EvaLuation of early CRRT and beta-blocker InTervention in patients with ECMO (ELITE) trial: Study protocol for a 2 × 2 partial factorial randomized controlled trial

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Abstract

Background

In critically ill patients requiring extracorporeal membrane oxygenation (ECMO) therapy, early initiation of continuous renal replacement therapy (CRRT) and beta-blockade of catecholamine-induced inotropic effects may improve outcomes.

Methods

A 2×2 partial factorial randomized controlled trial in eligible ECMO patients without a clear indication or contraindication to either interventions are centrally randomly assigned to (A) early or conventional-indicated CRRT, and/or (B) beta-blocker or usual care. The primary outcome is all-cause mortality at 30 days for both arms. A total of 496 participants provides 80% power to determine a 20% risk reduction in mortality at 30 days with 5% type I error.

Discussion

This trial will help define the role of early CRRT and beta-blockade in ECMO patients.

Trial registration:

ClinicalTrials.gov Identifier: NCT03549923, Registered on 8 June 2018. World Health Organization International Clinical Trials Registry Platform (WHO ICTEP) network: https://trialsearch.who.int/Trial2.aspx?TrialID=NCT03549923). The Ethics Committee of Beijing Anzhen Hospital Approval ID is 2018013.

Introduction

Introduction

Veno-arterial extracorporeal membrane oxygenation (VA-ECMO) provides short-term circulatory support for critically ill patients with severe cardiac shock, but mortality remains high (60% to 75 %)[1] and acute kidney injury (AKI) and fluid overload (FO) are frequent complications [2, 3] often managed with continuous renal replacement therapy (CRRT).[3,5-7] However, the optimal timing of CRRT is uncertain: the positive results of the early vs late initiation of renal replacement therapy in critically ill patients with acute kidney injury (the ELAIN) trial[8] were not confirmed in another study, the Artificial Kidney Initiation in Kidney Injury (AKIKI). [9] As critically ill patients have excessive sympathetic activation and autonomic dysfunction from high circulating catecholamines that may compromise cardiac function[10-15]. Beta-blockade could improve outcomes by improving myocardial oxygen consumption, ventricular remodeling, and left ventricular function[16,17]. A randomized, open, single center study in patients with septic shock requiring norepinephrine to maintain mean arterial pressure showed a benefit of esmolol on 28-day mortality[18]. The circulatory support offered by ECMO may avoid the negative inotropic effect of beta-blockers in the setting of cardiogenic shock.[19] We initiated the EvaLuation of early CRRT and beta-blocker

InTervention in patients with ECMO (ELITE) trial to determine the effects of early CRRT versus conventionally-indicated CRRT and/or beta-blockade on top of routine care.

Objectives:

To determine whether (A) early CRRT compared to conventional-indicated CRRT and (B) beta-blockade with esmolol compared to standard treatment, will reduce 30-day mortality in ECMO patients.

Methods

Study design

ELITE is a prospective, multi-center, open-label, randomized controlled trial, with a 2×2 partial factorial design to evaluate early CRRT support and beta-blockade on 30-day mortality in a broad range of ECMO patients admitted to hospitals in China from July 2018. In arm A, patients are randomized to early CRRT within 24 hours of initiation of ECMO or to control, regardless of whether there is a conventional indication, or to the control where patients only receive CRRT according to a conventional indication. In arm B, patients are randomized to intravenous esmolol group or usual care. The trial design and protocol adhere to the Recommendations

for Interventional Trials (SPIRIT) criteria[20.] (table 1) and checklist (see Additional file)

Eligibility

Broad inclusion criteria are used for both arms, whereby adult patients who have received ECMO for any reason within 24 hours and 7 days, for arms A and arm B, respectively, are eligible (Tables 2 and 3). Patients are excluded from arms A and B if they had a definite indication or contraindication to either CRRT or beta-blockers, respectively. As ECMO is often initiated by a specialist team to rescue and transfer patients to larger hospitals in China, a timeframe of 24 hours after ECMO implantation was used for early CRRT in arm A, while a relatively stable hemodynamic status (dopamine/dobutamine <5 μg/kg/min, with no administration of adrenaline or norepinephrine) and within 7 days after initiation of ECMO was required for eligibility into arm B.

Randomization

All eligible patients are centrally randomized in a 1:1 ratio to either early CRRT or conventional indication CRRT, and/or beta-blocker group or usual care (control) groups, via a computer-generated randomization schedule, stratified by age (<65 vs. ≥65 years) and implantation of ECMO for extracorporeal cardiopulmonary resuscitation (yes vs no). Investigators use a cellphone application to confirm eligibility and obtain the randomized treatment allocation.

Interventions

Patients assigned to early CRRT should have it applied concurrently with ECMO treatment and continued for ≥12 hours. Those assigned to standard therapy should receive CRRT according to 2012 Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for AKI stage 3 and have at least one of the following criteria met: severe hyperkalemia (> 6.5 mmol/L); metabolic acidosis (pH < 7.2); pulmonary edema unresponsive to diuretic therapy; requiring oxygen flow rate of > 5L/min to maintain an oxygen saturation (SpO_2) of >95%, or

requiring a forced inspired oxygen concentration (FiO_2) of >50% on ventilation; blood urea nitrogen level >112 mg/dL; or oliguria (urine output < 200 mL per 12 hours) for > 72 hours. CRRT can be initiated or discontinued according to the attending clinician's decision in managing the patient.

In arm B, patients assigned to the intervention group are to receive a continuous infusion of esmolol on top of conventional management, commencing at 25 mg/hour and increasing by 25 mg/hour every 20 minutes until the heart rate reduced to 75±5 bpm or an upper dose limit of 2000 mg/hour is reached. Esmolol infusion should be continued to maintain the heart rate threshold or according to the clinician's discretion until discharge from the intensive care unit (ICU) (or death, if sooner). Oral beta-blockers should be introduced before esmolol is withdrawn. Esmolol can be transiently stopped or completely withdrawn should a patient develops third-degree atrial-ventricular block , bradycardia (< 60 bpm), extreme left ventricular systolic dysfunction, aortic valve dysfunction, or severe cardiogenic pulmonary edema. Patients in the control group will not receive any type of beta-blockers, unless the clinician considers there is a strong indication. Concomitant diseases will be treated following current guidelines.

Outcomes

The primary outcome for both arms is all-cause mortality at 30 days. Secondary outcomes are all-cause mortality at 365 days; use of long-term RRT; success in weaning from ECMO, defined as survival after 24 hours from weaning; health-related quality of life according to scores on the EuroQoLEQ-5D-5L questionnaire at 365 days; length of stay at ICU and hospital; unplanned hospital readmission; separately on cardiac and non-cardiac death; any serious adverse event (SAE) in ICU (Table 4 outlines SAE definitions).

Data management

Data are collected on patient demography, medical history, concomitant therapy, duration of CRRT, and dose and duration of esmolol. Vital and health status are assessed at the time of weaning from ECMO, discharged from ICU and hospital, unplanned hospital readmission, EQ-5D scores, and SAEs, during follow-up via telephone, face-to-face, or remote medical consultation over 365 days. To improve monitoring adherence, the clinician will take time to explain about need of follow-up surveillance and encourage the participants to undergo routine examinations. Data are entered into a secure password protected electronic data capture system and checked for quality by research staff. All queries are listed for content and raised and resolved dates. All study records required by the coordinating center at the Heart Health Research Center (HHRC) and applicable regulatory bodies are maintained for 15 years.

Sample size

For each arm, a total of 496 patients (248 per group) are required based on the following assumption: a 70% 30-day mortality in the control group; a 20% relative risk reduction for each intervention (early CRRT and beta-blocker); no loss of follow-up or crossover; no interaction between interventions; and 5% type I error and 20% type II error.

Statistical analysis

All analyses will be conducted according to the intention-to-treat principle. Baseline characteristics between groups will be reported as frequencies and percentages for categorical variables, and as means and standard

deviations (SD) or medians and interquartile ranges (IQR) for continuous variables. The primary outcome will be compared between groups in a log-rank test. Other efficacy and safety endpoints will be reported with t test or Wilcoxon test, and chi-square test for continuous and categorial variables, respectively, as appropriate. All tests are two-sided, and the nominal level of α will be 5%.

In subgroup analysis by age and ECPR will be defined by the presence or absence of a pre-randomization variable and the primary outcome as in the main analysis. The main analysis for each subgroup will be an unadjusted test of interaction in a logistic model to determine whether the effect of treatment differs significantly across categories. The missing values will not be imputed unless substantial and reported with the number of observations used in the analysis.

Monitoring

The Data monitoring committee (DMC) consists of a critical care physician, nephrologist, and cardiovascular expert, all experienced in clinical research. Principal Investigator will report the process of the trial, quality of data collected, adverse events, and protocol deviation and violation to the DMC. The DMC will meet every 6 months during conduction of the trial. No interim analysis for efficiency is planned as the assumptions in sample size calculation is less likely to be changed.

Trial status

There have been 92 patients enrolled form 10 hospitals into study A and the enrollment is still ongoing(see Appendix for the hospital list). However, Study B was stopped in August 2019 in the absence of any patients being enrolled. Although we aimed to test the hypothesis that beta-blockers would protect the myocardium in ECMO patients, we found this too challenging to undertake as of these patients have low BP, which is a contraindication to such treatment and raised concerns of harms among investigators. Moreover, the short time window for enrollment was another barrier to recruitment, and by the time a patient is stable and without vasopressors, it is near the time to wean them off ECMO. Consequently, we decided to close recruitment into arm B.

Discussion

Being one of the most seriously ill groups in clinical practice, with high mortality and requiring heavy use of critical care resources, there are considerable challenges to generate reliable evidence to guide the management of ECMO patients. Our ELITE trial attempts to address two important clinical questions with strong pathophysiological mechanisms.

A multicenter retrospective cohort study has shown that FO is common in a pediatric population (Peak FO≥10% in 84.8%, ≥20% in 67.2%, and ≥50% in 29%)[21] where FO has consistently been shown to be associated with adverse outcomes, [22, 23, 24] while a meta-analysis of observational studies has shown lower mortality in those who receive CRRT[25]. These data suggest that early initiation of CRRT to avoid FO in the context of ECMO may be beneficial. The Kidney Interventions During Membrane Oxygenation (KIDMO) study showed that CRRT use was 43%, 16%, and 35% of patients for FO, for FO prevention, and for AKI, respectively after ECMO [26]. However, there has not been a randomized trial to support these approaches. So we designed this ELITE trial. As the closing of

arm B, the question of whether beta-blocker is efficient in patients with ECMO remains unaddressed and more effects should be made.

Other limitations of our trial include the lack of blinding, and for practical reasons, recruitment has been slow due to the small number of patients receiving ECMO despite the expectation of a least 10 cases treated annually across our network of 30 ICUs in China. We did not stratify our randomization by ECMO centers but will perform subgroup analysis to explore the effect between small and large centers.

In summary, the ELITE trial is the first randomized controlled trial of critically ill patients receiving ECMO support, powered to test the effects of early CRRT versus conventional timing of CRRT on 30-day mortality. The results should inform the management of this important patient group.

Declarations

Ethics approval and consent to participate

This trial complied with the Declaration of Helsinki regarding investigation in humans. Its ethical clearance, protocol (version 3.0 on September 25, 2019), and associated documents were approved by the Ethics Committee of Beijing Anzhen hospital (Approval ID: 2018013).Any significant modifications to the protocol will need approval from the ethics committee before implementation.

Informed consent and written consent forms of patients are mandatory before study participation. After the participant has been assessed as eligible, they or their guardians will be invited by the treating physicians to discuss the details and sign the informed consent. This trial does not involve collecting biological specimens for storage. Participants' data is stored using a participant identification number and the key to the identification code list is only available to the research team.

Ancillary and post-trial care

The trial insurance to cover for non-negligent harm associated with the protocol. This will include cover for additional health care, compensation, or damages.

Consent for publication

Written informed consent was obtained from the participants to publish this

manuscript and accompanying images.

Availability of data and materials

The datasets used and analyzed during the current study are available from

the corresponding author on reasonable request.

Competing interests

The authors declare no conflict of interest.

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Authors' contributions

Author contributions are consistent with the International Committee of Medical Journal Editors (ICMJE) Recommendations. XW, HW, CL and JZ participated in intervention of the study. CA and XD participated in the study design. XW, XD and ZW drafted and revised this manuscript. XH and JD are the principal investigators and conceived the study.

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Organization

Coordinating center: Heart Health Research Center (HHRC).

Steering committee: Jianzeng Dong, Xiaotong Hou, Craig Anderson, Xin Du, Hong Wang, Simon Finfer

End point adjudication committee: We would not adjudicate the primary or secondary endpoints

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Data monitoring committee (DMC): Bruce Neal, Jicheng Lv, Xiang Guo

Data management: Heart Health Research Center (HHRC).

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Tables

Table 1

	Study Period							
	CRRT Screening		Beta blocker Screening		Days post-randomization			
		CRRT Randomization		Beta blocker Randomization	Day 3	Day 7	Day 30	Day 365
Window for time for evaluation							±5 days	±35 days
Visit number		1		1	2	3	4	5
Informed consent		×		×				
Demographic data	×		×					
Physical measures	×	×	×	×				
Medical history		×		×				
Concomitant medications	×	×	×	×	×	×	×	×
Physical examinations[1]		×		×				
Vital signs[2]		×		×	×	×		
Complete blood count[3]		×		×	×	×		
Arterial blood gas[4]		×		×	×	×		
Biochemistry items[5]	×		×		×	×		
Coagulation indexes[6]		×		×	×	×		
UCG[7]		×		×	×	×		
Intake and output volume in 24 hours					×			
Medication, type and dose[8]		×		×	×	×	×	×
Mechanical ventilation and mode		×		×	×	×	×	

Left ventricular unloading method					×	×	×	
RRT	×				×	×	×	×
APACHEII score		×	×					
SOFA Score		×	×					
EQ-5D score								×
SAEs					×	×	×:	×

[1]Physical examinations: height（cm）,wight（kg）; [2]Vital signs: blood pressure（mmHg）,pulse（beats/min）, heart rate （beats/min）temperature（°C）, respiratory（/min）; [3] Complete blood count: white blood cell count（10^3/mm^3）, hemoglobin（g/dL）, platelet count（10^9/L）; [4] Arterial blood gas: PH（PaO2（mmHg）, PaCO2（mmHg）, K^+（mmol/L）, Na^+（mmol/L）, hematocrit（%）, lactic acid（mmol/L）; [5] Biochemistry items; creatine（μmol/L）, total bilirubin （μmol/L）; [6] Coagulation indexes: PT（s）, APTT（s）; [7] UCG: left ventricular ejection fraction（%）, left ventricular end diastolic diameter（cm）, Moderate and above pulmonary hypertension, moderate and above tricuspid regurgitation; 8 Medication: dopamine, dobutamine, epinephrine, norepinephrine, vasopressin, pituitrin, milrinone; beta blockers

Table 2. Inclusion and exclusion criteria for study A

Inclusion criteria
· Patients receiving VA-ECMO for any reason within 24 hours
· Provision of informed consent
Exclusion criteria
· Age < 18 years
· Receiving ECMO bridging to heart transplantation
· With convention indication of CRRT: AKI prior to enrollment caused by any reason, at least one of the following criteria is met:
a) Severe hyperkalemia (> 6.5 mmol/L)
b) Metabolic acidosis (pH < 7.2)
c) Pulmonary edema
d) Blood urea nitrogen level > 112 mg/dL
e) Oliguria (urine output < 200 mL/12h) for more than 72 hours
· CKD, with estimated GFR<30 mL/min
· Have already initiated CRRT
· Active hemorrhage/thrombotic thrombocytopenic purpura
· Receiving ECMO again during hospitalization or respiratory failure has already initiated VV-ECMO or extracorporeal carbon dioxide removal device before the initiation of VA-ECMO of this time

AKI: chronic kidney disease; CKD: chronic kidney disease; CRRT: continuous renal replacement therapy; ECMO: extracorporeal membrane oxygenation; GFR: glomerular filtration rate; VA-ECMO: veno-arterial extracorporeal membrane oxygenation; VV-ECMO: veno-venous extracorporeal membrane oxygenation.

Table 3. Inclusion and exclusion criteria for study B

Inclusion criteria
· Patients receiving VA-ECMO for any reason
· Dopamine/dobutamine <5 μg/kg/min, no administration of adrenaline or norepinephrine
· Within 7 days after initiation of VA-ECMO
Exclusion criteria
· Age < 18 years
· Receiving ECMO bridging to heart transplantation
· Contraindications or intolerance to beta-blockers
a) Moderate or severe bronchial asthma attack or history of bronchial asthma
b) Sinus bradycardia (heart rate < 60 bpm)
c) Type II second-degree or third-degree AVB
d) Allergy to esmolol
· Receiving ECMO again during hospitalization or respiratory failure has already initiated VV-ECMO or extracorporeal carbon dioxide removal device before the initiation of VA-ECMO of this time
· Have been on beta-blocker treatment after initiation of ECMO
· Women at child bearing age, pregnant or positive pregnancy test.

ECMO: extracorporeal membrane oxygenation; AVB: atrioventricular block; VA-ECMO: veno-arterial extracorporeal membrane oxygenation; VV-ECMO: veno-venous extracorporeal membrane oxygenation.

Table 4. Definition of SAEs

The SAEs include but are not limited to
Bleeding
· Bleeding requires transfusion for > 2 units
Severe arrhythmias which include
· Type II second-degree AVB or third-degree AVB
· Sustained ventricular tachycardia (> 30 s)
· Ventricular fibrillation
Ventilator associated pneumonia, which need to meet all the criteria below;
· At least 48 hours after endotracheal intubation
· Chest X-ray shows sustained or worsening shadowing (infiltrates or consolidations)
· Signs of pulmonary consolidation and/or crackles on auscultation, at least meet one of the following criteria
a) White blood cell count >10×10^9/L or <4×10^9/L
b) Temperature >37.5℃, purulent secretions
c) Positive cultures obtained directly from bronchial secretions
Bloodstream infection
· Positive cultures obtained from peripheral blood;
SSI
· Purulent drainage in the operated region with pain or tenderness, localized swelling, redness, and heat or fever, requiring operation, including superficial incisional wound SSI, deep incisional wound SSI and organ/space SSI
Any reason induced limb ischemia
· Physical examination demonstrating pain, pallor, pulseless, cold, motor or sensor deficit
· Requiring decannulation of ECMO catheter or surgical intervention
Stroke
· New onset abnormal neurological signs and symptoms last for at least 24 hours with radiographic evidence
Any other sever adverse events determined by the physicians

AVB: atrioventricular block; ECMO: extracorporeal membrane oxygenation; SAE: serious adverse events; SSI: surgical site infection.

Appendix

ELITE study centers:

Centers	Location	Number of patients enrolled
The Secondary Affiliated Hospital of Zhengzhou University	Zhengzhou, Henan province	35
The First Affiliated Hospital of Zhengzhou University	Zhengzhou, Henan province	17
The Second Hospital of Jilin University	Changchun, Jilin province	17
The People's Hospital of Guangxi Zhuang Autonomous Region	Nanning, Guangxi Zhuang Autonomous Region	8
Chinese PLA General Hospital	Beijing	3
Beijing Anzhen Hospital	Beijing	3
Zhongshan City People's Hospital	Zhongshan, Guangdong province	3
Sichuan Provincial People's Hospital	Chengdu, Sichuan province	3
Taizhou Hospital of Zhejiang Province	Taizhou, Zhejiang province	2
Zhongshan Hospital Affiliated to Fudan University	Shanghai	1

Figures

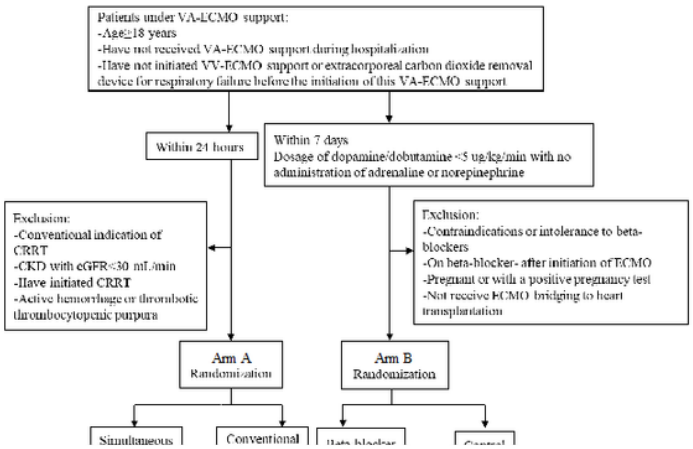

Figure 1

Study design

CKD: chronic kidney disease; CRRT: continuous renal replacement therapy; ECMO: extracorporeal membrane oxygenation; ICU: intensive care unit; VA-ECMO: veno-arterial extracorporeal membrane oxygenation.

Supplementary Files

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- ELITESPIRITchecklist.docx