms the basis of initial neonatal care [6]. Apnea of prematurity (AOP) is a condition characterized by the cessation of breathing in infants born before 37 weeks of gestation, often accompanied by bradycardia or cyanosis [7, 8].

AOP and its causes, including central hypoventilation and obstructive apnea, are significant concerns in neonatal care, necessitating interventions like the use of methylxanthines (e.g., caffeine and theophylline) to stimulate breathing [9]. Methylxanthines have been used in clinical practice since the 1970s to manage AOP, proving effective in reducing apneic episodes and the need for mechanical ventilation [10, 11]. Despite their benefits, these drugs require careful monitoring due to potential adverse effects, especially in extremely low birth weight infants who are more susceptible to complications [10]. Caffeine is preferred for its lower toxicity and wider therapeutic window, shown to reduce the rate of bronchopulmonary dysplasia, promote survival without neurodevelopmental disability, and facilitate extubation in preterm infants [12, 13]. The administration of caffeine, including dosing and monitoring, is tailored to each neonate's condition to optimize outcomes while minimizing risks [9, 14]. Management of apnea in preterm infants also involves strategies beyond pharmacotherapy, such as the application of continuous positive airway pressure (CPAP) to support breathing without invasive ventilation. CPAP, particularly in forms like bubble CPAP (b-CPAP), has been recognized for its effectiveness and cost efficiency in treating respiratory distress and apnea in preterm infants [15, 16]. The aim of study is to compare the efficacy and the safety of the Caffeine versus the Aminophylline in prophylaxis and treatment of apnea of prematurity in Preterm Neonates (<34 weeks).

Methods

A prospective, open-label, randomized controlled trial was conducted from October 2017 to January 2018 at Al-Yarmouk Teaching Hospital's Neonatal Intensive Care Unit (NICU), extending follow-up to the Child's Central Teaching Hospital for patients referred for weight gain until reaching 35 weeks of Gestational Age. The study received ethical approval from the neonatal department committees of both hospitals, and verbal consent was obtained from the parents. The investigation aimed to compare the effects of aminophylline and caffeine, both approved treatments for apnea of prematurity by the Ministry of Health of Iraq, on preterm newborns with less than 34 completed weeks of gestational age who could breathe spontaneously with or without resuscitation at birth. Exclusion criteria included major congenital anomalies, infants with pulmonary hemorrhage, and those unable to breathe spontaneously after birth and resuscitation. Randomization was based on the birth date, assigning newborns born on odd dates to the aminophylline group and those on even dates to the caffeine group. All infants underwent screening for hypoglycemia, hypocalcemia, and other conditions as deemed necessary, with treatment protocols for aminophylline (loading dose of 5 mg/kg, followed by maintenance doses of 2 mg/kg every 8 hours) and caffeine (loading dose of 20 mg/kg, followed by maintenance doses of 5 mg/kg/day). Baseline parameters including gestational age, birth weight, 5-minute APGAR score, gender, and maternal age were recorded. The study lacked surfactant availability at Al-Yarmouk Teaching Hospital. Medication discontinuation criteria were tachycardia (>200 beats/minute) and seizure development. Outcomes monitored included apnea occurrence, CPAP need and duration, mechanical ventilation necessity and duration, and adverse events such as tachycardia and seizures. Data were analyzed using SPSS v24, with continuous variables presented as means and discrete variables as numbers and percentages. The Chi-square test assessed associations between discrete variables, and T-tests or Mann-Whitney tests evaluated differences in means between groups. Odds ratios (OR) estimated the risk of unwanted outcomes, considering a p-value of ≤0.05 as significant.

Results

A total number of participants in this study was 55 preterm neonates admitted at the NICU of Al-Yarmouk Teaching Hospital, from them there were 10 preterm neonates referred and admitted to the Child`s Central Teaching Hospital. Mean gestational age of the 55 participants was 31.3 weeks with a standard deviation of + 2.1 weeks. The minimum gestational age was 26 weeks, and the maximum gestational age was 34 weeks. Mean Apgar score of the 55 participants was 8.1 with a standard deviation of + 1.6. The mean of the duration of treatment at the NICU of Al-Yarmouk teaching hospital was 6.4 days with a standard deviation of + 3.5 days. The minimum duration of treatment at the NICU of Al-Yarmouk teaching hospital was 1 day and the maximum duration of 18 days. Mean weight of the 10 participants at the time of admission at Child`s Central Teaching Hospital was (1.1kg+0.2), with a minimum weight of 0.8kg and a maximal weight of 1.5kg. Mean duration of admission of the 10 participants at Child`s Central Teaching Hospital was 23 days, with a standard deviation of 16.3 days. The minimal duration of admission was 5 days, and the maximal duration was 56 days.

Table 1: Characteristics of sampled patients that admitted to the NICU of Al- Yarmouk Teaching Hospital

Variables	Treatment Group						P value
	Total Sample		Aminophylline		Caffeine		
	N	100.0%	N	100.0%	N	100.0%	
Gestational Age (wk); M ± SD	31.3±2.1		31.5±2.0		31.2±2.2		0.669
Sex							0.221
Male	20	36.4%	8	28.6%	12	44.4%	
Female	35	63.6%	20	71.4%	15	55.6%	
M: F ratio		0.6		0.4		0.8	
Mother Age (y); M ± SD	25.2±7.4		24.7±7.5		25.7±7.4		0.599
Single vs. Twin							0.686
Single	44	80.0%	23	82.1%	21	77.8%	
Twin	11	20.0%	5	17.9%	6	22.2%	
Mode of Delivery							0.680
Normal Vaginal	29	52.7%	14	50.0%	15	55.6%	
Caesarian Section	26	47.3%	14	50.0%	12	44.4%	

Weight at Birth (Kg)	1.4±0.4		1.5±0.4		1.3±0.3		0.019
APGAR score 5 min; M ± SD	8.1±1.6		7.4±1.8		8.9±0.9		<0.001
Apnea	10	18.2%	7	25.0%	3	11.1%	0.182
Bradycardia	8	14.5%	4	14.3%	4	14.8%	0. 956
Cyanosis	10	18.2%	6	21.4%	4	14.8%	0.525
Tachycardia	0	0.0%	0	0.0%	0	0.0%	---
Sepsis	2	3.6%	0	0.0%	2	7.4%	0.142
CPAP	18	32.7%	14	50.0%	4	14.8%	0.005
Days on CPAP; M ± SD	1.6±1.2		1.7±1.2		1.3±1.2		0.504
Ventilator	11	20.0%	9	32.1%	2	7.4%	0.022
Days on Ventilator; M ± SD	1.4±1.2		1.5±1.2		0.8±0.4		0.397
Necrotizing Enterocolitis	3	5.5%	1	3.6%	2	7.4%	0.531
Intracranial Hemorrhage	0	0.0%	0	0.0%	0	0.0%	---
Days on treatment; M ± SD	6.4±3.5		6.1±3.6		6.8±3.4		0.440
Fate							0.271
Death	16	29.1%	10	35.7%	6	22.2%	
Discharged well/Referred	39	70.9%	18	64.3%	21	77.7%	

Table 2: Characteristics of participants admitted to Child`s Central Teaching Hospital

Total Sample			**Aminophylline**		**Caffeine**		**P value**
Variables	**N=10**	**100.0%**	**N=2**	**100.0%**	**N=8**	**100.0%**	
Gestational Age (wk); M ± SD	31.3±2.1		31.5±2.0		31.2±2.2		0.669
Sex							0.067
Male	7	70.0%	0	0.0%	7	87.5%	
Female	3	30.0%	2	100.0%	1	12.5%	
M: F ratio	2.3			0:2		7	
Weight on admission (Kg); M ± SD	1.1±0.2		1.1±0.3		1.1±0.2		0.790
Single vs. Twin							---
Single	10	100.0%	2	100.0%	8	100.0%	
Twin	0	0.0%	0	0.0%	0	0.0%	
Mode of Delivery							---
Normal Vaginal	7	70.0%	2	100.0%	5	62.5%	
Caesarian Section	3	30.0%	0	0.0%	3	37.5%	
Apnea	1	10.0%	0	0.0%	1	12.5%	0.378
Bradycardia	0	0.0%	0	0.0%	0	0.0%	---
Cyanosis	1	10.0%	0	0.0%	1	12.5%	0.378
Tachycardia	0	0.0%	0	0.0%	0	0.0%	---
Sepsis	0	0.0%	0	0.0%	0	0.0%	---
CPAP	0	0.0%	0	0.0%	0	0.0%	---
Necrotizing Enterocolitis	0	0.0%	0	0.0%	0	0.0%	---
Intracranial Hemorrhage	0	0.0%	0	0.0%	0	0.0%	---
Days of hospitalization; M ± SD	23.0±16.3		14.0±7.1		25.3±17.4		0.414
Completion of treatment	10	100.0%	2	100.0%	8	100.0%	---

Table 3: Risk estimation for developing certain studied outcomes in patients treated with Aminophylline compared to patients treated with caffeine

Outcomes of First Admission	**P value**	**ORb(95% CI)**
Apnea	0.192	2.667(0.611-11.643)
Bradycardia	0.956	0.958(0.214-4.292)
Cyanosis	0.527	10.568(0.389-6.319)
Poor feeding	0.274	10.944(0.590-6.404)
Sepsis	0.998	0.000(0.000)
CPAP	0.008	5.750(1.575-20.986)
Ventilator	0.034	5.921(1.144-30.653)
NEC	0.540	0.463(0.040-5.426)
Death	0.566	10.444(0.412-5.069)
Referral	0.147	0.325(0.071-1.487)

[a]for Wald statistic

[b]for all outcomes, null values are the negative outcomes; exposure level is Aminophylline and reference level is caffeine

Table 4: Distribution of sampled patients according to maternal age and to each of gestational age and to the mode of delivery

Mother Age < 18 y or > 34 y					
	Yes		No		
Variables	**N=16**	**100.0%**	**N=39**	**100.0%**	**P value**
Gestational Age					0.448*
Extreme preterm	1	6.3%	1	2.6%	
Very preterm	5	31.3%	18	46.2%	
Moderate to late preterm	10	62.5%	20	51.3%	
Mode of Delivery					0.147
Normal Vaginal	6	37.5%	23	59.0%	
Caesarian Section	10	62.5%	16	41.0%	

*after condensing gestational age into two groups; extreme to very preterm & moderate to late preterm

Table 5: Birth weight of studied patients according to having apnea or not, and to treatment group

Sample	Apnea						P value
	No			Yes			
	Weight at Birth (Kg)			Weight at Birth (Kg)			
	N	Mean	SD	N	Mean	SD	
Total Sample	45	1.43	0.40	10	1.39	0.37	0.760
Aminophylline Group	21	1.57	0.44	7	1.47	0.42	0.612
Caffeine Group	24	1.31	0.32	3	1.20	0.10	0.557

Discussion

This study, conducted in the NICU of Al-Yarmouk Teaching Hospital and followed up at the Child's Central Teaching Hospital, aimed to compare the efficacy and safety of aminophylline and caffeine in treating apnea of prematurity among neonates born before 34 weeks of gestation. Recognizing that approximately 70% of such infants exhibit clinically significant apnea, bradycardia, or desaturation during hospitalization, the research underlined the importance of diagnosing apnea of prematurity as a condition of exclusion, due to its potential association with various other conditions [17]. Throughout the admission period in the NICU of Al-Yarmouk Teaching Hospital, the study revealed no significant differences in most baseline characteristics between the aminophylline and caffeine groups, including mean gestational age, gender, mother's age, singleton or twin status, cyanosis, mode of delivery, and occurrence of intracranial hemorrhage (ICH), with all P values exceeding 0.05 [Table 2]. However, infants in the aminophylline group had a significantly higher mean birth weight than those in the caffeine group (1.5 kg vs. 1.3 kg, $p< 0.05$) [Table 2]. Despite 10 out of 55 neonates developing apnea, with a higher incidence in the aminophylline group, the difference was not statistically significant, aligning with previous studies by Henderson-Smart and Steer (2013), Hendy (2014), and Zonda (2016) [8, 17, 18]. The occurrences of bradycardia and tachycardia showed no significant statistical differences between the treatment groups, contrasting with findings from Henderson-Smart and Steer (2013) and Zonda (2016), which noted discrepancies in tachycardia rates between theophylline and caffeine treatments [8, 18]. The lack of significant difference in sepsis occurrences between groups, despite two cases in the caffeine group, also mirrored the broader findings of non-significant differences in adverse events between treatments Table 2. Significantly, infants on aminophylline were more likely to require CPAP and mechanical ventilation compared to those on caffeine, with P values less than 0.05, suggesting a higher propensity for aminophylline-treated infants to need respiratory support [Table 2]. This finding is partially supported by Zonda (2016), which indicated a reduced need for CPAP in some cases [8]. No significant differences were observed in the duration of CPAP use, mechanical ventilation, treatment of NEC, or treatment duration between the two groups, nor in outcomes related to mortality or discharge [Table 2], consistent with findings from Shivakumar *et al*. (2017) and Hendy (2014) [19, 20]. Upon transfer to the Child's Central Teaching Hospital, the continuation of treatment revealed no significant differences in gestational age, gender, weight at admission, apnea occurrence, cyanosis, or treatment success between the aminophylline and caffeine groups [Table 3]. All patients from this stage were singletons, with only one participant from the caffeine group experiencing an apneic and a cyanosis attack, both without statistical significance [Table 3]. Risk estimation for developing specific outcomes during NICU admission highlighted that infants treated with aminophylline were significantly more likely to require CPAP and mechanical ventilation compared to those receiving caffeine, with P values less than 0.05 [Table 4]. No significant associations were found between treatment groups and other outcomes such as apnea, bradycardia, cyanosis, sepsis, NEC, death, and referral, nor between maternal risk age and gestational age or mode of delivery [Table 4, Table 5]. Mean birth weight differences between apneic and non-apneic babies within each treatment group were also not significant [Table 5], underscoring the complexity of treating apnea of prematurity and the nuanced effects of aminophylline and caffeine in this vulnerable population.

Conclusion

Caffeine significantly reduces CPAP and mechanical ventilator use. There was no significant correlation between apnea incidence, fatality, and suggested adverse effects while taking caffeine, therefore it is deemed more effective and safe than Aminophylline.

Conflict of Interest
Not available.

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Not available.

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