Drug Design, Development and Therapy

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CLINICAL TRIAL REPORT

Effect of Norepinephrine and Phenylephrine on Tissue Oxygenation During Superficial Temporal Artery-Middle Cerebral Artery Bypass: A Randomized Controlled Trial

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Purpose: The current study aimed to compare the effects of norepinephrine and phenylephrine on tissue oxygenation and clinical outcomes in Moyamoya disease patients.

Patients and Methods: Sixty patients scheduled for superficial temporal artery-middle cerebral artery bypass were randomly assigned to either the norepinephrine group or the phenylephrine group. Standard doses of norepinephrine or phenylephrine were infused during surgery to maintain blood pressure fluctuating within ± 10% of baseline values. Cerebral oxygenation, muscle oxygenation, cardiac output, and urine volume were recorded at several timepoints: Before preoxygenation, After intubation, Skin cutting, Superficial temporal artery exposing, Middle cerebral artery exposing, and End of the surgery. Additionally, blood samples were collected from the superior vena cava and radial artery for blood gas analysis, to assess central venous oxygen saturation, blood lactate and calculate oxygen extraction rate. Length of hospital stay, incidence of neurological complications during hospitalization and mortality within 90 days were also recorded.

Results: Compared with phenylephrine group, the norepinephrine group exhibited significantly higher cerebral oxygenation, muscle oxygenation and cardiac output at Superficial temporal artery exposing, Middle cerebral artery exposing, and End of the surgery ($P<0.05$). No significant difference was observed between groups at any timepoints regarding urine output, central venous oxygen saturation, blood lactate levels, oxygen extraction rate. Length of hospital stay, incidence of neurological complications during hospitalization and 90-day mortality rate were comparable between groups.

Conclusion: The use of norepinephrine, in contrast to phenylephrine, for managing hypotension during superficial temporal artery-middle cerebral artery bypass significantly enhances tissue oxygenation, which may be related to the effective maintenance of cardiac output by norepinephrine.

Keywords: phenylephrine, norepinephrine, moyamoya disease, cerebral oxygenation, muscle oxygenation

Introduction

Moyamoya disease (MMD) is a cerebrovascular disorder characterized by progressive stenosis or occlusion at the end of the internal carotid artery and its branches, with secondary abnormal formation of posterior cerebral arteries. Superficial temporal artery (STA)-middle cerebral artery (MCA) bypass surgery is one of the most common procedures to treat MMD. Due to the vessel stenosis and occlusion, patients with MMD exhibit poor cerebral blood flow self-regulation and are highly dependent on systemic blood pressure.[1] The administration of vasopressors to maintain blood pressure at or above baseline level during surgery is particularly important for ensuring adequate cerebral perfusion pressure and minimizing postoperative neurological complications.[1,2] Phenylephrine (PE) has been demonstrated to be safely used in

Received: 10 February 2025
Accepted: 9 July 2025
Published: 25 July 2025

MMD patients.[1] However, as a pure α1-adrenergic agonist, PE leads to vasoconstriction and increased afterload, potentially reducing CO. Different from PE, norepinephrine (NE) has both α1 and β1 activity, meaning it increases blood pressure while preserving CO through β1-mediated inotropic effects. In recent years, NE has also gained increasing acceptance for cerebral revascularization in MMD patients.[3]

The impact of vasopressors on tissue oxygenation has long been a topic of concern in medical research.[4–6] Near-infrared spectroscopy (NIRS) offers a convenient, non-invasive and continuous method monitoring tissue oxygenation in brain and other tissues.[7] Previous studies have reported that intravenous administration of NE and PE may result in decreased cerebral oxygenation (ScO_2) and muscle oxygenation (SmO_2) levels.[8–12] However, there is a lack of comparative reports investigating the specific effects of NE and PE on tissue oxygenation in patients undergoing neurosurgery.

Therefore, this study aimed to compare the effect of norepinephrine and phenylephrine on tissue oxygenation and clinical outcomes in MMD patients undergoing superficial temporal artery-middle cerebral artery bypass.

Materials and Methods

This randomized double-blind clinical trial was conducted in compliance with the Declaration of Helsinki in the South District of The First Affiliated Hospital of the University of Science and Technology of China, Hefei, Anhui, China, after approved by the Clinical Research Ethics Committee of the same hospital (No: 2021-KY-060, Date: 09/04/2021, Chairperson Zuojun Shen). The study was registered with the China Clinical Trial Registry (No: ChiCTR2000041260, Date: 23/12/2020) before started and included 60 MMD patients scheduled for their first elective STA-MCA bypasses from May 1, 2021, to May 1, 2024. Informed consent was obtained from all participants prior to enrolment. All surgeries were performed by the same surgical team. Participants were aged 18–65 years, classified as American Society of Anesthesiologists (ASA) physical status II–III, in sinus rhythm, with hemoglobin levels >10 g dl^{-1}. Exclusion criteria included: (1) poorly controlled hypertension, systolic blood pressure >160 mmHg; (2) coronary artery disease; (3) heart failure; (4) heart valve disease; and (5) hepatic and renal insufficiency.

Randomization and Blinding

A computer-generated random number table was created using Excel software. Patients were randomly assigned in a 1:1 ratio to either the norepinephrine group (Group NE) or the phenylephrine group (Group PE). The randomization codes were enclosed in sealed envelopes. A nurse who was not involved in case management or data collection opened the envelope and prepared NE or PE (prepared in 50 mL syringes for continuous infusion or 20 mL syringes for intermittent injection) for the attending anesthesiologist. All patients, anesthesiologist and data collectors were blinded to group allocation.

Anesthetic Management

The anesthesiologist visited the patients in the surgical ward the day before surgery for preoperative anesthesia evaluation and got baseline blood pressure recorded. Baseline blood pressure defined as the blood pressure measured after resting in a supine position for 5 minutes.[13] Prior to surgery, 2000 mL of Ringer's lactate solution was infused. Pulse oximetry, ECG, capnography, temperature monitoring, and BIS were regularly monitored after patients' entering the operation room. YN-9002 tissue oxygen saturation monitor (Norwa Electronic Technology Co., Ltd., Hefei, Anhui, China) was applied to monitor the tissue oxygenation: one probe was placed on the forehead contralateral to the operation area (avoiding the frontal sinus) to detect ScO_2, the other on the left deltoid muscle for SmO_2 monitoring.[14] The baseline tissue oxygenation was recorded as the stable reading of the monitor for 10 minutes after cleaning local skin with alcohol gauze and pasting the monitoring electrode pads. Radial artery and internal jugular vein catheterization and pressure measurement were performed under local anesthesia. Internal jugular vein catheter was placed with a depth of 10–12 cm. The radial artery catheter was connected to FloTrac/Vigileo monitoring system (Vigileo FloTrac, Edwards Lifesciences, Irvine, CA, USA), and continuously monitored cardiac output (CO) and stroke volume variability (SVV). Anesthesia induction included intravenous administration of: etomidate 0.2mg kg^{-1}, sufentanil 0.3–0.5 μg kg^{-1}, rocuronium 1mg kg^{-1}, followed by tracheal intubation and mechanical ventilation. VT was set at 6–10mL kg^{-1}, ventilation frequency was 10–12 times/min, I: E=1:2, parameters were adjusted to maintain $PetCO_2$ at 40–45 mmHg. Anesthesia maintenance included: target-controlled infusion of propofol (Cp 1.5–2.5 μg mL^{-1}) and

remifentanil (Cp 2.0–4.0 ng mL^{-1}), along with inhalation of 1% sevoflurane, aiming to keep BIS between 40 and 60. Blood samples were collected simultaneously from the superior vena cava and radial artery for blood-gas analysis at the following timepoints: Baseline (before preoxygenation), After intubation, Skin cutting, STA exposing, MCA exposing, and End of the surgery. Tissue oxygen extraction rate (ERO_2) was calculated. $ERO_2=(SaO_2-SvO_2)/SaO_2$, SaO_2 is radical artery oxygen saturation, SvO_2 is superior vena cava oxygen saturation.

Inhalation Oxygen Concentration and Hemodynamic Management

Prior to anesthesia induction, patients were instructed to take at least 5 deep breaths through a mask with 100% oxygen 8 L min^{-1}. Following tracheal intubation, inhaled oxygen concentration was immediately adjusted to 60% and maintained until the end of the surgery.

Based on previous literature, the potency ratio of NE to PE is approximately 10:1.[10] Therefore, this study designed a 4 μg mL^{-1} of NE and 40 μg mL^{-1} of PE for intermittent injection, and a 40 μg mL^{-1} of NE and 400 μg mL^{-1} of PE for continuous intravenous infusion. After labelled with "study drug", NE or PE was placed in a 50 mL syringe for continuous infusing or in a 20 mL syringe for intermittent injection.

The blood pressure was continuously monitored and maintained within ± 10% of baseline blood pressure throughout the surgery.

In instances of hypotension, the anesthesiologist would administer a single injection of 1mL of the "study drug" intravenously, subsequently determine whether to initiate continuous intravenous infusion of the "study drug" as required. The initial infusion rate was 5mL h^{-1}, with adjustments made based on conditions to maintain the blood pressure fluctuations within ± 10% of baseline values. The specific infusion speed of the "study drug" was determined by the anesthesiologist, with recommended increment or decrement at 1–5 mL h^{-1}.

Before entering the room, the patient had received 2000 mL of Ringer's lactate solution intravenously. During the operation, adequate fluid was given to maintain SVV<10%, CI>2.5 L min^{-1} m^{-2}. The volume ratio of crystals/colloids was approximately 2:1.

All patients' hemoglobin levels, fluid status, anesthetic depth, inhaled oxygen concentration and blood pressure were strictly controlled.

Monitoring and Recording

ScO_2 and SmO_2 were selected as the primary outcome due to their critical roles in neurosurgical perfusion, while cardiac output, lactate, urine output, ERO_2, and SvO_2 were chosen as secondary markers of global hemodynamic indicators. The primary outcome was recorded on Baseline (before preoxygenation), After intubation, Skin cutting, STA exposing, MCA exposing, and End of the surgery. The secondary outcome included the following: (1) CO, uterine output, lactate (Lac), ERO_2, and SvO_2 at Baseline, After intubation, Skin cutting, STA exposing, MCA exposing, and End of the surgery; (2) length of hospital stay (LOS), incidence of neurological complications during hospitalization and mortality rate within 90 days. Neurological complications were got from the medical records include ischemic complications and cerebral hyperperfusion syndrome (CHS).[15,16] Ischemic complications include transient ischemic attack (TIA) and new infarction with imaging diagnosis. CHS was diagnosed if the patient demonstrated a focal seizure, or reversible deterioration of consciousness level with behavioral and/or speech abnormalities, or intracranial hemorrhage on CT, along with absence of a definite new infarction on a brain CT scan or diffusion-weighted MRI.

Sample Size Calculation

Prior to the study, a YN-9002 tissue oxygen saturation monitor was applied to measure ScO_2 and SmO_2 in 10 MMD patients undergoing STA-MCA bypass. The baseline values for ScO_2 and SmO_2 were found to be 75% and 70%, respectively, with a standard deviation of 5%. The prescribed testing level is 0.05 and the testing efficiency is 0.8. Calculated based on detecting a 5% difference in tissue oxygenation, a minimum of 17 patients were required for each group. Consequently, the study included 30 patients in the NE group and 30 in the PE group, resulting in a total of 60 patients.

Statistical Analyses

Statistical analysis was performed using SPSS 10.0. Quantitative variables were tested for normal distribution using the Shapiro–Wilk test. The quantitative variables with a normal distribution were expressed as mean ± standard deviation, and a comparison between two samples was performed using Student's *t*-test. Data with a non-normal distribution were expressed as the median and the interquartile range, and a comparison between two samples was performed using the Mann–Whitney U rank sum test. Comparisons between two groups at different timepoints were analyzed by two-way repeated measures analysis of variance. Mauchly's test assessed sphericity. If sphericity was violated, Pillai's trace results in multivariate test was applied (Both Pillai's trace and Greenhouse–Geisser have been used, and the results are consistent). If there was a significant difference between groups, we performed simple comparisons between groups for all timepoints with Bonferroni adjustments. The comparison of categorical data adopts the $\chi 2$ test or Fisher's exact test. Pearson's correlation analysis was employed to investigate the correlation between ScO_2 and CO as well as SmO_2 and CO. Two-tailed tests were conducted, with statistical significance defined as a P value less than 0.05.

Results

Ninety-one patients were screened for eligibility. Thirty-one patients were excluded due to non-compliance with inclusion criteria, refusal to participate, or cancellation of surgery. Sixty patients were randomized into one of the two study groups. Three patients both in the NE group (two NIRS malfunction, one changed operation type) and the PE group (two NIRS malfunction, one severe bradycardia) were respectively lost to follow-up, resulting in 54 patients available for analysis (Figure 1). The basic characteristics of the patients were comparable between groups (Table 1).

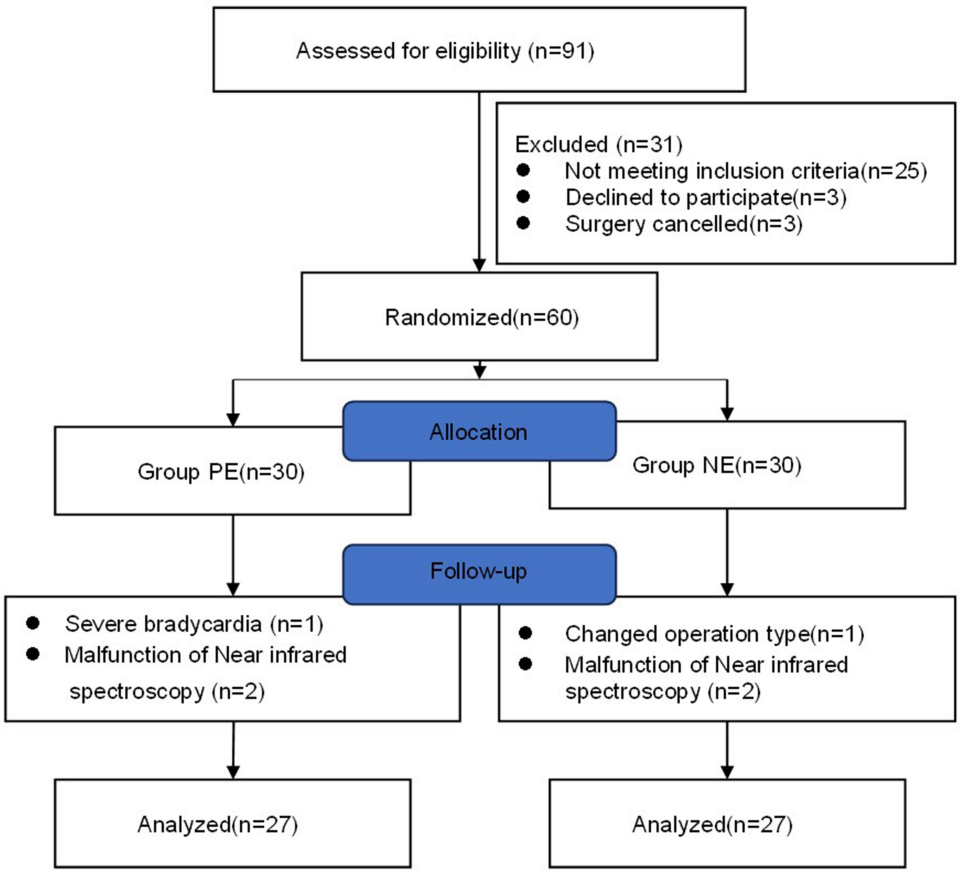

Figure 1 CONSORT flow diagram.
Abbreviations: PE, phenylephrine; NE, norepinephrine.

Table 1 Basic Characteristics of Patients

Characteristic	PE (n=27)	NE (n=27)	$t/\chi^2/F/Z$	*P*
Age (y)	48.8±7.6	47.4±10.1	0.566	0.574
Height (cm)	163.0±8.9	162.6±9.7	0.190	0.850
BMI (kg m^{-2})	24.1±3.0	24.7±2.8	−0.831	0.410
Sex (F/M)	18/9	15/12	0.701	0.402
ASA (II/III)	2/25	3/24	/	>0.999
Angiographic staging (II/III/IV/V/VI)	7/6/10/5/2	5/6/7/9/3	/	0.719
Hemoglobin (g L^{-1})	127.2±11.6	129.4±13.1	−0.650	0.519
Hypertension (n, %)	9(33)	11(41)	0.318	0.573
Diabetes (n, %)	0(0)	4(15)	/	0.111
Surgical duration (min)	289(260–325)	298(265–320)	−0.216	0.829
Fluid infusion volume (mL)	3313±648	3365±642	−0.295	0.769
Blood loss volume (mL)	117±48	107±43	0.745	0.460
MAP (mmHg)				
Baseline	100.6±11.1	105.4±9.2	2.514	0.120
After intubation	97.5±12.8	97.3±10.4	0.002	0.963
Skin cutting	100.4±9.5	96.8±7.2	2.167	0.148
STA exposing	96.6±8.1	97.6±6.8	0.224	0.638
MCA exposing	96.2±8.9	96.3±7.8	0.001	0.973
End of the surgery	95.4±10.1	98.2±6.6	1.291	0.262
SVV (%)				
Baseline	7.4±2.1	8.4±3.3	1.405	0.242
After intubation	6.4±3.7	6.7±2.1	0.136	0.714
Skin cutting	5.0±2.4	5.8±1.7	1.283	0.264
STA exposing	6.0±2.9	5.2±1.9	0.936	0.339
MCA exposing	6.7±2.9	6.3±2.2	0.188	0.666
End of the surgery	7.0±2.4	7.0±2.6	0.014	0.906

Note: Data are presented as mean ± SD or median (interquartile range) for continuous variables, and n (%) for categorical variables.

Abbreviations: PE, phenylephrine; NE, norepinephrine; BMI, body mass index; MAP, mean arterial pressure; STA, superficial temporal artery; MCA, middle cerebral artery; SVV, stroke volume variability.

Compared with Group PE, ScO_2, SmO_2 and CO were significantly higher at STA exposing, MCA exposing, and End of the surgery in Group NE (Table 2 and Figure 2). Other parameters, including SvO_2, ERO_2, Lac and uterine output, showed no significant difference between groups at any timepoints (Table 2).

As in Table 3, LOS was comparable between Group NE (15.3 ± 2.6 days) and Group PE (15.1 ± 2.9 days). In Group PE, one patient had stroke, two presented with HPS without persistent symptoms during hospitalization. In Group NE, one patient had stroke, three with HPS without persistent symptoms during hospitalization (Table 3). There was no death patient reported in both groups within 90 days after surgery (Table 3).

Pearson's correlation analysis revealed a positive correlation between ScO_2 and CO (r=0.298, $P<0.001$), SmO_2 and CO (r=0.228, $P<0.001$) (Figure 3).

Discussion

This study demonstrated that among MMD patients, the administration of NE to maintain blood pressure at equivalent levels resulted in higher levels of ScO_2, SmO_2 and CO compared with PE. Furthermore, a significant positive correlation was observed between ScO_2 and CO as well as SmO_2 and CO.

Previous studies have confirmed that NE and PE can cause a decrease in ScO_2,[8–12] but reports comparing the impact of NE and PE on ScO_2 are scarce. As far as we know, those include: 1. An animal experiment found that PE can cause a decline in ScO_2 in pigs under propofol–remifentanil anesthesia, while NE had no significant effect on ScO_2 with normal blood pressure subjects;[6] 2. In a recent obstetrics investigation, Wu et al reported that NE has its advantage in

https://doi.org/10.2147/DDDT.S517391

Table 2 Intraoperative Details of Patients

Variable	Patients (n)	Baseline	After Intubation	Skin Cutting	STA Exposing	MCA Exposing	End of the Surgery	P_{time}-value	P_{drug}-value	$P_{time \times drug}$-value
ScO_2 (%)								<0.001	<0.001	0.004
PE	24	74.5±3.6	77.7±6.5#	72.1±4.9	72.4±6.0#	72.8±6.0	71.9±6.3			
NE	27	76.4±4.5	80.4±5.9#	75.2±4.8	79.4±4.8*	79.4±5.3#,*	78.6±7.0#,*			
Mean difference (95% CI)		−1.8(−4.1, 0.5)	−2.7(−6.2, 0.8)	−3.1(−5.8, −0.3)	−7.0(−10.0, −4.0)	−6.6(−9.8, −3.4)	−6.6(−10.4, −2.9)			
P-value		0.118	0.126	0.028	<0.001	<0.001	<0.001			
SmO_2 (%)								<0.001	<0.001	0.032
PE	27	68.2±7.5	72.2±7.7#	67.5±7.4	67.2±6.3	66.8±6.8	67.2±7.5			
NE	24	70.9±7.0	75.1±7.5#	72.4±6.7	74.5±6.1#,*	75.4±5.8#,*	73.7±7.4*			
Mean difference (95% CI)		−2.7(−6.8, 1.4)	−2.9(−7.2, 1.3)	−4.9(−8.9, −0.9)	−7.3(−10.8, −3.8)	−8.6(−12.2, −5.0)	−6.5(−10.7, −2.3)			
P-value		0.199	0.174	0.017	<0.001	<0.001	0.003			
SvO_2 (%)								<0.001	<0.001	0.287
PE	22	72.7±4.3	78.4±5.7#	81.6±5.8#	81.5±6.0#	83.6±6.2#	82.4±6.3#			
NE	19	72.5±6.2	80.6±6.1#	84.0±3.9#	84.2±5.0#	84.8±4.3#	85.1±4.9#			
P-value		0.938	0.254	0.131	0.128	0.386	0.137			
ERO_2 (%)								<0.001	<0.001	0.238
PE	22	23.8±3.7	19.3±3.5#	16.0±4.2#	16.1±3.8#	14.0±4.2#	15.1±4.6#			
NE	20	24.6±5.8	17.6±6.2#	14.2±3.6#	13.8±4.2#	13.4±3.4#	13.3±3.9#			
P-value		0.714	0.297	0.151	0.077	0.616	0.21			
CO (L min^{-1})								<0.001	<0.001	0.057
PE	25	6.39±1.10	5.26±1.22	5.00±1.15	5.43±1.40	5.31±1.43	5.33±0.97			
NE	25	6.92±1.20	5.82±1.66#	5.58±1.37#	6.63±1.61#,*	6.71±1.62#,*	6.92±1.62#,*			
Mean difference (95% CI)		−0.52(−1.18, 0.13)	−0.56(−1.39, 0.27)	−0.58(−1.30, 0.14)	−1.20(−2.06, −0.34)	−1.40(−2.27, −0.53)	−1.58(−2.34, −0.82)			
P-value		0.114	0.181	0.112	0.007	0.002	<0.001			
Lac (mmol L^{-1})								<0.001	<0.001	0.320
PE	21	1.36±0.36	1.47±0.34	1.57±0.61#	1.67±0.63#	1.91±0.73#	2.17±0.82#			
NE	22	1.38±0.50	1.31±0.42	1.28±0.45	1.31±0.64	1.46±0.77	1.69±0.79			
P-value		0.860	0.188	0.080	0.065	0.056	0.059			
Uterine output (mL)								<0.001	<0.001	0.114
PE	21	/	171±203	689±284	1381±688	2029±635	2802±696			
NE	24	/	260±237	592±332	1154±440	1908±645	2633±837			
P-value		/	0.187	0.303	0.189	0.533	0.470			

Note: Data are presented as mean ± SD. *P<0.05 vs PE, #P<0.05 vs Baseline.

Abbreviations: STA, superficial temporal artery; MCA, middle cerebral artery; PE, phenylephrine; NE, norepinephrine; ScO_2, cerebral oxygenation; SmO_2, muscle oxygenation; SvO_2, superior vena cava oxygen saturation; ERO_2, oxygen extraction rate; CO, cardiac output; Lac, lactate.

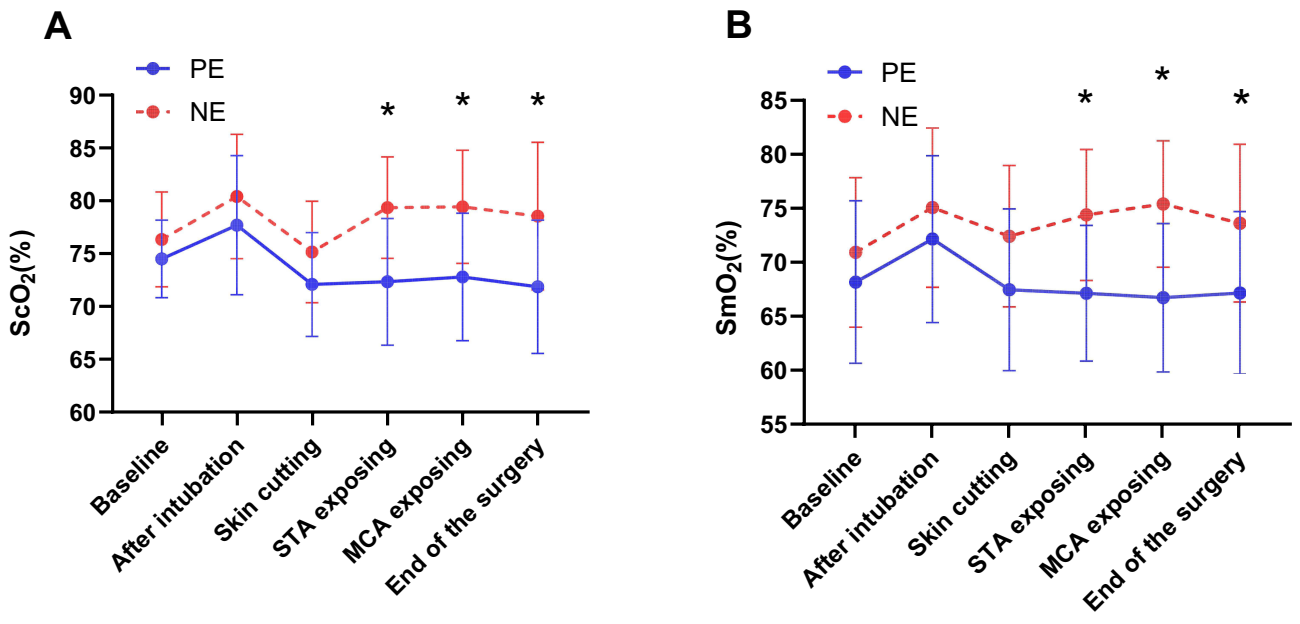

Figure 2 Time course of repeated measures of ScO_2 (**A**) and SmO_2 (**B**), represented by means and standard deviations. *P<0.05 vs PE.
Abbreviations: ScO_2, cerebral oxygenation; SmO_2, muscle oxygenation; PE, phenylephrine; NE, norepinephrine; STA, superficial temporal artery; MCA, middle cerebral artery.

maintaining ScO_2 of parturients compared with PE in counteracting hypotension following spinal anesthesia.[11] The findings of this trial confirm for the first time that in treating intraoperative hypotension, NE is better than PE in maintaining ScO_2 among neurosurgery patients. Unlike previous studies that used single intravenous injection[17,18] or short-term continuous intravenous infusion[11,19] of vasopressors, a particular feature of this trial is that we focused on a procedure (STA-MCA bypass) typically requiring high doses of vasopressor to maintain blood pressure within ± 10% of the baseline value in more than 5 hours. This design aims to better elucidate the effects of NE and PE on tissue oxygenation.

In contrast to NE, PE can adversely impact organ perfusion and contribute to the accumulation of tissue metabolites, such as lactate.[4] The latest guidelines from the Surviving Sepsis Campaign recommend norepinephrine as the first-choice vasopressor. Our data also indicated that patients in the PE group exhibited lower SmO_2, adding new evidence of the disadvantages of PE on peripheral oxygenation. Besides, although statistically insignificant at all timepoints, the blood lactate level in Group NE appeared to be lower than that in Group PE (Table 2), warranting further investigation with a larger sample.

In accordance with previous studies,[8,20] we found that intraoperative use of NE for hypotension management is superior in preserving cardiac output compared with PE. Furthermore, Pearson's correlation analysis of this trial revealed a positive correlation between ScO_2 and CO as well as SmO_2 and CO. So, we suggest that the different effect of NE/PE on CO may contribute to their different effect on ScO_2/ SmO_2, ie, the β-adrenergic agonistic activity of NE determines its advantage over PE on CO/ ScO_2/ SmO_2.

Table 3 Postoperative Outcomes of Patients

	PE (n=27)	NE (n=27)	t/χ^2	*P*
LOS (d)	15.1±2.9	15.3±2.6	−0.224	0.824
Neurological complications (n, %)	3 (11)	4 (15)	/	>0.999
90-day mortality (n, %)	0 (0)	0 (0)	/	/

Note: Data are presented as mean ± SD for continuous variables, and n (%) for categorical variables.
Abbreviations: PE, phenylephrine; NE, norepinephrine; LOS, length of hospital stay.

https://doi.org/10.2147/DDDT.S517391

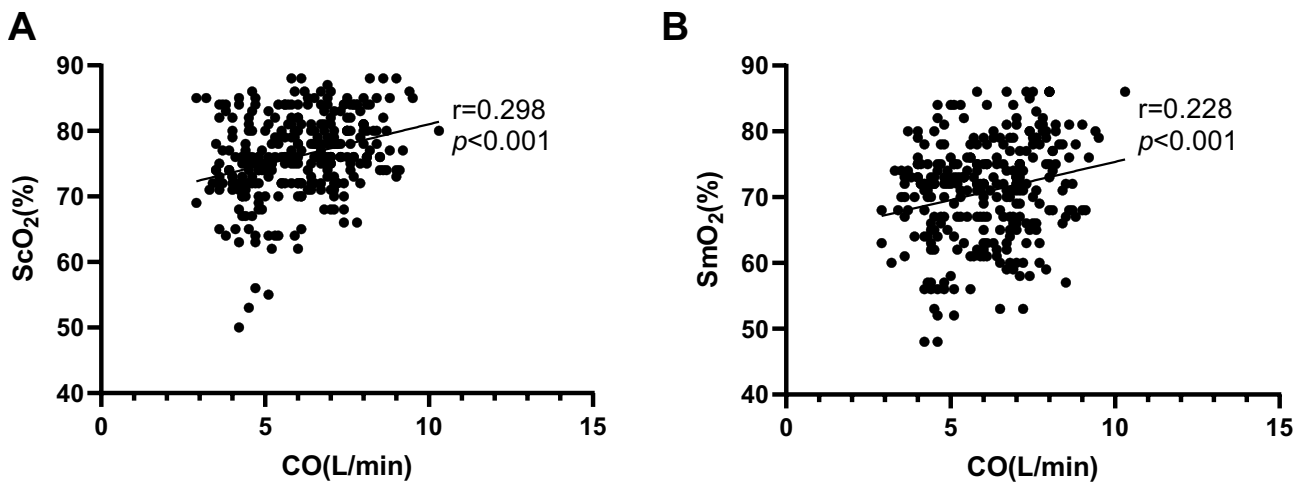

Figure 3 Pearson's correlation between ScO_2 and CO (**A**), SmO_2 and CO (**B**).
Abbreviations: ScO_2, cerebral oxygenation; SmO_2, muscle oxygenation; CO, cardiac output.

Mild pre-operative hypovolemia is common in surgical patients. Different from that, the patients in our study were in a normal volume state (2000 mL of Ringer's lactate solution was given before surgery for hemodilution). We know that the effect of PE on CO is determined by patients' overall blood volume status. PE increases venous return, preload, and cardiac output; meanwhile it also constricts arteries and increases afterload. In preload-independent patients, PE decreases CO mainly due to increased afterload (effect of enhancing venous return is weak in preload-independent patients). While in hypovolemic patients, CO does not change through increased venous return.[21] Differences in preload conditions may explain the contrasting outcomes on ScO_2 observed in our study compared to previous study.[10]

In this study, we have controlled the Hb/fluid infusion/BIS/MAP/inhaled oxygen concentration to ensure comparability between groups, as we know those would impact tissue oxygenation. This design offered us an opportunity to observe the effect of NE/PE on tissue oxygenation more clearly. According to Supplementary Table 1, the infusion rate and total infusion volume of the vasopressors in Group NE were higher than those in Group PE, indicating that the potency ratio of PE to NE was higher than 1:10. In fact, according to the results of this trial, the potency ratio of PE to NE was approximately 1:4.1. Different NE/PE producer and different fluid status of patients may partly explain the potency ratio difference of PE to NE from previous studies.[10,22] A 1:4.1 ratio drug preparation would be more appropriate for our future studies in the same context.

Although the levels of ScO_2 and SmO_2 in Group NE were higher than those in Group PE, no clinically significant decline in tissue oxygenation from preoperative baselines was observed at any point in either group (Table 2 and Figure 2). This suggests that both NE and PE can be safely used to manage intraoperative hypotension in patients with Moyamoya disease without causing a significant decrease in tissue oxygenation. That may also be the reason why we could not observe the differences in postoperative neurological complications, LOS, 90-day mortality rates, and cumulative all-cause mortality rates (Supplementary Table 2) between groups. In the future, evaluations of patients' postoperative cognitive status[23,24] might be introduced to further observe the impact of differences in tissue oxygenation on clinical outcomes.

This study has certain limitations. Firstly, the lack of retrograde catheterization of the jugular bulb precluded the jugular bulb oxygen saturation results to corroborate with NIRS, potentially explaining the discordance between SvO_2 and ERO_2 outcomes with ScO_2. Secondly, due to the disinfection scope of the surgical area, ScO_2 monitoring was only conducted on the contralateral side of the surgery. However, as the patients selected for this experiment were those who underwent STA-MAC bypass for the first time, their contralateral blood vessels remained in a diseased state without correction, the results of ScO_2 on the contralateral side of the surgery can still reflect the responses of MMD patients to different vasopressors. Finally, the relatively small sample size limits the generalizability of our findings. In fact, NE showed advantage in secondary outcomes (SvO_2, ERO_2 and Lac, Table 2), without statistical significance at any

timepoints, possibly due to the small sample size. Future studies should aim to include a larger patient cohort and explore outcomes related to S100B/neuron-specific enolase level, postoperative delirium, and cognitive function.

Conclusion

Both phenylephrine and norepinephrine can be safely administered to manage intraoperative hypotension in patients with Moyamoya disease undergoing superficial temporal artery cerebral artery bypass. Compared with phenylephrine, norepinephrine is superior in maintaining tissue oxygenation, possibly attributable to its advantage in cardiac output maintenance. Future research should explore whether the observed differences in tissue oxygenation impact long-term neurological outcomes, as well as further investigate the optimal dosing of phenylephrine relative to norepinephrine.

Data Sharing Statement

Individual deidentified participant-level data underlying the results reported in this article, as well as the study protocol and statistical analysis plan, will be made available upon reasonable request. Data are available beginning 3 months after online publication and for up to 24 months thereafter. To request data, please contact the corresponding author (Dr. Juan Li). Requests must include a methodologically sound proposal, and approval will be at the discretion of the study investigators.

Acknowledgments

We sincerely thank the patients for participation in the study.

Presentation: Oral presentation at Neuroanaesthesia Symposium 2025, 16–18 May 2025.

Funding

This work was supported by the Open Project Fund of Anhui Biomedical Optical Instrument Engineering Technology Research Center (grant number: 2023BMP09).

Disclosure

The authors report no conflicts of interest in this work.

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