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doi: 10.24488/twmuj.2021017

TWMUJ 6: 21-29, 2022

Original

Mallampati Classification and Frequency of Respiratory Depression After Cesarean Section With 0.15 MG Spinal Morphine

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(Accepted January 12, 2022)
(Advance Publication by J-STAGE March 28, 2022)

Background: Spinal anesthesia with intrathecal morphine is widely used for cesarean section (CS), and is associated with nocturnal desaturation. No studies have correlated respiratory depression (RD) in this population with the Mallampati (MMP) classification. We examine the value of MMP for preoperative risk stratification.

Method: MMP was assessed preoperatively in patients scheduled for elective CS under spinal anesthesia.

We defined RD events as follows within 24 hours postoperatively, measured by mainstream capnometry waveform analysis:

1. Bradypnea (RR ≤ 9 bpm for ≥ 120 seconds);
2. Apnea ($P_{ET}CO_2$ < 5 mmHg for ≥ 15 seconds up to 120 seconds);
3. Temporary hypopnea (5 mmHg ≤ $P_{ET}CO_2$ < 15 mmHg for ≥ 15 seconds up to 120 seconds);
4. Sustained hypopnea ($P_{ET}CO_2$ > 45 mmHg for ≥ 120 seconds).

Results: There were 100 patients with MMP 1-2, and 90 patients with MMP 3-4. Bradypnea was observed in 55 patients (MMP 1-2, 55%) vs. 55 patients (MMP 3-4, 61%), p = 0.394. Apnea was observed in 77 patients (MMP 1-2, 77%) vs. 75 patients (MMP 3-4, 83%), p = 0.276. Temporary hypopnea was observed in 68 patients (MMP 1-2, 68%) vs. 76 patients (MMP 3-4, 84%), p = 0.008. No sustained hypopnea events were noted in any patients.

Conclusions: Temporary hypopnea was more frequent in patients with MMP 3-4 vs. 1-2, following 0.15 mg intrathecal morphine for CS.

The study was registered at the University Hospital Medical Information Network Clinical Trials Registry (UMIN 000031410).

Keywords: intrathecal morphine, Mallampati classification, cesarean section, postoperative respiratory depression, perioperative risk stratification

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Introduction

Spinal anesthesia with intrathecal morphine is widely used for anesthetic management of cesarean section (CS).[1] Although morphine provides analgesia for as long as 12-24 hours postoperatively, delayed respiratory depression (RD) for 6-18 hours after administration has been noted.[2] The American Society of Anesthesiologists (ASA) guidelines recommend patients should be monitored for adequate ventilation for a minimum of 24 hours after administration of neuraxial opioids.[3] In previous studies, the reported incidence of delayed RD has been low (0.07-0.9%[4,5]), but the definition of RD has not been consistent across studies.

Recent studies using definitions based on continuous monitoring such as oxygen desaturation $SpO_2 < 90\%$[6] and high transcutaneous carbon dioxide concentration ($P_{TC}CO_2 > 50$ mmHg)[7] report much higher incidences of RD (23-32%). One of our own studies also found that severe hypoxemia ($SpO_2 < 90\%$) occurred in 35% of patients after the CS.[8] However, pulse oximetry alone may not be suited to detect RD at an early stage, especially with supplemental oxygen.[9] Capnography allows for a more direct assessment of ventilation, and a high frequency of apneic alert events (53% of patients) has been reported in this population.[10] Despite high rates of RD events reported with continuous monitoring, they are associated with fewer clinically adverse events.[6,7,10] Of note, a consensus statement from the Society for Obstetric Anesthesia and Perinatology (SOAP)[11] recommends no further respiratory monitoring is needed beyond routine postoperative monitoring for small doses of intrathecal morphine (0.05-0.15 mg) in healthy patients. For patients with airway risks (pre-existing obstructive sleep apnea: OSA, obesity, etc.), SOAP statement includes considerations for continuous rather than intermittent respiratory monitoring.

The Mallampati (MMP) classification is a simple method to assess airway risk at the bedside. MMP 3 or 4 indicates susceptibility to upper airway obstruction.[12,13] The relative risk of sleep apnea doubles with each increase in the MMP class.[14] In pregnant women, MMP increases by 1-2 levels due to edema around the airway,[15] and we have shown that 20% of postpartum patients have sleep apnea.[16] It is likely that pregnant women at higher risk for airway obstruction are in MMP 3 or 4, but the relationship between MMP and postoperative RD after CS has not been investigated. If there is a difference in the frequency of RD according to MMP, it may be possible to simplify the selection and preparation of postoperative respiratory monitoring strategies. In this study, we aimed to compare the frequency of RD events by capnometry after spinal anesthesia with 0.15 mg intrathecal morphine administration between patients with MMP 1 or 2 versus those with class 3 or 4.

Methods and Materials

A prospective observational study was conducted at St. Luke's International Hospital in Tokyo following approval by the Ethics Committee (17R-016, Clinical Trials Registry UMIN000031410). Two hundred patients were recruited between March 2018 and June 2019. Inclusion criteria were, scheduled CS, preoperative study consent, and administration of neuraxial anesthesia (spinal anesthesia alone or combined spinal and epidural anesthesia). Exclusion criteria were, emergent surgery, postoperative need for ventilatory support, conversion to general anesthesia, postoperative admission to the intensive care unit, or fetal complications. As inter-rater reliability is a concern in the evaluation of MMP, assessment of MMP was performed by a single researcher (SY) either on the day before or on the day of surgery. Samsoon and Young's modified MMP was used.[17] MMP was evaluated in a sitting position, without phonation, with maximum opening and protrusion of the tongue.

Primary endpoint

To find out prevalence of RD in patients receiving intrathecal morphine for CS. We defined RD as the presence of any of the following within the 24-hour postcesarean monitoring period:

#1. Bradypnea: respiratory rate of less than 10 breaths/min[3] for more than 2 minutes.[7]

#2. Apnea: maximal $P_{End\text{-}Tidal(ET)}CO_2$ value less than 5 mmHg for more than 15 seconds,[18] and less than 2 minutes.

#3. Temporary hypopnea (decrease in ventilation): maximum $P_{ET}CO_2$ value between 5 mmHg and 15 mmHg for at least 15 seconds,[18] lasting up to 2 minutes.

#4. Persistent hypopnea: $P_{ET}CO_2$ greater than 45 mmHg for more than 2 minutes.

Instances where $P_{ET}CO_2$ remained low for more than 2 minutes (exceeding criteria #2 and #3) were not considered RD events as this likely indicates discontinuation of monitoring.

A previous study that measured transcutaneous partial pressure of carbon dioxide, which approximates that of arterial blood, defined hypercapnia as 50 mmHg or higher for greater than 2 minutes.[7] The difference between arterial and end-expiratory carbon dioxide partial pressure for the capnometer used in this study (cap-ONE, Nihon Kohden, Japan) is reported to be 3 to 4 mmHg.[19] Accounting for this difference, the cutoff for $P_{ET}CO_2$ was set at 45 mmHg for 2 minutes for this study.

Secondary endpoints

Our secondary endpoint is the presence of any of the four previously defined RD events with desaturation of $SpO_2 < 90\%$[8] occurring within 1 minute before or after the RD event. Moreover, the following patient characteristics were noted for subsequent regression analysis as potential predictors of RD: body mass index (BMI), thyromental distance (TMD), STOP questionnaire score (S: snoring, T: tiredness or day somnolence, O: observed sleep apnea, P: hypertension).[20]

Methods for anesthesia

In the operating room, vital signs were measured according to ASA guidelines (pulse oximeter, non-invasive blood pressure monitoring: NIBP, electrocardiogram, thermometer). Every patient received spinal anesthesia without or with combined epidural anesthesia. A standard intrathecal mixture of 0.5% hyperbaric bupivacaine 12 mg/2.4 mL + fentanyl 20 mcg/0.4 mL + morphine 0.15 mg/0.15 mL was injected into the spinal subarachnoid space for each patient.

Measurement equipment and procedure

Postoperative vital signs measurements were performed using an automated blood pressure cuff, pulse oximeter, and mainstream capnometer (cap-ONE® YG-122 T Oral / Nasal adapter, OLG-3800 Capnography Monitor, Nihon Kohden, Japan) per institutional postoperative monitoring protocol for CS. No oxygen was administered unless ordered by the obstetrician in the event of $SpO_2 \leq 94\%$. Respiratory rate < 8 breaths/min and $P_{ET}CO_2 \geq 50$ mmHg on the capnometer were considered indications for immediate anesthesia consult. EarlySense® (EarlySense, Ramat Gan, Israel), a noninvasive piezoelectric sensor system placed under the patient's mattress, was utilized as an adjunct to detect bradypnea events.

Methods for identifying RD events

The capnography waveform, respiratory rate, end-tidal CO_2 values, SpO_2 values, and plethysmographic waveform were exported using dedicated software (PC-viewer, Nihon Kohden, Japan). All events that numerically match the study definitions of RD were identified. Three reviewers (KWM, HK, and NBR), each blinded to patients' MMP and other characteristics, independently screened the waveform data and excluded events that did not match defined criteria or were suspect of measurement artifact. RD events not excluded by at least two of the three reviewers were included in subsequent analyses.

Sample size calculation

Given the lack of prior studies on the relationship between MMP classification and RD, the necessary sample size was calculated based on interim data from the first 100 accrued patients. The interim analysis showed an approximately equal number of patients with MMP 1 or 2 (n = 47), and MMP 3 or 4 (n = 43), and the frequency of RD was 83% vs. 95% for bradypnea, 85% vs. 98% for apnea, and 77% vs. 81% for transient hypopnea, suggesting the existence of a small difference between the two groups. Calculations showed a sample size of 176 was necessary to detect a 15% difference (between 80% and 95%) in the frequency of RD with a group ratio of 1:1, at $\alpha = 0.05$ and $\beta = 0.2$. Accounting for potential patient dropouts, the final recruitment target was set at 200.

Statistical analysis

Descriptive data were noted as mean (± standard deviation), median (quartiles), and number of patients (%). Differences between the two groups were determined by t-test for continuous variables and χ^2 test for categorical variables. Binomial logistic regression analysis was used to identify predictors of RD events, including BMI,

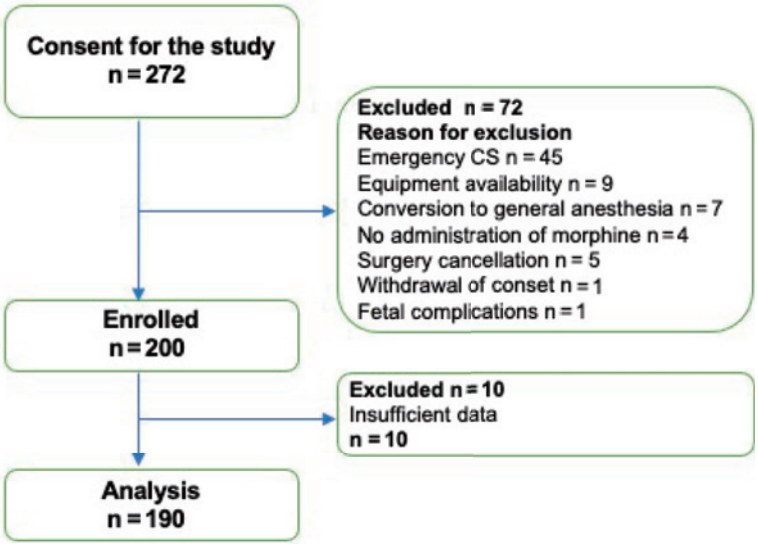

Figure 1. Flow diagram of participants through the study.

Table 1. Patient characteristics.

	MMP 1 or 2 (n = 100)	MMP 3 or 4 (n = 90)	p value (t-test or chi-square)
Age (years) mean±SD	36.9 ± 3.8	36.9 ± 4.3	0.881
Height (cm) mean±SD	159.7 ± 5.7	160.1 ± 4.5	0.548
Weight (kg) mean±SD	62.8 ± 7.59	64.3 ± 8.1	0.215
BMI (kg/m^2) mean±SD	24.6 ± 2.67	25.1 ± 3.1	0.315
Gestational age (weeks) mean±SD	37.8 ± 0.6	37.8 ± 0.6	0.80
Duration of surgery (hour: min) mean±SD	1:05 ± 0:17	1:08 ± 0:16	0.287
Blood loss (mL) mean±SD	905.6 ± 381	812.6 ± 477	0.144
STOP score ≥ 2, n (%)	7 (7)	17 (18.8)	0.014
Thyromental distance (cm) mean±SD	7.82 ± 0.99	7.51 ± 0.96	0.035
Pre-op respiratory rate (bpm) mean±SD	13.7 ± 1.3	14.2 ± 1.2	0.012
Pre-op SpO_2 (%) mean±SD	97.8 ± 0.9	97.7 ± 0.9	0.745
Duration of $ETCO_2$ monitoring (hours) mean±SD	19.3 ± 2.6	19.45 ± 2.7	0.717
Duration of SpO_2 monitoring (hours) mean±SD	20.5 ± 2.6	20.7 ± 2.6	0.614

SD, standard deviation; BMI, body mass index; op, operative; SpO_2, percutaneous oxygen saturation; $ETCO_2$, end-tidal carbon dioxide.
STOP score of 2 points or greater is considered positive.

TMD, and STOP score.[14, 21] All statistical tests were two-way, and p-values of less than 0.05 were considered significant. All statistical analyses were performed using IBM®SPSS®Statistics ver. 24.

Results

Consent was obtained from 272 patients. Seventy-two patients were excluded from the study due to the nature of surgery (emergent CS, n = 45), equipment availability (n = 9), conversion to general anesthesia (n = 7), no administration of morphine (n = 4), surgery cancellation (n = 5), withdrawal of consent (n = 1), and fetal complications (n = 1). Of the remaining 200 patients, 10 were excluded due to insufficient data, resulting in 190 patients for the final data analysis (**Figure 1**). There were 100 patients in the lower MMP group and 90 patients in the higher MMP group. **Table 1** shows patient characteristics.

Based on numeric criteria, 6,399 potential RD events were identified. Following waveform screening by three reviewers, 3,012 events were included in the final analysis. A total of 960 bradypnea, 316 apnea, 283 temporary hypopnea, and 0 sustained hypopnea events were in the

Table 2. Frequency of RD events.

Frequency of RD events	Total (n = 190)	MMP 1 or 2 (n = 100)	MMP 3 or 4 (n = 90)	p value
RD events, n (%)	178 (93.6)	93 (93)	85 (94.4)	0.683
Bradypnea, n (%)	110 (57.8)	55 (55)	55 (61.1)	0.394
Apnea, n (%)	152 (80)	77 (77)	75 (83.3)	0.276
Temporary hypopnea, n (%)	144 (75.7)	68 (68)	76 (84.4)	0.008
Sustained hypopnea, n	0	0	0	NA
Desaturation events, n (%)	80 (42.1)	40 (40)	40 (44.4)	0.536
RD events with Desaturation ($SpO_2 < 90\%$), n (%)	12 (6.3)	4 (4)	8 (8.8)	0.167
Bradypnea with $SpO_2 < 90\%$, n (%)	6 (3.2)	1 (1)	5 (5.5)	0.073
Apnea with $SpO_2 < 90\%$, n (%)	5 (2.6)	2 (2)	3 (3.3)	0.566
Temporary hypopnea with $SpO_2 < 90\%$, n	1 (0.5)	1 (1)	0	0.342
Oxygen administration, n (%)	34 (17.9)	17 (17)	17 (18.9)	0.734
Naloxone administration, n	0	0	0	NA

RD, respiratory depression; MMP, mallampati classification; SpO_2, percutaneous oxygen saturation; NA, not applicable.

Table 3. Potential predictors of RD.

	Odds ratio	95%CI:		p value
		lower limit	upper limit	
MMP, lower (1-2) vs. higher (3-4)	1.183	0.343	4.085	0.790
BMI	1.023	0.820	1.276	0.838
STOP score	3.506	1.132	10.856	0.030
TMD	1.426	0.735	2.767	0.294

CI, confidence interval.

lower MMP group, and 678 bradypnea, 402 apnea, 373 temporary hypopnea, and 0 sustained hypopnea were in the higher MMP group. The frequencies of RD (primary endpoint) and desaturation (secondary endpoint), are shown in **Table 2**. EarlySense® was able to capture 423 out of 1,638 bradypnea events (25.8%) and displayed a respiratory rate 71.6 ± 10.5% (mean, SD) of the time during the monitoring period.

Discussion

We found that overall RD as defined by the four criteria in this study was markedly more frequent (93-94%) than in the previous studies using continuous monitoring(23-53%).[6-8, 10] Moreover, we found a higher prevalence of temporary hypopneas in the MMP 3-4 group as compared to MMP 1-2 following administration of 0.15 mg intrathecal morphine for CS.

Prevalence of RD was much higher than previously reported data. The reason may be due to the utilization of a mainstream $ETCO_2$ sensor (more accurate than sidestream sensors[19]), over a longer period of time (an average of 19 hours), along with review of waveform data, may have led to higher sensitivity. To the best of our knowledge, no previous study of post-cesarean patients after administration of intrathecal morphine has included a full review of the capnometer waveform during the first nocturnal period.

Only one study has measured $ETCO_2$ continuously after CS. Weiniger et al.[10] used capnometry and pulse oximetry in post-CS patients who received 0.15 mg spinal morphine and reported that apneic events ($P_{ET}CO_2 < 5$ mmHg for 30-120 seconds, their primary outcome) occurred in 53% of 80 patients. We found much higher apneic events (80% vs. 53%) compared to this study, but the method was slightly different; we extracted apnea events of shorter duration (15-30 seconds) over a longer period (19 hours vs. 8 hours).

No study for CS patients has extracted bradypnea events by capnometry. Weiniger's study[10] does not report the frequency of alarm-triggered bradypnea (RR < 8 bpm). Terada et al.[22] found bradypnea (RR ≤ 10 bpm using continuous respiratory rate monitoring with a finger sensor) in 85% of patients after administration of 3 mg

epidural morphine (equivalent to 0.1 mg intrathecal morphine[23]), suggesting that bradypnea is more frequently detected by continuous monitoring.

The lack of sustained hypopnea in current study was not in accordance with our initial hypothesis. However, a recent report[24] studying post-surgical patients (not obstetric patients) receiving parenteral opioids demonstrated low $ETCO_2$ ($\leq$ 15 mmHg for $\geq$ 3 minutes) in 63% of patients, with no patients presenting with high $ETCO_2$ ($\geq$ 60 mmHg for $\geq$ 3 minutes). This is similar to what we found (low $ETCO_2$, 75.7% vs. high $ETCO_2$, 0%). In a state of hypopnea with reduced minute ventilation, partial pressure of carbon dioxide in arterial blood increases,[25] while exhaled carbon dioxide at the mouth tends to decrease.[26] The combination of decreased exhaled carbon dioxide during hypopnea and limitations of the measurement methods (a lack of observer verification, discrepancy between measured values and arterial blood concentration) may have hindered detection of sustained hypopnea (high $ETCO_2$) events.

Temporary hypopnea represents a low tidal volume, and is thought to be caused by a combination of factors, including irregular breathing patterns caused by opioids,[10, 27] and narrowing of the upper airway.[28] Weiniger et al.[18] defined temporary hypopnea as an alert state of RD before apnea. Evidence suggests patients with MMP 3-4 are at a higher risk for airway obstruction,[12, 13] which may have resulted in significantly higher temporary hypopnea in our present study.

The frequency of clinically significant desaturation ($SpO_2 < 90\%$) was 42%, which is much higher than 23% of patients with at least one desaturation event as reported by Ladha et al.[6] Ladha et al. used a more stringent standards, i.e., 30 seconds moving window with median $SpO_2 < 90\%$ to extract desaturation events, vs. our standard, which was simply an average of $SpO_2 < 90\%$ over a 60 seconds window.

A systematic review of studies on RD after neuraxial morphine or diamorphine in CS patients from 1990 to 2016 found that the prevalence of clinically significant RD (airway intervention, oxygen therapy, pharmacological therapy, or other interventions) was low (1.08-1.63 per 10,000) compared to RD reported by researchers (61 per 10,000).[29] Apnea occurred in 53% of patients in Weiniger's study mentioned above,[10] but only two patients received oxygen, and none required naloxone or any other intervention for the apneic events.

Standard SOAP monitoring guidelines allow respiratory rate and consciousness to be checked by clinical assessment every 2 hours for 12 hours after surgery, as long as it is safe to do so.[11] The same guidelines state that continuous monitoring, such as pulse oximetry and capnometry, should be considered in patients with obesity (BMI $\leq$ 40) and airway risks such as sleep apnea.

In our study, 18% of patients required oxygen administration. The median time of RD events was 9-13 hours, consistent with the pharmacologic profile of morphine which includes delayed and prolonged effects. Of note, RD and desaturation were measured even in MMP 1-2 patients, that were considered at low risk for airway events. Although airway assessment should be performed comprehensively with multiple indicators,[30] pregnant women with a MMP class 3 or higher can be considered to have significant airway risks, such as apnea, aspiration, and difficult intubation.[31] We believe it is advisable to monitor respiration continuously for 24 hours after surgery, especially in patients with MMP 3-4.

Every patient in the current study tolerated the capnometer well. While a capnometer may be a burden to the patient, given the fact that post-partum breast feeding starts as early as during the first day, capnometry remains the gold standard for respiratory monitoring. However, future studies should continue to investigate use of monitoring technologies that are more comfortable for the patient and resistant to various measurement artifacts.[32]

MMP classification and other outcomes

The MMP evaluates the anatomical relationship between tongue volume and oral cavity volume, and MMP is known to progress in parturients after delivery due to airway edema.[33, 34] Therefore, airway assessment in patients scheduled for CS should be performed immediately before surgery. For every one-class increase in MMP classification, the odds ratio for OSA increases by 2.[14] Moreover, Khan et al.[35] reported that the rate of oxygen desaturation increased with each increase in MMP class when sedatives were used.

Obese patients (BMI > 30) have greater risk for difficult intubation.[36] MMP tends to increase with BMI, and for every 5-point increase in BMI, the odds ratio for OSA

increases by 1.5.[13] Although elevated BMI is an established risk factor for OSA,[37] it has been reported that MMP may not correlate with BMI,[38] and we found no difference in BMI between MMP groups in our study of Japanese parturients.

A large U.S. study noted a difference in the mean pre-pregnancy BMI between races, White (26), Black (28), and Japanese (21),[39] and found that the BMI of Asian patients with OSA is lower than that of Caucasians with OSA.[40] This suggests that racial differences in craniofacial structure may be a factor in OSA and other airway and respiratory risks.[37]

MMP and TMD are predictors for difficult intubation, but data for obstetric patients is limited.[36] In our study, TMD in MMP 1-2 was significantly smaller than in the MMP 3-4 group. However, the difference was only 0.3 cm, which we consider it irrelevant for clinical practice.

Patients with a positive STOP score (≥ 2)[20] are significantly more likely to be in the MMP 3-4 group, indicating a higher risk of OSA. The relationship between OSA and RD is not clear, but the results suggest that STOP score may indicate a stronger predictor of RD in pregnant women, vs. MMP classification in the current study (**Table 3**).

Limitations

We gave a standard dose of 0.15 mg intrathecal morphine regardless of patient height or BMI. Therefore, we cannot speculate on any dose-effect relationship between intrathecal morphine and RD according to body habitus and inter-patient variability. Our population is predominantly Asian (Japanese), thus, we were unable to exclude any differences in racial sensitivity to opioids.[41]

Capnometry in non-intubated patients is susceptible to various artifacts or biases, thus, we have screened the raw results by three blinded investigators. For patient safety, the capnometer/pulse oximeter used in this study was configured to sound an audible alarm at the bedside when $SpO_2 \leq 94$ or respiratory rate < 8 breaths per minute. The audible alarm may have aroused the patient, possibly averted further deterioration and caused underestimation of the clinical impact of RD events. Moreover, initiation of supplemental oxygen may have resulted in further underestimation of RD events.

Preoperatively undiagnosed sleep apnea and other sleep disorders, as well as confounding effects from other postoperative analgesics could not be excluded, and may have impacted our results.

Conclusions

The frequencies of postoperative RD in patients who underwent CS with 0.15 mg spinal morphine were analyzed using multiple continuous monitoring modalities including $ETCO_2$, SpO_2, and the EarlySense® contactless monitor. Temporary hypopneas were significantly more frequent in the MMP class 3 and 4 group compared to patients with MMP class 1 and 2 in this study. However, RD events occurred frequently in every patient regardless of MMP classification. While MMP classification remains a useful assessment of airway anatomy, use of intrathecal morphine appears to pose an indiscriminate risk of RD. While risks of clinically significant harm appear to be minimal, continuous monitoring for 24 hours postoperatively may add an additional safety layer for every patient undergoing CS with spinal morphine.

Sources of Funding: Support was provided from institutional and/or departmental sources of St. Luke's International Hospital and Tokyo Women's Medical University.

Mainstream capnography monitors (cap-ONE® YG-122T Oral/Nasal adapter, OLG-3800 Capnography Monitor) were used on loan from Nihon Kohden, Japan, at no cost.

A non-invasive piezoelectric sensor system (EarlySense®) placed under the patient's mattress, was used on loan from EarlySense, Ramat Gan, Israel, at no cost.

Conflicts of Interest: YN is a consultant for Masimo Japan Corporation, Tokyo, Japan.

Author Contributions: SY and YN conceived the idea and designed the study, conducted the analysis and wrote the initial manuscript. KWM, NF, MO and YN assisted in creating the analysis methodology, and interpreting the results. KWM, HK and NBR independently read the waveform. All authors have approved the submitted version of the manuscript.

Acknowledgments: We would like to express our deep gratitude to Prof. Shiroh Isono, Department of Anesthesiology, Graduate School of Medicine, Chiba University for his professional advice.

Prior Presentations: Poster presentation at Anesthesiol-

ogy 2019, October 20, 2019, Orlando, FL.

Ethical Approval: Approval by the St. Luke's International Hospital Ethics Committee (17R-016).

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