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Prospective Observational Investigation of Capnography and Pulse Oximetry Monitoring After Cesarean Delivery With Intrathecal Morphine

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BACKGROUND: Intrathecal morphine provides excellent analgesia after cesarean delivery; however, respiratory events such as apnea, bradypnea, and hypoxemia have been reported. The primary study aim was to estimate the number of apneas per subject, termed "apnea alert events" (AAEs) defined by no breath for 30–120 seconds, using continuous capnography in women who underwent cesarean delivery.

METHODS: We performed a prospective, observational study with institutional review board approval of women who underwent cesarean delivery with spinal anesthesia containing 150-µg intrathecal morphine. A STOP-Bang obstructive sleep apnea assessment was administered to all women. Women were requested to use continuous capnography and pulse oximetry for 24 hours after cesarean delivery. Nasal sampling cannula measured end-tidal carbon dioxide ($Etco_2$) and respiratory rate (RR), and oxygen saturation (Spo_2) as measured by pulse oximetry. Capnography data were defined as "valid" when $Etco_2$ >10 mm Hg, RR >5 breaths per minute (bpm), Spo_2 >70%, or during apnea (AAE) defined as "no breath" ($Etco_2$, <5 mm Hg) for 30–120 seconds. Individual respiratory variable alerts were 10-second means of $Etco_2$ <10 mm Hg, RR <8 bpm, and Spo_2 <94%. Nurse observations of RR (hourly and blinded to capnography) are reported.

RESULTS: We recruited 80 women, mean (standard deviation [SD]) 35 (5) years, 47% body mass index >30 kg/m^2/weight >90 kg, and 11% with suspected obstructive sleep apnea (known or STOP-Bang score >3). The duration of normal capnography and pulse oximetry data was mean (SD) (range) 8:28 (7:51) (0:00–22:32) and 15:08 (6:42) (1:31–23:07) hours:minutes, respectively; 6 women did not use the capnography. There were 198 AAEs, mean (SD) duration 57 (27) seconds experienced by 39/74 (53%) women, median (95% confidence interval for median) (range) 1 (0–1) (0–29) per subject. Observation of RR by nurses was ≥14 bpm at all time-points for all women, r = 0.05 between capnography and nurse RR (95% confidence interval, –0.04 to 0.14). There were no clinically relevant adverse events for any woman. Sixty-five women (82%) had complaints with the capnography device, including itchy nose, nausea, interference with nursing baby, and overall inconvenience.

CONCLUSIONS: We report 198 AAEs detected by capnography among women who underwent cesarean delivery after receiving intrathecal morphine. These apneas were not confirmed by the intermittent hourly nursing observations. Absence of observer verification precludes distinction between real, albeit nonclinically significant alerts with capnography versus false apneas. Discomfort with the nasal sampling cannula and frequent alerts may impact capnography application after cesarean delivery. No clinically relevant adverse events occurred. (Anesth Analg 2019;128:513–22)

KEY POINTS

- **Question:** We investigated the number of apneas per subject (termed "apnea alert events") measured by capnography among women who underwent cesarean delivery and received intrathecal morphine.
- **Findings:** Capnography revealed 198 apnea events, mean (standard deviation) duration of 57 (27) seconds experienced by 39/74 (53%) women, although there were no clinically relevant adverse events.
- **Meaning:** The apnea events revealed by capnography were not confirmed by intermittent nursing assessments; the utility of capnography to detect clinically relevant apnea in this setting may be limited.

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This study was conducted at the Lucile Packard Children's Hospital, Stanford, California.

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Neuraxial morphine (intrathecal or epidural administration) provides high-quality analgesia after cesarean delivery and is recommended by the Society for Obstetric Anesthesia and Perinatology and the American Society of Anesthesiologists (ASA).[1–4] Neuraxial morphine in doses lower than required for intravenous analgesia has been safely and effectively administered for decades to millions of women undergoing cesarean delivery; however, there are concerns that neuraxial opioids may cause postoperative respiratory depression.[4–6]

The reported incidence of respiratory depression ranges from 0% to 32%.[7–11] This wide range is related to the varied definitions (including hypoxemia, bradypnea, apnea, or hypercarbia) and the measurement tools used.[3,10,12–14] The most commonly used measurements to detect respiratory depression after cesarean delivery are clinical observations of respiratory rate (RR), maternal sedation, and oxygen saturation (Spo_2) measured by pulse oximetry.[3] However, inadequacy of ventilation or apnea is most reliably detected using capnography.[15] To our knowledge, no study has applied capnography to women after cesarean delivery.

The primary aim of this study was to estimate the number of apneas per subject, termed "apnea alert events" (AAEs) defined by no breath (end-tidal carbon dioxide [$Etco_2$] <5 mm Hg for 30–120 seconds), using capnography in women who underwent cesarean delivery with spinal anesthesia that included 150-μg intrathecal morphine. In addition, we aimed to report individual respiratory variables derived from capnography and pulse oximetry, compare the hourly respiration rate recorded by the capnograph with hourly nursing observations, and report women's experience using capnography and pulse oximetry in this postoperative setting.

METHODS

Design, Setting, and Study Population

We conducted a prospective, observational cohort study at Lucile Packard Children's Hospital Stanford, a tertiary medical center in California with approximately 4500 deliveries per year and a cesarean delivery rate of approximately 31% during the study period April 2015 to April 2016. This study was approved by the Stanford University Research Compliance Office (6208, panel: 8, number: 30189), and written informed consent was obtained from all subjects participating in the study. The study was registered before subject enrollment at clinicaltrials.gov (NCT02417038; principal investigator: B.C.; April 10, 2015). We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for reporting this cohort study.

Women who were undergoing cesarean delivery with spinal anesthesia and who received the institution's standard spinal anesthetic (intrathecal heavy bupivacaine, 12 mg; fentanyl, 15 μg; and morphine, 150 μg) were approached for potential enrollment, and written informed consent was obtained.

Eligibility inclusion criteria included women with ASA physical status class II or III, between 18 and 45 years of age, gestational age >37 completed weeks, and singleton pregnancy. Women were excluded if they had contraindications for neuraxial anesthesia (bleeding diathesis, neuropathy, severe scoliosis, previous spine surgery, local anesthetic allergy), allergies to routine postoperative analgesic medication, history of current or chronic opioid use, inability to adequately understand the consent form, and blocked nose or nasal deformity. Obese women and women with suspected sleep-disordered breathing were not excluded.

At recruitment, women were asked to provide demographic and obstetric details, including prepregnancy weight, current weight, height, body mass index (BMI), any medical disease, parity, and gravidity. All women completed 2 questionnaires previously validated in nonpregnant subjects[16] and used in pregnant populations to detect obstructive sleep apnea (OSA) (8-item STOP-Bang questionnaire) and sleep complaints (19-item Pittsburgh Sleep Quality Index).[16–19] Women were also asked about previous diagnosis or investigations for OSA.[20] A preoperative venous blood gas sample was requested and taken when consent for this additional investigation was given.[21]

Recruited women were given a nasal sampling cannula, without supplementary oxygen/air and the pulse oximetry module connected to the Capnostream 20 (Medtronic, Boulder, CO) in the postanesthesia care unit (PACU). Women were requested to use the capnography and pulse oximetry as much as possible up to 24 hours after cesarean delivery. Women were informed that capnography and pulse oximetry data would be collected by investigators for research purposes however these data would not impact clinical care.

Data Sources

"AAEs" and individual respiratory variables were measured using the Capnostream 20 (Medtronic, Boulder, CO), a portable $Etco_2$ monitor that captures waveform patterns for $Etco_2$ and RR and has a pulse oximetry module to measure Spo_2 and heart rate continuously. The breath-to-breath respiratory data and pulse oximetry data collected were preserved as individual downloaded subject files containing the $Etco_2$, RR, and Spo_2 means at 10-second timeframes (14 women had data collected every 30 seconds) and stored on a local computer. The software used to download the data has been previously described.[22] Study investigators were available to address any concerns from women or nurses regarding the capnography, pulse oximetry, or any study methodology during the 24-hour monitoring period.

Hourly nursing observations of the RR and 2-hourly level of consciousness were recorded for 16 hours after cesarean delivery as per standard institutional care using a single reading at the time of assessment. Level of consciousness was assessed using descriptive measures and reported using a drop-down options menu in the electronic medical record (EMR): alert, lethargic, sedated, difficult to arouse, obtunded, unable to arouse, and unable to assess. We retrieved data regarding any oxygen administration, hypoxemia (Spo_2, <94%), naloxone requirements, or antiemetic use from the EMRs. Nurses were blinded to the data captured by the capnography during the data monitoring period, but nurses could see and record the Spo_2 values and respond if needed.

Postoperative pain, additional analgesics, and opioid-related side effects (pruritus and nausea) were recorded 1, 2, 4, 8, 12, and 24 hours after cesarean delivery. For

postoperative analgesia, all women received scheduled oral ibuprofen 600 mg and acetaminophen 650 mg every 6 hours for 48 hours after surgery. Women were asked to rate their pain on a 0–10 verbal numerical rating score (VNRS: 0 = no pain and 10 = worst pain imaginable). Breakthrough pain was treated with oral oxycodone: 5 mg if the VNRS was ≤4 or 10 mg if VNRS was >4 and women wanted treatment. Women were allowed up to 10-mg oxycodone every 4 hours, and if pain control was inadequate with oral medications or a woman was unable to tolerate oral medications, 4-mg intravenous morphine boluses were offered every 10 minutes (with a maximum of 20 mg in every 6 hours). Total additional opioid administration was calculated by adding the intravenous morphine dose to oxycodone (converted to total oral morphine equivalents using 2-mg oxycodone = 1-mg morphine).[10] Symptoms of pruritus and nausea, assessed by nurses, were treated based on standardized order sets. Any failure to respond or concerns related to side effects were referred to the duty anesthesiologist; thus, additional care may not be standardized but varied little within the group practice.

Women's Experience With the Capnography and Pulse Oximetry. At the end of the 24-hour monitoring period, the study investigators asked women open-ended questions about their experience with the capnography and pulse oximetry, their objective experience of wearing the nasal sampling cannula (numerical scale: 0 = never again and 10 = no problems), and if they would use it again after cesarean delivery if requested to (yes/no).

Respiratory Data Management

Capnography data retrieved were defined as "valid" when $Etco_2$ >10 mm Hg and RR >5 breaths per minute (bpm) and Spo_2 >70%, or "no breath" for a period of 30–120 seconds (Table 1). Pulse oximetry data were defined as valid when Spo_2 >70% for at least 30 seconds. No breath was a variable output from the capnograph that signified apnea identified during the monitoring period. The no breath variable was recorded when $Etco_2$ <5 mm Hg was measured for at least 30 seconds during the monitoring period. Apnea duration beyond 120 seconds was considered as a disconnection of the nasal cannula.[10] In this study, we designated the no breath variable as an AAE rather than as an apnea, as it was not verified by an independent observer.

The capnograph was used to identify both the RR and the presence/absence of breathing (apnea). The periods before and after AAEs were analyzed to ensure valid data as per definition (Table 1). We identified all alerts for apnea and the 3 individual variables: $Etco_2$, RR, and Spo_2 for the total duration of the capnography and pulse oximetry monitoring period. A 10-second mean below the predefined value was considered an alert.

Alerts for the individual respiratory variables were predefined: 10-second means of $Etco_2$ <10 mm Hg, RR <8 bpm,[23] and Spo_2 <94%.[23] $Etco_2$ <10 mm Hg was selected because it was considered to reduce the false alerts as it is closer to the apnea threshold.[22,24,25] A time search window was created for each 30- to 120-second AAE, from 5 minutes before the onset of the AAE and up to 5 minutes after the AAE terminated to identify whether the individual respiratory variable alerts occurred before, during, or after the AAE. The median (interquartile range [IQR]) for the number of alerts per minute is presented for each time period (5 minutes before AAE, during AAE, and 5 minutes after AAE), as well as during the 24-hour monitoring period. The absolute value of $Etco_2$ signified the following: normal ventilation (>10 mm Hg), individual variable alert (<10 mm Hg), and apnea (<5 mm Hg for at least 30 seconds but not >120 seconds).

Table 1. Definitions of the Individual Physiological Variable Alerts and Apnea Terms

Terminology	Definition
Valid capnography data	$Etco_2$ >10 mm Hg, RR >5 bpm, Spo_2 >70%, or during AAE
Valid pulse oximetry data	Spo_2 >70% or during apnea alert event
Apnea alert event (primary outcome)	$Etco_2$ <5 mm Hg for 30–120 consecutive seconds
Early warning alert	The time-point when the 10-s mean of a variable met the definitions for a trigger
Early warning alert triggers	
Bradypnea	10-s mean of RR <8 bpm
Hypocapnia	10-s mean of $Etco_2$ <10 mm Hg
Hypoxemia	10-s mean of Spo_2 <94%

Abbreviations: AAE, apnea alert event (defined as "no breath"/apnea lasting between 30 and 120 s); bpm, breaths per minute; $Etco_2$, end-tidal carbon dioxide measure by capnography Capnostream 20 (Medtronic, Boulder, CO); RR, respiratory rate measure by capnography; Spo_2, oxygen saturation as measured by pulse oximeter.

Study Outcome Measures

The primary study aim was to estimate the number of AAEs per subject.

Secondary study outcomes included the following:

1. The duration of AAEs throughout the 24-hour monitoring period.
2. The number of alerts for the individual respiratory variables ($Etco_2$, RR, and Spo_2) derived from capnography and pulse oximetry.
3. The individual respiratory variables values ($Etco_2$, RR, and Spo_2) 5 minutes before, during, and 5 minutes after AAEs.
4. The temporal relationship between alerts for the individual respiratory variables, 10-second means of $Etco_2$ <10 mm Hg, RR <8 bpm, Spo_2 <94%, and the AAEs.
5. The correlation between the RR recorded by capnography and the RR recorded by hourly nursing observations.
6. Women's experience using capnography and pulse oximetry. Women were specifically asked, "What was your experience?" (VNRS: 0 = worst ever and 10 = no problems at all) and "Which part of the monitoring bothered you?"
7. The incidence of suspected OSA from the STOP-Bang questionnaire (within the limitations of no validation in pregnant women) and the sleep quality assessed according to the Pittsburgh Sleep Quality Index.

Analysis of Variables Potentially Related to AAEs

Within the study cohort, we examined the potentially related variables (obesity and additional opioid administration) and compared respiratory variables (AAEs, $Etco_2$, RR,

and Spo_2) for obese women versus nonobese women and women receiving additional opioids (morphine and oxycodone) versus women not requiring additional opioids after cesarean delivery. Obesity[11] was defined as BMI >30 kg/m^2 or current weight >90 kg (when BMI was not available).

Statistical Methods

Continuous variables were summarized by either a mean and standard deviation (SD) or by the median (IQR) and minimum and maximum values. Categorical variables were summarized by a count and percentage.

The number of AAEs per subject was calculated, and the distribution of the number of AAEs per hour presented graphically for all women in the cohort. For some analyses, the unit was the AAE, and for others, it was the subject. Thus, when analyzing all AAEs, the total number of AAEs was the denominator. When analyzing all the subjects, the total number of subjects was the denominator. The hourly means for individual respiratory variables were calculated, using the means of all measurements during each hour per subject, and presented graphically. The duration of time that elapsed between the onset of the individual variable alert and the onset of the AAE, regardless of AAE duration, was measured for each variable, and these data are presented in a box plot. Pearson correlation coefficient between hourly mean respiration rate and hourly nurse observations was calculated and is presented with level of significance. SDs and/or confidence intervals (CIs) for repeated AAE measurements were estimated from the variance components of the residuals from repeated-measures analysis of variance models. We assessed the potential association between the variables potentially related to AAEs and other respiratory variables. These potentially related variables were obese subjects (obese versus nonobese) (yes/no), additional intravenous morphine (yes/no), and additional opioids (oral or intravenous) (yes/no) using Poisson regression. Least squares means (LSmeans) (model estimated means) are presented with level of significance and 95% CIs. The association among the hourly means of the individual variables, $Etco_2$, RR, and Spo_2, was compared between subcohort groups using repeated-measures analysis of variance. LSmeans (model estimated means) are presented with the level of significance and 95% CIs. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC) software. No imputation of missing data was performed. The required significance level of findings was $P < .05$. Nominal P values are presented, and no adjustments were made for multiple testing.

Sample Size Calculation

Statistical analyses planned were mainly descriptive in nature. Thus, the sample size calculation was based on precision analysis. We assumed that the error in the estimated mean would be <25% of the SD, and thus for a 95% CI, we estimated that we required a sample size of 62 subjects ($n = z_\alpha 2\sigma 2/E^2 \approx 62$). "$z_\alpha$" is the approximate value of the 97.5 percentile point of the normal distribution: 1.96. "σ" is the SD. "E" is the error in the estimated mean. It is assumed that $E = 0.25\sigma$. Accounting for potential dropouts, we decided to enroll 80 women.

RESULTS

There were 171 women approached, and 80 eligible women were recruited for the study; 6 women did not use the capnography and pulse oximetry (4 women did not use it at all and 2 only used it for 10 minutes) (Figure 1).

Demographic, medical, and obstetric characteristics of the study cohort are presented in Table 2 and Supplemental Digital Content 1, Table 1, http://links.lww.com/AA/C419. The principal items from the STOP-Bang and the Pittsburgh Sleep Quality Index are presented in Supplemental Digital Content 2, Table 2, http://links.lww.com/AA/C420.

The duration of valid data (hours:minutes), mean (SD) (range), was 8:28 (7:51) (0:00–22:32) for the capnography and 15:08 (6:42) (1:31–23:07) for the pulse oximetry. There

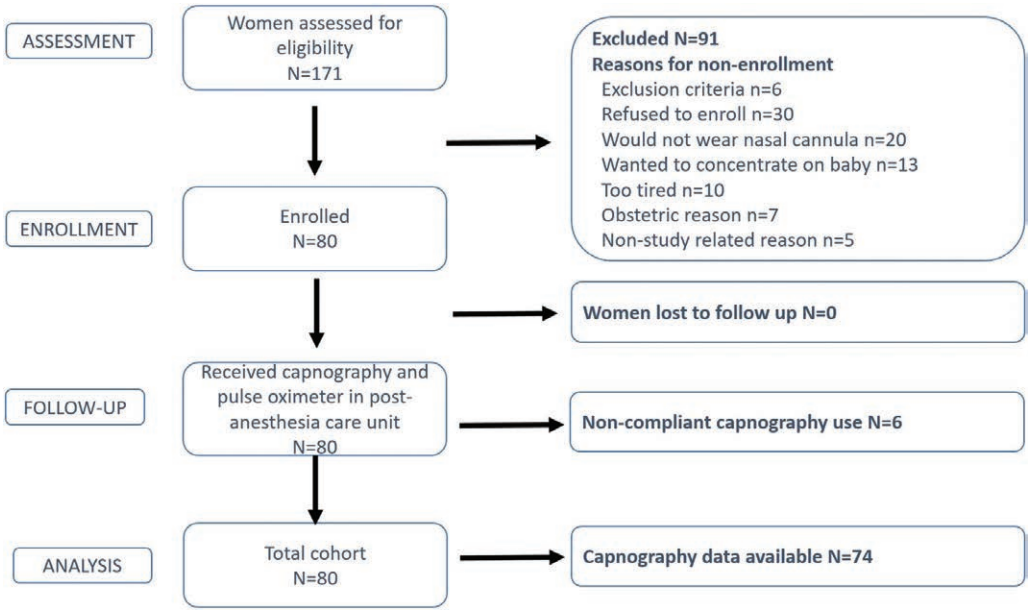

Figure 1. Study flow diagram of women who were assessed for enrollment and who participated in the study.

Table 2. Study Population Demographic and Obstetric Characteristics

Demographic and Obstetric Characteristics	
Maternal age (y), mean ± SD	34.5 ± 5.1
Gravida (number) , mean ± SD	2.6 ± 1.5
Parity (number) , mean ± SD	1.2 ± 0.8
Gestational age (wk) , mean ± SD	38.7 ± 0.7
Current weight (kg), mean ± SD (range)	80.0 ± 13.1 (53.1–113.0)
Current BMI (kg/m^2) , mean ± SD (range)	30 ± 5 (20–44)
ASA, n (%)	
I or II	78 (97.5)
III	2 (2.5)
Medical insurance type, n (%)	
Government-assisted	16 (20.0)
Private	64 (80.0)
Scheduled cesarean delivery, n (%)	65 (81.3)
Duration of cesarean delivery (min), mean ± SD	54.6 ± 16.6
Suspected or known OSA from history, n (%)	9 (11)
STOP-Bang score ≥3, n (%)	8 (10)
Time from surgery end to capnography start (min), mean ± SD	90.5 ± 69.2

Values are presented as mean ± SD and number (%).
Abbreviations: ASA, American Society of Anesthesiology; BMI, body mass index; OSA, obstructive sleep apnea; SD, standard deviation.

were 198 AAEs, mean (SD) duration of 57 (27) seconds experienced by 39/74 (53%) women, median (range) (95% CI for range) 1 (0–29) (0–1) per subject (Figure 2).

Of the women who experienced AAEs, 13 had 1 event, 7 had 2 events, 5 had 3 events, 3 had 4 events, 1 had 6 events, and 2 had 7 events. Eight women had ≥8 AAEs, 3 were obese (BMI [kg/m^2]: 31, 34, and 36), and none received additional morphine. The maximum number of AAEs was 29 in 1 woman who had no risk factors.

Supplemental Digital Content 3, Figure 1, http://links.lww.com/AA/C421, shows the hourly means of Spo_2 and RR for all women in the study cohort. Table 3 presents the number of alerts for individual variables ($Etco_2$, RR, and Spo_2) per minute during the 24-hour monitoring period, median (IQR). Table 3 also presents the mean(SD) of the individual values, 5 minutes before, during, and 5 minutes after the AAEs. For example, during the 5 minutes before AAE, we had a median of 1.2 RR alerts per minute, that is, 6 RR alerts for this 5-minute period. One hundred eighty-eight of 198 (94.9%) of the AAEs had a 10-second mean of $Etco_2$ <10 mm Hg at least once in the period from 5 minutes before the AAE started, and 107/198 (54.0%) of the AAEs had Spo_2 <94% at least once in the period from 5 minutes before the AAE started.

The temporal relationship between alerts for the individual variables and AAEs is presented in Figure 3. In a majority of cases, the Spo_2 alerted after the AAE, and the RR and $Etco_2$ alerted before the AAE.

Nursing RR observation was RR ≥14 bpm at all timepoints in all women during the 16-hour nurse monitoring period. The nurses-recorded RR median (IQR) was 18 (18–18), and the hourly mean(SD) of the capnography RR was 16 (14–18). The Pearson correlation coefficient was r = 0.05 (95% CI, –0.04 to 0.14; P = .25) between capnography-recorded RR and nursing-measured RR. One woman had a written comment in the nurse EMR that she reported lethargy, suggesting that she was tired but not sleepy or sedated because this was not noted. This woman had 29 AAEs, and the nurses reported her RR between 16 and 20/min postpartum, all Spo_2 measures were >94%, and she did not require naloxone. Postoperative nursing observations recorded oxygen administration through the nasal sampling cannula for 2 women at 11 and 16 hours, respectively, after cesarean delivery. One of these subjects had no AAEs, and the other had 7 AAEs during the 24-hour monitoring period. There was no apparent relationship between nurse-reported RR and Spo2 and nurse interventions, although precise statistical comparisons were not possible due to lack of temporality between readings. Five women had a nursing observation of Spo_2 <94%: 2 during the PACU stay and three 5–15 hours after cesarean delivery. Fifty-five women had a 10-second mean of Spo_2 <94% recorded by the pulse oximetry; thus, nurses identified and reported 5/55 (9.1%) of Spo_2 <94% events. Of the women with a nursing observation of Spo_2 <94%, 2 had no AAEs and 3 had 2 AAEs during the study period. The

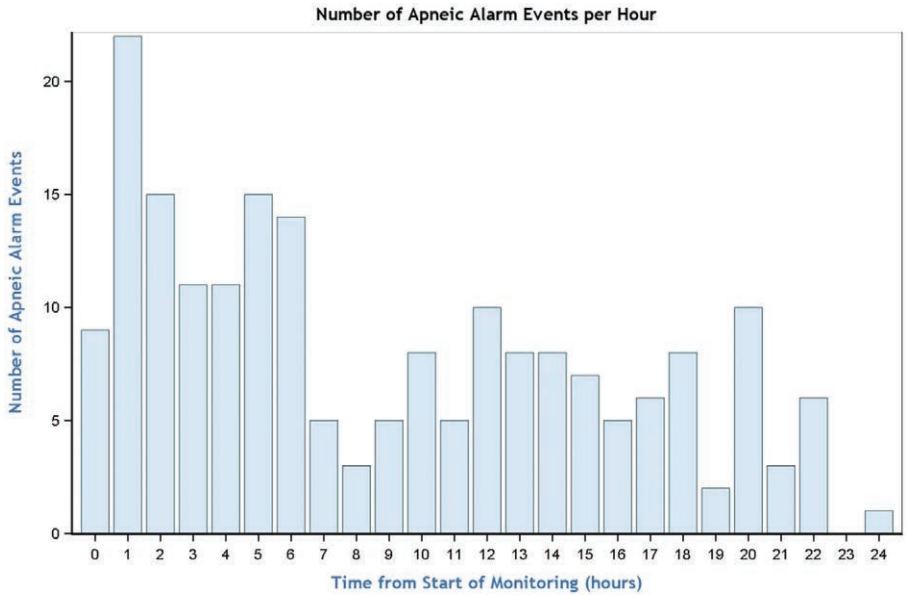

Figure 2. Number of AAEs per hour for all women. Mean (SD) time from start of monitoring to first apnea was 5:36 (5:48) hours:minutes. AAE indicates apneic alert event; SD, standard deviation.

Table 3. Alerts for the Individual Variables ($Etco_2$, RR, and Spo_2): 5 Minutes Before, During, 5 Minutes After the AAE, and During the Total Monitoring Period

Variables	5 min Before AAE	During AAE	5 min After AAE	Total Monitoring Period
No. alerts per minute				
$Etco_2$	0.4 (0.0–3.2)	5.1 (4.0–6.0)	0.7 (0.0–3.4)	1.4 (0.4–4.0)
RR	1.2 (0.0–3.6)	6.0 (5.4–6.0)	1.8 (0.4–4.8)	1.4 (0.5–4.1)
Spo_2	0.0 (0.0–1.0)	0.0 (0.0–0.0)	0.0 (0.0–0.4)	0.1 (0.0–0.6)
Individual variable values				
$Etco_2$	22.7 ± 11.9	7.8 ± 6.8	21.6 ± 12.8	16.0 ± 11.8
RR	10.7 ± 6.7	1.2 ± 1.9	9.4 ± 7.0	7.9 ± 6.2
Spo_2	95.6 ± 2.2	95.7 ± 2.2	95.3 ± 3.1	95.5 ± 1.4

Data are presented are mean ± SD and median (interquartile range).

All data (not only "valid" data) are presented.

Abbreviations: AAE, apnea alert event (defined as "no breath"/apnea lasting between 30 and 120 s); $Etco_2$, end-tidal carbon dioxide measure by capnography Capnostream 20 (Medtronic, Boulder, CO); RR, respiratory rate measure by capnography; SD, standard deviation; Spo_2, oxygen saturation as measured by pulse oximeter.

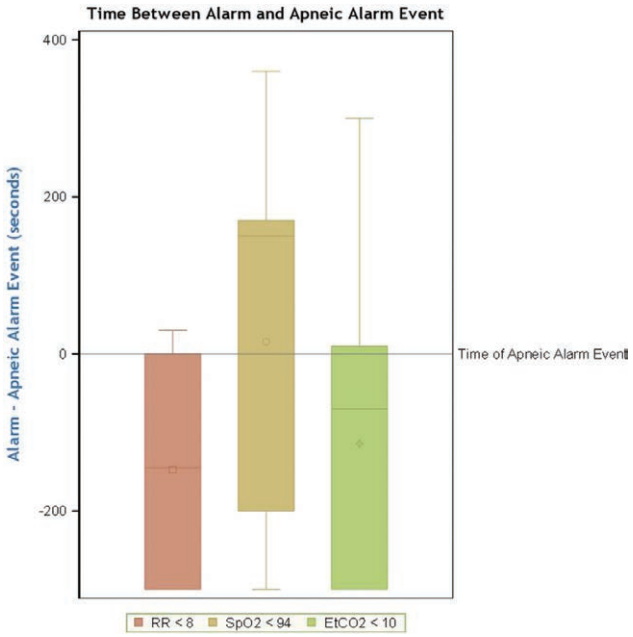

Figure 3. Timing of the alerts of individual variables in relation to the apnea alert events. A negative value indicates that the alert occurred before the AAE, and a positive value means that the alert occurred after the AAE. Data are presented in seconds, mean ± standard deviation (interquartile range) (total range). $Etco_2$ <10 mm Hg: −105.4 ± 168.3 (−300 to 10) (−300 to 330); RR <8 bpm: −147.4 ± 131.4 (−300 to 0) (−300 to 30); and Spo_2 <94%: 98.1 ± 276.4 (−200 to 340) (−300 to 420). AAE indicates apneic alert event; RR, respiratory rate.

precise time-points for these nurse measurements within the reported hour are not defined in parallel to the capnography and pulse oximetry; thus, we cannot align the nurse's Spo_2 readings to the capnography data.

No women received naloxone or any intervention for respiratory depression. Postoperative pain, additional analgesic requirements, and opioid-related side effects are presented in Supplemental Digital Content 4, Table 3, http://links.lww.com/AA/C422. There were 17 additional doses of intravenous morphine administered to 11 women after their cesarean delivery. No women received sedating antipruritic or antiemetic agents.

There were no problems reported with the capnography among 15 women (18.1%); 81.9% of the women had complaints with the capnography, including nose itching 16 (20.0%), looked "sick" to visitors 1 (1.3%), interfered with nursing 3 (3.8%), multiple reasons 37 (46.3%), including nose itching, nausea, forgot to put it back after it was removed (eg, after going to the bathroom), too many lines, looked sick to visitors, interfered with nursing; 3% of these women also complained about the pulse oximetry. Fifty-five subjects (68.8%) would wear the capnography and pulse oximetry again. Additional information regarding the capnography experience and sleep during the 24-hour monitoring period is presented in Supplemental Digital Content 5, Table 4, http://links.lww.com/AA/C423.

Analysis of Variables Potentially Related to AAEs

There were significantly fewer AAEs for obese women compared to nonobese women (0.25 [95% CI, 0.20–0.31] vs 0.40 [95% CI, 0.34–0.48]; $P < .0001$; rate ratio, 1.64 [95% CI, 1.23–2.18]). Comparisons between the LSmeans for women receiving and not receiving additional opioids (morphine and oxycodone) are presented in Supplemental Digital Content 6, Table 5, http://links.lww.com/AA/C424. The number of AAEs for women receiving (n = 11) versus women not receiving additional intravenous morphine was significantly different (0.34 [95% CI, 0.30–0.39] vs 0.15 [95% CI, 0.08–0.26]; $P = .0049$; rate ratio, 2.31 [95% CI, 1.29–4.15]) (Supplemental Digital Content 6, Table 5, http://links.lww.com/AA/C424). One woman receiving additional intravenous morphine had 1 AAE, 3:03 hours:minutes after intravenous morphine administration; 1 woman had 2 AAEs, the first occurred 9:40 hours:minutes after intravenous morphine administration; 1 woman had 3 AAEs, the first occurred 14:29 hours:minutes after intravenous morphine administration; and 1 woman had 6 AAEs, all occurred before intravenous morphine administration. There were 52 women (65%) who received additional opioids (calculated as morphine equivalents).[26] There was a significant difference in the number of AAEs for women who received additional opioids versus women who did not (LSmeans, 0.36 [95% CI, 0.30–0.42] vs 0.24 [95% CI, 0.18–0.31]; $P = .0108$; rate ratio, 1.50 [95% CI, 1.10–2.06]) (Supplemental Digital Content 7, Figure 2, http://links.lww.com/AA/C425). There was no apparent dose response.

DISCUSSION

The main finding in our prospective observational study of continuous capnography and pulse oximetry in women

who underwent cesarean delivery after receiving intrathecal morphine was that 53% of the women had AAEs. In the cohort of 80 women, we observed 198 AAEs that lasted on average 57 seconds. There were, however, no clinical consequences associated with the AAEs we report, and none was identified by hourly nursing observations. The duration of valid data capture was longer for pulse oximetry than capnography (15 vs 9 hours, respectively). Nursing observations recorded RR ≥14 bpm at all time-points in all women, and nursing RR was not correlated with capnography RR. Most women reported that the nasal sampling cannula bothered them for various reasons, although almost 70% reported that they would wear it again.

To identify apneas that may not be detected by routine nursing observations in our population, we used continuous assessments with capnography in a clinical environment, but we blinded staff to the measurements. The number of women who experienced apneas, 53%, was higher than reported previously. This likely relates to a combination of factors, including alert thresholds and lack of observer verification to identify artefacts and disconnections.[27] Abouleish et al[28] using pulse oximetry alert detected <1% incidence of desaturations but used a threshold of 85%, which is much lower than the 94% we used, and Daley et al[27] using vital signs with additional verified clinical observations reported apnea in almost 30% of women undergoing cesarean delivery who received epidural morphine 5 mg. Our alert thresholds for the respiratory variables were selected based on prior studies.[29,30] Alert thresholds for hypocarbia are often unreported, although a range of numerical options has been used ranging from 15 to 30 mm Hg.[24,31,32] A lower Spo_2 threshold is usually set when women receive supplementary oxygen. The selection of a suitable threshold has implications for false alerts because high thresholds that may alert early are overly sensitive and thus annoying for subjects and providers and potentially ignored by staff.[33] Previous studies showed that Spo_2 lags behind other variables as a reliable alert of respiratory depression, in part, due to the threshold value selected.[31,34] $Etco_2$ may have been "overly reliable" in previous studies of capnography due to the selection of a higher alert threshold. For this reason, we selected 10 mm Hg, which is lower than previous studies yet higher than the <5 mm Hg selected for the no breath apnea threshold.

We used capnography because it is considered reliable to measure apnea and bradypnea (decreased RR), combined with pulse oximetry to measure hypoxemia (decreased Spo_2).[15,35,36] Capnography measures $Etco_2$ that decreases if ventilation is reduced, whereas transcutaneous carbon dioxide (CO_2) measures $Paco_2$ that rises with hypoventilation. However, the clinical relevance of the AAEs we report using capnography, along with previous reports of hypercapnia,[10,36] hypoxemia,[28,37] and bradypneas,[38] is unclear. Burton et al[24] using capnography found that respiratory events (apnea and hypoxia) are more frequently associated with hypo- rather than hypercarbia. It is important to appreciate that the numerical values we reported for $Etco_2$ are not a quantitative assessment of $Paco_2$ levels or respiration adequacy,[39] and this is a limitation of using a nasal cannula to measure CO_2.[25] If quantitative arterial CO_2 levels are sought, transcutaneous CO_2 is superior[40,41]; however, only capnography can concurrently measure RR and identify apneas.[15]

Pulse oximetry is a less-reliable indicator than capnography and may only alert after the apneas have occurred. Our study supports this previous observation that the Spo_2 alerted more frequently after the AAE, and the majority of RR and $Etco_2$ alerts occurred before the AAE. In 2 of the earliest studies of continuous monitors after cesarean delivery in women receiving neuraxial morphine, there were no bradypneas identified in the presence of hypoxemia (Spo_2, <85%),[28] and Brose and Cohen[37] reported at least 1 episode of Spo_2 <85% in 71% of women who received neuraxial morphine after cesarean delivery. Both these studies reported no clinically significant respiratory depression. Subsequently, Pan and James[14] used continuous pulse oximetry, heart rate, and plethysmography after cesarean delivery and found no association between decreases in Spo_2 and RR.

We looked for a temporal trend in the capnography measurement and found that most of the AAEs occurred in the first 6 hours of monitoring. However, AAEs occurred throughout the monitoring period, consistent with data reporting depressed CO_2 response curves up to 24 hours after neuraxial morphine administration.[42] Brose and Cohen[37] showed that hypoxemia occurs without any temporal pattern, and Kato et al[38] reported onset of bradypnea between 1 and 13.5 hours after morphine administration for cesarean delivery. There was no temporal relationship between additional opioid administered and AAEs, bradypnea and hypoxemia, supporting previous findings with transcutaneous CO_2 monitoring.[10] There were fewer AAEs for obese women and those who received additional opioids. This was not a primary outcome and represents data on a small number of women; thus, firm conclusions cannot be drawn. However, our data support Crowgey et al[11] that neuraxial opioids may be safely administered to obese women and Bauchat et al[10] to permit additional systemic opioids for women who received neuraxial opioids for cesarean delivery.

It has been suggested that healthy young women who undergo cesarean delivery after receiving neuraxial opioids are at low risk of respiratory events, and that only nurse clinical observations are necessary.[4,37] The superiority of postoperative capnography or pulse oximetry monitoring versus intermittent clinical nurse assessments was confirmed in a recent meta-analysis.[34] Intermittent RR measures may miss apnea or bradypnea, unless slow onset of apnea occurs after period of bradypnea,[4] and excessive breaks between the nursing observations may mean that adverse clinical events are missed.[27,34,36,43] In our cohort, nursing observations were performed as per routine practice, hourly for 16 hours after cesarean delivery, more frequent than recommended by the ASA.[2] In keeping with our study, a recent study measuring transcutaneous CO_2 after cesarean delivery found no relationship between women with hypercapnia and the hourly nursing RR.[10]

We included all women regardless of BMI and report no discernible increase in the occurrence of apnea, bradypnea, and hypoxemia in these "at-risk" women. Women with risk factors such as suspected OSA and obesity (BMI >40 kg/m^2) have often been excluded from studies that examine

respiratory events after cesarean delivery with neuraxial opioid administration.[10,36] Crowgey et al[11] investigated respiratory depression after administration of neuraxial morphine for cesarean delivery, and almost two-thirds of their cohort was obese, using a similar BMI threshold for obesity to our study (>30 kg/m^2). They reported zero clinically relevant respiratory events, even among the obese women, as reported in our study. This complete absence of clinically relevant respiratory events after administration of neuraxial morphine for cesarean delivery was also noted in other studies, despite simultaneous reports of respiratory depression measured by capnography, transcutaneous CO_2, or naloxone requirements.[10,11,36]

The main limitation of our study was a lack of observer verification of the apnea events as true events, hence the term AAEs, defined as no breath ($Etco_2$, <5 mm Hg) for at least 30 seconds and up to 120 seconds.[10,44] To differentiate AAEs from disconnections and other potential artefacts,[31] we limited AAEs to 120 seconds[10] on the premise that any event longer than that was likely a disconnect.[37] Lack of observer verification lends this study more to a device evaluation rather than a clinical observation study. Capnography and pulse oximetry artefacts may have been caused by a number of factors, including coughing, swallowing, capnography/pulse oximetry displacement while mobilizing or caring for their neonate,[45] and hand movements.

We did not have a control group of women without neuraxial opioids after cesarean delivery. After cesarean delivery, many factors may affect respiration, including sleep deprivation, pregnancy-related OSA, and hormonal changes because pregnancy physiology is normalized. The highest risk period for respiratory depression may be during sleep, but we are not able to know which AAEs occurred during sleep. A future study is needed to look exclusively at respiratory depression during sleep.

We chose to disable the capnography and pulse oximetry alerts,[37] and therefore we cannot know if the nurses could have verified alerts or, alternatively, if they would experience alert fatigue.[46] If the alert settings had been activated for the capnography and pulse oximetry, then they would have triggered at least 198 times. Because the nursing staff was intentionally blinded to the capnography measurements, the device had no influence on nursing RR measurement and did not affect routine clinical care. We do not have sufficient information to state whether capnography is a useful device to detect respiratory depression or reduce associated morbidity in the busy postpartum floor setting. In a nonobstetric postoperative population in the PACU, observer confirmation of every capnography alert demonstrated that the majority of apnea alerts were true and that apneas occurred on average every 37 minutes.[47]

Most women complained that the nasal sampling cannula was bothersome, and women appear to prefer to use pulse oximetry rather than capnography based on the longer duration of use. However, we confirmed that capnography alerted for impending apneas earlier than pulse oximetry did,[15] suggesting that while capnography is less well-tolerated, it may be a more useful alert device if compliance can be ensured. Transcutaneous CO_2 monitors may be easier to wear because only 2 women withdrew consent in a prior study[36]; however, when offered a choice between the ear probe (with Spo_2) and the chest probe (CO_2 only), the chest probe was preferred.[10] We are only aware of 1 study that used capnography after cesarean delivery; however, women received neuraxial sufentanil and not morphine,[48] and the women's experience with the nasal sampling cannula was not discussed.

Although we made an assessment of variables potentially associated with AAEs, we did not adjust for confounding variables, such as OSA risk or BMI. Although OSA may be a significant contributor to postoperative respiratory events, the STOP-Bang screening tool has not been validated to identify OSA in the pregnant population.[18] We did not mandate a sleep position even for obese women and those with OSA, and all women reported sleeping with the bed angled upward. Hypoxemia is more likely to occur in the supine position while the women are asleep after the cesarean delivery, and this is more likely in obese women and those with OSA.[49] Sedated women may be at greater risk of respiratory events; however, in our cohort, only 1 woman had any recorded lethargy, so this association could not be assessed.

In conclusion, we identified 198 AAEs detected by capnography among 80 women who underwent cesarean delivery after receiving intrathecal morphine. There was poor correlation between capnography RR and nursing-observed RR. We had no clinically relevant respiratory adverse events in our study cohort. Absence of observer verification precludes distinction between real, albeit nonclinically significant alerts with capnography and false apneas. Continuous respiratory measurements by capnography could alert for apneas that intermittent hourly nursing observations may miss. However, maternal intolerance combined with frequent alerts may limit the widespread adoption of capnography after cesarean delivery, a setting where clinically significant respiratory depression is extremely rare. Future studies are needed to examine the role of capnography in at-risk subjects (eg, morbid obesity) and during at-risk periods (eg, while sleeping) when receiving sedatives or systematic narcotics. ■

DISCLOSURES

Name: Carolyn F. Weiniger, MBChB.
Contribution: This author helped with study design, study recruitment, data collection, data analysis, and manuscript preparation.
Conflicts of Interest: C. F. Weiniger is a principal investigator and an archival author. Oridion (now part of Medtronic) has provided travel support for conference presentation to Hadassah Hebrew University Medical Center, for which C. F. Weiniger has been a beneficiary. Covidien (now part of Medtronic) provided funding to support this investigator-initiated study. The company did not input the study design, study recruits, data analysis, or manuscript write-up.
Name: Seden Akdagli, MD.
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