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SOCIETY FOR NEUROSCIENCE IN ANESTHESIOLOGY AND CRITICAL CARE

ARTICLE OF THE MONTH

Ephedrine versus Phenylephrine Effect on Cerebral Blood Flow and Oxygen Consumption in Anesthetized Brain Tumor Patients: A Randomized Clinical Trial

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Welcome to the September 2020 edition of the SNACC Article of the Month. Our commentors this month are Hemanshu Prabhakar, MD, PhD; Charu Mahajan, MD, DM; and Indu Kapoor, MD.

Dr. Hemanshu Prabhakar is Professor in Department of Neuroanaesthesiology and Critical Care, at the All India Institute of Medical Sciences, New Delhi, India. He was awarded PhD from the same department in 2016. He has keen academic interests and is editor of several books on neuroanesthesia and neurocritical care. He is an active SNACC Member for many years and has enthusiastically involved himself in several committees of SNACC. His special interests are neuromonitoring, neuroendocopies, pituitary surgeries, and evidence-based practice.

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As always, readers are welcome to join us for further discussion and feedback on the SNACC **Twitter** feed, or on **Facebook**.

- Oana Maties, MD, Amie Hoefnagel, MD, Shilpa Rao, MD, and Nina Schloemerkemper, MD

Commentary

By Hemanshu Prabhakar, MD, PhD; Charu Mahajan, MD, DM; and Indu Kapoor, MD

During brain tumor surgeries maintenance of adequate cerebral perfusion pressure is of vital importance to ensure sufficient blood flow to meet metabolic demands. Under neurosurgical anesthesia, phenylephrine and ephedrine are popularly used to maintain systemic blood pressure. It has been suggested that phenylephrine reduces regional cerebral oxygen saturation compared with ephedrine, despite a marked increase in the mean arterial pressure.[1,2] The authors in this study, hypothesized that phenylephrine reduces cerebral metabolic rate of oxygen in selected brain regions compared with ephedrine. Using positron emission tomography, this randomized, double blinded study aimed to quantify the effects of phenylephrine and ephedrine on the cerebral metabolic rate of oxygen in brain tumor patients. The authors also assessed the effects of phenylephrine and ephedrine on cerebral blood flow, oxygen extraction fraction, and regional cerebral oxygen saturation.

This study was a prospective, single-center, parallel-group, double-blinded, randomized and controlled trial. All patients aged 18 to 75 years who were scheduled for elective craniotomy for supratentorial tumors with a minimum size of 3 cm (measured as the largest diameter in any plane on magnetic resonance imaging), were enrolled. Patients were randomized to receive the infusion of either ephedrine (2 mg/ml) or phenylephrine (0.1 mg/ml) in a 1:1 fashion.

On the day of surgery, patients were anesthetized in a room adjacent to the positron emission tomography (PET) scanner. All patients received anesthesia according to institutional guidelines. Accordingly, anesthesia was induced with propofol and remifentanil. A low dose of suxamethonium was administered to facilitate intubation. Anesthesia was maintained with a continuous infusion of propofol (4.8 to 12 mg/kg/h) and remifentanil (15 to 30 µg/kg/h). The bispectral index (BIS) was continuously monitored and maintained between 40 and 60. Controlled ventilation with 50% oxygen in air was applied and adjusted to achieve a pretreatment arterial carbon dioxide tension (Paco2) between 35 and 45 mmHg (i.e., normoventilation) and arterial oxygen tension (Pao2) greater than 100 mmHg. Cerebral oxygenation was monitored with near-infrared spectroscopy (INVOS cerebral oximeter) and continuously recorded during the PET examinations.

Pretreatment PET examinations were performed in the anesthetized patient before the administration of the study medication. The study medication was initially infused with a dedicated venous line at 30 ml/hr and titrated to increase the mean arterial pressure (MAP) to at least 60 mmHg or by 20% relative to the pretreatment MAP. PET measurements were repeated when the vasopressor treatment had raised the MAP to reach the desired plateau with stable values for 5 min. Infusion of the study medication was carefully titrated to avoid hypertension. After the PET examinations, the anesthetized patient, with ongoing infusion of study medication was transported to the neurosurgical suite, where surgery was initiated and the ICP and CPP were measured.

The authors have described in detail, various steps and procedures related to the PET examination of the patients.

The primary endpoint was the between-group difference in the cerebral metabolic rate of oxygen measured in the peritumoral surroundings and contralateral gray matter brain tissue. The secondary endpoints were the between-group differences in cerebral blood flow, oxygen extraction fraction, and regional cerebral oxygen saturation. Appropriate statistical analyses were done. A total of 24 patients were enrolled, whereas 265 of the 289 screened patients did not enter the study and were excluded for several reasons. The main results of this study were, peritumoral cerebral metabolic rate of oxygen values before and after vasopressor (ephedrine, 67.0 ± 11.3 and 67.8 ± 25.7 µmol/100 g/min; phenylephrine, 68.2 ± 15.2 and 67.6 ± 18.0 µmol/100 g/ min) showed no intergroup difference (difference [95% CI], 1.5 [−13.3 to 16.3] µmol/ 100 g/ min [P = 0.839]). Corresponding contralateral hemisphere cerebral metabolic rate of oxygen values (ephedrine, 90.8 ± 15.9 and 94.6 ± 16.9 µmol/ 100 g/ min; phenylephrine, 100.8 ± 20.7 and 96.4 ± 17.7 µmol/ 100 g/ min) showed no intergroup difference (difference [95% CI], 8.2 [−2.0 to 18.5] µmol/ 100 g/ min [P = 0.118]). Ephedrine significantly increased cerebral blood flow (difference [95% CI], 3.9 [0.7 to 7.0] ml/ 100 g/ min [P = 0.019]) and regional cerebral oxygen saturation (difference [95% CI], 4 [1 to 8]% [P = 0.024]) in the contralateral hemisphere compared to phenylephrine. The change in oxygen extraction fraction in both regions (peritumoral difference [95% CI], −0.6 [−14.7 to 13.6]% [P = 0.934]; contralateral hemisphere difference [95% CI], −0.1 [− 12.1 to 12.0]% [P = 0.989]) were comparable between groups.

This study demonstrates the changes in cerebral metabolic rate of oxygen in peritumoral and contralateral regions of interest were not different between ephedrine- and phenylephrine- treated patients. However, ephedrine caused a statistically significant increase in cerebral blood flow in contralateral hemisphere and in Paco2, regional cerebral oxygen saturation, and BIS when compared with phenylephrine. The difference in receptor affinity of the two vasopressors may explain the statistically significant increase in contralateral cerebral blood flow and statistically nonsignificant increase in

the cerebral metabolic rate of oxygen in both regions of interest after ephedrine treatment compared with phenylephrine treatment.[3] The findings in this study also suggest that infusion of phenylephrine and ephedrine may be associated with an uncoupling of the cerebral metabolic rate of the oxygen–cerebral blood flow relationship, which appeared to be present during propofol anesthesia and before vasopressor infusion.

The authors mention several limitations in the study, such as, small sample size, majority of screened patients were not included in the study, heterogeneity, including the uneven distribution of tumor pathology, may also have influenced the results. The study only included phenylephrine and ephedrine and generalizability of the findings is limited. Possible extracranial contamination of the regional cerebral oxygen saturation signal and absence of bilateral BIS and near-infrared spectroscopy measurements and thus comparison of both hemispheres are additional weaknesses of the study.

The authors concluded that the cerebral metabolic rate of oxygen changes in peritumoral and normal contralateral regions were similar between ephedrine- and phenylephrine- treated patients. In the normal contralateral region, ephedrine was associated with an increase in cerebral blood flow and regional cerebral oxygen saturation compared with phenylephrine. Possible concerns regarding the use of phenylephrine in patients with cerebral pathology, which is based on cerebral oximetry, may not be justified. The authors suggest that outcome studies are needed to further address this concern.

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