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Anemia and Postoperative Apnea in Former Preterm Infants

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To examine the association between anemia and postoperative apnea in former preterm infants, 24 former preterm infants of less than 60 weeks postconceptual age undergoing inguinal hernia repair were studied. A hematocrit of at least 25% was required for study participation. General endotracheal inhalational anesthesia, supplemented with neuromuscular blockade and controlled ventilation, was used. No barbiturates or opioids were administered. Respiratory pattern and heart rate were recorded for at least 12 h postoperatively using an impedance pneumograph. Tracings were analyzed for evidence of apnea, periodic breathing, and/or bradycardia by a pulmonologist unaware of the hematologic profile of the infant. Nineteen patients had a hematocrit of 30% or greater (group 1). Their mean (± standard deviation [SD]) gestational age was 33.5 ± 2.7 weeks and postconceptual age 45.5 ± 4.6 weeks. Five infants had a hematocrit less than 30% (group 2). Their mean gestational age (± SD) was 32.4 ± 3.2 weeks and postconceptual age 43.6 ± 5.5 weeks. Anemic infants had an 80% incidence of postoperative apnea *versus* 21% in infants with a normal hematocrit ($P < .03$). In the infants who developed postoperative prolonged apnea and/or bradycardia, a prior history of apnea was equally present in both groups (21% in group 1 and 20% in group 2). This study shows that anemia in former preterm infants can be associated with an increased incidence of postoperative apnea. (Key words: Anesthesia, pediatric: preterm. Complications: apnea; bradycardia; periodic breathing. Transfusion: anemia.)

SEVERAL RETROSPECTIVE AND PROSPECTIVE studies have established that former preterm infants are at risk for developing postoperative complications, including apnea.[1–5] Whether anemia contributes to these complications has not been studied in a controlled prospective manner.

The minimal acceptable hematocrit concentration for anesthesia and minor surgery has been set at 30%.[6] This value is arbitrary, and no scientific data are available to support the benefit of or adverse consequences from any specific hematocrit concentration. This issue is of special importance in pediatric anesthesia since former preterm infants with a low hematocrit frequently are scheduled for minor surgical procedures in which no or minimal blood loss is anticipated.

We designed this prospective study to evaluate whether an association exists between the incidence of postoperative apnea, periodic breathing, and/or bradycardia and preoperative hematocrit in former preterm infants.

Materials and Methods

Informed consent from parents and institutional approval for the study were obtained. Twenty-four otherwise healthy (ASA physical status 1 or 2) former preterm infants born at ≤ 37 weeks gestational age and undergoing general anesthesia for inguinal hernia repair were studied. All were less than 60 weeks postconceptual age at the time of operation. Infants with preexisting cardiac, neurologic, or metabolic diseases, as well as those receiving methylxanthines or caffeine, were excluded from participation in the study. Hemoglobin (Hb) and hematocrit were measured preoperatively using a Coulter S plus IV automated cell counter (Hialeah, FL). All infants were arbitrarily required to have a preoperative hematocrit of at least 25%.

General anesthesia with nitrous oxide, oxygen, and halothane supplemented with neuromuscular blockade using atracurium, controlled ventilation, and tracheal intubation was used in all cases. No perioperative barbiturates or opioids were administered. Heart rate, heart sounds, blood pressure, ECG, temperature, Hb oxygen saturation (Sp_{O_2}), and end-tidal carbon dioxide were monitored. Following induction of anesthesia, venous blood was obtained for measurement of reticulocyte count, quantitative fetal Hb (Hb F), Hb electrophoresis, and 2,3-diphosphoglycerate (2,3-DPG), and adenosine triphosphate (ATP) concentrations. Reticulocyte counts were done using a manual whole blood method with methylene blue; 1,000 red cells were counted and the result expressed as a percentage.

ATP and 2,3-DPG concentrations were measured using protein free supernatants prepared from whole blood collected in heparin. Assays were performed using the quantitative, enzymatic method of Sigma Diagnostics (St. Louis, MO) and read spectrophotometrically at 340 nm. A cellulose acetate Hb electrophoresis was performed; the proportion of Hb F migrating on the gel was quantitated using a densitometer and reported as percentage Hb F.

At the completion of surgery, residual neuromuscular blockade was antagonized with neostigmine 0.07 mg/kg and atropine 0.02 mg/kg. Full recovery of neuromuscular

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function was confirmed prior to tracheal extubation by monitoring train-of-four stimulation of the ulnar nerve and by observing the ability of the infant to sustain lifting of all limbs. The trachea was extubated in the operating room when the patient appeared fully awake. Any postoperative pain or discomfort was treated with acetaminophen 10 mg/kg orally or rectally as needed. All infants were monitored in the postanesthesia recovery room and on the ward with ECG and respiratory monitors equipped with alarms. Patterns of respiration and heart rate were continuously recorded using an impedance pneumograph (Healthyne 16000®) with an Oxford® recorder for at least 12 h postoperatively. A pulmonologist, unaware of the hematologic profile of the infants, examined the recorded data for apnea, periodic breathing, and bradycardia.

Brief apnea was defined as a respiratory pause of less than 15 s not associated with bradycardia. Prolonged apnea was defined as a respiratory pause of 15 s or longer or of less than 15 s if accompanied by bradycardia. Bradycardia was defined as a heart rate less than 100 beats per min for at least 5 s. Periodic breathing was defined as three or more periods of apnea 3–15 s separated by less than 20 s of normal respiration. The total time (minutes) of periodic breathing was then divided by the total sleep time (minutes) in the recording to determine the percent periodic breathing. Periodic breathing less than 1% was considered normal. The difference in the incidence of these events between infants whose hematocrit levels were $\geq 30\%$ and those whose levels were $< 30\%$ was compared using Fisher's exact test, and the hematologic and age differences were analyzed by the two-sample t test or by the nonparametric Mann-Whitney test if the samples failed the Wilks-Shapiro test for normality ($P < 0.05$). Differences were considered statistically significant if P values were < 0.05.

Results

Twenty-four former preterm infants were studied. Nineteen had a hematocrit of 30% or greater (group 1) and five had a hematocrit of less than 30% (group 2). There were no significant differences between the two groups in gestational and postconceptual ages or in historic evidence of preoperative apnea (table 1). The hematologic profile and the incidence of postoperative apnea, periodic breathing, and bradycardia in the two groups is also shown in table 1.

None of the infants studied had been transfused. No infants had an electrophoretic pattern consistent with sickle cell anemia or any other hemoglobinopathy. The reticulocyte count and Hb F concentration of infants in group 2 were significantly greater than those of infants in group 1 ($P < 0.05$ and < 0.03 respectively). The ATP and 2,3-DPG concentrations of infants in group 2 were less than those in group 1 ($P < 0.008$).

Postoperative pneumograms showed that infants in group 2 had a significantly greater incidence of prolonged apnea than did those in group 1 and that one infant in group 2 developed bradycardia ($P < 0.03$). None of these apneic episodes was diagnosed clinically, and no treatment was required.

Demographic data of infants who developed postoperative prolonged apnea and/or bradycardia in both

TABLE 1. Comparison of Age, Hematologic Profile, History of Apnea, and Postoperative Complications in the Two Study Groups

	Group 1 Hct ≥ 30% (n = 19)	Group 2 Hct < 30% (n = 5)	*P*
Gestational age (weeks)			
Mean ± SD	33.5 ± 2.7	32.4 ± 3.2	>0.1*
Range	28–36	28–36	
Postconceptual age (weeks)			
Mean ± SD	45.5 ± 4.6	43.6 ± 5.5	>0.1*
Range	40–54	34–51	
History of apnea	4 (21%)	1 (20%)	>0.99†
Hematologic profile			
Hematocrit % (range)	32.7–39.1	27.6–29.7	
Reticulocytes % (mean ± SD)	2.32 ± 1.34	4.42 ± 2.49	<0.05*
HbF% (mean ± SD)	36.7 ± 15.0	61.2 ± 33.8	<0.03‡
ATP μM/dl (mean ± SD)	50.8 ± 5.6	43.0 ± 3.3	<0.008‡
2,3-DPG μM/ml (mean ± SD)	1.55 ± 0.28	1.27 ± 0.21	>0.07‡
Postoperative complications			
Brief apnea	0	0	
Periodic breathing > 1%	0	1 (20%)	>0.2†
Prolonged apnea	4 (21%)	4 (80%)	<0.03†
Bradycardia	0	1 (20%)	>0.2†

* Mann-Whitney test.
† Fisher's exact test.
‡ Two sample t test.

TABLE 2. Demographic Data of Infants Who Developed Postoperative Apnea and/or Bradycardia *versus* Those Without Apnea

	Postoperative Apnea and/or Bradycardia (n = 9)	No Postoperative Apnea and/or Bradycardia (n = 15)	
Hematocrit (%)			
Mean ± SD	31.1 ± 3.2	35.2 ± 2.2	$p < .05$[a]
Range	27.6–35.3	32.7–39.1	
Gestational age (weeks)			
Mean ± SD	32.1 ± 2.8	34.0 ± 2.6	$p > .05$[a]
Range	28–36	28–36	
Postconceptual age (weeks)			
Mean ± SD	42.2 ± 4.3	46.9 ± 4.4	$p < .01$[a]
Range	39–51	41–54	
HbF %			
Mean ± SD	51.1 ± 26.8	36.1 ± 17.0	$p > .10$[b]
Range	20.3–75.3	11.4–68.4	
2,3-DPG (μM/ml)			
Mean ± SD	1.30 ± 0.26	1.61 ± 0.24	$p < .01$[a]
Range	1.00–1.80	1.25–2.00	
ATP (μM/dl)			
Mean ± SD	45.2 ± 5.8	51.6 ± 5.1	$p < .01$[b]
Range	37.2–54.4	44.5–59.9	
Prior history of apnea: n (%)	2 (22%)	3 (20%)	

[a] Mann-Whitney test. [b] Two sample t-test.

groups is shown in table 2. Infants who developed postoperative apnea and/or bradycardia had a significantly ($P < 0.01$) lower postconceptual age than did those who did not. The probability that such a difference in postconceptual age between groups 1 and 2 (table 1) existed but was not detected is 30%. Infants who developed apnea also had significantly lower hematocrit ($P < 0.05$) and ATP (< 0.01) and 2,3-DPG (< 0.01) concentrations.

Discussion

We undertook this study to better understand the relationships among postconceptual age, anemia, and apnea in an effort to improve our management of premature infants exposed to the stress of anesthesia and surgery. Our findings point to the presence of lower Hb, hematocrit, and ATP and 2,3 DPG concentrations in infants who developed postoperative apnea and bradycardia. In anemic infants, ATP and 2,3-DPG are measured together as a reflection of glucose metabolism and red cell viability. Progressive increases in 2,3-DPG and ATP over time are controlled by dietary phosphorus and the postgestational age of the infant and usually coincide with the transition from fetal to adult type Hb.[7]

The pathogenesis of apnea and periodic breathing in preterm infants is unclear, but it probably is multifactorial and reflects the immaturity of the mechanisms that control breathing. One of the factors believed to play a role in the development of apnea is anemia.[8] The diagnosis of anemia in preterm infants, however, is imprecise; Hb and hematocrit measurements alone, for example, are poorly correlated with physiologic determinations of oxygen delivery and response to transfusion.[9]

Premature infants are born with lower Hb concentrations and a higher Hb F fraction than are full-term infants. Furthermore, they experience a decrease in Hb concentration, which reaches a nadir at 1–3 months of age. This so-called "physiologic anemia" of prematurity is usually benign and self-limited, but in some infants it may result in signs and symptoms that include apnea[10] and poor weight gain.[11,12] In these infants transfusion with blood containing hemoglobin A (Hb A) corrects the anemia and is believed also to improve peripheral oxygen release, improve central nervous system oxygenation, and abrogate apneic episodes in some infants.[10,13,14] Some authors, however, have refuted these benefits[12,15] or have attributed them to simple correction of the preexisting hypovolemia that is often associated with anemia. Moreover, blood transfusions are not without their own significant risks and seldom are justified to correct anemia for surgery where no blood loss is anticipated.

In our study, infants who developed postoperative apnea did not increase their ATP and 2,3-DPG concentrations in response to anemia. Furthermore, their Hb F concentrations were significantly greater than in the nonapneic groups. These manifestations of stress erythropoiesis have been also described in infants with sudden infant death syndrome[16] and may play some role in predisposing the infant to central nervous system hypoxia and subsequent apnea. It is interesting that, besides being anemic, infants who developed apnea had a lower postconceptual age than did those without apnea (table 2). It

is impossible to rule out the possibility that the absence of apnea in infants with higher postconceptual age and Hb can be due simply to simultaneous maturation of the central nervous system and improvement in hematocrit.

The clinical significance of apneic episodes that are long enough to result in bradycardia but that abate before cardiorespiratory arrest develops remains unknown. Although one may argue that the spontaneous return of respiration is likely to occur in these infants, one may also argue that potential deleterious outcomes such as hypoxic–ischemic effects on the brain or sudden infant death may occur.

In conclusion, although it is generally accepted that preterm infants with inguinal hernia are at risk for incarceration and possible vascular compromise of the intestines and gonads, the risk of postoperative apnea is also significant especially in the presence of anemia. Our data suggest that anemic preterm infants with hematocrits of $< 30\%$ should have elective surgery delayed until such time as their hematocrit is greater than 30%. When surgery cannot be deferred, anemic infants must be observed and monitored very carefully in the postoperative period.

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