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RESEARCH PROTOCOL

The comparison of circuit lifespan between integration and separation approach in extracorporeal membrane oxygenation (ECMO) patient requiring continuous renal replacement therapy (CRRT) support, (E-CRRT Trial)

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The data and code were available upon reasonable request (Prasittiporn Tangjitaree, email address: pingmazz@gmail.com)

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ABSTRACT:

Background: The estimated incidence of acute kidney injury requiring continuous renal replacement therapy (CRRT) in patients necessitating extracorporeal membrane oxygenation (ECMO) is approximately 50%. Currently, two well-known techniques—integration and separation—are utilized for combining CRRT and ECMO circuits. The efficacy of these two techniques is still unknown. Therefore, this study aimed to compare the circuit lifespan of CRRT between the integration and separation techniques.

Methods: A multicentered randomized controlled study with an unblinded design will be conducted to determine circuit lifespan differences between integration and separation techniques.

Hypothesis: We hypothesize that the integration technique will yield a longer circuit lifespan for CRRT compared to the separation technique.

Trial registration: NCT05036616

Keywords: CRRT; ECMO; Circuit; Combination; Integration

INTRODUCTION

In contemporary critical care, extracorporeal membrane oxygenation (ECMO) has emerged as a pivotal life-saving intervention for critically ill patients. The severity of patients necessitating ECMO is often accompanied by multifactorial factors leading to acute kidney injury (AKI), including nosocomial infections, exposure to nephrotoxic drugs, hypotensive states, and systemic inflammatory conditions[1-4]. The incidence of AKI in critically ill patients can be as high as 80%, with up to 50% requiring renal replacement therapy within the first week[5-7]. Due to the state of hemodynamic instability, continuous renal replacement therapy (CRRT) is preferred.

The CRRT methods combined with ECMO have three main ways consisting of 1. In-line technique, 2. The separation technique, and 3. The integration technique. Currently, separation and integration are more popular methods, as shown in Figure 1 [8-10]. The separation technique offers advantages such as an independent circuit and easy circuit modifications[11]. However, it is associated with the risk of additional vascular access complications and catheter-related

bloodstream infections (CRBSI). On the other hand, the integration technique eliminates the need for additional vascular access for renal replacement therapy. Yet, concerns include the potential for air emboli, difficulties in managing pressure circuit issues, and limitations in certain CRRT machines that do not support integration techniques with pressure limitations[12].

Despite the absence of conclusive evidence supporting the superiority of either technique[13], a questionnaire study by Michael Thy, and et al.[14] revealed that method selection is often based on a physician's experience. This study aimed to address this gap by comparing the CRRT circuit lifespan, along with assessments of pressure at various points, CRRT machine alarms, 28-day mortality, and complications during CRRT when combined with ECMO for each technique. The objective is to provide substantive insights into the optimal approach for integrating CRRT with ECMO.

OBJECTIVES

Primary objective

The primary objective is to compare CRRT circuit lifespans.

Secondary objective

The secondary objectives are to compare serious adverse events, 28-day mortality, CRRT circuit pressure at various points, and the rate of CRRT machine alarms.

MATERIALS AND METHODS

Study design

This is a multicenter, open-label, randomized controlled study.

Study setting

This research was conducted in the surgical and medical intensive care units (ICU) of two tertiary care centers, including King Chulalongkorn Memorial Hospital and the Central Chest Institute of Thailand.

KEY MESSAGES:

- How to run CRRT during ECMO support is still unknown.
- Our study aimed to compare CRRT circuit lifespan between integration and separation technique in severe AKI patients requiring ECMO support.

Eligibility criteria

1. Patients aged 18 years or older,
2. Admitted to the intensive care unit,
3. Requiring ECMO (venovenous (VV-ECMO) or venoarterial ECMO (VA-ECMO), and
4. Presenting with AKI, which needs CRRT.

Exclusion criteria

1. Pregnancy
2. Heparin contraindication
3. AKI due to bilateral renal arterial thrombosis, renal vasculitis, glomerulonephritis, systemic vasculitis, or post-obstructive renal failure

Indication of ECMO treatment

1. Cardiogenic shock
2. Weaning from cardiopulmonary bypass after cardiac surgery
3. Post heart or heart-lung transplantation with acute primary graft failure
4. Chronic cardiomyopathy
5. Procedural support in high-risk cardiac intervention
6. Bridging to heart or heart-lung transplantation
7. Severe acute respiratory distress syndrome (severe ARDS)
8. Lung rest
9. Post lung transplantation
10. Lung hyperinflation
11. Severe pulmonary hemorrhage

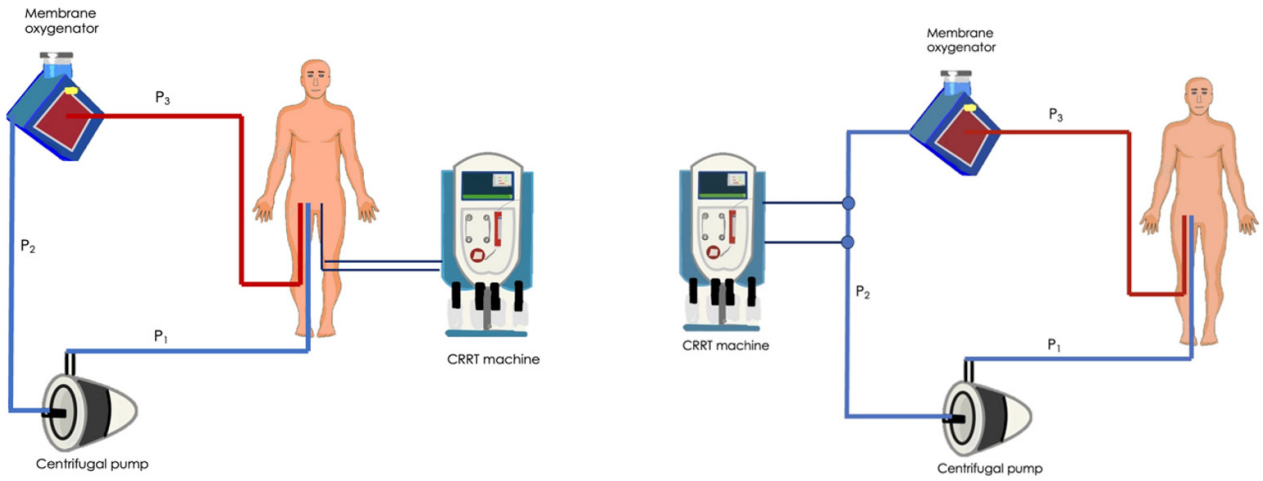

Figure 1. On the left shows the separation technique and the right is the integration technique.

Indication of CRRT

1. Severe acidosis with pH < 7.2 or serum bicarbonate < 15 mEq/L
2. Refractory volume overload, not diuretic-responsive
3. Persistent hyperkalemia (serum potassium > 6.2 mEq/L) even if received medication or hyperkalemia-related cardiac conduction abnormality by electrocardiogram
4. Oliguria or anuria, urine output < 0.5 mL per actual body weight sustained for more than 6 hours
5. Azotemia, blood urea nitrogen > 100 mg/dL, or uremia
6. Increased intracranial pressure

Recruitment and consent

The investigator will engage directly with the ICU team. The investigator team will assess patient eligibility based on predetermined criteria. If eligible, the patients or their surrogate decision makers (for vulnerable subjects) will be informed about the protocol of the study, and their informed consent will be sought for participation, if they agree to participate in the study.

Following consent from the patient or surrogate decision maker, the study protocol will be implemented, encompassing patient conditions, laboratory data, CRRT, and ECMO details. Demographic and clinical variables will be systematically recorded in a case record form.

Methods

1. Patients meeting eligibility criteria are pre-stratified by ECMO type (VV-ECMO or VA-ECMO) to address potential pressure-related influences on CRRT circuit longevity. Randomization, occurring in blocks of four within each ECMO type, establishes the separation and integration technique groups. This pre-stratification ensures a balanced representation of ECMO types across both groups. The type of ECMO is determined by a multidisciplinary medical team comprising cardiologists, cardiothoracic surgeons, and intensivists.
2. All patients undergo CRRT with either continuous venovenous hemodialysis (CVVHD) or continuous venovenous hemodiafiltration (CVVHDF). The decision about CRRT initiation is made by intensivists or nephrologists.
3. In the separation technique group, a nephrologist or intensivist inserts the dialysis catheter, proceeding with separate CRRT and ECMO. In the integration technique, perfusionists and the medical team integrate CRRT into the ECMO circuit.
4. The case record form is recorded during the first lifespan of the CRRT circuit, reasons for discontinuation of the ECMO or CRRT, vital signs, daily laboratory result, anticoagulant dose, citrate use in CRRT, dose of vasopressor/inotrope at least once per day, pressure in access and return cannula, alarm, and complications during CRRT in ECMO such as bleeding complications, hemolysis, or embolic event. The follow-up extends until the end of the first CRRT circuit. Mortality at 28-days post-randomization is documented. Both groups receive standardized care throughout the data collection process.

ECMO circuit

The Maquet Rotaflow ECMO System I or II, sourced from Germany, was employed as the primary apparatus in this study. Insertion of ECMO cannulas was conducted by either a cardiothoracic surgeon or a vascular surgeon. The return cannula specifications included 15-17 French in VA ECMO and 15-19 French in VV ECMO, while the drainage cannula dimensions were standardized at 25-27 French. Patient integration into the ECMO circuit was carried out by perfusionists with expertise in the field.

The initiation of ECMO commenced with an initial flow rate of 3-5 LPM, overseen by a collaborative effort involving a cardiologist, cardiothoracic surgeon, or intensivist. Systemic heparin, functioning as the systemic anticoagulant, was promptly administered, unless contraindications were present, to mitigate the risk of clotting within the ECMO circuit. The heparin dose is adjusted in units per hour to maintain an activated clotting time (ACT) of 180-220 seconds every 2 hours, and an activated partial thromboplastin time (aPTT) 1.5-2.5 times the normal frequency every 6-12 hours[15].

CRRT

The AKI definition was defined by the KDIGO 2012 guideline[16] as the serum creatinine increased at least 0.3 mg/dL from baseline within 48 hours, increased more than 1.5 times from baseline within 7 days, or urine output was less than 0.5 mL/kg/hour for 6 hours. The decision to initiate CRRT is made by intensivists or nephrologists.

The CRRT procedures in this study were conducted utilizing the Prismaflex system from Baxter, USA. The mode adopted was either continuous venovenous hemodialysis (CVVHD) or continuous venovenous hemodiafiltration (CVVHDF). Consistent with the KDIGO clinical practice guideline for acute kidney injury 2012[16], the prescribed CRRT dose was 25-30 mL/kg/hour.

The blood flow rate was set at a minimum of 100 mL/min, and regional citrate may be employed as the anticoagulant for the CRRT circuit in case of delayed heparin use in the ECMO circuit. The decision to use regional citrate depends on primary doctor judgment. However, in cases where patients presented with hyperlactatemia (arterial lactate exceeding 8 mmol/L) or exhibited an advanced stage of cirrhosis or acute liver failure, the use of regional citrate was contraindicated.

For the double lumen catheter (DLC) dedicated to CRRT, the DLC is an uncuffed, nontunneled dialysis catheter positioned at a depth of 16 cm from the skin exit site for the right internal jugular vein, 19 cm for the left internal jugular vein, and 25 cm for the femoral vein. DLC is placed in this order: right internal jugular vein, either femoral vein, left internal jugular vein, and either subclavian vein[16]. The selection depends on the position used for the ECMO insertion site. Proper site confirmation with a chest radiograph is conducted if the internal jugular or subclavian vein is used.

In the Integration group, pigtails that integrated the CRRT-ECMO circuit in the P2 segment, specifically the pre-oxygenator and post-blood pump sections of the ECMO circuit, measured 1.52 cm in diameter. These pigtails were seamlessly connected to the ECMO circuit via a

three-way stopcock, ensuring a streamlined integration of the two therapeutic modalities.

The complications during catheter insertion, including vascular injury, hematoma at the insertion sites, and pneumothorax, can occur but can be minimized with ultrasound guidance, expertise, and thorough attention in all cases. Concerns also arose regarding cardiac arrhythmia potentially occurring if the guide wire contacts the right atrium. However, awareness of guide wire depth and hemodynamic monitoring displays helps in early recognition. In the integration approach, air bubbles and blood loss might be occurred during combining systems. A multidisciplinary team, including a cardiothoracic surgeon or intensivist, remained bedside until blood flow was restored.

The CRRT machine operates with an access pressure range of -250 to +450 mmHg, triggering a high pressure alarm at +300 mmHg or higher, and a low pressure alarm at -250 mmHg or lower. Return pressure ranges from -50 to +350 mmHg, with a high pressure alarm set at +350 mmHg or higher. Transmembrane pressure (TMP) and pressure drop serve as indicators for filter clogging and clotting. A high TMP alarm is set at 300 mmHg or higher, and a high pressure drop alarm is set at 100 mmHg or higher. Blood leakage is detected using an infrared blood leak detector in the effluent line, while a bubble detection system utilizes ultrasonic technology to detect bubbles in the effluent line[18].

OUTCOME MEASUREMENT

Primary outcomes

CRRT circuit lifespan

Secondary outcomes

Serious adverse events, 28-day mortality, CRRT circuit pressure at various points, and rate of CRRT machine alarms.

Operative definitions

The primary outcome, circuit lifespan termination, is measured in hours from the initiation of blood flow into the renal replacement machine in the first circuit used until the completion of the circuit's designated usage period (maximum 72 hours as per manufacturer suggestion) or its premature clotting, meaning the circuit lifespan is less than 72 hours with the occurrence of circuit clotting, including visible clotting or a pressure drop > 100 mmHg, or clogging where TMP > 300 mmHg, events reported by trained nurses familiar with renal replacement therapy, or successful circuit completion is marked by improved renal function, characterized by urine output per day surpassing 1000 mL without diuretics or exceeding 2000 mL with diuretic use [19-20], or events affecting termination include ECMO discontinuation, extended circuit downtime, and participant mortality. Crossover between 2 techniques (integration to separation or vice versa) calculates circuit age only during the initial technique application, with recorded reasons for technique transition.

Nurse-recorded CRRT parameters, including access and return line pressures, transmembrane pressure (TMP), and pressure drop, are recorded hourly, with daily averages, while CRRT machine alarms (e.g. air detection alarm, blood leak detector, pressure alarm – high/low access or return pressure alarm, high TMP, or clotting) are documented. The 28-day mortality status was assessed, counting from the day of randomization.

Serious adverse events

Serious adverse events recorded during the data collection period for circuit lifespan include bleeding at the ECMO cannula or vascular access exit site, new onset of hemolysis during ECMO combined with CRRT treatment, systemic or major bleeding, new positive blood cultures with clinical correlation of infection (≥ 1 blood bottle), an air embolic event, and death.

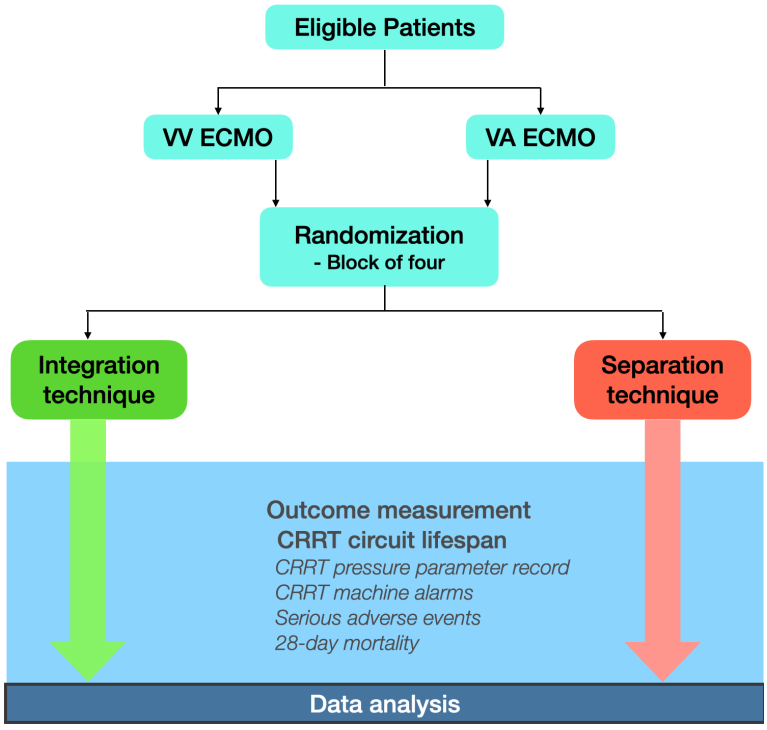

Figure 2. Flow chart of study protocol.

Timeline

Each participant will be followed up during the first circuit of CRRT, which will be used for primary outcome and secondary outcome collection. Follow-up will continue until 28 days after randomization for the assessment of mortality. The study began data collection on May 1st, 2021, and is planned to be completed within 4 years.

DATA ANALYSIS PLAN

Sample size estimation

The sample size for this study was determined based on data from Christian de Tymowski et al.[12], who reported a mean lifespan of 48 ± 51 hours for the integration group and 20 ± 33 hours for the dialysis catheter group in non-ECMO therapy. Setting the magnitude of the mean difference at 28 hours, with an anticipated longer circuit lifespan in the integration group compared to the separation group, and utilizing an alpha of 0.05, 80% power, and an allocation ratio of 1:1, sample size calculations were performed using the n4Studies [21] program. The calculated sample size was 37 participants per group, accounting for an estimated dropout rate of 5%. Consequently, the final sample size for each group was set at 40 participants.

OUTCOME ANALYSIS PLAN

The statistical analysis will be conducted using STATA version 18 software. Categorical data, including secondary outcome such as 28-day mortality, serious adverse events, and alarm settings, will be presented as frequencies and percentages and compared between two groups using the Chi-square test or Fisher's exact test. Continuous data, including primary outcome, and pressure at various points, will be reported as either mean or median, with the difference tested using the unpaired t-test or Mann-Whitney U test, depending on the data distribution.

For this primary analysis, intention-to-treat analysis will be employed to compare outcomes. Additionally, a per-protocol analysis will be conducted to support the findings of the noninferiority trial. The significance level was set at a p-value < 0.05.

Anticipated events include renal recovery until CRRT termination, ECMO discontinuation before CRRT circuit termination, or death during CRRT, potentially influencing the lifespan of CRRT. An adjusted circuit lifespan was predefined in the pre-analysis plan to exclude confounding events. Given that the primary outcome may be influenced by the use of anticoagulants, citrate, or non-citrate in the CRRT circuit, ECMO types, and study centers, preplanned subgroup analysis of these factors is conducted. Missing data handling involves single imputation. In cases where missing data exceed 40%, a complete case analysis is planned instead.

We plan to conduct an interim analysis after 40 participants. If there is a statistically significant difference observed, it may lead to the early termination of the trial. This could occur if there is clear evidence of the superiority of the standard treatment of combining CRRT with ECMO as outlined in the guidelines during the course of the research, or if there is significant evidence of harm or serious adverse events from the intervention.

DATA MANAGEMENT AND DATA MONITORING

Input data

The case record form is utilized for data collection, including baseline characteristics and outcomes. All data will be recorded and accessed only by the investigators to maintain data security and respect autonomy.

Monitoring method

Investigators plan to conduct regular meetings every month between investigators from both centers. These meetings will serve to discuss protocol adherence, reevaluate the understanding of critical care healthcare workers experienced in CRRT and ECMO management, monitor serious adverse events, address any issues encountered during data collection, work towards protocol improvement, and enhance participant recruitment. Additionally, they will review previous case records every three months to correct missing data and ensure data accuracy.

Serious adverse events (SAEs) and suspected unexpected serious adverse reactions (SUSARs) will be promptly reported to the Critical Care Nephrology Excellence Center at King Chulalongkorn Memorial Hospital, Bangkok, Thailand, and the Institutional Review Board (IRB) of the Faculty of Medicine of Chulalongkorn University.

Confidentiality

Informed consent is obtained in the surgical and medical ICU. All participants will not be specifically identified. A code number represents the patient's information rather than the patient's name, hospital number, or admission number. All data are recorded only in the case record form and on the investigator's personal computer. After the research, the data will be erased and destroyed.

Dissemination policy

We plan to disseminate the results in peer-reviewed journals related to critical care medicine or nephrology and at national or international conferences.

DISCUSSION

Given the absence of a standardized treatment approach for CRRT with ECMO, the authors undertook this study to identify the optimal method, considering CRRT lifespan while maintaining a favorable safety profile. The aim is to contribute valuable insights to guide clinicians in selecting the most suitable approach. If the results prove satisfactory and reliable, there is potential for cost reduction in CRRT filter sets by maximizing circuit lifespan and ICU workload reduction. Furthermore, the study seeks to elucidate the benefits and risks associated with each method, enhancing the evidence base for clinical outcomes.

This study's strengths lie in its status as one of the first randomized controlled trials comparing CRRT circuit lifespan and the pioneering comparison of both combination techniques in ECMO patients across both arms. Additionally, the study's multicenter design in tertiary centers features available perfusionists and cardiothoracic surgeons.

The study recognizes certain limitations, including a potentially prolonged participant recruitment period due to low ECMO cases. The trial is a single-blinded design, with only statisticians unaware of the specific interventions being employed, so outcomes are accepted for some bias.

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AUTHORS' CONTRIBUTIONS

(I) Conceptualization: Prasittiporn Tangjitaree; (II) Data curation: Prasittiporn Tangjitaree; (III) Formal analysis: Prasittiporn Tangjitaree; (IV) Funding acquisition: Prasittiporn Tangjitaree, Nattachai Srisawat; (V) Methodology: Prasittiporn Tangjitaree, Tanyapim Sinjira; (VI) Project administration: Prasittiporn Tangjitaree, Peerapat Thanapongsatorn; (VII) Visualization: Prasittiporn Tangjitaree; (VIII) Writing – original draft: Prasittiporn Tangjitaree; (IX) Writing – review & editing: Prasittiporn Tangjitaree, Peerapat Thanapongsatorn, Nattachai Srisawat.

ETHICS APPROVAL

The study received ethical approval from the IRB of Faculty of Medicine of Chulalongkorn University (COA No. 0607/2023), the Central Chest Institute of Thailand (REC 003/2022) and has been registered with U.S. Clinical Trials Registry (NCT05036616).

SUPPLEMENTARY MATERIALS

None

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