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Are All Preterm Infants Younger than 60 Weeks Postconceptual Age at Risk for Postanesthetic Apnea?

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Background: **Preterm and ex-preterm infants are at risk for life-threatening apnea after general anesthesia. The authors attempted to define the postconceptual age beyond which apnea is less likely to occur and to identify the factors that predispose to postanesthetic apnea.**

Methods: **Ninety-one infants younger than 60 weeks postconceptual age undergoing 101 general anesthetics were prospectively studied. All infants were admitted to the hospital for cardiorespiratory monitoring overnight. The presence of coexistent medical conditions that could influence the incidence of apnea was determined by a review of current and previous medical records and by history.**

Results: **Of 38 procedures performed in 35 infants younger than 44 weeks postconceptual age, 10 (26.3%) procedures in 9 infants were associated with postanesthetic apnea. In eight of these, apnea did not resolve spontaneously: four infants required stimulation, and four required continuous positive airway pressure by face mask. Apnea occurred after 2 of 63 procedures performed in infants 44 weeks postconceptual age or older. Both episodes occurred in one patient who had neurologic disease. Of the remaining 61 procedures in the latter age group, 7 were associated with episodes of bradycardia (lowest heart rate was 79 beats/min) postoperatively without apnea. These episodes lasted up to 5 s, were not associated with apnea or cyanosis, and resolved spontaneously in all cases. All infants with postanesthetic apnea and/or bradycardia experienced their first episode within 12 h after surgery.**

Conclusions: **Ex-preterm infants younger than 44 weeks postconceptual age are at greater risk for apnea after general anesthesia than are infants older than 44 weeks postconceptual age. Based on these results, the maximum long-run risk of postanesthetic apnea in preterm infants older than 44 weeks postconceptual age is 5% with 95% confidence. (Key words: Age factors: gestational; neonate; postconceptual; preterm. Anesthesia: neonatal; pediatric. Complications: apnea; respiratory.)**

SEVERAL reports have found an increased risk of life-threatening postanesthetic apnea in ex-preterm infants after general anesthesia.[1–6] This increased risk first was noted in a retrospective study by Steward.[1] Subsequently, a number of prospective studies confirmed the findings of Steward and attempted to define the postconceptual age beyond which postanesthetic apnea is less likely to occur.[2–5] However, there is no consensus regarding the likelihood of postanesthetic apnea in infants between 44 and 60 weeks postconceptual age. To define the age beyond which there is little likelihood of postanesthetic apnea, the authors undertook the following prospective study. The data obtained also were analyzed to identify preexisting conditions or anesthetic techniques that might increase the risk of postanesthetic apnea.

Methods

With approval from the Institutional Ethics Committee, 91 consecutive preterm infants younger than 37 weeks gestational age at birth and younger than 60 weeks postconceptual age at the time of surgery were studied. All preterm infants who were to receive postoperative ventilatory support, *i.e.*, patients scheduled for thoracic surgery or patients who were receiving ventilatory support before surgery, were excluded. All other ex-preterm infants who fulfilled the above criteria and underwent surgery over the 1-yr duration of the study were included. Gestational age was determined by questioning the parents and confirmed from documentation of physical examination at birth when previous medical records were available. Postconceptual age was the sum of the gestational and postnatal ages.

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The anesthetic management was individualized by the attending anesthesiologist. Anesthesia was induced intravenously with sodium thiopental. Succinylcholine was administered to facilitate tracheal intubation, and anesthesia was maintained with a volatile anesthetic in accordance with the usual institutional practice. Opioids and nondepolarizing muscle relaxants were administered when indicated to facilitate surgery and/or at the discretion of the attending anesthesiologist. In the majority of cases, however, succinylcholine was the only relaxant used because of the short duration of the surgical procedures. Nondepolarizing muscle relaxants, when administered, were antagonized at completion of surgery, and 100% O_2 was administered. Extubation was performed when the following criteria were present: leg lift,[7] regular coordinated respiration, and return of the gag reflex.

Cardiorespiratory monitoring was initiated upon arrival in the postanesthetic recovery unit and continued for a minimum of 24 h. Patients who experienced postanesthetic apnea were monitored continuously until a minimum of 12 apnea-free h had elapsed. All infants were monitored with an Edentec 2000W apnea impedance monitor with a computerized data storage and retrieval system. This monitor displays heart rate and respiratory rate and records events during an alarm. It has a respiratory sensitivity of 0.2 Ω with automatic sensitivity and 0.15 Ω with manual sensitivity for the impedance method of detection. It has an electrocardiogram sensitivity of 0.25–5 mV with automatic sensitivity and 0.15–10 mV with manual sensitivity. After recovery from anesthesia, monitoring was continued in a constant care unit with a nurse present in the room at all times. All episodes of apnea and bradycardia, color change including cyanosis or pallor, and the intervention required were recorded by the attending nurse. Apnea was defined as a respiratory pause of 15 s or longer.[8] Bradycardia was defined as a decrease in heart rate greater than 40 beats/min below the resting heart rate.[4]

The presence and severity of coexistent medical conditions that could influence the incidence of apnea were determined by a detailed examination of current and previous medical records and by questioning the parents of the infants in the study. These conditions included gestational age; postconceptual age; birth weight; weight at the time of surgery; ASA physical status; history of neonatal apnea; respiratory, cardiovascular, or neurologic disease; and necrotizing enterocolitis. Student's *t* test was used to compare the clinical variables (gestational age, birth weight, postconceptual age, weight at the time of surgery, hemoglobin concentration, and body temperature in recovery room) of the groups of patients with and without postanesthetic apnea. The incidence of postanesthetic apnea in the group of preterm infants younger than 44 weeks postconceptual age was compared with the incidence in those equal to or older than 44 weeks postconceptual age using Fisher's exact test. The incidence of postanesthetic apnea in infants with a history of neonatal apnea, necrotizing enterocolitis, or respiratory or neurologic disease was compared with the incidence in infants without such a history using Fisher's exact test. The incidence of postanesthetic apnea in patients receiving opioids and/or nondepolarizing muscle relaxants was compared with the incidence of postanesthetic apnea in patients not receiving these medications using Fisher's exact test. The minimal sample size required to predict a zero incidence of an event in the entire population was based on data from Hanley and Lippman-Hand.[9] Statistical significance was defined as $P < 0.05$.

Results

Ninety-one ex-preterm infants underwent 101 procedures (table 1). The age distribution of these infants detailed in figure 1 indicates that 38 procedures were performed in 35 infants younger than 44 weeks postconceptual age, 31 in 32 infants ≥44 and <50 weeks postconceptual age, and 30 in 30 infants ≥50 and <60 weeks postconceptual age. Because several patients returned for repeated surgery, the total number of infants studied (91) is less than the sum total of infants in the three age groups (97). The birth weight of the infants ranged from 0.57 to 3.3 kg, and their weight at the time of surgery ranged from 1.38 to 7.4 kg (table 2). Nondepolarizing muscle relaxants were used in 34 of 101 procedures and antagonized at completion of sur-

Table 1. Operations

Operation	Number of Procedures
Herniorrhaphy	59
VP shunt	11
Pyloromyotomy	8
Laparotomy	8
Bronchoscopy	2
Myelomeningocele repair	1
Miscellaneous minor procedures	12
Total	101

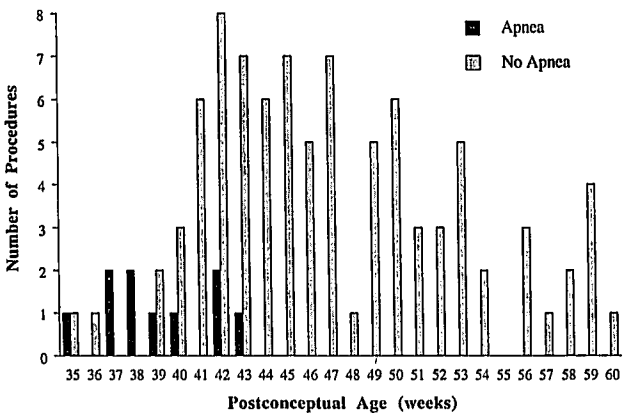

Fig. 1. Incidence of postanesthetic apnea with respect to postconceptual age. All episodes of postanesthetic apnea occurred in infants younger than 44 weeks postconceptual age with the exception of one who was excluded from the study (see text).

gery in all cases (table 3). Opioids were used in 10 procedures, fentanyl (1–2 μg/kg, intravenous) was given to four infants during surgery, and codeine (1 mg/kg, intramuscular) was given to six infants after surgery.

Ten infants had numerous episodes of apnea and bradycardia after 12 procedures (fig. 1). Of these 10, one required general anesthesia for the placement of ventriculoperitoneal shunts at 49 and 57 weeks postconceptual age. After both anesthetics, apnea and bradycardia occurred repeatedly but resolved with vigorous repeated stimulation. This infant had severe neurologic disease and therefore was excluded from the statistical analysis. The remaining nine infants (9.9% of the sample population studied) who experienced postanesthetic apnea after 10 procedures were younger than 44 weeks postconceptual age. Six of these nine infants had a history of apnea in the neonatal period, documented either in the medical records or by history from the parents. Breathing did not resume spontaneously after the apneic episodes in eight of these infants: four required repeated tactile stimulation, and four required 100% O_2 delivered by continuous positive airway pressure by face mask. None of these infants required tracheal intubation.

Table 2. Patient Demographics

Birth weight (kg)	1.69 ± 0.69 (0.57–3.3)
Weight at time of surgery (kg)	4.32 ± 1.44 (1.38–7.4)
Gestational age (weeks)	31.5 ± 3.7 (24–37)
Postconceptual age (weeks)	46.7 ± 6.0 (35.1–60)

Data are mean ± SD (range).

Table 3. Muscle Relaxants

	Number of Procedures Using the Relaxants
Succinylcholine	101
Atracurium	18
d-Tubocurare	7
Pancuronium	5
Gallamine	3
Vecuronium	1

Seven additional infants experienced episodes of bradycardia (lowest heart rate 79 beats/min) lasting 3–5 s. These infants were older than 44 weeks postconceptual age at the time of surgery. These episodes were not associated with apnea or color change and resolved spontaneously without intervention.

All infants with postanesthetic apnea and/or bradycardia experienced their first episode within 12 h of the operative procedure (range 5 min to 12 h). The time to the last apneic event ranged from 4 to 48 h.

Infants with postanesthetic apnea were significantly younger in terms of postconceptual age (39.4 ± 2.6 weeks *vs.* 47.5 ± 5.8 weeks, mean ± SD; $P = 0.0001$) and smaller (body weight 2.9 ± 0.6 kg *vs.* 4.5 ± 1.4 kg, mean ± SD; $P = 0.0008$) at the time of surgery than infants without apneic episodes. Of 38 procedures performed in 35 infants younger than 44 weeks postconceptual age, 10 procedures in 9 infants were associated with postanesthetic apnea. Of the 61 procedures performed in 60 infants 44 weeks postconceptual age or older at the time of surgery, there were no episodes of postanesthetic apnea. A history of neonatal apnea was present in 32 of the 91 infants included in this study. Of these 32 infants, 6 had apnea in the postanesthetic period and 26 recovered from anesthesia uneventfully. There was no significant difference in gestational age, birth weight, history of neonatal apnea, presence of neurologic or respiratory disease or necrotizing enterocolitis, and preoperative hematocrit among infants who experienced postanesthetic apnea compared with those who did not experience apnea ($P > 0.05$). The incidence of postanesthetic apnea did not correlate with the anesthetic technique or agents used, the use of opioids or muscle relaxants, or the body temperature on arrival in the recovery room.

Discussion

The incidence of postanesthetic apnea in the present study for all ex-preterm infants up to 60 weeks postconceptual age was 10.1%. This is consistent with pre-

viously published results.[1-4] The variability in the incidence of postanesthetic apnea among these studies may be attributed to several factors. The first is the inconsistency in reporting the incidence of apnea on the basis of postconceptual age.[1-3] In the present study, there was a 25% incidence of postanesthetic apnea in infants younger than 44 weeks postconceptual age, compared with a zero incidence in 61 infants 44–60 weeks postconceptual age ($P < 0.05$). Other factors include differences in patient populations and the presence of coexisting disease,[4] the small numbers of patients studied, differences in anesthetic techniques,[4] types of surgery, and the method and duration of apnea monitoring. We attempted to minimize the number of false-positive episodes of apnea by verifying each episode of recorded apnea with direct observation of respiration by a constant care nurse who was present in the room at all times during the monitored period. To determine the true incidence of postanesthetic apnea in ex-preterm infants, it is important to consider all of the above factors.

Postanesthetic apnea monitoring has been recommended for ex-preterm infants up to 44,[3] 46,[2] and 60 weeks[4] postconceptual age. Our data support the recommendation of Welborn *et al.*[3] to monitor ex-preterm infants up to 44 weeks postconceptual age for postanesthetic apnea. In the study by Liu *et al.*,[2] all infants who required postoperative ventilatory support were younger than 41 weeks postconceptual age, and those who did not require support were older than 46 weeks postconceptual age. The age distribution of their study population differed from ours in that Liu *et al.* did not report the results from infants between 41 and 46 weeks postconceptual age.[2] Therefore, they concluded that all ex-preterm infants younger than 46 weeks postconceptual age required monitoring for postanesthetic apnea. However, the present study included 42 infants between 41 and 46 weeks postconceptual age. Three of these 42 infants who were younger than 44 weeks postconceptual age experienced apnea. This supports the recommendation that ex-preterm infants up to 44 weeks postconceptual age be monitored for apnea after general anesthesia.[3]

Before 1987, we monitored ex-preterm infants who were younger than 44 weeks postconceptual age as inpatients for at least 12 h after surgery. In 1987, we extended the upper age limit of ex-preterm infants who required monitoring for postanesthetic apnea from 44 to 60 weeks postconceptual age after Kurth *et al.* reported postanesthetic apneas in five infants between 49 and 54 weeks postconceptual age and one infant between 55 and 60 weeks postconceptual age.[4] However, the results of the present study do not support the observations of Kurth *et al.* that postanesthetic apnea is common in ex-preterm infants between 45 and 60 weeks postconceptual age. Several possible explanations could account for the difference in results between the present study and that of Kurth *et al.* Coexisting diseases including central nervous system lesions may have been responsible for some of the episodes of apnea in ex-preterm infants older than 44 weeks postconceptual age in the study by Kurth *et al.* The only older ex-preterm infant in the present study who developed postanesthetic apnea had a documented intraventricular hemorrhage preoperatively. Second, differences in anesthetic technique may have contributed to the difference in the incidences of apnea between the two studies. The use of nondepolarizing muscle relaxants may be associated with an increased incidence of postoperative complications including apnea in ex-preterm infants.[5] Pancuronium was administered to 47 of the 49 patients (96%) in the series from Kurth *et al.* but to only 5% of infants in this study.[4] This also may suggest that the duration of surgery in the present study was shorter than that in the study by Kurth *et al.*, *i.e.*, exposure to anesthesia was reduced. However, the analysis of our data does not support a significant relationship between the use of nondepolarizing muscle relaxants and the incidence of postanesthetic apnea. These results are consistent with the findings of Liu *et al.*[2] Nonetheless, the importance of anesthetic technique as a determinant of postoperative apnea will remain unclear until a prospective randomized study is completed. Lastly, we may have underestimated the true incidence of postanesthetic apnea. Although our incidence of postanesthetic apnea in ex-preterm infants younger than 60 weeks postconceptual age (10.1%) is consistent with previously published data,[1-4] equipment and technical deficiencies may have led to an underestimation of the true incidence. We attempted to minimize this source of error by verifying all apneas with direct nursing observation. Obstructive apnea, however, cannot be detected by a pneumogram or by impedance monitoring; it requires evidence of cessation of respiratory gas flow. Because we did not measure respiratory gas flow, our incidence of postanesthetic apnea may have been underestimated. The extent of the error is small, however, because the incidence of obstructive apnea is reported to occur in only 3–6% of all apneic episodes in one series of in-

fants.[10] Even if such episodes had been undetected, none of them resulted in cardiorespiratory collapse or required intervention or resuscitation.

Bradycardia without apnea developed in seven infants who were older than 44 weeks postconceptual age. None of these episodes required intervention. It is reassuring to note that the minimum heart rate was 79 beats/min, the bradycardia lasted only 3–5 s, and most importantly, all episodes resolved without intervention. Although the sample size of infants who experienced bradycardia was small, it would appear that bradycardia is not predictive of postanesthetic apnea.

We found that coexisting respiratory or neurologic disease, a history of neonatal apnea, and the anesthetic agents administered were not associated with an increased incidence of postanesthetic apnea. Our results differ from a preliminary report by Mestad *et al.*,‡ who observed an association between respiratory disease and the incidence of postanesthetic apnea. This may be explained in part by a type II statistical error in the present study (only 40 patients in this study had preexisting respiratory disease). Based on the incidences of postanesthetic apnea in our study, $\alpha_2 = 0.05$ and $\beta = 0.20$ (power of 80%), we would require at least 376 infants with respiratory disease, 51 with neurologic disease, 99 with a history of neonatal apnea, 1,216 infants who received nondepolarizing muscle relaxants, and 162 who received opioids to establish relationships between these factors and postanesthetic apnea.[11]

We found that, with the exception of one infant with severe neurologic disease, none of the ex-preterm infants 44–60 weeks postconceptual age included in our study experienced postanesthetic apnea. However, the age of the infants was not distributed evenly between 44 and 60 weeks. More than half of the infants in this study were younger than 50 weeks postconceptual age. Because the likelihood of postanesthetic apnea increases as postconceptual age decreases, this skewed age distribution should favor an increased likelihood of postanesthetic apnea than a cohort with a homogeneous age profile. If our sample population represents the entire population of ex-preterm infants older than 44 weeks postconceptual age, the zero incidence of apnea in 61 ex-preterm infants predicts a maximum long-run risk of postanesthetic apnea of 5% with 95% confidence.[9]

‡ Mestad PH, Glenski JA, Binda RE: When is outpatient surgery safe in preterm infants (abstract)? ANESTHESIOLOGY 69:A744, 1988.

We found that all infants who had postanesthetic apnea experienced their first episode within 12 h after and their last episode between 4 and 48 h after discontinuation of anesthesia. These times are consistent with the results of previous studies.[1,2,4] Because the first episode of postanesthetic apnea can occur as late as 12 h after discontinuation of anesthesia, we recommend that all ex-preterm infants younger than 44 weeks postconceptual age be monitored for apnea overnight. In our practice, these infants are discharged home the morning after surgery if they have been apnea-free for at least 12 h.

All patients included in this study were admitted to the hospital for apnea monitoring overnight. However, 65 of the infants underwent surgical procedures that otherwise would have been performed on an outpatient basis. Of these infants, four experienced postanesthetic apnea: three after hernia repair and one after rectal biopsy (table 4). The incidence of apnea in infants undergoing procedures appropriate for an inpatient setting did not differ significantly from the incidence in infants undergoing procedures appropriate for an outpatient setting. Therefore, the type of surgery (minor outpatient *vs.* major inpatient procedures) was not predictive of the likelihood of postanesthetic apnea in the sample population studied.

With increases in the cost of medical care and hospitalization, there are parallel increases in the demand to perform minor surgical procedures in an ambulatory setting. However, our data demonstrate that, even after minor ambulatory procedures such as inguinal hernia repair, ex-preterm infants are at increased risk of complications that may be life-threatening if unrecognized and untreated (table 4). To avoid unnecessary hospital admission, we have defined the age group of ex-preterm infants who are at greatest risk for developing postanesthetic apnea. Our data suggest that ex-preterm infants younger than 44 weeks postconceptual age are at risk for postanesthetic apnea. It would be prudent to refer these infants to an institution equipped to provide intensive respiratory care to infants. In our practice, all ex-preterm infants younger than 50 weeks postconceptual age are monitored overnight as inpatients, even after minor surgical procedures performed under general anesthesia. This practice decreases the probability of discharging home ex-preterm infants at risk for postanesthetic apnea because of overestimation of postconceptual age. In our practice, ex-preterm infants older than 50 weeks postconceptual age are observed closely in the postanesthetic recovery unit for 2 h after

Table 4. Characteristics of Infants with Apnea Included in Statistical Analysis

Weight at Surgery (kg)	GA (weeks)	PCA (weeks)	Operation	ASA Physical Status	Neonatal Apnea History	Muscle Relaxant	Opioid
3.9	29	42	Inguinal hernia repair	I	No		
3.1	32	38.9	Ventricular peritoneal shunt	III	Yes		
3.0	33	38.2	Inguinal hernia repair	II	No		
2.6	36	37.5	Ventricular peritoneal shunt	II	Yes		
1.4	35	35.1	Colostomy	II	No	Curare	Fentanyl
2.8	28	39.3	Rectal biopsy	III	Yes		
2.9	28	40.6	Colostomy	III	Yes	Atracurium	Fentanyl
3.1	26	42.5	Inguinal hernia repair, circumcision	II	Yes	Atracurium	
3.2	33	37	Pyloromyotomy	I	No	Atracurium	
3.4	28	43	Bronchoscopy	III	Yes		

GA = gestational age; PCA = postconceptual age.

discontinuation of anesthesia. The decision to monitor these infants for an extended period with constant nursing and cardiorespiratory monitoring is individualized on the basis of coexistent cardiorespiratory or neurologic disease and their course in the immediate postrecovery period.

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