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Post-operative apnoea in the former preterm infant: a review

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Summary

Former preterm infants are known to be at increased risk for apnoea, periodic breathing, and bradycardia. When surgery cannot be postponed until respiratory function is more mature, special peri-operative considerations and measures are essential. In this article, the literature concerning this subject is reviewed, summarizing prospective and retrospective studies of risks associated with surgery in former preterm infants during the first year of life. This work is placed within the context of our ongoing studies of peri-operative risk in former preterm infants undergoing surgery at the Children's National Medical Center (CNMC), which have focused on three particular areas: (1) the effects of spinal versus general anaesthesia on the incidence of post-operative apnoea and bradycardia; (2) the possible contribution of anaemia of prematurity to surgical risk; and (3) the effect of peri-operative caffeine in preventing post-operative apnoea. Recommendations are made concerning surgical and anaesthetic management of infants who undergo surgery at < 44 weeks' post-conceptual age.

Keywords: anaesthesia: paediatric, preterm; complications: apnoea, bradycardia, periodic breathing; pharmacology: caffeine

Infants whose gestational age at birth is ≤ 37 weeks and who undergo general anaesthesia during the first 6 months of life are at increased risk for respiratory and/or cardiovascular complications during the peri-operative period, among the most common and most serious of which are apnoea, periodic breathing (PB), and/or bradycardia (Steward 1982; Liu *et al.* 1983; Welborn *et al.* 1986; Kurth *et al.* 1987). A retrospective study (Steward 1982) in healthy infants undergoing minor surgery found that 12% of the preterm infants had apnoea during anaesthesia and in the first 12 post-operative hours, although none required post-operative mechanical ventilation. In a prospective study (Liu *et al.* 1983) of 41 former preterm infants undergoing both minor and major surgical procedures, 18 infants, less than 41 weeks' post-conceptual age had post-operative apnoea, and some required post-operative mechanical ventilation. However, none of the infants greater than 46 weeks' post-conceptual age developed prolonged post-operative apnoea. These authors concluded that infants < 46 weeks post-conceptual age are at risk for post-operative apnoea, and that any such infant

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in whom surgery cannot be deferred should be hospitalized and monitored for 24 hours following surgery.

The incidence of apnoeic episodes in the preterm infant is inversely related to post-conceptual (gestational + postnatal) age; this may be due to the fact that auditory brain stem conduction time increases as gestational age decreases (Henderson-Smart, Pettigrew & Campbell 1983).

The significance of apnoeic episodes that are long enough to trigger a pre-set alarm limit or result in bradycardia, but self-correct before cardiorespiratory arrest develops, is unknown. Deleterious hypoxic-ischaemic effects on the brain may result from these episodes.

Prolonged apnoea is always pathologic. Periodic breathing (PB) by contrast, occurs in up to 95% of otherwise healthy preterm infants during sleep and is a result of inadequate development of ventilatory control (Kelly & Shannon 1979). During PB, there is a gradual reduction in ventilation and oxygenation that may lead to prolonged apnoea. Kelly and Shannon (1979) reported a marked increase in PB in infants with near-miss sudden infant death syndrome. Some preterm infants with PB demonstrate hypoventilation, a shift to the right of the CO_2 response curve, and a paradoxic response to hypoxia.

Inguinal hernias are common in former preterm infants, with an incidence of 13% among infants born at < 32 weeks gestational age (Peevy, Speed & Hoff 1986). Because of a high risk of incarceration, early surgical repair is usually indicated. Former preterm infants undergoing herniorrhaphy, therefore, provide an excellent opportunity for the study of peri-operative complications. In previously published studies of such infants, we sought to identify those infants undergoing the procedure as outpatients who were most likely to develop respiratory problems following their discharge home (Welborn *et al.* 1986). Respiratory difficulties were detected using impedance pneumography, which measures changes in resistance in the chest as respiration occurs. Recorded data were scanned and the pneumogram analysed for apnoea, PB, and bradycardia. *Brief apnoea* was defined as a respiratory pause of < 15 s not associated with bradycardia. *Prolonged apnoea* was a respiratory pause of ≥ 15 s, or < 15 s if accompanied by bradycardia. *Periodic breathing* was three or more periods of apnoea of 3–15 s duration, separated by less than 20 s of normal respiration. The severity of PB was interpreted by relating its duration to the total sleep time. PB less than 1% of the recording was considered normal. *Bradycardia* was a heart rate of < 100 beats/min for at least 5 s.

Eighty-six infants (38 preterm, 48 full-term) were studied. Seven of the 48 full-term infants were ≤ 44 weeks post-conceptual age. None had a history of apnoea or any other risk factor, and none developed post-operative prolonged apnoea or PB. Twenty-two of the 38 preterm infants were ≤ 44 weeks post-conceptual age. Eighteen had a history of apnoea, yet none showed prolonged pre-operative or post-operative apnoea on pneumogram. PB was noted in 14 former preterm infants with post-conceptual ages of ≤ 44 weeks, compared with none of those with a post-conceptual age of > 44 weeks ($P < 0.001$). Two of the 14 patients in the former group showed PB 5 h after surgery.

We concluded that preterm infants ≤ 44 weeks post-conceptual age are at risk for post-operative ventilatory dysfunction. When surgery cannot be delayed, we recommended that those infants should be admitted to hospital and their respiratory function monitored for at least 12 h after surgery.

In a prospective study using pneumography, Kurth *et al.* (1987) reported a 37% incidence of prolonged apnoea following anaesthesia in a group of former preterm infants whose post-conceptual ages ranged from 32–55 weeks. The initial episode of apnoea occurred as late as 12 h following anaesthesia. Some of the infants in Kurth's study had more complicated medical histories and extensive surgery than those in our study. They concluded that former preterm infants < 60 weeks post-conceptual age should be monitored for at least 12 h post-operatively.

Special considerations relating to peri-operative risk

Spinal vs general anaesthesia

Several authors have sought to demonstrate whether spinal anaesthesia places infants at less risk for apnoea and related complications than general anaesthesia. Abajian *et al.* (1984) reported a retrospective study of 36 preterm infants undergoing a variety of operative procedures under spinal anaesthesia. Thirty-one

blocks were successful after the first attempt; five required a second attempt. Six patients who had successful spinal anaesthetics required intravenous narcotic or nitrous oxide supplementation. There were no episodes of hypotension or bradycardia and no peri-operative complications. Harnik *et al.* (1986) studied 20 infants who underwent 21 inguinal hernia repairs under spinal anaesthesia. Eleven of the infants in this prospective study were < 44 weeks post-conceptual age, and eight weighed < 2500 g. In some patients spinal anaesthesia was supplemented with general anaesthesia. Apnoea and bradycardia developed in one infant, following injection of tetracaine, who had a pre-operative history of frequent apnoea. These were the only intra-operative complications. Post-operative apnoea developed in one patient 8 h after the procedure, when the patient became hypothermic. No child demonstrated cardiovascular instability. The authors concluded that subarachnoid blockade was a satisfactory alternative to general anaesthesia for selected preterm infants and suggested that it may avoid the post-operative respiratory complications associated with general anaesthesia.

In a prospective, double-blind study using pneumography we compared the effects of spinal and general anaesthesia on the incidence of post-operative apnoea and bradycardia in 36 otherwise healthy former preterm infants ≤ 51 weeks post-conceptual age undergoing inguinal hernia repair (Welborn *et al.* 1990). Patients were initially randomly divided into two groups: (1) general inhalational anaesthesia with neuromuscular blockade, and (2) spinal anaesthesia using 1% tetracaine 0.4–0.6 $mg \cdot kg^{-1}$ with an equal volume of 10% dextrose and 0.02 ml adrenaline 1:1000, and sedation with ketamine 1–2 $mg \cdot kg^{-1}$ intramuscularly prior to the injection of the spinal anaesthetic. A third group formed at a later date (group 2B) did not receive sedation (Table 1).

Five of the 16 patients receiving general anaesthesia developed prolonged apnoea with bradycardia; two of these five infants had no history of apnoea. Eight out of nine infants in Group 2A developed prolonged apnoea with bradycardia; two of these had no history of apnoea. None of the patients in Group 2B developed post-operative prolonged apnoea, PB, or bradycardia. We concluded that unsupplemented spinal anaesthesia is better tolerated by otherwise healthy former preterm infants than either general anaesthesia or spinal anaesthesia with ketamine sedation.

Table 1
Pre-operative data on infants receiving spinal v general anaesthesia

Variable	*Group 1 General (n = 16)*	*Group 2A Spinal + K (n = 9)*	*Group 2B Spinal (n = 11)*
Gestational age (week)			
Mean	31.8	31.4	31.3
Range	25–36	28–36	26–35
Conceptual age (week)			
Mean	43.3	41.2	40.5
Range	38–51	36–46	35–45
History of pre-operative apnoea	6	6	3
*Prolonged apnoea with bradycardia	5 (31%)	8 (89%)	0
PB > 1%	1	2	0
Intubation or ventilation	0	0	0

Fisher's exact test
*$P < 0.015$ (groups 1 v. 2A)
$P < 0.0001$ (groups 2A v. 2B)
$P < 0.06$ (groups 1 v. 2B)
K, ketamine; PB, periodic breathing

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Anaemia and peri-operative risk

A second variable that may place former preterm infants at risk for respiratory and cardiac complications is anaemia (Kattwinkel 1980). In the human fetus, HbF ($\alpha 2\ \gamma 2$), constitutes the major haemoglobin (Hb) fraction. It reaches a peak of 95% at 10 weeks gestation, remains at this level until 30 weeks, and then declines to 80% at term, when most of the remaining Hb is HbA ($\alpha 2\ \beta 2$). After birth, HbF gradually disappears. Preterm infants have more HbF than term infants and experience a fall in Hb concentration that exceeds that in term infants (Aranda, Gorman & Outerbridge 1977; Stockman 1986). Hb concentrations reach their lowest levels at 1 to 3 months of age, when values as low as 7 to 8 $g \cdot dl^{-1}$ are commonplace (Stockman 1986).

Separated from the hypoxic intrauterine environment, the preterm baby during the first week of life enters a stage of inactive red cell production. The

reticulocyte counts fall to 2% or less, and the Hb concentration decreases. As the Hb concentration falls below 10 $g \cdot dl^{-1}$, there is a stimulus to erythropoiesis. The reticulocytes increase over a two-week period and the anaemia is corrected (Seip 1955; Zaizov & Matoth 1976).

This phenomenon, which is relatively benign and self-limiting, has been termed the 'physiologic' anaemia of prematurity. Although some authors have shown that red blood cell transfusions decrease the incidence of apnoea and periodic breathing in premature infants (Kattwinkel 1977; Joshi *et al.* 1987; DeMaio *et al.* 1989), others have found no clinical benefit from such transfusion (Blank, Sheagren & Vajaria 1984; Keyes *et al.* 1989).

The high Hb-O_2 affinity of the preterm infant's blood also may impair the release of O_2 to the tissues (Stockman, Garcia & Oski 1977). If the fall in Hb concentration was an isolated phenomenon, it would diminish the availability of O_2 to the tissues. However, while Hb concentration is decreasing, there are changes that lead to a progressive rightward shift of the Hb-O_2 equilibrium curve that permits more O_2 to be extracted from saturated Hb. The rightward shift or increase in the P50 is due to an increase in the proportion of adult Hb relative to HbF as well as to an increase in the concentration of 2,3 diphosphoglycerate (2,3-DPG).

While specific post-operative complications have been identified in the former preterm infant (Steward 1982; Gregory & Steward 1983; Liu *et al.* 1983; Welborn *et al.* 1986; Kurth *et al.* 1987), it is not known whether anaemia, decreased oxygen-carrying capacity, or both, may contribute to the frequency of these complications.

To study these problems we conducted a prospective study involving 24 former preterm infants undergoing inguinal hernia repair, all of whom were < 55 weeks post-conceptual age with a pre-operative Hct $< 25\%$ (Welborn *et al.* 1991). General endotracheal inhalational anaesthesia, supplemented with neuromuscular blockade and controlled ventilation, was used; no barbiturates or opioids were administered. Following the induction of anaesthesia, reticulocyte count, per cent fetal haemoglobin (HbF%), 2,3-DPG, and adenosine triphosphate (ATP) levels were measured. Respiratory pattern and heart rate were recorded using impedance pneumography for at least 12 h post-operatively.

Nineteen infants had a Hct $\geq 30\%$ (group 1), and five infants had a Hct $< 30\%$ (group 2). The reticulocyte and HbF levels of infants with a Hct $< 30\%$ were significantly higher than those of infants with Hct $\geq 30\%$. However, the ATP and 2,3-DPG concentrations of infants in group 2 were lower than those of infants in group 1. Infants in group 2 had a significantly higher incidence of post-operative prolonged apnoea than those in group 1. Four of 19 infants in group 1 developed post-operative prolonged apnoea, one of whom had a history of apnoea; by contrast, four of five infants in group 2 developed post-operative prolonged apnoea and/or bradycardia, and none had history of apnoea (Table 2).

We concluded that anaemia in former preterm infants can be associated with an increased incidence of post-operative apnoea. Red cell transfusions cannot be recommended or justified in these infants because of potential complications. Therefore, it may be preferable to delay elective surgery until the Hct is above 30% by supplementing the feeds with iron. If surgery cannot be deferred, anaemic infants must be observed and monitored carefully in the post-operative period.

Peri-operative use of caffeine

The mechanism underlying the respirogenic effect of caffeine, theophylline, and other methylxanthines is not well established. It has been suggested that these drugs increase the sensitivity of the medullary respiratory centre to CO_2, since minute ventilation is increased.

Both theophylline and caffeine are widely used as respiratory stimulants in preterm infants and have gained acceptance in the management of neonatal apnoea.

Bory, Baltassat and Porthault (1978) reported that theophylline is biotransformed to caffeine by preterm infants and suggested that a significant part of the respirogenic effect of theophylline may be attributed to caffeine. Theophylline undergoes extensive demethylation and oxidation in adults and children (Baselt 1982). Demethylation and oxidation pathways are markedly deficient in neonates, who tend to methylate theophylline to produce caffeine (Boutroy, Vert & Royer 1979). Although caffeine and theophylline share several pharmacological actions of therapeutic interest, the former is a more potent central nervous system and respiratory stimulant

Table 2
Comparison of age, haematologic profile, history of apnoea and post-operative 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	
Post-conceptual age (weeks)			
Mean ± SD	45.5 ± 4.6	43.6 ± 5.5	> 0.1†
Range	40–54	34–51	
History of apnoea	4 (21%)	1 (20%)	> 0.99*
Haematologic profile			
Haematocrit % (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 $\mu m \cdot dl^{-1}$ (mean ± SD)	50.8 ± 5.6	43.0 ± 3.3	< 0.008‡
2,3-DPG $\mu m \cdot ml^{-1}$ (mean ± SD)	1.55 ± 0.28	1.27 ± 0.21	> 0.07‡
Post-operative complications			
Brief apnoea	0	0	
Periodic breathing > 1%	0	1 (20%)	> 0.2*
Prolonged apnoea	4 (21%)	4 (80%)	< 0.03*
Bradycardia	0	1 (20%)	> 0.2*

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

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and possesses fewer cardiac side-effects than the latter. Caffeine has a greater therapeutic index, is easier to administer, and has fewer peripheral effects than theophylline. In addition, it is associated with a more stable plasma concentration and therefore requires less therapeutic drug-level monitoring than theophylline (Aranda, Groudin & Sasyniuk 1981). Caffeine plasma concentrations as low as 3–5 $mg \cdot l^{-1}$ can eliminate apnoeic spells in neonates; concentrations of 8–20 $mg \cdot l^{-1}$ are required for an optimal response (Aranda *et al.* 1979). No toxicity has been observed with concentrations as high as 50 $mg \cdot l^{-1}$. Theophylline, by contrast, may cause cardiovascular side-effects at plasma concentrations as low as 13 $mg \cdot l^{-1}$.

The effectiveness of the methylxanthines in reducing apnoeic episodes in infants may be reinforced by their elimination half-life. The elimination rate of the methylxanthines is significantly lower in newborns than in older infants. In adults the half-life of caffeine and theophylline are 6 h and 9 h (Gal *et al.* 1978), respectively; in newborns, the half-life is prolonged (caffeine 37–231 h, theophylline 12–64 h). The half-life of caffeine reaches adult values by about 4 months of age.

Our prospective, double-blind, randomized study involved 20 preterm infants born at ≤ 37 weeks gestational age undergoing inguinal hernia repair at ≤ 44 weeks post-conceptual age (Welborn *et al.* 1988). A caffeine base 5 $mg \cdot kg^{-1}$ intravenously, given slowly immediately following the induction of general anaesthesia in a single dose, significantly reduced the incidence of prolonged post-operative apnoea in the study group compared with controls. However, it did not abolish all types of ventilatory dysfunction. No infants in the study group v. eight in the control group had prolonged apnoea with bradycardia, eight of the former v. one of the latter, had brief (< 15 s) episodes of apnoea (Table 3).

Although the dose of caffeine that we selected has been shown to be effective in other studies (Turmen, Davis & Aranda 1981), the resultant caffeine concentration (range 5–8.6 $mg \cdot l^{-1}$) was at the low end of the ideal therapeutic range (8–20 mg·l) (Aranda & Turmen

Table 3
Pre-operative data on study patients (n = 20)

	Group 1 Caffeine (n = 9)	*Group 2 Control (n = 11)*
Gestational age (week)		
Mean ± SD	29.8 ± 3	31.6 ± 3
Range	25–35	26–36
Conceptual age (week)		
Mean ± SD	40.6 ± 2	40.6 ± 2
Range	38–44	35–44
History of pre-operative apnoea	8 (89%)*	5 (45%)
Prolonged apnoea with bradycardia	None	8 (73%)**
PB > 1%	None	2 (18%)
Apnoea < 15 s	8 (89%)	1 (9%)
Intubation or ventilation	None	None
Plasma caffeine concentration Range in mg l^{-1}	5–8.6	Zero

*$P < 0.001$ (Fisher's exact test)
**$P < 0.002$ (Fisher's exact test)

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Table 4
Pre-operative data on study patients (n = 32)

	Group 1 Caffeine (n = 16)	*Group 2 Control (n = 16)*
Gestational age (week)		
Mean	30.0	30.4
Range	24–35	25–36
Conceptual age (week)		
Mean	40.9	40.5
Range	37–44	37–44
History of pre-operative apnoea	10 (63%)	8 (50%)
Prolonged apnoea with bradycardia	None	13 (81%)
PB > 1%	None	4 (25%)
Desaturation < 90%	None	8 (50%)
Intubation or ventilation	None	None
Plasma caffeine concentration Range in mg·l^{-1}	15–19	0

*$P < 0.05$ (Fisher's exact test)

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1979). We therefore conducted a second study in which the study group received caffeine base 10 mg·kg^{-1} intravenously immediately after induction of anaesthesia; those in Group 2 received saline as controls (Welborn *et al.* 1989).

Thirty-two preterm infants (≤ 44 weeks post-conceptual age) undergoing inguinal hernia repair were studied. General inhalational anaesthesia with neuromuscular blockade was used. None of the 16 patients who received caffeine 10 mg·kg^{-1} developed post-operative prolonged apnoea, PB, or bradycardia, and none had a post-operative SpO_2 of < 90%, the predetermined cut-off point for desaturation. In the 16 patients in the control group, 13 developed prolonged apnoea 4 to 6 h post-operatively. Eight infants had an SpO_2 of less than 90% at the time. Plasma caffeine ranged from 15–19 mg·l^{-1} in the study group, compared with 5–8.6 mg·l^{-1} in our earlier study (Table 4).

The higher concentration was well within the recommended therapeutic range. We recommend the use of caffeine base 10 mg·kg^{-1} in addition to monitoring for apnoea and bradycardia in all infants at risk for post-operative apnoea following general anaesthesia.

Recommendations

This review has underlined several difficulties in interpreting the existing data concerning peri-operative risk among former preterm infants. First, much of the data is derived from retrospective reviews of patients who developed complications or from those with pre-existing disease who underwent complex surgical procedures. Secondly, the total number of these reported cases, some 200, is very small. Thirdly, institutional differences regarding patient selection, care of the preterm infant, assignment of gestational age, type of surgery, type of anaesthetic management, number of patients studied, and the method and duration of recording and monitoring apnoea may influence study results and conclusions. Finally, the development of prolonged apnoea in preterm infants may be influenced by a host of non-surgery-related factors, including hypoglycaemia, hypoxia, hyperoxia, sepsis, anaemia,

hypocalcaemia and environmental temperature changes (Schute 1977).

In spite of their limitations, however, these studies, do enable basic conclusions and guidelines concerning anaesthetic management of the former preterm infant to be formulated. First, preterm infants must be observed very carefully for episodes of post-operative apnoea, bradycardia or both. The age at which the preterm infant no longer presents an increased risk must be determined on an individual basis, depending on his or her growth and development and the presence or absence of other medical conditions.

Elective surgery should be deferred if possible until the infant's respiratory control mechanism is more mature (44–46 weeks post-conceptual age) in otherwise healthy former preterm infants. When surgery cannot be deferred until the infant is developmentally more mature, certain measures should be taken to minimize the risk of ventilatory dysfunction All infants should be admitted to hospital and monitored for apnoea and bradycardia for at least 12 h after surgery. Out-patient surgery is not advisable for these infants. Secondly, we recommend the use of intravenous caffeine base 10 $mg \cdot kg^{-1}$ in all infants at risk for post-operative apnoea following general anaesthesia. Thirdly, spinal anaesthesia without sedation is associated with less apnoea than general anaesthesia or spinal anaesthesia with ketamine sedation. This option warrants further consideration. Infants with anaemia of prematurity are at increased risk of developing post-operative apnoea. It is therefore preferable to delay elective surgery and supplement the feeds with iron until the Hct is above 30%. When surgery cannot be deferred, anaemic infants must be observed and monitored most carefully in the post-operative period.

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