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ORIGINAL ARTICLE

An Experience in Tertiary Care Unit: Comparison between Efficacy of Caffeine Versus Aminophylline in Apnea of Prematurity

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ABSTRACT

Objective: To compare the efficacy of caffeine versus aminophylline in the treatment of Apnea of Prematurity amongst neonates in tertiary care unit.

Methods: The comparative cross-sectional research was conducted at Pediatric neonatology unit of The Children's Hospital & UCHS Lahore from October, 2020 to October, 2021. A total of 60 premature newborn babies fulfilling the selection criteria were enrolled after taking written informed consent from parents and were randomly divided into two groups of equal number i.e. 30 each. Non-Probability Consecutive Sampling. One group received intravenous aminophylline and the other group received intravenous caffeine when first episode of apnea was observed on clinical parameters. Patients were followed for up to 10 days during admission and efficacy was assessed.

Results: The mean gestational age of the premature newborn babies in aminophylline versus caffeine group was 29±1.51 versus 30±1.84 weeks. Efficacy of caffeine versus aminophylline was 87% versus 63% (p=0.037), need of oxygen was in 27% versus 57% (p=0.018), need of ventilation was 3% versus 17% (p=0.085), rate of complications was 16% versus 30% (p=0.819) and rate of mortality was 3% versus 20% (p=0.044) respectively.

Conclusion: In AOP, caffeine was superior in efficacy than aminophylline in terms of reduction in recurrence of apneic spells, oxygen requirement and mortality rates and were similar in efficacy in terms of need of ventilation and side effects.

Keywords: Apnea of prematurity, Efficacy, Caffeine, aminophylline

INTRODUCTION

Premature newborn babies have difficulty controlling their body temperature, acquiring new skills related to oral feeding, and breathing normally in their first few days of life. For many premature infants, overcoming apnea and establishing a regular breathing pattern is a significant developmental milestone[1]. Apnea of prematurity (AOP) is typically defined as the occurrence of breathing pauses lasting more than 15-20 seconds in infants born before 37 weeks of gestation. These pauses may be followed by a decrease in oxygen levels (SpO2 below 80% for 4 seconds) and a decrease in heart rate (bradycardia, where the heart rate drops below 2/3 of the baseline for 4 seconds)[2]. The pathogenesis of AOP remains incompletely known, however its onset or severity is likely impacted by underdeveloped pulmonary reflexes and respiratory reactions to low oxygen levels and high carbon dioxide levels. Moreover, several simultaneous illnesses or states of illness can exacerbate it[3]. The presence of several comorbidities and complicating conditions in premature neonates poses a significant challenge in establishing a causal relationship between apnea and adverse neurodevelopmental outcomes. Therefore, evaluating the impact of AOP on long-term neurodevelopment is challenging[4].

The only available treatments for AOP are posing in the prone position, therapy with methylxanthines, and the use of (NIPPV) or continuous positive airway pressure (CPAP). Transfusions of red blood cells and intake of carbon dioxide, and other reported therapies including sensory stimulation need more research because they are not commonly used[5]. There is a need to review the pathophysiology, processes underpinning treatment, and consequences of AOP in premature babies due to limited understanding of the causes and long-term impact on brain development, the optimal treatment for AOP remains uncertain[6]. Birth weight and gestational age are negatively linked with the prevalence of AOP. Almost all infants born before 29 weeks of gestation or weighing less than 1,000 g experience AOP. Additionally, 7% of newborns born at 34 to 35 weeks gestation, 15% at 32 to 33 weeks, and 54% at 30 to 31 weeks also get AOP[7]. The condition can be categorised into three distinct subtypes: mixed, obstructive, or central. Obstructive apnea accounts for between 10% to 25% of all occurrences of apnea, while central apnea accounts for the other cases. Between 10% and 25% of all apnea instances are central, 10% to 25% are obstructive, and 50% to 75% are mixed[8].

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One of these categories typically predominates in each individual newborn. While bradycardia appears to occur more commonly with prolonged periods of apnea, the incidence of bradycardia is comparatively low across these various categories. 10% of apneic occurrences lasting 10–14 seconds, 34% of those lasting 15–20 seconds, and 75% of those lasting more than 20 seconds have bradycardia[9]. A recent study showed that oxygen desaturation began before bradycardia (median interval 4.2 seconds), indicating that bradycardia typically develops after oxygen desaturation that is linked to apnea[10]. However, the revival from bradycardia frequently comes before the recovery from apnea in terms of oxygen saturation. Bradycardia may sometimes occur after an apnea without desaturation; this is not always caused by hypoxia but could be due to vagal nerve stimulation. AOP is a developmental condition that resolves on its own[11, 12].

Based on clinical observations, a comparative study between caffeine and aminophylline was initiated to determine the most effective treatment for apnea of prematurity. By identifying the superior treatment option, there is potential to significantly reduce rates of disability and mortality in premature infants, ultimately improving overall outcomes in this vulnerable population.

MATERIAL AND METHODS

Prior to conduct study ethical permission was taken under reference number (2020-140-CHICH on 21 November 2020). A total of 60 premature newborn babies fulfilling the selection criteria from the department of Neonatology, University of Child Health Sciences and The children's hospital, Lahore during October, 2020 to October, 2021 were enrolled. Inclusion criteria was premature newborn babies who were born <37 weeks post-last menstrual period and had their first apnea episode. While patients having major congenital malformations, who had metabolic derangements, sepsis, hypothermia, IVH and who required mechanical ventilation were excluded. The sample size of the study was 30 premature newborn babies for each group. Sample size was estimated using 80% power of study, 5% level of significance and assuming efficacy as 67% with aminophylline (group A) and 31.3% with Caffeine (group B)[13,14]. 30 premature newborn babies were allocated in aminophylline group and 30 were allocated in the caffeine group. In the aminophylline group, 5mg/kg body weight was loaded and 1.5mg/kg body weight was maintained every 12 hours. The caffeine group got 20mg/kg body weight of anhydrous caffeine at the start and 5 mg/kg 24 hours a day thereafter. Clinical indicators showed the initial apnea episode, prompting medication administration. The medicine was

administered through an intravenous route. Patients were observed for apnea up to 10 days during admission. Efficacy was defined as the reappearance of apnea after a time period of at least 3 days between the initial and subsequent apnea episodes.

The data was analysed using the statistical software IBM SPSS version 22. A Chi-square test was used to compare the efficacy between groups. An analysis was conducted to evaluate the influence of characteristics such as gestational age (28-37 weeks), gender, Apgar score, and birth weight on efficacy. Stratification was performed based on these variables, and a significance level of ≤0.05 was used.

RESULTS

A cohort of 60 neonates delivered prematurely were examined. The average gestational age of patients in the aminophylline group was 29±1.51 weeks, but in the caffeine group it was 30±1.84 weeks (p=0.316). At the 5-minute mark, the average APGAR score for babies in the aminophylline group was 5±0.83, whereas in the caffeine group it was 4±0.85 (p=0.471). The infants in the aminophylline group had an average birth weight of 1.8±0.33 kilogrammes, while those in the caffeine group had an average birth weight of 1.9±0.21 kilogrammes (p=0.568). The baseline oxygen saturation (SpO2) was 74±12.1% in the group receiving aminophylline and 76±11.1% in the group receiving caffeine (p=0.486). The aminophylline group consisted of 60% males and 40% females, whereas the caffeine group contained 46.6% males and 53.4% females.

Table 1: Association between gestational age and efficacy in caffeine and aminophylline

Gestational Age	Efficacy of Caffeine		Efficacy of Aminophylline	
	Yes	No	Yes	No
28-32 Weeks	15 (50%)	4 (13%)	18 (60%)	10 (34%)
33-<37 Weeks	11 (37%)	0 (0%)	1 (3%)	1 (3%)
Total	26 (87%)	4 (13%)	19 (63%)	11 (37%)
P Value	0.102		0.685	

Table 2: Association between weight and efficacy of caffeine and aminophylline

Weight	Efficacy of Caffeine		Efficacy of Aminophylline	
	Yes	No	Yes	No
<1 Kg	0 (0%)	0 (0%)	0 (0%)	1 (3%)
1-1.5 Kgs	0 (0%)	0 (0%)	8 (26.7%)	2 (6.7%)
1.6-2 Kgs	18 (60%)	3 (10%)	6 (20%)	6 (20%)
>2 Kgs	8 (27%)	1 (3%)	5 (16.3%)	2 (6.3%)
Total	26 (87%)	4 (13%)	19 (63%)	11 (37%)
P Value	0.815		0.257	

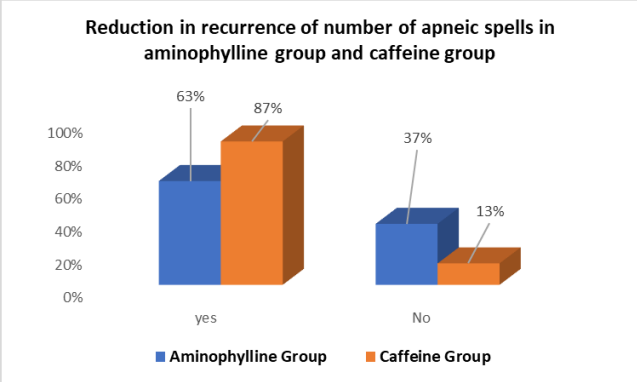

Figure 1: Reduction in recurrence of number of apneic spells in aminophylline group and caffeine group

Table 1 and figure 1 presents a comparison of the effectiveness of caffeine and aminophylline in various gestational age groups. Among cases falling within the 28-32 weeks category, caffeine demonstrated efficacy in 50% of instances, whereas aminophylline exhibited effectiveness in 60% of instances. Among cases falling between the 33-37 weeks range, caffeine demonstrated efficacy in 37% of instances, whereas aminophylline shown efficacy in a mere 3%. Generally, the effectiveness rates of both drugs differed depending on the different stages of fetal development, indicating potential variations in their efficacy across gestational age ranges.

Table 2 presents a comparison of the effectiveness of caffeine and aminophylline in various weight categories for newborns. Caffeine demonstrated efficacy in 60% of instances within the weight range of 1.6-2 kg, whereas aminophylline shown effectiveness in just 20% of patients within the same weight category. Across different weight categories, the effectiveness rates differed, highlighting the necessity for customized treatment strategies that are dependent on the weight of the newborn.

DISCUSSION

There are certain underlying principles for handling apnea of prematurity which incorporate close monitoring of infants while initiating supportive measures of care like tactile stimulation, constant positive pressure of airway or the mechanical ventilation. For stimulation of breathing, pharmacologic therapy can be used when needed. Methylxanthines are considered as the first-line agents preference for handling Apnea of prematurity[15]. In this study, efficacy of aminophylline versus caffeine was achieved in 63% premature newborn babies versus 87% respectively. Similar results were observed in a study done by Zulqarnain et al which revealed that in AOP caffeine was more effective compared to aminophylline in reducing the frequency of apneic spells. While in a study by Kondo et al. it was found that aminophylline was effective in 67% of infants in terms of preventing AOP[13,16]. Skouroliakou et al. assessed the efficacy of caffeine versus aminophylline in infants with AOP and revealed that in both groups there was a significant decrease in the apneic spells (p=0.001)[17]. In 2015, Jeong et al. did a study and found that caffeine was more effective than aminophylline in the short-term therapy of apnea in premature infants. In addition, he stated that caffeine was both efficacious and straightforward to administer[18]. Lookzadeh et al. also revealed superior efficacy of caffeine compared to aminophylline. With regards to need of supplemental oxygen, Lookzadeh et al. revealed that infants with AOP who received caffeine were less likely to need supplemental oxygen compared to those who received aminophylline i.e. 5% versus 25% and this difference was statistically significant (p=0.012)[19]. Lookzadeh et al. revealed that the use of aminophylline resulted in a reduced need of ventilation compared to caffeine i.e. 95% versus 75% and the difference was statistically significant i.e. p=0.012. These findings of Lookzadeh et al. are inconsistent with our study findings which revealed no significant difference between caffeine and aminophylline in terms of need of ventilation[19]. The difference may be because Lookzadeh et al. also included infants who were already on respiratory support and hence had more severe apnea as compared to infants enrolled in our study. Our study similarly revealed higher efficacy of caffeine in AOP, however, in our study the difference was of statistical significance, whereas Nagasato et al. did not find a significant difference. Shivakumar et al. conducted a comparison between caffeine and aminophylline and found that both substances were equally beneficial in reducing the frequency of apneic spells. Twenty A study conducted by Habibi et al. found that the advantages of caffeine usage were comparable to those of aminophylline[21]. Similar findings were reported by Najafian et al.[22]. In a study Khurana et al. revealed that in infants who had AOP and were treated with either caffeine or aminophylline, the rate of mortality in the caffeine group was 9% lesser compared to the aminophylline group, however, the difference was statistically insignificant (p=0.81)[23].

Future trials must be carried out on a larger sample size for confirmation of current study results and validation of efficacy of caffeine over aminophylline. The findings of the current study can help in facilitating clinicians to treat preterm babies and therefore

reduce the rate of disability and mortality associated with AOP by early and effective clinical intervention.

CONCLUSION

This study concludes that caffeine has significantly superior efficacy compared to aminophylline in terms of reduction in recurrence of apnea after a time interval of ≥3 days between the first and second apnea episode, need of oxygen and reduced rates of mortality. Caffeine was found to be linked with a better safety profile than aminophylline though this difference was not of statistical significance.

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