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Caffeine versus Aminophylline for Apnea of Prematurity: A Randomized Clinical Trial

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ABSTRACT

Background: Apnea of prematurity is often found in preterm neonates with gestational age less than 34-37 weeks or birth weight (BW) less than 1000 grams. The American Academy of Pediatrics defines apnea as a respiratory halt lasting at least 20 seconds, with bradycardia or cyanosis. Methylxanthines reduce the incidence of apnea. The purpose of this study was to compare the effect of caffeine and aminophylline on the incidence of the apnea in premature infants.

Methods: This randomized clinical trial study was conducted on 80 premature neonates at Shahid Sadoughi hospital in Yazd. The first group received the initial dose of 5 mg/kg aminophylline diluted in 5% dextrose with a maintenance dose of 2 mg/kg every 8 hours, while the second group received 30 mg/kg of caffeine diluted in 5% dextrose with a 24-hour maintenance dose of 10 mg/kg.

Results: There was no significant difference in frequency of apnea between the two groups (P = 0.121). However there was a significant difference in respiratory status between the two groups so that in caffeine group, oxyhood was less necessary for neonates (P = 0.012) and using continuous positive airway pressure (CPAP) was significantly less in aminophylline group (P = 0.012).

Conclusion: Our study showed that the frequency of apnea was less in the caffeine group, but there was no significant difference between the two groups. Aminophylline treatment in comparison with caffeine can reduce the need for CPAP in neonates with apnea.

Introduction

Apnea of prematurity is often found in preterm neonates with gestational age less than 34-37 weeks or birth weight (BW) less than 1000 grams.[1] The American Academy of Pediatrics defines apnea as a respiratory halt lasting at least 20 seconds, with bradycardia (less than 100 beats per minute) or cyanosis.[2] Apnea intervals have an inverse relationship with gestational age.[3] Also, certain conditions, such as hypoxia, metabolic disturbances, intracranial damage, and infections may lead to apnea.[4] Apnea can damage the growing brain of babies, and can also disrupt the function of some organs of the body such as gastrointestinal system[3]. Recurrent and prolonged apnea can lead to respiratory failure, intubation and finally mechanical ventilation.[4] Premature neonates usually experience a sudden drop in the oxygen saturation of the blood following apnea and may require immediate medical support.

Methylxanthines (such as aminophylline, theophylline, and caffeine) reduce the incidence of apnea and have been used in three last decades in neonatal intensive care units (NICUs).[5,6] Caffeine is a nonspecific antagonist of adenosine A1 and A2A receptors.[7] Caffeine stimulates respiratory system hence it is used to treat obstructive apnea for a long time. Studies have shown that caffeine is effective in treating apnea of prematurity for 80% of neonates with birth weight of less than 1000 gr and 26% of neonates with birth weight 1000-2500 gr.[8] These medicines improve the chemical receptor response to the partial pressure increase in carbon dioxide (PCO2), the function of the respiratory muscles and the central nervous system (CNS) stimulation.[4,5,9] Such drugs also reduce the need for mechanical ventilation, thus they can be useful before pulling out the respiratory tract.[4] Caffeine has good intestinal absorption and high drug treatment index, a long half-life, and less need for drug monitoring, which can be used on a daily basis. Caffeine can also prevent apnea and subsequently reduce the need for intubation.[10,11] Limited studies have investigated the effect of caffeine in comparison with aminophylline. The purpose of this study was to compare the effect of caffeine with aminophylline in treatment of apnea of prematurity.

Materials and Methods

This randomized clinical trial study was conducted from 2017 to 2018 in the NICU at Shahid Sadoughi hospital in Yazd. The university's ethics committee approved this study and we received the IR code. IRU.MEDICINE.REC.1397.78. Written informed consents of parents for each newborn participant was obtained.

Premature neonates with a gestational age under 34 weeks who experienced more than one episode of apnea during 24 hours or neonates with episodes of apnea requiring ventilation with bag were included in the study.

Neonates with congenital anomalies or secondary apnea related to sepsis, congenital cardiovascular disease, etc. as well as neonates whose mothers used pain relievers were excluded from the study.

Eighty eligible newborns whose data regarding their apnea was available were entered the study. Subjects were randomly divided into two groups. In each group 40 babies were treated with caffeine or aminophylline. Randomization was done using random numbers. The process was done by a researcher who was not involved in the study or the management of newborns. Prescribing treatment was conducted at the presence of a physician in the neonatal department.

The first group received the initial dose of 5 milligram per kilogram aminophylline diluted in 5% dextrose with a maintenance dose of 2 milligram per kilogram every 8 hours, while the second group received 30 milligram per kilogram of caffeine diluted in 5% dextrose with a 24-hour intravenous

Table 1. Characteristics and outcomes of caffeine and aminophylline groups

	Caffeine (n = 40)	Aminophylline (n = 40)	P-value
Gender			
Male	20	23	0.501
Female	20	17	
Gestational age, mean ± SD (weeks)	30.18±2.147	30.78 ± 1.968	0.196
Age, mean ± SD (day)	1.68 ± 1.366	1.48 ± 1.086	0.471
Birth weight, mean ± SD (gr)	1461.75 ± 512.445	1459.00 ± 410.770	0.979
Apgar score, mean ± SD			
1 min	7.83 ± 1.196	8.13 ± 1.137	0.254
5 min	8.65 ± 0.533	8.68 ± 0.616	0.847
Blood glucose during Apnea, mean ± SD	70.70 ± 10.246	73.90 ± 15.307	0.276

infusion maintenance dose of 10 milligram per kilogram. Within three days of starting the treatment, the response rate to the interventions and side effects were compared.

The following information were observed and recorded for this study: gender, age, birth weight, first and fifth minute APGAR, gestational age, neonatal respiratory status, blood glucose during apnea, number of apnea episodes within 72 hours, length of an episode of sleep in each neonate, heart rate, gastrointestinal complications (vomiting, abdominal distension, positive lavage), seizure, crying for more than an hour, and tachycardia. Continuous monitoring of vital information and oxygen saturation was carried out. Clinical evaluation was performed 24 hours after treatment with caffeine or aminophylline.

With a confidence interval level of 90% and a significant level of 5%, 80 participants were required. The difference in mean birth weight, age, gestational age, APGAR scores, and blood glucose during apnea were analyzed by independent t-test. Gender, respiratory status, apnea episodes during 72 hours, side effects of treatments were analyzed by chi-square test. $P < 0.05$ was considered statistically significant. The number of apnea episodes during 72 hours was analyzed using Fisher's test.

Results

In this study 43 male and 37 female premature neonates were investigated. The average gestational age of neonates who received caffeine or aminophylline was 30.18 ± 2.147 weeks or 30.78 ± 1.968 weeks, respectively ($P = 0.196$). The basic characteristics of the two intervention groups were almost the same (Table 1).

According to the Table 1, the frequency of apnea was less in caffeine group but there was no significant difference between treatment groups ($P = 0.12$). However there was a significant difference in respiratory status between the two groups, so that the oxyhood was less necessary in caffeine group ($P = 0.01$) and using continuous positive airway pressure (CPAP) was significantly less in aminophylline group (Table 2).

As shown in Table 3, data analysis using chi-square test showed that aminophylline or caffeine groups were not different in complications during treatment of apnea ($P > 0.05$).

Table 2. Comparison of primary outcomes between caffeine and aminophylline groups

Variable		Caffeine (n = 40)	Aminophylline (n = 40)	P-Value
Frequency of apnea within 72 h	Yes	7(17.5%)	13(32.5%)	0.121
	No	33(82.5%)	27(67.5%)	
Respiratory function	C PAP	38 (95%)	30 (75%)	0.012
	Oxyhood	2 (5%)	10 (25%)	

Table 3. Comparison of adverse effects between caffeine and aminophylline groups

Variable	Caffeine (n = 40)	Aminophylline (n = 40)	P-Value
GI intolerance	11(27.5%)	16(40%)	0.237
Tachycardia	5(12.5%)	6(15%)	0.745
Seizure	1(2.5%)	4(10%)	0.359
Crying more than one hour	3(7.5%)	4(10%)	1.000
Hyperglycemia	0(0%)	0(0%)	NA
Sleep disorder of neonate	0(0%)	1(2.5%)	1.000

NA: not applicable.

Discussion

The current study revealed that there was no significant difference between caffeine and aminophylline groups related to the frequency of apnea. Apnea occurs commonly in premature neonates and is defined as temporary cessation of breathing for more than 20 seconds, or less than 20 seconds with bradycardia (HR<80) or cyanosis in newborns less than 37 weeks of gestational age. Bradycardia and cyanosis usually occur after 20 seconds, but in premature neonates it may occur earlier.[12]

The prevalence of apnea has an inverse relationship with the gestational age at birth. Apnea is divided into three types. The first type is the central, which there is no respiratory effort, and it is about 10 to 25% of the cases. Obstructive respiratory apnea occurs despite respiratory effort and has a prevalence of 10 to 20%. Mixed type, includes 50 to 75% of the cases. Thirty five percent of all neonates below1800 grams (less than 34 weeks) experience at least one episode of apnea. Normally, neonates under the gestational age of 28 weeks will definitely experience apnea. Apnea usually occurs in the first few days of life, and after the seventh day the chances of developing apnea are very low.[13] The pathogenesis of apnea is related to the brain stem function. Breathing in newborns is markedly under the influence of sleep phase. In the REM phase, apnea occurs more clearly in preterm neonates.[14] When apnea repeats 2-3 times during an hour or when you need bag ventilation, it should be treated. Blood transfusion may be effective if hematocrit is less than 25%, or with repeated episodes of apnea, even within the therapeutic level. CPAP (4-6cmH2O) can be used to treat obstructive or concomitant apnea (usually for gestational ages of 32 to 34 weeks).[15]

Methylxanthines are the main treatment for apnea of prematurity, which can reduce the frequency of apnea and reduce the need for intubation. The mechanism of action of methylxanthine includes:

1. Stimulation of the respiratory center
2. Antagonistic effect on adenosine receptors (A1 and A2) in the CNS
3. Improved contraction and movement of thoracic diaphragm

Side-effects of methylxanthines, especially theophylline and aminophylline, include tachycardia, gastrointestinal intolerance (abdominal distension, intolerance to nutrition and vomiting), irritability and seizures.[16]

Other treatment is caffeine, which has longer half-life[9] and less toxicity compared to theophylline, and is better tolerated.[17] Caffeine is excreted by the kidneys. It has direct and indirect effects on the brain. Caffeine improves the ventilation by increasing the sensitivity to carbon dioxide, bronochodylation and improvement in the activity of the diaphragm. Mechanical ventilation is performed if other treatments are not effective.[18]

In a randomized clinical trial (RCT) study in India by Shivakumar[17], the safety of caffeine and aminophylline on apnea in newborns under 34 weeks from 2012 to 2015 in 240 preterms were studied and analyzed. In that study, caffeine was given at an initial dose of 20 mg/kg at a maintenance dose of 5 mg/kg/d and aminophylline 5 mg/kg and then 1.5mg/kg/d. Of the selected cases,

79 cases of caffeine and 77 cases of aminophylline were evaluated. Among the small for gestation age (SGA), the apnea episode was higher in the caffeine group during the first three days. During the first week of treatment, the caffeine group had a higher drop in oxygen saturation while aminophylline group had an increase in average heart rate. Generally, in that study, the complete removal of apnea (median six days) and the degree of saturation loss were similar in the two groups. There was no clear difference in gastrointestinal tolerance.

The second study was conducted in September 2017 by Atik et al. on the effects of caffeine on brain development. The study results showed that caffeine was associated with reduction of the cerebral palsy and cognitive delay incidence. Respiratory effects were beneficial for premature neonates, but further studies are needed to evaluate the effect of caffeine in different doses on brain development and to determine the maximum safe dose of caffeine for premature neonates.[19]

In an RCT study by Armanian in 2016, caffeine was prescribed for apnea prophylaxis in neonates weighing less than 1200 gr. Twenty six neonates received caffeine at an initial dose of 20 mg/kg and a maintenance dose of 5 mg/kg/d in the first ten days of life. There were 26 neonates in the control group. Four newborns in the caffeine group experienced an increase in apnea attacks versus 16 in the control group. The effect of prophylaxis on apnea was evident in premature neonates.[20]

In 1992, Scanlon et al. conducted a study on 44 neonates below 31 weeks at Birmingham hospital. In the first group, the initial dose of caffeine was 25 mg/kg and a maintenance dose was 6 mg/kg/d; in the second group, a high dose of caffeine was administered at a dose of 50 mg/kg and a maintenance dose of 12 mg/kg/d, and in the third group theophylline was administered at an initial dose of 7.5 mg/kg and a maintenance dose of 3 mg/kg/d. Two days after treatment, there was a clear response to treatment in all groups, but the response was clearly better in the high dose caffeine group and theophylline group (50% reduction in apnea). There was Continuous tachycardia (HR>195) at the theophylline level greater than 20 mg/L. The highest effect on HR was on day 4 of treatment, with a mean increase in HR of 3 in the first group and 5 in the second group and 12 in the third group. There was no complication with caffeine. In that study, the reduction in the number of apnea attacks in the first 8 hours of treatment was seen in the first and second groups. Regarding the effect of high dose caffeine was similar to theophylline and both were effective, this study suggested caffeine for apnea of prematurity(due to its high benefits, fewer side effects, easier administration than theophylline), and recommended it in neonates with inadequate clinical response.[21]

In a study by Henderson, the effects of theophylline and caffeine were evaluated in 108 premature neonates. The study revealed that caffeine was as effective as theophylline after one to three days starting treatment. Side effects such as tachycardia and intolerance to nutrition were lower for the caffeine group. Regarding the easier administration of caffeine and its lower complications, caffeine was recommended.[22]

A study in 2015 by Schellack et al. investigated 31 neonates for the effects of caffeine and aminophylline in preventing premature apnea in South Africa. Aminophylline was given at a dose of 6 mg/kg, then 2.5 mg/kg/dose, and caffeine at a dose of 10 mg/kg and then 2.5 mg/kg /d. The effect was evaluated by the number of apnea and its serum concentration. Gastrointestinal and cardiovascular status was examined in that study. The mean respiratory rate and heart rate in the aminophylline group were higher during the first five days of treatment. In the caffeine receiving group, the serum concentration of the drug was higher than the therapeutic range, but no symptoms were reported in the patients. The results showed

that caffeine was a good alternative to aminophylline, while oral administration might lead to many positive outcomes.[23]

In this study, there was no significant difference in response to treatment between the two groups of caffeine and aminophylline. A study in 2019 by korvadiya et al. on 40 Indian neonates with apnea of prematurity showed that there was no significant difference between the two groups treated with aminophylline and theophylline in terms of response to treatment and associated complications.[24] In a study by Habibi et al., it was observed that the benefits of caffeine use did not differ from those of aminophylline.[25]

Conclusion

In conclusion, the frequency of apnea was less in caffeine group, but there was no significant difference between the two groups. Aminophylline treatment in comparison with caffeine could reduce the need for CPAP in neonates with apnea, but there was not any difference between their side effects including the incidence of tachycardia, seizure, hypoglycemia, crying more than one hour, gastrointestinal intolerance or sleep disorders among groups.

Conflict of Interests

Authors have no conflict of interests.

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