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ORIGINAL ARTICLE

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Prophylactic infusion of phenylephrine is effective in attenuating the decrease in regional cerebral blood volume and oxygenation during spinal anesthesia for cesarean section

N. Hirose,[a] Y. Kondo,[a,b] T. Maeda,[a,b] M. Matsui,[a] M. Matsuda,[a] T. Suzuki[a]
[a]*Department of Anesthesiology, Nihon University School of Medicine, 30-1 Oyaguchi-Kamicho, Itabashi-ku, Tokyo 173-8610, Japan*
[b]*Department of Neurological Surgery, Nihon University School of Medicine, 30-1 Oyaguchi-Kamicho, Itabashi-ku, Tokyo 173-8610, Japan*

ABSTRACT
Background: Hypotension induced by spinal anesthesia for cesarean section causes a decrease in maternal regional cerebral blood volume and oxygenation. We used near-infrared spectroscopy to determine whether prophylactic infusion of phenylephrine attenuates these decreases.
Methods: Sixty patients undergoing bupivacaine spinal anesthesia for cesarean section were randomly divided into one of three intravenous infusion groups: saline (P0), phenylephrine 25 (P25) or 50 μg/min (P50). Mean arterial pressure, heart rate and near-infrared spectroscopy measurements were made at one-minute intervals for 20 minutes, and oxyhemoglobin, deoxyhemoglobin and total-hemoglobin concentrations and tissue oxygenation index were determined. Mean changes in the values between baseline and each measurement time after intrathecal injection were compared.
Results: Significant decreases in mean arterial pressure were seen in group P0 compared to P25 and P50 ($P < 0.01$). Heart rate decreased in a dose-dependent manner during phenylephrine infusion (P0 vs. P25 and P50, P25 vs. P50; $P < 0.05$). Significantly higher total-hemoglobin levels were observed in the phenylephrine groups versus the P0 group ($P < 0.01$). The largest decrease in tissue oxygenation index was found in the P50, followed by P0 and P25 groups (P0 vs. P25 and P50, P25 vs. P50; $P < 0.05$).
Conclusion: Prophylactic infusion of phenylephrine, especially at 25 μg/min, can effectively suppress decreases in regional cerebral blood volume and regional cerebral blood oxygenation after induction of spinal anesthesia for cesarean section.

Keywords: Cesarean section; Cerebral circulation; Near-infrared spectroscopy; Phenylephrine; Spinal anesthesia

Introduction

Hypotension is the most common complication during cesarean section under spinal anesthesia, and severe hypotension can cause adverse maternal symptoms, such as nausea and vomiting, secondary to cerebral hypoperfusion.[1,2] Studies using near-infrared spectroscopy (NIRS) reported significant decreases in regional cerebral blood volume (rCBV), total hemoglobin (total-Hb), regional cerebral blood oxygenation (rCBO), regional oxygen saturation (rSO_2), and tissue oxygenation index (TOI) indices, after spinal injection.[3–5] Our group has demonstrated that decreases in both total-Hb and TOI are related to the severity of hypotension, and may predict increased risk of adverse symptoms.[6] Other studies have demonstrated that phenylephrine infusion is effective in attenuating hypotension that occurs during spinal anesthesia.[7–9] These findings suggest that phenylephrine infusion may attenuate decreases in rCBV and rCBO that occur during spinal anesthesia.

The aim of this study was to determine the effect of prophylactic infusion of 25 and 50 μg/min phenylephrine on maternal rCBV and rCBO after induction of spinal anesthesia for cesarean section, as evaluated by NIRS. We hypothesized that both phenylephrine infusion doses would be effective for attenuating the decrease in rCBV and rCBO resulting from induction of spinal anesthesia.

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Correspondence to: Y. Kondo, Department of Anesthesiology, Nihon University School of Medicine, 30-1 Oyaguchi-Kamicho, Itabashi-ku, Tokyo 173-8610, Japan.
E-mail address: kondo.yuko@nihon-u.ac.jp

Methods

This double-blind, randomized, controlled study was approved by the Hospital Ethics Committee on Human Rights in Clinical Trials and Research of Nihon University Itabashi Hospital (Tokyo, Japan), and was registered in the ''UMIN Clinical Trial Registry'' (ID: 000012867).

After obtaining written informed consent, we evaluated 60 full-term pregnant patients, aged 20 years and older, of American Society of Anesthesiologists (ASA) grade II, who were scheduled for cesarean section under spinal anesthesia at Nihon University Itabashi Hospital. Exclusion criteria included hypertension, diabetes and renal dysfunction due to pregnancy, anemia (hemoglobin concentration <10 g/dL) and obesity (body mass index >30 kg/m^2). Based on a computer-generated random number table, patients were randomly divided into three groups according to the infusion regimens used after the induction of spinal anesthesia: saline (P0; control), phenylephrine 25 (P25) or 50 μg/min (P50). Group assignments were made from sealed opaque envelopes. An anesthesiologist who was not involved with the anesthetic management and data collection was responsible for preparing each test solution syringe. After adjusting the syringes so that each had the same volume of the required solution, in accordance with the instructions contained in the sealed envelope, a syringe was given to the attending anesthesiologist. Patients were unaware of their group assignment.

All patients fasted overnight and did not receive premedication. After arriving at the operating room, patients were equipped with monitors that included electrocardiogram (ECG) electrodes, an arm blood pressure cuff on the right arm for non-invasive blood pressure measurement, a pulse oximeter on the fingertip to measure oxygen saturation (SpO_2), a sampling tube for end-tidal CO_2 ($EtCO_2$) placed below the nostril, and an NIRS sensor placed on the left forehead. Patients were placed in the supine position on an operating table that was then tilted 15 degrees to the left. Subsequently, all patients were given 3 L/min oxygen using a face mask, and intravenous hydroxyethyl starch solution (6%) at a rate of 20 mL/kg/h (maximum 1000 mL until delivery, with an arbitrarily determined dose of crystalloid administered after delivery). After oxygenation for 3-min, baseline measurements of non-invasive mean arterial pressure (MAP), heart rate (HR), SpO_2, $EtCO_2$ and NIRS parameters were recorded (oxy-, deoxy- and total-Hb were zeroed). Spinal anesthesia and epidural catheterization were performed with the patient in the right lateral decubitus position. An epidural catheter was inserted at the L1/2 interspace. Spinal anesthesia was performed at the L3/4 interspace, with injection of hyperbaric bupivacaine at a dose determined by the individual anesthesiologist.

Immediately after intrathecal injection of bupivacaine, the patient was returned to the supine position and the operating table was tilted 15 degrees to the left. Hypotension, which was defined as MAP <80% of the baseline value or systolic blood pressure <90 mmHg, was treated with a 4 mg bolus of ephedrine if HR was less than 80 beats/min, or with a 50 μg bolus of phenylephrine if the HR was 80 beats/min or more. Each treatment was repeated every 2-min until the MAP recovered to baseline levels. If only bradycardia (HR <50) was observed, the patient was treated with a 0.5 mg bolus of atropine.

Adequacy of anesthesia was tested using pinprick sensation at 10-min after induction of spinal anesthesia. Patients in whom the height of the block was below T10 were excluded from the study. The operation was not started until all of the data sampling had been completed.

The volumes of all drug solutions were adjusted to 40 mL, in identical 50 mL syringes, to maintain blinding. Phenylephrine was diluted with normal saline to achieve the 25 and 50 μg/mL concentrations. Each solution was infused at 60 mL/h using a syringe pump during the 20-min period starting immediately after the intrathecal injection of bupivacaine. If the MAP increased by more than 20% from baseline, infusion of the solution was temporarily discontinued until it returned to baseline levels.

Throughout the study, all patients were monitored and their hemodynamic parameters, including MAP, HR, SpO_2 and $EtCO_2$, were recorded at 1-min intervals using a patient monitoring system (Life Scope™ BSM-6701, NIHON-KOHDEN Corporation, Tokyo, Japan). Changes in rCBV and rCBO were measured at the forehead using NIRS (NIRO pulse™, Hamamatsu Photonics, Hamamatsu, Japan). With this system, the NIR light from three laser diodes (775, 810, 850 nm) is directed at the head through a fiberoptic bundle, and the reflected light is transmitted to a multi-segment photodiode detector array. The NIRS system measures the concentrations of oxyhemoglobin (oxy-Hb), deoxyhemoglobin (deoxy-Hb), total-Hb (total-Hb = oxy-Hb + deoxy-Hb), and the TOI. Throughout the observation period, each of the parameters was measured continuously and recorded at 1-min intervals.

The primary outcomes were the difference among the groups in the mean variation value of the rCBV and rCBO, as estimated from the total-Hb[10,11] and TOI,[12] respectively, during the 20-min period after the spinal injection. Based on a previous study, we assumed that the incidence of hypotension, which was defined as a decrease in MAP by more than 20% from baseline, would be 80%, 25% and 15% in patients in the P0, P25 and P50 groups, respectively,[7] and that the decrease in both total-Hb and TOI would correlate with the

decrease in MAP.[6] We allocated previous data, including mean variation values of total-Hb and TOI, into three groups according to the same ratio for the incidence of hypotension reported above,[7] and calculated the effect sizes from the allocated data for the sample size calculation. From the calculated effect sizes, 0.49 and 0.44 in the comparison of total-Hb and TOI respectively, the sample sizes were determined to be 15 and 18 patients per group, for comparison of mean variation values of total-Hb and TOI among the groups, respectively, using a priori one-way analysis of variance (ANOVA) with $\alpha = 0.05$ and a power of 0.80. To take potential dropouts into consideration, this study enrolled 20 patients per group.

Patient characteristics and clinical data are presented as means (SD), medians (range), quartile deviation (QD) or number of cases (%). The time-series data of MAP, HR, SpO_2 and $EtCO_2$ at 1-min intervals are expressed as the measured values, while the NIRS measurements are expressed as variations from the baseline. The differences in patient characteristics and clinical data between the groups, and the baseline values of the time-series data, were analyzed by one-way ANOVA or the Kruskal–Wallis test. Inter-group comparisons of the incidence of hypotension and adverse symptoms were performed using a χ^2 test with Bonferroni correction ($P < 0.016$ was considered significant). The presence or absence of significant changes in the time-series data in each group was determined using one-way repeated measures ANOVA or the Friedman test. Inter-group comparisons of the mean values of MAP, HR, SpO_2 and $EtCO_2$, and the mean variations from baseline of NIRS measurements during the 20-min period after spinal injection were performed using the Tukey-Kramer or Steel-Dwass multiple comparison test. Statistical analysis was performed using JMP version 9 (SAS Institute, Cary, NC, USA). A P-value of <0.05 was considered significant.

Results

This study analyzed 56 patients (Fig. 1). Table 1 presents the patient characteristics and clinical data. The incidence of hypotension was significantly higher in the P0 compared with the phenylephrine groups. Bradycardia was observed in only one patient (P50 group). The incidence of adverse symptoms was significantly higher in the control versus the phenylephrine groups.

No significant differences were observed in baseline values of the time-series data between the groups, with the exception of oxy-, deoxy- and total-Hb (Table 2). Figs. 2 and 3 show the changes in the measurements from baseline, for the predefined time points. Table 3 presents the inter-group differences in mean values or mean variations during the 20 minute period after intrathecal injection. Oxy-hemoglobin decreased significantly in all groups (P0, P50; $P < 0.0001$, P25; $P = 0.002$), and there was a significant decrease in oxy-Hb levels in the P0 versus P25 group ($P = 0.023$), but no significant differences between the P0 and P50, and P25 and P50 groups. The only significant increase in deoxy-Hb was seen in the P50 group ($P < 0.0001$). Inter-group comparisons also showed that the phenylephrine infusion dose-dependently increased deoxy-Hb compared to P0 (P0 vs. P25, $P = 0.008$; P0 vs. P50, $P < 0.0001$; P25 vs. P50, $P = 0.016$). Total-Hb significantly decreased only in the P0 group ($P < 0.0001$). Inter-group comparison of total-Hb in both the phenylephrine groups showed there were significantly higher levels in both groups compared to the P0 group (P0 vs. P25, P0 vs. P50; $P < 0.0001$), with no significant differences noted between the phenylephrine groups. For TOI, there was a significant decrease in P0 and P50 groups ($P < 0.0001$). The largest decrease in TOI observed in inter-group comparisons was in the P50 group, followed in order by the P0 and P25 groups (P0 vs. P25; $P = 0.038$, P0 vs. P50; $P = 0.045$, P25 vs. P50; $P < 0.0001$). Mean arterial pressure decreased significantly only in the P0 group ($P = 0.0019$). In inter-group comparisons, although MAP was significantly higher in both the phenylephrine groups compared to the P0 group (P0 vs. P25, $P = 0.002$; P0 vs. P50, $P < 0.0001$), there was no significant difference between the phenylephrine groups. Heart rate decreased significantly only in the P50 group ($P = 0.0004$). In addition, phenylephrine infusion dose-dependently decreased HR compared to P0 (P0 vs. P25, $P = 0.0031$; P0 vs. P50, $P < 0.0001$; P25 vs. P50, $P = 0.0214$). There were no significant changes or differences in SpO_2 and $EtCO_2$ between any of the groups.

Discussion

The study showed that decreases in MAP in the control group (P0) led to significant decreases in total-Hb and TOI, suggesting that hypotension secondary to spinal anesthesia for cesarean section causes a decrease in maternal rCBV and rCBO. Total-hemoglobin and TOI were maintained in line with MAP in the P25 group, suggesting that a phenylephrine infusion at the rate of 25 μg/min was able to attenuate effectively the decreases in both rCBV and rCBO resulting from decreases in blood pressure after spinal anesthesia.

The changes found in the NIRS variables in the control group included a simultaneous decrease in total-Hb and TOI, in conjunction with a decrease in oxy-Hb, while deoxy-Hb levels remained unchanged, a finding consistent with our previous results.[4–6] This suggests that the decrease in rCBV and rCBO is related to the mild decline in blood supply resulting from the decrease in blood pressure.[6] The decrease in blood pressure after spinal anesthesia is primarily due to decrease in systemic vascular resistance (SVR), and not because of decreases

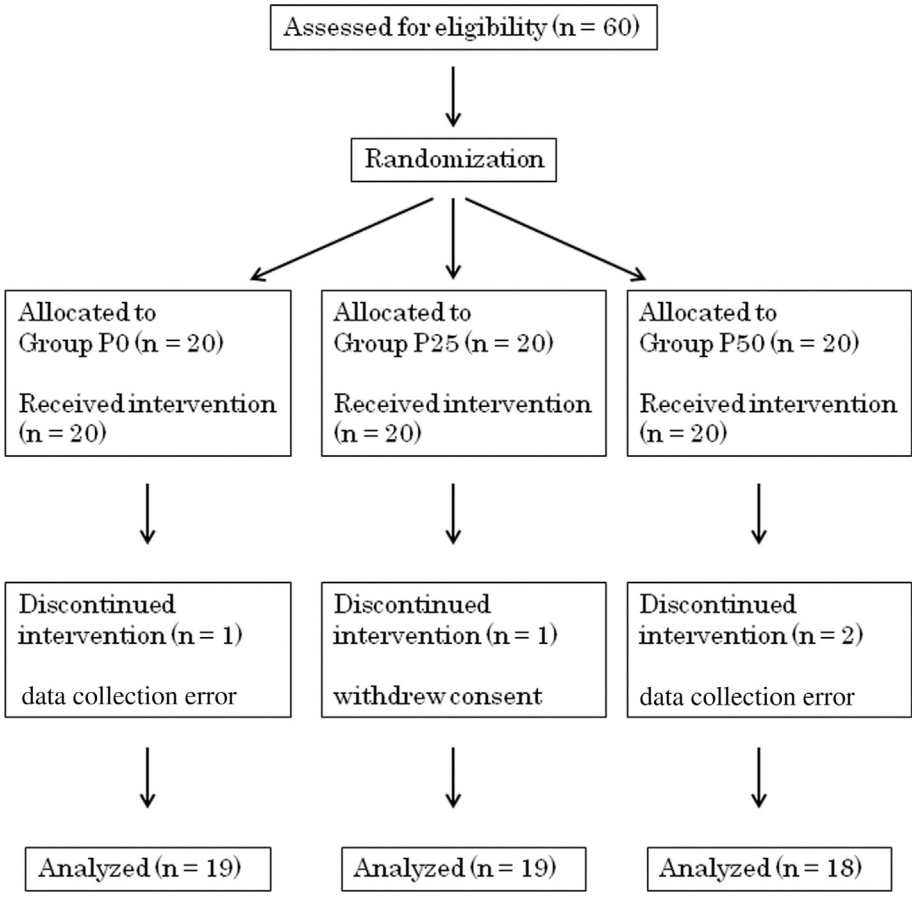

Fig. 1 Consort flow diagram

Table 1 Demographic and clinical data

	P0 (n=19)	P25 (n=19)	P50 (n=18)
[a]Age (y)	30.1 (4.8)	31.1 (5.7)	29.3 (5.4)
[a]Height (cm)	158.3 (5.4)	158.0 (6.1)	159.6 (8.3)
[a]Weight (kg)	61.2 (9.4)	64.3 (12.1)	62.4 (10.1)
[a]Gestational age (weeks)	37.8 (0.8)	38.4 (1.2)	38.2 (1.0)
[a]Dose of bupivacaine (mg)	11.5 (1.0)	10.0 (0.5)	11.0 (0.8)
[b]Block height (dermatome)	Th 4 (Th 3–7)	Th 3.5 (Th 3–6)	Th 4 (Th 3–8)
[a]Fluids, initial to 20 min after intrathecal injection (mL)	747.3 (135.9)	762.4 (184.8)	759.4 (172.2)
[c]Incidence of hypotension	12 (60)[*]	1 (5)	0 (0)
[c]Incidence of adverse symptoms, nausea	7 (37)[†]	1 (5)	0 (0)
[c]Interventional treatment			
Ephedrine	8 (42)	1 (5)	0 (0)
Phenylephrine	4 (21)	0 (0)	0 (0)
Atropine	0 (0)	0 (0)	1 (5)
[a]Total phenylephrine infusion dose (μg)	0 (0)	475 (20.4)	848 (45.2)

Data are presented as [a]mean (SD). [b]median (range) or [c]number (%). [*]P <0.0001 vs. P25 and P50. [†]P=0.0123 vs. P25, P=0.001 vs. P50. P0: control. P25: phenylephrine 25 μg/min. P50: phenylephrine 50 μg/min.

in stroke volume (SV) and cardiac output (CO).[13–15] Prophylactic phenylephrine infusion, which causes reflex bradycardia without a significant decrease in CO, can effectively maintain blood pressure.[8,9] The phenylephrine infusion rate required to maintain hemodynamic stability has been reported to lie in the range from 25 to 50 μg/min.[8,16] Our results showed that, compared to the control group, a phenylephrine infusion at 25 μg/min completely attenuated the decrease in MAP but also significantly decreased HR and attenuated the decrease in oxy-Hb, total-Hb and TOI. These observations suggest that a decrease in rCBV and rCBO secondary to a

Table 2 Baseline values of the time-series data

	P0 (n=19)	P25 (n=19)	P50 (n=18)
MAP (mmHg)	85.4 (10.5)	87.9 (12.5)	87.8 (9.8)
HR (beats/min)	76.9 (11.6)	73.9 (10.7)	73.4 (11.4)
SpO_2 (%)	98.3 (1.1)	98.7 (1.1)	98.7 (0.9)
$EtCO_2$ (mmHg)	36.5 (1.6)	36.2 (1.3)	36.4 (1.7)
TOI (%)	65.4 (5.1)	62.8 (3.8)	65.0 (4.9)

Data are presented as mean (SD). No significant differences were observed between the groups. MAP: mean arterial pressure. HR: heart rate. SpO_2: oxygen saturation. $EtCO_2$: end-tidal carbon dioxide. TOI: tissue oxygenation index.

decrease in blood pressure may have been due to shift in the distribution of circulating blood from the cerebral regions to the legs and trunk, because of the reduced SVR. Additionally, a phenylephrine infusion at 25 μg/min may be able to sufficiently suppress the decrease in SVR, despite the decrease in CO, thereby maintaining rCBV and rCBO.

Contrary to our expectations, we found that a phenylephrine infusion at 50 μg/min significantly decreased the TOI, although it maintained total-Hb and MAP. A comparison between the phenylephrine groups showed that the tendency for oxy-Hb to decrease and deoxy-Hb to significantly increase were dependent on the phenylephrine dosage, even though total-Hb and respiratory measurements in each of the groups remained stable to a similar extent. Based on the fact that the phenylephrine infusion had no impact on cerebral blood flow,[17] the changes observed in the NIRS variables suggest the possibility that phenylephrine might dose-dependently increase cerebral oxygen metabolism.[18,19] However, we consider this to be unlikely, because there is no particular evidence to suggest this. In contrast, Meng et al.[20] reported results that were similar to those of the present study, in which there was a simultaneous decrease in oxy-Hb and increase in deoxy-Hb, in conjunction with a decrease in cerebral tissue oxygen saturation ($SctO_2$) and CO, even though CBV remained unchanged after the bolus administration of phenylephrine as pressor treatment of anesthetized patients. Ogoh et al.[21] demonstrated that, while a 1.15 μg/kg/min phenylephrine infusion caused no changes in internal carotid artery blood flow, it significantly decreased frontal lobe oxygenation (ScO_2). The authors of both the previous studies suggested that the phenylephrine-induced decrease in $SctO_2$ and ScO_2 reflects an altered cerebral contribution of the arterial versus venous blood. Several studies have demonstrated that changes in ScO_2 partially reflect a change in frontal skin blood flow.[22,23] Ogoh et al.[21,24] demonstrated that phenylephrine infusion dose-dependently decreases forehead skin blood flow (SkBF) and that there is a significant correlation between the decrease in ScO_2 and decrease in SkBF during a phenylephrine infusion.

This present study also showed that the onset of nausea was significantly attenuated in both the phenylephrine groups, while there was a larger decrease in TOI with P50 infusion compared to P0, although the TOI level was maintained in the P25 group. These observations indicate that the decrease in TOI caused by the 50 μg/min phenylephrine infusion might be dependent on the specific effects of phenylephrine on cerebral and scalp circulation. It might not represent real or significant cerebral hypoxia,[20,21] and the decrease in TOI appears to exceed the inhibitory effect on decrease in TOI caused by a 25 μg/min phenylephrine infusion.

When evaluated by NIRS, a decrease of 10–20% in cerebral oxygen saturation (ScO_2 and TOI) or a decrease in oxy-Hb of 5 μmol/L, accompanied by a decrease in total-Hb from baseline, is suggestive of cerebral dysfunction and ischemia.[18,25–27] In contrast, according to the results of our previous studies in which no symptoms suggestive of an ischemic incident were seen in healthy parturients, despite a decrease in their oxy-Hb and TOI to below the above threshold,[4–6] it is still questionable whether the changes in NIRS variables found after spinal anesthesia have clinical significance. However, in comparison with the control group, in which 60% of patients received bolus doses of ephedrine or phenylephrine, the total-Hb and TOI were sufficiently maintained by infusion of phenylephrine, especially an infusion of 25 μg/min, in the present study. At the least, the results might suggest that prophylactic infusion of phenylephrine is more effective in the maintenance of rCBV and rCBO than symptomatic blood pressure management using bolus injection of pressor agents. The results suggest that prophylactic infusion of phenylephrine might be a safe management strategy in patients with certain cerebrovascular diseases, such as Moyamoya disease and Takayasu arteritis, in whom cerebrovascular circulation needs to be maintained during spinal anesthesia for cesarean section.[28–30]

There are several limitations to our present study. When using NIRS, it should be noted that the data merely reflect circulatory changes in the regional tissues of the frontal lobe, and may not correspond to the changes at other cerebral sites or the entire brain.[31] Although NIRS is regarded as a simple method for clinically evaluating cerebral circulation, several studies have demonstrated that there is poor correlation between NIRS and other measurements.[32,33]

In addition, since hemodynamic parameters were only evaluated using non-invasive blood pressure and

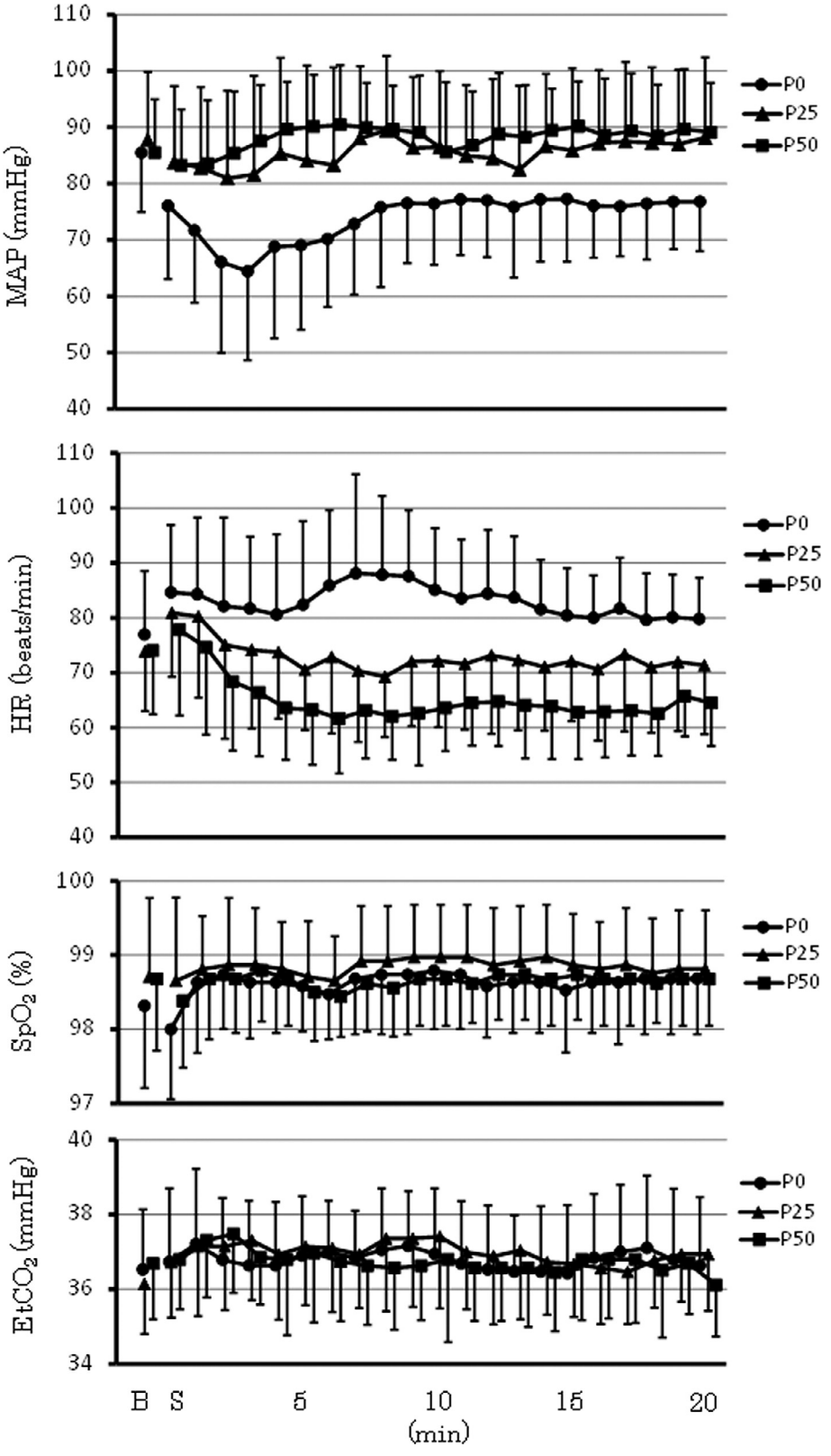

Fig. 2 Changes in cardiorespiratory parameters after induction of spinal anesthesia. MAP: mean arterial pressure; HR: heart rate; SpO_2: oxygen saturation by pulse oximetry; $EtCO_2$: end-tidal carbon dioxide; B: baseline, S: return to the supine position after spinal injection

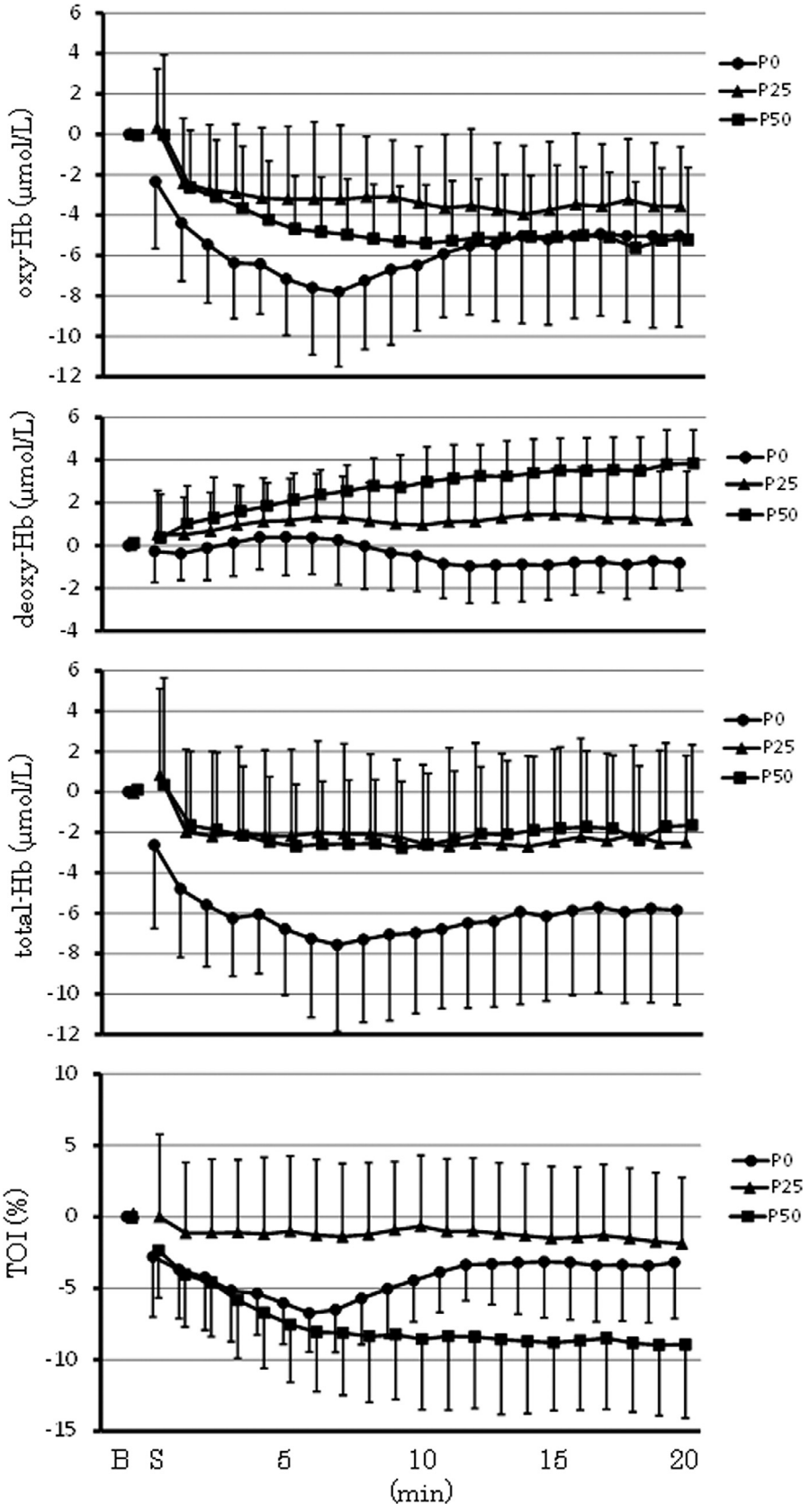

Fig. 3 Changes in near infrared spectroscopy parameters after induction of spinal anesthesia. Hb (oxy-, deoxy- and total-): hemoglobin concentration; TOI: tissue oxygenation index; B: baseline; S: return to the supine position after spinal injection

Table 3 Inter-group comparison of mean values or mean variation values in the 20 minute period after induction of spinal anesthesia

	P0 (n=19)	P25 (n=19)	P50 (n=18)
Oxy-Hb (μmol/L)[a]	−5.72 (2.86)	−3.12 (2.98)*	−4.46 (2.76)
Deoxy-Hb (μmol/L)[a]	−0.41 (1.29)	1.01 (1.73)*	2.33 (1.11)**,†
Total-Hb (μmol/L)[a]	−6.15 (0.81)	−2.08 (0.81)**	−2.12 (0.83)**
TOI (%)[b]	−4.27 [1.71]	−2.48 [0.75]*	−7.05 [3.69]**
MAP (mmHg)[a]	74.01 (2.26)	85.45 (2.26)*	90.62 (2.32)**
HR (beats/min)[b]	82.91 [7.21]	72.76 [9.91]*	64.43 [4.35]**,†
SpO_2 (%)[a]	98.62 (0.69)	98.82 (0.68)	98.63 (0.51)
$EtCO_2$ (mmHg)[a]	36.81 (1.32)	36.99 (1.14)	36.77 (0.79)

Data are presented as mean (SD) or median [QD]. *P <0.05, **P <0.01 vs P0. †P <0.05, ††P <0.01 vs P25. [a]Tukey-Kramer test, [b]Steel-Dwass test. Hb: hemoglobin concentration. TOI: tissue oxygenation index. MAP: mean arterial pressure. HR: heart rate. SpO_2: oxygen saturation. $EtCO_2$: end-tidal carbon dioxide.

ECG measurements, discussion of the relationship between NIRS and hemodynamics is a matter of speculation. Several studies have suggested that patient constitution and injection dose of local anesthetic have an impact on block height and the incidence of hypotension,[34,35] and it is therefore possible that non-standardization of the injection dose of bupivacaine in our patients could have impacted our results, although there were no significant differences in block height among the groups in this study.

In conclusion, we used NIRS to evaluate the effect of phenylephrine infusion on changes in maternal rCBV and rCBO after induction of spinal anesthesia for cesarean section. The results suggest that prophylactic infusion of phenylephrine, especially an infusion of 25 μg/min, can effectively suppress decreases in rCBV and rCBO after induction of spinal anesthesia.

Declaration of interest

None.

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