

# Comparative observational study of aminophylline with prophylactic and therapeutic uses for clinical outcomes in preterm infants

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**Objectives:** Aminophylline has been used for prevention or treatment of apnea in preterm infants with idiopathic apnea of prematurity. The aim of this study was to assess the clinical usefulness of prophylactic in comparison with therapeutic aminophylline therapy.

**Methods:** This retrospective observational study included infants born with a birth weight of  $< 2,500$  g or at  $< 36$  weeks of gestation. Infants born between August 2013 and July 2014 who received aminophylline therapy within 24 hr after birth were assigned to the prophylactic group, while infants born between August 2014 and July 2015 who received aminophylline therapy after obvious apnea were assigned to the therapeutic group. We compared clinical characteristics, including days of ventilator and oxygen therapy and bronchopulmonary dysplasia (BPD) between both groups.

**Results:** Sixty-four patients and 25 infants were identified in the prophylactic and therapeutic groups, respectively. The mean gestational age and birth weight were  $32.57 \pm 1.96$  weeks and  $1765 \pm 205$  g, respectively, in the prophylactic group and  $32.46 \pm 1.82$  weeks and  $1770 \pm 250$  g, respectively, in the therapeutic group. No significant differences in clinical characteristics were found between the two groups. Similar clinical outcomes, including days of ventilator and oxygen therapy, intraventricular hemorrhage (IVH), periventricular leukomalacia, and BPD, were observed between the two groups.

**Conclusions:** The present study showed that the prophylactic use of aminophylline does not improve the clinical outcomes, including BPD, IVH, and ventilator dependency as compared with therapeutic use. In other words, routine prophylactic use of aminophylline is unnecessary.

**Key Words:** Aminophylline, Apnea, Preterm infants

Apnea, defined as cessation of breathing for longer than 20 sec or for any duration if accompanied by cyanosis and bradycardia, is a common problem in preterm infants.<sup>1,2</sup> Many potential causes of neo-

natal apnea and bradycardia have been identified. However, idiopathic apnea of prematurity occurs in the absence of an identifiable predisposing disease. Aminophylline has been used for pre-

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vention or treatment of apnea in preterm infants with idiopathic apnea of prematurity.<sup>3,4</sup> However, effectiveness of prophylactic aminophylline in preterm infants is controversial.<sup>5,6</sup> Armanian et al., who investigated the prophylactic effect of aminophylline on apnea in preterm infants, reported that prophylactic aminophylline was effective in reducing the apnea incidence in higher-risk neonates.<sup>7</sup> However, in their studies, no significant differences in clinical outcome of persistent ductus arteriosus, intraventricular hemorrhage, and necrotizing enterocolitis were observed between the prophylactic aminophylline and placebo groups.

We investigated the effectiveness of prophylactic aminophylline by comparing the clinical outcome with that of therapeutic aminophylline. In prophylactic use, aminophylline was used before apnea developed, while aminophylline was used after apnea developed in therapeutic use in this study. Therefore we focused clinical characteristics including days of ventilator and oxygen therapy and bronchopulmonary dysplasia (BPD) rather than whether apnea has occurred or not.

## MATERIALS AND METHODS

### Materials

In accordance with our previous policy, aminophylline was administered prophylactically to infants born before July 2014 in our neonatal intensive care unit within 24 hr after birth. After this period we have been prescribing aminophyl-

line only to infants who show obvious apnea. Apnea is defined as cessation of breathing for longer than 20 sec or for any duration if accompanied by cyanosis and bradycardia. Infants with major congenital anomalies, and other obvious problems resulting in apnea and death within 7 days of life were excluded. Apnea events were detected by attending physicians and nurses and documented using pulse oximetry monitors.

On the basis of a different policy of aminophylline administration, infants were divided according to prophylactic and therapeutic periods. Infants born with birth weights of < 2,500 g or at < 36 weeks of gestation were enrolled and assigned to two groups. Infants born between August 2013 and July 2014 who received aminophylline therapy within 24 hr after birth were assigned to the prophylactic group. Infants born between August 2014 and July 2015 who received aminophylline therapy after obvious apnea were assigned to the therapeutic group.

### Methods

Demographic characteristics including gestational age and weight at birth, and sex were examined in both groups. For comparison of the outcome of aminophylline administration between prophylactic and therapeutic uses, the following parameters were analyzed: respiratory distress syndrome (RDS); patent ductus arteriosus (PDA, defined as the need for ibuprofen medication or surgical ligation), the duration of ventilator and oxygen therapy, intraventricular hemorrhage

(IVH), periventricular leukomalacia (PVL), and BPD. Data were collected until death or discharge from the NICU.

### Standard protocol approval, registration, and patient consent

Ethical approval for this study was granted by the institutional review board of our hospital (1801-013-163). The requirement for informed consent was waived because this study was conducted retrospectively.

### Statistical analysis

Data were stored in a dedicated access database and verified for accuracy. Statistical analyses were performed with the SPSS 15.0 software by using raw scores. The analyses presented here focus on the comparisons between the two groups (prophylactic and therapeutic groups). Statistical

comparison of the continuous and categorical variables was tested by means of t-test and chi-square test as appropriate for the data. In addition to univariate non-parametric statistical tests, the results of the t-test and chi-square tests were confirmed with the Mann-Whitney test and the Fisher's exact test. A p-value  $< 0.05$  was regarded as statistically significant.

## RESULTS

Sixty-four patients and 25 infants were identified in the prophylactic and therapeutic groups respectively. Demographic findings showed no significant differences between the two groups. The mean gestational age was  $32.57 \pm 1.96$  weeks in the prophylactic group, and  $32.46 \pm 1.82$  weeks in the therapeutic group. The mean birth weights

Table 1. Demographic characteristics of both groups

characteristic	Prophylactic group (n = 64)	Therapeutic group (n = 25)	P-value
Gender			
male/female (n)	33/31	14/11	0.815
Gestational age (wks) (median, range)	$32.57 \pm 1.96$	$32.46 \pm 1.82$	0.739
Birth weight (g )	$1765 \pm 205$	$1770 \pm 250$	0.625
delivery mode			
cesarean section (n)	53 (82.8%)	18 (72 %)	0.257
Apgar score			
1 min	$5.1 \pm 1.0$	$5.2 \pm 1.3$	1.000
5 min	$6.7 \pm 1.0$	$7.1 \pm 1.5$	0.770
the day of start aminophylline (d)		$11.08 \pm 6.18$	
the duration of aminophylline (d)	$29.68 \pm 21.79$	$29.52 \pm 22.28$	0.979

were  $1765 \pm 205$  g and  $1770 \pm 250$  g, respectively. The median time to initiation of aminophylline therapy was  $11.08 \pm 6.18$  days in the therapeutic group (Table 1). The median duration of aminophylline therapy in the prophylactic and therapeutic groups were  $29.68 \pm 21.79$  and  $29.52 \pm 22.28$  days respectively ( $P = 0.979$ ).

The incidences of RDS and PDA were similar between the two groups. The durations of ventilator therapy in the prophylactic and therapeutic groups were  $31.47 \pm 36.48$  and  $17.93 \pm 23.65$  days respectively. The durations of oxygen therapy in the two groups were  $35.95 \pm 38.85$  and  $26.88 \pm 28.75$  days, respectively (Table 2). Although the therapeutic group seemed to have shorter durations of ventilator and oxygen therapies, the difference between the two groups was not statistically significant ( $P = 0.108$  and  $P =$

$0.302$ , respectively). The outcomes such as IVH, PVL, NEC and BPD were similar between the two groups, indicating no significant difference between the two groups. Although three infants died in prophylactic group, there was no statistic significance. All these infants had less than 1,000 g of birth weight and died because of late onset sepsis.

## DISCUSSION

Apnea can lead to hypoxemia and bradycardia, particularly at very early gestational ages in pre-term infants. Prolonged apnea presents clinical concerns about harmful effects on the development of the brain or dysfunction of the intestine and other organs. Bucher et al. reported that ap-

**Table 2. Clinical Outcomes of Both Groups**

Outcome	Prophylactic group (n = 64)	Therapeutic group (n = 25)	P-value
RDS (n)	24 (37.5 %)	13 (52 %)	0.339
PDA (n)	22 (34.4 %)	8 (32 %)	1.000†
the duration of ventilator (d)	$31.47 \pm 36.48$	$17.93 \pm 23.65$	0.108
the duration of oxygen (d)	$35.95 \pm 38.85$	$26.88 \pm 28.75$	0.302
IVH (n)	2 (3.1 %)	0 (0 %)	1.000†
NEC (n)	3 (4.7 %)	1 (4 %)	1.000†
PVL (n)	4 (6.3 %)	2 (8 %)	0.646†
BPD (n)	30 (46.8 %)	9 (36%)	0.619*
Death (n)	3 (4.7 %)	0 (0%)	0.556

Abbreviations: RDS, respiratory distress syndrome; PDA, patent ductus arteriosus; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; PVL, periventricular leukomalacia; BPD, bronchopulmonary dysplasia.

\* : Chi-square

† : Fisher exact test

nea and hypoxemia were associated with electroencephalographic abnormalities and maybe the causes of leukomalacia.<sup>5</sup>

Methylxantines are most commonly used medications in apnea of preterm infants for more than 40 years.<sup>8,9</sup> Although caffeine has now largely replaced aminophylline in western countries, aminophylline is mainly used in some countries including China.<sup>10</sup> And there are also controversies about efficacy of caffeine compared to aminophylline.<sup>11</sup>

In our NICU, infants born before July 2014 were given aminophylline prophylactically within 2 hr after birth. Recently, the effect of prophylactic use of aminophylline has been reported. Armanian et al. reported that prophylactic aminophylline was effective in reducing the apnea incidence in higher-risk neonates and that the median time of hospitalization was shorter in the aminophylline group than in the placebo group.<sup>7</sup>

However, several studies reported no evidence of the benefit of using methylxanthines in preventing apnea in preterm infants. Henderson-Smart et al. reported that caffeine had no prophylactic effect on apnea of preterm infants.<sup>12</sup> In addition, they reported that the results such as oxygen therapy period, amount of time needed for intubation, and incidence of chronic lung disease, cerebral palsy, major disabilities or death showed no significant differences between the prophylactic and placebo groups. Our NICU changed the policy of aminophylline administration from prophylactic use to therapeutic use, which means administration of aminophylline to infants showing

obvious apnea. Therefore, we compared the outcomes of the prophylactic and therapeutic uses of aminophylline in infants born during two periods with different aminophylline administration policies with birth weight of < 2,500 g or < 36 weeks of gestational age.

In our study, the mean gestational ages and birth weights were not significantly different between the prophylactic and therapeutic groups. Demographic findings also showed no significant differences between the two groups. Prophylactic use of aminophylline did not improve the clinical outcomes including RDS, BPD, NEC, IVH and ventilator dependency as compared with the therapeutic use. In other words, the prophylactic routine use of aminophylline is unnecessary because it brought no significant difference in clinical outcomes between the two groups.

This study has important limitations. One is due to retrospective observational study and small number of infants included. Another is that the two groups included came from different periods, which might have affected the clinical outcomes. However, the policy in the care of preterm infants except the administration of aminophylline underwent no significant change. And the most important limitation is that we could not compare the serum concentrations of aminophylline between both groups.

In conclusion, this study is in close agreement with the previous data of Henderson-Smart et al., which suggested that methylxanthine caused no clinical improvement in the outcome of apnea in

preterm infants.<sup>12</sup> In addition, therapeutic use of aminophylline might be adequate for infants who show obvious apnea. In our knowledge, this is the first study to compare the outcome of the prophylactic and therapeutic uses of aminophylline therapy in Korea. Further studies with adequate sample size and prospective studies are needed to investigate the effectiveness and clinical outcomes of the prophylactic and therapeutic uses of aminophylline.

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