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Aminophylline in combination with caffeine citrate in neurodevelopmental treatment and follow-up of high-risk preterm infants using GMs assessment

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Abstract: To explore the application effect of aminophylline combined with caffeine citrate and GMs in the evaluation of neurodevelopmental treatment and follow-up in high-risk preterm infants. A retrospective analysis of 66 high-risk preterm infants admitted to Hengshui People's Hospital from January 2020 to June 2021 was conducted. The children who received only conventional treatment were set as the control group, while those who received aminophylline and caffeine citrate on the basis of conventional treatment were set as the experimental group, 33 cases each group; GMs were used to evaluate the neurodevelopmental function of the children, and the treatment effect was analyzed. The normal proportion of GMs assessment results in the twisting phase and restless movement phase of the experimental group was superior to the control group ($P<0.05$); The proportion of children with normal neurodevelopment in the experimental group was significantly higher than that in the control group ($P<0.05$). Aminophylline in combination with caffeine citrate can help promote the neurodevelopment of children and improve their physical health using GMs assessment in the treatment and follow-up of high-risk preterm infants.

Keywords: Aminophylline, caffeine citrate, GMs assessment, neurodevelopment.

INTRODUCTION

With the achievements in modern obstetric technology and neonatal medicine, the survival rate of high-risk neonates sees an immense improvement in recent years (Zhang *et al*., 2020; Fughhi *et al*., 2017; Megaly *et al*., 2018). However, clinical statistics reveal that neonatal brain damage caused by factors such as premature birth, asphyxia, and low birth weight has been rising, which are the major contributors for disability in children. As a result, the treatment and follow-up of high-risk preterm infants are attached great attention (Khurana *et al*., 2017; Conte *et al*., 2017; Lin *et al*., 2019). Due to the incomplete development of various organ systems, preterm birth infants are susceptible to apnea after birth, or even develop into respiratory distress syndrome in case of infection, leading to transient hypoxia and underdevelopment of cranial nerves (Minner *et al*., 2018; Escalante *et al*., 2019; Axelrod *et al*., 2016). At present, caffeine citrate and aminophylline are the mainstay for treatment of apnea in high-risk preterm infants. Nevertheless, shortcomings such as incomplete evaluation of children's neurodevelopment and incomplete prognostic follow-up have been found in previous studies. Multiple studies at home and abroad argued that the quality of general movements (GMs) serves as a new practical tool to assess the neurodevelopmental status of high-risk infants. Also, it is used to identify early cerebral palsy during follow-up and has demonstrated guidance value for prognosis. In order to further investigate the neurodevelopmental outcome of high-risk preterm infants, Hengshui People's Hospital has implemented GMs during the treatment and follow-up to ensure the accuracy and consistency of the evaluation of the treatment effects. The report is as follows.

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MATERIALS AND METHODS

Inclusion criteria

(1) Patients who conformed to the clinical diagnostic criteria for high-risk preterm infants in *Practical Neonatology* (Beladiya *et al*., 2019); (2) Child and parturient who had complete clinical medical records; (3) Gestational age less than 37 weeks.

Exclusion criteria

(1) Patients with congenital nervous system dysfunction; (2) Patients with intracranial hemorrhage at birth; (3) Patients with congenital heart disease; (4) Patients with secondary apnea; (5) Patients with inherited metabolic disease.

Case screening

A total of 66 cases of high-risk preterm infants admitted to our hospital from January 2020 to June 2021 were selected for retrospective analysis. The children who received only conventional treatment were set as the control group, while those received aminophylline and caffeine citrate on the basis of conventional treatment were set as the experimental group, 33 cases each group;

there was no statistical difference in terms of the gestational age, gender, and mode of delivery (cistern birth/cesarean section) between the two groups; the study was carried out with the approval of the ethics committee of Hengshui People's Hospital (approval No.2019-23-34).

All children in the control group were taken care of by a responsible personnel after admitting to NICU and placed in an incubator to keep airways unobstructed. They were given timely oxygen inhalation, antibiotics, anti-infection, vitamin K1 and other conventional treatment measures and the heart rate, respiration and blood oxygen saturation were monitored dynamically. The clinical manifestations of children were observed, and appropriate treatment was provided in time (Koch *et al*., 2017; Schmidt *et al*., 2017; Boltia *et al*., 2020).

On this basis, the children in the experimental group additionally received intravenous infusion of aminophylline (2ml, Henan Runhong Pharmaceutical Co., Ltd., SFDA approval no. H41022266), 2-4mg/kg each time based on body weight, which was diluted with 5-25% glucose injection. At the same time, caffeine citrate (Alfa Wassermann SpA, Italy, SFDA approval no. H20130109) was intravenously administered at the first load of 20mg/kg, and maintained at a dose of $5mg \cdot kg^{-1} \cdot d^{-1}$ after 24h, once a day; all children were followed up for more than 6 months.

Observation indicators

The GMs assessment was used to evaluate the neurodevelopmental status of children, including the twisting phase, the restless movement phase and the follow-up phase (Higgins *et al*., 2020).

STATISTICAL ANALYSIS

All data analysis was done by software SPSS22.0. The counting and measurement data were expressed in the form of [n (%)] and ($x \pm s$), and analyzed using X^2 and t tests, respectively. A p-value of <0.05 was claimed as a statistical difference.

RESULTS

Assessment of GMs in the twisting phase

The normal proportion of GMs in the writhing stage of the experimental group was significantly higher than that of the control group ($p<0.05$). The proportion of suspicious and abnormal GMs in the experimental group was lower than that of the control group, but there was no difference between the groups ($p>0.05$), see table 1.

Assessment of GMs in the restless movement phase

The normal proportion of GMs assessment results of children in the experimental group during restless movement was remarkably higher than that of the control group ($p<0.05$). The proportions of suspicious and abnormal GMs assessment in the experimental group were lower than those of the control group, but the difference was not significant ($p>0.05$), see table 2.

Follow-up results

The follow-up time of the control group was (8.71±2.06) months, the experimental group was (8.64±2.11) months, the difference between the groups was not significant ($p>0.05$), and the proportion of children with normal neurodevelopment in the experimental group was evidently higher than that in the control group ($p<0.05$), and the proportion of neurodevelopmental deviation and retardation of the experimental group was lower than that of the control group, but the difference between the groups was not significant ($p>0.05$), see table 3.

DISCUSSION

Human brain development thrives from 3 months of embryo to 2 years after birth, and the last three months of embryo is considered a critical period for brain development, in which brain cell proliferation, increase of gray matter volume, dendritic axon branching, glial proliferation and differentiation, and myelination are involved (Lista *et al*., 2016). However, due to the premature birth, the embryonic primary matrix degeneration, cerebrovascular watershed adjustment and the above-mentioned brain development process are not completed in normal order (Puia-Dumitrescu *et al*., 2019). Worse yet is owing to the child's weak physique, underdeveloped body functions, the tolerance of brain cells to high-risk factors such as hypoxia, ischemia, infection is reduced, the sensitivity is increased, and the susceptibility to various injuries such as white matter softening is increased. All these hinder the normal regulation of neonatal neurodevelopment and give rise to sequelae such as mental retardation, language impairment, dyskinesia, autism and abnormal behavior (Haid *et al*., 2018; Marotta *et al*., 2020; Shivakumar *et al*., 2017; Aranda *et al*., 2016).

Aminophylline and caffeine citrate are commonly used drugs for the treatment of primary apnea in premature infants. FIRMAN BROOKE (Firman *et al*., 2019) and HAIWEI DONG (Dong *et al*., 2014) confirmed that caffeine citrate and aminophylline have a vital role in neurodevelopmental promotion for high-risk preterm infants and demonstrate a guiding value for the prognosis of high-risk preterm infants.

In the present study, the results showed that the normal proportion of GMs assessment results in the writhing phase and the restless movement phase of the experimental group was significantly higher than that of the control group. To our best understanding, children with normal GMs assessment during the writhing phase

Table 1: Assessment of GMs in children with twisting stage [n (%)]

Groups	N	Normal	Suspicious	Abnormal
Control group	33	9 (27.27)	18 (54.55)	6 (18.18)
Experimental group	33	16 (48.48)	15 (45.45)	2(6.06)
X^2		4.191	0.546	2.276
P		0.041	0.460	0.131

Table 2: Assessment of GMs in children with restless exercise stage [n (%)]

Groups	N	Normal	Suspicious	Abnormal
Control group	33	14(42.42)	14(42.42)	5(15.15)
Experimental group	33	23(69.70)	9(27.27)	1(3.03)
X^2		2.982	1.668	2.933
P		0.026	0.196	0.087

Table 3: Neurodevelopmental outcomes of children [n (%)]

Groups	Normal	Developmental deviation	developmental retardation
Control group	15(45.45)	13(39.39)	5(15.15)
Experimental group	23(69.07)	9(27.27)	1(3.03)
X^2	3.970	1.091	2.933
P	0.046	0.293	0.087

and restless movement phase are at fewer odds to develop cerebral palsy, and the prognosis is promising, whereas children with suspicious and abnormal GMs require effective interventions, and follow-up monitoring is needed. The results of this study also indicate that the combination of aminophylline and caffeine citrate promotes the neurodevelopment of high-risk preterm infants, and the outcome is outstanding. Aminophylline has the strongest relaxing effect on bronchial smooth muscle, and it can also expand the bronchi and increase the vital capacity, especially for the bronchus in spasticity. In addition, aminophylline also expands the coronary arteries, increases the blood supply of the myocardium, and strengthens the contractility of the heart. Caffeine citrate, with highly fat-soluble property, can quickly penetrate into the cerebrospinal fluid, and is easily tolerated by high-risk preterm infants. It is characterized by long half-life, a small range of plasma depth fluctuations, and high safety profile. In the current study, the proportion of children with normal neurodevelopment in the experimental group was significantly higher than that in the control group, and the proportion of neurodevelopmental deviation and retardation in the experimental group was lower than that in the control group, but the difference between the groups was not significant, indicating that the combination of aminophylline and citrate therapy yields a good prognosis for high-risk preterm infants, and the combination of GMs assessment is more conducive to the prognostic and neurodevelopmental status of children. However, the GMs assessment in the present study only targeted infants within 6 months of age. Therefore, longer follow-up are expected be combined with the comprehensive developmental quotient (DQ) examination in the future.

Altogether, aminophylline in combination with caffeine citrate can help promote the neurodevelopment of children and improve their physical health using GMs assessment in the treatment and follow-up of high-risk preterm infants.

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