Early Use of Norepinephrine in Septic Shock Resuscitation (CENSER) : A Randomized Trial

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collection. Suthipol Udompanturak carried out the statistical analysis. Every authors read and approved the final manuscript.

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At a Glance Commentary: Recent evidence from animal studies and retrospective human studies has indicated the efficacy of early norepinephrine administration during septic shock resuscitation. However, there was limited information from prospective randomization trial to support this postulation. In this double-blind randomized controlled trial that enrolled 310 adults sepsis with hypotension, early norepinephrine administration resulted in significant higher shock control rate than standard treatment (76.1% vs 48.4%, respectively). The findings of this

study support the benefit of early administration of norepinephrine at the initiation of sepsis with hypotension resuscitation, together with fluid therapy.

ABSTRACT

Rationale: Recent retrospective evidence suggests the efficacy of early norepinephrine administration during resuscitation; however, prospective data to support this assertion are scarce.

Objectives: To conduct a Phase II trial evaluating the hypothesis that early low-dose norepinephrine in adults sepsis with hypotension increases shock control by six hours compared with standard care.

Methods: This single-center, randomized, double-blind, placebo-controlled clinical trial was conducted at Siriraj Hospital, Bangkok, Thailand. The study enrolled 310 adults diagnosed with sepsis with hypotension. The patients were randomly divided into two groups: early norepinephrine (n=155) and standard treatment (n=155). The primary outcome was shock control rate (defined as achievement of mean arterial blood pressure $\geq$65mmHg, with urine flow $\geq$0.5mL/kg/h for 2 consecutive hours, or decreased serum lactate $\geq$10% from baseline) by 6 hours after diagnosis.

Measurements and Main Results: The patients in both groups were well matched in background characteristics and disease severity. Median time from emergency room arrival to norepinephrine administration was significantly shorter in early norepinephrine group (93 vs. 192min; P<0.001). Shock control rate by 6 hours was significantly higher in early norepinephrine group (118/155[76.1%] vs. 75/155[48.4%]; P<0.001). 28 day mortality was not different between groups: 24/155 (15.5%) in the early norepinephrine group versus 34/155 (21.9%) in the standard treatment group (P=0.15). The early norepinephrine group was associated with lower incidences of cardiogenic pulmonary edema (22/155[14.4%] vs. 43/155[27.7%]; P=0.004) and new-onset arrhythmia (17/155[11%] vs. 31/155[20%]; P=0.03).

Conclusions: Early norepinephrine was significantly associated with increased shock control by 6 hours. Further studies are needed before this approach is introduced in clinical resuscitation practice.

Trial registration: ClinicalTrials.gov registration number; NCT01945983. (CENSER trial)

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INTRODUCTION

Septic shock is characterized by systemic vasodilatation and vascular leakage arising from systemic inflammation induced by serious infection.[1] Management, besides specific treatments consisting of antibiotics and source removal, includes effective restoration of the hemodynamic derangement and effective organ support. Generally, intravenous fluid is given first, followed by infusion of vasopressors when the blood pressure goal is not achieved after reaching the optimal intravascular volume.[2]

Recently, several studies advocated the benefits of administering norepinephrine at the beginning of resuscitation. A rat model of endotoxic shock[3] demonstrated that norepinephrine administration at the early stage of endotoxic shock, improved mean arterial pressure, aortic blood flow and sustained mesenteric blood flow. In humans, a retrospective study on a patient cohort with early norepinephrine administration revealed a shorter time to blood pressure goal achievement and favorable mortality outcome.[4] Another study demonstrated increased cardiac preload and cardiac output in patients with life-threatening hypotension who received early norepinephrine after fluid replacement.[5] Finally, a cohort analysis of patients who underwent septic shock resuscitation showed a mortality advantage from early norepinephrine use and illustrated the effect of delayed use of this agent.[6] Notably, all of these studies were retrospective, which means that they were all subject to unavoidable selection biases, such as hypotension severity, and fluid volume administered prior to norepinephrine initiation. Therefore, we performed a randomized controlled trial to examine the hypothesis that administering low dose norepinephrine at the beginning of sepsis induced

hypotension resuscitation accelerates shock control. Some of the results of these studies have been previously reported in the form of an abstract.[7]

METHODS

TRIAL DESIGN

This phase II, randomized, double-blind, placebo-controlled clinical trial was conducted at the Department of Medicine, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand during the October 2013 to March 2017 study period. Siriraj Hospital is Thailand's largest university-based national tertiary referral center. The trial was funded by Siriraj Critical Care Research Funding, and the funder had no role in the study design, analysis, or outcome assessment. The study protocol was developed by the investigator committee and approved by the Siriraj Institutional Review Board (SIRB) (approval no. Si 507/2013). The study complied with all of the principles set forth in the Declaration of Helsinki (1964) and its subsequent provisions. Informed consent to participate was obtained from each patient, or their legal guardian if the participant was unable to provide consent, prior to inclusion in the study. All participant screening and enrollment was performed by the co-investigators (Figure 1.). The details of the screening and enrollment processes are available in the study's supplement. The outcome evaluation, data management, and analysis were conducted by the principal investigator and a statistician, both of whom were blinded to the patient enrollment and treatment process.

PARTICIPANT ENROLLMENT, RANDOMIZATION, AND INTERVENTION ASSIGNMENT

Adults aged ≥18 years who presented at the emergency room with hypotension determined by mean arterial blood pressure (mABP) lower than 65 mmHg and infection as the suspected cause were eligible for enrollment if they met the diagnostic criteria for sepsis according to the Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2012.[8] Patients who met the septic shock diagnostic criteria for more than 1 hour before randomization and those who had acute cerebral vascular event, acute coronary syndrome, acute pulmonary edema, status asthmaticus, active cardiac arrhythmias, active gastrointestinal hemorrhage, pregnancy, seizure, drug overdose, burn injury, trauma, requirement for immediate surgery, or advanced-stage cancer were excluded. Patients who signed to refuse medical treatment, including fluid resuscitation, vasopressor and endotracheal intubation, were also excluded.

After enrollment, patients were randomly assigned in a 1:1 ratio by their sequential number of enrollment, to receive either early norepinephrine administration (early norepinephrine group) or placebo (standard treatment group), together with fluid resuscitation at the initiation of hypotension resuscitation. Randomization was performed using a computer-generated randomization table derived from www.randomization.com. This process was performed by an investigator (ST) who had no other role in patient enrollment or management. The other investigators, the patients, the patients' relatives, the attending physicians, and the nurses were all blinded to the study assignment. The study drug (norepinephrine or placebo) was prepared by a pharmacist, who had no other role in the trial. The study drugs were packaged in identically shaped containers labeled with sequential numbers according to the randomization table order. For the study drug, 4 mg of norepinephrine was mixed with 250 mL of 5% dextrose in water (5%D/W), giving a

final norepinephrine concentration of 16 µg/mL. For the placebo comparator, 250 mL of 5%D/W was prepared. The study drug was infused via either peripheral line or central venous catheter (when available) at an individually adjusted rate according to the patient's body weight to achieve a dose of norepinephrine of 0.05 µg/kg/min. The study drug was infused for a period of 24 hours without titration in both groups.

All eligible patients received treatment for septic shock according to the Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2012.[8] This included infusion of crystalloid solution, appropriate antibiotic therapy, source control, and organ support as directed by the attending physicians. The infusion rate and volume of intravenous fluid therapy was ordered according to the discretion of the treating clinician. If the hemodynamic goal (mABP $\geq$65mmHg) was not reached after optimal fluid (at least 30ml/kg) and study drug infusion, open label vasopressors were permitted when no attenuation of shock was observed.

After initial resuscitation in the emergency room, patients who required endotracheal intubation for mechanical ventilation, required initiation of renal replacement therapy and/ or required invasive hemodynamic monitoring were transferred to the medical intensive care unit (ICU). Hemodynamically stable patients with no indications for mechanical ventilator or renal replacement therapy support were transferred to the general medical ward. The nurse to patient ratio was 1:1 in ICU and 1:3 in general medical ward. All patients admitted to the ICU had an arterial line inserted for continuous blood pressure monitoring.

OUTCOME ASSESSMENT

The primary outcome of this study was shock control rate by 6 hours after diagnosis of sepsis with hypotension. Shock control rate was defined as achievement of sustained mABP of at least 65 mmHg,[9] together with evidence of adequate tissue perfusion. Patient's blood pressure was measured every 15 minutes after enrollment, either by automated non-invasive method or via an arterial line, when available. Target mABP achievement was defined as mABP of 65 mmHg or over, persisted for 2 consecutive measurements. Adequate tissue perfusion was defined as continuation of urine flow at >0.5 mL/kg/h for 2 consecutive hours, or decreased in serum lactate by more than 10% from the initial lactate level.[10–12]

The secondary outcomes were 28-day mortality and hospital mortality. Rate of respiratory failure requiring mechanical ventilator support, rate of renal failure requiring renal replacement therapy, and number of organ support-free days to day 28 were also recorded. The calculation of organ support-free days to day 28 was based on the formula proposed by Russell JA, et al.[13] (Supplement)

For safety outcome assessment, we recorded new onset of cardiac arrhythmia, organ ischemia, and cardiogenic or non-cardiogenic pulmonary edema from diagnosis of sepsis with hypotension to hospital discharge or death. Causes of death were classified into refractory septic shock, sequelae of multiple organ failure, recurrent infection, sudden cardiac death unrelated to septic shock, and other causes. The definition of all safety outcomes and causes of death are presented in the supplement. The adjudication of safety outcomes and causes of death was performed by the attending physician according to the pre-specified definitions. These assessments were performed prospectively on a day-by-day basis.

STATISTICAL ANALYSIS

According to our previous study,[12] the sample size calculation was based on a predicted rate of shock control by 6 hours after sepsis with hypotension resuscitation of 60% in the standard treatment group versus 80% in the early NE group. Enrollment of 150 participants per group would provide at least 80% power to assess the difference in the primary outcome between the two groups at a two-sided alpha error of 0.05. All primary and secondary outcomes analyses were based on the intention-to-treat principle. Patients who died before primary outcome assessment were considered treatment failure.

We used the Wilcoxon rank-sum test for continuous variables and the chi-square test or Fisher's exact test, where appropriate, for categorical variables. The primary outcome and safety outcomes were evaluated by the chi-square test. For the 28-day mortality analysis, time to death was calculated from date of septic diagnosis to date of death. Survival distributions in the two groups were estimated by plotting Kaplan–Meier curves. The hazard ratio of 28-day mortality was calculated by the Cox proportional hazards model. Values of $P<0.05$ were considered to indicate statistical significance. All data analyses were performed using SPSS Statistics version 18 (SPSS. Inc., Chicago, IL, USA).

RESULTS

PATIENTS

Four hundred and fifty-six patients with an mABP lower than 65 mmHg were screened. Of those, 320 patients satisfied the inclusion criteria and were randomized into either the early norepinephrine group or the standard treatment group. Seven patients in the study group and 3 patients in the control group later withdrew their consent to participate. Of the remaining 310 patients, 155 patients were randomly

allocated to each of the two groups (Figure 1). Patients' baseline characteristics, including age, underlying conditions, and disease severity, were well matched between groups. The following median baseline values indicate the severity of the study participants: APACHE-II score: 20 (interquartile range [IQR]:16–26), mABP: 56 mmHg (IQR:51–60), and serum lactate level: 2.8 mmol/L (IQR:1.8–5.3) (Table 1). No patients in either group required mechanical ventilator or renal replacement therapy before randomization.

There was no significant difference in median time from diagnosis to study drug initiation, or time from diagnosis to open-label norepinephrine initiation between early norepinephrine and standard treatment groups. Median time from emergency room arrival to norepinephrine administration was significantly shorter in the early norepinephrine group than in the standard treatment group (93 min [IQR:72-114] vs 192 min [IQR:150-298]; P<0.001) (Table 4). The proportion of patients that was admitted to the ICU was not different between groups (54.8% in the early norepinephrine group vs 51.6% in the standard treatment group, P=0.57). Among patients who were admitted to the ICU, the median time from diagnosis to ICU admission was similar between the study group and the control group (6 hours and 36 minutes [IQR:4:35-9:52] vs 6 hours and 35 minutes [IQR:5:15-10:34]; P=0.34). Among those who were transferred to the general medical ward, median time from diagnosis to admission was also not significant different between the early norepinephrine group and the standard treatment group (6 hours and 23 minutes [IQR:4:25-10:34] vs 6 hours and 45 minutes [IQR:4:24-10:54]; P=0.66) (Table 4).

OUTCOMES

The shock control rate by 6 hours after the initiation of resuscitation was higher in the early norepinephrine group than in the standard treatment group (76.1% vs. 48.4%; odds ratio [OR]: 3.4; 95% confidence interval [CI]: 2.09–5.53; P<0.001) (Table 2). For the individual endpoints by 6 hours, the achievement of target mABP (>65 mmHg), urine output (>0.5 mL/kg) and lactate clearance (>10%) were all significantly higher in the early norepinephrine group (all P<0.05). However, the rate of lactate normalization was not different between groups. There were more patients in the early norepinephrine group who achieved all targets by 6 hours than patients in the standard treatment group (31.0% vs. 17.4%; P=0.005). Similarly, there were more patients in the study group than in the control group who achieved both target mABP and target urine output (35.5% vs. 24.5%; P=0.04). In contrast, achievement of both target mABP and target lactate clearance >10% within 6 hours was not difference between the study and control groups (9.7% vs. 6.5%; P=0.3) (Table 2).

Median time from diagnosis to achieving target mABP $\geq$65 mmHg was shorter in the early norepinephrine group (3:30 hours vs. 4:45 hours; P<0.001). The median time from diagnosis to achieving shock control was 4 hours 45 minutes in the study group, which was significantly shorter than the 6 hours 2 minutes in the control group (P<0.001). Median of mABP was significantly higher in the early norepinephrine group during the 4th to 6th hour after diagnosis (P<0.05) (Figure 3A., available in the supplement).

Regarding the amount of intravenous fluid, there was no significant difference between groups for the total volume of fluid administered at any time. Open-label norepinephrine was used in 67.7% of study group patients, compared with 80% of control group patients (P=0.01). Although patients in the early norepinephrine group received a higher median norepinephrine dosage during the 2nd to 5th hours after

diagnosis, the norepinephrine dosage was the same between groups after the 6th hour (Figure 3B., available in the supplement). Other vasoactive agents, including epinephrine, dopamine, and dobutamine, were used in similar proportions when compared between groups. No patient in either group had cessation of study medication due to high blood pressure.

Mortality at 28 days was 15.5% in the early norepinephrine group and 21.9% in the standard treatment group (relative risk [RR]: 0.79, 95%CI: 0.53-1.11; P=0.15) (Table 2). The Kaplan–Meier curves of 28-day mortality are shown in Figure. 2. There was no difference between groups for the rates of mechanical ventilator support or renal replacement therapy (Table 2). The median number of organ support-free days to day 28 also did not differ between the two groups.

Patients in the early norepinephrine group had a lower rate of cardiogenic pulmonary edema (14.4% vs. 27.7%; P=0.004) and new-onset arrhythmia (11% vs. 20%; P=0.03). However, other complications, including limb ischemia, and intestinal ischemia, were similar between groups (Table 3). The leading cause of death was sequelae of multiple organ system failure, followed by refractory septic shock.

DISCUSSION

This double-blind randomized controlled trial revealed norepinephrine administration at the beginning of sepsis with hypotension resuscitation to be associated with a higher shock control rate by 6 hours compared with the standard treatment. Occurrence of organ failure, such as respiratory failure requiring ventilator support and renal failure requiring renal replacement therapy, did not differ between groups. However, two adverse events, cardiogenic pulmonary edema and new-onset arrhythmia, occurred in lower proportions in the early norepinephrine group.

This is the first study to assess the benefit of early norepinephrine administration for sepsis related hypotension resuscitation on surrogate short-term, shock control endpoints. Early norepinephrine administration improved mABP, urine output and lactate clearance by 6 hours. Our selected hemodynamic endpoints represent both macro- and micro-circulation restoration. A target mABP of ≥65 mmHg was selected to represent macro-circulation restoration, because a previous study reported that the targeted mABP higher than 65 mmHg did not improve mortality.[9] Data from a recent multicenter retrospective analysis showed that septic patients who had an mABP during ICU admission lower than 65 mmHg, had a significantly higher risk of mortality, acute kidney injury and myocardial injury.[14] For tissue perfusion evaluation, we used urine flow >0.5 mL/kg/h for 2 consecutive hours as evidence of adequate kidney blood flow and splanchnic circulation restoration. In those who had no urine or urine flow less than 0.5 mL/kg/h, lactate clearance >10% was used as the evaluative parameter. That evaluation protocol was based on evidence from a previous randomized controlled trial that found that shock resuscitation guided by serum lactate reduction associated with lower hospital mortality than those who did not monitor lactate clearance.[15] From our previous report, the achievement of both macro- and micro-circulation targets was associated with lower hospital mortality than the rate observed in patients who met only mABP target or no target at all.[12]

As noted from the disease pathophysiology, vasodilatation and leakage are prominent features. Thus, effective restoration of the perfusion deficit should begin with both fluid repletion and vasopressors. Several retrospective studies in patients with septic shock support this hypothesis.[4,6] Specifically, shorter hypotension duration and lower mortality were noted in patients with early norepinephrine administration.

The results of our study, which is the first randomized controlled trial, to investigate the effect of early norepinephrine, revealed a shorter shock interval in the early norepinephrine group than in the standard treatment group.

The lower occurrences of congestive heart failure and new-onset arrhythmia in the early norepinephrine group were not observed in other studies. A study in coronary blood flow during sepsis revealed increased perfusion together with increased oxygen demand.[16] Norepinephrine restored global perfusion, but did not further increase coronary blood flow. In an observational study, patients with septic shock and severe hypotension were given norepinephrine after median fluid resuscitation of 1000 mL. Using a noninvasive measurement (PiCCOplus), improved cardiac output was noted by the mechanism of increasing cardiac preload and cardiac contractility.[17] Thus, the lower cardiac events in our patients may be explained by decreasing oxygen demand resulting from shorter shock duration and improved cardiac contractility arising from early use of norepinephrine. However, the safety of early norepinephrine administration relative to lower incidence of congestive heart failure and new-onset arrhythmia, still needs to be confirmed.

Splanchnic hypoperfusion is an important concern when norepinephrine is given early. Vasoconstriction induced by norepinephrine may aggravate internal organ ischemia and lead to patient deterioration.[18,19] Recent studies examined this concern and revealed that norepinephrine did not alter perfusion to the gut and kidney.[20,21] Although no objective measurements were made in the present study, there was no difference in prevalence of organ failure between groups. Our study revealed similar rates of acute limb ischemia, intestinal ischemia, and gastrointestinal bleeding between groups, which may indicate prolonged inadequate tissue perfusion during septic shock resuscitation.

Fluid overload is a common complication during sepsis resuscitation. Systemic inflammation causes intravascular fluid leakage into the interstitial area, and subsequent large amounts of crystalloid resuscitation can fill up both intravascular and interstitial spaces, resulting in total body fluid excess. Early use of norepinephrine decreases the use of fluid replacement, possibly by constricting the dilated vascular bed, and shortens resuscitation duration. This was described in the above-mentioned and another recently reported animal studies[3,22] but not in our study. Possible explanations are that: 1) the study was carried out during 2013–2017 when the Surviving Sepsis Campaign Guidelines were used, meaning that fluid was given toward a target intravascular volume or central venous pressure; and 2) norepinephrine was used at a low dose (0.05 μg/kg/min) to avoid excessive vasoconstriction, a serious complication of norepinephrine, especially during inadequate preload, and this may result in sub-optimal increased cardiac preload and vasoconstriction that was sufficient to reduce hypoperfusion duration, but not resuscitation volume.

Concerning the timing of intervention, our study showed a remarkably shorter duration from emergency room presentation to study drug initiation than previous septic shock management studies. The reported median time from emergency room presentation to randomization in the ProCESS, ARISE, and PROMISE trials was 162 minutes among the early goal-directed therapy groups and 159 minutes among the standard treatment group.[23] In contrast, ours median time from emergency room arrival to administration of the study drug was 93 minutes. Hence, patients in early norepinephrine group received norepinephrine at least 1 hour earlier than the patients in the aforementioned trials.

This study has some limitations. First, we could not mask the effect of norepinephrine in the early norepinephrine group. The rapid increase in patient blood pressure may have provided clues to attending physicians. However, up to 20% of patients in the standard treatment group responded similarly to the placebo infusion. Second, due to the limited number of ICU beds available at our center, we had to transfer about 47% of patients that did not require mechanical ventilator or dialysis to the general medical ward. Moreover, some patients required adjustment of their norepinephrine infusion dosage and the use of vasopressors on the ward would be unlikely to occur at many institutions worldwide. Third, this study did not aim to evaluate mortality, so the effect of early norepinephrine administration on mortality cannot be inferred from the results of this study. Furthermore, we did not control the resuscitation fluid rate, which resulted in variation among patients. This may have affected the treatment outcome. Lastly, this is a single center trial, which could limit the generalizability of these findings to other care setting. Physician who decide to apply the results of this study to their routine clinical practice should carefully evaluate the context of this study and compare it with their own situation and setting. A multicenter trial with a larger population size, control of the rate of fluid resuscitation, and the timing of norepinephrine initiation is certainly required to assess the survival benefit of early norepinephrine as an intervention.

In conclusion, the results of this phase II clinical trial demonstrated significant association between early norepinephrine and increased shock control by 6 hours. Further studies are needed to confirm these findings before this approach can be introduced in clinical resuscitation practice. Future study should investigate the effect of early norepinephrine on organ dysfunction and mortality.

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Figure legends

Figure 1. Flow diagram describing the screening, recruitment, and randomization of patients.

Figure 2. Kaplan–Meier analysis of 28-day survival.
The hazard ratio for death in the early norepinephrine group compared with the standard treatment group was 0.69 (95%CI: 0.41–1.16; P=0.16).

Table 1. **Patients' Baseline Characteristics**.*

Characteristics	Early Norepinephrine (N=155)	Standard Treatment (N=155)
Age, median (IQR), y	65 (54–76)	68 (55–77)
Male gender, No. (%)	71 (45.8)	77 (49.7)
Body mass index, median (IQR), kg/m^2	21.6 (19.6–23.8)	22.1 (19.4–24.3)
APACHE II score, median (IQR)†	21 (15–26)	20 (16–26)
Time from emergency room arrival to diagnosis, median (IQR), min	23 (5–168)	25 (10–185)
Comorbidities, No. (%)		
Hypertension	77 (49.7)	85 (54.8)
Diabetes mellitus	51 (32.9)	53 (34.2)
Malignancy	41 (26.5)	41 (26.5)
Immunosuppression	38 (24.5)	34 (21.9)
Chronic kidney disease	27 (17.4)	37 (23.9)
Coronary artery disease	25 (16.1)	28 (16.8)
Stroke	19 (12.3)	15 (9.7)
Cirrhosis	14 (9)	13 (8.4)
Source of infection, No. (%)		
Urinary tract infection	47 (30.3)	45 (29)
Pneumonia	40 (25.8)	37 (23.9)
Intra-abdominal infection	31 (20)	33 (21.3)

Skin and soft tissue infection	15 (9.7)	12 (7.7)
Others	12 (7.7)	14 (9)
Unable to identify source of infection	10 (6.5)	14 (9)
Hemoculture positive for organism	25 (16.1)	27 (17.4)
Identified pathogens, No. (%)¶		
Gram positive cocci	20 (12.7)	21 (13.5)
Gram negative bacilli	87 (56.1)	73 (47.1)
Fungus	2 (1.3)	4 (2.6)
Virus	3 (1.9)	6 (3.9)
Unable to identify pathogen	39 (26.2)	51 (33.1)
Physiologic variables, median (IQR)		
Temperature, °C	38.0 (36.8–38.9)	38.1 (36.8–39.0)
Initial mean arterial pressure, mmHg	56 (50–59)	57 (52–62)
Initial heart rate, per min	110 (90–128)	108 (86–122)
Initial respiratory rate, per min	24 (22–30)	24 (24–32)
White cell count, per mm^3	11,990 (7070–19,890)	13,690 (6480–19,630)
Platelet count, per mm^3	169,000 (85,000–266,000)	157,000 (79,000–251,000)
Lactate, mmol/L	3.0 (1.8–5.7)	2.7 (1.8–4.8)
Lactate > 2 mmol/L, No./total No. (%)	106/155 (68.3)	102/155 (65.8)

*There were no significant differences between the two groups in baseline characteristics, excepted for initial mean arterial pressure, which was lower in the early norepinephrine administration group (P=0.02). IQR denotes interquartile range.

†The APACHE II score, a severity-determining score, ranges from 0 to 71. Higher scores indicate more severe disease.

¶ Data of identified pathogens were missing for 4 patients in the early norepinephrine group.

Table 2. Clinical Outcomes.*

Outcome	Early Norepinephrine (N=155)	Standard Treatment (N=155)	Odds Ratio or Relative Risk (95%CI)	P Value
Primary outcome, No. (%)			Odds ratio	
Achieved target mABP + tissue perfusion goal by 6 hours	118 (76.1)	75 (48.4)	3.4 (2.09–5.53)	<0.001
-Achieved target mABP + urine output + lactate clearance > 10% by 6 hours	48 (31.0)	27 (17.4)	2.13 (1.24-3.64)	0.005
-Achieved target mABP + urine output by 6 hours	55 (35.5)	38 (24.5)	1.69 (1.04-2.77)	0.04
-Achieved target mABP + lactate clearance > 10% by 6 hours	15 (9.7)	10 (6.5)	1.55 (0.68-3.57)	0.3
Secondary outcomes			Relative Risk	
Mortality at 28 days, No. (%)	24 (15.5)	34 (21.9)	0.79 (0.53–1.11)	0.15
Hospital mortality, No. (%)	35 (22.6)	38 (24.5)	0.95 (0.72–1.24)	0.69
Time from initial treatment to achieving target mABP + tissue perfusion goal, median (IQR), h:min	4:45 (3:30–5:56)	6:02 (4:20–9:18)		<0.001
Achieved target mABP by 6 hours, No. (%)	134 (86.5)	104 (67.1)	3.13 (1.77-5.53)	<0.001
Mean arterial pressure at 6 hours, median (IQR), mmHg	74 (69-79)	72 (66-78)		0.22
Time from initial treatment to achieving target mABP ≥65 mmHg, median (IQR), h:min	3:30 (2:09–5:00)	4:45 (3:15–7:00)		<0.001
Achieved target urine output within 6 hours, No. (%)	107 (69)	75 (48.4)	2.47 (1.55-3.95)	<0.001

-Achieved target urine output by 0-2 hours, No. (%)	13 (8.4)	12 (7.7)	1.09 (0.48-2.47)	0.84
Time from initial treatment to achieving target urine output, median (IQR), h:min	4:30 (3:00-5:52)	5:10 (4:00-9:37)		0.003
Achieved target lactate clearance > 10% by 6 hours, No. (%)	64 (41.3)	43 (27.7)	1.87 (1.16-3.02)	0.009
Lactate level < 2 mmol/L by 6 hours	73 (47.1)	62 (40.3)	1.32 (0.84-2.07)	0.23
Time from initial treatment to achieving target lactate < 2 mmol/L, median (IQR), h:min	6:00 (3:57-15:12)	8:45 (5:10-13:45)		0.003
Days alive and free of vasopressors to day 28, median (IQR), day†	26 (23–27)	25 (7–27)		0.35
Mechanical ventilator support, No. (%)	58 (37.4)	59 (38.1)	0.99 (0.79–1.24)	0.91
Days alive and free of mechanical ventilator to day 28, median (IQR), day†	28 (14–28)	28 (7–28)		0.42
Renal replacement therapy, No. (%)	19 (12.3)	23 (14.8)	0.89 (0.67–1.22)	0.51
Days alive and free of renal replacement therapy to day 28, median (IQR), day†	28 (20–28)	28 (20–28)		0.7
Days alive and free of organs support to day 28, median (IQR), day†	25 (0-27)	25 (0-26)		0.23

*IQR denotes interquartile range and h:min is hours:minutes.

†Days alive and free of vasopressors, mechanical ventilator, renal replacement therapy and organs support to day 28 were calculated based on method previously described in reference 13.

Abbreviation: mean arterial blood pressure (mABP)

Table 3. Adverse Events and Causes of In-Hospital Death.

Events	Early Norepinephrine (N=155)	Standard Treatment (N=155)	Relative Risk (95%CI)	P Value
Adverse events, No. (%)				
Cardiogenic pulmonary edema	22 (14.4)	43 (27.7)	0.70 (0.56–0.87)	0.004
Acute respiratory distress syndrome	17 (11)	14 (9)	1.12 (0.75–1.68)	0.56
New-onset cardiac arrhythmia	17 (11)	31 (20)	0.74 (0.56–0.94)	0.03
Hospital-acquired infection	22 (14.5)	21 (13.7)	1.03 (0.74–1.43)	0.85
Upper gastrointestinal hemorrhage	6 (3.9)	5 (3.2)	1.12 (0.58–2.15)	0.73
Acute limb and/or intestinal ischemia	5 (3.2)	3 (1.9)	1.35 (0.55–3.32)	0.47
Skin necrosis	1 (0.6)	1 (0.6)	1.0 (0.25-4.02)	1.0
Causes of in-hospital death, No. (%)				
Sequelae of multiple organ system failure	18 (11.6)	22 (14.2)	0.9 (0.66–1.22)	0.5
Refractory septic shock	4 (2.6)	6 (3.9)	0.83 (0.49–1.39)	0.52
Recurrent infection	6 (3.9)	4 (2.6)	1.26 (0.58–2.71)	0.75
Sudden cardiac death unrelated to septic shock	5 (3.2)	3 (1.9)	1.34 (0.55–3.31)	0.72
Other causes	2 (1.3)	3 (1.9)	0.83 (0.40–1.72)	0.66

Table 4. **Treatments Administered**.*

Data on Hemodynamic Management and Organ Support	**Early Norepinephrine (N=155)**	**Standard Treatment (N=155)**	**P Value**
Time from diagnosis to study drug initiation, median (IQR), h:min	1:10 (0:50–1:30)	1:10 (0:45–1:40)	0.66
Time from diagnosis to open label norepinephrine initiation, median (IQR), h:min	3:00 (2:12–4:30)	2:47 (2:05–4:33)	0.38
Time from diagnosis to any norepinephrine initiation, median (IQR), h:min	1:10 (0:50–1:30)	2:47 (2:05–4:33)	<0.001
Time from emergency room arrival to administration of any norepinephrine, median (IQR), h:min	1:33 (1:12-1:54)	3:12 (2:30-4:58)	<0.001
Vasopressors (open label)			
Norepinephrine, No. (%)	105 (67.7)	124 (80)	0.014
- Maximum dose, median (IQR), μg/kg/min†	0.1 (0.05–0.18)	0.1 (0.05–0.15)	0.59
Epinephrine, No. (%)	27 (17.4)	31 (20)	0.56
- Maximum dose, median (IQR), μg/kg/min†	0.41 (0.28–1.2)	0.4 (0.26–0.60)	0.41
Dopamine, No. (%)	6 (3.9)	3 (1.3)	0.31
- Maximum dose, median (IQR), μg/kg/min†	10.3 (4.7–14.7)	6.7 (4.9–7.2)	0.31
Dobutamine, No. (%)	5 (3.2)	5 (3.2)	1.0
- Maximum dose, median (IQR), μg/kg/min†	4.7 (2.4–6.7)	3.8 (3.3–4.3)	0.69
Fluid administered			
Fluid administered before study drug initiation, median (IQR), mL	800 (600–1000)	800 (500–1000)	0.34
Fluid administered before open label norepinephrine initiation, median (IQR), mL	2080 (1400–2600)	1900 (1345–2278)	0.32
Fluid administered before open label norepinephrine initiation, median (IQR), mL/kg	32.3 (24.5-45.9)	29.8 (21.8-40.9)	0.3

Fluid administered in first 1 hour, median (IQR), mL	800 (600–1000)	800 (600–1000)	0.64
Fluid administered in 0–6 hours, median (IQR), mL	2450 (1914–3200)	2600 (2154–3240)	0.33
Fluid administered in day 1, median (IQR), mL	5032 (3950–6060)	5025 (3855–5853)	0.66
Fluid administered in day 2, median (IQR), mL	1825 (964–2575)	1680 (987–2275)	0.28
Fluid administered in day 3, median (IQR), mL	845 (185–1733)	1000 (120–1755)	0.87
Central venous catheter insertion, No. (%)	67 (43.8)	71 (46.1)	0.68
Time from diagnosis to central venous catheter insertion, median (IQR), h:min, (n=138)	4:10 (2:45–8:30)	4:00 (2:30–6:40)	0.64
Initial central venous pressure, median (IQR), mmHg, (n=138)	8 (5–14)	9 (7–12)	0.41
ICU admission, No. (%)	85 (54.8)	80 (51.6)	0.57
Time from diagnosis to ICU admission, median (IQR), h:min, (n=165)	6:36 (4:35-9:52)	6:35 (5:15-10:30)	0.34
Time from diagnosis to general medical ward admission, median (IQR), h:min, (n=145)	6:23 (4:25-10:34)	6:45 (4:24-10:54)	0.66
ICU length of stay, median (IQR), day, (n=165)	2 (0-6)	1 (0-5)	0.57
Hospital length of stay, median (IQR), day, (n=310)	10 (6-21)	10 (7-17)	0.37

*IQR denotes interquartile range and h:min is hours:minutes.

†The median and IQR of vasopressor doses derived from the patients who received a dose more than zero.

Figure 1.

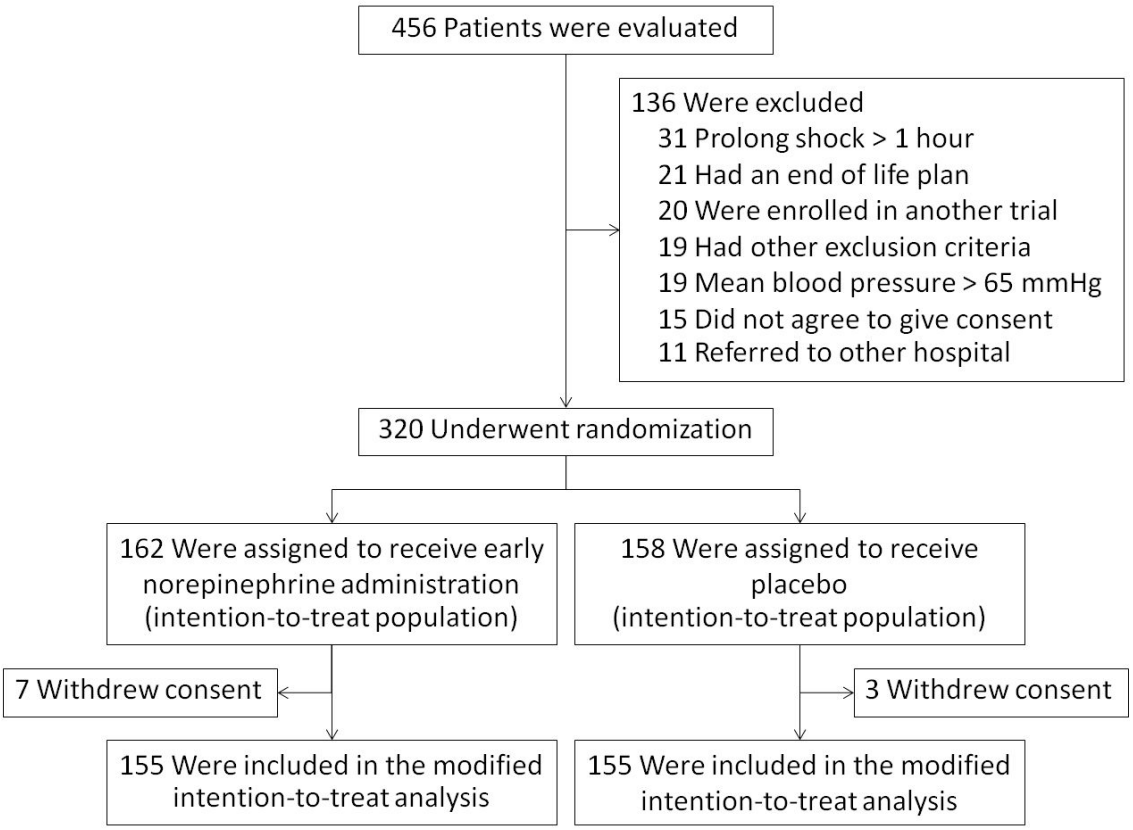
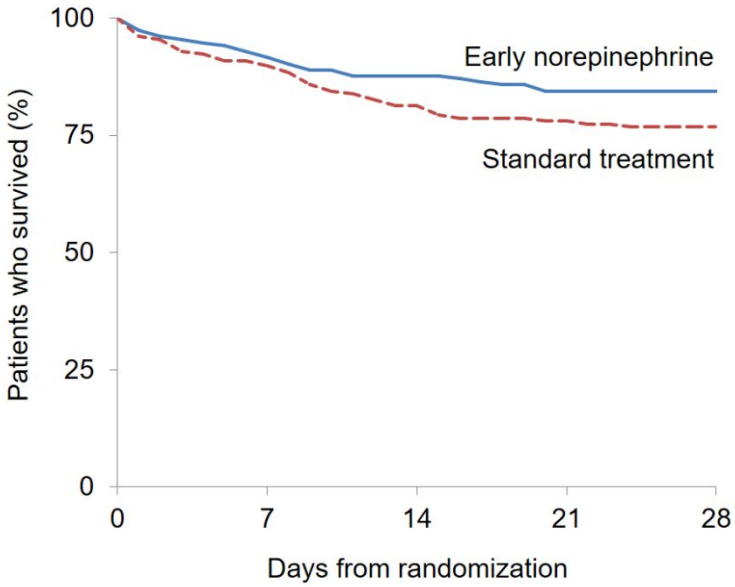


Figure 1. Flow diagram describing the screening, recruitment, and randomization of patients.

Figure 2.



No. at Risk					
Early Norepinephrine	155	142	136	131	131
Placebo	155	139	126	121	119

Figure 2. Kaplan–Meier analysis of 28-day survival.

The hazard ratio for death in the early norepinephrine group compared with the standard treatment group was 0.69 (95%CI: 0.41–1.16; P=0.16).

Supplementary data

Content

Definitions of comorbidities

Hypertension:

Hypertension was defined as previous documentation of blood pressure > 140/90 mmHg, and history of antihypertensive medication before the development of sepsis.

Diabetes mellitus:

Diabetes mellitus was defined as previous documentation of fasting blood sugar > 127mg/dL, and history of any oral hypoglycemic agents taken or history of insulin injection to control blood sugar level before the development of sepsis.

Malignancy:

Malignancy was defined as previous documentation of tissue pathology confirming a diagnosis of solid organ cancer or hematologic malignancy before the development of sepsis.

Immunosuppression:

Immunosuppression was defined as history of any chemotherapy or steroid use (dose equivalent to prednisolone > 20mg/d for > 7days) within 3 months before the development of sepsis.

Chronic kidney disease:

Chronic kidney disease was defined as history of low calculated glomerular filtration rate (< 60 ml/min/1.73m^2) before the development of sepsis.

Coronary artery disease:

Coronary artery disease was defined as history of previous myocardial ischemia, coronary artery angioplasty, and/or coronary bypass surgery at any time before the development of sepsis.

Stroke:

Stroke was defined as history of neurological deficit with documentation of computed tomography imaging showing ischemic or hemorrhagic stroke at any time before the development of sepsis.

Cirrhosis:

Cirrhosis was defined as previous diagnosis of cirrhosis with radiologic imaging confirmation of nodularity, irregularity, increased echogenicity, and atrophy of the liver, or presence of ascites at any time before the development of sepsis.

Definitions of safety outcomes

New-onset arrhythmia:

New-onset arrhythmia included the following arrhythmias: new-onset atrial fibrillation, atrial flutter, ventricular tachycardia, ventricular fibrillation, second and third-degree atrioventricular block, and junctional bradycardia.

Cardiogenic pulmonary edema:

Patients with chest X-ray showing bilateral pulmonary infiltration was diagnosed with cardiogenic pulmonary edema if there was evidence of left ventricular systolic or diastolic dysfunction together with early diastolic blood flow across mitral valve (E wave) to medial mitral valve annulus velocity (Ea wave) ratio greater than 15.[1]

Non-cardiogenic pulmonary edema:

Non-cardiogenic pulmonary edema was defined as bilateral pulmonary infiltration with left ventricular ejection fraction $\geq$ 55% and E/Ea ratio $\leq$ 15.

Definitions of causes of death

Refractory septic shock:

Refractory septic shock was defined as profound hypotension not responding to fluid resuscitation and high-dose vasopressors, and it resulted in death within 72 hours.

Death from sequelae of multiple organ failure:

Death from sequelae of multiple organ failure was defined as death from severe metabolic acidosis, electrolyte abnormality, or profound hypoxemia that occurred when the patient's hemodynamic status had been stabilized, but organ support, including mechanical ventilation and renal replacement therapy, was required.

Sudden cardiac death unrelated to septic shock:

Sudden cardiac death unrelated to septic shock was defined as death with evidence of new-onset acute myocardial ischemia occurring after the patient's hemodynamic status had been stabilized and the study drug was stopped, with no or low-dose vasopressors equivalent to norepinephrine less than 0.05 μg/kg/min.

Death from recurrent infection:

Death from recurrent infection was defined as death related to a new infection caused by a different organism at the previous infection site or infection of another organ system.

Deaths from causes not mentioned above:

Deaths from causes not mentioned above was defined as death precipitated by a cause other than the preceding 4 causes.

Patients screening and enrollment

1. The patient screening process started once the patient arrived in the emergency room (ER). The patient was evaluated by an emergency physician.
2. One of the co-authors (Tipa Chakorn) is an ER faculty staff member. She developed a system to alert the appropriate co-authors of the study when a patient candidate presented at the ER.
3. When patients with suspected sepsis/ septic shock came to the ER, the study co-authors that live within or in close proximity to the hospital were notified. Those responders were able to evaluate the patients of interest within 15 to 30 minutes.
4. If a patient fully satisfied the inclusion criteria and no exclusion criteria were met, the patient or the patient's legal guardian was approached. The study details were explained and written informed consent was request. Only patients that directly or indirectly provide consent were included.
5. Less than 3% of patients arrived at the ER without a relative or legal guardian. In this situation, we attempted to contact a family member to provide study information to request study participation.
6. If that process took longer than 1 hour, the patient was excluded. As shown in Figure 1., 31 patients were excluded due to the process taking longer than 1 hour.

Randomization processes

The randomization process included:

1. A co-author (ST) generated the randomization table from www.randomization.com. The table documented the sequential order of patient enrollment and the treatment group.
2. The randomization table was revealed to a research pharmacist. The study drugs (norepinephrine and placebo) were prepared by a pharmacist, who had no other role in the trial. Both study drugs were packaged in identically shaped containers. The study drug containers were labeled with serial numbers consistent with those listed on the randomization table.
3. The study drugs were then send for storage and ready use in the ER. Once a patient was enrolled and written informed consent was obtained, the assigned study drug was administered according to the sequential number. All co-authors that enrolled patients in this study were blinded to the randomization table during the study period.

Timeline for lactate measurement

1. The 1st lactate sampling (baseline lactate) was measured when the patient was diagnosed with sepsis with evidence of coexisting hypotension.
2. The 2nd lactate sampling was measured when patient blood pressure was increased to achieve mean arterial pressure > 65 mmHg for at least 1 hour, but no urine output or urine output less than 0.5ml/kg/hr.
3. The 3rd lactate sampling was measured at 6 hours after initiation of resuscitation.

Every patient had 1st and 3rd lactate sampling results; however, some patients either didn't have 2nd lactate sampling or the results were missing or otherwise unavailable.

To calculate lactate clearance, we compared the 2nd or the 3rd lactate level with the 1st lactate level according using the following equation:

Lactate clearance = 100 x {[1st lactate – 2nd or 3rd lactate]/1st lactate}

Organ support-free days calculation

Organ support included:

1. Mechanical ventilator for respiratory support
2. Vasopressor for cardiovascular support
3. Renal replacement therapy for renal support.

We calculated organ support-free days at day 28 according to method proposed by Russell JA, et al.[2] Briefly, we counted the number of days from the last day that the patient required organ support to day 28, and we calculated this for each organ. For patients who died before day 28, the organ support-free days value was recorded as 0 for that patients.

Figure 3. Mean arterial pressure (Figure 3A.) and summation of study and open label norepinephrine (Figure 3B.) over time.

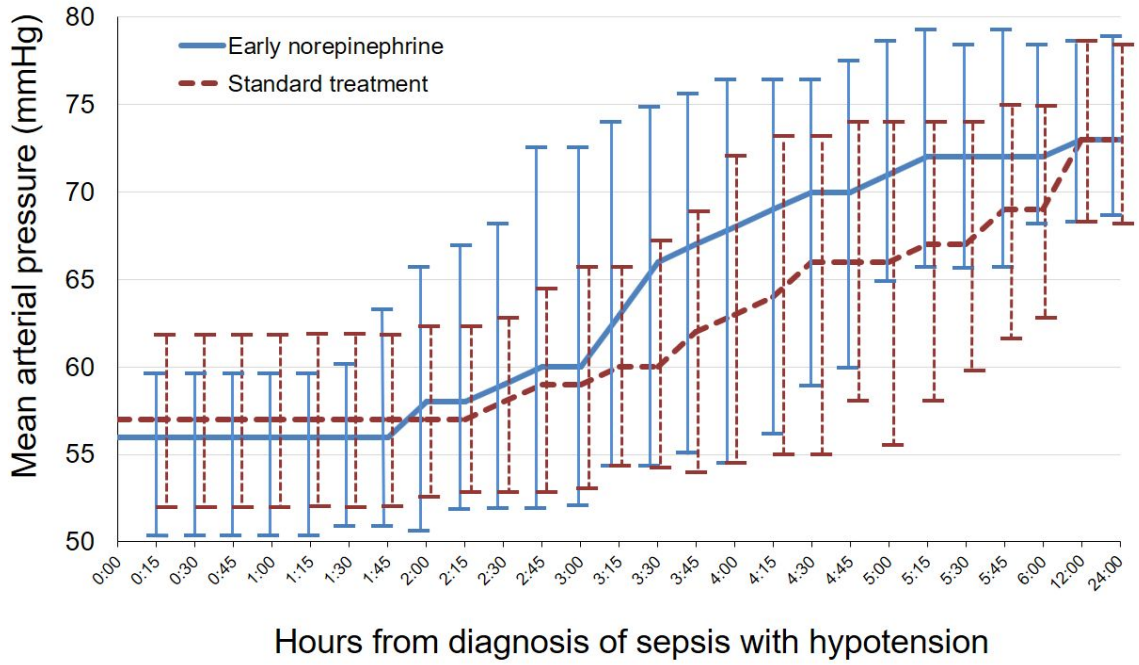


Figure 3A. Demonstrates median of mean arterial pressure and interquartile range (indicated by I bar) in the early norepinephrine group (blue line) and the standard treatment group (red doted line). Mean arterial pressure was significantly higher in the early norepinephrine group than in the standard treatment group during 3:30 to 6:00 hours diagnosis of sepsis with hypotension. ($P < 0.05$)

Figure 3. Mean arterial pressure (Figure 3A.) and summation of study and open label norepinephrine (Figure 3B.) over time.

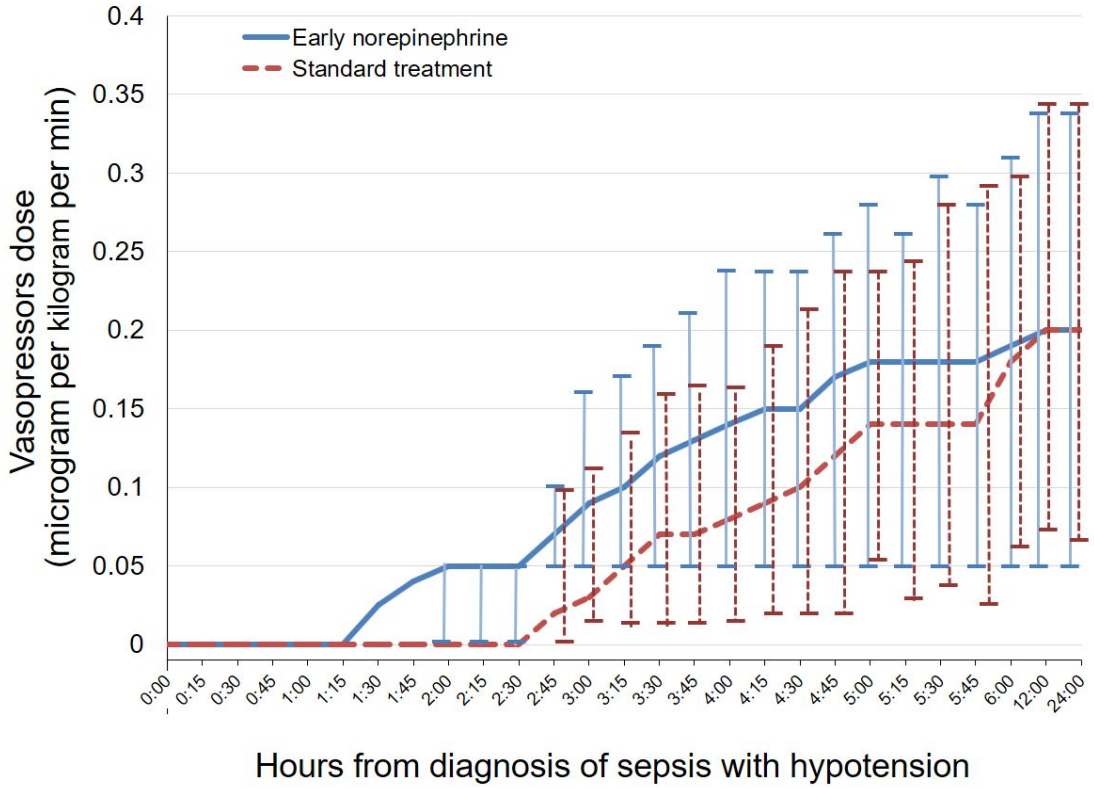


Figure 3B. Demonstrates median of summation of norepinephrine dose (study drug + open label norepinephrine) and interquartile range (indicated by I bar) in the early norepinephrine group (blue line) and the standard treatment group (red doted line). Patients in the early norepinephrine group received a significantly higher dose of norepinephrine than patients in the standard treatment group during 2:00 to 5:45 hours after diagnosis of sepsis with hypotension. (P <0.05)

Supplementary Table.

Clinical outcome: Detail of individual and composite endpoints assessment compared between groups.

Outcome	Early Norepinephrine (n=155), n(%)	Standard Treatment (n=155), n(%)	Odds Ratio or Relative Risk (95%CI)	P Value
Unable to achieve primary outcome target	37 (23.9%)	80 (51.6%)	0.29 (0.18-0.48)	<0.001
-No goals achieved by 6 hours	16 (10.4%)	35 (22.6%)	0.39 (0.21-0.75)	0.004
-Achieved only target mABP by 6 hours	16 (10.4%)	29 (18.7%)	0.52 (0.27-0.99)	0.05
-Achieved only target urine output by 6 hours	4 (2.6%)	10 (6.5%)	0.38 (0.12-1.25)	0.10
-Achieved only target lactate clearance >10% by 6 hours	1 (0.6%)	6 (3.9%)	0.16 (0.02-1.36)	0.06
-Achieved target urine output by 0-2 hours	13 (8.4%)	12 (7.7%)	1.09 (0.48-2.47)	0.84
-Achieved target urine output by 2nd to 3rd hours	22 (14.2%)	10 (6.5%)	2.40 (1.10-5.25)	0.03
-Achieved target urine output by 3rd to 4th hours	28 (18.1%)	16 (10.3%)	1.92 (1.01-3.71)	0.05
-Achieved target urine output by 4th to 5th hours	23 (14.8%)	24 (15.5%)	0.95 (0.51-1.77)	0.87

-Achieved target urine output by 5th to 6th hours	21 (13.5%)	13 (8.4%)	1.71 (0.82-3.56)	0.15

A P-value <0.05 indicates statistical significance

Abbreviation: CI, confidence interval

Supplementary references:

1. Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA, Waggoner AD, Flachskampf FA, Pellikka PA, Evangelista A. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. *J Am Soc Echocardiogr*. 2009;22(2):107-133.
2. Russell JA, Lee T, Singer J, De Backer D, Dijillali Annane. Days alive and free as an alternative to a mortality outcome in pivotal vasopressor and septic shock trials. *Journal of Critical Care*. 2018;47:333-337.