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Original Article

The effect of CPAP combined with caffeine citrate on apnea of prematurity

Shengxia Xiang, Dan Liu, Yumeng Ma, Nan Zhang, Hongyue Li, Xiaoli Du, Yumin Liu

Department of Pediatrics, The No. 4 People's Hospital of Hengshui City, Hengshui, Hebei province, China

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Abstract: Objective: To investigate the effect of continuous positive airway pressure (CPAP) combined with caffeine citrate on apnea of prematurity. Methods: A total of 200 premature infants with apnea treated in our hospital from January 2016 to September 2019 were included in this study. All the eligible premature infants were randomly assigned into control group (n = 100) and observation group (n = 100). Premature infants from control group underwent CPAP and aminophylline use, while infants in observation group received CPAP and caffeine citrate. The incidence of apnea, arterial blood gases analysis, success rate of ventilator weaning, time of mechanical ventilation, time of methylxanthine use and incidence of adverse reaction were compared between the two groups. Results: Compared with control group, the observation group had significantly reduced incidence of apnea ($P < 0.001$). Significantly improved degrees of arterial blood gases analysis were also found in observation group ($P < 0.001$). Moreover, the observation group had obviously higher success rate of ventilator weaning ($P < 0.001$). The time of mechanical ventilation and time of Methylxanthine use were obviously lower ($P < 0.001$). The incidence of adverse reaction was also significantly lower in observation group ($P = 0.002$). Conclusions: For treatment of apnea of prematurity, CPAP combined with caffeine citrate use is significantly superior to CPAP combined with aminophylline use in reducing the incidence of apnea and adverse reaction, increasing success rate of ventilator weaning, decreasing time of mechanical ventilation and time of methylxanthine use, and improving indexes of arterial blood gases. It is worth for clinical use.

Keywords: Apnea of prematurity, aminophylline, caffeine citrate, treatment

Introduction

Apnea of prematurity is considered as a common complication of preterm birth and it is characterized by insufficient respiratory drive or no air entering the lung [1, 2]. Apnea of prematurity is defined as a noninspiratory period lasting for less than 20 s by American Academy of Pediatrics, and is often accompanied by cyanosis and/or bradycardia. Epiderniologic studies demonstrated that apnea occurred more often with decreases in gestational age, and progressively increased over the first 4-5 weeks of life in preterm infants [3, 4]. It was reported that apnea of prematurity could lead to damage to the function of the intestine, developing brain, respiratory failure, and behavioral and neurological difficulties, which seriously threatened the life and prognosis in preterm infants [5, 6]. Therefore, once premature infants experience apnea, accompanied by changes of vital indexes, it has a very important significance for immediate medical support to reduce the incidences of mortality and sequelae.

It was reported that methylxanthine usage in neonates treated with mechanical ventilation could significantly reduce the apneic periods [7, 8]. Methylxanthine has been widely applied for treatment of apnea of prematurity due to its stimulation of breathing efforts [9]. Aminophylline and caffeine are the commonly available forms of methylxaanthines. Some studies reported that in contrast to aminophylline, caffeine citrate has more advantages in term of half-life, therapeutic index and intestinal absorption. So far, many clinical studies have been performed to discover a treatment for apnea of prematurity, but only a few have aimed at looking for drugs useful for treating apnea of prematurity [10, 11]. There were limited researches focused on safety and effectiveness

for caffeine citrate versus amionophylline in apnea of prematurity [12]. Moreover, the effect of methylxanthines in apnea of prematurity treated with continuous positive airway pressure was incompletely understood. In this context, this study was performed to conduct a comparison between caffeine citrate and amionophylline when used in standard doses and combined with mechanical ventilation to prevent and treat apnea of prematurity, and to determine any differences. The results of this study would provide experimental foundation for guideline of treatment in apnea of prematurity.

Materials and methods

Subjects

The study sample consisted of 200 infants admitted to department of Pediatrics at the No. 4 People's Hospital of Hengshui City from January 2016 to September 2019, who were born prematurely with a birth weight between 1000 g and 1500 g and had spontaneous breathing at 24 hours of life. The inclusion criteria were as follows: (1) The infants were born before 32 weeks of gestation; (2) The infants met the diagnostic criteria for apnea of prematurity [13], which was defined as discontinuance of breathing for more than 20 s or shorter but correlated with bradycardia (heart rate less than 100 bpm) or hypoxia (oxygen saturation less than 85%); (3) The data were completely recorded. The exclusion criteria were as follows: (1) Infants were combined with congenital disorders, perinatal asphyxia, metabolic disorders, disseminated infection, neuromuscular anomalies, malformation of the respiratory tract and perinatal asphyxia; (2) Methylxanthines were treated previously; (3) The infants were not available for follow-up. This study was approved by the hospital ethics committee and the parents of infants provided written informed consents.

The eligible candidates in this study were randomly divided into control group (n = 100) and observation group (n = 100). After experiencing apnea, infants received the therapy. The infants in two groups were provided the same respiratory management protocol. And the continuous positive airway pressure (CPAP) was initiated and settings were adjusted according to clinical parameters and arterial blood gases. SpO_2 was maintained between 88-92%. The parameters of neonatal ventilator were set as follows: Peak inspiratory pressure was regulated between 10 cm H_2O and 15 cm H_2O; Positive end-expiratory pressure was controlled from 4 cm H_2O to 6 cm H_2O; Respiratory rate was regulated between 35 times/min to 45 times/min; Inspiratory time was between 0.3 s to 0.5 s; The fraction of inspiration O_2 was 25-60%; Trigger pressure was adjusted from 0.2 cm H_2O to 0.4 cm H_2O. Based on CAPA, the infants in observation group received caffeine citrate: first loading dose of 20 mg/kg was given intravenously and maintenance doses of 5 mg/kg were given intravenously once daily; Aminophylline was used in infants in control group, with loading doses of 5 mg/kg given intravenously and maintenance dose of 2 mg/kg every 12 h. The treatment was conducted as far as the gestational age of 34 weeks.

Observed indexes

The incidence of apnea was compared between the two groups. Apnea was counted if a pause in breathing lasted for less than 20 s, combined with occurrence of cyanosis and/or bradycardia. Cyanosis was defined as SpO_2 less than 85% in neonate. Bradycardia was defined as heart rate decreasing by more than 20% from the baseline for 20 s.

The indexes of arterial blood gases were compared between the two groups. The blood sample of infants was withdrawn before and after treatment in order to determine the levels of PaO_2, $PaCO_2$ and SaO_2.

The success rate of ventilator weaning, time of mechanical ventilation and time of Methylxanthine use were compared between control group and observation group.

The incidence of adverse reaction was compared between the two groups. Adverse drug reaction in this study included tachycardia, gastrointestinal bleeding, retinopathy, bronchopulmonary dysplasia and hyperglycemia.

Statistical analysis

All data included in this study were analyzed using SPSS software, version 22.0. Measurement data were presented as mean ± SD and an independent-samples T test was used to evaluate comparison between two groups. Ca-

Table 1. The comparison of basic information between two groups

Groups	Cases	Gestational age (years)	Male/Female (Cases)	Birth weight (g)	singleton birth (Cases)	Family arrangement	
						Single parent	Two parent
Control group	100	30.1±0.8	55/45	1158.7±79.6	82	24	76
Observation group	100	29.9±0.7	58/42	1145.2±65.4	86	21	79
t/χ^2 value		1.881	0.183	1.310	0.595	0.258	
P value		0.061	0.669	0.192	0.440	0.612	

Table 2. Comparison of incidences of apnea, cyanosis and bradycardia between two groups

Groups	Cases	Apnea (cases)	Cyanosis (cases)	Bradycardia (cases)
Control group	100	41	36	38
Observation group	100	19	12	14
χ^2 value		11.520	15.790	14.970
P value		< 0.001	< 0.001	< 0.001

Table 3. Comparison of blood gas analysis results between two groups

Groups	$PaCO_2$ (mmHg)		PaO_2 (mmHg)		SaO_2 (mmHg)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group	72.1±8.5	56.2±5.7	52.7±4.3	75.4±7.6	40.8±5.6	64.2±3.5
Observation group	71.7±8.1	48.6±5.2	52.3±3.9	93.8±7.9	40.6±5.4	85.7±3.8
χ^2 value	0.314	9.850	0.689	16.780	0.257	41.620
P value	0.734	< 0.001	0.492	< 0.001	0.797	< 0.001

tegorical data were presented as percentages and the comparison between groups was conducted using the chi-square test. $P < 0.05$ was considered as statistically significant differences.

Results

Basic information

There were no significant differences between control group and observation group in clinical data including gestational age, gender, birth weight, singleton birth, and family arrangement. Therefore, both groups were comparable ($P > 0.05$, **Table 1**).

Comparison of apnea incidence

As shown in **Table 2**, the incidence of apnea in observation group was 19%, while it was 41% in control groups. And there were significant differences between the two groups ($P < 0.001$). The differences were also found in term of incidence of cyanosis and bradycardia (all $P < 0.001$).

Comparison of blood gas analysis results

Compared with those before treatment, $PaCO_2$ was significantly decreased and PaO_2 and SaO_2 were obviously increased after treatment in both groups (all $P < 0.001$). After treatment, $PaCO_2$ in observation group was significantly decreased and PaO_2 and PaO_2 and SaO_2 were remarkably increased in contrast to control group (all $P < 0.001$), as shown in **Table 3**.

Comparison of the success rate of ventilator weaning and time of mechanical ventilation

As seen in **Figure 1**, the success rate of ventilator weaning in observation group was significantly higher than that in control group (78% vs 95%, $\chi^2 = 12.370$, $P < 0.001$), and time of mechanical ventilation in observation group was obviously lower than that in control group (15.7±4.1 d vs 7.2±2.5 d, $t = 17.700$, $P < 0.001$).

Comparison of time of methylxanthine use

Compared with control group, the time of Methylxanthine use in observation group was significantly reduced (18.8±4.4 d vs 12.1±3.1 d, $t = 12.450$, $P < 0.001$), as seen in **Figure 2**.

Comparison of adverse reaction

As seen in **Table 4**, there were 7 cases of tachycardia, 4 cases of gastrointestinal bleeding, 2 cases of retinopathy, 2 cases of bronchopulmonary dysplasia, and 3 cases of hyperglycemia in

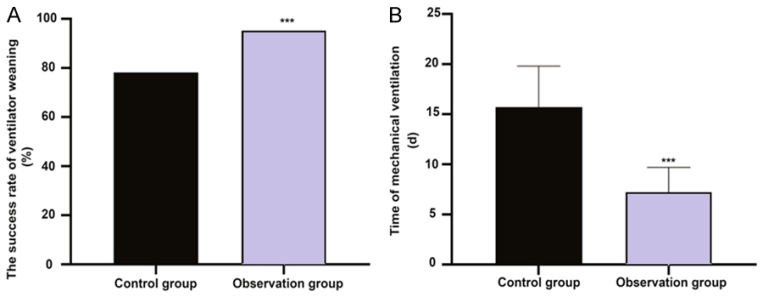

Figure 1. Comparison of the success rate of ventilator weaning and time of mechanical ventilation between two groups. A. The success rate of ventilator weaning; B. Time of mechanical ventilation. Compared with control group, ***P < 0.001.

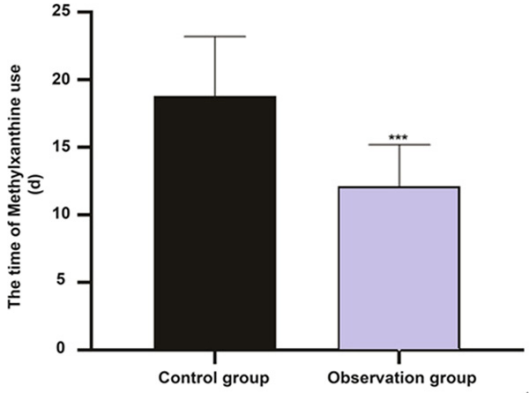

Figure 2. Comparison of time of methylxanthine use between two groups. Compared with control group, ***P < 0.001.

control groups, while there were 2 cases of tachycardia, 1 cases of hyperglycemia and 1 cases of gastrointestinal bleeding in observation group. The incidence rate of adverse reaction in observation group was significantly lower than that in control group (P = 0.002).

Discussion

In general, the mortality of low-weight preterm infants is higher than the normal infants [14]. It was reported that prematurity infants were subjected to various type of diseases after birth [15]. Apnea of prematurity is considered as one of the diseases with which preterm infants face [16]. It was shown that the incidence of apnea of prematurity was about 7% at gestational age less than 34 or 35 weeks and approximately 100% at gestational age less than 29 weeks [17]. Apnea of prematurity not only prolonged the time of hospitalization and raised health costs, but also had an influence on neurodevelopment, and even caused the mortality. So far, scholars have not reached a joint conclusion about the treatment of apnea of prematurity, and there were many controversies [18]. This study was performed to aim at providing guideline for prevention and treatment of apnea of prematurity.

Methylxanthines have been regarded as the major drugs for the treatment of preterm apnea via nasal continuous positive airway pressure (CPAP). But the dose, types, time and complications of application of these drugs have not been clearly understood. It was reported that methylxanthines use could prevent the attacks of apnea of prematurity [7]. The mechanism of action for methylxanthines included decreasing the depression of respiratory, increasing minute ventilation, improving the activity of bronchodilation and diaphragm, enhancing the sensitivity of detection of blood carbon dioxide and reducing periodic breathing [19, 20]. Caffeine citrate is one of methylxanthines drugs, which could easily pass through the blood brain barrier and enter the system of central nervous. At present, conflicting results on the comparison between caffeine citrate with other drugs for the treatment of preterm apnea have been reported. One study reported that for preterm ventilator patients, caffeine could lead to the failure of extubation. Some studies revealed that amionophylline and caffeine were equally effective for the treatment of apnea of prematurity infants [21]. Another study reported that prophylactic caffeine use could significantly prevent the preterm apnoeic attacks [22]. For early stages of prematurity infants less than 33 weeks, in contrast to theophylline, caffeine citrate was reported to be superior for treatment of apnea [23]. At present, the effect of caffeine citrate use in prevention and treatment of apnea of prematurity is still controversy. This study was an observational control trial in our hospital that was performed on prematurity infants with a weight between 1000 g and 1500 g and the gestational age of less than 32 weeks. The results showed that caffeine citrate use could obviously reduce the incidence of apnea in contrast

Table 4. Comparison of adverse drug reaction between two groups (Cases)

Groups	Tachycardia	Gastrointestinal bleeding	Retinopathy	Bronchopulmonary dysplasia	Hyperglycemia	Total incidence rate (%)
Control group	7	4	2	2	3	18
Observation group	2	1	0	0	1	4
χ^2 value						10.010
P value						0.002

to amionophylline, which indicated that caffeine citrate has more advantages over amionophylline in the treatment of apnea of prematurity. The similar results were reported by Skouroliakou et al. [24] and Steer et al. [25], and these researches were comparable with our study. Moreover, this study also revealed that the blood gas indexes such as $PaCO_2$, PaO_2 and SaO_2 in observation group were improved significantly in contrast to control group. And the success rate of ventilator weaning in observation group was higher than that in control group, while time of mechanical ventilation and time of methylxanthine use in observation group were less than those in control group, which also suggested the superiority of caffeine citrate over amionophylline during treatment process of preterm apnea. It was also indicated that the effect of caffeine citrate was more significant and caffeine citrate could significantly improve the low frequency fatigue of diaphragm, obviously promote recovery of prematurity infants, and reduce the time of drug use. These results were consistent with those reported by Zulqarnain et al. [26].

Previous study reported that methylxanthines had side effects and could adversely impact the brain development of prematurity infants by inhibiting adenosine receptors [24]. Lista et al. reported that there were 9.5% of patients with bronchopulmonary dysplasia, 2.3% of patients with tachycardia and 8.1% of patients with hepatic or renal functional impairment, which were manageable and prematurity infants were benefitted from caffeine citrate use for the treatment of apnea [27]. Zhao et al. reported that there were no significant differences in term of incidence of caffeine-associated adverse effects such as irritability, tachycardia, hyperglycemia, hypertension, difficulty in feeding, electrolyte disturbances and digestive disorders between low-dose caffeine group and high-dose caffeine group [28]. In this study, it was shown that the total incidence of adverse reaction including tachycardia, gastrointestinal bleeding, retinopathy, bronchopulmonary dysplasia, and hyperglycemia in observation group was lower than that in control group, suggesting that caffeine citrate was safer than amionophylline in the treatment of apnea of prematurity infants. These findings were similar to Henderson-Smart et al.'s results [29].

In conclusion, our research demonstrated that, compared with theophylline, caffeine citrate is more effective in for the treatment of apnea of prematurity in term of the incidence of apnea, arterial blood gases analysis, the success rate of ventilator weaning, time of mechanical ventilation, time of methylxanthine use and incidence of adverse reaction. The results of this study would help to confirm the recommendations to use caffeine citrate for apnea of prematurity. However, this study was limited by single-center research and small sample size. Attending physicians were not blinded. And the optimal use of caffeine citrate regarding the dose, duration and time of treatment should have been determined. Thus, further researches with multi-center, random control and larger sample sizes are necessary to explore the issues.

Disclosure of conflict of interest

None.

Address correspondence to: Shengxia Xiang, Department of Pediatrics, The No. 4 People's Hospital of Hengshui City, No. 485 Xinhua Road, Taocheng District, Hengshui 053000, Hebei Province, China. Tel: +86-0318-2176922; Fax: +86-0318-2176922; E-mail: xiangshengxia_9@163.com

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