Reducing the Incidence of Chronic Lung Disease in Very Premature Infants with Aminophylline

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ABSTRACT

Background: The objective of this study is to assess the safety and preventative effects of aminophylline on the incidence of chronic lung disease (CLD) in very premature infants.

Methods: This was a long follow-up randomized clinical trial. The prophylactic effect of aminophylline on the incidence of CLD was investigated in very premature infants. The study group received aminophylline for the 1st 10 days of life and control infants received no aminophylline during the 1st 10 days of life.

Results: Fifty-two infants participated (26 aminophylline, 26 controls). Premature infants on aminophylline had clearly shorter oxygen dependency time than those in the control group. Median time of oxygen dependency was 3 (0-9.5) days and 14 (3-40.5) days in group A and C, respectively (*P*: 0.001). Incidence of CLD was significantly different between the two groups. Only two infants (8.7%) on aminophylline developed CLD, when compared to 11 infants (44.0%), who did not receive aminophylline (*P*: 0.006). No side-effects were reported in the neonates (*P*: 1).

Conclusions: This study supports the preventative effects of aminophylline on the incidence of CLD in very premature infants. In other words, the more premature the infants, the greater will be the preventative effect of aminophylline on the incidence of CLD.

Keywords: Aminophylline, chronic lung disease, preterm neonates, prevention

Original Article

INTRODUCTION

Premature parturitions are those which happen at <37 weeks gestational (post-menstrual) age.[1] Due to the greatly improved methods of treating premature babies, more premature babies survive, particularly, extremely immature neonates.[2,3] Furthermore improvements in neonatal management reduce the mortality and morbidity of surviving premature infants.[1,4] Similarly, enhancement in assisted ventilation strategies, antenatal corticosteroids usage and postnatal surfactant administration has resulted in improved

outcomes for extremely premature infants.[5] Many efforts have been made to reduce damage and invasive procedures; even studies have been carried out to improve management and harm reduction with measurements of bilirubin through the skin (without phlebotomy).[6]

Occurrence of premature birth continues to rise; for example, in the USA the premature parturition rate is 12-13%.[7-9] Chronic lung disease (CLD) or bronchopulmonary dysplasia (BPD) happens in premature neonates with respiratory distress syndrome (RDS) who require respiratory support in the 1st days after birth.[2] However, as a result of the improved survival of extremely immature neonates the importance of CLD in the surviving neonatal populations increased.[2,10]

Aside from prematurity, factors such as assisted ventilation methods/oxygen therapy, intrauterine/postnatal infections, patent ductus arteriosus (PDA) and genetic basis is added into its multi-factorial and complex pathogenesis.[11-13] These factors usually are interrelated to lung inflammation and an arrest of pulmonary development.[14-16]

It seems that reducing the incidence of CLD will need a comprehensive multipurpose approach focusing on various aspects of the path that leads to CLD.[11]

Prematurity is the main risk factor in the development of CLD.[17,18] Langston *et al*. found that the saccular stage of lung development occurs between 23 and 32 weeks of gestation.[19] At this stage, due to poor lung-supporting structures, underdeveloped compliance, incompleted antioxidant system, fluid accumulation and surfactant deficiency, the lung seems to be most at risk to injury. Therefore, a very high risk of lung damage exists if birth takes place within this stage of lung development.[19] Then incidence of CLD in infants with RDS increases with a decrease of gestational age.[1] Accordingly the various incidences of CLD were found in different studies; it is found in 30% of infants with birth weight <1000 g,[20] 23% of infants <1500 g in a US study[21] and 26% of infants in a Canadian study.[22] Incidences of CLD may increase 2-3 times for each week of reduction in gestation.[23] Currently, it is estimated that 97% of CLD cases occur among preterm infants with birth weights of <1250 g.[24] Furthermore, growth retardation may have a considerable result on the susceptibility to lung damage.[25,26]

CLD, usually described as neonates being oxygen-dependent for at least 28 days after birth,[21] is a common unfavorable outcome of immature birth.[27]

Greenough and Ahmed proposed that "in the past, CLD/BPD developed after severe respiratory failure, usually associated by the PDA, pulmonary interstitial emphysema and/or infection, necessitating high-pressure ventilation and supplementary oxygen concentrations but new BPD, occurs in extremely premature infants who initially had minimal or even no signs of lung disease."[27,28]

CLD results in serious morbidity despite the decline in mortality rates among VLBW neonates.[3] CLD in premature neonates is presently a significant cause of mortality and long-term morbidity, such as recurrent pneumonia, growth retardation, decreased pulmonary function and poorer neurodevelopmental outcome.[21,29-31]

Based on what was described above, any attempt to reduce the incidence of CLD must be considered as an important and valuable work.[27] Surely prevention of premature birth is the best way to reduce the incidence of CLD. Nevertheless, the preventative effectiveness of different approaches have been investigated.[27]

Prenatal administration of corticosteroids, thyroid-releasing hormone and antioxidants has not been demonstrated to reduce BPD in clinical randomized trials.[32-34] Roberts and Dalziel analyzed the results of 21 randomized controlled trials (RCTs), in which Corticosteroids were given antenatally. They found reductions in incidence of RDS, intraventricular hemorrhage, necrotizing enterocolitis and death, however, no reduction in the incidence of CLD were reported.[32]

Furthermore, effectiveness of different postnatal approaches have been investigated such as assisted ventilation strategies modifications, administration of cromolyn sodium, thyroxine, antioxidants, macrolides, corticosteroids, inositol, surfactant, vitamin A, methylxanthines and estradiol/progesterone replacement.[27]

Schmidt *et al*. in a large RCT found that caffeine has a significant effect in reduction of BPD. Also, caffeine was associated with a reduction in cerebral palsy.[35,36]

Given the importance of the prevention of CLD in preterm neonates, the researcher(s) decided to

study the prophylactic effects of aminophylline on the incidence of CLD in high risk premature neonates (preterm neonate with a weight below 1200 g).

METHODS

Study design and participants

The present study was a long follow-up randomized clinical trial (RCT). Neonates admitted to the neonatal intensive care unit at Alzahra and Shahid Beheshti Hospitals in Isfahan-Iran, between March 2012 and April 2013 were included in this study. The prophylactic effect of aminophylline on the incidence of CLD was investigated in two groups of aminophylline (group A) and control (group C).

Inclusion criteria were infants being born premature and at-birth weight of equal and lower than 1200 g. Infants who had major congenital anomalies, asphyxia, occurrence of apnea and need for mechanical ventilation in the first 24 h of birth, congenital cyanotic heart disease, small for gestational age-intrauterine growth and sepsis in the 1st 10 days of birth were excluded. The infants in the study were randomly assigned to aminophylline (group A) and no aminophylline (group C), as described below. In order to select the neonates, randomly, those with an even digit at the end of their file numbers were placed in group A and neonates with their file numbers ending in an odd digit were assigned to group C.

Experimental procedure

In the aminophylline group (A), after considering the inclusion and exclusion criteria for the premature neonate with a weight equal and lower than 1200 g, 5 mg/kg of aminophylline, as a loading dose, was begun (parenteral) then each 8 h, 1/5 mg/kg, as a maintenance dose, was administered for the 1st 10 days of life.

However, in the control group (C), after considering the inclusion and exclusion criteria for the premature neonate with a weight equal and lower than 1200 g, no aminophylline was given in 1st 10 days of life.

The primary and secondary outcomes of the study in both groups were the duration of dependency on oxygen and the effect of preventative aminophylline on incidence of CLD respectively, with a long follow-up. Decisions regarding CLD were made uniformly in both groups. In short, Neonates were considered as having CLD/BPD if they had been oxygen dependent for at least 28 days after birth and the severity of CLD was judged according to the Table 1.[21] Aminophylline side-effects (tachycardia, hypertension) and also mortality for each neonate were recorded daily as other secondary outcomes.

Written informed consents were obtained from parents before the study, with approval of the protocol by the ethical committee of our university.

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The results were compared using the Chi-square, independent *t*-test and Mann-Whitney and Fisher's exact test. The data was analyzed with Statistical Package for the Social Sciences (SPSS) ver. 20.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

In our study, 52 neonates were randomized and completed the study [Figure 1] and the results were analyzed with the intention to promote treatment and health of premature neonates. Demographic characteristics were similar between the two groups [Table 2].

The primary outcome was clearly different between the two groups. Infants who had been placed in the aminophylline group (group A) had clearly shorter oxygen dependency time than the infants in the control group (group C). Median time of oxygen dependency in group A was 3 (0-9.5) days and in group C 14 (3-40.5) days [*P*: 0.001; Table 3]. Duration of oxygen dependency ranged from 0-30 days to 0-82 days in group A and C, respectively.

Average gestational ages in group A were 29.89 ± 1.93 and in group C, 28.59 ± 2.06. Average birth weights in group A were 1071.54 ± 117.56 g and in group C, 1007.69 ± 134.02, which means average gestational ages and birth weights were similar between the two groups [*P*: 0.10, *P*: 0.07, respectively; Table 2]. No side-effects were reported in neonates in both groups (*P*: 1). One and three neonates died in group C and A respectively [*P*: 0.31; Table 3].

Incidence of CLD was significantly different between the two groups. Only two infants (8.7%), who had been placed in aminophylline

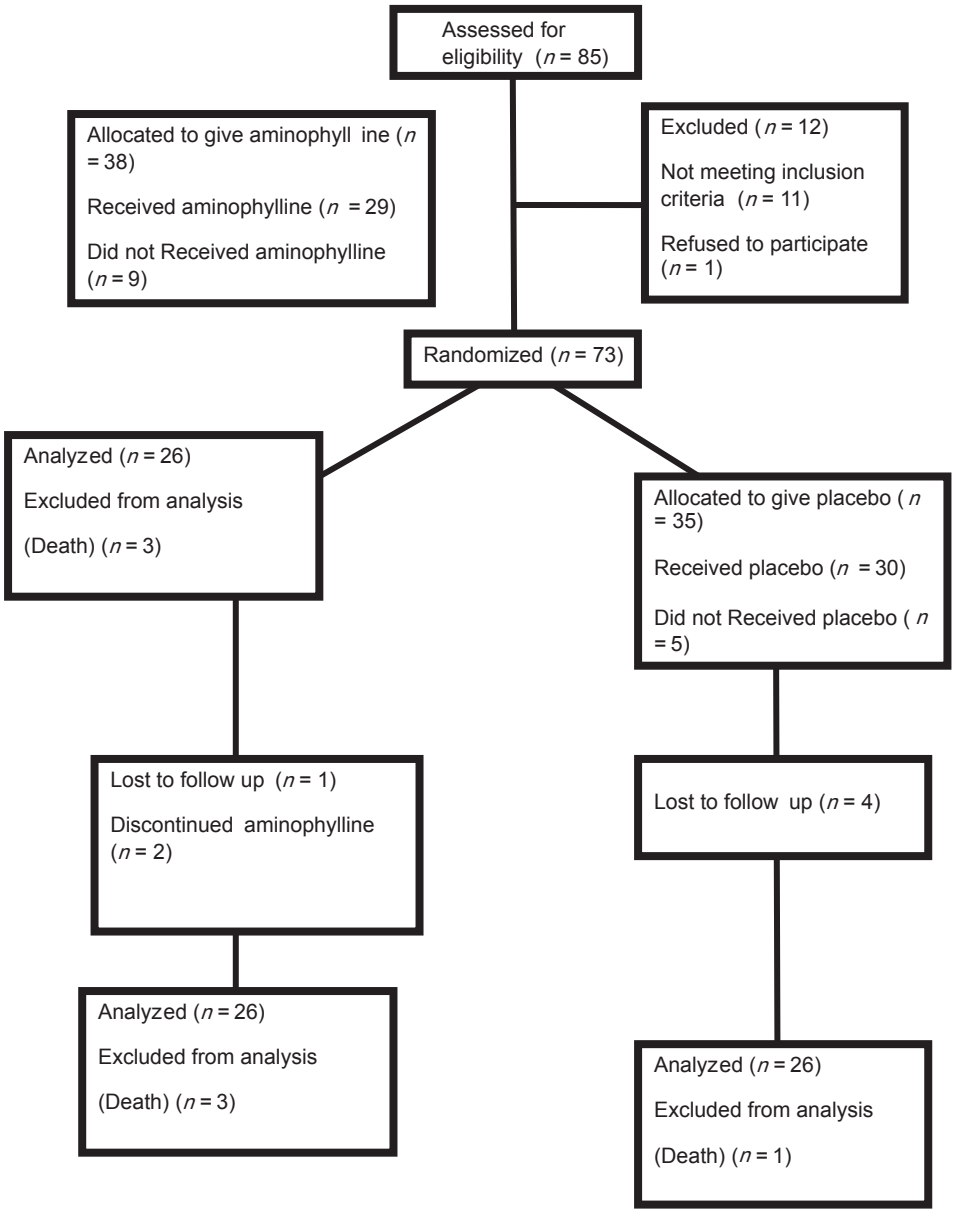

Figure 1: CONSORT diagram showing the flow of samples through each stage of study

group developed CLD, when compared to 11 infants (44.0%) who had not received aminophylline [*P*: 0.006; Table 3].

Birth weights of those infants who developed CLD in group C (not receiving aminophylline) ranged from 600 to 1150 g (average birth weights: 941.81 g) and gestational ages ranged from 25 to 30 weeks (average gestational ages: 27.18 weeks). Except one neonate who developed moderate CLD in group C, others developed mild CLD at 36 weeks' postmenstrual age (PMA) in both groups. Characteristics of infants who developed CLD are shown in Table 4.

DISCUSSION

In this study, prophylactic aminophylline was effective in the reduction of CLD incidence in very premature neonates (preterm neonate with a weight below 1200 g).

The effectiveness of different postnatal drugs in preventing the occurrence of CLD have been investigated in some clinical trials. In a review article Greenough and Ahmed[27] proposed that although using surfactant in infants with RDS has been associated with many benefits, but it had no effect on the incidence of CLD "possibly because

Table 1: Definition of bronchopulmonary dysplasia: Diagnostic criteria

Assessment	Gestational age	
	<32 weeks	**≥32 weeks**
Time point of assessment	36 weeks PMA or discharge to home, whichever comes first	>28 days but <56 days postnatal age or discharge to home, whichever comes first
	Treatment with oxygen>21% for at least 28 days plus	
Mild BPD/CLD	Breathing room air at 36 weeks PMA or discharge, whichever comes first	Breathing room air by 56 days postnatal age or discharge, whichever comes first
Moderate BPD/CLD	Need for <30% oxygen at 36 weeks PMA or discharge, whichever comes first	Need for <30% oxygen at 56 days postnatal age or discharge, whichever comes first
Severe BPD/CLD	Need for ≥30% oxygen or positive pressure (PPV or NCPAP), or both, at 36 weeks PMA or discharge, whichever comes first	Need for ≥30% oxygen or positive pressure (PPV or NCPAP), or both, at 56 days postnatal age or discharge, whichever comes first

From Jobe AH, Bancalari E: Bronchopulmonary dysplasia. Am J Respir Crit Care Med 163:1723, 2001. BPD=Bronchopulmonary dysplasia, NCPAP=Nasal continuous positive airway pressure, PMA=Postmenstrual age, PPV=Positive pressure ventilation, CLD=Chronic lung disease

Table 2: Characteristics of study infants

Characteristic	Aminophylline group	Control group	*P*
Gender			
Male (number [%])	13 (50.00)	11 (42.3)	0.58*
Female (number [%])	13 (50.00)	15 (57.7)	
Birth weight (g) (mean [SD])	1071.54± (117.56)	1007.69± (134.02)	0.07†
Gestational age (week) (mean [SD])	29.89± (1.93)	28.59± (2.06)	0.10†

*Chi-square tests, †Independent *t* test. SD=Standard deviation

Table 3: Primary and secondary outcomes in our study

Outcome	Aminophylline group (A)	Control group (C)	*P* value
n	26	26	-
Oxygen dependency time (days, median [IQR])	3 (0-9.5)	14 (3-40.5)	0.001*
CLD (%)	2 (8.7)	11 (44.0)	0.006‡
Side effects (%)	0 (0)	0 (0)	1
Death (%)	3 (11.5)	1 (3.8)	0.31†

*Mann-Whitney test, ‡Chi-square, †Fisher's exact test. IQR=Interquartile range, CLD=Chronic lung disease

Table 4: Characteristics of neonates with CLD

Group	GA (weeks)	BW (g)	Gender	Oxygen dependency time (days)	Severity of CLD at 36 weeks (PMA)
A	30	1150	M	28	Mild
A	28	860	M	30	Mild
C	25	600	F	60	Mild
C	28	940	M	30	Mild
C	26	910	M	45	Mild
C	27	800	M	60	Mild
C	28	1020	M	50	Mild
C	26	1000	M	30	Mild
C	26	1000	F	35	Mild
C	27	1150	M	82	Moderate
C	30	1040	F	32	Mild
C	28	1050	F	37	Mild
C	28	1150	F	44	Mild

CLD=Chronic lung disease, BW=Birth weight, GA=Gestational age, PMA=Postmenstrual age

of the increased survival of very prematurely born infants following surfactant administration."

Howlett and Ohlsson, Ng and Ohlsson showed that inositol and cromolyn sodium did not have any effect on reduction of CLD.[37,38] Also postnatal administration of antioxidants such as glutathionine, N-acetyl cysteine, melatonin, etc., had no association with developing CLD.[39-41] A study by Darlow and Graham found that postnatal vitamin A has a significant reduction effect in developing CLD at 36 weeks' PMA in extremely low birth weight infants.[42]

Some studies have investigated the effect of methylxanthines on CLD incidence. Lauterbach *et al*. tried pentoxifylline administration in VLBW neonates if they needed supplementary oxygen on the fourth postnatal day. They observed a significant reduction in occurrence of CLD compared with a placebo group (odds ratio [OR]

0.32, 95% confidence interval [CI] 0.11-0.94).[43] In addition, in a large study of Schmidt *et al*., caffeine usage caused a significant reduction in CLD development (OR 0.63, 95% CI 0.52-0.78). In that study they investigated neonates who needed respiratory stimulant to prevent apnea or to assist extubation throughout the 1st 10 postnatal days.[35,36] In the present study, incidence of CLD was significantly lower in the aminophylline receiving group than the control group, possibly due to improvement in respiration (with increasing diaphragmatic contractility) and the mild diuresis effect of aminophylline.

Replacement of estradiol/progesterone or thyroxine by some researchers failed to reduce the prevalence of CLD.[44,45] Schreiber *et al*. showed that the Nitric oxide administration in routine dose (starting at 10 ppm) reduced death or CLD/BPD and also intracranial hemorrhage, significantly.[46]

This study was designed to investigate preventive effects of aminophylline on the reduction of CLD development in the higher risk neonates. The results revealed that, among extremely premature infants, preventative effects of aminophylline on CLD become apparent. Further investigation should, of course, be carried out to corroborate the findings of the present study.

The major limitation of this study could be the rather small number of the infants included (52 premature neonates), even though the results clearly indicated a statistically significant difference between the experimental and control groups. On the other hand, the direct supervision of study by a neonatologist may be considered as the major strength of the study.

CONCLUSIONS

Apparently, with the study implemented among extremely premature infants, preventative effects of aminophylline on CLD become apparent. In fact, it seems the more premature the infants, the greater will be the preventative effect of aminophylline on the incidence of CLD.

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