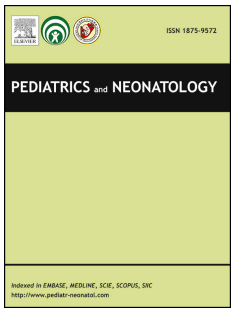

Effects of early aminophylline therapy on clinical outcomes in premature infants

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Abstract

Background

Aminophylline use and the association between clinical outcomes and therapy timing have been less investigated. The objective of this study was to determine the efficacy of early aminophylline use (within the first two days of life) in premature infants.

Method

A retrospective observational cohort of infants weighing <1500 g and <30 weeks of gestational age at Kaohsiung Veterans General Hospital received aminophylline either within the first two days of life (EA, early aminophylline group), after the third day of life (LA, late aminophylline group), or without aminophylline during the first month of life (WA, without aminophylline group). Demographic data and neonatal clinical outcomes were compared among the three groups.

Results

This study included 89 preterm infants (EA = 33, LA = 38, WA = 18). The EA group had a lower incidence of bronchopulmonary dysplasia (BPD) than the WA group (adjusted odds ratio [aOR] =8.86(1.56-59.32); P=0.024). Although there was no significant difference in BPD incidence between the EA and LA groups (aOR=2.66(0.51-13.81), P=0.244), a trend remained. Birth body weight less than 1000 g was also a significant risk factor for BPD (aOR=8.86(1.32–47.41), P=0.014). The duration of mechanical ventilation was shorter in the infants in the EA group compared to the WA group (estimated beta = -11.344(-19.57–-3.12); P=0.008).

Conclusion

Early aminophylline administration may be associated with a decreased incidence of BPD in preterm infants. However, the clinical benefits of aminophylline treatment require further investigation. In addition, a birth body weight of less than 1000 g was a crucial risk factor for BPD.

Keywords: apnea; bronchopulmonary dysplasia; prematurity; xanthines

Introduction

Apnea of prematurity is defined as an interruption of breathing for greater than 20 seconds, accompanied by hypoxia or bradycardia in neonates at less than 37 weeks of gestation.[1, 2] It is considered a developmental disorder in preterm infants that reflects the immaturity of respiratory control or the failure to maintain airway patency; however, the exact pathogenesis is not fully understood.[3] The incidence and severity of symptoms inversely correspond to gestational age and birth weight, and nearly all infants born at <29 weeks of gestation or <1000 g are affected.[1, 4] Episodes of apnea and bradycardia cease by 37 to 40 weeks of postmenstrual age (PMA) and may persist until 43 weeks of PMA in extremely premature infants.[5, 6] Although apnea of prematurity resolves with maturation, application of continuous positive airway pressure and pharmacologic treatments are widely used to reduce apneic events, which may interfere with cerebral hemodynamics and affect neurodevelopmental outcomes. Methylxanthine therapies, such as aminophylline, theophylline, and caffeine citrate, can stimulate the central nervous system and respiratory muscle function and have been the main pharmacological therapies for over 30 years.[7] Methylxanthines are competitive inhibitors of adenosine receptors and can excite respiratory neural output, increase ventilator response to carbon dioxide, enhance contraction of the diaphragm, decrease hypoxic inhibition of breathing, and decrease periodic breathing.[2, 8, 9]

The CAP trial,[10] which was randomized 2006 preterm infants with birth weights between 500 and 1250 g, reported that caffeine therapy was associated with a shorter duration of mechanical ventilation, a lower incidence of bronchopulmonary dysplasia (BPD), and a lower risk of patent ductus arteriosus (PDA) ligation. In addition, early caffeine administration (<3 days) compared with later (≥3 days) was related to the reduction of the mechanical ventilation time in a subsequent study of the CAP trial.[11] In two retrospective cohort studies, a lower incidence of BPD and a shorter duration of mechanical ventilation were observed in the group receiving early caffeine therapy.[12, 13] Caffeine citrate has been the preferred agent in recent years because it has a longer half-life, wider therapeutic margin, and lower frequency of adverse effects.[14-16] However, aminophylline still has clinical importance for treatment due to the cost of caffeine citrate and possible drug shortages, especially in developing

countries. Although caffeine and aminophylline have similar pharmacological mechanisms,[17] the benefits and efficacy of aminophylline have been less discussed and remain unclear. Therefore, we conducted a retrospective study to investigate the efficacy of early aminophylline administration in premature infants.

Methods

Study design and study participants

This was a retrospective observational cohort study of preterm infants admitted to the neonatal intensive care unit (NICU) at Kaohsiung Veterans General Hospital (KSVGH) between January 1, 2016 and September 31, 2020. The infants were eligible for inclusion in the study if they met the following criteria: (1) birth body weight <1500 g and gestational age <30 weeks, and (2) admission to our unit within 24 h after birth. Infants who died before the PMA of 36 weeks and those with major congenital anomalies were excluded. The study protocol was approved by the Institutional Review Board of KSVGH (IRB No. VGHKS21-CT6-05). All demographic information on the infants and their mothers was obtained from the KSVGH clinical database and medical records.

Data regarding the day of life (DOL) when aminophylline administration was initiated were also collected. The infants were categorized into three groups according to the starting date of aminophylline administration: early aminophylline (EA) group (0-2 days), late aminophylline (LA) group (≥3 days), and without aminophylline (WA) group (no aminophylline administered within DOL 30). Baseline demographics, clinical characteristics, and neonatal outcomes were compared among the three groups. Aminophylline therapy is usually initiated when episodes of apnea are recurrent (over 5 times in 24 hours), do not resolve spontaneously or with multiple tactile stimulations, are associated with bradycardia or hypoxemia (threshold of SpO2≤85 percent), or exclude other possible causes of apnea. All patients using aminophylline were administered 3 mg/kg/day, divided into two or three doses per day. A basic recruitment flowchart for this study is shown in Fig. 1.

BPD was defined as the requirement for supplemental oxygen or any respiratory support at a PMA of 36 weeks according to the Jensen 2019 definition.[18, 19] Other morbidities associated with prematurity, such as PDA, necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH), and retinopathy of prematurity (ROP), were also analyzed. NEC was defined as a modified Bell criteria stage IIa or higher.[20] The diagnosis of NEC was based on laboratory and radiographic findings of NEC or infants requiring either exploratory laparotomy or peritoneal drain placement for NEC. The presence of

intraventricular hemorrhage was evaluated using routine ultrasound imaging of the brain, interpreted by the attending neonatologist. ROP was diagnosed by an ophthalmologist via routine screening and was defined according to the international classification, including any stage of ROP with or without intervention.[21] Sepsis was defined as a positive blood culture and treatment with antibiotics during hospitalization.

Statistical analysis

All statistical analyses were performed using Statistical Analysis Software (SAS version 9.4; SAS System for Windows) and SPSS (version 20; SPSS Inc., Chicago, Illinois, USA). Comparisons among categorical variables were performed using the chi-square test or Fisher's exact test. All continuous variables are expressed as mean ± standard deviation (SD) and compared using a one-way analysis of variance. Clinical and demographic characteristics were significantly different among the three groups; thus, logistic and linear regression models controlling for variables were used to test the differences in the outcomes. Stepwise regression within the backward selection process started with a univariate analysis of the collected parameters to assess the influence of primary and secondary outcomes. Multivariate logistic regression analysis was used to examine the effect of significant outcomes from the univariate analysis of the three groups on the primary and secondary outcomes. Any variable with a significant univariate test with a p-value <.10 was selected as a candidate for the multivariate analysis. Some neonates only required continuous positive airway pressure (CPAP) and did not require intubation at birth but subsequently developed respiratory distress syndrome and required respiratory support within 2 days. Therefore, we included respiratory support on day two as an effect modifier in the model. Besides, PDA was associated with BPD development, so we added it as a factor for analysis.[22] The accuracy of the c-statistic was categorized as follows: 0.5, equal to chance; 0.7–0.8, acceptable; 0.8–0.9, excellent; and 0.9–1, outstanding. Two-sided 95% confidence intervals (CIs) and a p-value of less than 0.05 were considered statistically significant.

Results

During the study period, 193 very low birth weight (VLBW) infants (birth body weight <1500 g) were admitted to KSVGH's neonatal intensive care unit, and 89 preterm infants met the criteria for enrollment (birth weight = 999±260 g, gestational age = 26.9±1.8 weeks). Aminophylline was initiated less than three days after birth in 33 infants, over three days after birth in 38 infants, and not used in 18 infants. The baseline demographics and clinical characteristics of the infants and their mothers are summarized in Table 1. The mean birth weight (881±254 g), gestational age (26.2±2.0 weeks), and Apgar score were lower in the LA group. More infants in the LA group received intubation at birth and surfactant therapy. Respiratory support on day 2 in the three groups was described, including conventional mechanical ventilation (CMV), high-frequency oscillatory ventilation (HFOV), and CPAP, which showed a higher percentage of CPAP use in the EA group and more CMV use in the LA group. The duration of aminophylline use was 52.3±22.4 days in the EA group and 64.8±32.2 days in the LA group, which showed no significant differences between both groups (p=0.065). There were no significant differences in sex, sepsis during hospitalization, maternal age, preeclampsia, gestational diabetes mellitus, type of delivery, prenatal antibiotic administration, or use of antenatal steroids among the three groups.

The neonatal outcomes among the three groups are shown in Table 2. The primary outcomes were BPD, PDA, NEC, ROP, and IVH. The number of infants who developed BPD was significantly lower in the EA group (15%; p<0.005). The number of infants with ROP was also lower in the EA group (18%; p<0.005). The rates of PDA, NEC, and IVH did not differ significantly among the three groups. Secondary outcomes included duration of mechanical ventilation, noninvasive respiratory support, oxygen requirement, and length of stay. Infants receiving early aminophylline therapy had a significantly shorter duration of mechanical ventilation and lower oxygen requirements.

Due to the differences in baseline characteristics among the three groups, we adjusted the relative risk for confounding factors. The univariate logistic regression results indicated that the EA group had a lower incidence of BPD than the LA and WA groups (odds ratio [OR]= 4.48(1.18-16.95) and 6.92(2.20-21.77), P=0.027 and 0.001, respectively; Table 3). After multivariate logistic regression

analysis adjustment, the incidence of BPD was lower in the EA group than in the WA group (adjusted odds ratio [aOR]= 8.86(1.56–59.32), P=0.024), with no significant decrease compared to the LA group. Birth body weight <1000 g was an independent risk factor for BPD (OR= 6.75(2.49-18.28); P <0.001) and remained a major determinant after multivariate logistic regression analysis (aOR = 8.86(1.32-47.41); P=0.014). Respiratory support on day 2 was a significant factor for BPD. On day 2, HFOV use was a strong risk factor for BPD (aOR= 219.56(11.61–4152.87); P<0.001), and CMV use was a significant risk factor for BPD (aOR= 9.08(1.57-52.6); P=0.014) compared to CPAP use in multivariate analysis. Gestational age <28 weeks, use of surfactant therapy, and PDA were also risk factors related to BPD (OR= 4.75(1.54–14.63), 5.21(1.86–14.56), and 5.46(0.16-25.79); P=0.007, 0.002, and 0.032, respectively), but these factors became insignificant during the multivariate logistic regression analysis.

Regarding the incidence of ROP, the univariate linear regression results indicated that the number of infants receiving early aminophylline administration was lower than that in the late aminophylline administration group and the group without aminophylline use (OR= 4.50(1.25-16.17) and 4.50(1.51-13.38), P=0.021 and 0.007, respectively), but the three groups showed no significant difference after multivariate analysis. Other primary outcomes, including PDA, NEC, and IVH, showed no significant differences among the three groups after adjustment.

Among the secondary outcomes, the EA group had a significantly shorter duration of mechanical ventilation (estimated beta= -13.980(-23.69–-4.27); P=0.005) than the WA group according to the univariate linear regression analysis, and this remained significant in the multivariate linear regression analysis (estimated beta=-11.344(-19.57–-3.12); P=0.008; Table 4). In the univariate linear regression analysis, the other independent risk factors for increasing the duration of mechanical ventilation included gestational age <28 weeks (estimated beta= 21.037(14.50-27.57); P<0.001), birth body weight <1000 g (estimated beta= 21.669(15.26-28.08); P<0.001), intubation at birth (estimated beta= 16.320(9.24–23.40); P<0.001), and use of surfactant (estimated beta= 17.965(-10.86–25.07); P<0.001), but only gestational age <28 weeks remained significant after multivariate linear regression analysis (estimated beta= 8.901(0.56–17.24); P=0.037). The Apgar score at the first and fifth minutes

decreased the duration of mechanical ventilation in the univariate linear regression (estimated beta= -2.495(-4.59–-0.40) and -2.953(-5.53–-0.37); P=0.020 and 0.025, respectively), although it became insignificant in the multivariate linear regression analysis. Other secondary outcomes did not differ significantly among the three groups in univariate and multivariate linear regression analyses.

Discussion

To the best of our knowledge, this is the first study to explore the efficacy of early aminophylline administration within two days of life in preterm infants younger than 30 weeks of gestation. Our study revealed that early initiation of aminophylline therapy was associated with a reduced incidence of BPD, compared to the absence of aminophylline use in the first month of life. In addition, infants with early aminophylline administration had a shorter duration of mechanical ventilation than those who did not receive aminophylline in the first month of life.

Methylxanthines are widely used to treat premature apnea. Earlier trials and systematic reviews have shown the safety and efficacy of methylxanthines in the treatment of apnea, prophylaxis for infants at risk of apnea, and pre-extubation treatment.[17, 23-25] In recent years, caffeine has been an effective methylxanthine. Schmidt et al.[10] showed that caffeine therapy for apnea of prematurity could reduce the incidence of BPD, and Davis et al.[11] demonstrated that earlier initiation of caffeine therapy might be associated with a greater reduction in time on ventilation in a subgroup analysis of the CAP trial. A systematic review of 14 studies reported that early caffeine therapy can reduce the risk of BPD in cohort studies (RR= 0.80, 95% CI= 0.66 to 0.96) and randomized controlled trials (RR= 0.67, 95% CI= 0.56 to 0.81).[26] The time of initiation of early caffeine therapy varied, from the first two hours to three days postnatal.[26, 27] A few clinical reports explored the efficacy of aminophylline for BPD prevention or treatment. However, due to economic concerns, intravenous aminophylline is still widely administered in NICUs for apnea of prematurity in Taiwan. One randomized clinical trial found that premature infants with aminophylline use have a significantly lower incidence of BPD, possibly due to improvements in respiration and the mild diuretic effect of aminophylline.[28] He et al. hypothesized that theophylline may reduce the frequency of BPD by regulating the balance between pro-and anti-inflammatory cytokine expression.[29] Aminophylline is extensively metabolized in preterm infants, and caffeine is the major metabolic product by methylation.[9, 24] Thus, the pharmacologic effects of aminophylline may be similar to that of caffeine.

In our study, the infants in the EA group had less than half the incidence of BPD and ROP compared with the LA and WA groups. Infants in the EA group also had lower incidences of PDA and NEC.

Importantly, the incidence of BPD in the EA group remained significantly lower than in the WA group after adjustment for multivariate analysis. Although the EA group had a significantly lower incidence than the LA group, it might have a trend. In addition, body weight <1000 g and respiratory support on day 2 were independent risk factors for BPD. No significant differences were found in the primary outcomes for PDA, NEC, and IVH among the three groups. Owing to the lack of evidence regarding early aminophylline administration, we compared studies investigating early caffeine administration. Patel et al.[12] reported that infants receiving early caffeine therapy (<3 days) had a decreased incidence of BPD compared to infants receiving late caffeine initiation, with no significant differences in the incidence of NEC, ROP, and IVH. Taha et al.[13] also demonstrated that the early commencement of caffeine was associated with a reduction in BPD (36.1% vs. 46.7%). In a large, multicenter national cohort study, early (prophylactic) caffeine use possibly decreased the death rate and BPD and PDA rates in preterm neonates without severe adverse effects.[30] In our study, the incidence of BPD in the EA group was not statistically different from that in the LA group, but it still showed a decreasing trend. Compared to previous studies, the birth body weight was smaller in the LA group of our cohort.[12, 30] Most infants in the LA group (76%) weighed <1000 g compared to the EA group (34%) and the WA group (39%). Neonates in the LA group were also more likely to be ventilator-dependent, with a higher percentage of CMV and HFOV use on day 2. Since prematurity and low birth weight are the strongest predictors of BPD, lung immaturity could influence the results even after adjustments.[31] Our study also demonstrated that birth body weight <1000 g is an independent factor for BPD. In an Israeli national cohort, over 70% of infants with birth weights <1000 g developed BPD compared to 29.3% of those with birth weights around 1000-1500 g.[32] The type of respiratory support on day 2 was another important factor for BPD. This may represent the different severity of clinical conditions, so infants with CMV use had a higher risk of BPD, and infants with HFOV use had the highest risk compared with those with CPAP use. We included various clinical predictors for multivariate analysis adjustments, and the incidence of BPD was still significantly lower in the EA group than in the WA group, which had a similar distribution of body weight and gestational age. We believe that aminophylline still has the benefit of preventing BPD. Similar to caffeine, the reduction in BPD in the EA group may have contributed to earlier extubation, and anti-inflammatory and diuretic effects.[23]

However, Tey et al.[33] reported that the BPD rate was significantly higher in the aminophylline group (48.08% vs. 21.15%). They speculated that infants with severe apnea of prematurity might require longer CPAP support combined with aminophylline treatment. This is in contrast with our study and previous ones.[28] Tey's study enrolled preterm neonates with birth weights <1500 g, with a mean gestational age of 29 weeks and mean body weight of 1200 g.[33] We included infants with gestational age less than <30 weeks who were more likely to have apnea; the mean birth weight was 1000 g, smaller than Tey's study.[33] Besides, this study only matched the gestational age and did not adjust for other clinical factors, such as birth body weight, Apgar score, intubation or not at birth, antenatal steroid use, and surfactant use. The higher incidence of BPD in the aminophylline group may be due to more severe lung conditions that require more respiratory support.

On the other hand, the EA group had a lower incidence of ROP than the LA and WA groups in the univariate analysis, but there was no significant difference among the three groups. Similar to previous studies exploring the effect of early and late caffeine administration, there was no significant difference in the incidence of ROP.[12, 13] The CAP trial also reported no significant influence in ROP, whether caffeine was used or not.[10, 34] We analyzed the differences in the duration of respiratory support use in the three groups and found that the duration of mechanical ventilation was shorter in the EA group than in the WA group. Previous studies have pointed out that using caffeine earlier can result in fewer days on a ventilator than later use;[12, 30, 35] however, in our study, there was no statistically significant difference between the EA and LA groups, but it still had a decreasing trend. Neonates in the LA group appeared sicker initially and possibly needed longer ventilator support; however, compared with the WA group, they still had a shorter duration of mechanical ventilation.

The use of methylxanthines has been reported to be a risk factor for NEC,[36, 37] and early use of caffeine may increase the incidence of NEC.[13] However, a large retrospective cohort study revealed no increased risk of NEC with early caffeine administration.[30] Our results showed no significant difference among the three groups, perhaps because the dosage used in this study was relatively lower than the common dose (a loading dose of 5 mg/kg and a maintenance dose of 1.5 mg/kg every 8 hours).

The strength of our study is that few studies have investigated the association between clinical outcomes of aminophylline use in recent years, even though it is still used clinically. Our analyses were adjusted for all important clinical and significant variables in the univariate analysis. However, our study had several limitations. First, this was a single-center retrospective cohort study; therefore, it was difficult to clearly explain the indications for aminophylline use and how to determine the timing of initiation. The association between early aminophylline initiation and reduction in various neonatal morbidities may have been affected by treatment and selection bias. Second, the baseline characteristics of the groups were different. CPAP use on day 2 was significantly higher, and CMV use on day 2 was significantly lower in the EA group. This was a preexisting bias among the three groups, which might have affected the results. Even after using statistical models to adjust for the differences, we could not control all the factors that may reflect the severity of the disease or potentially affect the clinical outcome. Third, our sample size was relatively small, and we did not analyze the severity of the disease, such as different grades of IVH, or whether interventional treatments, such as medical or surgical treatment for PDA, were used. It was possible to limit the detection of clinically significant differences in the subgroup analysis. Owing to the above limitations, the evidence should be interpreted with caution. Nevertheless, we point out directions for future research.

In conclusion, our data indicate that early aminophylline administration may be associated with decreased BPD incidence in preterm infants. In addition to caffeine, aminophylline may also be an effective treatment for BPD. Other potential benefits of early aminophylline therapy include reduced duration of mechanical ventilation. Further studies, including large randomized multicenter prospective studies, are needed to confirm the protection of BPD against aminophylline and investigate the effect of early aminophylline use on neonatal outcomes and its long-term influence before suggesting routine early use of aminophylline in preterm infants.

Conflict of interest

The authors declare that they have no potential conflicts of interest.

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data processing

Data Availability Statement

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

Ethics approval

This study protocol was reviewed and approved by Institutional Review Board of Kaohsiung Veterans General Hospital, approval number [VGHKS21-CT6-05].

Contributors' statement

Yi-Ting Chu proposed the idea of the project, and conducted the literature review. All the authors contributed to the study design. Material preparation, data collection, and analysis were performed by Yi-Ting Chu, Chun-Hao Yin, Jin-Shuen Chen, Yao-Shen Chen, and Yee-Hsuan Chiou. The first draft of the manuscript was written by Yi-Ting Chu and all authors commented on previous versions of the manuscript. Jin-Shuen Chen, Yao-Shen Chen, Yee-

Hsuan Chiou, Chih-Chieh Yang and Hsiao-Ping Wang revised the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

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Table1. Baseline demographics and clinical characteri

Characteristics	Total n=89 (%)	Early Aminophylline (< 3 days) n=33 (%)	Late Aminophylline (≥ 3 days) n=38 (%)	Without Aminophylline n=18 (%)	p-value
Infants					
Gender- Male	50 (56%)	18 (55%)	19 (50%)	13 (72%)	0.285
Gestational age ,weeks (Mean±SD)	26.9±1.8	27.6±1.3	26.2±2.0	27.3±1.8	0.002
Birth body weight ,g (Mean±SD)	999±260	1087±235	881±254	1089±226	0.001
<1000 g	47(53%)	11(34%)	29(76%)	7(39%)	
1001-1499 g	42(47%)	22(66%)	9(24%)	11(61%)	
Singleton birth	59(67%)	26(79%)	21(56%)	12(67%)	0.112
Apgar score 1st min	5±2	5±2	4±2	5±2	0.022
Apgar score 5th min	7±2	7±1	6±1	7±1	0.035
Intubation at birth	44 (49%)	11 (33%)	24 (63%)	9 (50%)	0.043
Surfactant	54 (61%)	15 (46%)	30 (79%)	9 (50%)	0.009
Respiratory support on day 2					0.003
Conventional ventilation	47(53%)	10(30%)	26(68%)	11(61%)	
HFOV	8(9%)	3(9%)	5(13%)	0(0%)	
CPAP	34(38%)	20(61%)	7(19%)	7(39%)	
Sepsis during hospitalization	7(8%)	1(3%)	4(11%)	2(11%)	0.428
Duration of aminophylline, days (Mean±SD)	47.1±34.9	52.3±22.4	64.8±32.2	-	0.065
Mothers					
Age, years (Mean±SD)	33.4±5.3	34.0±4.8	33.5±5.2	31.8±5.5	0.362
Preeclampsia	19 (21%)	6 (18%)	10 (26%)	3 (17%)	0.609
Gestational diabetes mellitus	6 (7%)	2 (6%)	4 (11%)	0 (0%)	0.334
Antenatal steroid	79 (89%)	32 (97%)	33 (87%)	14 (79%)	0.103
Prenatal antibiotic use	55(62%)	19(58%)	24(67%)	12(67%)	0.795
Type of delivery					0.394
NSD	24 (27%)	7 (21%)	10 (26%)	7 (39%)	
C/S	65 (73%)	26 (79%)	28 (74%)	11 (61%)	

Data are presented as n (%). CPAP: continuous positive airway pressure; C/S: cesarean section; HFOV: high-frequency oscillatory ventilation; NSD: normal spontaneous delivery; SD: standard

deviation.

Table 3. Univariate and multivariate logistic regression analysis for primary outcomes in the study population , *n*=89.

Variables	Bronchopulmonary dysplasia				Retinopathy of prematurity			
	Univariate		Multivariate		Univariate		Multivariate	
	OR (95%CI)	p value	aOR (95%CI)	p value	OR (95%CI)	p value	aOR (95%CI)	p value
Gestational age < 28 weeks	4.52(1.74–11.77)	0.002			4.52 (1.74-11.77)	0.002		
Birth body weight < 1000 g	6.75(2.49-18.28)	<0.001	8.86 (1.32–47.41)	0.014	5.26 (2.01-13.76)	0.001	2.52 (0.71–8.97)	0.155
Aminophylline								
< 3 days	1		1		1		1	
≥ 3 days	4.48 (1.18-16.95)	0.027	2.66 (0.51–13.81)	0.244	4.50 (1.25-16.17)	0.021	1.52 (0.40–5.80)	0.540
Without	6.92 (2.20-21.77)	0.001	8.86 (1.56–59.32)	0.024	4.50 (1.51-13.38)	0.007	3.81 (0.77–18.86)	0.101
Apgar score 1st min					0.70 (0.54-0.91)	0.007		
Apgar score 5th min					0.67 (0.49-0.92)	0.012		
Intubation at birth					5.26 (2.05-13.52)	0.001		
Surfactant	5.21(1.86–14.56)	0.002			6.96 (3.00-31.26)	<0.001		
Respiratory support on day 2								
CPAP	1		1		1		1	
Conventional ventilation	18.18 (3.90-84.74)	<0.001	9.08 (1.57-52.6)	0.014	25.78 (5.50-120.83)	<0.001	16.61 (3.19-86.49)	0.014
HFOV	112.00 (8.87–1414.34)	<0.001	219.56 (11.61–4152.87)	<0.001	9.60 (1.27–72.53)	0.028	9.60 (1.11–82.56)	0.040
PDA	5.46 (0.1.16–25.79)	0.032						
Mothers								
Preeclampsia	0.31 (0.80–1.19)	0.089						
c-statistic			0.888 (0.82-0.95)	<0.001			0.786 (0.69-0.88)	<0.001
Hosmer-Lemeshow test			χ^2=3.607	0.730			χ^2=2.128	0.908

The OR is adjusted for all of the characteristics of infants and mothers mentioned in Table 1.

aOR: adjusted odds ratio; CI: confident interval; CPAP: continuous positive airway pressure; HFOV: high-frequency oscillatory ventilation; OR: odds ratio; PDA: patent ductus arteriosus

Table 2. Neonatal outcomes in the study population.

Variable	Total n=89 (%)	Early Aminophylline (<3days) n=33 (%)	Late Aminophylline (≥3days) n=38 (%)	Without Aminophylline n=18 (%)	p-value
Primary outcomes					
BPD	34 (38%)	5 (15%)	21 (55%)	8 (44%)	0.014
PDA	73 (82%)	25 (76%)	30 (79%)	18 (100%)	0.079
PDA, No./No. (%)					
Medical treatment	59/73(80%)	22/25(88%)	25/30(83%)	12/18(67%)	0.996
Surgical ligation	8/73(11%)	1/25(4%)	5/30(17%)	2/18(11%)	0.311
NEC(≥stage IIa)	4(4%)	0(0%)	4(11%)	0(0%)	0.06
ROP	34 (38%)	6 (18%)	19 (50%)	9 (50%)	0.012
Mild to moderate	9(10%)	2(6%)	4(10%)	3(16%)	0.477
Severe(≥stage 3)	25(28%)	4(12%)	15(40%)	6(34%)	0.033
IVH	11 (12%)	2 (6%)	6 (15%)	3(16%)	0.381
Mild to moderate	8(9%)	2(6%)	4(10%)	2(11%)	0.71
Severe(≥grade 3)	3(3%)	0(0%)	2(5%)	1(5%)	0.42
Secondary outcomes					
Duration of mechanical ventilation, days (Mean±SD)	17±19	6±11	25±20	20±18	<0.001
Duration of noninvasive respiratory support, days (Mean±SD)	30±14	28±16	32±13	27±12	0.372
Duration of oxygen requirement, days (Mean±SD)	58±32	43±27	73±31	53±27	0.004
Length of stay, days (Mean±SD)	82±26	73±22	92±28	76±20	0.306

Data are presented as n (%).

BPD: bronchopulmonary dysplasia; IVH: intraventricular hemorrhage; NEC: necrotizing enterocolitis; PDA: patent ductus arteriosus; ROP: retinopathy of prematurity; SD: standard deviation

Table 4. Univariate and multivariate linear regression analysis for the duration of mechanical ventilation in the study population , *n*=89.

Variables	Duration of mechanical ventilation					
	Univariate			Multivariate		
	Estimated beta	(95%CI)	p value	Estimated beta	(95%CI)	p value
Gestational age < 28 weeks	21.037	(14.50-27.57)	<0.001	8.901	(0.56–17.24)	0.037
Birth body weight < 1000 g	21.669	(15.26-28.08)	<0.001	6.859	(1.59–15.31)	0.110
Aminophylline						
< 3 days	-13.980	(-23.69–-4.27)	0.005	-11.344	(-19.57–-3.12)	0.008
≥ 3 days	-4.962	(-4.52–14.45)	0.301	-2.690	(-11.25–5.87)	0.533
Without		1			1	
Respiratory support on day 2						
CPAP		1			1	
Conventional ventilation	-9.104	(-20.55–2.35)	0.118	-2.575	(-12.72–7.57)	0.615
HFOV	-23.567	(-30.31–-16.83)	<0.001	-8.929	(-18.45–0.59)	0.066
Apgar score 1st min	-2.495	(-4.59–-0.40)	0.020	0.606	(-2.66–3.89)	0.714
Apgar score 5th min	-2.953	(-5.53–-0.37)	0.025	-0.979	(-4.79–2.83)	0.610
Intubation at birth	16.320	(9.24–23.40)	<0.001	3.730	(-2.96–10.42)	0.270
Surfactant	17.965	(10.86–25.07)	<0.001	1.852	(-8.27–11.97)	0.716
Mothers						
gestational diabetes mellitus	-13.930	(-29.37–1.51)	0.076	-3.716	(-15.64–8.16)	0.535

The estimated beta is adjusted for all of the characteristics of infant and mother mentioned in Table 1.

aOR: adjusted odds ratio; CI: confident interval; CPAP: continuous positive airway pressure; HFOV: high-frequency oscillatory ventilation

Figure 1. Flow Diagram of the Study Cohort