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Title: Effects of ephedrine and phenylephrine on cerebral oxygenation: Observational prospective study using near-infrared time-resolved spectroscopy

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Abstract

It has been reported that cerebral oxygenation (ScO_2) measured by near infrared spectroscopy is maintained or increased by treatment with ephedrine, whereas almost all previous reports demonstrated that phenylephrine reduced ScO_2 . As the mechanism of the latter, the interference of the extracranial blood flow, that is extracranial contamination, has been suspected. Accordingly, in this prospective observational study, we utilized time-resolved spectroscopy (TRS), in which the effect of extracranial contamination is thought to be minimal, and evaluated whether the same result was obtained.

We measured the changes in ScO_2 as well as the total cerebral hemoglobin concentration (tHb) after treatment with ephedrine or phenylephrine during laparoscopic surgery by using a tNIRS-1 (Hamamatsu Photonics, Hamamatsu, Japan), which is a commercial instrument utilizing TRS. Based on a mixed-effects model with random intercepts for ScO_2 or tHb including mean blood pressure, the mean difference and 95% confidence interval were evaluated as well as the predicted mean difference and its confidence interval using the interquartile range of mean blood pressure.

Fifty treatments with ephedrine or phenylephrine were done. The mean differences of ScO_2 were less than 0.1% and the predicted mean differences were less than 1.1% for the two drugs. The mean differences of tHb were less than 0.02 μM and the predicted mean differences were less than 0.2 μM for the drugs.

The changes in ScO_2 and tHb after treatments with ephedrine and phenylephrine were very small and clinically insignificant when measured by TRS. Previous reports about

phenylephrine may have been affected by extracranial contamination.

Key Words:

ephedrine, phenylephrine, cerebral oxygenation, near infrared spectroscopy, time-resolved spectroscopy

Introduction

Ephedrine and phenylephrine are widely used for the treatment of intraoperative hypotension. It has been reported that cerebral oxygenation (ScO_2) measured by near infrared spectroscopy (NIRS) is maintained or increased by treatment with ephedrine [1-4]. By contrast, almost all the previous reports demonstrated that phenylephrine reduced ScO_2 by from 3-20% [1-5]. The mechanism of the reduction in ScO_2 by phenylephrine has not been fully clarified. The most plausible mechanism for this reduction is a decrease in cardiac output induced by phenylephrine [3-5]. It increases sympathetic nerve activity reflexively, which constricts cerebral resistance vessels indirectly [3,4]. Another possible mechanism for the reduction in the measured values is the interference of the extracranial blood flow with the ScO_2 values, that is, extracranial contamination, which is an inherent limitation of NIRS [3,4].

Indeed, the value of ScO_2 measured by near-infrared spectroscopy is affected by scalp blood flow beneath the sensor [6]. In one previous study, ScO_2 measured using the INVOS 4100 (Covidien, Mansfield, MA) decreased by 19% after continuous infusion of phenylephrine while mean arterial pressure (MAP) was increased from the baseline by 30mmHg [7]. External carotid arterial blood flow and skin blood flow of the forehead also decreased by about 25% and there was a significant relationship with the decrease in ScO_2 . In another study, extracranial hypoxia-ischemia was induced by a circumferential pneumatic head cuff and the changes in ScO_2 were compared among the several near infrared spectroscopes that employed different algorithms [8]: the INVOS 5100C and

EQUANOX Classic 7600 (Nonin Medical Inc., Plymouth, MN), which employs spatially resolved spectroscopy (SRS), and the FORE-SIGHT (CAS Medical System, Brandford, CT), which employs the modified Beer-Lambert (MBL) law. After inflation of the head cuff, ScO_2 measured by the INVOS 5100C, FORE-SIGHT and EQUANOX Classic 7600 decreased by 16.6%, 11.8% and 6.8%, respectively. In another study using the same protocol, ScO_2 measured by the INVOS 5100C, FORE-SIGHT and NIRO-TRS (Hamamatsu Photonics, Hamamatsu, Japan), which utilizes time-resolved spectroscopy (TRS), decreased by 21.3%, 14.3% and 3.6%, respectively [9]. Thus, the influence of extracranial contamination depends on the difference of instruments (algorithms) and its effect seems to be minimal with the TRS method.

MBL and SRS employ continuous wave light and cannot measure the path lengths of the beams. On the other hand, TRS employs short pulse beams and yields a precise path length estimate, which enables measurement of the cerebral hemoglobin concentration [6]. Accordingly, ScO_2 was accurately calculated from the percentage of the oxygenated hemoglobin concentration compared with the total hemoglobin concentration. TRS is well-known for its superiority over the SRS and MBL methods with respect to the correctness and reproducibility of the measured data [10]. For example, as to the correctness, good correlation was observed between the hemoglobin concentration in the blood phantom and the total hemoglobin concentration measured by TRS [10]. For the reproducibility, it was demonstrated that standard deviations obtained by repeating measurements at six different positions on the forehead were 2.1% for the TRS method

and 5.1% for the SRS method [10]. In clinical settings such as cardiopulmonary bypass surgery [11] and carotid endarterectomy [12], it was reported that good correlation was observed between the ScO_2 measured by TRS and the jugular venous oxygen saturation.

In addition, the absolute value of the total cerebral hemoglobin concentration (tHb), reflects cerebral blood volume (CBV) [13,14]. CBV is another index of cerebral hemodynamics and indicates total arterial and venous blood volume in the brain [14]. As far as we know, there have been no studies to evaluate the changes in ScO_2 and tHb after treatment with ephedrine or phenylephrine by using an oximeter which utilized TRS. Accordingly, in this prospective observational study, we measured the changes in these variables after treatment with ephedrine or phenylephrine during laparoscopic surgery by using the tNIRS-1 (Hamamatsu Photonics, Hamamatsu, Japan), which is a commercial instrument using TRS.

Materials and Methods

This study was a prospective observational study approved by the ethics committee of the Hokkaido University Hospital (No. 017-0490). It was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and Good Clinical Practice. Written informed consent was obtained from all patients. It was registered in the UMIN Clinical Trials Registry prior to patient enrollment (UMIN000033310). Patients with ASA physical status classification 1 or 2 who were scheduled to undergo laparoscopic procedures in our university hospital were enrolled. Exclusion criteria were: 1) cardiovascular diseases of NYHA classification 2 or above, 2) cerebral diseases, 3) uncontrolled hypertension with systolic blood pressure of 160 mmHg or more, and 4) uncontrolled diabetes mellitus with HbA1c of 7.0% or more.

General anesthesia was performed using sevoflurane or desflurane with remifentanyl or propofol with remifentanyl. Neuromuscular blockade was achieved with rocuronium. After the induction of anesthesia, monitoring of invasive blood pressure from the radial artery was started. The sensors of the tNIRS-1 were placed on both sides of the forehead and the absolute values of cerebral oxygenated hemoglobin (O_2Hb) and deoxygenated hemoglobin (HHb) concentrations were continuously collected every 5 seconds. The tHb was obtained by summing O_2Hb and HHb. ScO_2 was derived from the percentage of O_2Hb compared with tHb. Left and right values were averaged.

During surgery, hypotension was treated with 4-8mg of ephedrine or 0.05-0.2 mg of

phenylephrine. The timing of treatment and selection of the drugs were entrusted to the judgement of the anesthesiologists in charge. After the treatment, we observed the changes in blood pressure and indices of tNIRS-1 with the anesthetic management for 10 minutes. When there were no additional treatments with drugs for this duration and when there were no changes in the concentrations of anesthetics, speed of infusion, setting of mechanical respiration, the patient's position and conditions of pneumoperitoneum for the same period, we recorded 1-minute averages of ScO_2 and tHb at two points, just before the injection of ephedrine or phenylephrine and when the MAP maximally increased.

Statistical Analysis

The primary objective was to observe the changes in ScO_2 after treatment with ephedrine or phenylephrine. The secondary objective was to evaluate changes in tHb after treatment with ephedrine or phenylephrine. In a previous study using a prototype near infrared TRS instrument, the NIRO-TRS, the standard deviation of ScO_2 was 2-5% [9]. For a two-sided 95% confidence interval with a normal mean, assuming a standard deviation of 5%, a sample size of 50 is required to obtain a half-width of at most 1.4%.

Continuous variables were expressed as median values [interquartile range (IQR)s]. We fitted the regression model of the change in ScO_2 or tHb including the ephedrine- or phenylephrine-induced change in MAP as an explanatory variable, and a random intercept of patients' identifiers to account for multiple measurements in the same patients. We presented the mean difference changes by 1 mmHg and changes of the IQR for each

explanatory variable with a 95% CI. R version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria at <https://www.R-project.org/>) was used to create charts and summarized the data.

Results

The study was performed in 23 patients. However, 2 patients were excluded due to insufficient acquisition of the tNIRS-1 data. Among the remaining 21 patients, 50 treatments with ephedrine were done in 18 patients and 50 treatments with phenylephrine were done in 14 patients. Patient demographic data are shown in Table 1. There was a trend for older patients to be treated with phenylephrine. Among inhaled anesthetics, desflurane was used for 10 patients and sevoflurane for 8 patients. Desflurane was used for 7 patients treated with ephedrine and 9 patients treated with phenylephrine.

Table 2 shows the intraoperative physiological values and cerebral oxygenation indices. After injection of ephedrine, median MAP increased by about 10 mmHg. Heart rate slightly increased, but there were almost no changes in SpO₂, ETCO₂ or body temperature, which parameters may affect ScO₂ values [15]. Median ScO₂ increased by only 0.5% (Figure), while median tHb decreased by only 0.3 μ M. After injection of phenylephrine, median MAP increased by about 17 mmHg. Heart rate decreased by 5 bpm, but there were almost no changes in other parameters. Median ScO₂ decreased by 1.2% (Figure), while median tHb did not change.

Based on the mixed-effects model with random intercepts for MAP with ephedrine, the mean difference and its 95% confidence interval of changes in ScO₂ and tHb were 0.100% [95%CI: 0.039, 0.155] and 0.018 μ M [95%CI: -0.004, 0.040], respectively (Table 3). With phenylephrine, the mean difference by 1 mmHg and its 95% confidence interval of

changes in ScO₂ and tHb were 0.047% [95%CI: -0.0003, 0.093] and 0.02 μ M [95%CI: 0.001, 0.038] (Table 3), respectively. The mean difference changing by IQR and its confidence interval determined by the interquartile range of MAP in ephedrine were 1.099 % [95%CI: 0.427, 1.701] for ScO₂ and 0.203 μ M [95%CI: -0.042, 0.435] in tHb (Table 3), respectively. The mean difference changes by the IQR and their confidence intervals determined by the interquartile range of MAP for phenylephrine were 0.421 % [-0.003, 0.840] for ScO₂ and 0.177 μ M [0.01, 0.343] for tHb, respectively (Table 3).

Discussion

In this prospective observational study, we observed the changes in ScO₂ and tHb after bolus injection of ephedrine or phenylephrine by using near-infrared TRS, which is considered to be the least susceptible to extracranial contamination among those measuring instruments using various algorithms. It is reported that normal tHb is about 85 μ M [16]. Therefore, the changes in ScO₂ and tHb were very small and seemed to be clinically insignificant, although MAP sufficiently increased.

Several reports have indicated that ScO₂ is maintained or increased by treatment with ephedrine [1-4], which is consistent with our results. Ephedrine increases [1] or preserves [2] cardiac output. The blood flow velocity of the middle cerebral artery measured by transcranial Doppler sonography did not change after the continuous infusion of ephedrine in a healthy volunteer, although MAP increased by about 20 mmHg [17]. Recent studies using positron emission tomography (PET) and magnetic resonance

imaging (MRI) have demonstrated that the continuous infusion of ephedrine increases cerebral blood flow in both the peritumoral area and contralateral hemisphere in anesthetized brain tumor patients [18,19]. These findings support the concept that ScO_2 is maintained or increased by treatment with ephedrine. In addition, external carotid artery flow measured by duplex ultrasonography was maintained after bolus injection of ephedrine in healthy volunteers [20]. Accordingly, constant results may be obtained whatever algorithms of NIRS are used.

In our study, the decrease in ScO_2 after phenylephrine treatment was small and clinically insignificant, which was inconsistent with previous studies [3-5]. First, almost all previous studies except two used INVOS devices [2,4], in which the influence of extracranial contamination was reported to be more than 15% of the ScO_2 values [8,9]. In the remaining 2 reports, the Oxiplex TS (ISS, Inc., Champaign IL., USA), a quantitative frequency NIRS device [2,21], was used. There has been no information about extracranial contamination with the use of that device; however, the decrease in ScO_2 measured was less than 5% [2,21]. Second, it was consistently demonstrated that cerebral blood flow increased after treatment with phenylephrine, regardless of whether the methodology was transcranial Doppler sonography [22], duplex ultrasonography [20], PET [18] or MRI [19]. It is reported that cerebral oxygen saturation can be expressed as a function of SaO_2 , the blood hemoglobin concentration, cerebral blood flow, and the cerebral metabolic rate for oxygen, assuming that the ratio of blood components between the cerebral arterial and cerebral venous vascular beds remains constant [23]. Accordingly,

an increase in cerebral blood flow may rather work in the direction of an increase in ScO_2 . On the other hand, if the ratio of blood components changes, possibly due to cerebral vasoconstriction, there is possibility of a decrease in ScO_2 contrary to the increase in cerebral blood flow. However, whether the ratio really changes has not been proven yet. In addition, a recent report using MRI demonstrated that brain tissue oxygen tension was increased to around 1.2 times by treatment with phenylephrine, whereas ScO_2 measured by the INVOS decreased by about 4% [19].

CBV was calculated by using a conversion formula with tHb and blood Hb[13,14].

The formula used was:

$$\text{CBV} = \text{tHb} \times \text{MW}_{\text{Hb}} \times (\text{blood Hb} \times \eta \times \rho \times 100000)^{-1}$$

where MW_{Hb} is the molecular weight of hemoglobin, 64500; η is the cerebral-to-large-vessel hematocrit ratio, 0.85; and ρ is the density of cerebral tissue, 1.04.

Because it was supposed that blood Hb did not change for less than 5 min during the measurement periods in our study, changes in tHb could reflect changes in CBV. It is reported that CBV, but not cerebral blood flow, influences intracranial pressure and that changes in cerebral blood flow do not reliably predict changes in CBV [15]. In our study, tHb showed almost no changes after bolus injection of ephedrine or phenylephrine. There are few reports about the effects of these drugs on CBV. A study using MRI showed that CBV was increased by ephedrine or phenylephrine in both the peritumoral area and

contralateral hemisphere in anesthetized brain tumor patients [19]. However, only one study using NIRS (Oxiplex TS) showed that phenylephrine caused a decrease in CBV of 3% during hypocapnia, although there were no changes during normocapnia or hypercapnia [21]. In our study, the patients were managed by normocapnia and the result was the same as in that study.

As one of the limitations of this study, there were 11 patients who received both of the drugs several times. Accordingly, a crossover effect of two drugs cannot be excluded and it might be that the effect of treatment averaged out. Second, the timing of treatment and selection of the drugs were entrusted to the judgement of the anesthesiologists in charge. Therefore, the choice of ephedrine or phenylephrine may have been subjected to individual bias. Third, no definition or cause of hypotension was provided. In our study, the median MAP at the time of treatment was at the 50 mmHg level in both groups. Accordingly, the degree of hypotension might not have been severe. Fourth, the degree of increase in blood pressure was different for the two drugs. If the increase in blood pressure induced by ephedrine was the same as that induced by phenylephrine, the changes in ScO_2 and tHb might be greater. Fifth, we used sevoflurane, desflurane or propofol for the maintenance of anesthesia. Because the effect of cerebral circulation is different among anesthetics [15], the responses of ScO_2 and tHb might be different, although the actual changes were small regardless of their type. Finally, we did not strictly fix the $PaCO_2$ values at the time of treatment. However, as shown in Table 2, the median pre and post $ETCO_2$ values were from 38-40 mmHg. Accordingly, we consider that the

effect of PaCO₂ was minimal.

In conclusion, this prospective observational study using near-infrared time-resolved spectroscopy, which is considered to be the least susceptible to extracranial contamination among various algorithms, under the anesthetic management of patients with ASA physical status 1 or 2 showed that the differences in ScO₂ and tHb were very small and clinically insignificant after bolus injection of ephedrine or phenylephrine. Previous reports about phenylephrine may have been affected by extracranial contamination. Accordingly, we may be able to choose either one for the maintenance of general circulatory states such as the blood pressure and heart rate during anesthetic management. In the future, it will be necessary to perform a randomized controlled study using only one drug for each patient under the same physiological and anesthetic conditions using this spectroscopy.

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Figure legend

Figure

Box plot of ScO₂ values with the treatment using ephedrine or phenylephrine

pre: at the injection of ephedrine or phenylephrine

post: when the mean arterial pressure (MAP) maximally increased

white horizontal bar indicates median value.

Statements & Declarations

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Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Author Contributions

Conceptualization: [Yasunori Kubo, Yuji Morimoto]; Methodology: [Yasunori Kubo, Tomonori Kubo, Yuji Morimoto]; Formal analysis and investigation: [Isao Yokota, Takayuki Toki, Yasunori Kubo, Yuji Morimoto]; Writing - original draft preparation: [Yasunori Kubo, Takayuki Toki]; Writing - review and editing: [Yuji Morimoto]

Ethics approval

This study was approved by the ethics committee of the Hokkaido University Hospital (No. 017-0490). This was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and Good Clinical Practice.

Consent to participate

Written informed consent was obtained from all individual participants included in the study.

Table 1 Patient demographic data

	All	Ephedrine	Phenylephrine
Number	21	18	14
Age (years)	64 [57, 73]	64 [56, 73]	73 [63, 75]
Sex Female/Male	10/11	9/9	7/7
Height (m)	162 [159, 168]	162 [159,168]	162 [156, 163]
Weight (kg)	63 [55, 71]	65 [57, 71]	62 [52, 71]
ASA PS 1/2	10/11	8/10	8/6
Comorbidities			
None	8	7	6
Hypertension	9	8	5
Hyperlipidemia	5	4	4
Obesity	4	4	2
DM	4	4	2
RA	1	1	1
Diseases			
Colon cancer	12	11	6
Gastric cancer	5	4	5
Uterine cancer	2	2	2
Pancreatic cancer	2	1	1
Surgery time (min)	186 [139, 269]	220 [142, 278]	218 [168, 361]
Anesthetic time (min)	292 [237, 339]	313 [240, 349]	312 [258, 460]
Anesthetic methods			
Inhaled	18	15	13
Intravenous	3	3	1

The values of age, height, weight surgery time and anesthetic time are shown as medians [interquartile range]. The numbers of comorbidities, diseases, and anesthetic methods are the ones for all 21 patients, 18 ephedrine-treated patients and 14 phenylephrine-treated patients.

Table 2 Intraoperative physiological values and cerebral oxygenation indices

	Ephedrine	Phenylephrine
Number	50	50
Time (min) between pre and post	4 [3.5]	2 [2, 3]
mean arterial pressure (mmHg)		
pre	56 [52, 62]	57 [53, 61]
post	70 [62, 74]	74 [67, 80]
changes	10 [6, 17]	17 [14, 23]
systolic arterial pressure (mmHg)		
pre	82 [78, 90]	85 [79, 92]
post	103 [94, 114]	114 [102, 124]
diastolic arterial pressure (mmHg)		
pre	42 [39, 47]	42 [39, 47]
post	50 [47, 55]	54 [51, 59]
Heart rate (bpm)		
pre	60 [56, 65]	66 [60, 69]
post	62 [57, 67]	61 [58, 65]
SpO ₂ (%)		
pre	99 [97, 100]	98 [96, 100]
post	99 [98, 100]	98 [97, 100]
ETCO ₂ (mmHg)		
pre	38 [35, 39]	39 [37, 40]
post	39 [37, 41]	40 [38, 41]
body temperature (°C)		
pre	36.6 [36.5, 37.1]	36.5 [36.4, 36.8]
post	36.6 [36.5, 37.1]	36.5 [36.4, 36.8]
ScO ₂ (%)		
pre	59.4 [57.1, 63.3]	62.3 [59.3, 64.4]
post	60.5 [57.5, 63.8]	60.5 [59.5, 64.6]
changes	0.55 [0.10, 1.17]	-1.20 [-2.00, -0.12]
tHb (μM)		
pre	49 [43, 57]	55 [49, 57]
post	48 [43, 58]	55 [49, 57]
change	-0.30 [-0.70, 0.10]	0.00 [-0.30, 0.27]

pre: at the injection of ephedrine or phenylephrine

post: when the mean arterial pressure (MAP) maximally increased

SpO₂: oxygen saturation of peripheral artery, ETCO₂: end-tidal carbon dioxide partial pressure

The values are shown as medians [interquartile range].

Table 3 Mixed effects model with random-intercepts for MAP

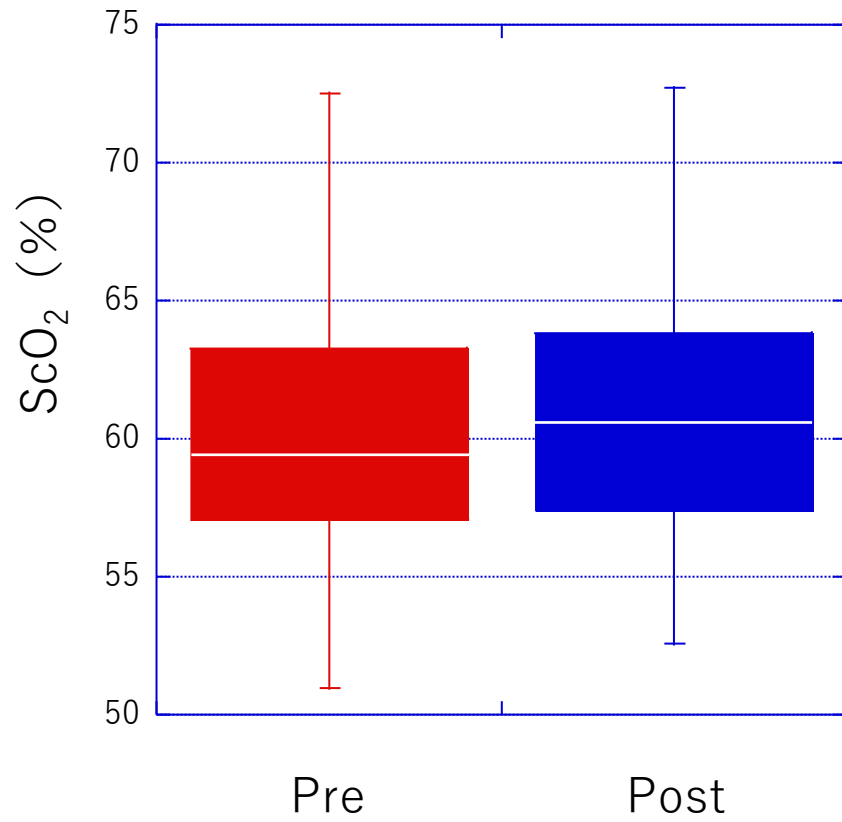
change in ScO₂ (%)

	inter-quartile range	mean difference change by 1 mmHg	95%CI		mean difference change by IQR of each exploratory variable	95%CI	
Ephedrine							
change in MAP	6-17	0.100	0.039	0.155	1.099	0.427	1.701
Phenylephrine							
change in MAP	14-23	0.047	-0.0003	0.093	0.421	-0.003	0.840

change in tHb (μM)

	inter-quartile range	mean difference change by 1 mmHg	95%CI		mean difference changing by IQR of each exploratory variable	95%CI	
Ephedrine							
change in MAP	6-17	0.018	-0.004	0.040	0.203	-0.042	0.435
Phenylephrine							
change in MAP	14-23	0.020	0.001	0.038	0.177	0.010	0.343

Ephedrine



Phenylephrine

