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Effect of Caffeine and Aminophylline on Apnea of Prematurity

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ABSTRACT

Background: The most common type of apnea among premature newborns is idiopathic apnea of prematurity. Recurrent apnea can lead to hypoxemia and central nervous system damage. Although caffeine and theophylline are the most commonly prescribed drugs in this field, there is disagreement about which medicine is preferred. The purpose of this study was to compare the therapeutic effect and side effects of caffeine and aminophylline in the treatment of idiopathic apnea of prematurity.

Methods: This randomized clinical trial study was conducted on 67 premature neonates with the definite diagnosis of idiopathic apnea of prematurity. In this regard, subjects were divided into two groups, namely aminophylline recipient group (n=31) and caffeine recipient group (n=36). The two groups were compared regarding the frequency of recurrent apnea and side effects of drugs.

Results: Regarding gender distribution, 15 (48.4%) patients in the aminophylline recipient group, and subjects in the 20 (55.6%) caffeine recipient group were male. After the treatment, apnea recurred only in one case (0.1%) of aminophylline recipient group. Moreover, 7 patients (58.3%) in the aminophylline recipient group and 5 cases (41%) in the caffeine recipient group suffered from gastrointestinal side effects (P=0.3).

Conclusion: The obtained results of the present study revealed that there was no significant difference between the two groups.

Keywords: Aminophylline, Apnea, Caffeine, Prematurity

Introduction

One of the most common problems of newborns is apnea of prematurity. The term apnea refers to the cessation of breathing for more than 15-20 seconds or less than 15 seconds if it is accompanied by cyanosis or bradycardia (1). The incidence of apnea is reversely correlated with gestational age (1, 2). Most of newborns with 28 weeks of gestational age or less, 84% of newborns with the weights of less than 1kg regardless of the gestational age, 54% of newborns with 30-31 gestational age, 15% of newborns with 32-33 gestational age and 7% of newborns within the age range of 34-35 gestational age experienced apnea (3, 4). Apnea is usually seen in the first or second weeks of the life. Bradycardia and cyanosis are the symptoms, which are seen in the cases of apnea. Bradycardia usually occurs when apnea lasts longer than 20 seconds. In 95% of the cases, bradycardia starts 1-2 seconds after apnea and it often has a sinus rhythm type. Although numerous factors, such as pulmonary, cerebral, and infectious diseases, can lead to apnea, the most common type of apnea among premature newborns is idiopathic apnea of prematurity. This type of apnea is caused by the lack of physiological evolution of respiratory system. In these patients, the pathological conditions, such as infections and cerebral hemorrhage do not play a role in its creation (1, 2). Severe and persistent apnea can lead to the evolutionary disorder of the brain (1). The therapeutic approach toward apnea include prone head-elevated position, continuous positive airway pressure (CPAP), and high-flow nasal cannula (HFNC), as well as the administration of some drugs (e.g., methylxanthines and doxapram)

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(1-4). Although methylxanthines have been used as main drugs for the treatment of prematurity apnea for a long time, there is a dearth of research on the efficiency and safety of the drugs (4). Aminophylline and caffeine are among the commonly used methylxanthines (4). However, there is a disagreement on this issue that which drug is more suitable for treatment and prevention of prematurity apnea (5-7). Some reports indicated that caffeine has fewer side effects and higher efficiency, compared to aminophylline (7, 8). Regarding the given importance of idiopathic apnea of prematurity treatment and presence of discrepancies in this issue, the present study was conducted to compare the therapeutic and side effects of aminophylline and caffeine.

Methods

This double-blind randomized clinical trial was conducted on 67 premature neonates with the definite diagnosis of idiopathic apnea of prematurity. The present study was performed at Kosar Hospital of Qazvin, Qazvin, Iran, in 2016. This hospital is the only referral center for treating premature neonates in Qazvin Province that is affiliated to Qazvin University of Medical Sciences, Qazvin, Iran. The inclusion criteria for percipients were 1) the gestational age of less than 37 weeks, 2) existence of apnea attack (the cessation of breathe for more than 15-20 seconds or less than 15 seconds if accompanied by cyanosis or bradycardia), and 3) lack of any pathologic conditions (1). The exclusion criteria included newborns with any risk factors (e.g., cerebral hemorrhage, sepsis, respiratory distress syndrome, pulmonary diseases) and any congenital malformations (e.g., diaphragmatic hernia). After the approval of project by the Ethics Committee of Qazvin University, the eligible premature neonates (87 premature neonates) were divided randomly into two groups, namely aminophylline recipient group (31 patients identified by blue card) and caffeine recipient group (36 patients identified by green card). Initially, the type of treatment was written on the cards and then placed in identical envelopes by someone who was not involved in the project.

The parents of the eligible patients randomly selected one of the cards after entering the hospital. Sampling continued in succession until the researchers reached their desired sample size. Project executives and parents were not informed of the treatment type. The aminophylline recipient group received intravenous aminophylline (5-7 mg/kg at first and then 1-2 mg/kg each 6-12 h; Caspian Tamin Pharmaceutical Company, Rasht, Iran; IRC: 128041754) and the caffeine recipient group received intravenous caffeine (20 mg/kg at first and then after 24 h, maintenance dose of 5 mg/kg/24h was divided into two doses (Chemi Daro Pharmaceutical Company, Tehran, Iran; IRC: 1228140013) (2). The treatment duration for both groups was 5-7 days.

During this time the investigated patients were controlled carefully regarding apnea recurrence, cyanosis, bradycardia, cessation of breathing, amount of oxygen saturation and also short-term complications (e.g., vomiting and gastrointestinal bleeding). These data were recorded in pre-prepared checklist by someone who did not know about the type of treatment. After the treatment began, the lack of apnea relapse, oxygen saturation ≥ 95%, no bradycardia, no cessation of breathing, and absence of cyanosis were considered complete recovery. The recurrence of apnea was defined when the symptoms of apnea (cessation of breathing for more than 15-20 seconds or less than 15 seconds if accompanied by cyanosis or bradycardia) were observed again despite drug therapy. Apnea was diagnosed through clinical examination by a neonatologist, monitoring device, and pulse oximetry. The neonates unresponsive to drugs or those who felt bad during the treatment were included in the next stage of the treatment (e.g. use of CPAP or intubation). The results were presented in statistical tables and numerical indicators. The obtained data were analyzed in SPSS (version 16) using the Chi-square test. P-value less than 0.05 was considered statistically significant.

Ethics statement

The Ethics Committee of the Research Department in the Qazvin University of Medical Sciences, Qazvin, Iran, approved the study (project no. 11170). All parents were provided information regarding the research method in simple language. The premature neonates were included in the study after their parents agreed and signed the informed consent form.

Results

Out of 67 premature neonates with idiopathic prematurity apnea, 35 (52.2%) were male. Among these neonates, 2 (3%) and 62 (92.5%) cases had bradycardia and cyanosis, respectively. however, no symptoms were observed in 3 (4.5%) of the investigated neonates. Regarding gender distribution, 15 (48.4%) patients in the

Table 1. Comparison of variables between aminophylline and caffeine groups

Variables[1]	Groups		P
	Aminophylline (n=31)	Caffeine (n=36)	
Gender (male/female)	15/16	20/16	0.6
Weight (gram)			
<1000	4 (12.9)	7 (19.4)	
1000-1500	5 (16.1)	13 (36.1)	0.07
1500-2000	10 (32.3)	11 (30.6)	
>2000	12 (38.7)	5 (13.9)	
Gestational age (weeks)			
< 30	8 (25.8)	12 (33.3)	
30-32	8 (25.8)	11(30.6)	0.6
32-34	7 (22.6)	8 (22.2)	
>34	8 (25.8)	5 (13.9)	
Onset of apnea (day)			
First day	9 (29)	19 (52.8)	0.06
2-7	20 (64.5)	13 (36.1)	
>7	2 (6.5)	4 (11.1)	
Duration of apnea (second)			
10-15	8 (25.8)	11 (30.6)	0.5
>15	23 (74.2)	25 (69.5)	
Associated symptoms			
Bradycardia	2 (6.5)	0 (0)	0.1
Cyanosis	29 (93.5)	33 (91.7)	

[1]Chi-square test

Table 2. Comparison of complications between aminophylline and caffeine groups

Variables[1]	Groups		P
	Aminophylline (n=31)	Caffeine (n=36)	
Gastrointestinal disturbance	7 (22.6)	5 (13.9)	0.3
Recurrent apnea	1 (0.03)	0 (0)	-

[1]Chi-square test

aminophylline recipient group, and subjects in the 20 (55.6%) caffeine recipient group were male. There was no significant difference between the two groups in terms of gender, weight, gestational age, first day of apnea, duration of apnea, and related symptoms (P>0.05; Table 1). After the initiation of the treatment, the recurrence of apnea was observed in only one case (0.03%) from aminophylline group. In addition, 7 (58.3%) neonates in aminophylline recipient group and 5 (41%) of caffeine recipient group had gastrointestinal side effects, such as vomiting and gastrointestinal bleeding (P=0.3). Out of 12 neonates with gastrointestinal side effects, 10 neonates had the gestational age of less than 34 weeks (Table 2).

Discussion

The obtained results of the present study indicated that the therapeutic effects and side effects of aminophylline and caffeine were similar. Apnea is one of the common problems of premature neonates, which is caused by the immaturity of respiratory control center (1). During such attacks, the cessation of breathing occurs and the oxygen saturation (SpO2) falls to less than 80% for more than 4 seconds and heart rate becomes slower than 67% of baseline for more than 4 seconds. These changes may lead to neurological evolutionary complications (4). Therefore, it is often recommended to treat these neonates to reduce their apnea attacks and to prevent permanent nervous side effects (1, 2, 4). One of the recommended treatments is to use the methylxanthine drugs, such as aminophylline and caffeine (1-4). These drugs reduce the frequency of apnea attacks by increasing the number of breaths, lowering the threshold of sensitivity to hypercapnia, and also increasing the contractility of diaphragm (4). There are disagreements about which drug is more suitable and results of previously conducted studies are paradoxical (6-12). The study of Henderson-Smart et al. on 108 premature neonates with prematurity apnea showed that there is no significant difference between the effects of treatment with caffeine and aminophylline (6). In contrast, the investigation of 53 premature neonates with prematurity apnea

by Laubscher et al. revealed that caffeine treatment could significantly improve respiratory function and reduce the demand for oxygen after 24 h (9). They also reported that the respiratory effort of both groups was identical after 7 days. These researchers concluded that although both drugs improved respiratory function, a faster response was achieved using caffeine, compared to aminophylline (9). Although both caffeine and aminophylline are used for the treatment of apnea of prematurity, the report of Skouroliakou et al. showed that the prophylactic effect of caffeine among premature neonates is better than that of aminophylline (5). Other reports indicated that the prophylactic prescription of caffeine to neonates could lead to survival without the development of neurologic side effects at 18-20 months corrected age, compared to control group. In addition, these reports revealed that prophylactic caffeine reduces the need for patent ductus arteriosus (PDA) treatment (10-12). In the present study, the treatment effects on both caffeine and aminophylline recipient groups were identical and there was no significant difference between the two groups in terms of apnea improvement. The recurrence of apnea was observed in one case of aminophylline recipient group. Moreover, both drugs were evaluated in terms of their side effects (13-17). Hoecker et al. reported that the loading dose of 25mg/kg of caffeine citrate results in the vasoconstriction of cerebral and intestinal veins and reduces blood flow velocity (13). This study suggests that these pathophysiologic changes could provide the conditions for the creation of periventricular leukomalacia, hemorrhage, and necrotizing enterocolitis (13). Saliba et al. reported that administering the loading dose of 10mg/kg caffeine through nasogastric tube reduces the likelihood of cerebral and intestinal side effects (14). The main side effects of aminophylline, are seizures and hypokalemia and the side effects such as tachycardia, tachypnea, glucose instability, jitteriness, restlessness, tremors, irritability, vomiting, gastrointestinal bleeding and feeding intolerance are less common in caffeine (7, 15). The physiological effects of aminophylline and caffeine are similar. They increase energy consumption, raise oxygen demand, reduce growth and delay weighing of preterm neonates. Therefore, it is recommended to administer extra caloric supplementation when the patient receives the high doses of the drug (16, 17). In the present study, none of the mentioned side effects were observed and only 12 cases (7 cases of aminophylline recipient group and 5 cases of caffeine recipient group) had gastrointestinal side effects. The differences in the results of above-mentioned studies could be related to certain factors, including the dose of drug, route of drug administration, age of neonates, and start date of treatment. Although most of studies recommend caffeine administration, there was no significant difference between the two drugs in terms of therapeutic effects and their side effects. The limitations of the present study included: lack of serum drugs measurements and failure to determine the long-term effects of drugs.

Conclusion

The obtained results of the present study revealed that there was no significant difference between the two groups.

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Conflicts of interests

There are no conflicts of interest.

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