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Comparison of the Efficacy of Caffeine with Aminophylline for Management of Infants having Apnea of Prematurity

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ABSTRACT

Objective: To compare the efficacy of caffeine with aminophylline for management of infants having apnea of prematurity. **Study design:** Randomized Controlled Trials. **Settings:** Department of Pediatrics, Allied Hospital, Faisalabad. **Study duration:** April 2024 to September 2024. **Materials & Methods:** A total of 140 patients (70 in each group), both male and female infants with birth weights greater than 500 g and gestational ages between 23 and 35 weeks who had multiple episodes of preterm apnea over the course of a 24-hour period were included. Neuromuscular abnormalities, prenatal asphyxia, cerebral hemorrhage, metabolic disorders, anemia, disseminated infections, congenital illnesses, and neonates whose mothers took painkillers were not included. Using a computer-generated random number table, the patients were split into two equal groups at random. A group of seventy patients had 30 mg/kg of caffeine mixed with 5% dextrose. They also got an intravenous maintenance dose of 10 mg/kg every 24 hours. Within three days of beginning treatment, bradycardia, hypoxia, and breathing were recorded, and the treatment's effectiveness was evaluated. **Results:** The average age of patients in group A was 10.69 ± 5.01 hours, whereas the average age of patients in group B was 11.84 ± 4.91 hours. There were 73 (52.14%) females and 67 (47.86%) males. The mean gestational age in groups A and B was 32.92 ± 1.55 weeks and 31.84 ± 1.42 weeks, respectively. The average blood sugar level was 82.34 ± 9.42 mg/dl. Weight at birth was 1234.54 ± 234.72 grams on average. At one minute and five minutes, the mean Apgar score was 7.72 ± 1.43 and 8.13 ± 0.89, respectively. 45 patients (64.29%) in group B (aminophylline) and 62 patients (85.71%) in group A (caffeine) showed efficacy. The statistically significant p-value is 0.003. **Conclusion:** According to the study's findings, caffeine is a safer and more effective treatment for preterm apnea than aminophylline.

INTRODUCTION

The organs of premature newborns are undeveloped both physically and functionally. Apnea is exacerbated by an immature respiratory control system, which is less sensitive to variations in carbon dioxide levels. This is among the most common situations that premature infants in the neonatal intensive care unit (NICU) encounter.[1] Apnea of prematurity (AOP) is common in premature babies. It is when the baby stops breathing for a short time and then has bradycardia and desaturations.[2] An imbalance between sympathetic and parasympathetic outputs and infants' immature respiratory drive may be the cause of this instability in the cardiovascular and respiratory systems.[3]

The frequency of AOP goes down as gestational age goes up. For example, 85% of babies were born before 34 weeks of pregnancy, and almost all babies were born before 30 weeks of pregnancy or weighed less than 1000g at birth.[2] Preterm newborns may develop retinopathy and bronchopulmonary dysplasia as a result of uncontrolled or persistent AOP, which may even raise infant mortality. Thus, early and efficient clinical management is essential when taking into account the possible short-term and long-term implications of apnea.[4]

There is no single "first-line" strategy or gold standard of care for treating apnea in preterm newborns, despite the fact that there are numerous choices available. The current standard of care for apnea is methylxanthine therapy, which includes aminophylline/theophylline and caffeine.[5] Adenosine A1 and A2A receptors are nonspecifically antagonistic to caffeine. Since caffeine stimulates the respiratory system, it has traditionally been used to treat obstructive apnea. They can be helpful prior to removing the respiratory tract since they also lessen the requirement for mechanical ventilation. Caffeine has a lengthy half-life, a high drug treatment index, good intestinal absorption, and a low requirement for drug monitoring.[6]

Aminophylline functions as an antagonist of the adenosine receptor. Aminophylline can increase diaphragmatic contractility by stimulating the respiratory impulse's core drive. There have also been reports of tachycardia, food intolerance, hypertension, hyperglycemia, and hyponatremia as side effects of aminophylline.[1] For the treatment of preterm apnea, caffeine and aminophylline were 85.7% and 67.4% effective, respectively, while the rates of apnea recurrence were 14.3% and 32.6% for caffeine and aminophylline, respectively.[7]

Apnea is common in prematurely born infants. It is typically treated with theophylline and aminophylline. In this study, the effects of caffeine and aminophylline on preterm apnea are compared. In Pakistan, caffeine and aminophylline are not interchangeable when it comes to treating preterm apnea. The results of this study will be helpful in determining the most effective course of treatment for apnea of prematurity: Aminophylline or caffeine.

MATERIALS AND METHODS

After receiving approval from the ethical review committee, this randomized controlled experiment was carried out from April to September 2024 at the Department of Pediatrics, Allied Hospital, Faisalabad. P1 = 85.7%[7], P2 = 67.4%[7], research power = 80%, level of significance = 5%, and sample size = 140 (70 in each group) were calculated using the WHO sample size calculator. Both male and female infants with birth weights greater than 500 g and gestational ages between 23 and 35 weeks who had multiple episodes of preterm apnea (breathing cessation lasting longer than 20 seconds or brief but associated with hypoxia (oxygen saturation <85%) or bradycardia (heart rate <100 bpm) over the course of a 24-hour period were included. Neuromuscular abnormalities, prenatal asphyxia, anemia, cerebral hemorrhage, disseminated infections, congenital illnesses, and neonates whose mothers took painkillers were not included.

Parents' informed consent was obtained before enrolling patients who met the inclusion criteria. The patients were randomly assigned to two equal groups using a computer-generated random number table. Seventy patients in group A received 30 mg/kg of caffeine dissolved in 5% dextrose, with an intravenous maintenance dose of 10 mg/kg given every 24 hours. Within three days of beginning treatment, bradycardia, hypoxia, and breathing were recorded, and the treatment's effectiveness (no recurrent episodes of apnea within 72 hours of treatment) was evaluated. A carefully created proforma was used to gather all of the data.

SPSS version 25 was used to enter and evaluate the data. APGAR scores at 1 & 5 min, blood glucose levels during apnea, age, gestational age, birth weight, and the mean and standard deviation of numerical data were among the descriptive statistics evaluated. For efficacy and gender, frequency and percentage were computed. The chi-square test was used to compare the effectiveness of the two groups. Stratification was used to account for effect modifiers like as gender, APGAR scores at 1 & 5 min, blood glucose levels during apnea, age, gestational age, birth weight. The chi-squared post-stratification test was used. A p-value of less than 0.05 was deemed significant.

RESULTS

11.79 ± 4.93 years was the average age. The average age of patients in group A was 10.69 ± 5.01 hours, whereas the average age of patients in group B was 11.84 ± 4.91 hours. There were 73 (52.14%) females and 67 (47.86%) males. An average gestational age of 32.61 ± 2.97 weeks was recorded. The mean gestational age in groups A and B was 32.92 ± 1.55 weeks and 31.84 ± 1.42 weeks, respectively. The average blood sugar level was 82.34 ± 9.42 mg/dl. Weight at birth was 1234.54 ± 234.72 grams on average. At one minute and five minutes, the mean Apgar score was 7.72 ± 1.43 and 8.13 ± 0.89, respectively. The distribution of patients by various variables is shown in Table I.

45 patients (64.29%) in group B (aminophylline) and 62 patients (85.71%) in group A (caffeine) showed efficacy. The statistically significant p-value is 0.003. (Table II).

Table III displays the stratification of efficacy by gender, age, gestational age, birth weight, APGAR scores at 1 & 5 min, and blood glucose level during apnea.

Table I

Distribution of different variables (n=140).

		Group A (n=70)	Group B (n=70)
		Number (%)	Number (%)
Age (hrs)	≤12	46 (65.71%)	45 (64.29%)
	>12	24 (34.29%)	25 (35.71%)
Gestational age (weeks)	23-30	28 (40.0%)	27 (38.57%)
	31-35	42 (60.0%)	43 (61.43%)
Gender	Male	34 (48.57%)	33 (47.14%)
	Female	36 (51.43%)	37 (52.86%)
Birth weight (grams)	501-1500	25 (35.71%)	26 (37.14%)
	>1500	45 (64.29%)	44 (62.86%)
Blood glucose levels (mg/dl)	≤70	21 (30.0%)	23 (32.86%)
	>70	49 (70.0%)	47 (67.14%)
Apgar score at 1 min	<7	29 (41.43%)	28 (40.0%)
	8-10	41 (58.57%)	42 (60.0%)
Apgar score at 5 min	<7	27 (62.79%)	25 (35.71%)
	8-10	43 (37.21%)	45 (64.29%)

Table II

Comparison of efficacy (n=140).

	Group A (n=70)		Group B (n=70)		P-value
	Yes	No	Yes	No	
Efficacy	60 (85.71%)	10 (14.29%)	45 (64.29%)	25 (35.71%)	**0.003**

Table III

Stratification of efficacy with respect to age, gestational age, birth weight, Apgar score at 1 and 5 minutes, blood glucose level during apnea and gender.

		Group A (n=70) Efficacy		Group B (n=70) Efficacy		P-value
		Yes	No	Yes	No	
Age (hrs)	≤12	39 (84.78%)	07 (15.22%)	30 (66.67%)	15 (33.33%)	0.044
	>12	21 (87.50%)	03 (12.50%)	15 (60.0%)	10 (40.0%)	0.029
Gestational age (weeks)	23-30	22 (78.57%)	06 (21.43%)	16 (59.26%)	11 (40.74%)	0.121

	31-35	38 (90.48%)	04 (9.52%)	29 (67.44%)	14 (32.56%)	0.009
Gender	Male	27 (79.41%)	07 (20.59%)	20 (60.61%)	13 (39.39%)	0.093
	Female	33 (91.67%)	03 (8.33%)	25 (67.57%)	12 (32.43%)	0.011
Birth weight (grams)	501-1500	17 (68.0%)	08 (32.0%)	09 (34.62%)	17 (65.38%)	0.017
	>1500	43 (95.56%)	02 (4.44%)	36 (81.82%)	08 (18.18%)	0.040
Blood glucose levels (mg/dl)	≤70	15 (71.43%)	06 (28.57%)	07 (30.43%)	16 (69.57%)	0.007
	>70	45 (91.84%)	04 (8.16%)	38 (80.85%)	09 (19.15%)	0.116
Apgar score at 1 min	<7	25 (86.21%)	04 (13.79%)	19 (67.86%)	09 (32.14%)	0.099
	8-10	35 (85.37%)	06 (14.63%)	26 (61.90%)	16 (38.10%)	0.016
Apgar score at 5 min	<7	23 (85.19%)	04 (14.81%)	18 (72.0%)	07 (28.0%)	0.245
	8-10	37 (86.05%)	06 (13.95%)	27 (60.0%)	18 (40.0%)	0.006

DISCUSSION

There are some fundamental guidelines for managing preterm apnea that include careful observation of the newborn while supportive care techniques like tactile stimulation, continuous positive airway pressure, or mechanical ventilation are started. When necessary, pharmaceutical therapy might be utilized to stimulate breathing. Methylxanthines are thought to be the preferred first-line treatment for preterm apnea.[7]

In this study, aminophylline was more effective than caffeine in 64.31% of preterm newborns compared to 85.71%. Similar findings were noted in a research by Zulqarnain et al.[5] that showed caffeine was superior than aminophylline in lowering the frequency of apneic spells in AOP. For the treatment of preterm apnea, caffeine and aminophylline were 85.7% and 67.4% effective, respectively, while the rates of apnea recurrence were 14.3% and 32.6% for caffeine and aminophylline, respectively.[7]

In contrast, aminophylline was found to be helpful in avoiding AOP in 67% of newborns in a research by Kondo et al.[8] When comparing the effectiveness of caffeine and aminophylline in treating babies with AOP, Skouroliakou et al. found that both groups saw a significant reduction in apneic spells (p=0.001).[9]

According to a 2015 study by Jeong et al., caffeine was superior to aminophylline for treating premature infants' apnea in the short run. Furthermore, he claimed that caffeine was easy to give and effective.[10] Additionally, Lookzadeh et al. found that caffeine was more effective than aminophylline. Lookzadeh et al. found that infants with AOP who got caffeine had a lower likelihood of requiring supplementary oxygen than those who received aminophylline, namely 5% versus 25%, and that this difference was statistically significant (p=0.012).[11] According to Lookzadeh et al., using aminophylline reduced the demand for ventilation by 95% compared to 75% when compared to caffeine, and the difference was statistically significant (p=0.012). These Lookzadeh et al. findings contradict the results of our investigation, which showed no discernible change in the demand for ventilation between aminophylline and caffeine.[11] The reason for the discrepancy could be that, in contrast to the infants in our study, Lookzadeh et al.[11] also included infants who were already receiving breathing support and so had more severe apnea.

Caffeine was also found to be more effective in lowering AOP in our investigation; nevertheless, the difference was statistically significant, while Nagasato et al.[12] did not detect any. When Shivakumar et al.[12] compared caffeine with aminophylline, they discovered that both drugs were similarly effective at lowering the frequency of apneic episodes. According to a research by Habibi et al., the benefits of caffeine use were similar to those of aminophylline.[13] Najafian et al.[14] obtained similar results. According to a research by Khurana et al., newborns with AOP who received either caffeine or aminophylline had a 9% lower death rate in the caffeine group than in the aminophylline group; however, the difference was not statistically significant (p=0.81).[15]

Caffeine was found to be more beneficial than other drugs in a local investigation[16] that examined the means of the rates of apnea in both groups over a period of seven days. With a significant p-value, the coffee group had fewer patients with tachycardia and tachypnea, as well as shorter hospital stays and oxygen inhalation times. When it came to fewer adverse effects, caffeine outperformed aminophylline. A different local study[17] found that the rate of complications was 16% for caffeine versus 30% for aminophylline, the rate of mortality was 3% for caffeine versus 20% for aminophylline, the need for oxygen was 27% versus 57% (p=0.018), and the effectiveness of caffeine versus aminophylline was 87% versus 63% (p=0.037).

With a significant p-value of 0.03, Birader S. et al.'s study[18] revealed that the caffeine group experienced 2.3 apnea events on average per day, compared to 3.8 occurrences per day for the aminophylline group. Additionally, there were fewer cases of tachycardia, food intolerance, and a decreased need for mechanical ventilation in the caffeine group (12% vs. 24%). Infants treated with caffeine had a shorter hospital stay (average of 22 days) than those treated with aminophylline (average of 28 days). This study found that when it comes to treating AOP in preterm newborns, caffeine citrate is more efficient and has less side effects than aminophylline. Shorter hospital stays, fewer and milder apnea episodes, less side effects, and less need for artificial ventilation are all results of it.

This study's limitations include the fact that it was limited to a single hospital and that the results might not be broadly applicable. To draw broad conclusions, research from more hospitals around the nation is required. Furthermore, because it was costly and inaccessible in many places, the patients' levels of both medications were not assessed. Since caffeine improves neurodevelopmental outcomes but severe apnea has a detrimental effect, more research is needed to determine whether caffeine is effective in shielding the brain from long-term neurodevelopmental impairment of any kind.

Suggestions: The results have important ramifications for clinical practice, especially in situations where both medications are accessible. NICUs may be encouraged to use caffeine as the first-line treatment for AOP due to its demonstrated benefits over aminophylline. This could result in better clinical outcomes for preterm infants, such as shorter hospital stays and probably fewer medical expenses.

CONCLUSION

According to the study's findings, caffeine is a safer and more effective treatment for preterm apnea than aminophylline. When choosing the medication regimen to begin treatment with, these outcomes should be considered. Caffeine is advised as the first line of treatment for neonatal apnea of prematurity.

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