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Intensive care with extracorporeal membrane oxygenation rewarming in accident severe hypothermia (ICE-CRASH) study: A protocol for a nationwide prospective, observational study in Japan

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Title: Intensive care with extracorporeal membrane oxygenation rewarming in accident severe hypothermia (ICE-CRASH) study: A protocol for a nationwide prospective, observational study in Japan

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Abstract

Introduction: Accidental hypothermia (AH) is a rare but critical disease, leading to death in severe cases. In recent decades, extracorporeal membrane oxygenation (ECMO) has been successfully used to rewarm hypothermic patients with cardiac arrest or circulation instability. However, data on the efficacy of rewarming using ECMO for patients with AH are limited. Therefore, a large-scale, nationwide, multicenter, prospective study is warranted. The primary objective of this study will be to clarify the efficacy of rewarming using ECMO for patients with AH. Our secondary objectives will be to evaluate the incidence of complications, such as bleeding, thrombosis, during ECMO use and to identify the most appropriate management of ECMO for AH.

Methods and analyses: The ICE-CRASH study is taking place in 35 tertiary emergency medical facilities in Japan. The inclusion criteria are patients ≥18 years old with a body temperature ≤32 °C. We will include patients with AH who present to the ED from December 2019 to March 2022. The research personnel at each hospital will collect several variables, including patient demographics, rewarming method, ECMO data, and complications. Our primary outcome is to compare the 28-day mortality rate between the ECMO and non-ECMO (other treatments) groups among patients with severe AH. Our secondary outcomes are to compare the following values between the ECMO and non-ECMO groups: length of stay in the intensive-care unit and complications. In addition, in cases of ECMO rewarming, we will evaluate the relationship between the information regarding ECMO and the prognosis.

Ethics and dissemination: This study received research ethics approval from Asahikawa Medical University (18194 & 19115). The study was approved by the institutional review board of each hospital, and the requirement for informed consent was waived due to the observational nature of the study.

Trial registration number: UMIN Clinical Trials Registry; UMIN000036132. Registered 1

April 2019.

Keywords: accidental hypothermia, mortality, extracorporeal membrane oxygenation (ECMO), complication,

Strengths and limitations of this study

1. This study will be the first large-scale, prospective study of ECMO rewarming for patients suffering from accidental hypothermia (AH).

2. This study will evaluate the efficacy of ECMO rewarming compared to non-ECMO rewarming for hypothermic patients with cardiac arrest or circulatory instability.

3. This study will also collect blood samples to determine the relationship between coagulation fibrinolysis and ECMO-related complications and identify optimal ECMO rewarming management approaches for hypothermic patients.

4. However, this study is not a randomized trial, which means that the adjustment for confounding factors is not complete.

Introduction

Accidental hypothermia (AH) is a rare condition but can be life-threatening in severe cases [1 2]. Thanks to technological advances over the past few decades, veno-arterial extracorporeal membrane oxygenation (V-A ECMO) has become a viable rewarming treatment for patients with severe hypothermia with cardiac arrest or severe circulatory instability [3 4 5 6]. Recently, the resuscitation guidelines from both the European Resuscitation Council and the American Heart Association have recommend the use of ECMO in AH patients with cardiac arrest [7 8]. However, there has been limited evidence concerning the utility of ECMO rewarming in patients with AH because of the low frequency of eligible patients. In addition, ethical implications restrict the utility of randomized controlled trials. Thus, previous studies on patients with AH rewarmed by ECMO have been case reports or single-center retrospective analyses [4 5 6].

A recent study using the nationwide Japanese Diagnosis Procedure Combination inpatients database showed that V-A ECMO was associated with a higher survival rate and more favorable neurological outcomes than conventional cardiopulmonary resuscitation (CPR) alone in hypothermic patients with cardiac arrest [9]. However, this study has several issues. First, whether or not ECMO should be initiated in hypothermic patients with circulatory instability remains unclear. Second, this study did not clarify whether ECMO or other warming methods should be used in patients with AH. At present, there are no clinical guidelines on this point. Third, this study did not describe the complications associated with ECMO rewarming in hypothermic patients. The use of ECMO for hypothermic patients with noncardiac arrest is highly debatable, as ECMO is a highly invasive treatment with potentially serious complications [5]. Therefore, a large-scale, nationwide, multicenter, prospective study is warranted to resolve these issues.

Objectives

The primary objective of this study will be to clarify the efficacy of ECMO rewarming for hypothermic patients with cardiac arrest or circulatory instability. We hypothesized that the ECMO rewarming method is more beneficial in terms of survival than conventional rewarming methods. Our secondary objectives are to evaluate the incidence of adverse effects, such as bleeding, thrombosis, and infectious disease, during and after V-A ECMO rewarming for hypothermic patients with cardiac arrest or circulatory instability. The results will help identify the most appropriate management approach with ECMO for patients with AH.

Methods and analyses

Study design and setting

The Intensive Care with ExtraCorporeal membrane oxygenation Rewarming in Accidentally Severe Hypothermia (ICE-CRASH) study is a prospective, nationwide, observational study of patients with AH. The registry started in December 2019, with a planned three years of patient recruitment. The study is taking place at 35 tertiary emergency medical facilities that provide emergency and intensive care treatments to patients with AH in Japan.

Eligibility criteria

- Inclusion criteria

The ICE-CRASH study consists of patients whose body temperature measured at the emergency department (ED) is less than 32 °C. Investigators will enroll consecutive patients ≥18 years old with AH, including those with cardiac arrest. We will include patients with AH who present to the ED from December 2019 to March 2022.

- Exclusion criteria

The following patients will be excluded: patients <18 years old and those with cardiac arrest who are not eligible for resuscitation, according to the judgment of the emergency physician at each institution.

Data collection and quality control

A trained investigator or research assistant at each center will collect the following data: age, sex, any pre-existing conditions, activities of daily living (ADL), causes underlying the hypothermia, alcohol intake, anticoagulants, Charlson comorbidity index (CCI), Glasgow coma scale (GCS), Sequential Organ Failure Assessment (SOFA) score [10], laboratory data,

body temperature, blood pressure, heart rate, respiratory rate, electrocardiogram, cardiac arrest during pre-hospital, duration in the intensive-care unit (ICU), length of hospital stay, mortality and Cerebral Performance Category (CPC) score at discharge, event days (ventilator, renal replacement therapy, and catecholamine days), amount of transfusion, and mortality at 28 days after admission (Table 1). These data will be recorded in the electronic data capture system (NorthNet; https://www.crmic-huhp.jp/northnet/edc/).

Rewarming methods will be divided into active external rewarming (warmed blanket and warmed bath) and active internal rewarming (warmed fluid infusion, lavage, hemodialysis, intravascular catheter, and extracorporeal membrane oxygenation [ECMO]). The selection of the rewarming method will be decided based on the attending physician's judgement. When rewarming using ECMO is selected, the registry will also record additional information regarding ECMO as follows: the size of the ECMO cannula, the ECMO flow, presence of distal perfusion, usage and types of anticoagulants, patient status at the start of ECMO (CPA or non-CPA), time from the scene until ECMO initiation, duration using ECMO, and presence of weaning from ECMO.

In addition, registry data will be collected concerning the incidence of complications (ventricular fibrillation, bleeding, pneumonia, acute pancreatitis, acute kidney injury) and complications due to ECMO (infection or thrombosis of cannula). Complications will include events that occur within seven days after admission. Bleeding is defined as any amount requiring a transfusion. Pneumonia is defined as an obvious shadow on chest radiography or computed tomography (CT). Pancreatitis is defined as cases meeting at least two of the following conditions: 1) abdominal pain, 2) elevation of pancreatic enzyme levels in the blood, and 3) edema of the pancreas or peripancreatic effusion on ultrasound/CT. Acute kidney injury is defined as acute kidney injury network (AKIN) classification stage ≥2.

Furthermore, the ICE-CRASH study will collect blood samples from patients with AH

at each participating institution and perform additional tests related to coagulation and fibrinolysis.

Outcomes

Our primary outcome is the comparison of the survival rate between the ECMO and non-ECMO (other treatments) groups for severe hypothermic patients. Our secondary outcomes are the examination of the incidence of complications in the ECMO group (ventricular fibrillation, bleeding, thrombosis, pneumonia, acute pancreatitis, lower limb ischemia, acute kidney injury) and the clarification of the relationship between the time to ECMO initiation and the prognosis in the ECMO group.

Statistical plan

Sample size estimation

The sample size was calculated based on similar previous studies [4 5 6]. Based on the results of previous retrospective observational studies, we assumed proportions of surviving patients at 28 days after admission among patients with AH of 50% in the ECMO group and 85% in the non-ECMO group. For a power of 80% and a type 1 error of 5%, the number of patients required is at least 33 in each group. Taking into account the sample of patients who dropped out during the process, the total number needed was calculated to be 70 patients.

Statistical analyses

Categorical variables will be presented as frequencies and percentages, and continuous variables will be presented as the means with the standard deviation or medians with the interquartile range (25th to 75th percentile). Intergroup comparisons will be carried out using Fisher's exact test for categorical data and the Mann-Whitney U test for continuous data. For the primary outcome, Kaplan-Meyer curves in combination with the log-rank test and the multivariate Cox proportional hazard model, after adjusting for demographic and clinical variables, will be used to evaluate the association between ECMO rewarming and survival in patients with AH.

Ethics and dissemination

This study will be conducted in accordance with the Declaration of Helsinki. It has received research ethics approval from Asahikawa Medical University (18194 & 19115) and is registered with the UMIN Clinical Trials Registry (UMIN000036132). It has also been approved by the Ethics Committee of each participating hospital. The need for informed consent will be waived due to the observational nature of the study. However, if blood samples

are collected for additional studies, written informed consent will be obtained from each patient as appropriate.

The results of the study will be disseminated to the participating hospitals, submitted to peer-reviewed journals for publication, and presented at scientific congresses.

Discussion

Since the successful use of ECMO for AH with cardiac arrest has been reported, many studies have reported the efficacy of ECMO rewarming in patients with AH [3 4 5 6]. In recent years, some studies have suggested the utility of predictive scores, such as the HOPE score [11] and ICE score [12], for deciding to initiate ECMO rewarming in hypothermia patients. However, these scores were based on data obtained from retrospective studies and thus included significant issues, such as publication and selection bias. For example, few of these retrospective studies focused on complications associated with ECMO usage, especially hemorrhagic and thrombotic complications. Furthermore, even when they reported complications, the studies may have underestimated them.

Although previous studies have shown that deep hypothermia inhibited the platelet function and coagulation [13 14], in the clinical application of ECMO, many centers routinely use anti-coagulants, such as heparin, to prevent thrombosis. However, no study has examined the appropriate use of heparin when performing ECMO for hypothermia. In the ICE-CRASH study, we will collect blood samples and perform additional coagulation and fibrinolysis tests to evaluate the relationship between thrombotic and bleeding complications during and after rewarming. In the future, these results may lead to the development of a new management approach for hypothermia specific to ECMO that differs from conventional ECMO management. If a safer and less-complicated method of ECMO management can be developed, ECMO may become the method of choice for hypothermic patients with non-cardiac arrest, in whom ECMO use has previously been discouraged due to its invasiveness.

According to studies regarding extracorporeal resuscitation (ECPR) for out-of-hospital cardiopulmonary arrest patients, the longer it takes to initiate ECPR, the poorer the neurological prognosis [15 16]. Some studies have shown that the optimal cut-off time from cardiac arrest to ECMO initiation is 40 to 59 minutes [17 18]. Recent review suggests that ECPR

is not offered if the no-flow duration is unknown or prolonged to the extent that brain recovery is doubtful [19]. However, this did not apply to patients with AH resulting in cardiac arrest [20 21]. Retrospective studies have shown that hypothermic patients with cardiac arrest or circulatory instability who required long-distance transport, resulting in a delayed introduction of ECMO, actually had a good neurological outcome[20 21]. Furthermore, a recent study showed that the parameter "un-witnessed cardiac arrest" was not associated with a worse outcome [11]. Although these results are very encouraging, the maximum permissible time until the initiation of ECMO remains unclear. In the ICE-CRASH study, we will collect data on the time to the initiation of ECMO and CPR to clarify the relationship between the time to ECMO and the prognosis. These results may provide strong evidence supporting the feasibility of long-distance transport for the introduction of ECMO for patients with AH in the future, even in remote areas where ECMO cannot be introduced immediately.

Furthermore, the ICE-CRASH study will collect data associated with the ECMO rewarming rate. A recent retrospective study showed that a slower ECMO rewarming rate was associated with a better survival rate [22], while another study showed the opposite result [23]. The optimal ECMO rewarming rate thus remains unclear. Eventually, the ICE-CRASH study will be able to provide results that will help establish safer and more optimal ECMO management methods for patients with severe hypothermia.

Authors' contributions:

ST conceived and designed the ICE-CRASH study and is the principal investigator, MH developed the study protocol. ST and MH drafted and revised the manuscript, and all authors critically reviewed the content and approved the final manuscript.

Funding statement:

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Competing interests

None declared.

Patient and public involvement

No patient or public involvement.

Patient consent for publication

Not required

Provenance and peer review

Not commissioned; externally peer reviewed.

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Table 1. Variables collected in this study

Pre-hospital	In-hospital	Rewarming Time/Method	Outcome	Complications
Age, years	Body temperature	Time required for rewarming	Length of ICU stay	Bleeding/thrombosis
Sex	GCS	Active external rewarming	Length of hospital stay	Pneumonia
Time from EMS alert to ED arrival	CPA or non-CPA	Warmed blanket	Mortality at discharge	Pancreatitis
Location (indoor or outdoor)	Blood pressure	Warmed bath	CPC	Acute kidney injury
Causes underlying the hypothermia	Heart rate	Active internall rewarming	Event days	
ADL	ECG	Warmed fluid infusion	Ventilator	
Charlson comorbidity index	Respiratory rate	Lavage	Renal replacement therapy	
	Laboratory tests	Hemodialysis	catecholamine	
	Arterial blood gas analysis	Intravascular catheter	Transfusion	
	SOFA score	ECMO	Mortality at 28 days after admission	
		(Cannula size, flow, distal perfusion, anticoagulant, time to initiate ECMO, duration, weaning)		

EMS, emergency medical service; ED, Emergency department; ADL, Activities of daily living; GCS, Glasgow Coma Scale; CPA, Cardiopulmonary Arrest; ECG, Electrocardiogram; SOFA, Sequential Organ Failure Assessment; ECMO, Extracorporeal membrane oxygenation; CPC, Cerebral Performance Category;

Reporting checklist for protocol of a clinical trial.

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Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	P1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	P3
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	#3	Date and version identifier	P3
Funding	#4	Sources and types of financial, material, and other support	P14
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	P14

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	n/a
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	n/a
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n/a
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	P5
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	n/a
Objectives	#7	Specific objectives or hypotheses	P6
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	P7
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	n/a
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will	P7

		perform the interventions (eg, surgeons, psychotherapists)	
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	P8
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	n/a
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	n/a
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	P10
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	n/a
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	P11
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	n/a
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	n/a

Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	n/a
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	n/a
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	n/a
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	n/a
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	n/a
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	P8
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	P11
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	n/a

Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	n/a
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	n/a
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	n/a
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	P11
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	n/a
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	P11
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	n/a

Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	P15
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	n/a
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	P12
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

BMJ Open

Intensive care with extracorporeal membrane oxygenation rewarming in accident severe hypothermia (ICE-CRASH) study: A protocol for a multicenter prospective, observational study in Japan

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Title: Intensive care with extracorporeal membrane oxygenation rewarming in accident severe hypothermia (ICE-CRASH) study: A protocol for a multicenter prospective, observational study in Japan

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Abstract

Introduction: Accidental hypothermia (AH) is a rare but critical disease, leading to death in severe cases. In recent decades, extracorporeal membrane oxygenation (ECMO) has been successfully used to rewarm hypothermic patients with cardiac arrest or circulation instability. However, data on the efficacy of rewarming using ECMO for patients with AH are limited. Therefore, a large-scale, multicenter, prospective study is warranted. The primary objective of this study will be to clarify the effectiveness of rewarming using ECMO for patients with AH. Our secondary objectives will be to compare the incidence of adverse effects between ECMO rewarming and non-ECMO rewarming and to identify the most appropriate management of ECMO for AH.

Methods and analyses: The ICE-CRASH study is taking place in 35 tertiary emergency medical facilities in Japan. The inclusion criteria are patients ≥18 years old with a body temperature ≤32 °C. We will include patients with AH who present to the ED from December 2019 to March 2022. The research personnel at each hospital will collect several variables, including patient demographics, rewarming method, ECMO data, and complications. Our primary outcome is to compare the 28-day survival rate between the ECMO and non-ECMO (other treatments) groups among patients with severe AH. Our secondary outcomes are to compare the following values between the ECMO and non-ECMO groups: length of stay in the intensive-care unit and complications. Furthermore, in patients with cardiac arrest, the CPC score at discharge will be compared between both groups.

Ethics and dissemination: This study received research ethics approval from Asahikawa Medical University (18194 & 19115). The study was approved by the institutional review board of each hospital, and the requirement for informed consent was waived due to the observational nature of the study.

Trial registration number: UMIN Clinical Trials Registry; UMIN000036132. Registered 1

April 2019.

Keywords: accidental hypothermia, mortality, extracorporeal membrane oxygenation (ECMO), complication,

Strengths and limitations of this study

1. This study will be the first large-scale, prospective study of ECMO rewarming for patients suffering from accidental hypothermia (AH).
2. This study will evaluate the effectiveness of ECMO rewarming compared to non-ECMO rewarming for hypothermic patients with cardiac arrest or circulatory instability.
3. This study will also collect blood samples to determine the relationship between coagulation fibrinolysis and ECMO-related complications and identify optimal ECMO rewarming management approaches for hypothermic patients.
4. However, this study is not a randomized trial, which means that the adjustment for confounding factors is not complete.

Introduction

Accidental hypothermia (AH) is a rare condition but can be life-threatening in severe cases [1 2]. Thanks to technological advances over the past few decades, veno-arterial extracorporeal membrane oxygenation (V-A ECMO) has become a viable rewarming treatment for patients with severe hypothermia with cardiac arrest or severe circulatory instability [3 4 5 6]. Recently, the resuscitation guidelines from both the European Resuscitation Council and the American Heart Association have recommend the use of ECMO in AH patients with cardiac arrest [7 8]. However, there has been limited evidence concerning the utility of ECMO rewarming in patients with AH because of the low frequency of eligible patients. In addition, ethical implications restrict the utility of randomized controlled trials. Thus, previous studies on patients with AH rewarmed by ECMO have been case reports or single-center retrospective analyses [4 5 6].

A recent study using the nationwide Japanese Diagnosis Procedure Combination inpatients database showed that V-A ECMO was associated with a higher survival rate and more favorable neurological outcomes than conventional cardiopulmonary resuscitation (CPR) alone in hypothermic patients with cardiac arrest [9]. However, this study has several issues. First, whether or not ECMO should be initiated in hypothermic patients with circulatory instability remains unclear. Second, this study did not clarify whether ECMO or other rewarming methods should be used in patients with AH. At present, there are no clinical guidelines on this point. Third, this study did not describe the complications associated with ECMO rewarming in hypothermic patients. The use of ECMO for hypothermic patients with noncardiac arrest is highly debatable, as ECMO is a highly invasive treatment with potentially serious complications [5]. Therefore, a large-scale, multicenter, prospective study is warranted to resolve these issues.

Objectives

The primary objective of this study will be to clarify the effectiveness of ECMO rewarming for hypothermic patients with cardiac arrest and those with unstable circulation. We hypothesized that the ECMO rewarming method is more beneficial in terms of survival than conventional rewarming methods. Our secondary objectives are to compare the incidence of adverse effects, such as bleeding, thrombosis, and infectious disease between ECMO rewarming and non-ECMO rewarming. Furthermore, in this study, we will collect blood samples and perform additional tests related to coagulation and fibrinolysis to investigate the relationship between bleeding or thrombotic complications and anticoagulant use.

The results will help identify the most appropriate management approach with ECMO for patients with AH.

Methods and analyses

Study design and setting

The Intensive Care with ExtraCorporeal membrane oxygenation Rewarming in Accidentally Severe Hypothermia (ICE-CRASH) study is a prospective, multicenter, observational study of patients with AH. The registry started in December 2019, with a planned three years of patient recruitment. The study is taking place at 35 tertiary emergency medical facilities that provide emergency and intensive care treatments to patients with AH in Japan.

Eligibility criteria

- Inclusion criteria

The ICE-CRASH study consists of patients whose core body temperature measured at the emergency department (ED) is less than 32 °C. Investigators will enroll consecutive patients ≥18 years old with AH, including those with cardiac arrest. We will include patients with AH who present to the ED from December 2019 to March 2022.

- Exclusion criteria

The following patients will be excluded: patients <18 years old and those with cardiac arrest who are not eligible for resuscitation, according to the judgment of the emergency physician at each institution.

Data collection and quality control

A trained investigator or research assistant at each center will collect the following data: age, sex, any pre-existing conditions, activities of daily living (ADL), causes underlying the hypothermia, alcohol intake, anticoagulants, Charlson comorbidity index (CCI), Glasgow coma scale (GCS), Sequential Organ Failure Assessment (SOFA) score [10], laboratory data,

core body temperature, temperature measurement site, blood pressure, heart rate, respiratory rate, electrocardiogram, cardiac arrest during pre-hospital, duration in the intensive-care unit (ICU), length of hospital stay, mortality and Cerebral Performance Category (CPC) score at discharge, event days (ventilator, renal replacement therapy, and catecholamine days), amount of transfusion, and mortality at 28 days after admission (Table 1). The laboratory data consist of the following: an arterial blood gas analysis, including the lactate level, blood count, biochemical tests, and coagulation test. Measurement of the body temperature is based on the core body temperature. If for some reason the core body temperature cannot be measured, the peripheral body temperature will be measured, and data on the measurement site (bladder, rectum, esophagus, axilla, and others) will be collected. These data will be recorded in the electronic data capture system (NorthNet; https://www.crmic-huhp.jp/northnet/edc/).

Rewarming methods will be divided into active external rewarming (warmed blanket and warmed bath) and active internal rewarming (warmed fluid infusion, lavage, hemodialysis, intravascular catheter, and extracorporeal membrane oxygenation [ECMO]). The selection of the rewarming method will be decided based on the attending physician's judgement. When rewarming using ECMO is selected, the registry will also record additional information regarding ECMO as follows: the ECMO setting (venous-arterial or venous-venous), the size of the ECMO cannula, the ECMO flow, presence of distal perfusion, usage and types of anticoagulants, patient status at the start of ECMO (CPA or non-CPA), time from the scene until ECMO initiation, duration using ECMO, and presence of weaning from ECMO.

In addition, registry data will be collected concerning the incidence of complications (ventricular fibrillation, bleeding, pneumonia, acute pancreatitis, acute kidney injury) and complications due to ECMO (infection or thrombosis of cannula). Complications will include events that occur within seven days after admission. Bleeding is defined as any amount requiring a transfusion. Pneumonia is defined as an obvious shadow on chest radiography or

computed tomography (CT). Pancreatitis is defined as cases meeting at least two of the following conditions: 1) abdominal pain, 2) elevation of pancreatic enzyme levels in the blood, and 3) edema of the pancreas or peripancreatic effusion on ultrasound/CT. Acute kidney injury is defined as acute kidney injury network (AKIN) classification stage ≥2.

Furthermore, the ICE-CRASH study will collect blood samples from patients with AH at each participating institution and perform additional tests related to coagulation and fibrinolysis.

Outcomes

Our primary outcome is the comparison of the survival rate between the ECMO and non-ECMO (other treatments) groups for severe hypothermic patients. Our secondary outcomes are to compare the CPC score at discharge between the ECMO and non-ECMO groups for hypothermic patients with cardiac arrest; to compare the incidence of complications (ventricular fibrillation, bleeding, thrombosis, pneumonia, acute pancreatitis, lower limb ischemia, acute kidney injury) between the ECMO and non-ECMO groups; and to clarify the relationship between the time to ECMO initiation and the prognosis in the ECMO group.

Statistical plan

Sample size estimation

The sample size was calculated based on similar previous studies [4 5 6]. Based on the results of previous retrospective observational studies, we assumed proportions of surviving patients at 28 days after admission among hypothermic patients with cardiac arrest of 50% in the ECMO group and 15% in the non-ECMO group [4 5]. For a power of 80% and a type 1 error of 5%, the number of patients required is at least 33 in each group. Taking into account the sample of patients who dropped out during the process, the total number needed was calculated to be 70 patients. Similarly, we assumed proportions of surviving patients at 28 days after admission among hypothermic patients with circulatory instability (non-cardiac arrest) of 85% in the ECMO group and 55% in the non-ECMO group [5]. Based on the same calculation, the number of patients required was determined to be at least 43 in each group, and the total number needed was calculated to be 90 patients.

This study is a registry study, so it will be conducted until at least March 2022, after which enrollment may continue in order to increase the number of cases.

Statistical analyses

Categorical variables will be presented as frequencies and percentages, and continuous variables will be presented as the means with the standard deviation or medians with the interquartile range (25^{th} to 75^{th} percentile). Intergroup comparisons will be carried out using Fisher's exact test for categorical data and the Mann-Whitney U test for continuous data. We will use propensity matching between the ECMO and non-ECMO groups to adjust for the patient background as much as possible for statistical analyses. We will then compare the survival rates of the ECMO and non-ECMO groups.

Ethics and dissemination

This study will be conducted in accordance with the Declaration of Helsinki. It has received research ethics approval from Asahikawa Medical University (18194 & 19115) and is registered with the UMIN Clinical Trials Registry (UMIN000036132). It has also been approved by the Ethics Committee of each participating hospital. The need for informed consent will be waived due to the observational nature of the study. However, if blood samples are collected for additional studies, written informed consent will be obtained from each patient as appropriate.

The results of the study will be disseminated to the participating hospitals, submitted to peer-reviewed journals for publication, and presented at scientific congresses.

Discussion

Since the successful use of ECMO for AH with cardiac arrest has been reported, many studies have reported the efficacy of ECMO rewarming in patients with AH [3 4 5 6]. In recent years, the resuscitation guidelines from both the European Resuscitation Council and the American Heart Association have recommend the use of ECMO in AH patients with cardiac arrest [7 8]. However, at present, there are no global guidelines concerning the use of ECMO in AH patients with circulatory instability. The present findings may support the creation of guidelines concerning the use of ECMO in AH patients with circulatory instability.

Previous studies have shown that severe hypothermia inhibited the platelet function and coagulation [11 12]. However, few retrospective studies have focused on complications associated with ECMO usage, especially hemorrhagic and thrombotic complications. Thus, the incidence of these complications from using ECMO rewarming in patients with AH remains unclear. In this study, we will collect blood samples and perform additional coagulation and fibrinolysis tests to evaluate the relationship between thrombotic and bleeding complications during and after rewarming. These results may lead to the development of a new management approach for hypothermia specific to ECMO.

According to studies regarding extracorporeal resuscitation (ECPR) for out-of-hospital cardiopulmonary arrest patients, the longer it takes to initiate ECPR, the poorer the neurological prognosis [13 14]. However, this did not apply to patients with AH resulting in cardiac arrest [15 16]. A recent study showed that the parameter “un-witnessed cardiac arrest” was not associated with a worse outcome [17]. However, the maximum permissible time until the initiation of ECMO remains unclear. In the present study, we will collect data on the time to the initiation of ECMO and CPR to clarify the relationship between the time to ECMO and the prognosis. These results may provide evidence supporting the feasibility of long-distance transport for the introduction of ECMO for patients with AH in the future.

Furthermore, a recent retrospective study showed that a slower ECMO rewarming rate was associated with a better survival rate [18], while another study showed the opposite result [19]. The optimal ECMO rewarming rate thus remains unclear. The present study will collect data associated with the ECMO rewarming rate. The results may help establish safer and more optimal ECMO management methods for patients with severe hypothermia.

Authors' contributions:

ST conceived and designed the ICE-CRASH study and is the principal investigator, MH developed the study protocol. ST and MH drafted and revised the manuscript, and all authors critically reviewed the content and approved the final manuscript.

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Competing interests

None declared.

Patient and public involvement

No patient or public involvement.

Patient consent for publication

Not required

Provenance and peer review

Not commissioned; externally peer reviewed.

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Table 1. Variables collected in this study

Pre-hospital	In-hospital	Rewarming Time/Method	Outcome	Complications
Age, years	Core body temperature (measurement site)	Time required for rewarming	Length of ICU stay	Bleeding/thrombosis
Sex	GCS	Active external rewarming	Length of hospital stay	Pneumonia
Time from EMS alert to ED arrival	CPA or non-CPA	Warmed blanket	Mortality at discharge	Pancreatitis
Location (indoor or outdoor)	Blood pressure	Warmed bath	CPC score at discharge	Acute kidney injury
Causes underlying the hypothermia	Heart rate	Active internal rewarming	Event days	
ADL	ECG	Warmed fluid infusion	Ventilator	
Charlson comorbidity index	Respiratory rate	Lavage	Renal replacement therapy	
	Laboratory tests (blood counts, biochemical tests, and coagulation test)	Hemodialysis	catecholamine	
	Arterial blood gas analysis (including lactate)	Intravascular catheter	Transfusion	
	SOFA score	ECMO	Mortality at 28 days after admission	
		(Venous-Arterial or Venous-Venous, Cannula size, flow, distal perfusion, anticoagulant, time to initiate ECMO, duration, weaning)		

EMS, emergency medical service; ED, Emergency department; ADL, Activities of daily living; GCS, Glasgow Coma Scale; CPA, Cardiopulmonary Arrest; ECG, Electrocardiogram; SOFA, Sequential Organ Failure Assessment; ECMO, Extracorporeal membrane oxygenation; CPC, Cerebral Performance Category;

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	P1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	P3
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	#3	Date and version identifier	P3
Funding	#4	Sources and types of financial, material, and other support	P14
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	P14

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	n/a
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	n/a
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n/a
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	P5
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	n/a
Objectives	#7	Specific objectives or hypotheses	P6
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	P7
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	n/a
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will	P7

		perform the interventions (eg, surgeons, psychotherapists)	
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	P8
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	n/a
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	n/a
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	P10
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	n/a
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	P11
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	n/a
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	n/a

Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	n/a
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	n/a
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	n/a
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	n/a
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	n/a
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	P8
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	P11
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	n/a

Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	n/a
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	n/a
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	n/a
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	P11
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	n/a
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	P11
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	n/a

Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	P15
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	n/a
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	P12
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a