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Low Dose Aminophylline Effectively Decreases the Risk of Post-Operative Apnea in Premature Infants

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Background: Retinopathy of prematurity (ROP) is the most common reason behind surgical procedures in premature newborns. Anesthesia in these patients is life-threatening due to post-operative apnea of prematurity (POA). This study aimed to determine the predisposing factors to POA in premature infants and to explore the role of prophylactic aminophylline in decreasing the incidence of POA.

Materials and Methods: Fifty patients with prematurity who were candidates for elective eye surgery (less than one hour) were selected and received aminophylline (3 mg/kg) 5 minutes after the induction of anesthesia with sevoflurane. Patients were kept in the recovery room for 2 hours post-operation in an incubator and were monitored for SPO2, apnea, bradycardia and other signs of desaturation and apnea.

Results: There were no statistically significant differences in the gestational age and weight, sex, postconceptual age and weight and other demographic characteristics between the experimental and control groups. Gestational age<28 weeks, postconceptual age<60 weeks, birth weight, operation weight and anemia (OR=1.91; 95% CI: 1.24-3.73; P=0.012) were the predisposing factors associated with postoperative apnea. Treatment with aminophylline as compared with the placebo was associated with a significantly decreased risk of post-operative apnea (OR=0.53; 95% CI 0.28–0.98; P=0.034).

Conclusion: Aminophylline can be used prophylactically to decrease the risk of postoperative apnea with no major adverse effects.

Key words: Retinopathy of prematurity, Post-operative apnea of prematurity, Aminophylline

Abbreviations: ROP: retinopathy of prematurity; AOP: Apnea of prematurity; POA: post-operative apnea; NICU: neonatal intensive care unit.

INTRODUCTION

The prevalence of prematurity in newborns is on the rise in developing countries due to the advances in prenatal and postnatal care, and cesarean deliveries. Prematurity is a common cause of neonatal intensive care unit (NICU) admissions and incubation. Prematurity is threatened by prolongation of NICU stay and adverse effects of oxygen therapy including retinopathy of prematurity (ROP) (1). ROP is the most common reason behind surgical procedures in premature infants, exposing them to anesthesia side effects such as apnea (2). Premature newborns are prone to cardiopulmonary events such as AOP (3). AOP is characterized by cessation of respiration in premature infants for more than 20 seconds or of any duration accompanied by bradycardia or cyanosis. AOP is a complex disease with a multifactorial pathogenetic cascade, which has been partially understood (4). It is probably related to the immaturity of the central

nervous system (CNS) (5). Approximately, 25% of preterm infants may develop AOP due to an immature respiratory system (6). Premature infants are also prone to POA, that can increase mortality and the need for prolonged post-operative intubation (7). Risk factors for AOP include post-conceptual age, gestational age, birth weight, history of respiratory distress syndrome, anemia, pre-existing conditions, use of opioids and muscle relaxants, and history of apnea (8). Prophylactic methylxanthines (such as theophylline and caffeine) have been used in preterm infants to stimulate breathing and reduce the incidence of AOP in NICUs (9,10); but their advantage in preventing POA has yet to be confirmed. The aim of this study was to determine the predisposing factors of POA in premature infants and to explore the role of prophylactic aminophylline in decreasing the incidence of POA and preventing subsequent re-intubation.

MATERIALS AND METHODS

Patient Selection and Data Collection:

This study was approved by the hospital ethics committee and performed in accordance with the ethical standards laid down in an appropriate version of the 2000 Declaration of Helsinki. Information about the study was provided comprehensively both orally and written to parents. Guardians of patients gave their written informed consents prior to their inclusion in the study as requested by the University Hospital Ethical Board Committee.

In this experimental study, 50 premature infants, who were candidates for elective eye surgery (less than one hour) were enrolled and randomly assigned to two groups. The experiment group infants received a loading dose of aminophylline (3 mg/kg IV) after induction of anesthesia as prophylactic dose (not followed by a maintenance dose). The control group received normal saline solution instead. Apnea was defined as cessation of breathing lasting > 20 seconds or < 20 seconds in combination with bradycardia, cyanosis or pallor. The inclusion criteria were: birth age<36 weeks, weight at the time of operation < 2500 g, the surgery had to be the first operation to be done under general anesthesia, and no intubation or mechanical ventilation 1 week prior to operation.

All patients' information and their demographic characteristics namely age, weight, history of respiratory distress syndrome, history of allergy, and physical exam were extracted from their medical records. The exclusion criteria were airway obstruction, hypocarbia, hypercarbia, hypothyroidism, neuromuscular blockage, temperature abnormalities, dehydration, electrolyte (calcium, magnesium, phosphorus) imbalance, hypoglycemia, aspiration, sepsis, pulmonary hemorrhage, or intracranial hemorrhage.

Anesthesia:

In the operating room, all premature infants were monitored using electrocardiography (ECG), pulse oximetry, heart rate (HR), precordial stethoscope, temperature monitoring, bispectral index (BIS) and end-tidal CO2 (ETCO2). Standard inhalation anesthesia was induced using 8% sevoflurane. Sevoflurane was used to provide faster induction, quick spontaneous breathing, better maintenance of hemodynamic balance, and less cardiovascular side effects. Besides, sevoflurane provides rapid induction and emergence compared to other volatiles. No premedication with opioids, lidocaine, sedative-hypnotics, or muscle relaxants was performed in this study.

Right after the induction of anesthesia with sevoflurane, an intravenous line (IV-line) was obtained. Single dose aminophylline (3 mg/kg) was administered 5 minutes after the induction of anesthesia. Patients were immediately monitored for any clinical signs of aminophylline toxicity including tachycardia (according to age and 30% increase in basal HR), arrhythmia, and seizure. Hypothermia and subsequent apnea or delayed awakening were avoided by covering the head and neck areas and the upper extremity using vibrils. Besides, the room temperature was adjusted at 28-30° C.

Anesthesia was maintained by 50% N2O-50% oxygen at a flow rate of 3 L/min plus sevoflurane (3-6%) based on

patient hemodynamics and BIS (maintained 40-60). Ventilation was provided by inserting an appropriate laryngeal mask airway (LMA) at proper depth of anesthesia (based on BIS 40-60, stable hemodynamics and central pupils). Thereafter, LMA was attached to a Mapleson F semi-closed anesthetic system where controlled ventilation was assisted manually. To prevent CO2 re-breathing, a fresh gas inflow rate of approximately 2.5 times of minute ventilation was provided and ETCO2 was maintained at 30-35mmHg. The bag compliance, chest movement, oxygen saturation (SPO2), and airway pressure were used to monitor efficient ventilation. Airway pressure was maintained at 10-12 cmH2O in order to prevent gastric over-distension and subsequent decrease in depth of anesthesia. In order to maintain deep level of anesthesia, BIS level was set at 40-60.

Time to retain spontaneous breathing and awakening was shortened (based on BIS monitoring), due to rapid decrease of inhaled sevoflurane concentration during emergence. In average, spontaneous breathing was retained for 5 minutes after the discontinuation of Sevoflurane.

Considering high metabolic demand and high ratio of body surface area (BSA) to weight, maintenance intravenous fluids were calculated on the basis of a formula derived from data by Holliday and Segar (11). To prevent hypoglycemia, 5% dextrose in 0.45% normal saline was administered at maintenance rates. Blood sugar (BS) was assessed once at the beginning of the operation and then every 30 minutes afterwards. BS less than 90 mg/dl was treated with 5% infusion of dextrose.

The infants were extubated post-operation if they had safe extubation criteria, such as flexing the hip and knees to hold the feet off the bed and normal airway protective reflexes, alert mental status, hemodynamic stability, and adequate arterial oxygen saturation with inspired oxygen fraction <0.4 L/min.

Monitoring of apnea

Apnea is defined as discontinuation in pulmonary airflow for more than 10-20 seconds, that could be accompanied by bradycardia (heart rate <80-100 beats per minute) or decrease in blood oxygen saturation. Apnea is accompanied by both airflow and respiratory efforts, in which no chest movements are observed. Monitoring of apnea continued for 12 hours post operation in the recovery room and ward. The anesthesiologist closely observed these movements in the recovery room. Any decrease in frequency and number of ventilation was assumed as apnea and treated with oxygen, face mask and Mapleson F system, which is best for controlled ventilation. This prevents any further progression of bradycardia or arrest. In the recovery room, patients were kept in an incubator for 2 hours post-operation and were monitored for SPO2 (hypoxia was recorded if SPO2<90%), apnea, bradycardia and hypothermia and thereafter transferred to the ward. Patients were visited twice at 6 and 12 hours post-operation in order to record any apnea, hemodynamic instability, and signs of aminophylline toxicity including seizure, arrhythmia and agitation.

Monitoring for post operative apnea (observation/computer) under face mask included: decrease in chest movements, decrease in passive bag movements, decrease in negative airway pressure of ventilator monitor, and decrease in flow waves on ventilator monitors (bradypnea). Desaturation events were determined based on apparent life threatening events (ALTE) definition which included: color change (cyanosis or pallor), tone changes (limpness or stiffness), bradycardia, and difficult ventilation.

Statistical Analysis:

Data were expressed as mean± standard deviation (SD) and categorical data were presented as numbers. Comparisons between the two groups were conducted using unpaired t-tests. Statistical significance was defined as $P < 0.05$. Logistic regression analyses were used to calculate univariate crude odds ratio (OR) with 95% confidence intervals (CIs) with apnea as the outcome factor. Stepwise multivariate regression model was used to estimate adjusted OR with 95% CIs for significant risk factors associated with apnea in premature infants. Sample

size was calculated based on α=0.05, power of 80%, and clinical difference of 60% between the two groups. The sample size was 25 patients for each group.

RESULTS

Fifty premature infants with a gestational age of 31.5±7.5 weeks (mean± SD) (range 26-34 weeks), postconceptual age of 42.5±12.8 weeks (range 28-42 weeks), birth weight of 955±552 g (range 782-1520 g), and weight at operation of 1850±965 g (range 850-4200) were included in the study. They were randomly divided into two groups based on accidental randomization. The age distribution of the control group was similar to that of the case group. There were no statistically significant differences in gestational age and weight, sex, postconceptual age and weight or other demographic characteristics between the experimental and control groups (Table 1). Type of delivery was not different between the two groups (P>0.05). Past history of NICU admission and respiratory disease were not significantly different between the two groups either (P>0.05). There was no clinical sign of aminophylline toxicity in any patient.

Table 1. Characteristics of preterm infants in aminophylline and control groups

	Aminophylline (25)	Control (25)	p-value
Gestational age (weeks)	28.5±5.2	30.7±6.2	0.12
Birth weight (kg)	890±545	920±510	0.6
Postconceptual age (weeks)	46.5±7.2	47.7±5.4	0.86
Weight at operation (g)	1820±420	1770±550	0.075
Sex (Female/male)	52%/48%	46%/54%	>0.05
Type of delivery			
NVD	14(56%)	12 (48%)	>0.05
CS	11 (44%)	13(52%)	>0.05
NICU admission			
History of NICU	32%	40%	>0.05
Days of NICU	12.5±8.6	10.4±8.5	>0.05
History of respiratory diseases	28%	24%	>0.05
History of anemia	60%	64%	>0.05
History of blood transfusion	32%	36%	>0.05

Results for primary outcome (apnea) were analyzed in two groups. From 25 infants who received aminophylline prophylaxis, 2 patients developed post-operation apnea compared to 14 cases out of 25 infants in the placebo group. Incidence of apnea spells and desaturation events is listed in Table 2.

Table 2. Incidence of apnea and desaturation events in premature infants post operation

	Aminophylline	control
Apnea		
↓Chest movements	1(4%)	5(20%)
↓Bag movements	1(4%)	3(12%)
↓Negative airway pressure	0	4(16%)
↓Flow (bradypnea)	0	2(8%)
Desaturation events		
Hypoxia	2(8%)	4(16%)
Cyanosis/pallor	1(4%)	3(12%)
Limpness/stiffness	0	2(8%)
Bradycardia	0	5(20%)

The OR was adjusted for gestational age and weight, sex, post-conceptual age and weight at operation. Table 3 shows the ORs for several potential risk factors of postoperative apnea in premature infants undergoing operation. In multivariate regression analysis model Gestational age<28 weeks, postconceptual age<60 weeks, birth weight, operation weight and anemia were the predisposing factors significantly associated with postoperative apnea (Table 3). This relationship remained significant after adjustment for gender, birth weight and duration of NICU admission. Treatment with aminophylline as compared with the placebo was associated with a significantly decreased risk of post-operative apnea (POA) (OR=0.53; 95% CI 0.28–0.98; P=0.034), which persisted after adjustment for gestational age (OR= 0.78; 95% CI, 0.42-0.97; P=0.001) and operation weight (OR= 0.61; 95% CI, 0.36- 0.95; P=0.02) and other potential confounders.

Table 3. ORs for several potential risk factors of postoperative apnea among premature infants undergoing operation (CI: confidence interval).

	Odds Ratio	95% CI	P-value
Gestational age <28 w	2.12	1.23-3.86	0.023
Birth weight	1.85	1.37-2.31	0.033
Postconceptual age<60 weeks	1.92	1.44-2.98	0.009
Operation weight	1.63	1.11-2.45	0.026
Sex	0.95	0.67-1.55	0.071
Anemia	1.91	1.24-3.73	0.012
NICU admission	0.85	0.55-1.61	0.065

DISCUSSION

POA is more common in preterm than term infants (12). These episodes of ineffective breathing can lead to hypoxemia and bradycardia. Incidence of cardiac arrest has declined during the past decades in infants but apnea spells are on the rise (13). Respiratory neuronal system is invariably sensitive to anesthesia in premature infants; therefore apnea may occur post-operatively. These incidents could cause re-intubation, mechanical ventilation, and hypoxemia, which adversely affect neuropsychological status of these patients (14). POA increases the duration of post-operative NICU admission and health care cost.

The most important responsibility of anesthesiologists is to maintain an open and secure airway and oxygenation. This responsibility is more important in infants, and quick, and proper intervention is mandatory. To decrease the risk of post-operative apnea, avoiding hypothermia, hypoglycemia, replacement with Sevoflurane (15), and maintenance of appropriate depth of anesthesia are necessary. In fact, applying only one of these items may not be enough. On the other hand, anesthesia aggravates respiratory impulses in immature CNS making them vulnerable to POA (16). Therefore, we used aminophylline to instigate CNS or respiratory impulses to prevent POA in immature infants.

Methylxanthines have been effective in reducing the number of apnea attacks and decreased the use of mechanical ventilation two to seven days after starting treatment (17). Aminophylline (18) and caffeine have been used to decrease apnea of prematurity (19,20). Caffeine appears to have similar short-term effects on apnea as does aminophylline although IV caffeine is too expensive to be available in all settings; therefore our study suggests aminophylline as a possible cost-effective alternative (21,22). Besides, premature infants vary tremendously in their response to methylxanthines. This variation may affect clinical outcomes such as apnea, need for IPPV, neonatal morbidity, length of hospital stay and long-term development (23). In our study, aminophylline significantly decreased the risk of apnea event in premature infants compared to controls. We chose aminophylline at a lower dose (3 mg/kg) compared to previous studies (5 mg/kg) to eliminate toxicity issues (no toxicity was observed in our patients), and its clinical efficacy was not compromised by dose modification.

Anesthetic drugs and immaturity of respiratory muscles including diaphragm and intercostal muscles contribute to apnea. Methylxanthines have been used to increase minute ventilation in response to CO2 rise and prevention of apnea in infants with increased risk of apnea. Aminophylline is a stimulator of central respiratory centre. It also increases diaphragm contractions in infants. Diaphragm is the main respiratory muscle in infants. Preterm infants' diaphragm muscle mainly contains fast-twitch muscle fibers, which become quickly exhausted in repetitive contractions. Type I muscle fibers are fatigue resistant and thus suitable for fast and repetitive contractions; but these fibers are scarce in diaphragm muscle of premature infants. Besides, contributing factor in preterm infants may reduce calcium release from sarcoplasmic reticulum (SR), which would lower the calcium available for activating contractile muscles. Aminophylline stimulate CNS, myocardium, and muscles through increase in intracellular cAMP and intracellular calcium (24). Aminophylline may increase ventilation and improve contractile function of the diaphragm (25). Methylxanthines (such as caffeine or aminophylline) have been used to stimulate breathing and reduce apnea through inhibition of Adenosin receptors A1 and A2a (26).

In conclusion, aminophylline could be administered as prophylaxis for POA. Monitoring alone may not compensate for any unpredictable apnea in the recovery room, therefore aminophylline used as prophylaxis could be life saving in hospital settings. Although the toxicity issue of prophylactic aminophylline is still debatable, and further study and measuring of its blood level could definitely elucidate this issue. Sufficient experience and professional judgment in order to avoid mortality and morbidity in premature infants is absolutely mandatory.

Conflict of interest

The authors of this article declare no conflict of interest, no financial, consulting, and personal relationships with any other people or organizations that could influence (bias) the author's work. All necessary ethical approvals were obtained and the study was reviewed and approved by the university hospital ethics committee and performed in accordance with the ethical standards laid down in an appropriate version of the 2000 Declaration of Helsinki.

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