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High-dose Caffeine Suppresses Postoperative Apnea in Former Preterm Infants

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Thirty-two former preterm infants (≤44 weeks postconceptual age) undergoing inguinal hernia repair were prospectively studied. General inhalational anesthesia with neuromuscular blockade was used. No barbiturates or opioids were given. Infants were randomly divided into two groups. Group 1 received iv caffeine 10 mg/kg immediately after induction of anesthesia. Group 2 received iv saline. Respiratory pattern, heart rate, and Sp_{O_2} were monitored using an impedance pneumograph and a pulse oximeter, respectively, for at least 12 h postoperatively. Tracings were analyzed for evidence of apnea, periodic breathing, and/or bradycardia by a pulmonologist unaware of the drug given. None of the patients who received caffeine developed postoperative bradycardia, prolonged apnea, or periodic breathing, and none had postoperative Sp_{O_2} less than 90%. In the control group 13 (81%) developed prolonged apnea 4–6 h postoperatively. Fifty percent of the patients had Sp_{O_2} less than 90% at the time. This study shows that iv caffeine 10 mg/kg is effective in the control of apnea in otherwise healthy expremature infants between 37 and 44 weeks of postconceptual age. It is still recommended, however, that all infants at risk be monitored for at least 12 h for apnea and bradycardia following general anesthesia. (Key words: Anesthesia: pediatric. Complications: apnea; bradycardia; periodic breathing. Pharmacology: caffeine).

FORMER PRETERM INFANTS are prone to develop apnea and/or bradycardia in the postoperative period.[1–5]

Recently, the use of caffeine as a respiratory stimulant has been shown to be effective in the management of neonatal apnea and postoperative ventilatory dysfunction in a small series of former premature infants.[6] An iv caffeine dose of 5 mg/kg resulted in a significant reduction in the incidence of prolonged postoperative apnea (≥15 s or shorter apnea with bradycardia), but short apnea (<15 s) persisted possibly because the caffeine blood concentration achieved was at the lower end of the ideal therapeutic range.

We designed a prospective, double-blind, randomized study to examine the effectiveness of a higher dose of iv caffeine in the control of postoperative apnea following anesthesia and surgery in former preterm infants.

Materials and Methods

Informed consent and institutional approval for the study were obtained. Thirty-two otherwise healthy (ASA physical status 1 or 2) former premature infants born at ≤37 weeks gestational age undergoing general anesthesia for inguinal hernia repair were studied. All were ≤44 weeks postconceptual age at the time of operation (range, 37–44 weeks). Infants with preexisting cardiac, neurologic, or metabolic diseases, as well as those already receiving methylxanthines, were not included.

No preoperative medication was used. Heart rate and heart sounds, arterial blood pressure, ECG, temperature, hemoglobin oxygen saturation (Sp_{O_2}), and end-tidal CO_2 were monitored. General anesthesia with a volatile anesthetic supplemented with neuromuscular blockade was used in all cases. The trachea of each patient was intubated. No barbiturates, opioids, or local anesthetics were administered in the perioperative period.

Infants were randomly divided into two groups. Group 1 patients received iv caffeine 10 mg/kg injected over a 2-min period. The drug was administered immediately following induction of anesthesia, so that its peak effect would be evident at the end of surgery. Patients in group 2 received iv saline and served as controls. The solutions were supplied by the hospital pharmacy in a double-blind fashion. At the completion of surgery, a venous blood specimen was drawn to measure serum caffeine concentration using the Emit® caffeine assay. All patients had the neuromuscular blockade antagonized using atropine 0.02 mg/kg and neostigmine 0.07 mg/kg iv, and the trachea was extubated in the operating room when the patient was fully awake. Postoperative pain/discomfort was treated by the administration of acetaminophen 10 mg/kg orally as needed. The patterns of respiration, heart rate, and Sp_{O_2} were continuously monitored and recorded using an impedance pneumograph (Healthdyne 16000®) with an Oxford® recorder and Nellcor N-200® pulse oximeter, respectively, for at least 12 h postoperatively on monitored beds on the ward. The recorded data were analyzed for evidence of apnea, periodic breathing, bradycardia, and hemoglobin desaturation in all patients.

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TABLE 1. Age, Number of Infants with Apnea, PB, Desaturation, and Postoperative Ventilation in Groups 1 and 2

	Group 1 Caffeine (n = 16)	Group 2 Control (n = 16)
Gestational age (weeks)		
Mean ± SD	30.0 ± 3.4	30.4 ± 3.7
Range	24–35	25–36
Postconceptual age (weeks)		
Mean ± SD	40.9 ± 2.0	40.5 ± 1.9
Range	37–44	37–44
History of preoperative apnea	10 (63%)	8 (50%)
Temperature (° C) on admission to recovery room (range)	35.5–37.5	35.5–37.5
Duration of surgery (range in minutes)	35–55	35–55
Postoperative prolonged apnea or apnea with bradycardia	0	13 (81%)*
Postoperative PB > 1%	0	4 (25%)
Postoperative hemoglobin saturation < 90%	0	8 (50%)*
Postoperative intubation or ventilation	0	0
Postoperative caffeine level mg/l (range)	15–19	0

* $P < 0.05$, Fisher's exact test.

This was done by a pulmonologist who was blinded to patient group assignment.

Brief apnea was defined as a respiratory pause of less than 15 s not associated with bradycardia. Prolonged or potentially life-threatening apnea was defined as a respiratory pause of 15 s or longer, or less than 15 s if accompanied by bradycardia. Bradycardia was indicated by heart rate less than 100 beats/min for at least 5 s, and periodic breathing (PB) 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 PB was then divided by the total sleep time (minutes) in the recording to determine the percent of PB. PB less than 1% was considered normal. Hemoglobin desaturation was defined as an Sp_{O_2} less than 90%. The incidence of these events in the two groups were compared using Fisher's exact test. Results were considered significant if P values were less than 0.05.

Results

Thirty-two former preterm infants were studied. Sixteen received caffeine (group 1) and 16 received saline and served as controls (group 2). There were no significant differences between the two groups in gestational or postconceptual ages, or in the presence of preoperative apnea by history (table 1).

The incidence of postoperative apnea, PB, and hemoglobin desaturation in the two groups is shown in table 1. None of the patients who received caffeine developed postoperative bradycardia, prolonged apnea, or PB, and none had postoperativeSp_{O_2} less than 90%. In the control group 13 patients (81%) developed prolonged apnea 4–6 h postoperatively. Of those, two infants developed prolonged apnea (>15 s) with bradycardia. In the remaining 11 infants, the diagnosis of prolonged apnea was based on the presence of apnea lasting <15 s associated with bradycardia. Fifty percent of the patients had Sp_{O_2} less than 90% at the time apnea was recorded. Four infants developed PB. None of these apneic episodes was diagnosed clinically. All were detected when the alarms were activated or subsequent to the patients' discharge by analysis of the pneumographic tracings. None of the patients in either group required tracheal intubation or controlled ventilation postoperatively. The difference in the incidence of life-threatening or prolonged apnea with bradycardia and desaturation between the two groups is statistically significant ($P < 0.05$).

Discussion

Premature infants undergoing general anesthesia within the first few months of life are prone to develop apnea and/or bradycardia in the postoperative period.[2–6] The incidence of perioperative apneic episodes is inversely correlated with gestational age and weight.

Although the cause of apnea after anesthesia is unknown, recent studies have speculated that the respiratory center in preterm infants is easily inhibited by trace concentrations of anesthetics, endorphins, or hypoxemia,[7]; thus, central respiratory stimulants and opiate antagonists, such as methylxanthines and naloxone, when given postoperatively, may prevent apnea.[8,9]

Methylxanthines have been widely used by neonatologists for the management of apnea of prematurity. Although therapeutic blood concentrations and pharmacokinetic profiles in premature infants have been established for both theophylline[10] and caffeine,[11,12] caffeine has the distinct advantage of being a more potent CNS and respiratory stimulant, and possesses fewer cardiac side effects than does theophylline.[13] Other reasons for our selection of caffeine in the present study include a wider therapeutic index, ease of administration, less fluctuation in plasma concentrations, less need for therapeutic monitoring, and fewer peripheral effects.[14]

In adults and children, theophylline undergoes extensive demethylation and oxidation.[15] In contrast, demethylation and oxidation pathways are markedly deficient in neonates, who, instead, tend to methylate theophylline to produce caffeine.[16]

The elimination rate of all methylxanthines is significantly decreased in the newborn infant. In adults the half-lives of caffeine and theophylline are 6 h[17] and 9 h,[18] respectively, but in newborns the elimination half-lives are prolonged (caffeine 37–231 h, theophylline 12–64 h). In a study of the maturation of caffeine elimination, Aranda *et al.*[17] found that the caffeine elimination half-life decreases with age and reaches adult values by about 4 months of age.

In a previous study[6] of otherwise healthy premature infants, we found that the administration of 5 mg/kg iv caffeine significantly reduced the incidence of prolonged postoperative apnea. However, it did not totally abolish all types of ventilatory dysfunction. Although the dose of caffeine that we selected (5 mg/kg) has been shown to be effective in other studies,[19] the resultant caffeine concentration (5–8.6 mg/l) was on the low side of the ideal therapeutic range (8–20 mg/l).[12]

Although naloxone is used in newborn infants to reverse respiratory depression that results from therapeutic opioids given to the mother,[20] its role in the prevention of apnea in the postoperative period is yet to be established.

The significance of apneic episodes that are long enough to result in bradycardia and arterial oxygen desaturation but eventually self-correct before cardiorespiratory arrest develops remains enigmatic. Although one may argue that the spontaneous return of respiration is the most likely outcome in these infants, potential deleterious hypoxic–ischemic effects on the brain,[21] or even relationship to sudden infant death syndrome (SIDS) in many children have been suggested.[22] Failure to detect and/or treat breathing irregularities in these high-risk infants may increase the likelihood of sudden death.

This study shows that iv caffeine 10 mg/kg is effective in the control of brief and prolonged apnea in otherwise healthy expremature infants between 37 and 44 weeks of postconceptual age. The caffeine concentration achieved (15–19 mg/l) with this dose is well within the recommended therapeutic range for this drug and requires one single iv administration. We recommend the use of caffeine 10 mg/kg in addition to monitoring for apnea and bradycardia in all infants at risk of postoperative apnea following general anesthesia.

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