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EDITORIAL

Terlipressin or norepinephrine, or both in septic shock?

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Vasopressor therapy is one of the cornerstones in the management of septic shock when intravenous fluid resuscitation is insufficient to maintain a mean arterial pressure (MAP) above 65 mmHg [1]. Norepinephrine is the recommended first-choice vasopressor, but hyporesponsiveness represents a significant clinical problem and high doses are sometimes required to achieve the target MAP. Such high-dose catecholamine therapy may increase the risk of life-threatening arrhythmias, immunosuppression, and mortality [2–4].

In response to concerns about high-dose norepinephrine therapy in septic shock, adjunctive treatment with vasopressin has been suggested [1]. In the Vasopressin and Septic Shock Trial (VASST), adding low-dose vasopressin (0.01–0.03 U/min) to existing norepinephrine treatment did not decrease mortality in patients with septic shock compared with norepinephrine mono-therapy [5]. However, among patients with less severe shock and among those enrolled within 12 h there appeared to be a possible survival benefit with vasopressin, suggesting that early initiation may be beneficial.

Yet, the Vasopressin vs Norepinephrine as Initial Therapy in Septic Shock (VANISH) trial found no difference in kidney failure-free days or mortality with early (within 6 h) initiation of vasopressin therapy (up to 0.06 U/min) compared with norepinephrine alone among 409 septic shock patients [6].

In addition to vasoconstriction via vasopressin V1-receptor activation, vasopressin may cause unwanted side effects via activation of V2-receptors in the renal collecting ducts (antidiuretic effect) and on endothelial cells (prothrombotic effect via Von Willebrand factor release), V3-receptors in the pituitary gland (increased ACTH secretion) and oxytocin-receptors on vascular endothelial cells (increased nitric oxide synthase activity causing vasodilation). Terlipressin, a synthetic vasopressin analogue with greater selectivity for the V1-receptor, may therefore be an attractive alternative to vasopressin.

Experimental animal data suggest that terlipressin attenuates fluid accumulation and prolongs survival time compared with vasopressin [7]. In addition, data from small randomised controlled trials suggest that terlipressin improves short term renal function in patients with type 1 hepatorenal syndrome [8] and that it may even improve survival in patients with liver cirrhosis and septic shock compared with norepinephrine [9]. However, data on the safety and efficacy of terlipressin therapy in septic shock patients without liver failure are scant.

In a recent article in *Intensive Care Medicine*, Liu et al. report the results of a randomised, multicenter, double blind, controlled trial comparing norepinephrine alone

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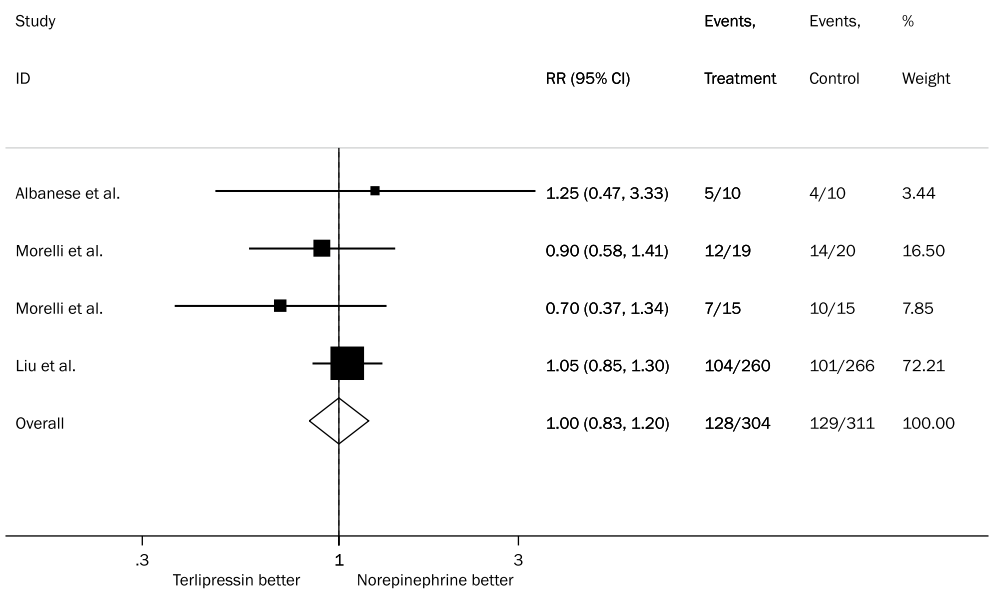

Fig. 1 Meta-analysis of mortality in randomised trials comparing terlipressin (Treatment) with norepinephrine (Control) in adult patients with septic shock

with early terlipressin infusion (20–160 μg/h) plus norepinephrine in patients with septic shock [10]. The study was stopped due to futility after enrolment of 50% of scheduled patients. In the 526 randomised and analysed patients, they found no difference in 28-day mortality (primary outcome; 38 vs. 40%, $P=0.63$), vasopressor-free days or change in SOFA score during the first week after randomisation. This informative study hence confirms the findings of previous pilot investigations showing no mortality benefit when terlipressin is used alone or is added to norepinephrine (Fig. 1) [11–13].

The striking difference in serious adverse events, particularly digital ischemia, reported by Liu et al., requires attention. Overall, 1.5% of patients treated with norepinephrine alone suffered from digital ischemia; an identical incidence to VANISH trial patients receiving norepinephrine only. However, in the study by Liu et al., digital ischemia occurred in 13% of patients receiving terlipressin (c.f. 5.4% with vasopressin in the VANISH trial). In addition, the authors found a greater prevalence of diarrhea (2.7% vs 0.3%), but importantly not acute mesenteric ischemia, in the terlipressin group.

The high incidence of digital ischemia may have several possible explanations. Firstly, the risk of terlipressin-induced ischemic events increases with hypovolemia. In the study by Liu et al., most cases of digital ischemia occurred in the first 24 h. Unfortunately, the amount of pre-randomisation fluid administration was not reported. It is therefore unclear whether patients were "adequately" fluid resuscitated before entering the trial.

Secondly, some studies demonstrate that cardiac index is significantly decreased with terlipressin but not with norepinephrine [11, 12]. An increase in systemic vascular resistance at the expense of cardiac index may indeed compromise organ blood flow and contribute to adverse ischemic events. But since cardiac index was not measured by Liu et al., we can only speculate about whether such hemodynamic alterations contributed to the high rate of adverse events.

Finally, terlipressin is known to have a longer effective half-life than both norepinephrine and (arginine) vasopressin, but the pharmacokinetics of lysin-vasopressin, the active metabolite of terlipressin, during continuous infusion in septic shock has not been established. Preliminary safety with low-dose infusion (approximately 110 μg/h) was reported in one small trial but adverse events other than atrial fibrillation were not assessed [13]. However, in patients with liver cirrhosis and septic shock who received up to 312 μg/h, the overall rate of adverse events was 41% with 29% experiencing "peripheral cyanosis" [9]. In view of the high rate of serious adverse events, the maximum terlipressin infusion rate should likely be significantly less than 160 μg/h in patients with septic shock.

In all, it appears that the terlipressin doses used to treat patients with hepatorenal syndrome may be too high in patients with septic shock. If there is a place for terlipressin infusion in such patients, a safe dose range needs to be established first. In the meantime, how should clinicians manage vasopressors in septic shock?

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ORIGINAL

Terlipressin versus norepinephrine as infusion in patients with septic shock: a multicentre, randomised, double-blinded trial

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Abstract

Purpose: Recent clinical data suggest that terlipressin, a vasopressin analogue, may be more beneficial in septic shock patients than catecholamines. However, terlipressin's effect on mortality is unknown. We set out to ascertain the efficacy and safety of continuous terlipressin infusion compared with norepinephrine (NE) in patients with septic shock.

Methods: In this multicentre, randomised, double-blinded trial, patients with septic shock recruited from 21 intensive care units in 11 provinces of China were randomised (1:1) to receive either terlipressin (20–160 μg/h with maximum infusion rate of 4 mg/day) or NE (4–30 μg/min) before open-label vasopressors. The primary endpoint was mortality 28 days after the start of infusion. Primary efficacy endpoint analysis and safety analysis were performed on the data from a modified intention-to-treat population.

Results: Between 1 January 2013 and 28 February 2016, 617 patients were randomised (312 to the terlipressin group, 305 to the NE group). The modified intention-to-treat population comprised 526 (85.3%) patients (260 in the terlipressin group and 266 in the NE group). There was no significant difference in 28-day mortality rate between the terlipressin group (40%) and the NE group (38%) (odds ratio 0.93 [95% CI 0.55–1.56]; $p = 0.80$). Change in SOFA score on day 7 was similar between the two groups: − 7 (IQR − 11 to 3) in the terlipressin group and − 6 (IQR − 10 to 5) in the NE group. There was no difference between the groups in the number of days alive and free of vasopressors. Overall, serious adverse events were more common in the terlipressin group than in the NE group (30% vs 12%; $p < 0.001$).

Conclusions: In this multicentre, randomised, double-blinded trial, we observed no difference in mortality between terlipressin and NE infusion in patients with septic shock. Patients in the terlipressin group had a higher number of serious adverse events.

Trial registration: This trial is registered at ClinicalTrials.gov: ID NCT01697410.

Keywords: Terlipressin, Norepinephrine, Septic shock, SOFA score

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Introduction

Despite the significant progress made in intensive care medicine, septic shock remains associated with high morbidity and mortality [1–3]. To correct hypotension in septic shock, norepinephrine (NE) is the first-line recommended vasopressor [4]. However, achieving the arterial blood pressure target may require high doses of NE, which may result in myocardial injury and alter the sepsis-associated immunomodulation [5].

Vasopressin, an endogenously released peptide hormone, has emerged as a potential adjunct to NE in case of refractory hypotension or when the dose of NE needed to reach the arterial blood pressure target is judged to be high [4]. The recent Vasopressin (Arginine vasopressin, AVP) and Septic Shock Trial (VASST) failed to show benefit of vasopressin compared to NE [6], while the VANISH randomized clinical trial demonstrated that early vasopressin reduced the use of renal replacement therapy in patients with septic shock [7]. Vasopressin may stimulate multiple receptors, namely V_1 receptors, V_2 receptors, oxytocin receptors, and purinergic receptors, and activation of the V_1 receptor leads to vasoconstriction and arterial blood pressure increase [8]. However, AVP has no selectivity for the V_1 receptor and may have side effects due to activation of the other receptors [9, 10]. Terlipressin, a synthetic, long-acting vasopressin analogue, has a much higher affinity to the V_1 receptor than to other receptors [8]. Preliminary clinical analysis has shown that terlipressin effectively reduces the NE requirements in patients with septic shock [11, 12]. A recent meta-analysis found that the use of terlipressin and vasopressin, compared to NE, may decrease mortality in patients with septic shock [13]. However, another meta-analysis failed to confirm these results [14]. Until now, there has been no trial powered enough to evaluate the effect of terlipressin on mortality, organ dysfunction or safety in septic shock patients.

To determine the efficiency of terlipressin versus NE in septic shock, we conducted a multicentre, randomised, double-blind trial with 28-day mortality as the primary outcome.

Take-home message:

Up to now, this multicenter, randomized, double-blind trial is the largest study regarding efficacy and safety of continuous terlipressin infusion in septic shock.We did not find a significant reduction in 28-day mortality rate with terlipressin. Terlipressin is effective in reversing sepsis-induced arterial hypotension. Furthermore, compared to norepinephrine, terlipressin treatment improved serum creatine and SOFA score. Digital ischemia must be intensively monitored during terlipressin treatment. The dosing regimen and safety of continuous terlipressin infusion in septic shock need to be further investigated.

Methods

Study design and participants

This prospective, multicentre, randomised, double-blind trial was conducted between January 2013 and February 2016 in 21 intensive care units in 11 provinces of China. The medical ethics research committee of the First Affiliated Hospital of Sun Yat-sen University approved the study with subsequent sanctioning of all participating hospitals.

Patients older than 18 years diagnosed with septic shock during their ICU stay were considered for enrolment. Septic shock was defined by the presence of two or more diagnostic criteria for the systemic inflammatory response syndrome. Proven or suspected infection, and hypotension despite adequate fluid resuscitation (sepsis-induced hypotension defined as systolic blood pressure (SBP) < 90 mmHg or mean arterial pressure < 70 mmHg or an SBP decrease > 40 mmHg or > 2SD below normal for age in the absence of other causes of hypotension) [15]. Exclusion criteria included (1) unstable coronary syndrome (acute myocardial infarction during this episode of shock based on the combination of history, electrocardiogram and enzyme changes, (2) previous use of terlipressin for arterial blood pressure support during the current ICU admission, (3) malignancy or other irreversible disease or condition for which mortality was estimated to be very high (defined by investigator), (4) acute mesenteric ischaemia either proven or suspected, (5) Raynaud's phenomenon, (6) pregnancy, (7) organ transplantation. For all patients informed consent was obtained and signed by their next of kin, or another surrogate decision maker, before entering the study. The trial was registered with ClinicalTrials.gov, number NCT01697410.

Randomisation and masking

We randomly assigned patients who met eligibility criteria to receive either terlipressin or NE. Randomisation was done with sequentially numbered, opaque, computer-generated sealed envelopes. The allocation sequence was concealed from the researchers. To reduce the impact on the results from heterogeneity of septic shock and inter-hospital variation as much as possible, stratification by the investigating centre in combination with block randomisation (block size = 10) according to the sequence of recruitment was employed in the enrolment process. Eligible patients were randomly assigned in a 1:1 ratio in each hospital with randomisation stratified by study centre. The random number was written on the sealed randomisation envelopes. Once the patient was included in the study, the sealed envelope was handed over to an independent pharmaceutical nurse who worked in an isolated pharmacy. This pharmaceutical nurse prepared the study medication according to the allocated group written on a card inside the envelope, wrote the random number of the included patient on a confidential

medication form, and then resealed the envelope. Subsequently, the sealed envelope and medication form were locked in an independent safe box in the pharmacy. The study drug was prepared in a standard 50-mL syringe and the drug solution was colourless and transparent. The clinical staffs, investigators, researchers, patients and their families who were involved in this study were strictly masked to the treatment assignment during the trial period. Clinicians who enrolled the subjects were not involved in data collection. To prevent advance knowledge of treatment assignment and subversion of the allocation sequence, the trial entry sheet of the case report form (CRF) was filled out and informed consent was obtained before disclosing the unique participant number and allocation; the unique number generated could not be changed or deleted afterward.

Procedures and sepsis management

Terlipressin (1 mg) or NE (11 mg) was dissolved in a 50-mL syringe containing 5% dextrose in water, with final concentrations of 0.02 mg of terlipressin per mL and 0.22 mg of NE per mL. The terlipressin or NE infusion was colourless and transparent. Therefore the study drug could not be identified by appearance of the syringe. Infusion was started at 1 mL/h and titrated to achieve the target blood pressure. The maximum infusion rate of the study drug was 8 mL/h. Thus, the terlipressin infusion was started at 20 μg/h and titrated to a maximum of 160 μg/h, whereas the NE infusion was started at 4 μg/min and titrated to a maximum of 30 μg/min. In several previous studies, a 1-mg terlipressin bolus was given to maintain blood pressure in septic shock every 6 h [8, 11]. The half-life terlipressin is 6 h [8]. Therefore, the maximum dosage of continuous terlipressin infusion was 4 mg/day in our study. The study drugs were manufactured and distributed by Hybio Phamaceutical (Shenzhen, China) to the participating hospital pharmacies.

An initial target mean arterial pressure of 65–75 mmHg was recommended. However, the ICU physician was allowed to modify the target arterial blood pressure of each patient. The study drug was given first to achieve the target blood pressure. During the initiation and titration of the study drug, the bedside nurse was allowed to administer open-label NE in case the recommended mean arterial pressure was not reached on maximal study drug infusion. Other open-label vasopressors such as dopamine and epinephrine were allowed to be added if the maximum doses of both the study drug and the open-label NE were not effective to achieve or maintain the target blood pressure. Tapering of open-label vasopressors was permitted only when the target mean arterial pressure had been reached during the study drug infusion. Tapering of the study drug was commenced only when the target mean arterial pressure had been maintained for 12 h without any open-label vasopressors. However, the ICU physician or nurse could modify the titration speed according to the variation of arterial blood pressure.

The study drug infusion was interrupted if any of the following serious adverse events occurred: acute ST-segment elevation confirmed by a 12-lead electrocardiogram, serious or life-threatening (haemodynamically unstable) cardiac arrhythmias, acute mesenteric ischaemia, digital ischaemia or severe diarrhoea. If the clinical team noted any of the aforementioned adverse events that they considered to be related to the study drug, the study drug was discontinued for at least 12 h and a serious adverse event was reported. The study drug could be resumed if the adverse event had been controlled and the event was deemed to be unrelated to the study drug or the study protocol as judged by the investigators.

If vasopressor support was required during the same admission to the ICU after a patient had been already weaned from the study drug, the study drug was preferentially re-infused, as long as no exclusion criterion was met. The treatment of sepsis followed the current international guidelines [13].

Outcomes

The primary outcome was death from any cause and was assessed 28 days after the start of study drug infusion. Secondary outcomes included changes in the Sequential Organ Failure Assessment (SOFA) score on day 7 after randomisation and days alive and free of vasopressor during 28 days after randomisation. We also evaluated the incidence of serious adverse events.

Statistical analysis

On the basis of a previous study [1], a sample size of 1000 patients was originally calculated to show a reduction in 28-day mortality rate from 50% to 40% by terlipressin treatment, with a two-sided test (error = 5%; power = 80%). Considering a possible drop-out rate of 10%, the trial would need to enrol 1100 patients. An independent data and safety monitoring committee reviewed the safety and efficacy data. Formal interim analyses were scheduled after approximately 30%, 50%, 80% and 100% of intention-to-treat patient data had accrued. An O'Brien–Fleming approach was used for sequential stopping rules for safety and efficacy according to the Lan–DeMets method [16]. The study would continue until the final analysis if a stopping boundary was not crossed at the interim analysis.

The primary analysis, which compared 28-day mortality between the two treatment groups, was performed using an unadjusted chi-square test. The analyses were performed on data from the modified intention-to-treat population, defined as all randomly assigned patients with at least once infusion except those who could be

excluded without the risk of bias [17] (patients who were confirmed to be ineligible and did not receive the study infusion) and those for whom we did not have consent for the use of data (Fig. 1). Results are presented as absolute and relative risks and 95% confidence intervals.

A logistic regression procedure and significant covariates that predicted outcomes were used to adjust raw values for 28-day mortality. Age, illness severity (Acute Physiology and Chronic Health Evaluation II [APACHE II] score at baseline), serious coexisting conditions and other baseline covariates that predicted outcome were entered into the model. Results are presented as odds ratios and 95% confidence intervals. Parametric procedures (independent *t* test) and repeated-measures analysis of variance were used to compare all secondary outcomes.

The data analyst and investigators remained unaware of the treatment assignments while undertaking the final analyses. Analysis was conducted with the use of SAS software (version 9.1.3), and all *p* values were two-sided. Guangzhou Hipower Pharmaceutical R&D Co. Ltd as a data monitoring committee supervised the study.

Role of funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation or writing of the report. The corresponding author had full access to all the study's data and had the final responsibility for the decision to submit for publication.

Results

Enrolment started in January 2013. Two planned interim analyses were conducted after approximately 300 and 600 patients had been enrolled. In the second interim analysis, the data and safety monitoring board reviewed intention-to-treat data on the 28-day mortality rate. Two-sided O'Brien–Fleming boundaries were used to assess potential early stopping of the trial. Using SAS software, this interim analysis fulfilled the stopping rules of $p<0.0036$ for efficacy and $p>0.2235$ for futility. The observed *p* value (see results below) fell within the futility region. On the basis of all available data, the data and safety monitoring board recommended cessation of the trial. Recruitment was stopped early at 50% enrolment in February 2016.

Between 1 January 2013 and 28 February 2016, among 684 eligible patients, 617 were randomised after providing informed consent. Among these 617 patients, 13 withdrew their consent, 21 did not receive the study drug infusion because of rapid improvement, 13 were confirmed ineligible and 35 were withdrawn from care without infusion. Thus 535 patients underwent randomisation and infusion of the study drug. Out of these 535 patients, five withdrew their consent and four were lost to follow-up. Thus, 526 patients were included in the final primary analysis: 260 patients were randomised to the terlipressin group and 266 to the NE group (Fig. 1). The baseline characteristics of the two groups are shown in Table 1. Enrolled patients were severely ill, as indicated by the APACHE II and SOFA scores and the serum lactate concentration at inclusion, the incidence of organ dysfunction and the incidence of comorbidities. The most common sites of infection were lung and abdomen, with an incidence of 51% and 54%, respectively, and with mixed pathogens or Gram-negative organisms accounting for the majority of cases (Table 1).

Arterial blood pressure and serum lactate during the first 7 days of the study in the two treatment groups are shown in Fig. 2.

Outcomes

There was no significant difference in the primary outcome between the terlipressin group and the NE group (40% vs 38%, respectively; $p=0.633$) (Table 2). The absolute risk difference between the terlipressin group and the NE group was 2% (95% CI −9.8% to 18.8%). The relative risk was 1.053 (95% CI 0.742–1.496). The results remained nonsignificant after multivariate logistic regression analysis (odds ratio for death in the terlipressin group at 28 days, 0.93 [95% CI 0.55–1.60]). Compared to baseline, the SOFA score on day 7 after randomisation was improved in both groups ($p<0.05$). The change in SOFA score on day 7 after randomisation was similar between groups, −7 (IQR −11 to 3) in the terlipressin group and −6 (IQR −10 to 5) in the NE group (Table 2). Days alive and free of vasopressor were similar between groups (Table 2).

More patients in the terlipressin group had serious adverse events than in the NE group (30% vs 12%, $p<0.01$; Table 3). Thirty-three out of 260 (12.6%) patients who received terlipressin infusion experienced digital ischaemia after the start of infusion versus only one in the NE group ($p<0.0001$) (Table 3). Globally, 76% of digital ischaemia emerged during the first 24 h after the start of infusion. Out of the 33 patients, 31 (94%) with digital ischaemia received an open-label vasopressor in addition to the study drug to maintain the target arterial blood pressure. No patient with digital ischaemia required surgical intervention. Severe diarrhoea was more common in the terlipressin group than in the NE group ($p<0.05$). There were no significant differences in the overall rates of serious arrhythmia, intestinal ischaemia and hyponatraemia between the two groups (Table 3).

Furthermore, we did some post hoc analyses of other outcomes, the results of which were presented in the supplement.

Discussion

To the best of our knowledge, our study of continuous terlipressin infusion in patients with septic shock is the largest

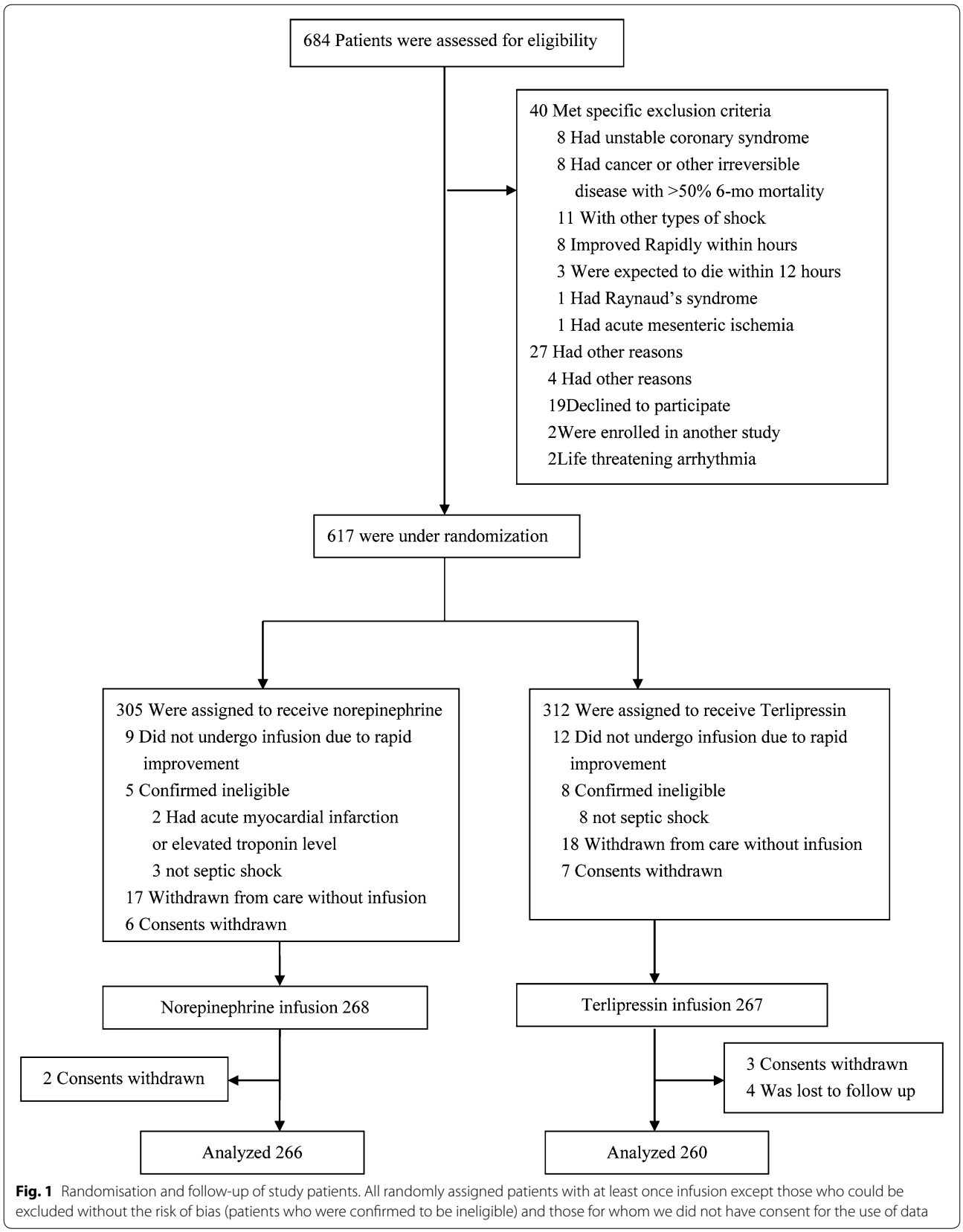

Fig. 1 Randomisation and follow-up of study patients. All randomly assigned patients with at least once infusion except those who could be excluded without the risk of bias (patients who were confirmed to be ineligible) and those for whom we did not have consent for the use of data

Table 1 Baseline characteristics of the modified intention-to-treat population

	Norepinephrine group ($n=266$)	Terlipressin group ($n=260$)
Age (years)	61.09 ± 16.20	60.93 ± 15.86
Height (cm)	164.54 ± 8.23	164.65 ± 7.68
Weight (kg)	60.72 ± 10.53	61.48 ± 11.56
Male	169 (63.53%)	162 (62.30%)
Female	97 (36.46%)	98 (37.69%)
Pre-existing diseases *N* (%)		
Congestive heart failure	6 (2.25%)	3 (1.15%)
Hypertension	72 (27.06%)	70 (26.92%)
Coronary artery heart disease	24 (9.02%)	16 (6.15%)
Liver diseases	39 (14.66%)	41 (15.77%)
Chronic obstructive pulmonary disease	15 (5.63%)	19 (7.30%)
Chronic renal failure	14 (5.26%)	8 (3.07%)
Nervous system disease	16 (6.01%)	20 (7.69%)
Diabetes	34 (12.78%)	47 (18.07%)
Trauma	7 (2.63%)	12 (4.61%)
Cancer	70 (26.31%)	76 (29.23%)
Immunodepression	13 (4.87%)	16 (6.15%)
Corticosteroid use	46 (17.29%)	44 (16.92%)
Treatment *N* (%)		
Ventilator	196 (73.68%)	194 (74.61%)
Dobutamine	25 (9.39%)	22 (8.46%)
Renal replacement therapy	39 (14.66%)	39 (15%)
Dopamine/norepinephrine	229 (86.09%)	235 (90.38%)
Norepinephrine dosage (μg/kg/min)	0.48 ± 0.36	0.46 ± 0.28
Dopamine dosage (μg/kg/min)	7.5 ± 3.1	7.8 ± 3.6
Transfusion	14 (5.26%)	15 (5.76%)
Organ dysfunction[a] *N* (%)		
Respiratory	218 (81.95%)	216 (83.07%)
Cardiovascular	266 (100%)	260 (100%)
Renal	138 (51.87%)	139 (53.46%)
Hepatic	120 (45.11%)	132 (50.76%)
Hematologic and coagulation	132 (49.62%)	142 (54.61%)
Neurologic	94 (35.34%)	89 (34.23%)
Operation		
Selective	59 (22.18%)	48 (18.46%)
Emergency	86 (32.33%)	89 (34.23%)
APACHE II score	19.09 ± 8.26	19.08 ± 7.01
SOFA score	11.45 ± 3.63	11.34 ± 3.67
Baseline BE (mmol/l)	− 3.10 ± 6.51	− 3.61 ± 6.27
Heart rate (/min)	118.14 ± 24.23	118.32 ± 23.93
Mean arterial pressure (mmHg)	67.61 ± 14.68	67.74 ± 14.21
Baseline serum lactate level (mmol/l)	3.81 ± 3.62	4.01 ± 3.23
Baseline arterial pH	7.36 ± 0.36	7.38 ± 0.31
PaO_2/FiO_2	193.24 ± 118.25	194.24 ± 117.61
Source of infection[b] *N* (%)		
Lung	134 (50.37%)	139 (53.36%)
Abdomen	143 (53.75%)	146 (56.15%)
Blood	26 (9.77%)	23 (8.84%)
Urinary tract	32 (12.03%)	41 (15.76%)

Table 1 continued

	Norepinephrine group ($n=266$)	Terlipressin group ($n=260$)
Others	37 (13.90%)	40 (15.38%)
Pathogen type in cultures *N* (%)		
Gram-positive	38 (14.28%)	33 (12.69%)
Gram-negative	95 (35.71%)	109 (41.92%)
Fungus	31 (11.65%)	25 (9.61%)
Mixed organisms	56 (21.05%)	61 (23.46%)
No pathogen	102 (38.34%)	92 (35.38%)

Data presented as *n* (%) or mean ± SD. *p* values are comparisons between norepinephrine group and terlipressin group

APACHE Acute Physiology and Chronic Health Evaluation, *SOFA* Sepsis-related Organ Failure Assessment

[a] Organ failure for each organ system was considered to be present if the SOFA score was not zero

[b] Other sources of infection included central nervous system, bones and joints, cardiac system and reproductive organs. As some patients suffered from several infectious sites at the same time, the sum of incidence exceeds 100%

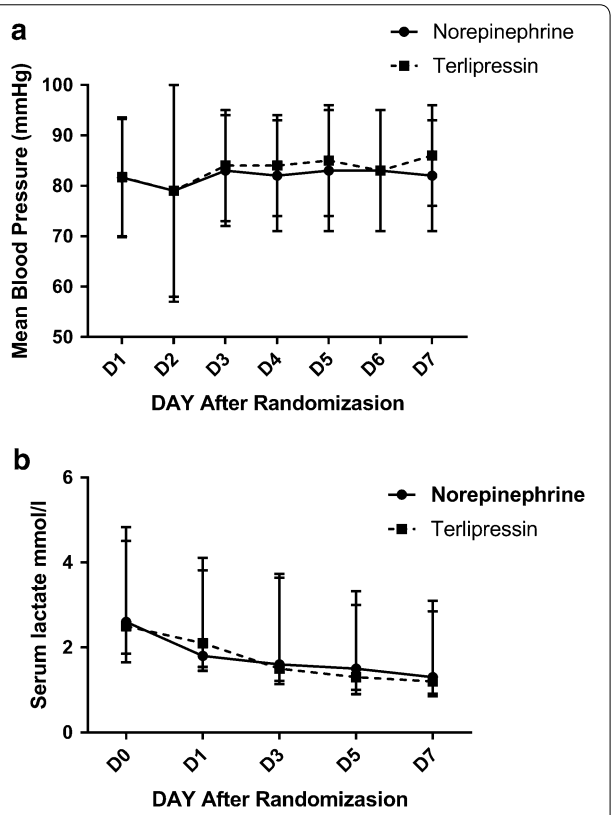

Fig. 2 Mean arterial pressure and serum lactate of two groups. **a** Mean arterial pressure of the two groups during 7 days after randomisation; values are mean ± standard deviation. **b** Serum lactate of the two groups during 7 days after randomisation; values are median and interquartile range

randomised, controlled, double-blind, multicentre study conducted so far. Continuous administration of terlipressin compared to NE in patients with septic shock did not decrease 28-day mortality. The changes in SOFA score on day 7 after randomisation were similar in the two groups. Serious adverse events were more common in the terlipressin group.

We set up the study to detect an absolute difference in 28-day mortality of 10% from an expected 50% as indicated in previous trials [1]. However, the observed mortality rates in both the terlipressin and NE groups were lower compared to previous studies [1, 2]. The reduction of mortality rates might be possibly due to an overall improvement in the care of patients with septic shock over the years. Furthermore, the mortality rates of septic shock varied among studies from different regions [1, 7, 18]. The current study showed the 28-day mortality of septic shock in mainland of China. The absolute difference of 28-day mortality rate between the groups was, however, only 2%.

The SOFA score is the predominant severity score currently used during sepsis [3]. A higher SOFA score is associated with an increased probability of death [19]. Rapid improvement in SOFA score has been associated with lower mortality rates [20, 21]. The current trial demonstrates that compared to baseline, the SOFA score on day 7 after randomisation was improved in both the terlipressin group and NE group. Furthermore, the improvements of SOFA score on day 7 after randomisation were similar between groups. Animal experiments showed evidence that terlipressin might protect organ function by improving myocardial contractility, renal function and vascular leakage in septic shock [22–24]. The VANISH randomized clinical trial was the latest trail to evaluate the effect of early vasopressin vs norepinephrine on renal function in patients with septic shock. Among adults with septic shock, the early use of vasopressin compared with norepinephrine reduced the use of renal replacement therapy [7]. In the post hoc analyses of our trial (presented in the supplement), we found a greater reduction of serum creatinine on days 5 and 7 after randomisation in the terlipressin group compared to the NE group. However, we failed to demonstrate a reduction in renal replacement therapy or acute kidney injury

Table 2 Analysis of the rates and risks of death from any cause and secondary outcomes

Variable	Norepinephrine group ($N=266$)	Terlipressin group ($N=260$)	p
28-day mortality *N* (%)	101/266 (38%)	104/260 (40%)	0.633
Days alive and free of vasopressor	14.66 ± 11.13	15.50 ± 11.14	0.424
Change of SOFA score from D0 to D7[a]	−6 (−10 to 5)[b]	−7 (−11 to 3)[b]	0.123

SOFA Sepsis-related Organ Failure Assessment

[a] D0 was defined as the day at randomisation. D7 was defined as the 7 days after randomisation. Those who died before day 7 were scored 24 at day 7 and those who were discharged from ICU before day 7 were scored 0 at day 7

[b] Data is presented as median (interquartile range). Repeated-measures analysis of variance was used for these data. The SOFA score on day 7 was significantly lower compared to that on day 0 in both groups ($p=0.000$). The p value for the interaction term (between group and time) was 0.515

Table 3 Serious adverse events in patients with septic shock

Variable *N* (%)	Norepinephrine group ($n=266$)	Terlipressin group ($n=260$)	p
Acute myocardial infarction or ischaemia	4 (1.39%)	2 (0.68%)	0.45
Life-threatening arrhythmia	6 (2.08%)	7 (2.38%)	1.00
Acute mesenteric ischaemia	1 (0.35%)	3 (1.02%)	0.62
Hyponatraemia	18 (6.25%)	25 (8.5%)	0.56
Digital ischaemia	1 (0.35%)	33 (12.6%)	< 0.0001
Diarrhoea	1 (0.35%)	8 (2.72%)	0.037
Overall	31 (11.65%)	78 (30%)	< 0.01

with terlipressin. Recently, in a phase IIa randomised, placebo-controlled trial in septic shock patients, selepressin, a novel selective vasopressin V_{1A} agonist, may improve fluid balance and shorten the time of mechanical ventilation [25]. Our post hoc analyses failed to find the benefits of terlipressin on fluid balance and mechanical ventilation.

One of the main results of our study was the significantly higher rate of serious adverse events, in particular the digital ischaemia, in the terlipressin group compared to the NE group. However, no patient needed surgical interventions for digital ischaemia. Previous reports show that serious ischaemic adverse events associated with terlipressin, such as skin ischaemia involving the extremities, scrotum, trunk and abdominal skin, are rarely observed [26]. At least two reasons may be responsible for the high rate of terlipressin-associated digital ischaemia in our septic shock patients. Firstly, 94% patients with digital ischaemia received terlipressin and open-label NE treatment at the same time. Such a combination may cause massive peripheral vasoconstriction, thus promoting the risk of ischaemia. Secondly, the dosage of terlipressin with a maximum of 4 mg/day in our trial was higher than the maximum of 1–2 mg/day reported in previous studies [11, 12, 27, 28]. High dosage may lead to increased vasoconstriction and ultimately in peripheral ischaemia. It is noteworthy that other adverse effects including myocardial infarction or ischaemia and life-threatening arrhythmia were rare in both groups of our study. Exclusion of patients who had acute coronary syndromes could account for the lack of adverse cardiovascular effects in our trial.

Several limitations of our trial should be mentioned. Firstly, terlipressin is a synthetic, long-acting vasopressin analogue with high affinity to the V_1 receptor. No equivalent dose of terlipressin compared to NE or vasopressin has been reported. We could not measure the serum level of terlipressin as a guide to estimate the dose and duration effect. Secondly, the sample size was originally designed for the primary endpoint. As a result of the small difference in the primary endpoint between the two groups, the trial was terminated at 50% enrolment. Therefore, the study might be underpowered for the outcomes analysis. Thirdly, the SOFA score of circulation was calculated according to the dosage of NE or dopamine. In this trial, however, the investigators were blinded to the experimental drugs. Therefore, on the basis of our protocol, they treated all the experimental drugs as NE, and subsequently calculated SOFA score according to infusion dose of the drug. This method might disturb the accuracy of SOFA score. Furthermore, the relatively high number of exclusions after randomisation in our modified intention-to-treat population might influence the accuracy of our conclusions.

In conclusion, we evaluated the effect of continuous terlipressin infusion (maximum 4 mg/day) compared to

NE in patients with septic shock. We did not find a significant reduction in 28-day mortality rate with terlipressin. Change in SOFA score on day 7 after randomisation was similar in both the norepinephrine and terlipressin group. We observed higher rates of serious adverse events, in particular digital ischaemia, in the terlipressin group as compared to the NE group. The dosing regimen and safety of continuous terlipressin infusion in septic shock need to be further investigated.

Electronic supplementary material
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Author contributions
ZL and JC contributed eaqually to this work. ZL, JC and XG designed the research; QK, JC, QL, XH, ZT, YK, KL, LZ, QS, TS, LZ, XW, XH, CW, BW, JL, SY, QG, KQ, XS and YW performed the research and collected data; AL analysed the data; ZL wrote the manuscript. All authors read and approved the final manuscript.

Compliance with ethical standards

Conflicts of interest
We declare no competing interests.

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It makes sense to continue to use norepinephrine as first line therapy. As doses rise, then early use of vasopressin appears to be the logical second line vasopressor. It has been tested in multiple randomised controlled trials and a recent meta-analysis found its use led to lower rates of atrial fibrillation and possibly lower rates of mortality and requirement for renal replacement therapy [14]. However, digital ischemic events were higher in that analysis too, reminding us that adequate fluid resuscitation, repeated assessment of cardiac output and targeting the lowest acceptable MAP for each individual patient to avoid high-dose vasopressors where possible, remain important components in the management of septic shock.

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