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Effects of intravenously administered indocyanine green on near-infrared cerebral oximetry and pulse oximetry readings

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Background: Intravenously administered indocyanine green (ICG) may cause misreadings of cerebral oximetry and pulse oximetry in patients undergoing carotid endarterectomy under general anesthesia. The present study determined the effects of two different doses (12.5 mg vs. 25 mg) of ICG on regional cerebral tissue oxygen saturation ($SctO_2$) and percutaneous peripheral oxygen saturation (SpO_2).

Methods: Twenty-six patients receiving ICG for videoangiography were divided into two groups according to the dosage (12.5 mg and 25 mg, n = 13 in each group). Heart rate, arterial blood pressure, $SctO_2$, and SpO_2 were measured before and after an intravenous bolus administration of ICG.

Results: Following the dye administration, no changes in heart rate or arterial blood pressure were noted in either group. $SctO_2$ was increased in both groups; however, the magnitude of the increase was greater (21.6 ± 5.8% vs. 12.6 ± 4.1%, P < 0.0001) and more prolonged (28.4 ± 9.6 min vs. 13.8 ± 5.2 min, P < 0.0001) in the 25 mg group than in the 12.5 mg group. In contrast, SpO_2 was decreased in both groups; the magnitude of the decrease was greater in the 25 mg group than in the 12.5 mg group (4.0 ± 0.8% vs. 1.6 ± 1.0%, P < 0.0001). There were no differences in the time to reach the peak $SctO_2$ or to reach the nadir SpO_2 between the two groups.

Conclusions: In patients given ICG for videoangiography, a 25 mg bolus results in a greater and more prolonged increase in $SctO_2$ and a greater reduction in SpO_2 than a 12.5 mg bolus, with no differences in the time to reach the peak $SctO_2$ or to reach the nadir SpO_2.

Key Words: Cerebral oximetry, Cerebral oxygenation, Indocyanine green, Near-infrared spectroscopy, Pulse oximetry.

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Introduction

It is well established that intravenously administered vital dyes having absorption spectra used by optical-technology-based monitors interfere with oximetry readings. They may then result in misreadings of percutaneous oxygen saturation (SpO_2) measured via pulse oximetry, although it is transient [1,2].

Cerebral near-infrared spectroscopy (NIRS), which provides real-time information on the balance between cerebral oxygen supply and demand, also uses infrared light to estimate regional

cerebral tissue oxygen saturation ($SctO_2$) [3,4]. It is now being increasingly used to guide intraoperative optimization of cerebral oxygenation in patients undergoing procedures associated with a high risk of adverse neurologic outcomes [5]. However, among others, methylene blue [6] and indigo carmine [7] may interfere with NIRS-based cerebral oximetry readings.

Indocyanine green (ICG) is a strong near-infrared absorber having preferable fluorescent characteristics. It has been used to visualize the blood stream during neurosurgery [8], being particularly useful for observing the patency of extracranial–intracranial bypass [9], for complete aneurysm clipping [10], or for the intraoperative evaluation of carotid endarterectomy (CEA) [11]. Many new intraoperative applications of ICG and ICG angiography are emerging [12,13].

We have recently documented a constant and immediate increase in $SctO_2$ readings with the INVOS® device in patients undergoing neurosurgery during which an IV bolus of 12.5 mg ICG (approximately 0.25 mg/kg) was administered for videoangiography [14]. However, two dosages of ICG (12.5 mg or 25 mg) are frequently used in clinical practice, while its recommended dose for standard diagnostic procedures ranges between 0.1 and 0.5 mg/kg with a maximum daily dose of 5 mg/kg [10]. The magnitude and the duration of $SctO_2$ misreading may vary as a function of different doses of ICG. The current study aimed to determine the oximetry readings ($SctO_2$ and SpO_2) using two different doses (12.5 mg vs. 25 mg) of ICG during CEA under general anesthesia. Cerebral oximetry and near-infrared-ICG videoangiography have been used simultaneously for many years in patients undergoing neurovascular surgeries on a routine basis in our hospital.

Materials and Methods

After receiving the University Hospital Ethics Committee approval, written informed consent was obtained from all of the patients. Twenty-six patients of American Society of Anesthesiologists (ASA) physical status I–III scheduled for CEA under general anesthesia with tracheal intubation were assigned to either the 12.5 mg group or the 25 mg group, based on a computer-generated randomization list. Exclusion criteria included liver or renal insufficiency, known iodine or ICG hypersensitivity, and ASA physical status IV or V.

Patients were premedicated with midazolam 0.1 mg/kg orally 60 min before being transported to the operating room. Upon arrival in the operating room, standard monitoring including electrocardiography, noninvasive measurement of systemic blood pressure, pulse oximetry, capnography, and bispectral index monitoring (BIS® system; Aspect Medical Systems, Newton, MA, USA) was applied throughout the procedure. A 20-gauge radial arterial catheter was placed in either wrist of each subject under local anesthesia with 1% lidocaine to monitor blood pressure and to take blood samples if necessary. Pulse oximetry finger probe (Ohmeda Biox 3700, Ohmeda, Louisville, CO, USA) was placed on the index finger of the hand. Two adhesive cerebral oximeter probes were applied to the forehead before induction of anesthesia to continuously measure $SctO_2$ using the INVOS® 5100B cerebral oximeter (INVOS®, Somanetics; Troy, MI, USA). $SctO_2$ values contralateral to the side of surgery were used to determine cerebral oxygenation.

After preoxygenation, anesthesia was induced with IV propofol (1 to 2 mg/kg) and remifentanil (1 μg/kg), and maintained with sevoflurane (1.5 to 2.0%) and remifentanil (0.03 to 0.12 μg/kg/min). Rocuronium was used for initiation and maintenance of muscle relaxation. Patients were mechanically ventilated after tracheal intubation with an oxygen/air mixture at 0.5 fraction of inspired oxygen to maintain the end-tidal carbon dioxide tension between 35 and 40 mmHg throughout the surgery.

During the surgery, near-infrared-ICG videoangiographic recording was performed before and/or after the excision of the plaque and closure of the ICA. Upon the surgeon's request, patients were given ICG (Indocyanine green®, Dongin-Dang Pharmaceuticals, Seoul, Korea) intravenously by the anesthesiologist as a bolus of 12.5 mg (approximately 0.25 mg/kg dose) or 25 mg (approximately 0.5 mg/kg dose, 25 mg dose dissolved in 10 ml of 0.9% NaCl) to visualize the blood flow within the internal carotid artery.

Heart rate, arterial blood pressure, $SctO_2$, and SpO_2 were recorded by an independent investigator immediately before anesthetic induction and just before administration of ICG (baseline), and every min thereafter until the recovery of baseline $SctO_2$ value. The time from dye injection to the maximum changes (peak or nadir) and to the recovery of baseline values (duration) of $SctO_2$ and SpO_2, the highest readings of $SctO_2$ (peak) or the lowest readings of SpO_2 (nadir), and the magnitude of their maximum changes after ICG injection were also recorded.

Statistical analysis

The sample size calculation was based on the primary endpoint of $SctO_2$ value after ICG injection. A power analysis suggested that a sample size of 10 patients in each group should be adequate to detect an absolute 5% difference in the highest $SctO_2$ value with a two-sided significance level (alpha) of 0.05 and a power of 0.8. Data are expressed as mean ± SD (range). Both between and within group comparisons of $SctO_2$, SpO_2, and hemodynamic data were analyzed using two-way repeated measures analysis of variance followed by Scheffé post hoc test as required. Normal distribution was determined using the Kolmogorov–Smirnov test. Categorical data were analyzed using the Fisher's exact test. Other data were compared between the groups us-

ing a paired Student's t-test. All analyses were performed using StatView software version 4.0 (Abacus Concepts, Berkeley, CA, USA). A P value < 0.05 was considered statistically significant.

Results

Consecutive ICG videoangiographic examinations were performed in 26 patients; 21 before and the remaining 5 after arteriotomy. The patient characteristics including the baseline $SctO_2$ and SpO_2 were comparable between the two groups (Table 1).

Table 1. Demographic and Intraoperative Variables

Variables	12.5 mg Group (n = 13)	25 mg Group (n = 13)	P value
Male/Female	9/4	10/3	0.658
Age (yr)	67.1 (56–77)	68.1 (58–78)	0.750
Weight (kg)	62.3 ± 11.5	64.9 ± 9.0	0.525
Hemoglobin (g/dl)	13.3 ± 1.0	12.4 ± 2.3	0.189
Underlying diseases			
Hypertension	7	8	0.691
Diabetes	2	6	0.089
MAP before ICG (mmHg)	74.7 ± 8.7	69.8 ± 7.7	0.139
HR before ICG (beats/min)	64.6 ± 14.4	74.5 ± 12.4	0.074
$SctO_2$ before ICG (%)	62.0 ± 4.2	60.5 ± 6.4	0.473
SpO_2 before ICG (%)	98.7 ± 1.6	98.2 ± 1.3	0.334

Data are expressed as mean (range), mean ± SD or numbers. ACEI: angiotensin converting enzyme inhibitor, Ag II a: angiotensin II antagonist, MAP: mean arterial pressure, HR: heart rate, $SctO_2$: regional cerebral tissue oxygen saturation, SpO_2: percutaneous peripheral oxygen saturation.

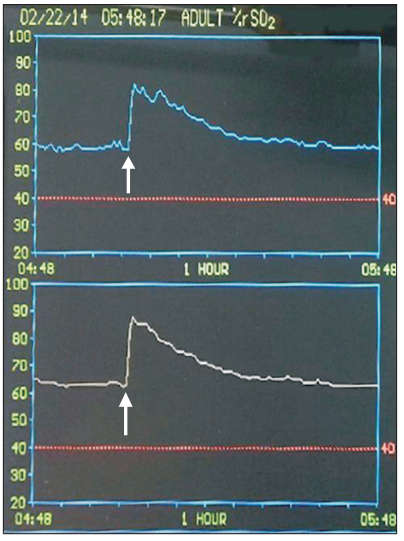

Fig. 1. A rapid but transient increase in near-infrared cerebral oximetry reading (upper, left; lower, right) after intravenous indocyanine green injection as a bolus (25 mg, administered at the point indicated by the arrow).

No changes in heart rate or arterial blood pressure were noted following the dye administration in either group.

Fig. 1 illustrates the typical changes in $SctO_2$ after a 25 mg bolus injection of ICG in a patient by replicating the INVOS monitor display. Following the administration, $SctO_2$ was significantly increased in both groups; however, the magnitude of the increase of was greater (21.6 ± 5.8% vs. 12.6 ± 4.1%, P < 0.0001) and more prolonged (28.4 ± 9.6 min vs. 13.8 ± 5.2 min, P < 0.0001) in the 25 mg group than in the 12.5 mg group (Fig. 2). No differences were noted between the two groups in the time to reach the greatest changes in $SctO_2$ (43.0 ± 10.9 s vs. 50.0 ± 30.0 s, P = 0.437). Also, there were no significant differences in the degree of maximum increases in $SctO_2$ between the non-operative and operative sides in either the 12.5 mg group (12.6 ± 4.1% vs. 12.7 ± 3.4%, P = 0.910) or the 25 mg group (21.6 ± 5.8%

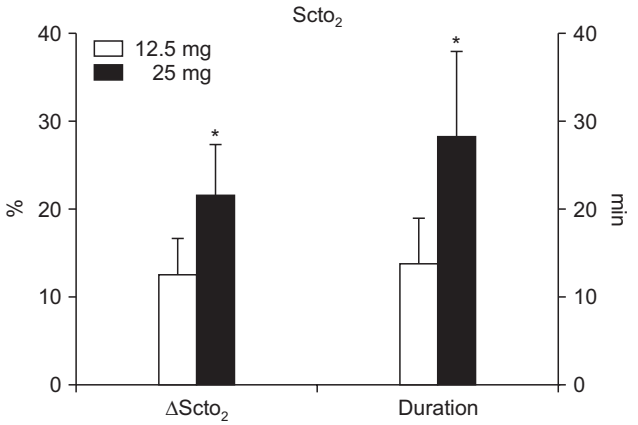

Fig. 2. The magnitude ($\Delta SctO_2$) and duration of the increase in regional cerebral oxygen saturation ($SctO_2$) via cerebral oximetry after intravenous indocyanine green injection as a bolus (12.5 mg or 25 mg). Data shown are expressed as mean ± SD. *P < 0.05 vs. 12.5 mg.

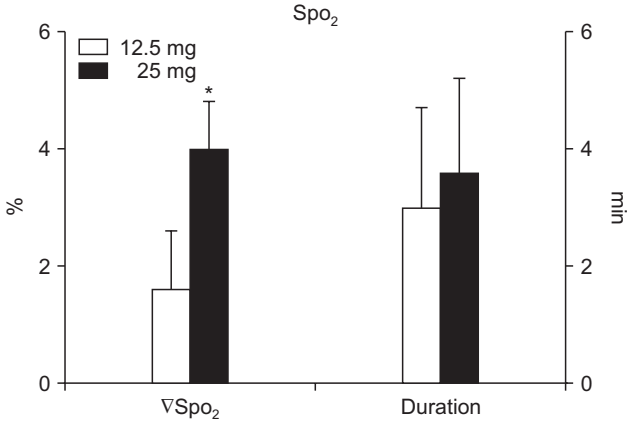

Fig. 3. The magnitude (∇SpO_2) and duration of the decrease in percutaneous peripheral oxygen saturation (SpO_2) via pulse oximetry after intravenous indocyanine green injection as a bolus (12.5 mg or 25 mg). Data shown are expressed as mean ± SD. *P < 0.05 vs. 12.5 mg.

vs. 19.7 ± 3.6%, P = 0.054).

In contrast, SpO_2 was significantly decreased in both groups (P < 0.005); the magnitude of the decrease was greater in the 25 mg group than in the 12.5 mg group (4.0 ± 0.8% vs. 1.6 ± 1.0%, P < 0.0001). There were no differences between the two groups in the time to reach the nadir SpO_2 (47.5.0 ± 20.0 s vs. 57.5 ± 37.4 s, P = 0.404) (Fig. 3) and the time to recover to the baseline $SctO_2$ (3.6 ± 1.6 min vs. 3.0 ± 1.7 min, P = 0.374).

An immediate increase in $SctO_2$ was observed in all of the patients, whereas a decrease in SpO_2 was observed in all but one patient (96.2%). Overall, the highest $SctO_2$ values were 86 and 95% and the lowest SpO_2 values were 94 and 92% in the 12.5 and 25 mg groups, respectively.

Discussion

Our study demonstrated that, when given as a single IV bolus using the INVOS cerebral oximeter, the higher dose (25 mg) of ICG led to greater and more prolonged increases in $SctO_2$ with a greater reduction in SpO_2, reaching the peak or the nadir within a minute (approximately one or two circulation times). These results are contradictory to those previously obtained with methylene blue [6] or indigo carmine [7], where $SctO_2$ was significantly decreased. Collectively, interference with the $SctO_2$ measurement (i.e., the magnitude, duration, and direction of the changes) by the vital dyes may vary according to the dosage as well as the type of the dye.

The INVOS cerebral oximeter uses two near-infrared wavelengths (730 and 805 nm) and measures the spectral absorbance of an admixture of arterial, capillary, and venous blood (hemoglobin or cytochrome aa3) in the brain [15]. Regional oxygen saturation is calculated as the ratio of oxyhemoglobin to total hemoglobin determined by the differential light absorption with subsequent computer suppression of the input from superficial tissues [3]. Any substance that absorbs infrared light of the same wavelength produced by the light emitting diodes may affect the absorption of light as it traverses the blood and tissues.

ICG has a dose- and time-dependent effect on plasma light absorbance (range 700–850 nm) with a spectral absorption peak at 805 nm and an emission peak around 835 nm, which is within the NIR window [16], whereas indigo carmine has an absorption peak at 620 nm with a dramatic decline around 700 nm [1]. Deoxyhemoglobin absorbs more infrared light at 730 nm, with the isobestic point for deoxyhemoglobin/oxyhemoglobin (wavelength at which oxy- and deoxyhemoglobin species have the same molar absorptivity) at 810 nm. Taken together, ICG would reduce the ratio of infrared light absorption at 730 nm/805 nm with a resultant increase in $SctO_2$, while indigo carmine would increase the ratio with resultant dampening of $SctO_2$.

Fluorescent lights have been shown to interfere with pulse oximetry readings [17]. ICG becomes strongly NIR-fluorescent after IV administration, with an absorption and an emission peak within the range of wavelengths used by the INVOS device [16]. In this context, one may ascribe the enhanced $SctO_2$ readings to a strong fluorescence signal emitted by ICG. This is, however, unlikely because the emission detected by the INVOS device would be a reduction in oxy-hemoglobin and $SctO_2$.

ICG increased $SctO_2$, whose peak was shown within one minute after the administration in the present study; while indigo carmine caused a nadir in 7 min (5–9 min) in a previous study [7]. The peak effects may be related to the highest concentration of the drug within the blood compartment in the brain tissue, since neither indigo carmine nor ICG normally penetrates the blood-brain barrier. Both dyes reach their peak concentrations in the brain within a minute when administered intravenously or intraarterially [18,19]. The discrepancy in the time to reach the peak $SctO_2$ between the two dyes cannot be readily explained. ICG may increase $SctO_2$ very rapidly (within one minute), since the wavelength of light (i.e., 805 nm) emitted by the INVOS System is very close to the absorption peak of ICG with a resultant extremely high absorbance.

Cerebral oximetry, in contrast to SpO_2 monitoring based on transmission oximetry, uses reflectance oximetry to measure the oxygen saturation of the tissues underneath the sensor. The light passes not only through parts of the frontal brain, but also through the overlying skull and scalp, and the oximetry signal may thus be contaminated by extracranial blood sources [20]. One may argue if cross clamping of the carotid artery during the surgery may redistribute the blood flow between extracranial and intracranial tissues and thereby increases the extracranial blood volume where hemoglobin oxygen saturation would be higher compared to that in the intracranial blood, $SctO_2$ would be increased. However, in the present study, the changes in contralateral and ipsilateral $SctO_2$ values after ICG did not differ in either group. Moreover, videoangiography was not performed during the carotid artery occlusion, but it was performed before the occlusion and/or following the reperfusion. It is unlikely that the redistribution of blood flow contributed to the elevated $SctO_2$ reading.

ICG-induced increase in $SctO_2$ was dose-dependent by the 12.6–21.6% absolute changes (20–36% relative changes), which lasted for up to 28 minutes with the higher dose. The relative increase in $SctO_2$ > 20% after carotid declamping has been associated with the onset of cerebral hyperperfusion syndrome in patients undergoing CEA under general anesthesia [21], whereas the relative decrease in $SctO_2$ > 20% after carotid cross-clamping has been associated with cerebral ischemia [22]. As such, the elevation of $SctO_2$ readings temporarily induced by ICG may obscure the interpretation of $SctO_2$ changes during the surgery, preventing the use of proper therapeutic interventions

(e.g., shunt placement or other pharmacological or physiological intervention) to correct the changes in $SctO_2$ and to improve postoperative outcomes. Moreover, administration of the dye is usually repeated in every patient because angiography is performed twice, i.e., before and after arteriotomy, in CEA procedures.

In the present study, the change in $SctO_2$ lasted longer than that in SpO_2. The pulse oximeter measures hemoglobin saturation in the arterial bed using two wavelengths of light (660 and 925 nm), while ICG has an absorption peak at 805 nm. The INVOS device measures regional cerebral tissue oxygen saturation (i.e., venous, capillary, and arterial blood) using two near-infrared wavelengths (730 and 805 nm). Differences in blood beds evaluated by the monitors, and the employed wavelengths and the analysis methods of the two devices (i.e., pulse oximeter and cerebral oximeter) may, at least in part, account for the differences in their interaction with ICG. Consequently, cerebral oxygenation monitoring using NIRS is more sensitive to changes in ICG than pulse oximetry. A dampened $SctO_2$ reading persisted for 20–40 min with indigo carmine in a previous study [5], while an elevated $SctO_2$ reading was maintained for 13.8 ± 5.2 min with ICG 12.5 mg and 28.4 ± 9.6 min with ICG 25 mg in the present study. We speculate that the effects of the two dyes on $SctO_2$ persist until the dyes are completely cleared up from the circulation (i.e., 5 to 6 half-lives) because of their higher sensitivity.

In conclusion, in patients undergoing CEA under general anesthesia, an IV bolus of 25 mg ICG for videoangiography resulted in a greater and more prolonged increase (for up to 28 min with a higher dose) in $SctO_2$ and a greater decrease in SpO_2 than an IV bolus of 12.5 mg ICG, with no differences in the time to reach the peak $SctO_2$ or the nadir SpO_2. Anesthesiologists should be alert when cerebral oximetry and IV-administered ICG are being used simultaneously.

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