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# *Postoperative Apnea in Former Preterm Infants: Prospective Comparison of Spinal and General Anesthesia*

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**Thirty-six former preterm infants undergoing inguinal hernia repair were studied. All were ≤51 weeks postconceptual age at the time of operation. Patients were randomly assigned to receive general or spinal anesthesia. Group 1 patients received general inhalational anesthesia with neuromuscular blockade. Group 2 patients received spinal anesthesia using 1% tetracaine 0.4–0.6 mg/kg in conjunction with an equal volume of 10% dextrose and 0.02 ml epinephrine 1: 1000. In the first part of the study, infants randomized to receive spinal anesthesia also received sedation with im ketamine 1–2 mg/kg prior to placement of the spinal anesthetic (group 2 A). The remainder of group 2 patients did not receive sedation (group 2 B). Respiratory pattern and heart rate were monitored using an impedance pneumograph for at least 12 h postoperatively. Tracings were analyzed for evidence of apnea, periodic breathing and/or bradycardia by a pulmonologist unaware of the anesthetic technique utilized. None of the patients who received spinal anesthesia without ketamine sedation developed postoperative bradycardia, prolonged apnea, or periodic breathing. Eight of nine infants (89%) who received spinal anesthesia and adjunct intraoperative sedation with ketamine developed prolonged apnea with bradycardia. Two of the eight infants had no prior history of apnea. Five of the 16 patients (31%) who received general anesthesia developed prolonged apnea with bradycardia. Two of these five infants had no prior history of apnea. When infants with no prior history of apnea were analyzed separately, there was no statistically significant increased incidence of apnea in children receiving general *versus* spinal anesthesia with or without ketamine sedation. Because of the small numbers of patients studied, and the multiple factors that may influence the incidence of postoperative apnea (*e.g.*, prior history of neonatal apnea), standard postoperative respiratory monitoring of these high-risk infants is still recommended following all anesthetic techniques. (Key words: Anesthesia: pediatric. Anesthesia techniques: spinal. Complications: apnea; bradycardia; periodic breathing.)**

AS A GREATER NUMBER of preterm infants survive the early neonatal period, more are presenting for anesthesia and surgery. While some continue to be extremely ill and require multiple emergency operations to survive, most are relatively well but require elective operations. For example, inguinal hernias are particularly common in former preterm infants with an incidence of 13% among those born less than 32 weeks gestational age.[1] Because of a high risk of incarceration, early surgical repair is indicated.

Former preterm infants are prone to develop apnea and/or bradycardia following operations performed under general anesthesia.[2–6] Although several reports on the use of spinal anesthesia in infants recently have been published,[7,8] none of the studies prospectively documented the absence of ventilatory and cardiovascular dysfunction. We designed a prospective, observer-blinded, randomized study using pneumography to compare the effects of spinal and general anesthesia upon the incidence of postoperative apnea, bradycardia, and periodic breathing (PB) in former preterm infants.

## Materials and Methods

Informed consent and institutional approval for the study were obtained. Thirty-six otherwise healthy (ASA physical status 1 or 2) former preterm infants (born at ≤37 weeks gestational age) undergoing anesthesia for inguinal hernia repair were studied. All were ≤51 weeks postconceptual age at the time of operation (range 35–51 weeks). Infants with pre-existing cardiac, neurologic, or metabolic diseases, as well as those receiving methylxanthines or caffeine, were excluded from participation in the study.

Patients received no preanesthesic medications nor did they receive perioperative barbiturates or opioids. Heart rate, heart sounds, blood pressure, ECG, temperature, and hemoglobin oxygen saturation ($Sp_{O_2}$) were monitored. Patients were randomly assigned to receive general (group 1) or spinal (group 2) anesthesia. Patients in group 1 received general inhalational anesthesia consisting of halothane, $N_2O$, and $O_2$ with neuromuscular blockade and controlled ventilation. Neuromuscular blockade was reversed at the end of the surgical procedure with neostigmine 0.07 mg/kg and atropine 0.02 mg/kg. Full recovery of neuromuscular function was confirmed by monitoring train-of-four stimulation of the ulnar nerve and by observing the ability of the infant to sustain lifting of all limbs prior to tracheal extubation.

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Group 2 patients received spinal anesthesia. All spinal blocks were performed with the patient in the lateral decubitus position with the neck extended to prevent airway occlusion and a subsequent decrease in oxygenation.[9] Under sterile conditions, a lumbar puncture was performed with a midline approach through either the fourth or fifth lumbar interspace, using a 22-G, 1½ inch, disposable Quincke needle with a stylet. One percent tetracaine 0.4–0.6 mg/kg in conjunction with an equal volume of 10% dextrose and 0.02 ml epinephrine 1:1000 in a 1-ml tuberculin syringe was used as the agent for all spinal anesthetics in this study. The infant was then placed in the supine position and an iv infusion of lactated Ringer's solution with 5% dextrose was started in a lower extremity following the onset of spinal blockade. During the early part of the study, all infants received im ketamine 1–2 mg/kg for sedation prior to performance of lumbar puncture and their results are presented separately (group 2 A). As we gained experience, and because of an observed high incidence of side effects when ketamine was administered, spinal blocks were administered without prior sedation (group 2 B). Group 2 B infants were comforted by a pacifier dipped either in sugar solution or peach schnapps as needed. To minimize arousing of the child during surgery, the blood pressure cuff was also applied to the anesthetized lower extremity.

The infants were transported to the postanesthesia recovery room following the completion of surgery. Postoperative pain or discomfort was treated with acetominophen 10 mg/kg orally. The patterns of respiration and heart rate were continuously monitored and recorded using an impedance pneumograph (Healthdyne 16000®) with an Oxford® recorder for at least 12 h postoperatively. All children were also monitored on the ward with ECG and respiratory monitors equipped with alarms. A pulmonologist, blinded to patient group assignment, examined the recorded data for evidence of apnea, bradycardia, and PB.

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 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, 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 (min) of PB was then divided by the total sleep time (min) in the recording to determine the percent of PB. PB less than 1% was considered normal. The difference in the incidence of these events among the groups was compared using Fisher's exact test. Age, temperature on admission to recovery room, and duration of surgery were compared by analysis of variance. Results were considered significant if $P$ values were less than 0.05.

## Results

Thirty-six infants were studied. Sixteen received inhalation anesthesia *via* endotracheal tube with neuromuscular blockade (group 1), nine received spinal anesthesia plus im ketamine sedation (group 2 A), and eleven had spinal anesthesia with no sedation (group 2 B). There

TABLE 1. Age, Number of Infants with Apnea, Bradycardia, Periodic Breathing, and Postoperative Ventilation in the Study Patients

| | Group 1 General Anesthesia (n = 16) | Group 2A Spinal + Ketamine (n = 9) | Group 2B Spinal Anesthesia (n = 11) |
|---|---|---|---|
| Gestational age (weeks) | | | |
| Mean ± SD | 31.8 ± 3.9 | 31.4 ± 3.2 | 31.3 ± 2.6 |
| Range | 25–36 | 28–36 | 26–35 |
| Postconceptual age (weeks) | | | |
| Mean ± SD | 43.3 ± 3.9 | 41.2 ± 2.9 | 40.5 ± 3.4 |
| Range | 38–51 | 36–46 | 35–45 |
| History of preoperative apnea | 6 (37.5%) | 6 (66.7%) | 3 (27.3%) |
| Temperature on admission to recovery room | | | |
| Range | 35.5–37.5 | 35.5–37.5 | 35.5–37.5 |
| Mean | 36.5 | 36.5 | 36.4 |
| Duration of surgery | | | |
| Range (min) | 35–55 | 35–55 | 35–55 |
| Mean | 41.9 | 41.7 | 42.3 |
| Postoperative prolonged apnea or apnea with bradycardia* | 5 (31%) | 8 (89%) | 0 |
| Postoperative PB > 1% | 1 | 2 | 0 |
| Postoperative intubation or ventilation | 0 | 0 | 0 |

PB = Periodic Breathing.
* $P < 0.015$ (groups 1 *vs.* 2A).
$< 0.0001$ (groups 2A *vs.* 2B).
$< 0.06$ (groups 1 *vs.* 2B).

were no significant differences between the three groups in gestational and postconceptual ages, or history of preoperative apnea (table 1). Five (31%) of the patients who received general anesthesia developed prolonged apnea with bradycardia; two of the five infants had no prior history of apnea (table 1). None of the patients who received spinal anesthesia without ketamine sedation developed postoperative bradycardia, prolonged apnea, or PB. Eight (89%) of the nine infants who received spinal anesthesia with preoperative ketamine sedation developed prolonged apnea with bradycardia; two of the eight infants had no prior history of apnea. In all cases, the diagnosis of prolonged apnea was based on the presence of apnea lasting <15 s associated with bradycardia. One infant in group 1 and 2 infants in group 2 A developed PB > 1%. None of these apneic episodes were observed clinically. All were detected when the alarms were activated or subsequent to the patient's discharge by analysis of the pneumographic tracings. None of the patients in the three groups required tracheal intubation or controlled ventilation postoperatively. The overall difference in the incidence of prolonged apnea with bradycardia between groups 1 and 2, subgroups 2 A and 2 B, and groups 1 and 2 B is statistically significant (table 1). If patients with a prior history of apnea are separated, however, the incidence of postoperative apnea among these subgroups is not statistically significant (table 2).

## Discussion

All infants with inguinal hernias are at risk of incarceration and the subsequent vascular compromise of both intestines and gonadal tissue. This is especially true in preterm infants and early repair is usually recommended.[1,10] Former preterm infants represent a significant operative risk mainly related to the presence of immature organ systems.[11] Several retrospective and prospective studies[2–6] have established that the former preterm infant undergoing general anesthesia is at risk for respiratory and cardiovascular complications in the perioperative period, mainly in the form of apnea, PB, and bradycardia. The risk of these events appear to be related to a weak central respiratory drive and is inversely related to postconceptual age.[5] Some solutions for the problem of postoperative apnea and periodic breathing in the former preterm infants are to defer elective operations until the infant is greater than 44–46 weeks postconceptual age,[2,3,5,6] employ postoperative respiratory and ECG monitoring of infants 44 weeks postconceptual age or less,[2–6] administer perioperative iv caffeine,[12,13] or use spinal anesthesia.[7,8]

In a retrospective chart review of 36 premature infants undergoing a variety of operative procedures under spinal anesthesia, Abajian *et al.*[7] reported that 31 blocks were successful after the first attempt, while five required a second attempt. Four patients who had otherwise successful spinal anesthetics received local anesthesia injected into the hernia sac or spermatic cord to decrease discomfort during traction. Two additional patients required iv or nitrous oxide supplementation. There were no episodes of hypotension, bradycardia, or any other intraoperative complications. Although no postoperative monitoring for apnea was employed, the authors did not observe any postoperative complications. They concluded that spinal anesthesia can be safely and reliably performed in that group of patients but that the superiority of spinal to other forms of anesthesia remained to be demonstrated.

In a prospective study by Harnik *et al.*,[8] 20 high-risk infants underwent 21 inguinal hernia repairs under spinal anesthesia. Eleven of these infants were less than 44 weeks postconceptual age, while eight were under 2,500 g in weight. Intravenous or halothane supplementation (*via* mask) of the spinal anesthetic was necessary for several patients. The only reported intraoperative complication was apnea and bradycardia in one patient following injection of the tetracaine; that infant had a history of frequent apnea prior to surgery. Postoperative apnea developed in one patient 8 h after the procedure when the patient became hypothermic (T 34.2° C). No children experienced cardiovascular instability. The authors concluded that subarachnoid blockade was a satisfactory alternative to general anesthesia for selected premature infants and suggested that it may avoid the increased incidence of postoperative respiratory complications associated with general anesthesia.

The observation that high-risk infants are less likely to

TABLE 2. The Incidence of Postoperative Apnea in Premature Infants with and without a Prior History of Apnea

| | Group 1 General Anesthesia (n = 16) | Group 2A Spinal + Ketamine (n = 9) | Group 2B Spinal Anesthesia (n = 11) |
|---|---|---|---|
| No prior history of apnea* | 2/10 (20%) | 2/3 (67%) | 0 |
| Prior history of apnea† | 3/6 (50%) | 6/6 (100%) | 0 |
| Total number of patients | 5/16 (31%) | 3/9 (89%) | 0 |

* $P = 0.05$ (group 2A *vs.* 2B).

† $P < 0.02$ (group 2A *vs.* 2B).

develop apnea or bradycardia when spinal rather than general anesthesia is used has not been demonstrated in a controlled, randomized, prospective manner with the use of postoperative pneumography. Some episodes of apnea and bradycardia could have been missed without documented pneumography. In our study the patients were otherwise healthy former preterm infants undergoing inguinal hernia repair. None of the 11 infants who received spinal anesthesia without sedation developed postoperative prolonged apnea. However, most infants (eight of nine) who received im ketamine sedation to supplement spinal anesthesia developed postoperative apnea. Whether other forms of sedation would have resulted in a lower incidence of postoperative apnea requires further investigation. Like the reports by Liu *et al.*,[3] and Kurth *et al.*,[5] a history of neonatal apnea correlated with the occurrence of postoperative apnea in the total number of patients: the incidence of postoperative prolonged apnea was 60% in infants who had a prior history of apnea, and 19% in those without a prior history of apnea. The small number of patients studied makes it difficult to speculate on the incidence of postoperative apnea in any subgroup of infants (*e.g.*, those without prior history of apnea) when spinal *versus* general anesthesia are used. For example in our study 20% of the infants who developed apnea following general anesthesia and 67% of those following spinal anesthesia with ketamine sedation had no prior history of apnea (table 2). This difference did not reach statistical significance. However, the difference regarding postoperative prolonged apnea was statistically significant in the comparison of the groups receiving spinal anesthesia with and without ketamine sedation (2 B *vs.* 2 A) for both infants with ($P < .02$) and without ($P = .05$) prior history of apnea. The extremely high incidence of postoperative prolonged apnea in infants who received spinal anesthesia with ketamine sedation may caution against the use of ketamine for sedation in premature infants. Early in our study we chose im ketamine as a sedative to facilitate performance of the lumbar puncture. Because we did not have iv access prior to placement of the block, im ketamine seemed to be the most appropriate choice for sedation. Although there is little information available regarding the respiratory effects of ketamine in preterm infants, there is evidence in older children that iv ketamine does not affect functional residual capacity or oxygen saturation, even in iv doses of 2 mg/kg.[14] Ketamine was used by Harnik[8] in a similar group of infants with no reported complications. However, more recent work by Hamza *et al.*[15] examining the ventilatory response to $CO_2$ following the iv bolus administration of ketamine 2 mg/kg followed by an iv ketamine infusion of 40 $\mu g \cdot kg^{-1} \cdot min^{-1}$ indicates that while respiratory rate, tidal volume, end-tidal $CO_2$, and minute ventilation were preserved, ventilatory control was significantly altered. This altered ventilatory depression may be severe in the infants with immature respiratory controls. Our results suggest that ketamine may not be an acceptable agent for sedating infants who are at an increased risk for apnea. Other forms of sedation, *e.g.*, $N_2O$, should be investigated in infants who are not comforted by nonpharmacologic methods.

The clinical significance of apneic episodes long enough to result in bradycardia but that abate before cardiorespiratory arrest develops remains unknown.[13] 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[16] or sudden infant death may occur.[17,18]

In summary, this study shows that spinal anesthesia without ketamine sedation was not associated with postoperative apnea, whereas infants receiving either general anesthesia or spinal anesthesia plus ketamine sedation experienced a 31% and 89% incidence of postoperative apnea, respectively. Because of the small number of infants examined in this series and the multiple factors that may influence the incidence of postoperative apnea (*e.g.*, prior history of neonatal apnea) we believe that it is prudent to continue cardiorespiratory monitoring for at least 12 h postoperatively in all high-risk infants who are younger than 44–46 weeks[2,3] postconceptual age following all anesthetic techniques.

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