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Life-threatening Apnea in Infants Recovering from Anesthesia

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To determine whether prematurely born infants with a history of idiopathic apneic episodes are more prone than other infants to life-threatening apnea during recovery from anesthesia, the authors prospectively studied 214 infants (173 full term, 41 premature) who received anesthesia. Fifteen premature infants had a preanesthetic history of idiopathic apnea. Six of these required mechanical ventilation because of idiopathic apneic episodes during emergence from anesthesia. Two were ventilated for other reasons, and seven recovered normally. Infants ventilated for apnea were younger (postnatal age 1.6 ± 1.2 months, mean ± SD; conceptual age 38.6 ± 3.0 weeks) than those who recovered normally (postnatal age 5.6 ± 2.7 months; conceptual age 55.1 ± 11.3 weeks) ($P < 0.01$). No other premature or full-term infant was ventilated because of postoperative apneic episodes. The authors conclude that anesthetics may unmask a defect in ventilatory control of prematurely born infants younger than 41–46 weeks conceptual age who have a preanesthetic history of idiopathic apnea. (Key words: Anesthesia: outpatient; pediatric. Recovery: ventilation. Ventilation: apnea.)

THE PROGRESSIVE DECREASE in the mortality of prematurely born infants has led to an increase in the number of these babies who present for anesthesia and surgery. Prematurely born infants are more likely than full-term infants to have apneic episodes following anesthesia.[1] Ideally, infants who might develop life-threatening apnea postoperatively should be identified prior to anesthesia and surgery. We have observed that postanesthetic apneic episodes associated with cyanosis, bradycardia, or pallor seem to occur more frequently in prematurely born infants who have a preanesthetic history of idiopathic apnea. To document the validity and incidence of this clinical observation, we prospectively studied children under 12 months of age (postnatal age) who received anesthesia.

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Methods

The study population consisted of infants who were anesthetized during a one year period beginning March 1, 1981. This included infants anesthetized for general surgical, urologic, neurosurgical, orthopedic, thoracic, plastic, and radiologic procedures.

Immediately following each anesthetic, data sheets were completed by the anesthetist. Factors recorded were gestational and postnatal ages, birth and preanesthetic weights, American Society of Anesthesiologists (ASA) physical status classification, prenatal, perinatal and medical histories, operative procedure, duration of anesthesia, anesthetic drugs, postanesthetic complications, and indications for postanesthetic ventilatory assistance.

The following definitions were utilized: Infants born before 37 weeks of gestation were classified as premature, while those who had a gestational period of 37 weeks or greater were considered full-term infants. Conceptual age was defined as gestational age plus postnatal age. Apnea was defined as the cessation of breathing for longer than 20 s or a shorter period associated with bradycardia, cyanosis, or pallor.[2] Apneic episode were defined as idiopathic if the following causes were eliminated: airway obstruction, hypocarbia, neuromuscular block, narcotic overdose, temperature abnormalities, dehydration, anemia, hypocalcemia, hypoglycemia, aspiration, sepsis, pulmonary hemorrhage, intracranial hemorrhage, and seizures. A preanesthetic history of idiopathic apnea was defined as idiopathic apneic episodes occurring between birth and the commencement of anesthesia that required stimulation or resuscitation.

The anesthetic management of the patients was not standardized because the authors felt that the care of each infant should not be compromised by limiting the responsible anesthesiologist's choices of techniques or pharmacologic agents. Infants received no premedication except for methohexital, which was administered rectally to some older infants and to patients who had CT scans. Ventilation was controlled in all infants who were intubated during anesthesia. No end-expiratory pressure was utilized. At the end of anesthesia, atropine and neostigmine were administered to patients who received muscle relaxants. Full reversal of the neuromuscular effects of relaxants was confirmed by the presence of four twitches and no fade after train-of-four nerve stimulation.[3]

Heart sounds, heart rate, the electrocardiogram, respirations, and temperature were monitored continuously on all patients from the commencement of anesthesia until the infants were transported to the recovery area. Blood pressure was measured routinely by oscillometry, unless the placement of an arterial line was indicated. In this case, pressure was measured directly.

Following the administration of anesthetic drugs, 100% oxygen was administered until the infants were extubated or admitted to the recovery area. Postoperative ventilation was planned for infants who required respiratory support preoperatively and those with surgically related problems necessitating postoperative respiratory support. In all other infants, spontaneous respirations were allowed to return at the end of anesthesia. Infants were extubated only after they were awake and ventilating adequately on 100 per cent oxygen. Ventilation was judged adequate when spontaneous respirations were sustained and when an infant's appearance and vital signs were normal. Immediately after extubation, 100% oxygen was administered by mask and ventilatory status was reassessed. If ventilation remained adequate, the patients were allowed to breathe room air and ventilation was evaluated again. Respiratory support was instituted when necessary. If apnea occurred more than 20 min after the first spontaneous postoperative breath, infants were taken to the intensive care unit and mechanically ventilated overnight.

Data were reviewed and statistical analysis performed using the Student's *t* test for unpaired data and chi-square analysis. The results are expressed as the mean ± SD. Significance was defined as $P < 0.05$.

Results

Two hundred and fourteen cases were studied during the 1-year period (Table 1). Ninety-two per cent of these patients were intubated. All full-term infants under 3 months and prematurely born infants under 7 months were intubated with the exception of those infants who had CT scans under rectally administered methohexital.

One hundred and seventy-three cases were full-term infants. Ten received postoperative respiratory support because they were ventilated preoperatively or because they had surgically related problems necessitating this type of therapy. Four other infants had a preanesthetic history of idiopathic apnea. None of these four required respiratory support before or after anesthesia.

Forty-one cases were prematurely born infants. Eighteen required postoperative respiratory support. Ten of these 18 were ventilated mechanically because they required this therapy preoperatively or because they had surgically related problems necessitating postoperative respiratory support. Seven others were ventilated because of postanesthetic idiopathic apneic episodes. Although all had a preanesthetic history of apnea, none were intubated

TABLE 1. Distribution of Premature and Full-term Infants

	Premature (n = 41)	Full-term (n = 173)	Total (n = 214)
History of idiopathic apnea	15	4	19
Postanesthetic respiratory support	18	10	28
Indications			
Idiopathic postoperative apnea	7	0	7
Previous postoperative apnea	1	0	1
Other medical and surgical indications	10	10	20

or mechanically ventilated prior to arrival in the operating room. Six left the operating room intubated because of life-threatening apneic episodes, which continued to occur more than 20 min after the first spontaneous postoperative breath. One of these infants (7 months postnatal age; 58 weeks conceptual age) also had persistent obstructive apneic episodes. This infant was deaf, blind, and brain damaged. The infant (1.5 months postnatal age; 38 weeks conceptual age) who was extubated successfully before leaving the operating room initially appeared to recover normally. However, he was apneic and cyanotic 10 min following admission to the recovery room. After mouth-to-mouth resuscitation followed by ventilation with an Ambu bag, spontaneous respirations resumed. This infant then was reintubated and transferred to the pediatric intensive care unit, where he recovered without further incident.

One other infant (2 months postnatal age; 45 weeks conceptual age), was electively ventilated postoperatively because of an earlier history of postoperative ventilation for apneic episodes immediately following anesthesia. This infant and the infant with brain damage were excluded from the statistical analysis because they had these mitigating considerations.

Prematurely born infants with a preanesthetic history of apnea required postoperative ventilatory support for apnea more frequently than all other infants ($P < 0.0005$) (Table 2). The incidence of respiratory support was higher in these infants even when they were compared only with prematurely born infants without a history of apnea ($P < 0.01$).

There was no significant difference in birth or preanesthetic weight, gestational age, ASA physical status, duration of anesthesia, or operative procedures between the prematurely born infants with a history of idiopathic apnea who required respiratory support and those who did not. However, there was a significant difference in the postnatal and conceptual ages between the two groups ($P < 0.01$) (Table 3). All infants requiring postoperative respiratory support were less than 41 weeks conceptual age and 4 months postnatal age, whereas those who did

TABLE 2. Gestational Age, Preanesthetic History of Apnea, and Ventilatory Status of Infants Recovering from Anesthesia*

	Recovery from Anesthesia	
	Apnea	Normal
Prematurely born infants		
Apnea history†	6	7
No apnea history	0	16
Full-term infants		
Apnea history	0	4
No apnea history	0	159

* Ten prematurely born infants and 10 full-term infants who were ventilated for surgical or medical reasons other than postanesthetic apnea are excluded.

† Two infants in this group who became apneic after anesthesia are excluded (see text).

not were older than 46 weeks conceptual age and 4 months postnatal age.

Drugs administered during anesthesia to the prematurely born infants with a preanesthetic history of apnea included: halothane, nitrous oxide, succinylcholine, curare, pancuronium, atropine, neostigmine, methohexital, thiopental, and fentanyl. The need for postanesthetic respiratory support did not correlate with the use of any particular agent (Table 4).

Discussion

A gradual decrease in the frequency of apneic episodes occurs as gestational age increases or as prematurely born infants mature.[4–6] Our finding that respiratory support for life-threatening apneic episodes after anesthesia decreased as conceptual age increased is consistent with this. All prematurely born infants younger than 41 weeks conceptual age with a preanesthetic history of apnea required postanesthetic respiratory support, whereas those who were older did not.

Apneic episodes in prematurely born infants have been attributed to immaturity of the respiratory system.[7] Analysis of the proportion of type I and type II muscle fibers in specimens of diaphragm and intercostal muscles of premature and full-term infants revealed that the percentage of type I fibers increases as infants mature.[8] Because type I muscle fibers have a higher resistance to fatigue, these investigators concluded that some instances of apnea may be due to fatigue of the respiratory muscles. The recent study of Henderson-Smart *et al.*[9] demonstrated that the auditory brain stem conduction time increased as gestational age decreased. This increase in conduction time correlated with the frequency of apneic episodes. They concluded that apnea is probably related to immature brain stem function.

TABLE 3. Relation of Age to Recovery from Anesthesia in Premature Infants with a Preanesthetic History of Apnea

	Recovery Period	
	Respiratory Support (n = 6)	Normal Recovery (n = 7)
Gestational age (weeks)		
Mean ± SD	31.6 ± 3.1	31.1 ± 2.5
Range	25–36	28–36
Postnatal age (months)		
Mean ± SD	1.6 ± 1.2*	5.6 ± 2.7
Range	0–3	3–11
Conceptual age (weeks)		
Mean ± SD	38.6 ± 3.0*	55.1 ± 11.3
Range	33–40.8	46.7–79.9

* $P < 0.01$, compared with the mean of infants recovering normally.

In infants who have a history of neonatal apnea, both alveolar hypoventilation during quiet natural sleep and an abnormal response to hypercapnia and hypoxia have been demonstrated.[10,11] We postulate that residual anesthetic drugs may have been sufficient to further depress the ventilatory responses to carbon dioxide and hypoxia in our infants who experienced postoperative apneic episodes. These residual drugs also may have accentuated the decrease in muscle power and endurance of the respiratory muscles of these infants.

Anesthetic drugs are known to affect the ventilatory control mechanism. Several investigators have demonstrated that narcotics as well as potent inhalation anesthetics such as halothane decrease tidal volume, increase Pa_{CO_2}, and depress the ventilatory response to CO_2.[12,13] In addition, potent anesthetic agents alter the level of Pa_{CO_2} at which spontaneous respirations cease ("apneic threshold").[14]

The ventilatory response to hypoxia also is altered by anesthetics. Low concentrations of halothane severely depress the hypoxic stimulus to respiration, whereas higher doses abolish this response.[15] Even nitrous oxide, in concentrations of 35–50%, has been shown to depress the ventilatory response to hypoxia.[16]

The results of our study indicate that prematurely born infants with a preanesthetic history of unexplained apneic episodes have a high risk of developing idiopathic life-threatening apnea during recovery from anesthesia. All of our prematurely born infants with this history who were under 41 weeks conceptual age required postanesthetic ventilation.

The variation in the anesthetic management of the patients and the wide range of surgical procedures indicates that the postanesthetic apnea that we observed is not a result of a specific operation or anesthetic technique.

Ideally, infants at risk of becoming apneic during recovery from anesthesia should be identified prior to anesthesia and surgery so that appropriate personnel, equipment, and facilities will be available to take care of any problem that may arise. Since the postnatal course of these infants frequently is associated with significant med-

TABLE 4. Ages, Operations, Drugs, and Postanesthetic Respiratory Status of Prematurely Born Infants with a History of Apnea Who Were Included in the Statistical Analysis

Ages					Drugs Administered during Anesthesia											Recovery Period	
Gestational (wk)	Postnatal (mo)	Conceptual (wk)	Operation	Drugs Received prior to Anesthesia	Halothane	Nitrous oxide	Succinylcholine	Pancuronium	Curare	Atropine	Thiopental	Methohexital	Fentanyl	Neostigmine	Others	Respiratory support	Normal recovery
30	4	46.7	Bilateral inguinal hernia repair and orchiopexy	Theophylline	+	+											+
28	3	40.7	Bilateral inguinal hernia repair	Theophylline	+	+	+			+						+	
28	3	40.7	Bilateral inguinal hernia repair	Theophylline		+			+	+	+			+		+	
32	1.5	38.4	Bilateral inguinal hernia repair		+	+	+	+		+				+		+	
32	3.5	48.6	Bilateral inguinal hernia repair and orchiopexy		+	+	+		+	+				+			+
30	5	52	Bilateral inguinal hernia repair		+	+											+
36	1	40.8	Ventricular-peritoneal shunt	Theophylline Phenobarbital		+			+	+			+	+	Oxacillin	+	
36	3	50.9	Ventricular-peritoneal shunt revision		+	+		+		+				+	Oxacillin		+
30	6.5	53	CT scan									+					+
28	6	54.8	CT scan	Chlorothiazide Hydralazine								+					+
32	11	79.9	Bronchoscopy and esophagoscopy		+	+	+								Lidocaine		+
33	1	38	Esophagoscopy and dilatation		+	+									Oxacillin	+	
33	.03	33	Tracheoesophageal fistula repair and colostomy		+	+		+		+			+	+	Cefazolin	+	

ical problems, elective surgery often is postponed until these perinatal problems are resolved. When surgery finally is scheduled, many of these infants will appear "normal." Frequently they are admitted to the hospital as outpatients for minor surgical procedures such as an inguinal herniorrhaphy. Distinguishing these babies from others of the same postnatal age requires a careful birth and perinatal history.

The increasing pressure to reduce hospital costs has popularized the concept of outpatient surgery for minor surgical procedures. In view of our findings, it would be prudent to refer infants with a history of apnea, particularly those under 46 weeks conceptual age, to institutions with facilities equipped to provide appropriate postoperative care for these infants. These infants should not undergo surgical procedures as outpatients. Instead, they should be admitted to the hospital postoperatively and closely monitored for 24 h.

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