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ORIGINAL ARTICLE

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A prospective observational study of the change in regional cerebral oxygen saturation during cesarean delivery in women receiving phenylephrine prophylaxis for spinal hypotension

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ABSTRACT

Background: Spinal hypotension causes decreased regional cerebral oxygen saturation (ScO_2) in women undergoing cesarean delivery. In this study we aimed to measure the change in ScO_2 using near infrared spectroscopy in women receiving a prophylactic phenylephrine infusion during cesarean delivery under spinal anesthesia.

Methods: This was a prospective, observational cohort study. Fifty-three women had ScO_2 measurements at the following time points: preoperatively, in the supine position with 30° of left lateral tilt; one and five minutes after spinal anesthesia; at the time of skin incision; immediately after delivery; one minute after commencing the oxytocin infusion; at completion of surgery, and one hour after surgery. Spinal anesthesia and a prophylactic phenylephrine infusion were administered according to a standard treatment protocol. Statistical analysis used the Wilcoxon Signed Rank test with Bonferroni's correction for multiple comparisons.

Results: Blood pressure was maintained within 20% of baseline throughout surgery. The baseline mean (range) ScO_2 was 61.5% (54.0–66.3%). It decreased significantly at all subsequent measurement points. The maximum decrease was five minutes after spinal anesthesia. Thirty-four (64.2%) of the parturients exhibited ScO_2 values <20% of baseline, or a decrease to below an absolute value of 50%. There was no significant correlation between systolic blood pressure and mean ScO_2.

Conclusion: Spinal anesthesia with phenylephrine infusion during cesarean delivery is associated with a significant decrease in ScO_2 levels, maximal five minutes later. Further studies are required to establish the clinical significance of this finding.

Keywords: Cerebral autoregulation; Cesarean delivery; Complications; Morbidity; Spinal anesthesia

Introduction

The incidence of spinal hypotension during cesarean delivery (CD) is as high as 70–80%,[1] and may cause dizziness, faintness and nausea and vomiting, secondary to cerebral hypoperfusion.[2]

Near infrared spectroscopy (NIRS) is a direct non-invasive spectroscopic method that uses the near infrared portion of the electromagnetic spectrum (800–2500 nm) to measure blood oxygenation in the frontal lobe microvasculature.[3] Its advantages include simple bedside performance and lack of interference with other measurements.[3]

Near infrared spectroscopy has previously demonstrated that spinal hypotension causes decreased brain oxygen saturation during CD.[4,5] When ephedrine was administered to treat spinal hypotension, cerebral oxygen saturation (ScO_2) returned to baseline values.[6,7] Current standard practice is to use a prophylactic phenylephrine infusion to prevent spinal hypotension during CD.[8,9]

There are few studies discussing the effect of phenylephrine on ScO_2.[7,10,11] In a randomized controlled study

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that evaluated the fall in average frontal lobe ScO_2 over 60 minutes after administration of spinal anesthesia, a prophylactic phenylephrine infusion and a prophylactic ephedrine infusion were compared in 24 women. Phenylephrine infusion was associated with a decrease in mean ScO_2 of $-8.6 \pm 2.8\%$,[12] despite similar blood pressure maintenance in both groups, while mean ScO_2 using ephedrine infusion was unchanged.

We performed a prospective observational pilot study to investigate the change in mean frontal lobe ScO_2 at different time points intra- and postoperatively in women receiving a prophylactic phenylephrine infusion during CD. Based on results from a preliminary study in our hospital, the primary aim of the study was to measure mean ScO_2 levels five minutes after initiation of spinal anesthesia. The secondary aims were to measure: (1) change in mean ScO_2 from baseline at the following time points: 1-min after initiation of spinal anesthesia (1-min), 5-min after spinal anesthesia (5-min), at skin incision (SI), immediately after baby delivery (BD), 1-min after initiation of oxytocin infusion (OX), at surgery completion (SE) and one hour after surgery in the post-anesthesia care unit (PACU1); (2) the decrease of mean frontal ScO_2 below the theoretical cerebral hypoperfusion threshold; (3) systolic blood pressure (SBP) during surgery compared to baseline; (4) the correlation between SBP and mean frontal lobe ScO_2.

Methods

This prospective observational study was performed at the Beilinson Campus of the Rabin Medical Centre, Petah Tikva, Israel, a tertiary university hospital with 10 000 deliveries per annum, between October 2015 and March 2016. The Institutional Review Board approved this study and all participants provided written informed consent. As per institutional policy, the study was registered on clinical trials.gov (registration number NCT02473978).

Consecutive women undergoing elective CD under spinal anesthesia with a prophylactic phenylephrine infusion were included. Exclusion criteria were women under the age of 18 years, American Society of Anesthesiologists (ASA) physical score >2, preeclampsia or chronic hypertension, unfamiliarity with the Hebrew language, and allergy to phenylephrine. Women in whom the surgeon assessed significant intraoperative hemorrhage, or who required blood products or methergine for uterine atony, were excluded from analysis.

In the ward, an intravenous cannula (18-gauge) was inserted 2.5 h before surgery and 500 mL of Ringer's Lactate was infused over two hours. Sodium citrate (30 mL) and Ringer's Lactate solution (500 mL) were given 30 minutes before surgery.

Women were placed supine with left uterine displacement, using a wedge, in the operating room (OR). Standard monitoring with non-invasive blood pressure (NIBP), pulse oximetry and electrocardiogram (S/5 Anesthesia Delivery Unit, Instrumentarium Corp., Datex-Ohmeda, Finland) was instituted. Baseline NIBP was measured in the 30° left lateral supine position on arrival in the OR and at 1-min intervals until the end of surgery. Near infrared spectroscopy sensors (INVOS Cerebral/Somatic Oximeter|Covidien, Boulder Colorado USA) were connected to the right and left side of the forehead, immediately below the hairline, according to the manufacturer's guidelines, to measure right- and left-sided (ScO_2R; ScO_2L) frontal cerebral oxygen saturation. No women received routine supplemental oxygen.

Spinal anesthesia was performed in the sitting position. A 26-gauge needle (B Braun Pencil Point Spinal Needle) was inserted at the L3–L4 or L4–L5 interspace, and hyperbaric bupivacaine 12 mg (AstraZeneca, England), fentanyl 20 μg (Panpharma, France) and preservative-free morphine sulphate 0.1 mg (Rafa Laboratories, Israel) were injected. After injection, women were placed in the supine position with left uterine displacement.

Immediately after completion of spinal injection, a phenylephrine infusion (Omega, Canada) was administered at an initial rate of 50 μg/min. The phenylephrine dose was titrated according to a standard protocol: if SBP fell 20% from baseline or below 90 mmHg, or faintness, dizziness, nausea or vomiting occurred, the initial dose was increased by 20%; if SBP increased more than 20% from baseline the initial dose was decreased by 20%. The phenylephrine infusion was continued throughout surgery and was not tapered after delivery, due to our institutional protocol of uterine exteriorization and associated nausea and vomiting seen at this time. The phenylephrine infusion was stopped after skin stapling. The sensory level to pinprick test was checked and surgery commenced when the block had reached the T4 dermatome. Immediately after delivery, oxytocin 20 IU in 1L Ringer's Lactate was infused at 200 mL/h. No other uterotonics were given. All parturients received dexamethasone 4 mg (Omega, Canada) and ondansetron 4 mg (Fresenius Kabi, Germany) after delivery.

In the PACU, the Ringer's Lactate infusion with oxytocin was changed to a bag containing 10 IU/L and infused at 200 mL/h. All women received intravenous tramadol 100 mg (Grunenthal GMBH, Germany) with 10 mg metoclopramide (Rafa laboratories, Israel), 1000 mg intravenous paracetamol (Bristol Myers Squibb, USA) and intramuscular diclofenac 75 mg (Teva Pharmaceutical, Israel).

Demographic data (maternal age, weight, parity, gravidity) and neonatal Apgar score were recorded. Frontal lobe ScO_2 was recorded preoperatively in the 30° left lateral supine position on arrival in the OR (BL), 1-min after initiation of spinal anesthesia (1-min), 5-min after

spinal anesthesia (5-min), at skin incision (SI), immediately after baby delivery (BD), 1-min after initiation of oxytocin infusion (OX), at surgery completion (SE) and 1 h after surgery in the PACU (PACU1). There was no difference between left- and right-sided cerebral oxygen saturation, so the average of both frontal lobe ScO_2 measures was used and recorded as mean cerebral saturation. The theoretical cerebral hypoperfusion threshold was defined as an absolute decrease of frontal lobe ScO_2 to <50% or a decrease of more than 20% from baseline on either right or left side of the brain.[13,14] The NIBP values at these time points were also recorded. Total phenylephrine dose was noted.

The primary outcome of this pilot study was the change from baseline of mean frontal lobe ScO_2, as measured by NIRS at 5-min. Secondary outcomes were:

1. Change from baseline of mean frontal lobe ScO_2 at all other time points.
2. Decrease of frontal lobe ScO_2 below the cerebral hypoperfusion threshold.
3. Systolic blood pressure measurements throughout surgery compared to baseline.
4. Correlation between systolic blood pressure and mean frontal lobe ScO_2.

Based on previous research to detect a decrease in mean frontal lobe ScO_2 readings from baseline to lowest mean ScO_2 of more than 6%, assuming a common standard deviation of 8% and allowing for 20% of potential dropouts, 56 women were required to obtain a power of a least 0.8 ($\beta = 20\%$; two-tailed $\alpha = 5\%$).[3,4] Statistical analysis was performed using the SPSS software version 23.0 (IBM, Chicago, IL). Variables were analyzed with statistical tests according to the Kolmogorov–Smirnov test of normality. According to the Kolmogorov–Smirnov test of normality, both normally and non-normally distributed data were observed (Supplementary file). Nonparametric tests were therefore used for all data.

The primary outcome; comparison of mean baseline ScO_2 with other time points; and the decrease of ScO_2 below the theoretical cerebral hypoperfusion threshold, were measured using the Wilcoxon Signed Rank test with Bonferroni's correction for multiple comparisons and presented as boxplots.

The SBP measurements were compared with baseline using the Wilcoxon Signed Rank test with Bonferroni's correction for multiple comparisons; and data are presented as boxplots. The correlation between SBP and mean frontal lobe ScO_2 was measured using the Spearman correlation test. Seven comparisons were used for each variable: baseline to 1-min; baseline to 5-min; baseline to SI; baseline to BD; baseline to OX; baseline to SE; baseline to PACU1. The *P*-value was corrected as per $0.05/7 = 0.007$.

Results

We enrolled 59 women, and three were excluded (Fig. 1). The outcomes for 56 women are reported. Demographic data, neonatal data, and total phenylephrine dosage are shown in Table 1.

Oxygen saturation was 96–98% during the measurement period.

For the primary outcome, at 5-min after spinal anesthesia, the mean frontal lobe ScO_2 had decreased significantly compared to baseline, from 61.5% (54–66.3) to 55% (48–60.8) ($P < 0.005$).

Secondary outcomes are listed in Fig. 2. Compared to baseline, mean frontal lobe ScO_2 decreased significantly at all time points during surgery, starting five minutes after the spinal. At the end of surgery, after discontinuation of the phenylephrine infusion, there was a non-significant increase in mean frontal lobe ScO_2 compared to baseline, however in the PACU one hour after completion of surgery, mean frontal lobe ScO_2 was again significantly reduced compared to baseline.

For the theoretical cerebral hypoperfusion threshold, 34 (64.2%) women had cerebral hypoperfusion at least once during the study period (Table 2). Twenty-six parturients (49.1%) had cerebral hypoperfusion five minutes after spinal anesthesia. In the PACU, one hour after surgery, seventeen (32.1%) women remained below the theoretical cerebral hypoperfusion threshold.

Systolic blood pressure measurements are shown in Fig. 3. Baseline SBP was 121 (114.5–137) mmHg, and no statistically significant decrease in blood pressure occurred throughout surgery. However, at the end of surgery, after ScO_2, was discontinued phenylephrine infusion was discontinued, and SBP decreased significantly ($P < 0.007$) from 121 (114.5–137) to 106 (92–114.5) mmHg. One hour after surgery, blood pressure remained significantly lower ($P < 0.007$) than the baseline (from 121 (114.5–137) to 116 (109.5–124) mmHg).

There was no significant correlation between SBP and mean frontal lobe ScO_2 (R_S 0.03 for SBP, $P=0.6$), although our study was not powered to evaluate this.

Discussion

In this prospective pilot study, NIRS was used to measure mean frontal lobe ScO_2 in women receiving a prophylactic phenylephrine infusion. Despite preservation of blood pressure to within 20% of baseline measurements, the mean frontal lobe ScO_2 significantly decreased after spinal anesthesia and remained below baseline at all measured time-points until the phenylephrine infusion was discontinued. It decreased further one hour postpartum. Mean frontal lobe ScO_2 was below the theoretical cerebral hypoperfusion level at some point during surgery in more than a third of women.

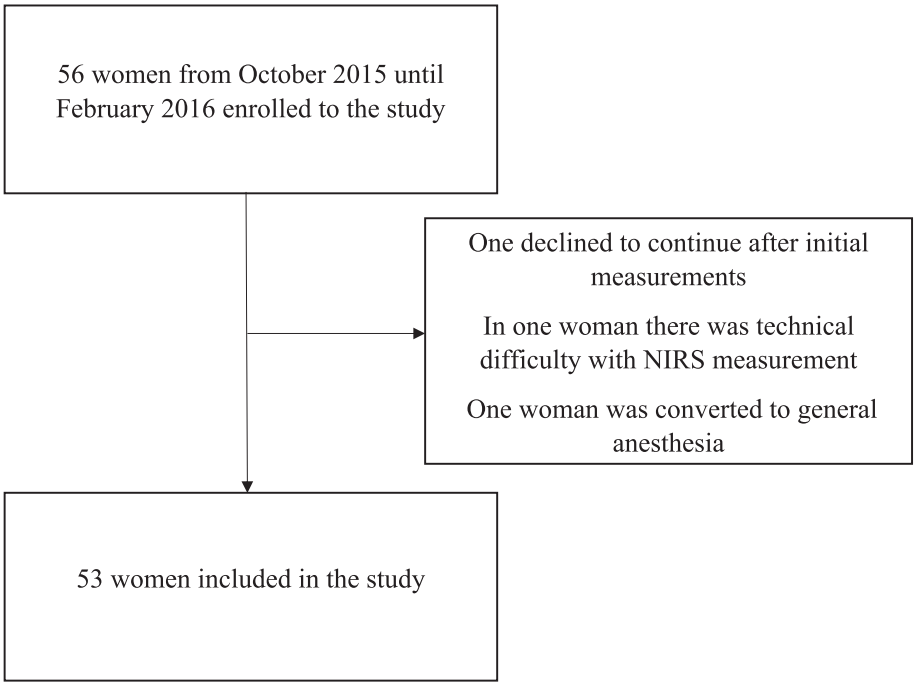

Fig. 1 Study patient flowchart. NIRS: near infrared spectroscopy

Table 1 Maternal and neonatal demographic data, duration of surgery, phenylephrine dose and length of stay in the postoperative care unit

Parameter	n=53
Age (y)	35 (29.5–38)
Weight (kg)	74 (66–85)
Parity (n)	1 (0.5–2)
Gravity (n)	3 (2–4)
Gestation week	38.1 (37.4–38.5)
PACU (min)	173 (151–228)
Surgery (min)	24 (19.5–29.5)
Phenylephrine dose (mg)	1.5 (1.28–1.78)
Umbilical artery pH	7.37 (7.35–7.39)
Apgar 1-min	9 (9–9)
Apgar 5-min	10 (10–10)

Data presented as median (25–75th percentiles). PACU: post-anaesthesia care unit.

The fall in mean frontal lobe ScO_2 corroborates the findings of Foss et al., who showed decreased frontal lobe ScO_2 after spinal anesthesia in conjunction with phenylephrine infusion over the 60 minutes after spinal anesthesia.[7] Our study investigated specific perioperative time-points and the magnitude of the mean frontal lobe ScO_2 change at each time-point.

The mechanism for the decrease in mean frontal lobe ScO_2 is unclear and likely multifactorial. In one study measuring ScO_2, a third NIRS sensor was placed on the thigh to determine the effect of spinal block on the lower extremities.[15] Spinal anesthesia caused redistribution of blood flow to the lower extremities, leading to decreased mean frontal lobe ScO_2, since reduced mean frontal lobe ScO_2 values corresponded with increased regional saturation of the thigh.

A further explanation of the findings may be occult spinal hypotension. Previous studies have shown the relationship of spinal-induced hypotension and decreased ScO_2.[7,15] In one study of 35 parturients using low-dose spinal anesthesia, women who developed hypotension had a preceding decrease in mean frontal lobe ScO_2.[6] In two other studies, women who received spinal anesthesia for CD had decreased mean frontal lobe ScO_2 that was inversely correlated with NIBP readings.[15] Although we attempted to maintain blood pressure within a narrow range, it is possible that the blood pressure measured every minute missed intermittent hypotensive episodes. A study comparing intermittent versus continuous NIBP monitoring during CD found that intermittent monitoring every three minutes missed hypotensive episodes in 30% of episodes.[16] Another consideration is that intraoperative shivering or movement may have interfered with the reading. Cerebral blood flow changes produced by deafferentation may also be a cause.[17] In early research on the effect of deafferentation on cortical areas activated by movement of proximal muscles, regional cerebral blood flow was measured with positron emission tomography and ^{15}O-labeled water. The authors found that movement-related change in cerebral blood flow was reduced after deafferentation.[17] A final explanation for the decreased mean frontal lobe ScO_2 may be the direct effect of phenylephrine. Studies in healthy volunteers receiving phenylephrine infusion showed a decrease in mean

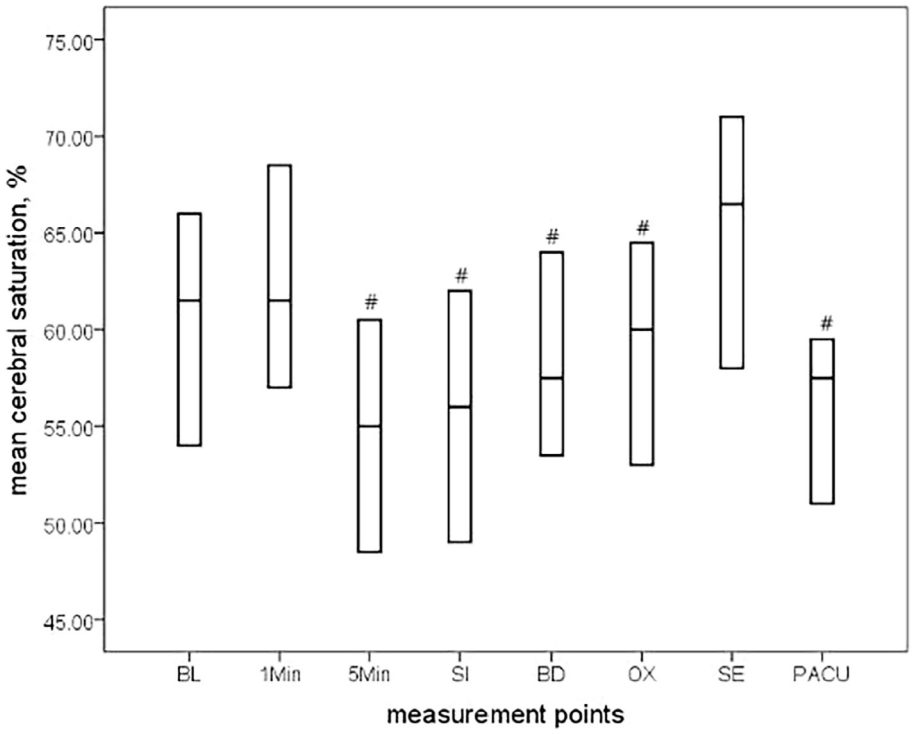

Fig. 2 Cerebral oxygen saturation according to time. BL: baseline; SI: skin incision; BD: baby delivery; OX: oxytocin infusion; SE: surgery completion; PACU: postoperative anesthesia care unit

Table 2 Cerebral hypoperfusion threshold at different measurement points

Measurement point	Cerebral hypoperfusion threshold n=53		
	Any side	Left-sided	Right-sided
1-min	4 (7.6)	4 (7.6)	2 (3.8)
5-min	26 (49.1)	21 (39.6)	19 (35.9)
SI	24 (45.3)	20 (37.7)	16 (30.2)
BD	16 (30.2)	12 (22.6)	13 (24.5)
OX	13 (24.5)	11 (20.8)	11 (20.8)
SE	8 (15.1)	5 (9.4)	6 (11.3)
PACU1	17 (32.1)	14 (26.4)	11 (20.8)
Total number of patients	34 (64.2)	29 (54.7)	27 (50.9)

Cerebral hypoperfusion threshold = absolute decrease of cerebral saturation <50% or decrease more than 20% from baseline. Data presented as number (percent). Points of measurement:; 1-min – one minute after initiation of spinal anesthesia. 5-min – five minutes after spinal anesthesia; SI: skin incision; BD: baby delivered; OX: one minute after beginning of oxytocin infusion; SE: surgery completion; PACU1: one hour after surgery.

frontal lobe ScO_2 when compared to the same volunteers who received a saline infusion.[18] Anesthetized, non-obstetric patients who received phenylephrine boluses to correct hypotension demonstrated a paradoxical decrease in frontal lobe ScO_2, apparently from a direct effect.[10,11] One study that compared prophylactic phenylephrine versus prophylactic ephedrine during CD found that ephedrine administration was associated with maintenance of mean frontal lobe ScO_2 compared to baseline ($+2.1 \pm 2.8\%$; mean $\pm$ SE), whereas phenylephrine was associated with decreased mean frontal lobe ScO_2 ($-8.6 \pm 2.8\%$; P=0.005), with a 10.7% difference in mean frontal lobe ScO_2 between groups (P=0.0106).[7]

The mechanism for decreased mean frontal lobe ScO_2 produced by phenylephrine may be via decreased cardiac output or cerebral vasoconstriction. Phenylephrine is known to cause a dose-dependent decrease in cardiac output.[19] In a previous study performed in our institution, measuring cardiac output at different time points during CD performed under spinal anesthesia with a prophylactic phenylephrine infusion, the pattern of changes in stroke volume at different time points corresponded to the changes in mean frontal lobe ScO_2 seen in the current study.[19] In the study comparing ephedrine and phenylephrine boluses, phenylephrine decreased cardiac output while ephedrine maintained it; and there

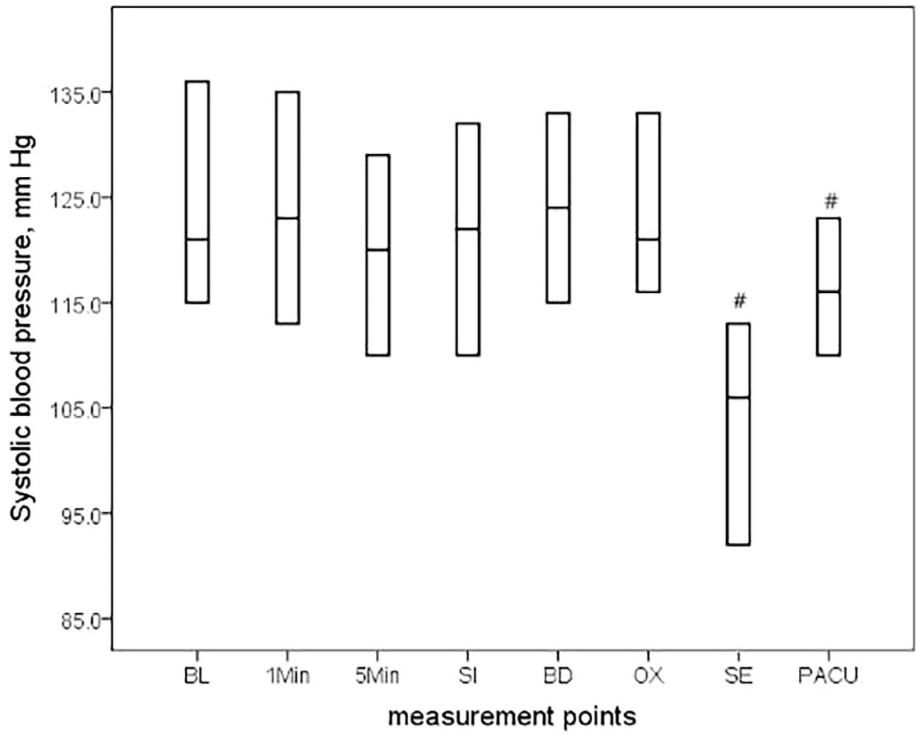

Fig. 3 Systolic blood pressure measurements. BL: baseline; SI: skin incision; BD: baby delivery; OX: oxytocin infusion; SE: surgery completion; PACU: postoperative anesthesia care unit

was a significant correlation between mean frontal lobe ScO_2 and cardiac output (P <0.0010).[10] Decreased cardiac output to the brain may cause a compensatory increase in cerebral oxygen extraction, leading to decreased mean frontal lobe ScO_2.[20]

However, phenylephrine may cause a decrease in mean frontal lobe ScO_2 via mechanisms other than those that change cardiac output. In a study of eight healthy volunteers receiving a phenylephrine infusion at one intervention and normal saline infusion at a different intervention, cardiac output, mean frontal lobe ScO_2, middle cerebral artery mean blood velocity, and right internal carotid artery and internal jugular venous blood flow assessed using duplex ultrasound were measured. Compared to saline administration, phenylephrine infusion was associated with a decreased mean frontal lobe ScO_2, an increased mean cerebral artery velocity, an increased internal jugular venous blood flow, and no changes in either cardiac output or internal carotid artery blood flow.[18] The authors postulated that these changes could be due to cerebral vasoconstriction.

We noted that the mean frontal lobe ScO_2 remained low even one hour after surgery. There are several possible explanations for this phenomenon. In a previous study in our institution measuring perioperative cardiac output changes after spinal anesthesia with a phenylephrine infusion, we found that both cardiac output and non-invasive blood pressure remained below baseline when measured in the PACU one hour after surgery.[18] Clinical experience in our hospital has shown that spinal block takes approximately two hours to resolve, and so some deafferentation which remained may have influenced NIRS readings.

Our study has several limitations. Firstly, we did not measure cardiac output. We did not study short- and long-term neurological sequelae using cognitive tests in our patients. There were a few cases where patients with a low mean frontal lobe ScO_2 complained of weakness, tiredness or agitation, but these complaints were not quantified. We did not measure time intervals between spinal initiation and delivery of the baby or progression of sensory levels intraoperatively or postoperatively. We did not give oxygen supplementation to women intraoperatively: in a previous study, oxygen supplementation was shown to be effective in attenuating the decrease in mean frontal lobe ScO_2 readings after spinal anesthesia.[21] Therefore our results may not be able to be extrapolated in centers that routinely give oxygen supplementation. Likewise, our fluid supplementation is different from others. Large variations in fluid supplementation exist,[8,22] and the effect of crystalloid co-loading on hemodynamics is still debated.[22–25]

Finally, the mean frontal lobe ScO_2 readings may be inaccurate, as a recent study showed NIRS readings were prone to extracranial contamination and a recent study has put into question the accuracy of NIRS measurement.[26,27]

In conclusion, we observed a fall in mean frontal lobe ScO_2 in parturients undergoing CD under spinal anesthesia with a prophylactic phenylephrine infusion. This

was observed at almost all points during surgery and at one hour postpartum, with one third of parturients having at least one mean frontal lobe ScO_2 reading below the theoretical cerebral hypoperfusion level. Though the findings of this pilot study are interesting, it is not possible to generate conclusions. Larger randomized controlled studies are needed to elucidate the cause, and long-term outcome studies to assess its clinical significance.

Declaration of Interests

Dr Weiniger is an editor of the International Journal of Obstetric Anesthesia but took no role in the assessment of this submission. There was no funding support received for this research.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijoa.2018.09.005.