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Original Research Article

Efficacy of caffeine citrate combined with mechanical ventilation in the treatment of apnea of prematurity and its influence on neurodevelopmental outcomes

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Abstract

Purpose: *To investigate the efficacy of caffeine citrate when combined with mechanical ventilation in the treatment of apnea of prematurity and its influence on neurodevelopmental outcomes.*
Methods: *One hundred and sixty (160) premature infants with apnea admitted in Guangdong Second Provincial General Hospital, Guangzhou, China were enrolled in this study, and divided into control and study groups. Children in the control group underwent mechanical ventilation combined with aminophylline therapy, while children in the study group were administered mechanical ventilation combined with caffeine citrate. Blood gas and pulmonary function indices, as well as clinical symptom and neurodevelopmental improvements were assessed. Also, the incidence of adverse reactions were recorded during treatment.*
Results: *Blood gas indices including oxygen partial pressure (PaO_2) and pulse oxygen saturation (SPO_2) levels in the study group were significantly higher, but partial pressure of carbon dioxide ($PaCO_2$) level was lower ($p < 0.05$); furthermore, tidal volume, respiratory rate and peak expiratory flow (PEF) in the study group were higher than in the control group ($p < 0.05$). On the other hand, the disappearance time of apnea, invasive mechanical ventilation time and oxygen inhalation time in the study group were shorter than in the control group ($p < 0.05$). Mental development index (MDI) and psychomotor development index (PDI) values in the study group were significantly higher than in the control group ($p < 0.05$), while the incidence of bronchopulmonary dysplasia, feeding intolerance, tachycardia and hyperglycemia in the study group was significantly lower than in the control group ($p < 0.05$).*
Conclusion: *The combination of caffeine citrate and mechanical ventilation aids improvement in the neurodevelopmental outcome of children, as well as reduction in the incidence of adverse reactions. However, further clinical trials are required prior to application of this strategy in clinical practice.*

Keywords: *Preterm infants, Apnea, Caffeine citrate, Mechanical ventilation therapy, Neurodevelopmental outcome*

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INTRODUCTION

Premature delivery is a common phenomenon in clinical practice [1]. In recent years, with the increase in factors such as advanced maternal age, multiparous status and multiple pregnancies, the birth rate of premature infants has also been on the increase. With the development of perinatal medicine and treatment techniques for severe neonatal disease, the survival rate of premature infants has also been greatly elevated. However, the short-term and long-term complications caused by premature birth cannot be ignored, seriously threatening the safety and intellectual development of premature children [2].

At present, there is no specific clinical treatment for premature infants with brain injury. Hence, with the increasing number of premature infants nowadays, it is particularly essential to know how to effectively treat premature infants with apnea, and reduce defects in cognitive and motor development in premature infants in order to improve their quality of life [3]. Currently, there are drug therapy and non-drug therapy in the clinical treatment for apnea of prematurity. The therapeutic drugs contain aminophylline, caffeine and other central respiratory stimulants. Non-drug treatment programs mainly include measures such as auxiliary ventilation, maintaining body temperature, and correcting anemia [4]. Previous studies have found that drug therapy and mechanical ventilation are the treatment regimens for the disease, and different degrees of therapeutic effects have been achieved [5].

In the past decade in China, aminophylline has been the first-line drug for the prevention and control of apnea of prematurity, while caffeine is the first-line drug abroad. Studies have confirmed that both drugs can effectively control the incidence of apnea of prematurity, but in terms of adverse reactions, the incidence of apnea of prematurity is low when treated with caffeine regimen [6]. With the marketing of caffeine in China, the therapeutic effect of caffeine has become a current research hotspot. The present study attempts to investigate the efficacy and safety of caffeine citrate or aminophylline, when combined with mechanical ventilation in treating apnea of prematurity.

METHODS

General patient profile

From preterm infants with apnea admitted to Guangdong Second Provincial General Hospital, Guangdong, China from January 2020 to June 2022, and those who met the study criteria were selected as study subjects.

Inclusion criteria

All premature infants hospitalized in neonatal intensive care unit (NICU) of the hospital with ① gestational age < 34 weeks; ② children who have primary apnea within 7 days after birth, and are in line with the diagnostic criteria for primary apnea [7]; ③ guardians of children who voluntarily signed informed consent for the study; ④ patients who have undergone mechanical ventilation treatment.

Exclusion criteria

(1) Patients with severe diseases such as congenital heart disease, intracranial hemorrhage, sepsis, respiratory tract infection, necrotizing enteritis, electrolyte imbalance and respiratory distress syndrome or apnea caused by severe diseases; (2) patients with severe system malformations, such as respiratory, digestive and nervous system malformations; (3) children with cerebral ischemia and hypoxic-ischemic encephalopathy; (4) guardians who are reluctant to sign informed consent or adverse outcomes in discharge cases.

A total of 160 children who met the research criteria were selected for the study, and they were divided into a control group and a study group via the random number table, with 80 children in each group. The general baseline data for all the subjects are shown in Table 1. All procedures performed in studies involving human participants were approved by the Ethics Committee of Guangdong Second Provincial General Hospital (approval no. 2023-KY-KZ-108-01), and complied with guidelines of the 1964 Helsinki Declaration and its later amendments for ethical research involving human subjects [8].

Treatments and procedures

After enrollment, most children were given general conventional treatment in the neonatal intensive care unit (NICU) ward, including warming, conventional nutritional support and fluid replacement therapy. Meanwhile, the vital signs and blood gas analysis of the children were monitored, and the control group was treated with mechanical ventilation (nasal continuous positive airway pressure) and aminophylline using conventional treatment.

Initial setting: Positive end expiratory pressure (PEEP): 4 - 6 cmH_2O (1 cm H_2O = 0.098 kPa),

Table 1: General baseline profile of the study participants (mean ± SD, n = 80)

Group	Male to female ratio	Mean gestational age (weeks)	Mean weight (g)	Mode of delivery	
				Spontaneous delivery	***Cesarean section***
Control	48/32	32.80±1.87	163.46±320.12	26	54
Study	41/39	32.27±1.57	1648.54±260.73	31	49
t/χ^2	1.241	1.95	0.327	0.681	
P-value	0.265	0.053	0.744	0.409	

P < 0.05 indicates that there was no statistically significant difference between groups

ventilation frequency 30 - 40 times /min, forced inspiratory oxygen (FiO_2): 0.21-0.5. Blood gas analysis was performed 10 min after each adjustment of PEEP and FiO_2 until PaO_2 was maintained at 8 - 9.33 kPa (60 ~ 70 mmHg) or pulse oxygen saturation was 95 - 97 %. Weaning was performed following the completion of treatment. Aminophylline treatment plan: the first dose is 5mg/kg, continuous intravenous infusion for 30 min, and the maintenance dose is 2.5mg/kg after 12 h, each time via slow intravenous injection at 12-h intervals.

The treatment regimen in the study group was nasal continuous positive airway pressure and caffeine citrate. Mechanical ventilation treatment was the same as in the control group. Caffeine citrate (Chiesi Farmaceutici SpA, H20181129, strength: 20 mg/1mL) was administered via intravenous injection. The first loading dosage was 20 mg/kg, and the injection time was controlled within 30 min. Children were administered 5 mg/kg dose every 24 h via continuous intravenous injection.

The rate of intravenous infusion was not too fast, and the time was set to 10 min. During the treatment, if the child had recurrent episodes of apnea, the maintenance dose was adjusted to 10 mg/kg. During the treatment period, if apnea occurred frequently in both groups, the treatment was changed to invasive ventilation. Caffeine citrate was discontinued 1 week after the apnea disappeared.

Evaluation of parameters/indices

Blood gas indices

Blood gas indices were statistically analyzed and compared before and after treatment, including partial pressure of oxygen (PaO_2), partial pressure of carbon dioxide ($PaCO_2$) and pulse oximetry oxygen saturation (SPO_2). The detection instrument was a blood gas analyzer, and the shuffled examination and results were provided by the clinical laboratory of the hospital.

Pulmonary function parameters

Lung function test was performed after drug withdrawal. Lung function meter was used to record the minute lung tidal volume (tidal volume = inspiratory time × air supply flow rate, the longer the inspiratory time, the greater the tidal volume), respiratory rate per minute, peak expiratory flow (PEF), PEF detection method, and the maximum flow value during the exhalation of children.

Improvement of clinical symptoms

Apnea disappearance time, mechanical ventilation time and oxygen therapy time in the two groups were statistically analyzed.

Neurodevelopment of the children

The neurodevelopment of the children was investigated and assessed using the Infant Mental Development Scale (CDCC) before and after treatment [9], including mental development index (MDI) and psychomotor development index (PDI). The former included 121 items and the latter included 61 items, which were measured before and after treatment. The specific evaluation criteria were as follows: *Excellent*: more than 120 points; *Intermediate and superior*: 110 - 119 points; *Moderate intelligence*: 90 - 109 points; *Lower middle intelligence*: 80 - 89 points; *critical state*: 70 - 79 points; *mental retardation*: < 69 points.

Incidence of adverse reactions

The adverse reactions in the two groups were recorded during treatment, including bronchopulmonary dysplasia, feeding intolerance, tachycardia and hyperglycemia.

Statistical analysis

All data in this study were processed and analyzed using SPSS 23.0 software. The Enumeration data are expressed as number of cases/percentages. The measurement data were checked for compliance with the normal distribution, and presented as sample means.

Independent sample t-test was used to determine statistically significant differences and $p < 0.05$ indicated that the difference was statistically significant.

RESULTS

Blood gas indices

The levels of blood gas indices in both groups are shown in Table 2. Before treatment, the levels of each of the blood gas indices in the two groups were not statistically significant (t = 0.776, 0.684, 0.135, p = 0.439, 0.495, 0.893). After treatment, PaO_2 and SPO_2 levels in the two groups increased, respectively, compared with pretreatment levels ($p < 0.05$). However, $PaCO_2$ levels in the two groups decreased after treatment ($p < 0.05$) but the decrease was more pronounced in the study group.

Pulmonary function indices

Compared with the control group, the tidal volume, respiratory rate and PEF in the study group were significantly higher than in the control group, and the differences were statistically significant ($p < 0.05$) as shown in Table 3.

Clinical symptoms

The level of improvement in clinical symptoms in the two groups is shown in Table 4. Compared with the control group, apnea disappearance time, invasive mechanical ventilation time and oxygen inhalation time in the study group were significantly shortened ($p < 0.05$).

Neurodevelopment

The neurodevelopment data for the children in the two groups are shown in Table 5. The MDI and PDI values of the two groups before treatment were similar (t = 1.622, 0.569, p = 0.107, 0.570). After treatment, the two values for the study group were significantly higher than for the control group ($p < 0.05$).

Incidence of adverse reactions

The adverse reactions in the two groups during the treatment are shown in Table 6. Compared with control group, the incidence of bronchopulmonary hypoplasia (3.75 vs 15.00 %), feeding intolerance (8.75 vs 32.50 %), tachycardia (12.50 vs 45.00 %) and hyperglycemia (15.00 vs 27.50 %) in the study group were substantially lower ($p < 0.05$).

Table 2: Comparison of blood gas indices (mean ± SD, n = 80)

Group		PaO_2 (mmHg)	$PaCO_2$ (mmHg)	SPO_2 (%)
Control	Pre-treatment	52.59±6.20	60.49±7.63	81.37±8.83
	Post-treatment	66.67±5.25	46.37±4.84	90.54±5.86
Study	Pre-treatment	51.81±6.53	59.72±6.72	81.18±8.96
	Post-treatment	72.44±6.75	42.86±4.46	95.55±3.78
t		6.040	4.770	6.417
P-value		0.000	0.000	0.000

Table 3: Comparison of pulmonary function indices (mean ± SD, n = 80)

Group	Tidal volume (mL)	Respiratory rate (beats/min)	PEF (L/min)
Control	7.20±0.85	40.22±4.30	30.37±1.10
Study	8.59±0.61	44.29±4.08	38.46±0.71
t	11.884	6.141	55.473
P-value	0.000	0.000	0.000

Table 4: Comparison of improvement in clinical symptoms (mean ± SD, n = 80)

Group	Apnea disappearance time	Invasive mechanical ventilation time	Oxygen therapy time
Control	6.97±1.53	10.29±1.99	17.67±2.58
Study	2.59±0.56	8.32±1.89	14.08±2.09
t	24.123	6.411	9.687
P-value	0.000	0.000	0.000

Table 5: Comparison of neurodevelopment (mean ± SD, n = 80)

Group	Time	MDI	PDI
Control	Pre-treatment	90.29±9.16	87.83±8.53
	Post-treatment	91.63±8.70	93.07±8.68
Study	Pre-treatment	87.99±8.68	87.05±8.75
	Post-treatment	101.35±9.35	104.95±9.39
t value		6.799	8.313
P-value		0.000	0.000

Table 6: Comparison of adverse reactions {n (%)}

Group	Case	Bronchopulmonary dysplasia	Feeding intolerance	Tachycardia	Hyperglycaemia
Control	80	12（15.00）	26（32.50）	36（45.00）	22（27.50）
Study	80	3（3.75）	7（8.75）	10（12.50）	12（15.00）
χ^2		5.959	13.782	20.625	3.735
P-value		0.015	0.000	0.000	0.053

DISCUSSION

There is no uniform conclusion on the etiology of apnea of prematurity and the intervention strategy. In recent years, it has been recognized that the occurrence of primary apnea may be related to the imperfect development of the respiratory center of the medulla oblongata in the brainstem, that is, an abnormal neuronal cell structure in the brainstem. It is reflected as less synaptic connections on nerve cells, dysmyelination, etc. The smaller the gestational age, the lighter the birth weight, and the higher the incidence of the disease [10].

Although there is no direct evidence that apnea in premature infants is associated with adverse outcomes of neurological development, studies have found that the occurrence of apnea in premature infants indeed gives rise to local hemodynamic abnormalities in the brain of children, which in turn aggravates neurological damage [11]. In certain relevant diagnosis and treatment guidelines in various countries, methylxanthines have been recommended as the main drugs for use in intervention attempts in apnea of prematurity, especially aminophylline and caffeine [12].

Metabolism studies on these types of drugs were conducted as early as in the 1980s. These studies found that the metabolic process of these drugs varies greatly according to the degree of development of the premature infants and adults [13]. Related studies also revealed that the metabolic processes are completely different between very low birth weight premature infants and adults. Caffeine citrate is a research focus in apnea studies. Studies have found that some children will still have recurrent apnea after caffeine treatment, which is needed to integrate with mechanical ventilation therapy or administered at an increased dose [14].

Caffeine is a psychoactive substance, and its use has different impacts on the central nervous, respiratory and cardiovascular systems, such as relieving fatigue, improving alertness as well as motor performance [15]. As shown in previous studies, caffeine increases the sensitivity of the respiratory center to carbon dioxide concentration and enhances nervous systems excitability by reducing the inhibitory effect of adenosine on respiration through the antagonization of A1 receptors in the brain [16]. Nonetheless, animal studies have indicated that caffeine citrate protected animal white matter injury model to a certain extent, through a mechanism that may be related to the inhibition of inflammatory emergency response and reduction of apoptosis [17].

In China, aminophylline is mainly used to treat apnea of prematurity, but in recent years, with advances in research, caffeine citrate has also been gradually applied in clinical treatment [18]. This study sought to compare the efficacy of aminophylline or caffeine citrate, when combined with mechanical ventilation, in the treatment of apnea of prematurity, and to evaluate the safety of the two regimens.

As demonstrated by the results of the present work, improvement of blood gas and pulmonary function-related indices in the study group treated with caffeine citrate was significantly better than in the control group. The results showed that both regimens were effective in the treatment of apnea of prematurity. However, caffeine citrate showed better efficacy, possibly because the use of caffeine citrate actively stimulated the respiratory system of children, achieved bronchiectasis, and increased ventilation, thereby promoting blood gas-related indices in children. The shorter apnea disappearance time, mechanical ventilation time

and oxygen inhalation time of the patients in the study group compared with control group, indicate the stronger therapeutic effect of caffeine citrate when combined with mechanical ventilation.

Both caffeine citrate and aminophylline are methylxanthines, and their mechanisms of action in apnea are similar. However, the findings suggest that caffeine citrate regimen had a faster onset of action, and this may be related to the higher lipid solubility of caffeine, rapid penetration into the cerebrospinal fluid, and a faster onset of action. In addition, the neurodevelopment of both groups was compared. The higher MDI and PDI values in the study group indicate that caffeine citrate combined with mechanical ventilation would better protect the brain tissue of premature infants with apnea as well as repair brain injury. This may be related to the faster recovery of respiratory function in the study group, with the result that adequate blood oxygen was then supplied to the brain.

The adverse reactions results in both groups during the treatment showed that the incidence of bronchopulmonary hypoplasia, feeding intolerance, tachycardia and hyperglycemia in the study group was significantly lower than in the control group. Thus, caffeine citrate combined with mechanical ventilation did not increase the incidence of adverse reactions.

CONCLUSION

Caffeine citrate/mechanical ventilation therapy improves blood gas indices and pulmonary function in premature infants with apnea, compared with aminophylline treatment. The combination therapy also produces greater improvement in clinical symptoms, as well as the development of the nervous system in children. However, its specific mechanism of action, as well as its effect on other relevant indicators of children requires further research.

DECLARATIONS

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Ethical approval

None provided.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them. Yingxian Liu and Yanpi Xie designed the study and carried them out; Yingxian Liu, Yanpi Xie, Chuming You and Qiong Meng supervised the data collection, analyzed and interpreted the data; Yingxian Liu, Yanpi Xie, Dongjun Liu and Zhenyu Liang prepared the manuscript for publication and reviewed the draft of the manuscript. All authors read and approved the manuscript.

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