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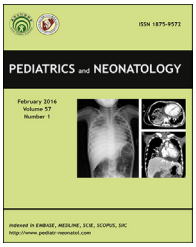

ORIGINAL ARTICLE

Neurodevelopmental Outcomes in Very Low Birth Weight Infants Using Aminophylline for the Treatment of Apnea

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aminophylline;
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neurological outcomes

Background: Aminophylline has been widely used in the treatment of apneic episodes in premature infants. Animal models suggest caution in the use of aminophylline as it may increase the cerebral metabolic rate and decrease the rate of anoxic survival in neonates. This study aimed to evaluate the neurological outcomes in very low birth weight (VLBW) infants treated with aminophylline for apnea in our neonatal intensive care unit.
Methods: All VLBW infants (body birth weight $<$ 1500 g) admitted to our neonatal intensive care unit between January 2000 and December 2011 were enrolled in this retrospective study. Clinical characteristics and outcomes of these infants were reviewed and recorded. Scores on the Bayley Scales of Infant Development at 6 months, 12 months, and 18 months of corrected age were also recorded. The controls (who did not receive aminophylline) were matched for gestational age with the aminophylline group.
Results: The baseline characteristics of the aminophylline group and the control group were similar. The neurodevelopmental outcomes as well as rates of patent ductus arteriosus, brain injury, severe retinopathy of prematurity, and necrotizing enterocolitis were not significantly different between the two groups. Only bronchopulmonary dysplasia remained significantly higher in the aminophylline group after adjusting for risk factors (48.08% vs. 21.15%; adjusted odds ratio: 12.50; $p < 0.001$).
Conclusion: Aminophylline therapy for apnea of prematurity had no apparent and additional risk on the neurodevelopmental outcomes of VLBW infants at a corrected age of 18 months.

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Further studies with a larger sample size are needed to confirm the adverse neurological effects of aminophylline treatment.

1. Introduction

Apnea is a common problem in preterm infants, probably due to prematurity or an associated illness. Apnea of prematurity (AOP) is found in 50% to 80% of preterm infants at < 30 weeks of gestation, with an even higher incidence in extremely low birth weight infants.[1,2] AOP is defined as breathing pauses that last for > 20 seconds or < 20 seconds accompanied with bradycardia or oxygen desaturation.[3,4] Such frequent hypoxic and bradycardic spells could lead to significant decrements in brain oxygen delivery during the critical phase of brain growth and development.[5,6] Treatment for AOP includes the application of nasal continuous positive airway pressure (NCPAP) and administration of methylxanthines, such as aminophylline, theophylline, and caffeine. Methylxanthines are inhibitors of adenosine receptors; adenosine has been shown to protect the brain from energy failure and cell death during experimental hypoxia and ischemia in animal models.[7–11] Animal models suggest caution in the use of methylxanthines because they could increase the cerebral metabolic rate and decrease the rate of anoxic survival in neonates.[8] Whether or not methylxanthines adversely affect the neurodevelopment of preterm infants is unknown.

At present, it appears that caffeine is the most effective methylxanthine for the treatment of AOP.[2,12] For instance, one large, randomized, controlled trial on the use of caffeine for AOP treatment found that caffeine decreases the rates of bronchopulmonary dysplasia (BPD).[13] In a subsequent study, the authors also successfully demonstrated that caffeine improved the rate of survival without neurodevelopmental disabilities.[14] However, data on the outcomes of aminophylline treatment for AOP are still scarce. Therefore, we conducted this retrospective study to evaluate the neurodevelopmental outcomes of aminophylline in very low birth weight (VLBW) infants treated for AOP in our neonatal intensive care unit (NICU).

2. Methods

2.1. Study design

This was a retrospective, observational study, which used data collected from inpatient and outpatient medical records.

2.2. Study participants

All VLBW infants (birth body weight < 1500 g) admitted to the NICU of Kaohsiung Medical University Hospital, Kaohsiung, Taiwan between January 2000 and December 2011 were enrolled in this retrospective study. Clinical characteristics and outcomes of the infants who received aminophylline for the treatment of apnea during hospitalization were reviewed and recorded. We defined AOP as breathing pauses that lasted for > 20 seconds or < 20 seconds accompanied with bradycardia (heart rate < 100 bpm) or oxygen desaturation. Treatment was started if an infant had five or more apneic attacks requiring intervention within 24 hours (including those in whom AOP and NCPAP had been applied). Methylxanthine administration was based upon the following standard regimen — an aminophylline loading dose of 5–8 mg/kg (administered intravenously over 30 minutes) and maintenance doses of 1.5–3 mg/kg every 8 hours to 12 hours that were administered either intravenously or enterally. The aminophylline dosage was adjusted to maintain a serum concentration of 5–12 mg/dL or when clinical toxicity (e.g., tachycardia, tachypnea, or jitteriness) was noted.[15] Therapy was continued until AOP regressed. The control group comprised infants who had AOP (< 5 apneic attacks within 24 hours or in whom AOP could be managed well with NCPAP or tactile stimulant) but did not receive aminophylline treatment. To minimize the influence of confounding factors between the infants with and without aminophylline, we matched the groups for gestational age and then compared the outcomes between them.

2.3. Assessment of neurodevelopmental outcomes

When the infants reached a corrected age of 6 months, 12 months, and 18 months, scores of the second version of the Bayley Scales of Infant Development (BSID-II) for mental and psychomotor development were evaluated.[16] The mental development index (MDI) and psychomotor developmental index (PDI) were used as scales of cognition and motor development, respectively. Neurodevelopmental impairment was defined as either an MDI or PDI score of < 70 (2 standard deviation below the mean of 100) on the BSID-II. Infants were excluded if they died prior to 18 months of corrected age or if their complete BSID-II data at 6 months, 12 months, and 18 months of age were unavailable.

2.4. Definition of neonatal variables

Patent ductus arteriosus (PDA) was defined by spontaneous closure or therapeutic injection of a prostaglandin inhibitor or surgical ligation. Cranial ultrasonography was performed after hospitalization. Brain injury was defined as the presence of one of the following: (1) Grade III or higher intraventricular hemorrhage (including subependymal and intraventricular, graded according to the classification of