RESEARCH ARTICLE

Apnea in Preterm and Term Infants After Deep Sedation and General Anesthesia

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ABSTRACT

OBJECTIVES: Determine the incidence of apnea in preterm and term infants after deep sedation (DS) compared with general anesthesia (GA).

METHODS: A retrospective chart review was performed on infants who underwent elective DS or GA from January 2008 to December 2013, were <60 weeks postmenstrual age if preterm or <50 weeks postmenstrual age if term, and were monitored for apnea as inpatients after DS or GA. Gestational age, postmenstrual age, chronologic age, anesthetic and sedative medications, procedure indication, and postsedation events were collected.

RESULTS: There were 61 DS encounters (24 preterm and 37 term) and 175 GA encounters (120 preterm and 55 term) that met inclusion criteria. No recorded apneic events in either preterm or term infants were recorded after DS. After GA, 1.7% of infants had apneic events (2.5% preterm and 0 term; $P = .57$ versus DS). All events occurred within 2 hours of monitoring in recovery.

CONCLUSIONS: None of the infants had apnea after DS. Rates from the literature would suggest that 2 to 6 of the preterm DS subjects should have experienced postsedation apnea. Sampled GA subjects had a rate of 2.5% in preterm infants exhibiting apnea after GA. Although the post-DS apnea rate is lower than what has been previously published, the small sample size and limitations of a retrospective design prevent us from directing a change in postsedation monitoring recommendations. However, we do support the need for prospective studies with strict monitoring criteria to reveal the true risk of post-DS apnea.

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Preterm and term infants who undergo general anesthesia (GA) are known to be at risk for apnea and bradycardia in the 12 to 48 hours after anesthesia. Preterm infants <60 weeks postmenstrual age (PMA) (gestational age plus chronological age)[1] have an incidence of apnea with or without bradycardia of 10%, which decreases to 0% at ~60 weeks PMA.[2] The incidence of apnea in infants age <44 weeks PMA is 25%, making this the group of infants who are at the highest risk for postanesthesia apnea.[2,3] Patient factors that increase the risk of apnea and bradycardia include younger estimated gestational age (EGA) and anemia.[3–6] The incidence of apnea and bradycardia after anesthesia in term infants has not been extensively described but appears to be less than that of preterm infants.[3] There are case series of postanesthesia apnea in term infants ranging from 39 to 44.5 weeks PMA, and in these reports, apnea appears to be much less common by 60 weeks PMA.[3,7] Similar to preterm infants, there are known risk factors for term infants to exhibit apnea postanesthesia, including anemia, a history of respiratory distress, and bronchopulmonary dysplasia.[2–4,6]

Many hospitals derive guidelines and policies for postsedation monitoring in infants from this anesthesia research. However, because published recommendations for the PMA at which infants no longer need postanesthesia monitoring vary (ranging from 46 to 60 weeks for preterm and 44 to 47 weeks for term infants), hospital policies regarding monitoring are variable.[2,3,8,9] Additionally, there are guidelines in which researchers recommend that infants with certain comorbid conditions, such as a bronchopulmonary dysplasia, receive more prolonged monitoring, leading to additional inconsistencies in hospital discharge policy.[3,6]

There is little research available on the risk of apnea in infants after lighter depths of suppressed consciousness compared with GA. Therefore, we sought to describe the incidence of apnea in preterm and term infants who underwent deep sedation (DS) compared with present-day GA. On the basis of the authors' anecdotal experience, it was hypothesized that the rate of apnea after DS is less than that after GA.

METHODS

A retrospective chart review was performed on all infants who underwent DS and were <6 months chronologic age between January 2008 and December 2013. Inclusion criteria were any infant <6 months of age at the time of sedation who also met the following age criteria: preterm (<37 weeks EGA) infants <60 weeks PMA or term (≥37 weeks EGA) infants <50 weeks PMA. The EGA was obtained either from the sedation and/or anesthesia paperwork or any previous medical documentation when available. If documentation simply noted the patient to be "term," for purposes of PMA calculation, an EGA of 37 weeks was used. Patients were excluded if they were on mechanical ventilation immediately before or after DS; if they were not monitored for at least 4 hours after the initial recovery period; if they had incomplete records that did not allow for determination of EGA or PMA; or if we were unable to determine if any events occurred after. Patients undergoing anesthesia or sedation at our institution recover using American Society of PeriAnesthesia Nurses guidelines for monitoring and the nurse-to-patient ratio. Those having anesthesia in the operating room (OR) recover in the postanesthesia care unit (PACU), whereas those receiving sedation either recover in the sedation unit or an area adjacent to the procedure area.[10] Once recovered, patients are transferred to the children's hospital, where they are in a monitored environment.

For the anesthesia comparison group, a retrospective chart review was performed on all infants who underwent elective GA for a surgical procedure, were <6 months of age between January 2008 and December 2013, and admitted after the procedure. The same inclusion criteria of age <6 months, preterm <60 weeks PMA, or term <50 weeks PMA were applied. The exclusion criteria were also the same.

An apneic event was defined as present when documented in nursing vital sign flowsheets or in nursing or physician documentation. If the duration of the apnea was available, only those events with a cessation of breathing for >15 seconds were counted as apnea. Events of any duration were counted if associated with bradycardia and/or desaturations.[1–3] Similarly, desaturation events were defined as present if recorded in nursing notes or vital sign records as oxygen desaturation <90%.

Data collected or calculated included the diagnostic test or procedure requiring sedation or anesthesia, EGA, PMA, chronologic age, anesthetic or sedative medication used, events during sedation, events after sedation or anesthesia, and the duration of the postprocedure monitoring. Sedation depth scores were not collected. Hospital policy requires the documentation of the Ramsay Sedation Scale to assess sedation depth.[11] However, to differentiate between the deepest 3 levels of sedation, the scale requires the patient to be stimulated, which may cause the child to move and disturb the procedure. Therefore, stimulation is often not performed, indicating that the score may be less accurate in reflecting true patient sedation depth. This must be considered when reviewing the data and comparing among different studies or personal experience.

The Institutional Review Board at the University of Kentucky approved this study. Clopper-Pearson exact method was used to obtain 95% confidence intervals (CIs) for event rates. Fisher's exact tests were used to compare present-day anesthesia with DS. Kruskal-Wallis and χ^2 tests were used to make comparisons with respect to infant characteristics (Table 1). All tests were 2 sided at the 5% significance level, and analyses were conducted in SAS version 9.4 (SAS Institute, Inc, Cary, NC).

RESULTS

We identified 226 sedation encounters in patients <6 months of age at the time of sedation. Of these, 88 met criteria for postsedation monitoring on the basis of their PMA or EGA. Of these 88 sedation encounters, 61 were monitored for >4 hours postsedation, of which 37 were term and 24 were preterm infants. One was excluded because of a lack of EGA information. Of the 61 included sedation

TABLE 1 Infant Characteristics

	DS		GA	
	Preterm Infants (n = 24)	Term Infants (n = 37)	Preterm Infants (n = 120)	Term Infants (n = 55)
EGA, wk, range (median)	23–36.9 (34)	37.0–40.4 (38.5)	25.1–36.6 (32)[a]	37–39.4 (37)[b]
PCA, wk, range (median)	39.4–60.0 (47.0)	39.6–49.9 (44.8)	37–58.7 (45.8)[a]	38.3–50 (45.8)[c]
Chronological age, wk, range (median)	3.4–26.0 (15.9)	2.6–12.9 (6.0)	3.9–32.6 (13.9)[a]	1.3–13 (8.1)[b]
Male sex, n (%)	10 (42)	19 (51)	107 (89)[b]	50 (91)[b]
Length of observation, h, range (median)	4–>24 (23.5)	4.1–>24 (23.0)	5–>24 (23.5)	9–>24 (23)

PCA, postconceptional age.
[a] Not significant versus the preterm sedation group.
[b] $P < .001$ versus the same-aged sedation group.
[c] $P < .03$ versus the term sedation group.

encounters (Fig 1A), 1 preterm infant was sedated 2 separate times, and 1 term infant was sedated 4 separate times, resulting in 61 sedation encounters on 57 patients. Each sedation encounter is reported separately.

Age and sex characteristics of infants receiving sedation along with the duration of postsedation monitoring are shown in Table 1 and Fig 2A. Infants were monitored from 4 to >24 hours, with a median of 23 hours. Fourteen (38%) term and 5 (21%) preterm infants were in the highest-risk age group of <44 weeks PMA. The indication for the sedation and the medication used can be seen in Table 2. MRI of the head was the most common procedure for both preterm and term infants. Propofol was overwhelmingly the most common sedating medication used.

There were 252 infants identified who were <6 months of age when put under GA. Of these infants, 201 met the criteria for postsedation monitoring on the basis of their PMA. Three of these infants were left intubated postoperatively, and 23 were not monitored for >4 hours and were therefore excluded. In total, 55 term and 120 preterm infants who underwent GA were included (n = 175; Fig 1B) The ages and sexes of the infants can be seen in Table 1 and Fig 2B, with the indications for surgery and the anesthetics given in Table 2. All infants underwent hernia repair, the majority of which were bilateral. Eight (15%) term and 43 (36%) preterm patients who underwent anesthesia were in the highest-risk age group of <44 weeks PMA. Medications used during anesthesia were at the discretion of the anesthetic team. All infants were administered inhalational anesthetics, and >50% were additionally given propofol, whereas ~25% of the preterm infants and >30% of the term infants received a narcotic. Approximately 75% of the infants had a caudal block placed.

There were no recorded postsedation apneic events for either preterm or term infants receiving DS. For preterm infants receiving GA, 3 had apneic events and 1 had a desaturation event. The initial apneic events in the 3 patients occurred in the PACU within the first 2 hours of recovery. Two of these 3 preterm infants had no significant comorbidities: 1 had hydronephrosis, and the other was on reflux medication.[3,4,6] The third was relatively anemic, with a hemoglobin of 8.5 g/dL discovered postoperatively. The patient with hydronephrosis had an EGA of 30.1 weeks (PMA of 44.3 weeks); was in the OR for 42 minutes for bilateral inguinal hernia (BIH) repair and circumcision; received sevoflurane, fentanyl, and propofol without a caudal block; and did receive fentanyl doses postoperatively for pain. The infant with reflux had an EGA of 30.4 weeks (PMA of 44.4 weeks); was in the OR for 80 minutes for repair of BIH and umbilical hernia; and received desflurane, fentanyl, and propofol intraoperatively without a caudal block nor narcotics postoperatively. The third infant had an EGA of 27 weeks (PMA of 41.6 weeks),

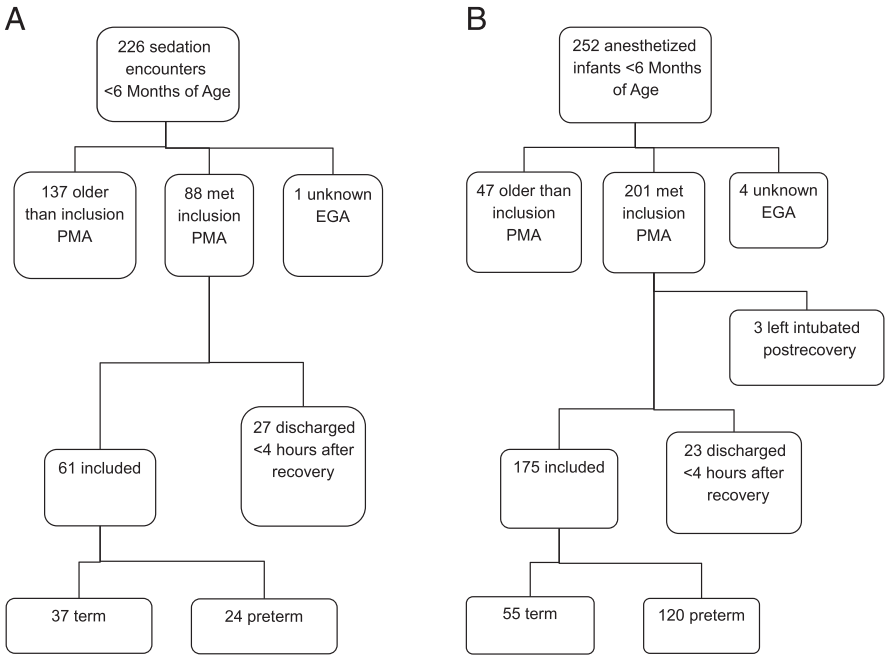

FIGURE 1 A, Sedation patients. B, Anesthesia patients.

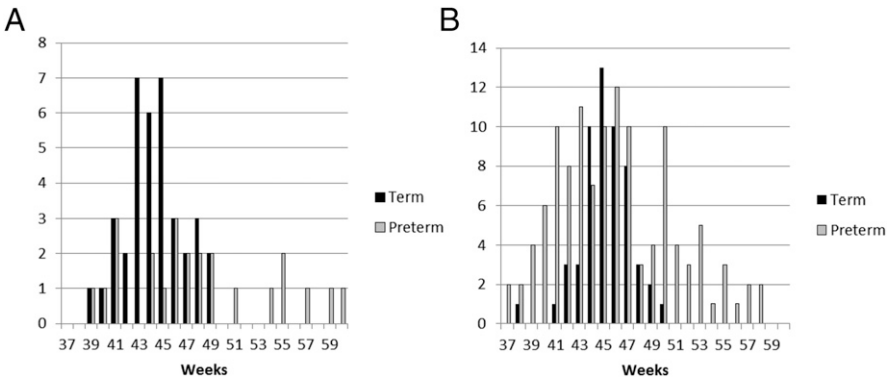

FIGURE 2 A, PMA distribution of sedation patients. B, PMA distribution of anesthesia patients.

was in the OR for 60 minutes for repair of BIH, and received sevoflurane, propofol, and a caudal block but no narcotics after surgery. His hemoglobin of 8.5 several days after surgery was discovered when he was unable to come off oxygen because of persistent apnea and desaturations. He was transfused with packed red blood cells and was weaned to room air within 36 hours. Of the term infants receiving GA, there was 1 patient (EGA 37 weeks and PMA 43.4 weeks without comorbidities) with recorded saturations of 80% to 83% despite 1 L of oxygen via nasal cannula. He received oxygen starting at 2 hours postoperation and was weaned to room air 3 hours later. He had received sevoflurane and propofol without a caudal block in the OR for a 54-minute BIH repair and did not receive perioperative narcotics.

Table 3 shows the rates of apneic events for all groups along with the 95% CIs for the true probability of apnea. When comparing present-day anesthesia to DS, there was no significant difference revealed in the rate of apneic events after DS in preterm infants, term infants, or both ($P = 1.00$, 1.00, and .57, respectively).

DISCUSSION

This retrospective study reveals that for this group of patients, the recorded incidence of apneic events in preterm and term infants who underwent DS or GA and were admitted for prolonged monitoring appears to be no different than in similar populations of infants undergoing GA in other reports.[2,3] The incidence of documented apnea in preterm and term infants after DS in this relatively small sample over 6 years was 0. However, because 2 of the infants undergoing DS accounted for 6 of the 61 sedation encounters, this may have contributed to a lack of events because these 2 infants may have brought a decreased apnea risk to all 6 encounters. On the basis of the historical literature of preterm infants receiving GA, the expected number of patients to experience postsedation apnea was 2 to 6 (assuming a 10%–25% rate) of preterm infants and up to 4 term infants (assuming a 10% rate).[2,3] In the GA group, we found 3 preterm infants who had documented apnea postoperatively, yielding an incidence of 2.5%. Even this appears to be lower than what is described in the literature, but it is closer to the more recent data from Davidson et al,[6] who reported an overall apnea rate of 4% in preterm infants who underwent inguinal herniorrhaphy with GA. Again, on the basis of historical literature, 12 to 30 preterm infants and as many as 5 term infants would have been expected to experience apnea after GA.[2,3] If we use exact binomial tests to compare the DS event rates seen here to the rates of events after anesthesia in the most conservative early historical literature, the rate of apnea for both preterm and term infants after DS is less than the historically expected 10% ($P = .003$). However, we were not able to illustrate statistical significance in the apnea incidence between those infants who underwent current GA compared with DS at our hospital.

It is perhaps intuitive to suspect that after sedation, infants would have fewer apneic events than after GA. GA by definition suppresses the central nervous system further than does sedation. This, along with its increased potential for hemodynamic effects, would logically result in an increased risk for apnea over patients receiving DS. Of the GA patients evaluated in this study, 79% received >1 class of agent or medication, whereas 87% of procedural sedation patients received only a single agent. The combined medications and medication classes, particularly narcotics, may increase the postanesthetic risk for apnea.[7,12] The invasive nature of the surgical procedure itself may also be an additional risk above that of the less invasive procedures for which infants receive DS.[7,12] Some evidence reveals that preterm infants respond differently to painful stimuli than do term infants.[11,13,14] Additionally, in this infant age group, the indication for surgical intervention is often hernia repair, for which the predominant sex undergoing GA is male (~90% in our anesthesia population versus 50% of the sedation group). It is well described that preterm male infants have worse outcomes than female infants, including higher rates of mortality and pulmonary morbidity, and this sex difference in the anesthesia group may contribute to their postanesthesia risk for apnea.[5,15–17] Lastly, infants who are sedated by the pediatric intensive care team at our institution undergo a prescreening process by which more complex patients, including those on oxygen or continuous positive airway pressure and bilevel positive airway pressure with airway anomalies or heart disease, are referred to anesthesia for sedation. This process may additionally screen out infants who have an increased risk for postsedation apnea.

It was somewhat surprising that present-day rates of apnea after anesthesia were lower than what is historically described. However, this and the lower rate of apnea after DS may have several possible explanations. First, the determination of apnea depended on the documentation of apnea in the medical record. Infants may have experienced apnea that wasn't documented either because of the lack of clinical significance at the time, the low sensitivity of apnea and bradycardia

TABLE 2 Indication and Medications for Sedation

	Preterm Infants (n = 24)[a]	Term Infants (n = 37)[a]
	n (%)	n (%)
Indication for sedation		
MRI, head	18 (75)	22 (92)
MRI, spine	3 (12)	4 (11)
Bronchoscopy	1 (4)	4 (11)
Lumbar puncture	—	6 (16)
Dressing change	2 (8)	—
BMA	—	2 (5)
MRI orbits	1 (4)	—
EGD	—	1 (3)
Liver biopsy	—	1 (3)
Echocardiogram	—	1 (3)
CT, abdomen and pelvis	1 (4)	—
PICC	—	1 (3)
Sedation medications		
Propofol	21 (87)	32 (86)
Propofol, fentanyl	1 (4)	4 (11)
Chloral hydrate	2 (8)	—
Propofol, chloral hydrate	—	1 (3)
Indication for surgery	Preterm infants (n = 120)	Term infants (n = 55)
BIH repair	52 (43)	26 (47)
BIH repair plus other procedure[b]	36 (30)	6 (11)
Unilateral inguinal hernia repair	21 (17)	18 (33)
Unilateral inguinal hernia repair plus other procedure[b]	11 (9)	5 (9)
Anesthetic medication[c]		
Sevoflurane and/or desflurane	120 (100)	55 (100)
Propofol	74 (61)	40 (73)
Fentanyl or morphine	28 (23)	20 (36)
Rocuronium or succinylcholine	20 (16)	6 (11)
Caudal block	96 (79)	38 (69)

BMA, bone marrow aspiration; CT, computed tomography; EGD, esophagogastroduodenoscopy; PICC, peripherally inserted central catheter; —, not applicable.

[a] The total number of procedures exceeds the number of sedation encounters because >1 procedure occurred during several of the sedation encounters.

[b] Circumcision was the most common additional procedure in term infants, and hydrocele repair was most common in term infants.

[c] The total number of medications exceeds the number of anesthesia encounters because >1 medication was administered during all of the encounters.

monitors, or an expectation that infants would have apnea, especially in the PACU. Many of the events described in the literature happened in the immediate postsurgical time period, while the infant was still in the care of the anesthesia team, and therefore may not be documented. At what threshold did each bedside caregiver feel that an event warranted diagnosing and documenting as apnea? An argument might be made that if an event wasn't documented, then it wasn't clinically significant. However, these same "insignificant" events that occur in the home environment might lead to more significant events when not in the presence of a health care provider. This is not to say that the diagnosis or documentation of apnea has changed over time, only that there are challenges in performing retrospective analysis when the question involves precise documentation.

TABLE 3 Rate of Apneic Events With 95% CIs After Sedation or Anesthesia

	Preterm, Rate (95% CI)	Term, Rate (95% CI)	Preterm and Term, Rate (95% CI)
DS	0 (0–0.143)	0 (0–0.095)	0 (0–0.059)
GA[a]	0.025 (0.005–0.071)	0 (0–0.065)	0.017 (0.004–0.049)

[a] Not significant compared with DS.

All infants admitted to the hospital for observation after sedation and/or anesthesia are to be in a monitored environment, according to hospital policy. It is difficult to determine, on the basis of medical records, exactly what the extent of the monitoring was for each individual patient. Some had definite documentation that they were on an apnea and/or bradycardia monitor that should alarm if the infant met predetermined criteria for apnea, and others were also documented to be on pulse oximetry. However, there is no way to verify that all infants were indeed placed on such monitors. Also, apnea and/or bradycardia monitors traditionally used for postoperative monitoring purposes are less sensitive for obstructive apnea. In addition, to determine the effect of an apneic event on oxygen saturations, all infants would need pulse oximetry monitoring to determine if a brief respiratory pause event led to desaturation and therefore met diagnostic criteria for apnea.

Finally, anesthesia practices have changed in the years since many of the early descriptions of preterm infants having apnea postoperatively were established. Halothane was the most common inhalational agent in the majority of early studies, whereas sevoflurane and desflurane were the most common agents used in the patients evaluated here.[4,7–9,18] Desflurane enables a more rapid, immediate recovery in 1 study compared with halothane.[19] The use of caudal blocks may impact postoperative apnea. In our anesthesia group, a majority of infants had

a caudal block placed for postoperative pain control (76% total; 79% preterm and 69% term), which, although they still received inhalational anesthetics, may have decreased the incidence of apnea, as seen in a 2012 study by Brenner et al.[12]

There are several limitations in this study. Being a retrospective chart review, there is a possibility for omissions in the medical record from both a lack of documentation of an observed event and events being unwitnessed. Given that there were 3 patients in the anesthesia group who had apneic events that occurred in both the PACU and on the wards, we know that apneic events do get documented even in the immediate postoperative period, but the threshold for each infant and provider cannot be standardized in a retrospective study. The GA group, and particularly the sedation group, had small sample sizes and therefore were not powered to find rare clinical events. Another limitation is the number of patients who fell within the PMA range for inclusion yet were not monitored for at least 4 hours after the initial recovery period. Twenty-seven DS infants (14 term and 13 preterm) and 23 anesthesia infants (10 term and 13 preterm) were discharged within 4 hours; of course, there was no way to determine if these infants had apneic events after discharge. There was no documentation in the record as to why these infants were discharged early. Our hospital policy regarding the PMA at which infants should stay for postanesthesia monitoring changed to include older infants in the middle of the dates of this study, which may account for some of the earlier discharges in older infants. Apneic events are most likely to occur in the hours immediately after anesthesia, as was seen in the 3 preterm infants with apnea in this study who each had their first episode of apnea within the first 2 hours after the operation. None of the DS or GA patients who were discharged before 4 hours of monitoring had any apneic events during the time they were monitored. Another possible limitation is the inability to accurately account for the depth of sedation in the DS group. It will be important in prospective studies to accurately reflect the depth of sedation with a validated scale.

This study cannot be used to directly address and impact the current guidelines of monitoring infants after sedation. The results do bring to light the possibility that infants undergoing DS perhaps do not incur the same risk for apnea as those undergoing GA. To warrant any change in current practice, a large, multicenter, prospective study would need to be undertaken, with strict, consistent monitoring practices and definitions of clinically significant apnea. The addition of capnography to the prolonged monitoring equipment would further assist in capturing all apnea events. In the meantime, hospital policies regarding postsedation and postanesthesia monitoring for young, former preterm and term infants should certainly remain cautiously conservative.

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