Title: Changes of cerebral oxygenation indices measured by near infrared time-resolved spectroscopy during spinal anesthesia for cesarean section: Simultaneous measurement with cerebral blood flow

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Short running title: cerebral hemodynamics in cesarean section

Abstract

Aim: To measure the changes in cerebral oxygenation indices by near infrared time-resolved spectroscopy and the cerebral blood flow simultaneously after spinal anesthesia for cesarean section.

Methods: This prospective observational study was conducted for 25 pregnant women scheduled for elective cesarean section under spinal anesthesia. During a period of 15 min after spinal anesthesia, cerebral oxygenation (ScO_2), and the total cerebral hemoglobin concentration (tHb) were measured using near infrared time-resolved spectroscopy and mean cerebral blood flow velocity (Vm) was measured using transcranial Doppler ultrasonography. Next, in the women who had nausea during the observed period, we compared these values when nausea was detected with those when it was not.

Results: Mean arterial pressure (MAP) decreased to around 60 mmHg (by 25% compared to the control) 6 min after spinal anesthesia. Compared to the control, ScO_2 decreased by about 3% after 6 min and then gradually increased. The tHb, which reflects cerebral blood volume started to decrease just after spinal anesthesia and this continued until 12 min (the decrease was about 12%). Vm decreased by about 7%. In the 14 women who had nausea, MAP, Vm and ScO_2 values when nausea was detected were significantly lower than when it was not.

Conclusion: The changes in cerebral hemodynamics may be small after spinal anesthesia in ordinary cesarean section compared to the reduction of systemic arterial

blood pressure. There might be greater decreases in cerebral blood flow and oxygenation when nausea occurred in the pregnant women who experienced it after spinal anesthesia.

Key Words: cerebral blood flow; cerebral oxygenation; cesarean section; near infrared time-resolved spectroscopy; spinal anesthesia; nausea

Introduction

In cesarean section, hypotension is usually seen just after spinal anesthesia. This hypotension is regarded as the most important cause of nausea observed during the same period [1, 2], because it may lead to cerebral hypoperfusion and brainstem ischemia, which is thought to activate the circulatory, respiratory, and vomiting centers grouped together in the medulla [3]. However, few studies have evaluated the cerebral perfusion after spinal anesthesia for cesarean section. In one study, cerebral hemodynamics were measured for 15 minutes after spinal anesthesia by using transcranial Doppler ultrasonography (TCD)[4]. The study concluded that the effects on the cerebrovascular hemodynamic parameters were unlikely to be clinically significant because they did not affect indices for perfusion pressure or flow.

An alternative method to evaluate cerebral hemodynamics is near infrared spectroscopy (NIRS)[5]. First, we can noninvasively measure cerebral oxygenation (ScO_2) by NIRS. Currently, ScO_2 monitoring is widely used to detect cerebral perfusion abnormalities in cardiac and non-cardiac surgeries [6, 7]. In addition, it was reported that the intraoperative decrease in ScO_2 was related to postoperative delirium and/or cognitive dysfunction, especially in cardiac surgery [6, 7]. Some different principals are adopted in commercially available NIRS monitoring: the Modified Beer-Lambert law (MBL) and spatial resolved spectroscopy (SRS) have been the representative methods [6, 7]. Second, in some oximeters, relative changes in the total cerebral hemoglobin concentration (tHb) can be measured. The tHb reflects cerebral blood volume (CBV) by using a conversion

formula with tHb and blood hemoglobin (Hb): CBV=0.73 × tHb /blood Hb [8]. CBV is another index of cerebral hemodynamics other than ScO_2 and cerebral blood flow (CBF) and indicates total arterial and venous blood volume in the brain [9]. Hence, CBV directly influences intracranial pressure and the changes in CBV and CBF do not always vary in parallel [9].

By spinal anesthesia using hyperbaric bupivacaine for cesarean section, a study using NIRS that adopted the MBL and SRS methods (NIRO pulse™, Hamamatsu Photonics, Hamamatsu, Japan) revealed that ScO_2 and tHb were decreased by 4% and 6 μmol/L, respectively[10]. Another study using the same NIRS platform demonstrated that the maximum changes in ScO_2 and tHb correlated with changes in mean arterial pressure (MAP) and that lower values of them were associated with an increased risk of nausea and dizziness [11].

Recently, NIRS using a new theory, i.e., the time-resolved spectroscopy (TRS) method (tNIRS-1 tissue oximeter, Hamamatsu Photonics, Hamamatsu, Japan) became available[12]. The TRS method is considered to be superior to the conventional NIRS that adopts the MBL and SRS methods in regard to the correctness and reproducibility of the measured data[12 13]. Moreover, in the TRS method, the absolute tHb values can be obtained, unlike with the MBL and SRS methods. The oximeter with TRS method has already been applied to robot-assisted laparoscopic surgery [13], parturition [14] and cesarean section [15] and good results were obtained. However, detailed analyses of factors such as minute diachronic changes in ScO_2 and tHb were not done in the cesarean section study.

In this study, accordingly, we measured ScO_2 and tHb after spinal anesthesia for

cesarean section by using a tNIRS-1, and their detailed time courses were evaluated. Next, CBF velocity (which reflects CBF) was measured by TCD. As far as we know, this is the first study to measure both cerebral oxygen indices and CBF after spinal anesthesia for cesarean section. Our hypothesis was that changes in these cerebral hemodynamic indices would be small compared to the change in systemic blood pressure. Finally, for the pregnant women who had nausea during the observed period, we compared these values when nausea was detected with those when it was not.

Materials and Methods

This prospective observational study was approved by the ethics committee of the Hokkaido University Hospital (No. 017-0280), and written informed consent was obtained from all the pregnant women. It was registered in the UMIN Clinical Trials Registry prior to patient enrollment (UMIN000031828).

Anesthesia and perioperative management were conducted for 25 pregnant women scheduled for elective cesarean section in Hokkaido University Hospital. Pregnant women with hypertension, diabetes, renal dysfunction, cerebral disease including pre-eclampsia, obesity (body mass index>30) and under treatment with ritodrine were excluded.

After entering the operating room, noninvasive monitoring of MAP in the upper arm, heart rate and SpO_2 was started. The respiratory rate was also monitored with a Nellcor^{TM} respiratory monitor (PM1000N, Medtronic, Minneapolis, USA). The sensors of the tNIRS-1 were placed on the left side of the forehead and the absolute values of cerebral oxygenated hemoglobin (O_2Hb) and deoxygenated hemoglobin (HHb) concentrations were continuously collected every 5 seconds. tHb was obtained by summing O_2Hb and HHb. ScO_2 was derived from the percentage of O_2Hb compared with tHb. The mean blood flow velocity (Vm) of the middle cerebral artery was measured through the left temporal window with a transcranial Doppler apparatus (EZ-Dop, DWL, Singen, Germany).

With the pregnant woman in the lateral position, an epidural catheter was inserted at around the T11-12 intervertebral space. As a test dose, 1.5% lidocaine (a 3mL bolus) was given; however, no additional administration was performed during the observation period. Next, a subarachnoid puncture was performed at the L 3-4 intervertebral space and 1.5-2.5 mL of 0.5% hyperbaric bupivacaine was administered and 10-20 mcg of fentanyl was added optionally. After spinal anesthesia, each patient was returned to the supine position and oxygen was administered via a mask. Intravenous infusion was performed at the rate of about 20 ml/kg/h during the measurement. When systolic blood pressure fell below 80% of the initial value or 90 mmHg, 4-8mg of ephedrine was administered. In addition, left uterine displacement and/or the Trendelenburg position were added for safety when the increase in blood pressure induced by ephedrine was insufficient. Women with a cold test result indicating inadequate analgesia at dermatome Th10 or below were excluded. When tachypnea (respiratory rate > 25 breaths/min) continued, they were also excluded.

During 15 minutes after spinal anesthesia. MAP, SpO_2, tNIRS-1 indices were recorded every 2 minutes, and TCD indices were recorded every 4 minutes. The women were asked about nausea at least every one minute and the duration of the nausea was recorded.

Statistical Analysis

The primary objective was to observe the changes in tNIRS-1 indices such as ScO_2 and tHb after spinal anesthesia for cesarean section. In a previous study measuring ScO_2 after

spinal anesthesia for cesarean section by using a NIRO pulse^{TM}, the standard deviation (SD) of baseline ScO_2 was 6.2% [11]. For a two-sided 95% confidence interval with a normal mean, assuming an SD of 6.2%, a sample size of 25 is required to obtain a half-width of at most 2.4%. In another study using a prototype near infrared TRS, the TRS-10 system (Hamamatsu Photonics, Hamamatsu, Japan), the SD of CBV was around 0.3 $mL.100g^{-1}$ [8]. For a two-sided 95% confidence interval with a normal mean, assuming an SD of 0.3 $mL.100g^{-1}$, a sample size of 25 is required to obtain a half-width of at most 0.12 $mL.100g^{-1}$. The normality of all ScO_2 and tHb data was ascertained using the Shapiro-Wilk test. Accordingly, to evaluate these objectives, one-way repeated-measures analysis of variance (ANOVA) and a post hoc test were performed followed by Bonferroni multiple comparison for each time point. Sphericity was tested with Mauchly's test. If sphericity was violated, we used Greenhouse-Geisser correction.

The secondary objective was to evaluate the time courses of Vm. The normality of all Vm data was ascertained and one-way repeated-measures ANOVA and Bonferroni multiple comparison were performed.

The third objective was to observe the relationship between nausea and systemic and cerebral circulation in the pregnant women who complained of nausea. For this, MAP, Vm and ScO_2 when nausea was observed were compared with their values when nausea was not observed, using an unpaired t-test.

As the physiological parameters, we evaluated the time courses of MAP and SpO_2. The normality of all MAP data was ascertained and one-way repeated-measures ANOVA and Bonferroni multiple comparison were performed. For SpO_2, the normality was not

ascertained so the Friedman test was utilized and Bonferroni multiple comparison was performed.

Data of normality were expressed as mean ± SD and others as the median (25%-75% interquartile range). Statistical analysis was performed using SPSS ver. 25.0 (Armonk, USA). A P-value <0.05 was considered statistically significant.

Results

Patient demographics and clinical data are shown in Table. There were no pregnant women who were excluded due to inadequate analgesia or tachypnea. There was no abnormal pregnancy such as placenta previa. The number of women who had nausea during the observed period was 14 and the median time of complaining of nausea in these women was 2.5 (2-4.3) minutes. All the newborns had Apgar scores of 8 or more at both 1 and 5 minutes. In the Trendelenburg position the blood pressure at the head level becomes higher than that at the upper arm. However, the influence of this position on the results of this study would be small because there were only 2 cases in this position.

Changes in MAP are shown in Fig. 1A. MAP decreased to about 60 mmHg (by 25% compared to the control) 6 minutes after spinal anesthesia and significant changes were observed in one-way repeated-measures ANOVA ($F=11.55$ $P<0.01$). The median SpO_2 value at both the control and T2 was 98%. It became 99% at T4 and increased to 100% after T6 until T14, probably due to oxygenation after the spinal anesthesia. Although there was a significant difference in the Friedman test ($P<0.01$), these changes were small and might not have affected the changes in ScO_2 and Vm according to the physiological relationship between SaO_2 and these values [9, 16].

Changes in ScO_2 and tHb are shown in Fig. 1B and 1C. One-way repeated-measures ANOVA revealed significant changes in ScO_2 over time ($F= 6.16$; $P<0.01$). It significantly decreased to 58.8 ± 4.9% six minutes after spinal anesthesia (a decrease of about 3% compared to the control). Then it gradually increased. One-way repeated-

measures ANOVA of the changes in tHb also revealed a significant difference ($F= 30.47$; $P<0.01$). It started to decrease just after spinal anesthesia and continued to do so until 12 minutes. The decrease compared to the control was about 6 μmol/L (about 12% of the control level). Changes in Vm are shown in Fig. 1D. Although Vm at T8 decreased by about 7% compared to the control, there was no significant difference in the change ($F=0.91$; $P=0.44$).

Finally, for the 14 pregnant women who had nausea during the observed period, we compared the values of MAP, Vm and ScO_2 when nausea was detected with those when it was not (Fig. 2). All the values when nausea was detected were significantly lower than when it was not detected.

Discussion

As far as we know, this is the first study to measure both cerebral oxygen indices and CBF after spinal anesthesia for cesarean section. The changes in cerebral hemodynamics were small after spinal anesthesia in ordinary cesarean section compared to the reduction of systemic arterial blood pressure. There might be greater decreases in cerebral blood flow and oxygenation when nausea occurred in the pregnant women who experienced it after spinal anesthesia.

ScO_2 measured by the TRS method decreased by only 3% in pregnant women after spinal anesthesia with hyperbaric bupivacaine, while MAP decreased by 25%. This decrease was comparable with that of a previous study in which ScO_2 measured by the SRS method decreased by 4% after spinal anesthesia with hyperbaric bupivacaine [10]. On the other hand, a decrease of more than 5% was observed after spinal anesthesia with hyperbaric bupivacaine in about 70% of pregnant women when ScO_2 was measured with an INVOS 3100 (Somanetics, Troy, USA) [17]. The devices of the INVOS series are believed to use the MBL method mainly [18] although the manufacturer has not disclosed the algorithms used. It was reported that spectroscopy utilizing the MBL method may overestimate changes in cerebral oxygenation [18].

The tHb decreased by about 6 μmol/L. This is the same as the result measured by the SRS method [10]. This decrease was about 12% compared to the control. This is a new finding because the absolute value of tHb can be measured only by the TRS method. According to the formula for CBV and tHb [8], the decrease in CBV may be less than 12%

because it is supposed that blood Hb was decreased by the infusion. Intracranial volume consists of 10% cerebral blood, 5% cerebrospinal fluid (CSF), and 85% cerebral tissue according to the Monro–Kellie doctrine,[19]. Therefore, an about 10% decrease in CBV only affects 1% of total intracranial volume. It is reported that the decrease in CBV after spinal anesthesia in cesarean section is due to a decrease in systemic vascular resistance [20]. Accordingly, this decrease may reduce cerebral venous blood pooling although the exact mechanism is unknown.

Finally, Vm decreased by 7%. This small decrease in Vm might have been because the level to which MAP decreased was around the lower threshold of cerebral autoregulation; i.e., about 65-70mmHg of MAP [9]. Thus, it was concluded that the decreases in cerebral oxygen indices and CBF were small and clinically insignificant compared to the decrease in systemic blood pressure after spinal anesthesia in ordinary cesarean section.

It is reported that ScO_2 can be expressed as a function of SaO_2, blood Hb, CBF and the cerebral metabolic rate for oxygen[16]. In our study, SpO_2 values (substituted for SaO_2) were stable throughout the observed period. If the blood Hb is dominant for regulating ScO_2, a reincrease in ScO_2 should not be found because it is natural to think that blood Hb is decreased by the infusion. On the contrary, decreases in Vm were larger than for SCO_2. It is generally accepted that CBF and cerebral metabolism are tightly coupled [9]. Accordingly, the decrease in ScO_2 may be small due to the reduction of the cerebral metabolic rate accompanied by the decrease in CBF.

Hypotension is regarded as the most important cause of nausea after spinal anesthesia for cesarean section because it may lead to cerebral hypoperfusion and brainstem

ischemia [3]. However, there seems to be no clinical evidence about it[4]. In our study, MAP, Vm and ScO_2 were significantly lower when the pregnant women complained of nausea than when they had no nausea. This suggested that there might be greater decreases in cerebral blood flow and oxygenation when nausea occurred in the pregnant women who experienced it after spinal anesthesia. On the other hand, a recent meta-analysis reported that the women treated with ephedrine had a higher incidence of nausea and vomiting that those using phenylephrine [21]. Moreover, a recent retrospective study demonstrated that women who had a female neonate, a history of severe nausea and vomiting in the first trimester, and a history of premenstrual syndrome and motion sickness before pregnancy experienced a significantly higher rate of nausea and vomiting after spinal anesthesia for cesarean section [22]. Accordingly, further study will be necessary to clarify the causes of nausea after spinal anesthesia for cesarean section.

A recent guideline recommends the use of phenylephrine for the hypotension after spinal anesthesia in elective cesarean section due to there being less neonatal acidosis than with ephedrine [23]. However, another guideline [24] and meta-analysis [21] state that both phenylephrine and ephedrine may be effective for treating hypotension during cesarean section with spinal anesthesia. In addition, it was reported that phenylephrine administration reduced ScO_2 in anesthetized patients whereas it was preserved after ephedrine treatment [25, 26]. In a study on cesarean section with spinal anesthesia, administration of ephedrine maintained ScO_2, whereas phenylephrine reduced ScO_2, with a greater than 10% difference between the groups [27]. Accordingly, we chose ephedrine as an inotropic agent for our study. In our study, the mean umbilical cord blood pH was 7.27

and all the neonates had Apgar scores of 8 of more at both 1 and 5 minutes after birth. Recent findings suggest that the reduction in ScO_2 caused by phenylephrine may be due to vasoconstriction in the extracranial region [9]. It was also reported that the influence of extracranial contamination was much less in NIRS using TRS than in that using MBL[18]. Therefore, to examine the effect of phenylephrine on ScO_2 by using a tNIRS-1 will be necessary as the next step.

This study has some limitations. First, the changes in cerebral hemodynamics measured by NIRS are in the frontal lobe just beneath the sensor on the forehead [7]. The middle cerebral artery supplies blood to that part of frontal lobe. Accordingly, the measurement sites of NIRS and TCD are not necessarily the same, but are not far apart. However, it is a fact that neither the NIRS and nor TCD measurements in our study estimate the changes in the whole brain including the brainstem, in which the vomiting centers exit. However, the measurement methods of NIRS and TCD utilized in our study are the most standard methods. Therefore, we believe that we could observe representative changes in cerebral oxygenation and blood flow after spinal anesthesia for cesarean section. Next, it was performed for ordinary cesarean section in women without severe complications. On the other hand, the ScO_2 values before parturition were significantly lower in pregnant women with severe pre-eclampsia than in healthy ones [28]. In contrast, the ScO_2 values were significantly higher in pre-eclamptic women than in normotensive ones before anesthesia [15] and just after spinal anesthesia [29]. A recent review indicated that regulation of CBF is altered in pregnancy and is further altered by hypertension and hypertensive

disorders of pregnancy, including pre-eclampsia, although the mechanisms have not been fully elucidated [30]. In a study using a prototype TRS (TRS-20, Hamamatsu Photonics, Hamamatsu, Japan), the ScO_2 decreased by more than 10% after massive bleeding due to placenta previa [15]. Pregnant women with such complications should be evaluated as the next step. Finally, changes in $PaCO_2$ affect the CBF [9]. Although the end-tidal CO_2 concentration ($EtCO_2$) is used as a substitute for it, we did not monitor this. Instead, we monitored the respiratory rate. Because there were no patients who had tachypnea, we believe that the $PaCO_2$ level was maintained within the acceptable range in our patients.

In conclusion, we simultaneously evaluated the changes in cerebral oxygen indices measured by near infrared time-resolved spectroscopy and CBF measured by transcranial Doppler ultrasonography after spinal anesthesia for ordinary cesarean section in women without severe complications. These changes were small compared to the reduction of systemic arterial blood pressure. Further study will be necessary to clarify the changes in cerebral hemodynamics in pregnant women with complications such as pre-eclampsia or massive bleeding during cesarean section. There might be greater decreases in cerebral blood flow and oxygenation when nausea occurred in the pregnant women who experienced it after spinal anesthesia.

Disclosure

Conflicts of interest: None of the authors have any conflicts of interest.

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References

1 Balki M, Carvalho JC. Intraoperative nausea and vomiting during cesarean section under regional anesthesia. *Int J Obstet Anesth*. 2005; **14**: 230-41.

2 Jelting Y, Klein C, Harlander T, Eberhart L, Roewer N, Kranke P. Preventing nausea and vomiting in women undergoing regional anesthesia for cesarean section: challenges and solutions. *Local Reg Anesth*. 2017; **10**: 83-90.

3 Borgeat A, Ekatodramis G, Schenker CA. Postoperative nausea and vomiting in regional anesthesia: a review. *Anesthesiology*. 2003; **98**: 530-47.

4 Postma IR, van Veen TR, Mears SL, Zeeman GG, Haeri S, Belfort MA. The effect of neuraxial anesthesia on maternal cerebral hemodynamics. *Am J Perinatol*. 2014; **31**: 787-93.

5 Sun S, Liu NH, Huang SQ. Role of cerebral oxygenation for prediction of hypotension after spinal anesthesia for caesarean section. *J Clin Monit Comput*. 2016; **30**: 417-21.

6 Thiele RH, Shaw AD, Bartels K*, et al.* American Society for Enhanced Recovery and Perioperative Quality Initiative Joint Consensus Statement on the Role of Neuromonitoring in Perioperative Outcomes: Cerebral Near-Infrared Spectroscopy. *Anesth Analg*. 2020; **131**: 1444-55.

7 Yoshitani K, Kawaguchi M, Ishida K*, et al.* Guidelines for the use of cerebral oximetry by near-infrared spectroscopy in cardiovascular anesthesia: a report by the cerebrospinal Division of the Academic Committee of the Japanese Society of Cardiovascular Anesthesiologists (JSCVA). *J Anesth*. 2019; **33**: 167-96.

8 Ohmae E, Ouchi Y, Oda M*, et al.* Cerebral hemodynamics evaluation by near-infrared time-resolved spectroscopy: correlation with simultaneous positron emission tomography measurements. *NeuroImage*. 2006; **29**: 697-705.

9 Patel PM, Drummond JC, Lemkuil BP. Cerebral Physiology and the Effets of Anesthetic Drugs. In: Gropper MA, (ed) *Miller's Anesthesia*. 9th edn. Philadelphia: Elsevier 2020; 294-332.

10 Kondo Y, Sakatani K, Hirose N*, et al.* Effect of spinal anesthesia for elective cesarean section on cerebral blood oxygenation changes: comparison of hyperbaric and isobaric bupivacaine. *Adv Exp Med Biol*. 2013; **765**: 109-14.

11 Hirose N, Kondo Y, Maeda T, Suzuki T, Yoshino A. Relationship between regional cerebral blood volume and oxygenation and blood pressure during spinal anesthesia in women undergoing cesarean section. *J Anesth*. 2016; **30**: 603-9.

12 Fujisaki S, Osaki T, Suzuki T*, et al.* A clinical tissue oximeter using NIR time-resolved spectroscopy. In: Elwell CE, Leung TS, Harrison DK, (eds) *Oxygen Transport to Tissue XXXVII, Advances in Experimental Medicine and Biology 1st ed*. New York:

Springer 2016; 427-33.

13 Tanaka N, Yamamoto M, Abe T*, et al.* Changes of Cerebral Blood Volume During Robot-Assisted Laparoscopic Radical Prostatectomy: Observational Prospective Study Using Near-Infrared Time-Resolved Spectroscopy. *J Endourol*. 2019; **33**: 995-1001.

14 Suzuki K, Itoh H, Mukai M*, et al.* Measurement of maternal cerebral tissue hemoglobin on near-infrared time-resolved spectroscopy in the peripartum period. *J Obstet Gynaecol Res*. 2015; **41**: 876-83.

15 Yamazaki K, Suzuki K, Itoh H*, et al.* Cerebral oxygen saturation evaluated by near-infrared time-resolved spectroscopy (TRS) in pregnant women during caesarean section - a promising new method of maternal monitoring. *Clin Physiol Funct I*. 2013; **33**: 109-16.

16 Yagi Y, Yamamoto M, Saito H*, et al.* Changes of Cerebral Oxygenation in Sequential Glenn and Fontan Procedures in the Same Children. *Pediatr Cardiol*. 2017; **38**: 1215-9.

17 Berlac PA, Rasmussen YH. Per-operative cerebral near-infrared spectroscopy (NIRS) predicts maternal hypotension during elective caesarean delivery in spinal anaesthesia. *Int J Obstet Anesth*. 2005; **14**: 26-31.

18 Kato S, Yoshitani K, Kubota Y, Inatomi Y, Ohnishi Y. Effect of posture and extracranial contamination on results of cerebral oximetry by near-infrared spectroscopy.

J Anesth. 2017; **31**: 103-10.

19 Wilson MH. Monro-Kellie 2.0: The dynamic vascular and venous pathophysiological components of intracranial pressure. *J Cereb blood Flow Metab*. 2016; **36**: 1338-50.

20 Kondo Y, Hirose N, Maeda T, Yoshino A, Suzuki T. Relationship between changes in regional cerebral blood volume and oxygenation and changes in cardiac output and systemic vascular resistance during spinal anesthesia in women undergoing cesarean section. *J Anesth*. 2019; **33**: 579-86.

21 Xu C, Liu S, Huang Y, Guo X, Xiao H, Qi D. Phenylephrine vs ephedrine in cesarean delivery under spinal anesthesia: A systematic literature review and meta-analysis. *Int J Surg (London, England)*. 2018; **60**: 48-59.

22 Semiz A, Akpak YK, Yılanlıoğlu NC*, et al.* Prediction of intraoperative nausea and vomiting in caesarean delivery under regional anaesthesia. *J Int Med Res.* 2017; **45**: 332-9.

23 Kinsella SM, Carvalho B, Dyer RA*, et al.* International consensus statement on the management of hypotension with vasopressors during caesarean section under spinal anaesthesia. *Anaesthesia*. 2018; **73**: 71-92.

24 Practice Guidelines for Obstetric Anesthesia: An Updated Report by the American Society of Anesthesiologists Task Force on Obstetric Anesthesia and the

Society for Obstetric Anesthesia and Perinatology. *Anesthesiology*. 2016; **124**: 270-300.

25 Meng L, Cannesson M, Alexander BS*, et al.* Effect of phenylephrine and ephedrine bolus treatment on cerebral oxygenation in anaesthetized patients. *Brit J Anaesth*. 2011; **107**: 209-17.

26 Nissen P, Brassard P, Jørgensen TB, Secher NH. Phenylephrine but not ephedrine reduces frontal lobe oxygenation following anesthesia-induced hypotension. *Neurocrit Care*. 2010; **12**: 17-23.

27 Foss VT, Christensen R, Rokamp KZ, Nissen P, Secher NH, Nielsen HB. Effect of phenylephrine vs. ephedrine on frontal lobe oxygenation during caesarean section with spinal anesthesia: an open label randomized controlled trial. *Front Physiol*. 2014; **5**: 81.

28 Guerci P, Vial F, Feugeas J*, et al.* Cerebral oximetry assessed by near-infrared spectrometry during preeclampsia: an observational study: impact of magnesium sulfate administration. *Crit Care Med*. 2014; **42**: 2379-86.

29 Karademir A, Erdogan Kayhan G. Cerebral oxygen saturation monitoring in preeclamptic pregnant women undergoing cesarean section with spinal anesthesia: a prospective, observational study. *J Clin Monit Comput*. 2019; **33**: 833-41.

30 Jones-Muhammad M, Warrington JP. Cerebral Blood Flow Regulation in Pregnancy, Hypertension, and Hypertensive Disorders of Pregnancy. *Brain Sci.* 2019; **9**:224

Figure legends

Figure 1 Changes in mean arterial pressure (MAP) and cerebral hemodynamics over time

A Changes in MAP

B Changes in ScO_2

C Changes in tHb

D Changes in Vm

Data are expressed as mean ± SD.

Compared with control, * indicates $P<0.01$, # indicates $P=0.01$ and $ indicates $P=0.03$ by Bonferroni multiple comparison.

Control: before spinal anesthesia in the supine position

Tx: x minutes after spinal anesthesia in the supine position

Figure 2 Comparison of MAP (A), Vm (B) and ScO_2 (C) with or without nausea in the 14 patients who complained of nausea

For MAP and ScO_2, the values were 31 with nausea and 81 without nausea. For Vm they

were 17 with nausea and 39 without nausea.

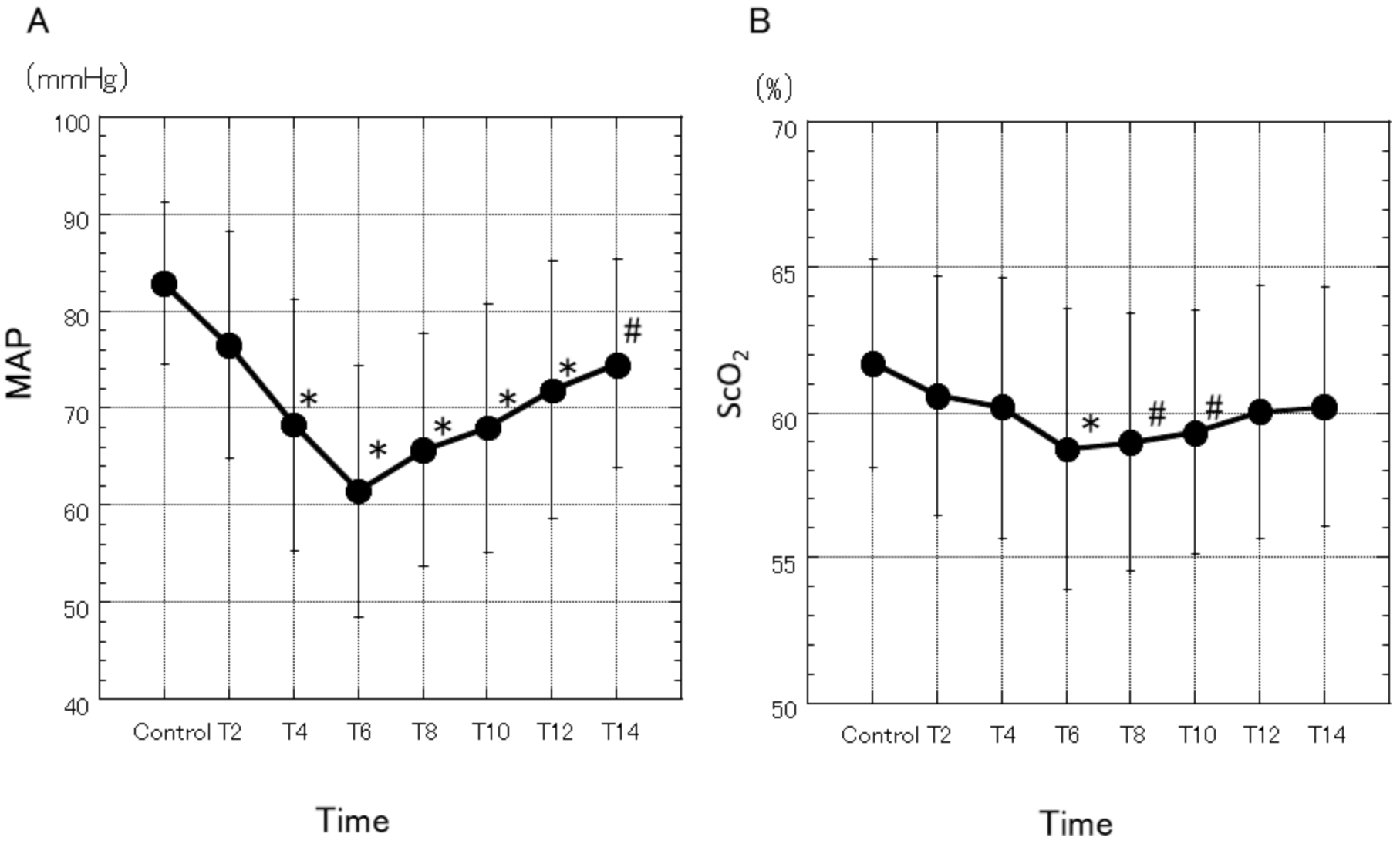
Data are expressed as mean ± SD.

In all the variables, $P<0.01$ was observed by the unpaired t-test.

Table Demographic and clinical data

Age (years)	32.4±5.7
Height (cm)	157.0±5.0
Weight (kg)	60.0±8.5
Gestational age (weeks)	38 (35-38)
Dose of bupivacaine (mg)	10 (10-10)
Dose of fentanyl (μg)	15 (5-20)
Block height, dermatome	Th4 (Th3-Th4)
Fluids (ml)	1000 (850-1150)
Blood Loss (including amniotic fluid)	837±296
Dose of ephedrine (mg)	8 (4-8)
left uterine displacement +/-	9/16
Trendelenburg position +/-	2/23
Nausea +/-	14/11
Birth weight (g)	2740±448
Apgar score	
1min	8 (8-8)
5min	8 (8-9)
Umbilical cord blood pH	7.27±0.06

Data of normality were expressed as mean ± standard deviation (SD) and others as median (25%-75% interquartile range; IQR) except American Society of Anesthesiologists Physical Status Classification (ASA-PS).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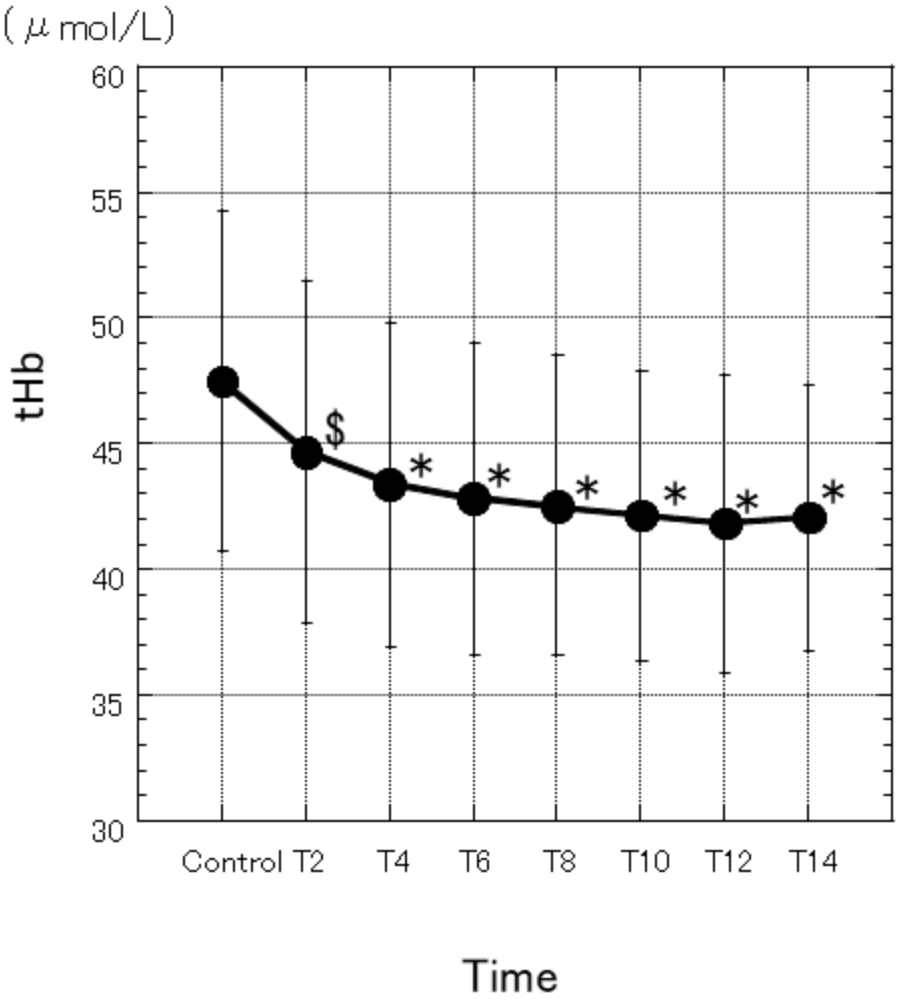
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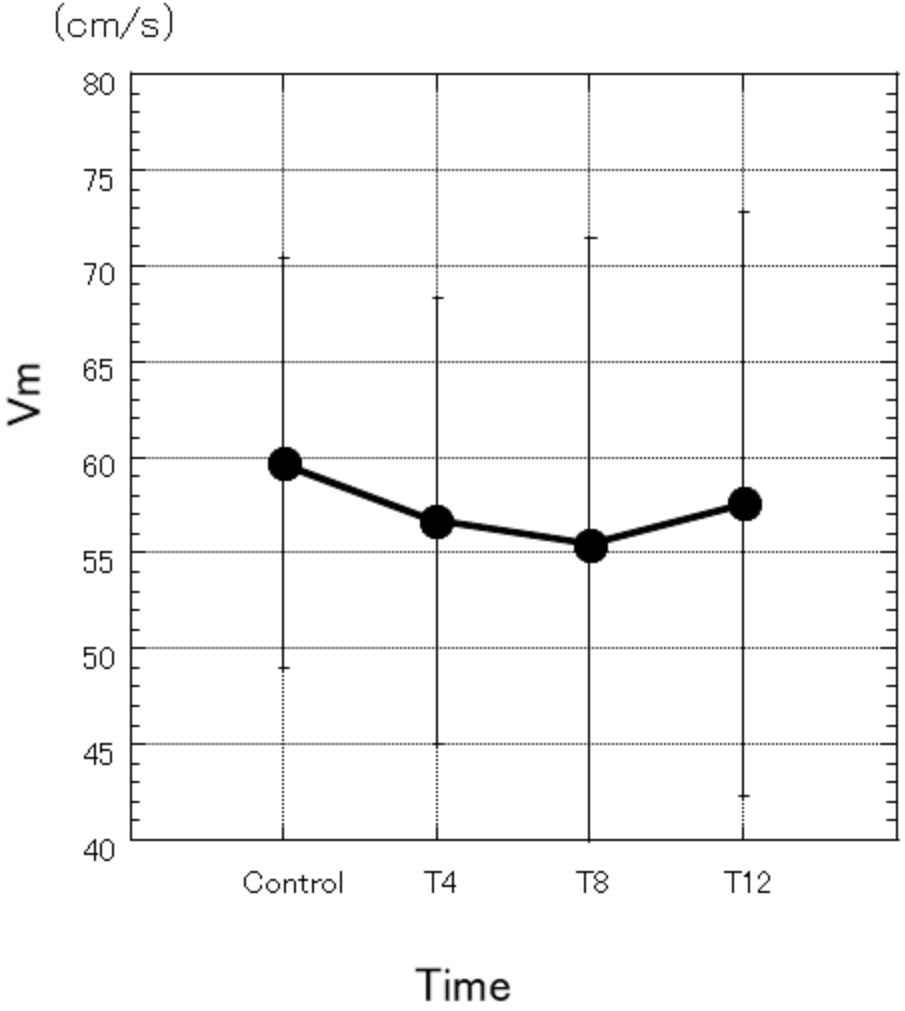
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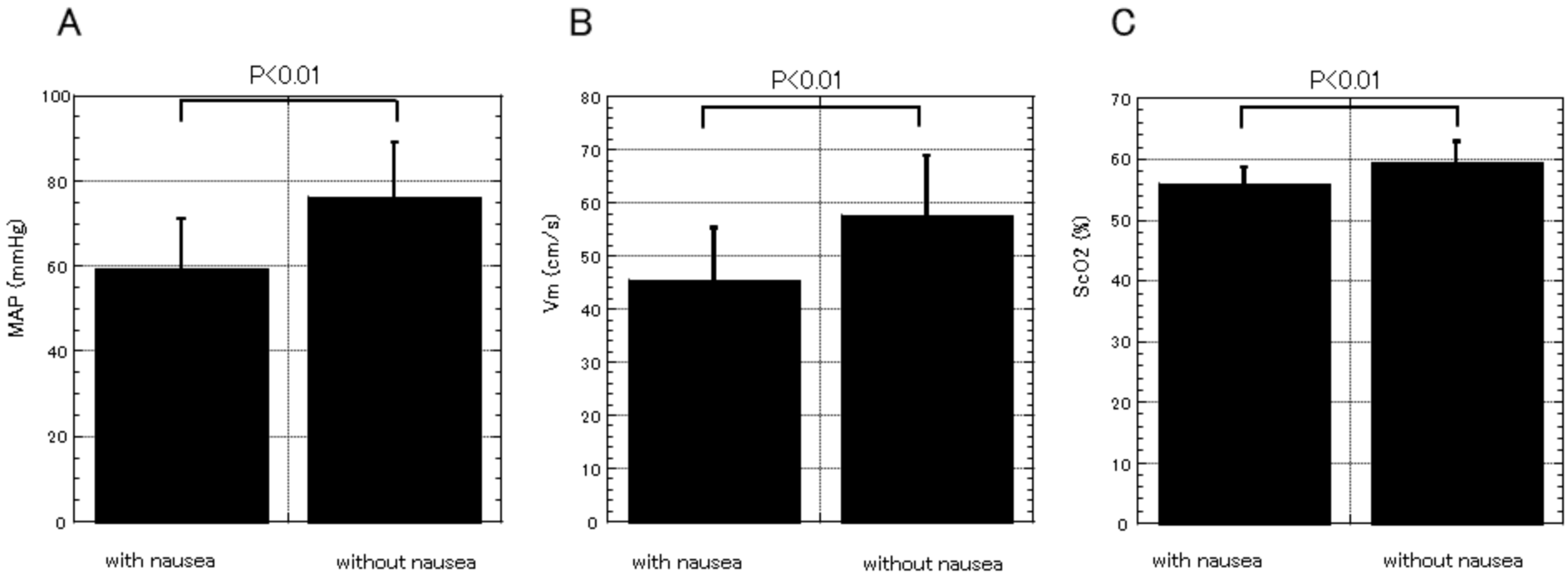
40
Vm
Control T4 T8 T12
Time


A
P<0.01
MAP (mmHg)
100
80
60
40
20
0
with nausea
without nausea
B
P<0.01
Vm (cm/s)
80
70
60
50
40
30
20
10
0
with nausea
without nausea
C
P<0.01
ScO2 (%)
70
60
50
40
30
20
10
0
with nausea
without nausea