Published in final edited form as:

Int J Obstet Anesth. 2017 November ; 32: 48–53. doi:10.1016/j.ijoa.2017.06.003.

A prospective study of post-cesarean delivery hypoxia after spinal anesthesia with intrathecal morphine 150 µg

Karim S. Ladha^{a,*}, Rie Kato^{b,*}, Lawrence C. Tseng^c, Brian T. Bateman^d, and Toshiyuki Okutomi^e

^aAssistant Professor, Department of Anesthesiology, University of Toronto and Toronto General Hospital, 3 Eaton North - 200 Elizabeth St, Toronto, Ontario, Canada

^bAssociate Professor, Division of Obstetric Anesthesia, Center for Perinatal Care, Child Health and Development, Kitasato University Hospital, 1-15-1 Kitasato, Minami-ku, Sagamihara, Kanagawa 252-0303, Japan

^cAssociate Professor, Department of Anesthesiology, Perioperative and Pain Medicine, Brigham and Women's Hospital, Harvard Medical School, 75 Francis Street, Boston MA, USA

^dAssociate Professor, Department of Anesthesiology, Perioperative and Pain Medicine, Brigham and Women's Hospital, Harvard Medical School, 75 Francis Street, Boston MA, USA

^eClinical Professor, Division of Obstetric Anesthesia, Center for Perinatal Care, Child Health and Development, Kitasato University Hospital, 1-15-1 Kitasato, Minami-ku, Sagamihara, Kanagawa 252-0303, Japan

Abstract

Introduction—Delayed respiratory depression is a feared complication of intrathecal morphine in patients undergoing cesarean delivery. The incidence, timing and risk factors for hypoxia in this population are not known.

Methods—Patients undergoing cesarean delivery under spinal anesthesia at a tertiary care center from October 2012 to March 2016 were included in the study. The Berlin sleep apnea Questionnaire was completed before surgery. Oxygen saturation was recorded every second for 24 hours after the initiation of spinal anesthesia. Desaturation events were defined as a median saturation of <90% (mild) or <85% (severe) across a 30 second period. Multivariable logistic regression was used to determine predictors of a desaturation event.

Results—A total of 721 patients were included in the analysis. Within this cohort, 169 women (23%) experienced at least one mild desaturation event, 91 (13%) experienced two or more mild desaturations, and 26 (4%) suffered a severe desaturation event. After the administration of intrathecal morphine, the median times to first mild or first severe desaturation were 7.4 (IQR 4.1–

Corresponding Author: Dr Rie Kato, Kitasato University Hospital, 1-15-1 Kitasato, Minami-ku, Sagamihara, Kanagawa 252-0375, Japan, Phone: +81-42-778-8606, Fax: +81-42-778-8647, rie.kato@nifty.com.

*The first two authors contributed equally to this work and are co-first authors

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimersthat apply to the journal pertain.

13.5) h and 12.0 (IQR 5.4–19.6) h, respectively. Patients who screened positive for sleep apnea had increased odds of having a mild desaturation event (OR 2.31, 95% CI: 1.40 to 3.79, $P=0.001$), as did patients who were obese (OR 1.80, 95% CI 1.05 to 3.09, $P=0.033$).

Conclusions—Mild hypoxemia occurred frequently in women receiving intrathecal morphine 150 µg for post-cesarean analgesia. Desaturations were observed most frequently 4–8 hours after administration of intrathecal morphine. Obesity and a positive Berlin questionnaire were risk factors for hypoxemic events.

Keywords

Cesarean delivery; Oxygen; pulse oximeter; Oxygen; desaturation; Opioid; intrathecal morphine

Introduction

Intrathecal morphine (ITM) is commonly used for patients undergoing cesarean delivery (CD).¹ Although pruritus, urinary retention and nausea are common adverse effects of ITM, delayed respiratory depression is especially concerning, due to its potential for significant morbidity and mortality.² The incidence of bradypnea associated with ITM for post-cesarean analgesia is reported to be as low as 0–0.26%.^{3–5} However, the rate estimations provided in these studies may not fully account for the extent of opioid-induced respiratory depression, because respiratory rate was not monitored continuously. In addition, patients may be hypoxic and hypercarbic without exhibiting bradypnea.⁶

There are limited data on the incidence of hypoxia following ITM in patients undergoing CD because postoperative pulse oximetry is not typically measured. Furthermore, few studies have investigated the impact of patient characteristics, for example obstructive sleep apnea (OSA), on the rate of hypoxia following the administration of neuraxial opioids.⁷ The physiologic changes of pregnancy may predispose women to OSA.⁸

Defining populations at risk for hypoxia following ITM may allow for more targeted surveillance through the use of continuous pulse oximetry. The aim of this study was to analyze the timing and incidence of hypoxic events in parturients receiving ITM 150 µg for post-cesarean analgesia, and to identify factors associated with postoperative hypoxia.

Methods

This study was approved by the medical research Ethics Board at Kitasato University School of Medicine (B12-98) and Partners Institutional Review Board, and registered at the UMIN Clinical Trials Registry (UMIN000018487).

Patients undergoing CD under spinal anesthesia at Kitasato University Hospital, a tertiary care center located in Sagami-hara, Japan, from October 2012 to March 2016 were considered for inclusion into the study. This included all elective and non-elective cases scheduled between 0745 to 1930 hours. Parturients were included irrespective of gestational age. Women who were American Society of Anesthesiologist's physical status ≥ 2 ; on supplemental oxygen preoperatively; a non-elective case that prevented obtaining informed consent; undergoing a cesarean hysterectomy or radiological intervention; or administered

additional anesthetics or analgesics intraoperatively, other than single-shot spinal anesthesia, were excluded.

Patients were positioned in the right lateral decubitus position and dural puncture was performed at the L3/4 or L4/5 vertebral interspace with a 25- or 27-gauge pencil-point spinal needle. Subsequently, 0.5% hyperbaric bupivacaine 2.4 mL, fentanyl 10 µg and morphine hydrochloride 150 µg were administered. Postoperative pain management was changed during the study time period. From October 2012 to September 2013, a transversus abdominis plane (TAP) block (0.375% ropivacaine 20 mL each side) was performed after surgery unless the patient refused it. At the patient's request for additional analgesia, flurbiprofen 50 mg (intravenous), diclofenac 50 mg (rectal) and/or pentazocine 15 mg (intramuscular) was administered at the discretion of the obstetrician in charge. From October 2013 to March 2016, a TAP block was performed only when a patient requested it. Acetaminophen 1g (intravenous) and flurbiprofen 50 mg (intravenous) were administered every 8 hours for at least 24 hours after surgery. When the patient requested additional analgesia, flurbiprofen 50 mg (intravenous) and/or pentazocine 15 mg (intravenous) was administered at the discretion of the obstetrician in charge.

Oxygen saturation was recorded every second from the time the patient was transferred to the obstetric ward after surgery until 24 hours after the initiation of spinal anesthesia. The saturation probe was secured with tape on the annular finger of the non-dominant hand. The recording was interrupted when the patient left her bed to see her baby in the neonatal intensive care unit or ambulated on the first postoperative day. Data were recorded and stored in the pulse oximeter (Nellcor Oximax N-600X, Covidien Co. Japan) set at the patient's bedside and clinicians were able to see these readings. The pulse oximeter was programmed to alarm when the pulse rate was >140 beats/min or <40 beats/min or SatSeconds™ (Covidien Co. Japan) exceeded 50. SatSeconds™ is calculated by $(90 - \text{SpO}_2) \times \text{time (s)}$. Interventions in the event of low oxygen saturation (SpO_2) were not dictated by protocol, but were noted on the medical record. Patients who received supplemental oxygen were excluded from the analysis.

Demographic information collected included patient age, height and weight; and time of operation. The Berlin Questionnaire was administered to patients before surgery. Data extracted from the medical record included past history, a diagnosis of preeclampsia, administration of magnesium or ritodrine, and interventions in the event of low SpO_2 .

The median oxygen saturation was calculated for overlapping 30-second intervals within the 24 hour period. If the median oxygen saturation was less than 90% in a 30 second window, then the patient was considered to have a mild desaturation event. The duration of a desaturation event was defined as the number of contiguous windows in which the median was less than 90%. Additionally, if the median oxygen saturation was less than 85% in a particular window, then the patient was considered to have a severe desaturation event, with the duration calculated in the same manner. These values were selected based on their use in prior studies.^{9,10} If more than half of the oxygen saturation measurements were deemed by the machine to be artifact or of poor quality, then the window was excluded from the

analysis. The definition and algorithm to determine whether a reading was artifactual is propriety company information, and not publically available.

Unadjusted univariate analysis was undertaken and differences between the groups were tested using t-tests for continuous variables and chi-square tests for categorical variables. Multivariable logistic regression was used to determine predictors of having a hypoxic event. The predictors included in the model were advanced maternal age (defined as age >35, obesity (defined as a body mass index [BMI] >30 kg/m²), afternoon surgery, a positive result on the Berlin Questionnaire, whether the patient had a diagnosis of preeclampsia, and if the patient had received a TAP block, ritodrine or magnesium. Potential predictors were defined prior to analyzing the data and all covariates were included in the model without further selection. Statistical tests were two-tailed and a *P* value of <0.05 was considered to be significant. All analyses were performed in Stata (version 12; StataCorp, College Station, TX, USA).

Results

Eight-hundred-and-thirty-two of 838 patients consented to participate in the study. Patients were excluded for having a saturation recording failure (n=31) or requiring intraoperative anesthetics or analgesics during surgery (n=33). Interventions for low SpO₂ included encouragement of breathing and supplemental oxygen. All patients who were encouraged to breathe were given oxygen. Eighteen patients (six of whom had preeclampsia) received oxygen postoperatively and were excluded from analysis. A patient flowchart is shown in Fig. 1. After exclusions, 721 patients were included in the analysis and their demographic information is presented in Table 1. Within this cohort, 169 women (23%) experienced at least one mild desaturation event, 91 (13%) experienced two or more mild desaturations, and 26 (4%) suffered a severe desaturation event.

After the administration of ITM, the median times to the first mild and severe desaturations were 7.4 h (IQR 4.1–13.5) and 12.0 h (IQR 5.4–19.6), respectively. Fig. 2 displays a histogram showing the time after anesthesia for the first desaturation. There was a similar time trend when examining all desaturation events, with the number of events peaking 4–8 h after anesthesia (Fig. 3). The median duration of mild and severe desaturation was 52 (IQR 45–70) and 47 (IQR 44–55) s, respectively. Desaturations occurred more frequently in the evening hours (Fig. 4).

In univariate analysis, there were no differences in age or time of day of surgery between patients who did and did not experience a desaturation. However, patients who experienced a mild desaturation had a higher BMI, were more likely to be obese and to screen positive on the Berlin Questionnaire. Patients who experienced a severe desaturation were more likely to be positive on category 1 of the Berlin Questionnaire. Tables 1 and 2 describe the characteristics of the study cohort and the differences between the groups.

In multivariable logistic regression analysis, age and an afternoon CD were not significant predictors of having a mild desaturation. Patients who screened positive for OSA had increased odds of having a mild desaturation event (OR 2.31, 95% CI 1.40 to 3.82,

$P=0.001$). Obese patients had an increased odds of having a mild desaturation event (OR 1.80, 95% CI 1.05 to 3.09, $P=0.033$). There were no statistically significant predictors of having a severe desaturation event in the setting of relatively few events. The point estimate from this analysis suggested a two-fold increase in severe desaturation associated with obesity. The results from the regression analysis are shown in Table 3.

Discussion

In this prospective study of postoperative oxygen saturation, 23% and 4% of parturients undergoing CD with spinal anesthesia containing morphine 150 µg experienced mild and severe desaturation episodes, respectively. Obese and OSA-screen positive patients were more likely to have mild desaturation episodes. No factors were associated with severe desaturation episodes, although the study power for this was limited. Desaturation episodes generally occurred several hours after the administration of ITM and occurred more frequently in the evening hours.

The incidence of desaturation episodes was significantly greater than that reported by Dalchow et al., who found no episodes of desaturation after intrathecal diamorphine 300 µg in women undergoing CD.¹¹ However, their study looked for a sustained desaturation of SpO₂ <90% for more than two minutes. In our study, the incidence of desaturation episodes was greater than the number of bradypnea episodes previously described after ITM.³⁻⁵ We attribute this to the enhanced detection of episodes due to continuous pulse oximetry, with respiratory rate being a less sensitive measure of respiratory depression than hypoxia and hypercarbia. Our findings are consistent with the 32% incidence of hypercapnic events (transcutaneous CO₂ >50 mmHg for 2 min) in post-cesarean delivery patients who had received ITM 150 µg.¹² Our results are also consistent with other studies in which delayed respiratory depression occurred 4 to 12 hours after the administration of ITM.^{13,14}

Obesity and a positive Berlin Questionnaire were both predictors of having a mild desaturation event. The Berlin Questionnaire, a validated screening tool to detect OSA, consists of three parts related to snoring (category 1), day-time somnolence and fatigue (category 2), and hypertension and obesity (category 3).¹⁵ While no factor was associated with severe desaturation, the number of total severe events was likely too low for the number of possible predictors in the regression model. It may be reasonable to infer that those at risk of having a mild desaturation episode are also at increased risk of having a severe desaturation episode, given the point estimate for a severe desaturation episode associated with obesity.

Because desaturation can occur during normal pregnancy, the additional contribution of ITM 150 µg is unclear. The prevalence of OSA (defined as an apnea-hypopnea index ≥5) during the third trimester of pregnancy has been estimated to be 19.7%,¹⁶ but the actual prevalence in our population is unknown and may differ by ethnicity and race, which would be relevant to the current study. There have been no investigations, to our knowledge, of post-cesarean desaturation in women not receiving ITM.

While pulse oximeter probe misalignments or desaturation artifacts can occur clinically, we believe these effects to be minimal in our study for several reasons. These include the method of saturation probe attachment, the exclusion of unreliable SpO₂ measurements by signal interference and pulse loss indicators, and critical review and adjudication of the medical record.

Our study has several limitations inherent to its design that should be considered when interpreting the results. Firstly, because the pulse oximeter alarmed with patient desaturation, either the sound or a care provider may have aroused the patient, thus reducing the duration and magnitude of hypoxia. Secondly, medical staff was not blinded to oximetry readings and could intervene if oxygen saturation was low. We excluded the 2.5% of patients who were given supplemental oxygen, as this would have interfered with subsequent desaturation episodes. This likely resulted in an underestimation of the incidence of desaturation. Thirdly, this study was performed at a single institution in Japan and therefore the results may not be generalizable to other centers or patient populations. The prevalence of obesity¹⁷, OSA, and even sensitivity to ITM may differ in other populations.

The results of this study demonstrate that hypoxia after CD under spinal anesthesia with morphine 150 µg is common. Patients who are obese and screen positive for OSA by the Berlin Questionnaire are at increased risk. The risk of hypoxia seems to be increased several hours after the administration of ITM and during evening hours. Our findings provide some guidance for defining which parturients are at high risk for desaturation and when these patients should be more closely monitored.

Acknowledgments

Funding

This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

References

1. Aiono-Le Tagaloa L, Butwick AJ, Carvalho B. A survey of perioperative and postoperative anesthetic practices for cesarean delivery. *Anesthesiol Res Pract*. 2009; 2009:510642. [PubMed: 21217809]
2. Lee LA, Caplan RA, Stephens LS, Posner KL, Terman GW, Voepel-Lewis T, et al. Postoperative opioid-induced respiratory depression: a closed claims analysis. *Anesthesiology*. 2015; 122:659–65. [PubMed: 25536092]
3. Abouleish E, Rawal N, Rashad MN. The addition of 0.2 mg subarachnoid morphine to hyperbaric bupivacaine for cesarean delivery: a prospective study of 856 cases. *Reg Anesth*. 1991; 16:137–40. [PubMed: 1883770]
4. Kato R, Shimamoto H, Terui K, Yokota K, Miyao H. Delayed respiratory depression associated with 0.15 mg intrathecal morphine for cesarean section: a review of 1915 cases. *J Anesth*. 2008; 22:112–6. [PubMed: 18500606]
5. Crowgey TR, Dominguez JE, Peterson-Layne C, Allen TK, Muir HA, Habib AS. A retrospective assessment of the incidence of respiratory depression after neuraxial morphine administration for postcesarean delivery analgesia. *Anesth Analg*. 2013; 117:1368–70. [PubMed: 24257387]
6. Bailey PL, Rhondeau S, Schafer PG, Lu JK, Timmins BS, Foster W, et al. Dose-response pharmacology of intrathecal morphine in human volunteers. *Anesthesiology*. 1993; 79:49–59. [PubMed: 8342828]

7. Orlov D, Ankichetty S, Chung F, Brull R. Cardiorespiratory complications of neuraxial opioids in patients with obstructive sleep apnea: a systematic review. *J Clin Anesth.* 2013; 25:591–9. [PubMed: 23994284]
8. Venkata C, Venkateshiah SB. Sleep-disordered breathing during pregnancy. *J Am Board Fam Med.* 2009; 22:158–68. [PubMed: 19264939]
9. Ehrenfeld JM, Funk LM, Van Schalkwyk J, Merry AF, Sandberg WS, Gawande A. The incidence of hypoxemia during surgery: evidence from two institutions. *Can J Anaesth.* 2010; 57:888–97. [PubMed: 20680710]
10. Sun Z, Sessler DI, Dalton JE, Devereaux PJ, Shahinyan A, Naylor AJ, et al. Postoperative hypoxemia is common and persistent: A prospective blinded observational study. *Anesth Analg.* 2015; 121:709–15. [PubMed: 26287299]
11. Dalchow S, Lubeigt O, Peters G, Harvey A, Duggan T, Binning A. Transcutaneous carbon dioxide levels and oxygen saturation following caesarean section performed under spinal anaesthesia with intrathecal opioids. *Int J Obstet Anesth.* 2013; 22:217–22. [PubMed: 23707035]
12. Bauchat JR, McCarthy R, Fitzgerald P, Kolb S, Wong CA. Transcutaneous carbon dioxide measurements in women receiving intrathecal morphine for cesarean delivery: A prospective observational study. *Anesth Analg.* 2017; 124:872–8. [PubMed: 28099291]
13. Chaney MA. Side effects of intrathecal and epidural opioids. *Can J Anaesth.* 1995; 42:891–903. [PubMed: 8706199]
14. Bailey PL, Lu JK, Pace NL, Orr JA, White JL, Hamber EA, et al. Effects of intrathecal morphine on the ventilatory response to hypoxia. *N Engl J Med.* 2000; 343:1228–34. [PubMed: 11071674]
15. Netzer NC, Stoohs RA, Netzer CM, Clark K, Strohl KP. Using the Berlin Questionnaire to identify patients at risk for the sleep apnea syndrome. *Ann Intern Med.* 1999; 131:485–91. [PubMed: 10507956]
16. Pien GW, Pack AI, Jackson N, Maislin G, Macones GA, Schwab RJ. Risk factors for sleep-disordered breathing in pregnancy. *Thorax.* 2014; 69:371–7. [PubMed: 24262432]
17. Federation WO. World map of obesity. <http://www.worldobesity.org/resources/world-map-obesity/> (accessed May. 26, 2017)

Highlights

- In this study, mild desaturation after 150 µg intrathecal morphine was common
- Desaturation occurred most frequently 4–8 hours after intrathecal morphine
- Obesity and a positive Berlin questionnaire were predictive of mild desaturation

Fig. 1.
Flow chart outlining patient inclusion and exclusion criteria

Fig. 2.

Histogram demonstrating the distribution of the timing of the first event, for both mild and severe desaturation, after the administration of single-shot spinal anesthesia

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Fig. 3.

Histogram showing the distribution of all desaturation events, for both mild and severe desaturation, in relation to the administration of single-shot spinal anesthesia.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Fig. 4.

Histogram displaying the distribution of all desaturation events, for mild and severe desaturation, by the time of day. “00” on the x-axis represents midnight.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 1

Baseline characteristics and univariate associations with mild desaturation

	No desaturation	At least one mild desaturation	P-value
n	552	169	
Age, mean (SD)	34.1 (5.0)	34.8 (4.9)	0.098
Advanced maternal age	277 (50.2%)	91 (53.8%)	0.40
Obese	49 (8.9%)	34 (20.1%)	<0.001
BMI, mean (SD)	25.3 (3.7)	27.0 (4.7)	<0.001
Preeclampsia	37 (6.7%)	8 (4.7%)	0.35
Afternoon delivery	169 (30.6%)	52 (30.8%)	0.97
Positive Berlin Questionnaire			
category 1	112 (20.3%)	65 (38.5%)	<0.001
Positive Berlin Questionnaire			
category 2	67 (12.2%)	34 (20.1%)	0.009
Positive Berlin Questionnaire			
category 3	113 (20.5%)	46 (27.2%)	0.066
Positive Berlin Questionnaire			
overall	68 (12.3%)	44 (26.0%)	<0.001
TAP block	472 (85.5%)	147 (87.0%)	0.63
Pentazocine	10 (1.8%)	1 (0.6%)	0.26
Ritodrine	91 (16.5%)	23 (13.6%)	0.37
Magnesium	21 (3.8%)	10 (5.9%)	0.24

All values displayed as n (%) unless otherwise specified

SD: standard deviation. BMI: body mass index. TAP: transversus abdominis plane.

Table 2

Baseline characteristics and univariate associations with severe desaturation

	No desaturation	At least one severe desaturation	P-value
n	695	26	
Age, mean (SD)	34.3 (5.0)	34.5 (5.1)	0.78
Advanced maternal age	354 (50.9%)	14 (53.8%)	0.77
Obese	77 (11.1%)	6 (23.1%)	0.060
BMI, mean (SD)	25.7 (4.0)	27.1 (4.7)	0.082
Preeclampsia	44 (6.3%)	1 (3.8%)	0.61
Afternoon delivery	212 (30.5%)	9 (34.6%)	0.66
BMI, mean (SD)	25.7 (4.0)	27.1 (4.7)	0.082
Positive Berlin Questionnaire			
category 1	164 (23.6%)	13 (50.0%)	0.002
Positive Berlin Questionnaire			
category 2	95 (13.7%)	6 (23.1%)	0.18
Positive Berlin Questionnaire			
category 3	154 (22.2%)	5 (19.2%)	0.72
Positive Berlin Questionnaire			
overall	106 (15.3%)	6 (23.1%)	0.28
TAP block	596 (85.8%)	23 (88.5%)	0.70
Pentazocine	11 (1.6%)	0 (0.0%)	0.52
Ritodrine	110 (15.8%)	4 (15.4%)	0.95
Magnesium	30 (4.3%)	1 (3.8%)	0.91

All values displayed as n, (%) unless otherwise specified. SD: standard deviation. BMI: body mass index. TAP: transversus abdominis plane

Table 3

Results of the multivariable logistic regression predicting a desaturation event

	Mild desaturation			Severe desaturation		
	OR	95% CI	P-value	OR	95% CI	P-value
Advanced maternal age	1.14	(0.80 to 1.63)	0.47	1.11	(0.50 to 2.46)	0.79
Obese	1.80	(1.05 to 3.09)	0.033	2.16	(0.72 to 6.45)	0.17
Preeclampsia	0.43	(0.19 to 1.01)	0.053	0.51	(0.06 to 4.08)	0.53
Afternoon delivery	0.98	(0.67 to 1.44)	0.92	1.22	(0.53 to 2.81)	0.64
Positive Berlin	2.31	(1.40 to 3.82)	0.001	1.31	(0.43 to 4.00)	0.62
Questionnaire overall						
TAP block	1.25	(0.74 to 2.11)	0.41	1.37	(0.40 to 4.68)	0.98
Pentazocine	0.28	(0.04 to 2.25)	0.23	–		
Ritodrine	0.72	(0.42 to 1.26)	0.25	0.98	(0.31 to 3.13)	0.87
Magnesium	1.89	(0.80 to 4.49)	0.15	0.84	(0.10 to 7.17)	0.53

OR: odds ratio. CI: confidence interval. TAP: transversus abdominis plane