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Clinical paper

Early post-resuscitation outcomes in patients receiving norepinephrine versus epinephrine for post-resuscitation shock in a non-trauma emergency department: A parallel-group, open-label, feasibility randomized controlled trial

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Abstract

Background: Post-resuscitation shock is the main cause of early death in post-cardiac arrest patients. To date, no randomized trial compares the efficacy between norepinephrine and epinephrine in post-resuscitation shock patients.

Objectives: This study aimed to assess the feasibility of the study protocol, and explore potential differences in efficacy and adverse events between norepinephrine and epinephrine in post-resuscitation shock patients.

Methods: This single-center, parallel-group, open-label, feasibility randomized controlled trial included adult non-traumatic cardiac arrest patients who had post-resuscitation shock within one hour after successful resuscitation. Patients were randomized to receive norepinephrine or epinephrine in a 1:1 ratio. Feasibility outcomes were reported descriptively and narratively. Exploratory analyses were performed to compare the efficacy and adverse events.

Results: A total of 40 patients were equally allocated. Most feasibility goals were achieved. All patients received the allocated intervention with no withdrawals. Ten (50%) patients in the norepinephrine group and 15 (75%) patients in the epinephrine group achieved the target blood pressure by the protocol with a median time of 42 and 39 min, respectively. However, the protocol deviated in 10 (25%) patients and the recruitment rate did not reach the acceptable threshold. The vasopressor dose to achieve the target blood pressure was significantly lower in the norepinephrine group. No significant differences in mortality rates and adverse outcomes were observed in the exploratory analyses.

Conclusion: It is feasible to conduct the definitive trial comparing early post-resuscitation outcomes in patients receiving NE versus EPI for post-resuscitation shock. Some protocol modifications are necessary.

Keywords: Post-resuscitation shock, Vasopressor, Norepinephrine, Epinephrine

Introduction

Post-resuscitation shock, as a consequence of post-cardiac arrest syndrome, is the main cause of early death in post-cardiac arrest patients.[1] The condition occurs in 50–70% of post-cardiac arrest patients.[2] Achievement of adequate tissue perfusion during the early post-cardiac arrest phase has a critical impact on survival and neurological outcomes of cardiac arrest patients.[1]

In post-resuscitation shock, maintenance of mean arterial pressure (MAP) $\geq$ 65 mmHg and systolic blood pressure (SBP) $\geq$ 90 mmHg utilizing crystalloid fluids, vasopressors, or inotropes is generally recommended.[3,4] Nevertheless, a gap of evidence exists concerning the most appropriate type of vasopressor for post-resuscitation shock. The latest recommendation in favor of norepinephrine (NE) was based on indirect evidence derived from patients with critical illness, septic shock, and cardiogenic shock.[3] Conversely, epinephrine (EPI) has also been widely used as the

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first-line vasopressor for post-resuscitation shock in various institutions, especially in Thailand. Recent retrospective studies reported higher mortality rates, unfavorable neurological outcomes, and cardiovascular complications among individuals receiving EPI compared to those receiving NE in post-resuscitation shock.[5,6] However, the imbalance of baseline characteristics and confounding factors between groups might have led to biases against EPI. EPI acts on alpha and beta-adrenergic receptors, causing vasoconstriction and positive inotropic effects, while NE has a less potent inotropic effect.[7] By these mechanisms, EPI seems to be more suitable for reversing post-resuscitation shock than NE, especially when post-resuscitation myocardial dysfunction occurs.

Currently, there is no randomized controlled trial (RCT) directly comparing the efficacy of NE and EPI in post-resuscitation shock. Therefore, we conducted a pilot feasibility study to ensure the practicality of the protocol and explore the potential efficacy and adverse events of NE and EPI for the definitive RCT.

Methods

Study design and setting

This study was a single-center, parallel-group, open-label, feasibility RCT conducted in the non-trauma ED of Siriraj Hospital.

Out-of-hospital cardiac arrest (OHCA) patients were transported to the ED in two modes: the emergency medical services (EMS) or private vehicles. The EMS providers were capable of providing pre-hospital advanced cardiopulmonary resuscitation (CPR) according to the 2020 American Heart Association Guidelines.[4]

Siriraj Hospital is a 2,000-bed academic tertiary hospital. The non-trauma ED has more than 20,000 visits per year, accepting only critical patients with emergency severity index level 1 and 2, requiring immediate life-saving interventions or having unstable vital signs.[8] The ED provided comprehensive advanced cardiac life support. Extracorporeal CPR (E-CPR) could be initiated in the ED in conjunction with the decision of cardiologists and cardiothoracic surgeons. Cardiology consultation was readily available.

For post-resuscitation care, EPI was routinely administered to maintain MAP $\geq$ 65 mmHg and SBP $\geq$ 90 mmHg in our institution. Central venous access and arterial lines could be accessed by emergency physicians. Post-cardiac arrest patients were preferably admitted to intensive care units (ICUs). However, if ICUs were not available, the patients would be admitted to general wards in a designated area where intensive care could be provided and later transferred to the ICUs when available and indicated. Targeted temperature management (TTM) could be initiated only at the ICUs and was selectively performed in our setting due to limited resources.

The study protocol was approved by Siriraj Institutional Review Board, with the certification of approval number Si 270/2022, and was registered in Thaiclinicaltrials.org, with the reference number TCTR20220418001. This research was written following Consolidated Standards of Reporting Trials 2010 reporting guidelines.[9]

Participants

The trial included all adult (age $\geq$ 18 years), non-traumatic OHCA or emergency department cardiac arrest (EDCA) patients who had post-resuscitation shock in the ED, defined as MAP < 65 mmHg or SBP < 90 mmHg within 1 hour after return of spontaneous circulation (ROSC). Patients were excluded if one of the following criteria was met: ST-elevation myocardial infarction (STEMI), cardiogenic shock, anaphylaxis, E-CPR initiated before ROSC, pregnancy, patients with Do-Not-Resuscitate orders, and cancer patients who were receiving palliative treatment. Patients with STEMI or cardiogenic shock were excluded because NE had established efficacy over EPI in this population.[10,11] Cardiogenic shock was diagnosed by the consultant cardiologist when the cause of arrest was most likely cardiac in origin with evidence of severe systolic dysfunction or mechanical failures. Patients could be withdrawn from the trial for any reason by the treating physicians or legal representatives at any time.

Sample size

Based on the previous observational study,[5] which showed the rate of death or re-arrest in the ED of 33.3% among patients receiving EPI and a rate of 15.6% among patients receiving NE, 92 patients in each group for the definitive trial would have 80% power to show the difference at a two-sided alpha level of 0.05. For this feasibility study, approximately 20% of the population needed in the definitive trial was recruited, which were 20 patients in each arm.

Enrollment and randomization

After ROSC, the legal representatives of the candidate cardiac arrest patients were approached by the investigators, regardless of hypotension status, to verbally explain the trial recruitment process and the trial protocol in advance. When post-resuscitation shock occurred, written informed consent was immediately obtained from the legal representatives. The patients were then randomly assigned in a 1:1 ratio to receive NE or EPI, using computer-generated, permuted blocks of 4, sealed in sequentially numbered opaque envelopes prepared by the research facilitator who was not involved in the recruitment process or patient care. The nurses then started infusing the allocated vasopressors per protocol in an open-label fashion.

Intervention and trial protocol

After randomization, patients received either NE or EPI infusion and titration to achieve the target blood pressure (BP), defined as MAP $\geq$ 65 mmHg and SBP $\geq$ 90 mmHg. For simplicity, non-weight-based, rounded dosing with fixed concentration was used in this study. An average patient weight of 60 kilograms (kg) was used to establish the vasopressor dose titration protocol.[12]

For the NE group, 4 mg of norepinephrine bitartrate diluted in 250 ml of 5% dextrose in water (concentration: 16 mcg/ml) was administered via a large peripheral vein or, more preferably, a central venous catheter if available. The initial infusion rate was 10 ml/h (~2.67 mcg/min), up-titrated by 10 ml/h every 5–10 min until reaching the target BP. If MAP remained above 90 mmHg for at least 10 min, NE could be titrated down 3–5 ml/h every 5–10 min as deemed appropriate by the treating physicians.

For the EPI group, 10 mg of epinephrine bitartrate diluted in 100 ml of normal saline (concentration: 100 mcg/ml) was administered via a large peripheral vein or, more preferably, a central venous catheter, as usual care. The initial infusion rate was 5 ml/h (~8.33 mcg/min), up-titrated by 5 ml/h every 5–10 min until reaching the target BP. If MAP remained above 90 mmHg for at least 10 min, EPI could be titrated down 1–2 ml/h every 5–10 min as deemed appropriate by the treating physicians.

The vasopressor dose was up-titrated according to protocol until reaching the target BP or meeting specific termination criteria. These criteria included death or re-arrest, NE infusion rate $\geq$ 50 ml/h or EPI infusion rate $\geq$ 35 ml/h, significant supraventricular or ventricular

arrhythmias, cardiogenic shock diagnosed by the consulting cardiologists, and initiation of extracorporeal membrane oxygenation (ECMO). If the target BP was reached or any termination criteria were met, treating physicians had the discretion to decide whether to continue up-titration, discontinue, switch the vasopressor, or add the second vasopressor as clinically directed. These criteria were established to alert the treating physicians for possible adverse effects of the study intervention such as arrhythmia or potential refractory shock. The upper vasopressor dose limits in the termination criteria were set according to the usual dosing practices in our institution.

Cardiac point-of-care ultrasound (POCUS) was performed by the attending emergency physicians 30 min after the intervention to evaluate the global left ventricular (LV) contractility function, graded to normal, minimally impaired, and significantly impaired function.[13] Other aspects of post-cardiac arrest care such as fluid therapy, inotropes, mechanical ventilation strategy, and targeted temperature management (TTM) were conducted at the discretion of the treating physicians.

Outcome measures

The primary outcomes were the feasibility and acceptability of the enrollment and the trial intervention protocol. Predefined acceptability criteria were established. To complete the definitive trial in 2 years, the expected recruitment rate of $\geq$ 8 patients per month was set, aiming for over 90% success in intervention receipt. Protocol deviation, in terms of dose titration per protocol and the initiation of the second vasopressor before meeting the termination criteria, and withdrawals for safety reasons were expected to be < 20% and 10%, respectively. More than 25% of the patients achieving the target BP before reaching the termination criteria and a median time within 120 min were set to ensure protocol effectiveness, safety, and acceptability. All primary outcomes were reported descriptively and narratively.

Secondary outcomes were death within 3 h after ROSC, re-arrest within 3 h, death within 6 h, 28-day mortality, significant supraventricular tachyarrhythmias (SVT) and ventricular tachyarrhythmias (VT), refractory shock, the achievement of the target BP, and the vasopressor dose when the target BP was achieved. Significant SVT was defined as sinus tachycardia, atrial fibrillation, atrial flutter, or supraventricular tachycardia with a ventricular rate of more than 150/min. Significant VT included both sustained and non-sustained VT. Refractory shock was defined as either persistent hypotension (SBP < 90 mmHg or MAP < 65 mmHg) despite the dosage of NE or EPI $\geq$ 30 mcg/min (0.5 mcg/kg/min in an average 60-kg patient) or requiring a second vasopressor to achieve the target BP. If a second vasopressor was present, the vasopressor dose when the target BP was achieved would be reported as the sum of both vasopressor doses in the NE-equivalent dose.[14]

Statistical analysis

All data were analyzed according to an intention-to-treat principle. Demographic data and baseline characteristics were reported by treatment arms. Continuous variables were explored using the Shapiro-Wilk and Kolmogorov-Smirnov tests, which showed non-normality for all continuous variables in the study. Continuous variables were expressed as median and interquartile range (IQR). For categorical variables, frequency and percentage were reported.

To explore the potential differences in efficacy and adverse events between the interventions, exploratory analyses were performed for secondary outcomes using the Mann-Whitney U test for continuous variables and Chi-square or Fisher exact test for categorical variables as appropriate. For all statistical analyses, a *p*-value of less than 0.05 was considered statistically significant unless defined otherwise.

Result

Baseline characteristics

The trial enrolled patients from May 2022 to June 2023. There were 196 cardiac arrest patients during the study period. After exclusion, as shown in Fig. 1, a total of 40 patients were randomized, resulting in 20 patients in each study arm.

Baseline characteristics are presented in Table 1. The predominant gender was female. Almost all patients presented with initial non-shockable rhythm. Approximately half of the OHCA patients in both groups were transported to the ED by private vehicles. The majority of the presumed etiologies of cardiac arrest were respiratory and metabolic derangement. Only a few patients received TTM. There was no missing data, except the LV contractility which cardiac POCUS was not performed in 4 patients.

Primary outcomes

Table 2 summarizes the primary outcomes and the expected values assessing patient enrollment and trial protocol feasibility and acceptability. Most feasibility goals were achieved. All patients successfully received the allocated interventions with no withdrawals. A total of 10 (50%) patients in the NE group and 15 (75%) patients in the EPI group achieved the target BP before reaching the termination criteria. The median time to achieve the target BP was under 120 min. However, two feasibility outcomes exceeded acceptable thresholds. The average recruitment rate was 3.3 patients per month. Ten (25%) patients experienced protocol deviation, primarily due to a lower up-titration dose than what was prespecified in the protocol.

Secondary outcomes

Table 3 depicts the secondary outcomes and exploratory analyses for potential differences in efficacy and adverse events. For mortality, there were no statistical differences in the rate of death during the early post-resuscitation period at 3 and 6 h between the NE and EPI groups. The rate of re-arrest within the first 3 h was numerically but not statistically higher in the NE group. There was no difference in 28-day mortality between groups. Two patients in each group were alive after 28 days. The Cerebral Performance Category scale at discharge was 3 and 5 for patients in the NE group, and 2 and 3 for patients in the EPI group.

The study did not identify any disparity in the incidence of significant arrhythmias. The incidence of refractory shock was numerically lower in the NE group. The target BP was ultimately achieved in 14 (70%) patients in the NE group and 16 (80%) patients in the EPI group, without statistical difference between groups. However, the median vasopressor dose when the target BP was achieved was significantly lower in the NE group. Cardiac POCUS at 30 min after ROSC did not demonstrate significant differences between groups in global left ventricular contractility function.

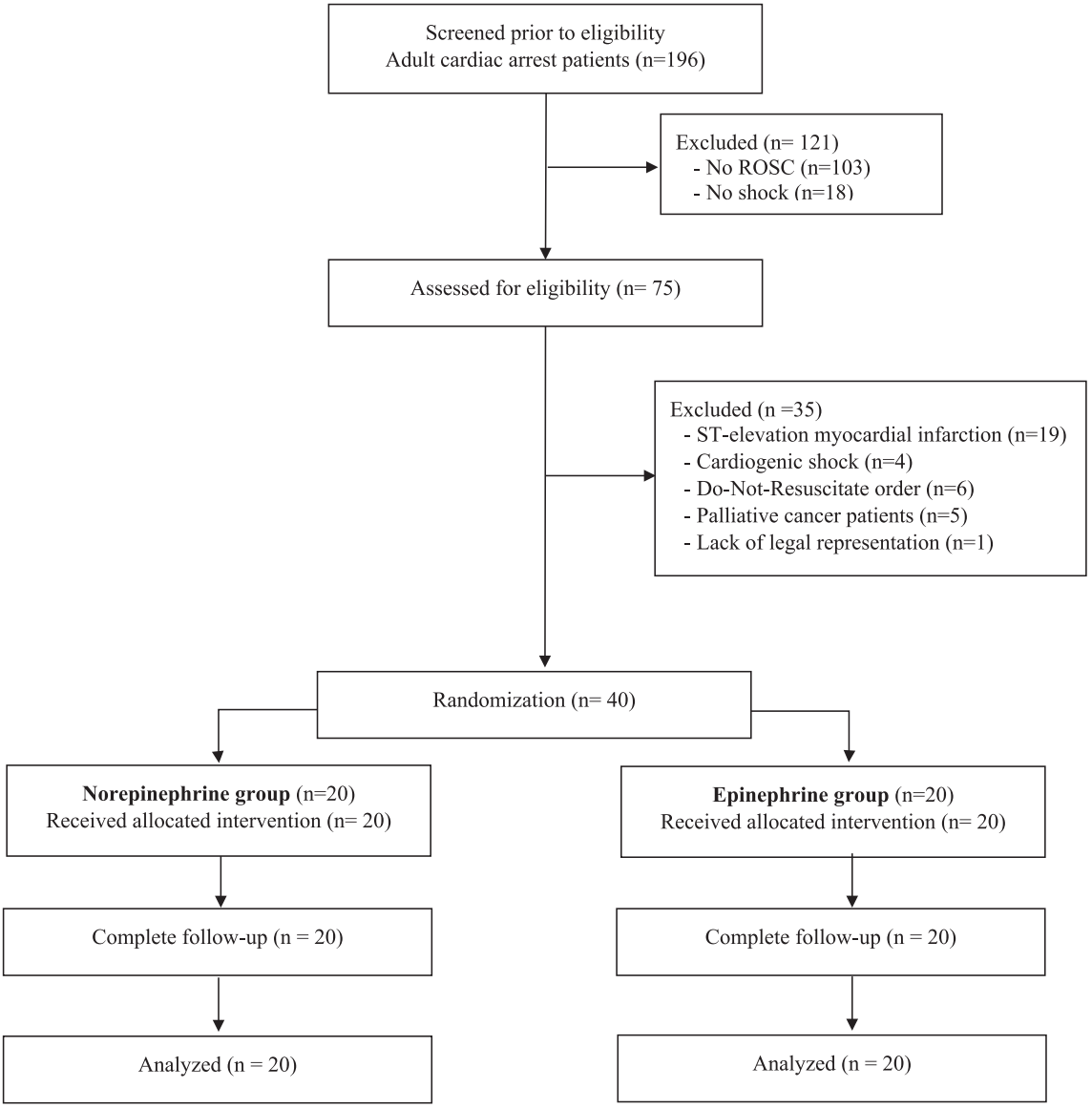

Fig. 1 – Study flow diagram.

Discussion

The feasibility and acceptability of the protocol were assessed for the definitive RCT aiming to compare the efficacy of NE and EPI in early post-resuscitation shock. The recruitment rate fell below expectations due to an insufficient number of cardiac arrest patients. A longer enrollment period would be required for the definitive trial. Even though the rate of protocol deviation was more than the predefined expectation, the target BP was still achieved before reaching the termination criteria in 63% of the patients. In addition, the median time to achieve the target BP was less than 1 hour after ROSC in both groups. Although there was no specific recommendation regarding the cut-off for time to achieve the target BP in post-cardiac arrest patients, a delay in reaching the target MAP was associated with higher mortality.[15] Gaieski and colleagues reported a 28% reduction in mortality when the target BP was achieved within 6 h after ROSC.[16]

The median dose of NE required to achieve the target blood pressure was significantly lower than that of EPI. However, previous observational studies reported no significant difference in doses of the vasopressors.[5,6] Pharmacologically, EPI has less α_1- affinity but more β_1-affinity relative to NE at an equivalent dose.[17] Given the majority of the patients in this study exhibited preserved LV contractility which inferred vasodilatory shock, this could explain the higher dose of EPI required to achieve the effective vasoconstriction. It also implied the efficacy of NE over EPI in post-resuscitation shock in cardiac arrest from non-cardiac causes. On the other hand, the initial dose, the up-titration dose, and the threshold for adding the second vasopressor were substantially higher in EPI according to the protocol. The ability to reach a higher dose in a shorter time of EPI might also result in higher dose utilization compared to NE. Therefore, the definitive trial should establish a comparable initial dose, titration dose, and protocol termination dose between NE and EPI to eliminate the possibility of differences arising from unequal dosing.

Table 1 – Baseline characteristics.

Characteristics	Norepinephrine (n = 20)	Epinephrine (n = 20)
Age (years), median (IQR)	74 (60–79)	66 (58–75)
Male, n (%)	9 (45)	5 (25)
Charlson Comorbidity Index, median (IQR)	5 (4–6)	4.5 (3–6)
Type of cardiac arrest, n (%)		
OHCA	15 (75)	16 (80)
EDCA	5 (25)	4 (20)
Witnessed status in OHCA, n (%)		
Witnessed by bystander	9 (60)	10 (63)
Witnessed by EMS	0 (0)	0 (0)
Unwitnessed	5 (33)	6 (38)
Unknown	1 (7)	0 (0)
Bystander CPR in OHCA, n (%)	6 (40)	5 (31)
Initial rhythm, n (%)		
Ventricular fibrillation	0 (0)	1 (5)
Pulseless ventricular tachycardia	0 (0)	0 (0)
Pulseless electrical activity	12 (60)	9 (45)
Asystole	8 (40)	9 (45)
Unknown shockable rhythm	0 (0)	0 (0)
Unknown non-shockable rhythm	0 (0)	1 (5)
Modes of transportation for OHCA, n (%)		
EMS transport	7 (47)	9 (56)
Private vehicle	8 (53)	7 (44)
Presumed etiology of cardiac arrest, n (%)		
Cardiac	0 (0)	0 (0)
Respiratory	9 (45)	10 (50)
Metabolic derangement	7 (35)	8 (40)
Hypovolemic/hemorrhage	1 (5)	0 (0)
Unknown	2 (10)	2 (10)
Other	1 (5)	0 (0)
Time from ROSC to shock (min), median (IQR)	10 (0–32)	17 (3–36)
Initial hemodynamic parameter, median (IQR)		
MAP (mmHg)	53 (48–58)	50 (46–59)
SBP (mmHg)	72 (62–78)	66 (60–79)
HR (beats per minute)	105 (86–120)	99 (80–117)
Disposition, n (%)		
ICU	5 (25)	5 (25)
General ward	7 (35)	9 (45)
Died in the ED	8 (40)	6 (30)
ECMO, n (%)	0 (0)	0 (0)
Targeted temperature management	1 (5)	2 (10)

Abbreviations: *CPR* cardiopulmonary resuscitation, *ECMO* extracorporeal membrane oxygenation, *ED* emergency department, *EDCA* emergency department cardiac arrest, *EMS* emergency medical service, *EPI* epinephrine, *HR* heart rate, *IQR* interquartile range, *ICU* intensive care unit, *LV* left ventricle, *MAP* mean arterial pressure, *OHCA* out-of-hospital cardiac arrest, *ROSC* return of spontaneous circulation, *SBP* systolic blood pressure.

Table 2 – The primary outcomes and the expected values for the feasibility and acceptability of the enrollment and the trial protocol.

Primary outcomes	Total (n = 40)	Norepinephrine (n = 20)	Epinephrine (n = 20)	Expected value
Recruitment rate (patients/month)	3.3			>8
Interventions successfully initiated, n (%)	40 (100)	20 (100)	20 (100)	>90%
Protocol deviation, n (%)	10 (25)	4 (20)	6 (30)	<20%
Withdrawal rate, n (%)	0 (0)	0 (0)	0 (0)	<10%
Target BP achieved before reaching the termination criteria, n (%)	25 (63)	10 (50)	15 (75)	>25%
Time to achieve the target BP (min), median (IQR)		42 (21–61)	39 (27–94)	<120

Abbreviation: *BP* blood pressure, *mcg* microgram, *min* minute, *IQR* interquartile range.

Table 3 – Secondary outcomes and the exploratory analyses of potential differences in efficacy and adverse events between norepinephrine and epinephrine.

Secondary outcomes	Norepinephrine (n = 20)	Epinephrine (n = 20)	*p*-value
Death within 3 h, n (%)	4 (20)	3 (15)	1.000
Re-arrest within 3 h, n (%)	8 (40)	4 (20)	0.168
Death within 6 hn (%)	4 (20)	3 (15)	1.000
28-day mortality, n (%)	18 (90)	18 (90)	1.000
Significant supraventricular arrhythmia, n (%)	0 (0)	1 (5)	1.000
Sinus tachycardia, n (%)	0 (0)	0 (0)	
Atrial fibrillation / Atrial flutter, n (%)	0 (0)	1 (5)	
SVT, n (%)	0 (0)	0 (0)	
Significant ventricular arrhythmia, n (%)	1 (5)	0 (0)	1.000
NSVT, n (%)	0 (0)	0 (0)	
VT, n (%)	1 (5)	0 (0)	
Refractory shock, n (%)	3 (20)	8 (47)	0.108
Vasopressor dose > 0.5 mcg/kg/min	0 (0)	8 (40)	
Second vasopressor received	3 (15)	2 (10)	
Target BP ultimately achieved, n (%)	14 (70)	16 (80)	0.465
Vasopressor dose when the target BP was achieved (mcg/min), median (IQR)	8.7 (5.3–10.7)	25.0 (16.7–41.7)	<0.001
Left ventricular contractility after 30 min, n (%)			0.440
Normal	15 (75)	14 (70)	
Minimally impaired	2 (10)	4 (20)	
Significantly impaired	0 (0)	1 (5)	
Not performed	3 (15)	1 (5)	

Abbreviations: *BP* blood pressure, *IQR* interquartile range, *kg* kilogram, *mcg* microgram, *min* minute, *NSVT* non-sustained ventricular tachycardia, *SVT* supraventricular tachycardia, *VT* ventricular tachycardia.

The previous retrospective studies reported significantly lower mortality in the NE group during the early post-resuscitation period, in contrast to this study.[5,6] Significant arrhythmias in the NE and EPI groups were also trivial compared to the previous study.[5] The conflicting results might be related to the exclusion of patients with cardiogenic shock and ST-elevation myocardial infarction, in which epinephrine was associated with a trend toward higher mortality and a higher incidence of arrhythmias.[10,11] The incidence of refractory shock tended to be higher in the EPI group, consistent with the previous studies.[5,10] Several cellular and metabolic derangements caused by EPI were also proposed as a cause of the higher rate of refractory shock.[7,10,19] Surprisingly, the rate of re-arrest within 3 h was numerically twice as high in the NE group. This could be attributed to the relatively lower initial dose and titrating dose of NE compared to the dose of EPI. A retrospective study also reported higher odds of re-arrest when the initial vasopressor dose after ROSC was less than 0.25 mcg/kg/min.[18] An interim analysis for the definitive trial should closely monitor this particular issue. In addition, based on the early death and re-arrest rate from this pilot study, a total of 82 patients are required in each arm for the definitive trial.

Overall, these findings support the feasibility of the definitive trial. Protocol modifications are deemed necessary, particularly concerning the equivalent protocolized dose titration between the vasopressors. An extended recruitment period is anticipated.

Limitations

This study has several limitations. First, the study was conducted in a developing country with less established public first aid, limited EMS systems, and limited availability of ICUs, which might contribute to a lower incidence of initial shockable rhythms and the higher mortality observed in this study. Post-cardiac arrest care provided to the patients did not fully meet the standards published in international guidelines. This limits the generalizability of the study results. Second, there are variations in the vasopressor doses, concentrations, and titration practices among different institutes and countries. The concentration and the initial dose of EPI described in this study were relatively high compared to the standards in other parts of the world. The lack of standardization in vasopressor administration could complicate the interpretation of the results and limit the ability to directly apply the findings to clinical practice in other settings. Last, the small sample size of this feasibility study poses a limitation to the result interpretation. A larger definitive trial would provide more robust and reliable evidence.

Conclusion

It is feasible to conduct the definitive trial comparing early post-resuscitation outcomes in patients receiving norepinephrine versus epinephrine for post-resuscitation shock. It is crucial to ensure an equivalent dose titration protocol for both vasopressors. An interim analysis is recommended to closely monitor adverse outcomes, focusing on the incidence of re-arrest in the early post-resuscitation period. An extended recruitment period is anticipated.

CRediT authorship contribution statement

Wasin Pansiritanachot: Data curation, Formal analysis, Methodology, Validation, Writing – original draft, Writing – review & editing. **Orapim Vathanavalun:** Investigation, Methodology, Resources, Visualization, Writing – original draft. **Tipa Chakorn:** Conceptualiza-

tion, Project administration, Supervision, Validation, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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