EFFECT OF PRALIDOXIME ADMINISTRATION DURING CARDIOPULMONARY RESUSCITATION ON BRAIN TISSUE OXYGEN TENSION AFTER RESTORATION OF SPONTANEOUS CIRCULATION IN A SWINE MODEL OF CARDIAC ARREST

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ABSTRACT

Purpose: *Previous studies suggested that epinephrine reduced brain tissue O_2 tension ($PbtO_2$) after restoration of spontaneous circulation (ROSC) via α1-adrenoceptor stimulation. Another previous study reported that pralidoxime had α1-adrenoceptor inhibitory action together with non-adrenergic vasopressor action. We sought to investigate the effects of pralidoxime administered during cardiopulmonary resuscitation (CPR) as a sole vasopressor on $PbtO_2$ after ROSC. We hypothesized that pralidoxime administration would lead to a comparable ROSC rate and higher $PbtO_2$ after ROSC when compared to epinephrine administration.*

Methods: *After 7 min of ventricular fibrillation, 24 pigs randomly received either pralidoxime or epinephrine during cardiopulmonary resuscitation (CPR). Cerebral measurements, including $PbtO_2$, were measured from the parietal cortices during the 60min post-ROSC period.*

Results: *Coronary perfusion pressure (CPP) during CPR was significantly higher in the epinephrine group than in the pralidoxime group ($P = 0.012$). All animals in the epinephrine group achieved ROSC, while 7 (58.3%) did in the pralidoxime group ($P = 0.037$). The areas under the curves for $PbtO_2$ during the post-ROSC period did not differ between the two groups.*

Conclusions: *Pralidoxime alone was significantly inferior to epinephrine in increasing CPP and achieving ROSC. In addition, pralidoxime administration did not improve $PbtO_2$ during the post-resuscitation period as compared with epinephrine.*

Key words: *Brain Tissue oxygen ● pralidoxime ● cardiac arrest*

Introduction

Hypoxic brain injury is a well-known determinant of neurologic outcome following cardiac arrest. To improve the likelihood of neurologically favorable survival, it is critically important to ensure sufficient cerebral oxygenation and prevent secondary hypoxic brain injury after restoration of spontaneous circulation (ROSC).

Epinephrine still remains the first-line drug used during cardiopulmonary resuscitation (CPR) Panchal, A.R et al. [1]. Several studies have indicated that epinephrine, though it increases coronary perfusion pressure (CPP) and myocardial blood flow and thereby facilitates ROSC, affects the brain adversely after ROSC Ristagno et al. [2]. In a study that investigated the effects of epinephrine administered during CPR on cerebral oxygenation in a pig cardiac arrest model, Ristagno et al. reported that epinephrine reduced cerebral cortical microcirculatory blood flow and brain tissue O_2 tension ($PbtO_2$) after ROSC as compared to saline placebo [2], via α1-adrenoceptor stimulation. Pralidoxime is well-known as an antidote for organophosphate poisoning. Multiple studies suggested that pralidoxime, when administered together with epinephrine, improves CPP and ROSC rate [3-5]. Jung et al. reported that the pralidoxime has non-adrenergic pressor action together with αadrenoceptor inhibitory action in anesthetized normal rats [4]. Given the reported pressor effects and α-adrenoceptor inhibitory action reported in these studies, pralidoxime may increase CPP and help restore spontaneous circulation without adversely affecting $PbtO_2$ after ROSC. However, to our knowledge, no study

has evaluated the effects of this drug administered during CPR as a sole vasopressor drug on $PbtO_2$ after ROSC.

In the present study, we sought to investigate the effects of pralidoxime administered during CPR as a sole vasopressor on $PbtO_2$ after ROSC. We hypothesized that pralidoxime administration would lead to a comparable ROSC rate and higher $PbtO_2$ after ROSC when compared to epinephrine administration.

Methods

This study was conducted in 24 healthy Yorkshire/Landrace cross pigs weighing 24.9 ± 2.8 kg and was approved by the Animal Care "Biomedical Research Center" and Use Committee of Chonnam National University Hospital (CNUH IACUC-20012) and Bukhara State Medical Institute. Animal care and experiments were conducted according to the author's Institutional Animal Care and Use Committee guidelines.

After intramuscular injection of ketamine (20 mg/kg) and xylazine (2.2 mg/kg) followed by inhalation of a mixture of sevoflurane (2–5%) and O_2, tracheal intubation (6.5 mm internal diameter) was performed. Then, the animals were ventilated using an anesthesia machine on a 70/30 mixture of N_2O/O_2 and sevoflurane (titrated to prevent signs of pain) with a tidal volume of 10 ml/kg and a respiratory rate adjusted to maintain normocapnia. Endtidal carbon dioxide ($ETCO_2$) was monitored by placing a sample line between the intubation tube and ventilator circuit. A 7.0-F catheter was inserted from the left femoral artery to the aorta for arterial pressure monitoring and blood sampling. A 6.0-F introducer sheath was advanced through the right external jugular vein for drug administration, right atrial pressure monitoring, and pacemaker catheter insertion. Another 7.0-F catheter was inserted into the left internal jugular vein and advanced retrogradely into the jugular bulb for jugular venous blood sampling. Burr holes (10 mm in diameter) were created bilaterally on the skull over the parietal cortices. Through the burr holes, the dura mater was carefully incised enough to visualize the cerebral cortical microvessels. The animal's rectal temperature was monitored and maintained at

38°C during the preparation period. Immediately after the preparation procedures, the animals were randomly assigned by using information in a closed envelope to either the epinephrine group or the pralidoxime group. An investigator prepared either epinephrine (0.02 mg/kg) or pralidoxime chloride (40 mg/kg) solution in equal volumes (20 ml), while the remainder of the investigators remained blinded to the group assignment.

Experimental protocol

Ventricular fibrillation (VF) was induced by delivering a 60 Hz and 30 mA alternating current through the pacemaker catheter placed in the right ventricle. Mechanical ventilation was suspended immediately after induction of VF. After 7 min of untreated VF, CPR was started using a pneumatic, piston-driven chest compressor (Life-Stat; Michigan Instruments, Grand Rapids, MI, USA) at a rate of 100 compressions/min to a depth of approximately 20% of the anteroposterior chest diameter. During CPR, ventilation was performed using a bagvalve device with an O_2 flow rate of 15 l/min and at a rate of 10 breaths/min. Coincident with the start of CPR, either an epinephrine or pralidoxime solution was administered into the right atrium according to the group assignment. During CPR, epinephrine solution was administered intravenously every 3 min in the epinephrine group, while saline placebo was administered every 3 min in the pralidoxime group. Defibrillation was attempted with a 150-J biphasic waveform transthoracic shock every 2 min if indicated. CPR was continued until ROSC was attained or for 14 min. The resuscitation efforts were discontinued if ROSC was not achieved within 14 min of CPR.

Following ROSC, mechanical ventilation was resumed with 100% oxygen. The animals were observed for 1 hour under general anesthesia with 1% sevoflurane. After 15 min following ROSC, the ventilatory rate was adjusted to maintain an $ETCO_2$ of 40 mmHg. No hemodynamic drug was administered during this period. After completion of the experimental protocol, the animals were euthanized with potassium chloride under general anesthesia.

CPP was calculated from the difference between aortic end-diastolic pressure and right atrial end-diastolic pressure. Cerebral microcirculatory blood flow and $PbtO_2$ were measured on the cerebral cortices exposed through burr holes. $PbtO_2$ was measured with an optical oxygen sensor (Oxygen Dipping Probe DP-PSt7; PreSens-Precision Sensing GmbH, Regensburg, Germany). Cerebral hypoxia was defined as a $PbtO_2$ of <20 mmHg [67]. Cerebral microcirculatory blood flow was assessed by observing cerebral cortical microcirculation videos, which were obtained using a hand-held digital microscope (GScopeTM G5; Genie Tech, Seoul, Korea) positioned over the burr holes. Microvascular flow index (MFI) and the number of perfused capillaries were determined by the method of Spronk et al. [8-9]. The number of perfused capillaries after ROSC was expressed as a percentage of the number of perfused capillaries relative to that at the pre-arrest baseline (%Capillary number). Arterial and jugular venous blood samples were obtained and examined for blood gases and lactate levels (GEM Premier 3000; Instrumentation Laboratory Company, Lexington, MA, USA) at pre-arrest baseline and at 3, 15, and 60 min after ROSC.

Statistical analysis

The normality of continuous variables was examined with the Shapiro-Wilk and Kolmogorov-Smirnov tests. Normally distributed continuous variables were summarized by their means ± standard deviation, and independent two-sample t-tests were used for intergroup comparison, while non-normally distributed continuous variables were summarized by their medians, and interquartile ranges (IQR) and Mann-Whitney U tests were used. Categorical variables were compared using Fisher's exact test. Areas under the curves (AUC) were calculated and expressed as mean ± standard error or median (IQR). A two-tailed P value of <0.05 was considered statistically significant.

Results

Table 1 shows the pre-arrest baseline measurements. There were no significant inter-group differences at the pre-arrest baseline. CPP during CPR was significantly

higher in the epinephrine group than in the pralidoxime group (AUC of CPP for the first 2 min of CPR, 19.2 [10.7 - 24.0] mmHg · min and 5.1 [2.4 – 11.5] mmHg · min in the epinephrine and pralidoxime groups, respectively, P = 0.012). All animals in the epinephrine group achieved ROSC, while 7 (58.3%) did in the pralidoxime group (P = 0.037). The epinephrine group animals received 1 (1 – 2) mg of epinephrine during CPR. The duration of CPR was significantly shorter in the epinephrine group than in the pralidoxime group (2 [2 – 4] min and 11 [4 – 12] min, respectively, P = 0.002).

All the animals that achieved ROSC were hemodynamically stabilized and survived the 60min post-ROSC period. During the post-resuscitation period, mean arterial pressure was maintained above 65 mmH in all of the animals (Figure 1). None had hypoxemia or hypocapnia during this period. No significant intergroup differences were found in the AUC for mean arterial pressure, PaO_2, and $PaCO_2$. Figure 2 and Table 2 show cerebral measurements after ROSC. $PbtO_2$ was higher in the pralidoxime group throughout the 60min post-resuscitation observation period, but the differences in AUC for $PbtO_2$ did not reach statistical significance. Five animals (45.5%) in the epinephrine group experienced cerebral hypoxia during the 60-min post-ROSC period, while none did in the pralidoxime group (P = 0.106) Neither the AUC for MFI nor that for %Capillary number differed between the two groups. The AUCs for arterial and jugular venous lactate also did not differ between the two groups (P = 0.759 and 0.920, respectively)

Discussion

In the present study, pralidoxime was significantly inferior to epinephrine in increasing CPP and achieving ROSC. Pralidoxime administration did not improve $PbtO_2$ during the postresuscitation period as compared with epinephrine. These findings were in contrast to our hypothesis that pralidoxime administration would lead to comparable ROSC rate and higher $PbtO_2$ after ROSC when compared to epinephrine administration.

The reasons why pralidoxime did not increase CPP during CPR and thereby improve ROSC rate are not clear. In contrast to the previous studies in which pralidoxime was administered together with epinephrine [3-5], this drug was administered as a sole vasopressor during CPR. Pralidoxime may have vasopressor action but this may be insufficient to achieve CPP enough to restore spontaneous circulation. On the other hand, this may be attributable to its vasodepressive action caused by α-adrenoceptor inhibition reported by Jung et al. [6]. The vasodepressive action might have been greater than non-adrenergic pressor action of this drug when used as a sole vasopressor. To evaluate the exact reason why pralidoxime fail to improve CPP in the present study, a further study comparing pralidoxime and saline placebo is required.

Several studies have suggested that cerebral hypoxia is not uncommon after ROSC Elmer et al. [10-11]. Although the impact of cerebral hypoxia after ROSC on neurologic outcome in cardiac arrest survivors remains elucidated, a number of studies in patients with severe traumatic brain injury have suggested that cerebral hypoxia leads to unfavorable outcomes [12-15]. The reason why pralidoxime could not improve $PbtO_2$ after ROSC is unclear. $PbtO_2$ is determined by multiple factors, including cerebral O_2 delivery, diffusion from cerebral capillaries to neurons, and cerebral O_2 consumption. We postulate that the benefits from α-adrenoceptor inhibitory effect of pralidoxime (probably on cerebral O_2 delivery) were not great enough to improve $PbtO_2$.

In this study, epinephrine administration resulted in significantly higher CPP and thereby improved ROSC rate. However, in the present study, 45.5% of the animals in the epinephrine group experienced cerebral hypoxia during the post-resuscitation period. These results are in line with those of clinical studies suggesting increased ROSC rates after epinephrine at the expense of poor neurological outcomes [16-17]. Given the fact that the majority of cardiac arrest survivors suffer from brain injury, further efforts to develop novel therapeutics to prevent cerebral hypoxia are required.

This study has several important limitations. First, it was conducted on young, healthy anesthetized pigs. Thus, the findings are not directly extrapolated to clinical cardiac arrest patients. Second, our study was preliminary in nature, and thus sample size calculation a priori was not conducted. Therefore, the sample size may have been insufficient. Third, $PbtO_2$, MFI, and %Capillary number were measured in a small area of the parietal cortex.

Thus, the results might not accurately reflect changes in the whole brain.

Conclusions

In the present study, pralidoxime alone was significantly inferior to epinephrine in increasing CPP and achieving ROSC. In addition, pralidoxime administration did not improve $PbtO_2$ during the post-resuscitation period as compared with epinephrine.

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Table 1. Pre-arrest baseline measurements.

Variable	Pralidoxime (N =12)	Epinephrine (N = 12)	P value
Systolic arterial pressure (mmHg)	123.92 ± 12.32	126.82 ± 17.25	0.852
Diastolic arterial pressrue (mmHg)	85.25 ± 13.11	83.73 ± 15.51	0.864
Mean arterial pressure (mmHg)	102.25 ± 11.67	102.82 ± 14.88	0.925
Mean right atrial pressure (mmHg)	8.08 ± 1.78	6.73 ± 2.15	0.203
Heart rate (/min)	89.25 ± 9.98	87.27 ± 13.34	0.743
$ETCO_2$ (mmHg)	38.83 ± 2.59	38.09 ± 1.92	0.722
Arterial pH	7.51 ± 0.03	7.52 ± 0.02	0.276
$PaCO_2$ (mmHg)	42 (41 - 44)	41 (39 - 42)	0.134
PaO_2 (mmHg)	160.57 ± 26.48	171.82 ± 27.31	0.591
Arterial lactate (mmol/l)	0.76 ± 0.22	1.01 ± 0.27	0.065
Jugular venous lactate (mmol/l)	1.06 ± 0.31	1.38 ± 0.64	0.239
$PbtO_2$ (mmHg)	32.16 ± 6.83	34.12 ± 6.69	0.624
Microvascular flow index	3	3	NA
Number of perfused capillaries (N)	13 ± 5	13 ± 3	0.327

Data are presented as the means ± standard deviation or medians with interquartile ranges. Microvascular flow index at pre-arrest baseline was 3 in all animals. $PaCO_2$, partial pressure of arterial CO_2; PaO_2, partial pressure of arterial O_2; $PbtO_2$, brain tissue O2 tension; NA, not applicable.

Table 2. Comparisons of the areas under the curves for cerebral measurement parameters.

	Pralidoxime (N = 7)	Epinephrine (N = 12)	P value
$PbtO_2$ (mmHg・min)			
The 60-min post-ROSC period	2539.419 ± 301.826	1713.663± 249.566	0.147
First 10-min post-ROSC period	625.204 ± 77.712	450.108± 61.505	0.284
Subsequent 50-min post-ROSC period	1915.429 ± 260.574	1281.996± 215.457	0.233
%Capillary number (%・min)			
The 60-min post-ROSC period	5545.884 ± 545.197	3845.438± 461.057	0.110
First 10-min post-ROSC period	1143.714 ± 90.609	850.188± 97.169	0.180
Subsequent 50-min post-ROSC period	4402.170 ± 526.492	2995.251± 406.270	0.190
Microvascular flow index (unit・min)			
The 60-min post-ROSC period	55.786 ± 7.699	55.625 ± 6.824	1.000
First 10-min post-ROSC period	16.357 ± 2.058	20.227 ± 1.481	0.363
Subsequent 50-min post-ROSC period	39.429 ± 8.149	35.712 ± 6.680	1.000

Data are presented as mean ± standard error. %Capillary number, percent of counted number of perfused capillaries relative to that at the pre-arrest baseline.

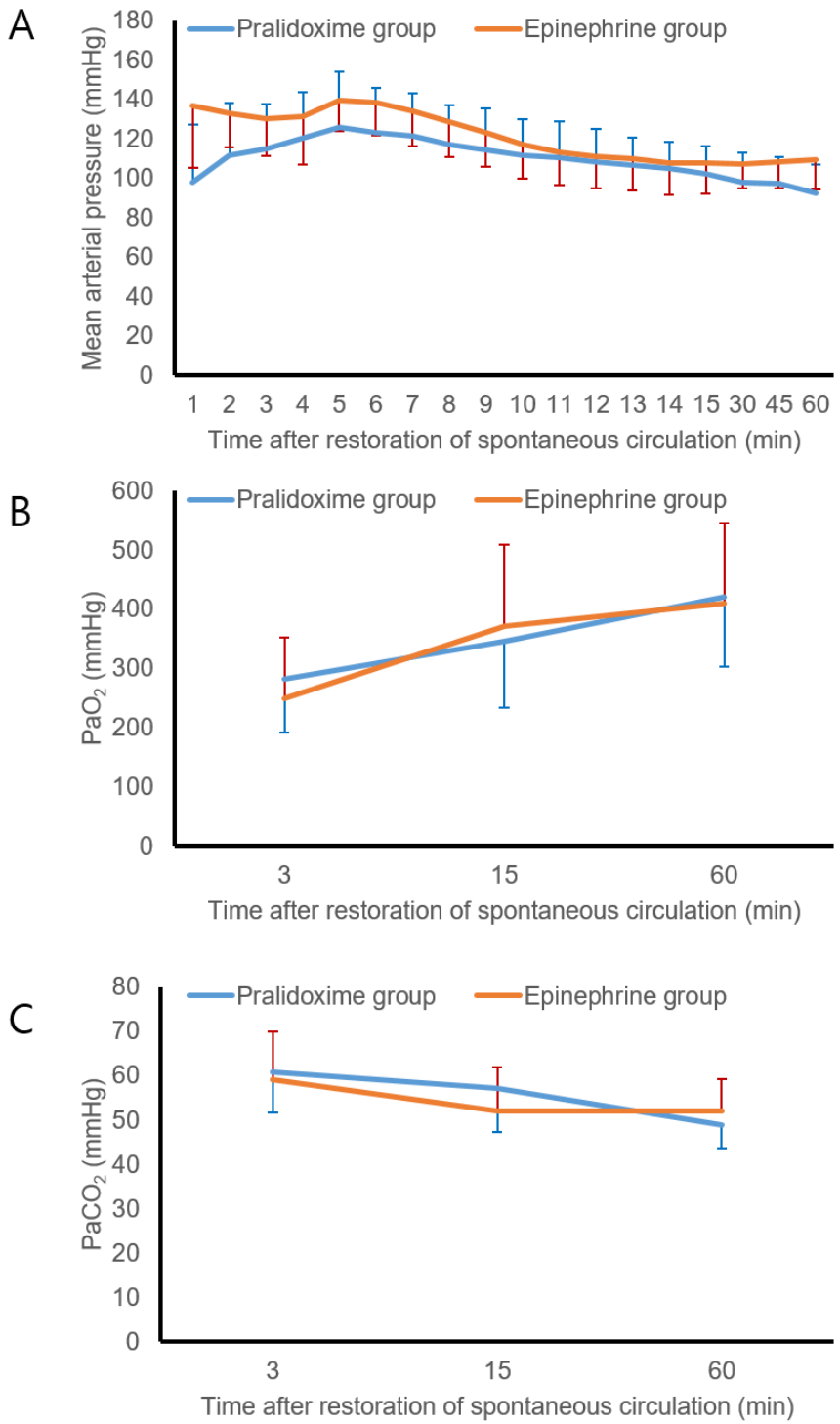

Figure 1. Mean arterial pressure (A), PaO_2 (B), and $PaCO_2$ (C) after the restoration of spontaneous circulation. Error bars represent the standard deviation. $PaCO_2$, partial pressure of arterial CO_2; PaO_2, partial pressure of arterial O_2.

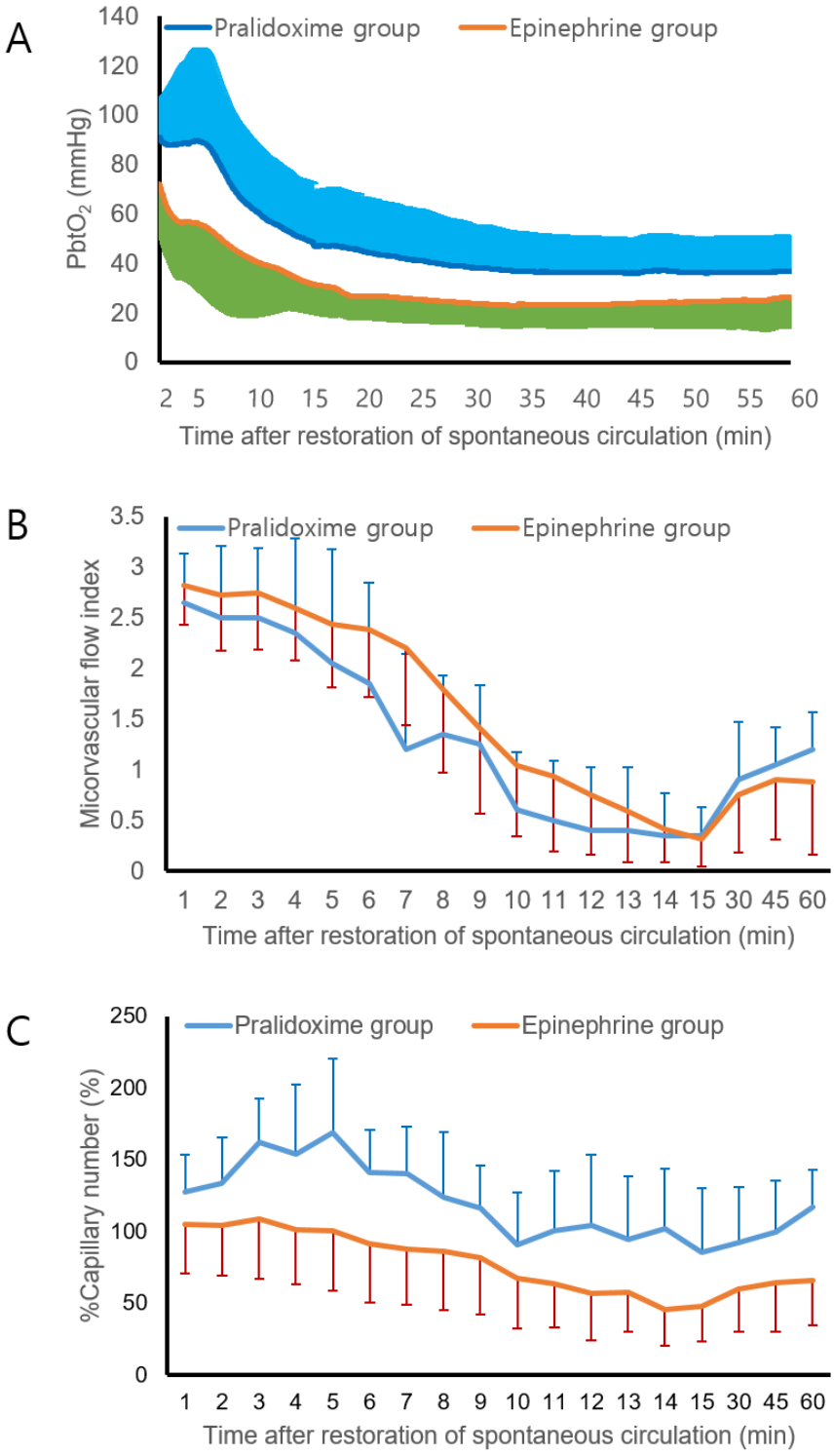

Figure 2. Brain tissue O_2 tension (PbtO2, A), microvascular flow index (B), and %Capillary number (C) after the restoration of spontaneous circulation. Error bars represent the standard deviation. %Capillary number, percent of counted number of perfused capillaries relative to that at the pre-arrest baseline.