Original Article

Effects of Epinephrine, Norepinephrine, and Phenylephrine on Cerebral Oxygen Saturation in Patients Undergoing Cardiopulmonary Bypass: A Randomized Clinical Trial

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ABSTRACT

Background: Epinephrine, norepinephrine, and phenylephrine may have different effects on cerebral O_2 saturation when used to treat intraoperative hypotension. The present study aimed to evaluate these effects on cerebral O_2 saturation in patients undergoing cardiopulmonary bypass (CPB) during heart surgeries.

Methods: The current randomized clinical trial enrolled 114 adult patients, 90 of whom were eligible for randomization into 3 groups (each=30) receiving epinephrine, norepinephrine, and phenylephrine if they experienced hypotension (mean arterial pressure [MAP]<60 mm Hg) during surgery. Cerebral oximetry as the primary outcome, hemodynamic parameters, consisting of heart rate, MAP, and arterial blood gas (ABG), and lactate levels were recorded prior to surgery and 120, 150, and 180 seconds after vasopressor administration during CPB.

Results: The 3 study groups were similar regarding demographic variables. Hemodynamic parameters, including ABG, and lactate levels showed no statistically significant differences between the groups (P>0.05). Additionally, cerebral O_2 saturation at baseline and 120, 150, and 180 seconds after vasopressor administration was not statistically different between the 3 groups (P>0.05).

Conclusions: The administration of epinephrine, norepinephrine, or phenylephrine in adult patients undergoing cardiac surgery with CPB support yielded no statistically significant differences in clinical and hemodynamic parameters. ***(Iranian Heart Journal 2023; 24(2): 6-13)***

KEYWORDS: Vasopressor, Cardiopulmonary bypass, Cardiac surgical procedures, Oximetry

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Cardiopulmonary bypass (CPB) is a non-physiological and complex procedure and one of the basic pillars in cardiac surgery that can have inadvertent systemic effects, such as the activation of the inflammatory response due to the contact of plasma proteases and blood cells with cardiopulmonary pump surfaces, the activation of complement and hemostatic systems, and the emboli formation of fibrin, fat, and platelets. [1] A longer bypass duration is related to more unwanted side effects in the body organs, which may be associated with various complications, such as severe hypotension, changes in blood sugar, cerebral and renal complications, liver damage, pulmonary problems, heart rhythm disturbances, bleeding, and even death. [2] One of the most significant and probable complications during the bypass pump is hypotension, which may impair the perfusion of vital organs. [3]

The main cause of hypotension at the beginning of CPB is a sharp decrease in peripheral vascular resistance, which can be due to a decreased blood viscosity secondary to the dilution of the blood with the priming solution. Likewise, a decrease in vascular tone secondary to the dilution of circulating catecholamine and temporary hypoxia induced by the initial circulation of the priming fluid can decrease vascular tone.

Although acceptable limits for blood pressure are somewhat statistically different, a mean arterial pressure (MAP) of 70 to 90 mm Hg is acceptable. However, maintaining a MAP exceeding 60 mm Hg during CPB is essential for the adequate perfusion of the coronary, cerebral, and renal arteries.

A decrease in MAP below 50 mm Hg and lower can convert cerebral blood flow into a pressure-dependent variable; nonetheless, the change can be prevented by inhibiting hypotension, preventing the perfusion pressure of vital organs, and maintaining a MAP above 60 mm Hg. [4] The maintenance of MAP within the mentioned limits by increasing the blood flow of the bypass pump and the administration of vasoconstrictors can prevent cerebral and other complications. [5] Although the sympathomimetic effects of these drugs on MAP are obvious, their adverse effects, which may be due to increased vascular resistance or cardiac output, as well as their effects on cerebral oxygenation or cerebral blood flow, are still unclear. Previous studies have reported contradictory results. Numerous investigations have shown that during CPB, tissue perfusion pressure and O_2 delivery can be disrupted up to varying degrees, which may cause the temporary or permanent impairment of organ functions postoperatively. [6]

A change in blood pressure during CPB, especially with the aim of blood pressure reduction, is frequent and can be associated with organ impairment and complications, which may be fatal. Therefore, vasopressors play a salient role in preventing and treating hypotension and improving the perfusion of vital organs, such as the brain. [7]

Vasopressors have different mechanisms of action, and their effect on the cerebrovascular blood supply can vary. Most studies have used norepinephrine and phenylephrine to increase blood pressure and subsequently improve cerebral blood flow. Indeed, epinephrine, which is widely used in heart surgery, has been less studied. In this study, we sought to compare the effects of epinephrine, norepinephrine, and phenylephrine on cerebral oxygenation during CPB in patients undergoing open-heart surgery. [8]

METHODS

The present single-blind randomized clinical trial investigated the effects of epinephrine, norepinephrine, and phenylephrine on cerebral oxygenation during CPB. The study population consisted of candidates for open-

heart surgery (coronary artery bypass and cardiac valve surgeries).

The study protocol was approved by the institutional review board and was registered in the Iranian Registry of Clinical Trials (2019.514.43582N1). Informed written consent was obtained from the entire study population before surgery.

Sample size calculation was performed based on previous studies [9] and considering an α type error of 0.05 and a study power of 80%. The sample size was calculated to be 30 patients in each group (http://www.stat.ubc.ca/~rollin/stats/ssize/b2.html). Totally, 114 adult patients were enrolled. Among them, 90 patients were eligible for randomization into 3 groups (each group=30) using online randomization software (http://www.graphpad.com/quickcalcs/randomize3/). The main researcher was not aware of the random allocation list, and the list was concealed. If a patient's blood pressure dropped below 60 mm Hg during surgery and after non-pharmacological measures proved ineffective, the patient was recruited into the study and was randomly assigned to 1 of the 3 groups of epinephrine, norepinephrine, and phenylephrine (Fig. 1). Care was taken to ensure that all the patients had the same condition in terms of anesthesia, surgery, and CPB as much as possible.

During the surgical operation, membrane oxygenators and arterial filters were used.

Before the implantation of the aortic clamp and to induce chemical arrest, cold del Nido cardioplegia solutions were administered into the coronary arteries antegradely, retrogradely, or directly, depending on the type of surgery, in all the patients. If indicated, the protocol was repeated every 60 to 90 minutes. Cerebral oxygenation was recorded continuously during surgery. During CPB support, anesthesia was maintained with the intravenous administration of anesthetics. In all 3 groups, efforts were made to maintain the hematocrit level between 24% and 27%. To that end, blood transfusion units were used if clinically indicated.

Ninety patients out of the 114 cases developed hypotension at least once during CPB support. These patients were initially treated with non-pharmacological measures, such as an increase in pump flow, depending on the patient's body temperature. In the event of no response and after blood pressure drops below 60 mm Hg, the patients received norepinephrine (5–10 µg), epinephrine (5–10 µg), or phenylephrine (40–60 µg) based on their assigned group to raise and keep blood pressure over 60 mm Hg.

For each patient, MAP and arterial and cerebral O_2 saturation levels were recorded before anesthesia induction, before CPB initiation, during CPB support, and at the end of surgery in the operating room.

During CPB support, cerebral O_2 saturation was measured before inotropic medication and then 120, 150, and 180 seconds after the administration of inotropes. The mean cerebral O_2 saturation was calculated and recorded as an index for medication effectiveness.

Arterial blood gas samples were taken during CPB.

In cases where the above samples were taken more than once (depending on bypass duration), their mean was calculated and recorded in the patient's profile. In the course of bypass support, MAP, PaO_2, and cerebral oximetry were monitored and recorded constantly. Body temperature was constantly monitored with nasopharyngeal sensors. O_2 saturation was measured using digital pulse oximetry. Cerebral oximetry was performed using a cerebral oximetry monitoring device (Somanetics, Troy, MI, USA).

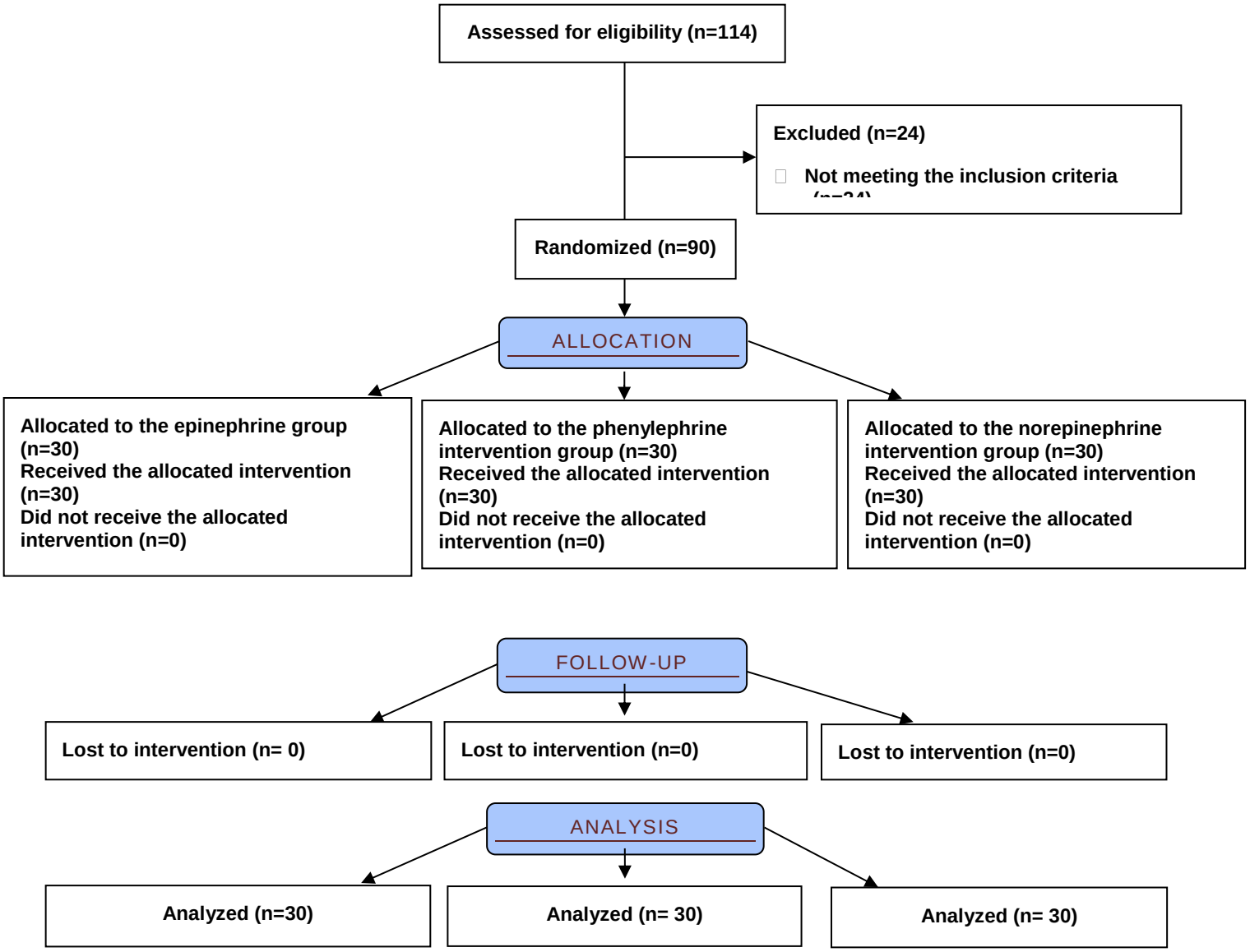

Figure 1: The figure illustrates the CONSORT flow diagram.

Statistical analysis was performed using IBM SPSS Statistics for Windows, version 22.0 (SPSS Inc, IBM Corp, Armonk, NY). Descriptive statistics, consisting of the mean, the standard deviation, and the frequency, were used to describe the key characteristics of the main study variables. For the statistical analyses, appropriate tests, including the χ^2 test, the dependent *t* test, and the repeated measures analysis of variance (ANOVA), were employed.

RESULTS

Results from the comparison of the patients' interquartile range of age, weight, height, ventricular ejection fraction, and blood flow between the epinephrine, norepinephrine, and phenylephrine groups revealed no statistically significant differences ($P>0.05$) (Table 1 & Table 2).

Results from the comparison of the means of pH, PaO_2, hemoglobin, lactate, and bicarbonate levels between the epinephrine,

norepinephrine, and phenylephrine groups at different time points (before, during, and after CPB) revealed no statistically significant differences (P>0.05) (Table 3).

Results from the comparison of the frequency of arrhythmias and the need for defibrillation after weaning from CPB between the epinephrine, norepinephrine, and phenylephrine groups did not reveal any statistically significant differences (P>0.05) (Table 4).

Results from the comparison of the mean medicine consumption (µg) and the duration of postoperative mechanical ventilation (h) between the epinephrine, norepinephrine, and phenylephrine groups yielded no statistically significant differences (P>0.05) (Table 5).

Results from the comparison of MAP and cerebral O_2 saturation between the epinephrine, norepinephrine, and phenylephrine groups at different time points (before the medication, and 120, 150, and 180 seconds after the medication) did not reveal any statistically significant differences (P>0.05) (Table 6).

Intragroup variations of pH, bicarbonate, PaO_2, MAP, and cerebral O_2 saturation at different study time points were not statistically significant in repeated measures ANOVA (P>0.05). However, lactate and hemoglobin changes were significant within each study group before, during, and after CPB (P<0.05).

Table 1: Comparison of age, height, and the ventricular ejection fraction interquartile between the 3 study groups

Variable	Median (Interquartile range)			*P* value (the Kruskal–Wallis test)
	Epinephrine	Norepinephrine	Phenylephrine	
Age (y)	62 (56.50-66.25)	53 (42.25-63.50)	59 (48.50-67.25)	0.06
Height (cm)	164 (157-170.25)	167(165.6-175)	168 (157-170)	0.23
Ventricular ejection fraction (%)	45 (35-51.25)	47.50 (40-50)	47.50 (35-50)	0.85

Table 2: Comparison of weight, body mass index, and blood flow between the 3 study groups

Variable	Mean (SD)			*P* value (ANOVA)
	Epinephrine	Norepinephrine	Phenylephrine	
Weight (kg)	70.16 ±7.34	72.10±40.70	68.12±16.41	0.47
Body mass (m^2)	1.0±79.22	1.0 ±83.24	1.0±72.19	0.18
Blood flow (mL/min)	4319.52±86.89	4379.354±80.71	4191.379±86.45	0.22

Table 3: Comparison of the means of pH, bicarbonate, arterial blood O_2, lactate, and hemoglobin before, during, and after CPB between the 3 study groups

Variable	Phase	Mean ±SD			*P* value (ANOVA)
		Epinephrine	Norepinephrine	Phenylephrine	
pH	Before CPB	7.37±0.36	7.35±0.43	7.36±0.39	0.22
	During CPB	7.0 ±37.5	7.0±38.58	7.0±41.41	0.54
	After CPB	7.0±37.6	7.0±36.45	7.0±37.39	0.29
Bicarbonate (mmol/L)	Before CPB	21.23±2.63	21.17±2.51	19.2±93.72	0.15
	During CPB	22.3±53.27	21.96±1.84	21.2±46.96	0.41
	After CPB	22.3±66.39	21.96±2.62	20.2±86.73	0.11
PaO_2 (mm Hg)	Before CPB	263.200±72.59	253.33±89.67	263.700±70.26	0.84
	During CPB	263.70±70.26	253.33±89.67	263.7±70.26	0.17
	After CPB	225.73±37.93	297.108±700.21	215±83.82	0.27
Lactate (mg/dL)	Before CPB	1.08±1.01	0.0±98.48	1.0±1.71	0.89
	During CPB	1.08±1.01	0.98±0.48	1.79±0.01	0.54
	After CPB	3.2±8.21	1.1±83.55	21.1±1.55	0.06
Hemoglobin (g/dL)	Before CPB	11.65±1.51	12.1±22.67	12.1±22.42	0.25
	During CPB	8.41±1.57	9.26±2.13	8.88±1.26	0.16
	After CPB	9.1±27.29	13.2±46.40	9.1±28.96	0.29

CPB, Cardiopulmonary bypass
Note: For patients whose CPB duration exceeded 1 hour, the tests were performed several times, and the mean was calculated.

Table 4: Frequencies of arrhythmias and the need for defibrillation after disconnection from CPB between the 3 study groups

Variable	N (%)			*P* value
	Epinephrine	Norepinephrine	Phenylephrine	
Arrhythmias	28 (32.9)	30(33.3)	27 (31.8)	0.05
	2 (2.2)	0 (0)	3 (2.2)	
Need for defibrillation	30 (34.1)	30 (33.3)	27 (31.8)	0.1
	0 (0)	0 (0)	3 (2.2)	
Total cases	30 (33.3)	30 (33.3)	30 (33.3)	

CPB, Cardiopulmonary bypass

Table 5: Median (interquartile) of medicine consumption (µg) and the duration of postoperative mechanical ventilation (h) between the 3 study groups

Variable	Median (interquartile range)			*P* value (the Kruskal–Wallis test)
	Epinephrine	Norepinephrine	Phenylephrine	
Medicine consumption (µg)	25 (20-40)	30 (20-40)	* 30 (20-40)	0.559
Duration of postoperative mechanical ventilation (h)	11 (8.5-15.50)	11 (7.75-15.25)	10 (6-11)	0.15

* Equivalence of phenylephrine with epinephrine and norepinephrine was done by dividing the obtained numbers by 30.

Table 6: Comparison of MAP and cerebral O_2 saturation at different time intervals between the study 3 groups

Variable	Time Interval	Mean ±SD			*P* value
		Epinephrine	Norepinephrine	Phenylephrine	
MAP (mm Hg)	Before the medication	48/20±4.48	46.5±60.90	44.63±57.47	0.84
	120 s after the medication	46.5±93.48	47.6±26.11	45.6±40.52	0.46
	150 s after the medication	47.8±56.59	47.6± 17.5	43.7±55.2	0.22
	180 s after the medication	44.7±80.81	46.6±83.26	47.9±11.14	0.76
Cerebral O_2 saturation (%)	Before the medication	59.10±2.16	62.8±19.21	59.8±86.66	0.38
	120 s after the medication	61.8±1.81	63.9±92.69	57.8±83.63	0.38
	150 s after the medication	61.9±4.47	63.8±75.74	57.8±83.76	0.11
	180 s after the medication	64.11±13.46	62.10±94.16	58.9±67.37	0.49

*Cross-statistical testing between the norepinephrine and phenylephrine groups showed a significant difference (*P*=0.029).

DISCUSSION

The present study assessed 90 patients out of 114 eligible cases undergoing cardiac surgery under CPB support in 3 groups: epinephrine, norepinephrine, and phenylephrine. Based on the data collected, the following results were achieved.

Most patients were candidates for coronary artery and valve replacement surgeries. Cerebral oxygenation in the groups receiving epinephrine, norepinephrine, or phenylephrine during open-heart surgery revealed that although the use of the mentioned vasopressors at different time intervals was associated with some degree of cerebral oxygenation, no statistically significant differences were noted between the 3 groups. It appears that cerebral oximetry during CPB was within normal limits.

In 2016, Hagen et al [6] determined the effect of norepinephrine on cerebral oxygenation during CPB and found no statistically significant correlations between the administration of norepinephrine (to maintain MAP around 80 mm Hg) and changes in cerebral O_2 saturation by the end of CPB, which is consistent with findings from the present study. We found no statistically significant differences in the mean and standard deviation of cerebral oxygenation at different time intervals (before the medication administration and 120, 150, and 180 seconds after medication administration).

In another research by Brassard et al [1] in 2014, the effects of norepinephrine and phenylephrine on the cerebral oxygenation of patients with diabetes mellitus (DM) comorbidities were evaluated during CPB. After the administration of norepinephrine to restore MAP during CPB, reduced cerebral oxygenation was noticed, associated with diminished frontal lobe oxygenation in patients with DM but not in those without DM. Similarly, phenylephrine administration was associated with a further decrease in frontal lobe oxygenation in the patients, especially those with DM.

The administration of epinephrine, norepinephrine, and phenylephrine did not affect serum lactate and pH levels in the study patients after CPB. Our literature review showed that no study had evaluated the effects of epinephrine, norepinephrine, and phenylephrine on serum lactate and pH levels in patients undergoing open-heart surgery.

Comparison of the effects of epinephrine, norepinephrine, and phenylephrine on time to restore normal heart rhythm and the need for defibrillation, pacemakers, and antiarrhythmic medicine use after declamping in patients undergoing open-heart surgery showed that only 3 cases (2.2%) in the phenylephrine group needed defibrillation. Still, statistical tests revealed no significant differences between the other 2 groups. The finding could be due to the effect of phenylephrine as an α-adrenergic receptor agonist, which may cause reflex bradycardia. [12] Additionally, no statistically significant differences were noted between the 3 groups in terms of the need for defibrillation or antiarrhythmic medicine use.

The activation of neutrophils and their subsequent presence in pulmonary blood circulation causes deep endothelial, epithelial, and interstitial damage to the lungs. The damage may cause decreased lung capacity and impaired gas exchange by increasing endothelial capillary permeability. Despite improvements in CPB techniques and intensive postoperative care, pulmonary function impairment after cardiac surgery is still an issue, probably related to low PaO_2 or high PCO_2. The condition might continue for several days and lead to mechanical ventilation. [13] In the present study, none of epinephrine, norepinephrine, and phenylephrine could reduce the duration of mechanical ventilation.

Results from the effects of epinephrine, norepinephrine, and phenylephrine on maintaining a MAP of 60 mm Hg to 80 mm Hg were compared, showing no statistically significant differences in the mean and standard deviation of MAP at different time intervals (before the medication and 120, 150, and 180 seconds after medication administration). A significant reason justifying the discrepancy between the results of the present study and those reported previously is different doses of epinephrine, norepinephrine, and phenylephrine, as well as different aortic clamping times among patients, which can definitely affect the outcome.

CONCLUSIONS

The findings from the present study indicate that the administration of epinephrine, norepinephrine, or phenylephrine during

CPB is not associated with a statistically significant difference in clinical variables, including hemodynamic parameters, arterial blood gas, lactate levels, and cerebral O_2 saturation in patients undergoing cardiopulmonary bypass surgery. Therefore, each of the abovementioned medicines can be used interchangeably in the event of systolic hypotension during CPB support.

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