Early restricted oxygen therapy after resuscitation from cardiac arrest (ER-OXYTRAC): protocol for a stepped-wedge cluster randomised controlled trial


ABSTRACT

Introduction Cardiac arrest is a critical condition, and patients often experience postcardiac arrest syndrome (PCAS) even after the return of spontaneous circulation (ROSC). Administering a restricted amount of oxygen in the early phase after ROSC has been suggested as a potential therapy for PCAS; however, the optimal target for arterial partial pressure of oxygen or peripheral oxygen saturation (SpO2) to safely and effectively reduce oxygen remains unclear. Therefore, we aimed to validate the efficacy of restricted oxygen treatment with 94%–95% of the target SpO2 for patients with PCAS.

Methods and analysis ER-OXYTRAC (early restricted oxygen therapy after resuscitation from cardiac arrest) is a nationwide, multicentre, pragmatic, single-blind, stepped-wedge cluster randomised controlled trial targeting cases of non-traumatic cardiac arrest. This study includes adult patients with out-of-hospital or in-hospital cardiac arrest who achieved ROSC in 39 tertiary centres across Japan, with a target sample size of 1000. Patients whose circulation has returned before hospital arrival and those with cardiac arrest due to intracranial disease or intoxication are excluded. Study participants are assigned to either the restricted oxygen (titration of a fraction of inspired oxygen with 94%–95% of the target SpO2) or the control (98%–100% of the target SpO2) group based on cluster randomisation per institution. The trial intervention continues until 12 hours after ROSC. Other treatments for PCAS, including oxygen administration later than 12 hours, can be determined by the treating physicians. The primary outcome is favourable neurological function, defined as cerebral performance category 1–2 at 90 days after ROSC, to be compared using an intention-to-treat analysis.

Ethics and dissemination This study has been approved by the Institutional Review Board at Keio University School of Medicine (approval number: 20211106). Written informed consent will be obtained from all participants or their legal representatives. Results will be disseminated via publications and presentations.

STRENGTHS AND LIMITATIONS OF THIS STUDY

➢ A nationwide stepped-wedge cluster randomised controlled trial is currently being conducted in 39 tertiary care centres across Japan.
➢ The trial is recruiting patients with out-of-hospital or in-hospital cardiac arrest, with a target sample size of 1000.
➢ A fraction of inspired oxygen is titrated to 94%–95% of target peripheral oxygen saturation (restricted oxygen group) or 98%–100% (control group) for 12 hours after return of spontaneous circulation (ROSC).
➢ Favourable neurological function, defined as cerebral performance category 1–2 (1–5 scale, where 1 means normal neurological function) at 90 days after ROSC, will be compared between the two groups.
➢ Small clinical effects of the restricted oxygen strategy cannot be validated with the planned sample size.
INTRODUCTION

Cardiac arrest, an emergency and critical condition, should be appropriately managed to prevent unfavourable clinical outcomes.\(^1\)\(^2\) Administering strenuous resuscitative efforts while transporting a patient from the site of cardiac arrest to a hospital leads to the return of spontaneous circulation (ROSC) from cardiac arrest, whereas haemodynamic instability and neurological dysfunction are known to emerge even after ROSC, a condition known as postcardiac arrest syndrome (PCAS).\(^1\)\(^3\) While targeted temperature management (TTM) after ROSC improves the neurological outcomes of patients with PCAS,\(^4\)\(^5\) various studies have failed to elucidate an effective treatment that would help patients with PCAS regain optimal neurological functions.

Avoiding supraphysiological oxygen in patients with ROSC following cardiac arrest has been suggested as a potential therapy for PCAS by several observational studies.\(^6\)\(^–\)\(^10\) Meta-analyses and prospective observational studies have reported that a lower partial pressure of arterial oxygen (PaO_2) within 6–24 hours after ROSC, particularly <300 mm Hg, is associated with favourable neurological outcomes and decreased mortality in patients with PCAS.\(^10\) Accordingly, the American Heart Association, the European Resuscitation Council and the European Society of Intensive Care Medicine guidelines for cardiopulmonary resuscitation have recommended 92%–94% of peripheral oxygen saturation (SpO_2) as a lower threshold of target oxygenation in patients achieving ROSC.\(^11\)\(^–\)\(^15\) However, studies validating the safety and effectiveness of restricted oxygen administration with a lower SpO_2 target in patients with PCAS are limited.\(^14\)\(^15\)

A recent randomised controlled trial (RCT) demonstrated the ineffectiveness of a low PaO_2 target (68–75 mm Hg) in patients with ROSC from out-of-hospital cardiac arrest (OHCA), although the control target (98–105 mm Hg) was lower than the usual practice reported in observational studies and continuous measurements of PaO_2 to avoid hyperoxia would not be a standard practice.\(^16\) Another RCT reported higher in-hospital mortality following restricted oxygen administration from the scene to the intensive care unit (ICU) admission using a target SpO_2 of 90%–94%, in which suboptimal power was considered because of early trial termination due to the coronavirus disease 2019 (COVID-19) pandemic.\(^17\)\(^18\)

An individual-level patient data meta-analysis of RCTs on restricted oxygen for OHCA revealed that conservative oxygen therapy was associated with reduced mortality at the last follow-up; however, low or very low certainty of evidence could not conclude its clinical utility.\(^19\)

Furthermore, these studies only included patients with OHCA; thus, the therapeutic effects of restricted oxygen administration with a low SpO_2 target remain unclear among patients with in-hospital cardiac arrest.\(^16\)\(^18\)

In the present study, we aimed to elucidate the effectiveness of early restricted oxygen therapy within 12 hours after ROSC using 94% of target SpO_2 in patients with cardiac arrest. Considering that the tight adjustment of oxygen levels with continuous PaO_2 measurement is impractical, oxygen titration is conducted based on SpO_2 monitoring in this trial. We hypothesised that early restricted oxygen therapy with 94%–95% of target SpO_2 is associated with a higher rate of favourable neurological functions, defined as cerebral performance category (CPC) 1 or 2, at 90 days after ROSC than liberal oxygen therapy with 98%–100% of target SpO_2.

METHODS AND ANALYSIS

Trial design and setting

The early restricted oxygen therapy after resuscitation from cardiac arrest (ER-OXYTRAC) trial is a multicentre, pragmatic, single-blind, stepped-wedge cluster RCT that will include adult patients diagnosed with PCAS following ROSC after cardiac arrest. The ER-OXYTRAC trial is being conducted in 39 tertiary care centres, including academic and community hospitals, in both urban and rural areas across Japan. The geographical location is shown in figure 1.

Participants and interventions

A flowchart of the patient enrolment process is shown in figure 2. The inclusion criteria for patients are as follows: (1) those aged ≥20 years; (2) those with non-traumatic out-of-hospital or in-hospital cardiac arrest; and (3) those who achieve ROSC at a hospital. The patients are included regardless of the place of cardiac arrest, rhythm type during cardiac arrest (shockable vs non-shockable) and witness status. Cardiac arrest needs to be confirmed by healthcare providers, including emergency medical service personnel, nurses and physicians.

The exclusion criteria are as follows: (1) patients in whom ROSC is confirmed before hospital arrival (for patients with OHCA); (2) patients not receiving ventilator support after ROSC; (3) patients whose Glasgow Coma Scale is >8 when ROSC is confirmed; (4) patients receiving extracorporeal membrane oxygenation when ROSC is confirmed; (5) patients who are not expected to survive >24 hours when ROSC is confirmed; (6) patients in whom an aetiology for cardiac arrest is considered an intracranial disease; (7) patients in whom intoxication is considered the aetiology of cardiac arrest; (8) patients with cerebral dysfunction before cardiac arrest, defined as a CPC of 3 or 4; (9) patients diagnosed with COVID-19 and required medications for COVID-19; (10) patients in whom withholding or withdrawal of treatment is based on advanced directives or relatives when ROSC was confirmed; (11) patients with other diseases, such as chronic lung and congenital diseases, which require stricter control of oxygen administration or adjustment.
of target \( \text{SpO}_2 \); (12) patients in whom \( \text{SpO}_2 \) is considered not to have been correctly measured by a clinical physician (eg, \( \text{SpO}_2 \) is 5% lower or higher than arterial oxygen saturation); (13) patients who participate in other clinical trials that require a therapeutic intervention; (14) patients who need to be arrested, detained or put in custody by law enforcement or legal agencies; (15) patients who refuse to participate in the trial; and (16) patients deemed ineligible to participate by a clinical physician. ROSC is confirmed in patients with continuous spontaneous circulation for >10 min.

The investigators will explain the study verbally and in writing and provide the consent form approved by the institutional review board to potential trial participants or their legally authorised representatives to obtain voluntary written consent. If written consent cannot be immediately obtained from a legally authorised representative, explanations and consent will be provided over the phone and written consent will be obtained later.

Participants will be assigned to either of the two groups: (1) restricted oxygen group (target \( \text{SpO}_2 \) is 94%–95%) or (2) control group (target \( \text{SpO}_2 \) is 98%–100%).

Figure 1  Geographical location of the participating institutions. The ER-OXYTRAC trial will be conducted in 39 tertiary care centres, including academic and community hospitals, in both urban and rural areas across Japan. ER-OXYTRAC, early restricted oxygen therapy after resuscitation from cardiac arrest.
adjustment of the amount of oxygen administered (fraction of inspiratory oxygen (FiO₂)) is summarised in figure 3. In both the restricted oxygen and control groups, FiO₂ is decreased by 5% when SpO₂ is higher than the upper limit of target SpO₂ and increased by 5% when SpO₂ is lower than the lower limit of target SpO₂. Other treatments, including adjustment of tidal volume, positive endoexpiratory pressure and driving pressure, will be provided according to the clinical physician’s discretion. SpO₂ will be measured with any device and at any location (eg, fingertip, forehead and earlobe). SpO₂ is evaluated at least every 10 min and when any treatment that can cause a change in SpO₂ is conducted. An arterial blood gas assay is conducted every 3 hours after ROSC, and when PaO₂ is ≥ 300 mm Hg, FiO₂ is decreased regardless of SpO₂. This adjustment of FiO₂ as a study intervention is conducted until 12 hours after ROSC; thereafter, FiO₂ is adjusted by a clinical physician.

In both the restricted oxygen and control groups, allocated interventions are not discontinued nor modified when SpO₂ within the target ranges cannot be obtained by adjusting FiO₂ (SpO₂ is lower than the lower limit of the target with 100% of FiO₂ or higher than the upper limit of the target with 21% of FiO₂). When any disease or condition requiring stricter control of oxygen administration emerges, the allocated interventions are discontinued and FiO₂ is adjusted appropriately by a clinical physician. After the treatment for such diseases or conditions is completed, the allocated interventions are reinitiated and continued until 12 hours after ROSC. In the
restricted oxygen group, when hypoxia (PaO₂ < 60 mm Hg) or adverse events, such as haemodynamic instability, due to hypoxia emerges when SpO₂ is 94%–95%, the target SpO₂ is changed to 98%–100%. Trial monitoring experts, who are independent of the conduct of the trial, will ensure that the trial is conducted in accordance with the protocol.

Other than the adjustment of FiO₂, any treatments after ROSC, including the adjustment of the ventilator setting, are provided based on the decision of a clinical physician. When treatments that can change SpO₂ are conducted, SpO₂ is measured immediately and FiO₂ is adjusted following the allocated interventions. TTM is conducted on all participants. The temperature target, TTM methods, TTM duration and medications, including sedatives and muscle relaxants, during TTM are decided by a clinical physician.

Outcome measures
The primary endpoint is CPC at 90 days after the intervention. The secondary endpoints are as follows: (1) survival at 30 days after intervention initiation; (2) survival at 90 days after intervention initiation; (3) hospital-free days until 90 days after intervention initiation; (4) ICU-free days until 90 days after intervention initiation; (5) ventilator-free days until 90 days after intervention initiation; (6) renal replacement therapy (RRT)-free days until 90 days after intervention initiation; (7) oxygen-free days until 90 days after intervention initiation; (8) Clinical Frailty Scale at 90 days after intervention initiation; (9) presence of hyperoxia, defined as PaO₂ ≥ 300 mm Hg, within 12 hours after intervention initiation; and (10) presence of hypoxia, defined as PaO₂ < 60 mm Hg, within 12 hours after intervention initiation.

The hospital-free, ICU-free, ventilator-free, RRT-free and oxygen-free days were defined as the number of days from day 1 to day 90 after intervention initiation when the patient was alive and free from support for at least 24 consecutive hours. If patients die within 90 days or are still supported after 90 days, zero will be assigned.
Randomised assignment of interventions and participant timeline

This study adopts a stepped-wedge cluster randomisation design, and the intervention is allocated per cluster that includes at least five institutions. Before the initiation of the study, the participating institutions will submit an estimated annual number of patients with OHCA and in-hospital cardiac arrest, an estimated frequency of cardiogenic cardiac arrest, the average transportation time for patients with OHCA and TTM methods. Stratified randomisation of the institution by the submitted information is conducted by a statistician who is not involved in the trial, and five clusters are generated. The study period is divided into six periods (the first to sixth period), and the timing of crossover of the intervention (control to restricted oxygen) is randomly assigned to each cluster from the first day of either of the second to sixth periods. SpO₂, peripheral oxygen saturation.

Statistical methods

We hypothesised that restricted oxygen therapy with 94%–95% of target SpO₂ until 12 hours after ROSC is associated with a higher rate of favourable neurological functions, defined as CPC of 1 or 2, at 90 days after ROSC than liberal oxygen therapy with 98%–100% of target SpO₂. Based on previous studies, we estimated that the incidence of a CPC 1 or 2 at 90 days after ROSC was 12% in the control group and the absolute difference from the restricted oxygen therapy was 10%. To evaluate the difference in the incidence between the groups, a two-sided significance level of 0.05 and a power of 0.80 are set. We adopt a stepped-wedge cluster randomisation design, in which each study institution is randomly allocated into five different clusters. The study period is divided into

accurately. Participants will be followed-up for 90 days after intervention initiation. If a participant is discharged from the hospital before 90 days, the investigators will contact the participant via telephone to obtain information regarding their status.

Owing to the nature of the trial, participants, care providers and outcome assessors cannot be blinded to the assigned intervention. However, the statisticians who will analyse the data will be blinded to group allocation.
six periods (first to sixth period), and the study intervention is initiated as a control (target SpO2 is 98%–100%) and then changed to restricted oxygen (target SpO2 is 95%–95%) at the beginning of one of the second to sixth periods that is predetermined prior to study initiation (crossover design). When at least five study institutions are allocated into each cluster and intercluster and intracluster correlations are estimated at 0.008 and 0.1, respectively, 6 cases in each institution (30 cases in each cluster) in each divided period would be needed, leading to a total of 900 cases. Assuming that approximately 10% of the patients will drop out because of withdrawal or other reasons, 1000 patients will be required.

We will report patient flow according to the Consolidated Standards of Reporting Trials flowchart for stepped-wedge cluster RCTs as per the allocated sequence and period. The final analysis will be performed after collecting the 90-day outcomes of the participants. Eligibility for the analysis is decided by the primary investigator and statisticians, who are not involved in the conduct of the trial. The intention-to-treat cohort includes all eligible patients admitted to the eligible wards. The proportion of patients with CPC 1 or 2 will be compared between the groups at the individual level using a generalised linear mixed model with binary distribution. The jackknife method will be used to estimate SEs to account for grouping within clusters. A log-link function will be incorporated to estimate the relative risk as a measure of effect. The best model with a unique covariance structure that produces the lowest Bayesian information criterion value will be selected. The covariance structures considered in the model are the unstructured covariance structure, Toeplitz covariance structure and variance component structure. The Kenward-Roger method will be applied to adjust for the denominator degree of freedom for tests of the fixed effects. Results will be expressed as a relative risk with a 95% CI and p value.

Secondary analysis will be conducted to interpret the primary analysis rather than test a hypothesis. Secondary endpoints will be compared between the groups in a model similar to the one used in the primary analysis. Moreover, subgroup analyses will be conducted by...
dividing the participants based on adjusted mortality and institutional characteristics, including geographical location, transportation time and temperature for TTM, which were used for cluster generation.

Interim analysis will be conducted after 500 cases are registered when their survival/death is confirmed at 90 days. Participant enrolment will continue during the interim analysis. In the interim analysis, the proportion of CPC 1 or 2 will be compared between the groups and statistical significance will be evaluated. To maintain a two-sided significance level of <0.05, the multiplicity of testing will be adjusted using the Pocock boundary. The Data and Safety Monitoring Committee (DSMC) will assess the results of the interim analyses and make recommendations on the continuation, modification or termination of the trial. Based on the recommendations by the DSMC, the primary investigator will make the final decision to continue or terminate the trial. When trial continuation is decided, the results of the interim analysis will remain concealed.

There are no plans to conduct additional analyses. Although researchers at the participating centres may conduct ancillary studies using data obtained from this trial, specific analysis methods have not been determined. If many missing values cannot be ignored, sensitivity analysis will be performed using multiple imputations of the missing values.

Oversight and monitoring
This trial is led by the Japanese Association for Acute Medicine. The steering committee consists of four clinical researchers who supervise the implementation of the trial and check its progress. The steering committee and a clinical research centre within the principal institution designed the study. Another clinical research centre at an institution, to which a member of the steering committee belongs, developed the clinical trial data management system and will monitor the registered data. The endpoint adjudication committee consists of three clinical researchers at different institutions.

DSMC comprises three clinical researchers at different institutions who are independent from the sponsor and have competing interests. DSMC receives any reports of severe adverse events; assesses the relationship between the study intervention and severe adverse events; and recommends the continuation, modification or termination of the trial. The DSMC will assess the results of the interim analyses and make recommendations on the continuation, modification or termination of the trial. The DSMC will hold a meeting at least every year, assess the clinical trial data management system and evaluate the safety of continuing the trial.

All investigators at participating institutions are mandated to collect, assess, record and manage solicited and spontaneously reported adverse events. The DSMC, which is independent of the conduct of the trial, monitors the study to ensure the reliability of the trial in terms of the protection of human rights, safety and welfare of the participants. If the principal investigator is notified of a severe adverse event related to the trial intervention, a prompt report will be presented to the DSMC and ethics review board of the principal institution. In addition, the principal investigator will take appropriate action and promptly share information on the severe adverse event with other investigators involved in the trial. The DSMC and ethics review board of the principal institution will review and examine the report and send written recommendations made in response to it to the principal investigator.

Patient and public involvement
Patients were involved in the design of this research. During the feasibility stage, the choice of outcome measures and methods of recruitment were informed by discussions with patients who were participating as members of the institutional review board.

ETHICS AND DISSEMINATION
The clinical trial is conducted according to the principles of the Declaration of Helsinki and the Ethical Guidelines for Medical and Health Research Involving Human Subjects published by the Ministry of Health, Labour and Welfare of Japan and the Japanese Ministry of Education, Culture, Sports, Science and Technology. The study was approved by the Institutional Review Board at Keio University School of Medicine, the principal hospital (approval number: 20211106); the approval process was initiated in 2021. Written informed consent to participate will be obtained from all participants or their legally acceptable representatives (online supplemental files 1,2). The insurance company will provide compensation to trial participants who suffer from health issues related to flaws in the trial protocol during the first year after trial participation.

The need for protocol changes will be initially discussed by the steering committee, followed by a meeting including representatives from all participating institutions. When a decision is reached to change the protocol, the revised protocol will be discussed by the institutional review board of the principal institution. After obtaining approval from the institutional review board, the revised protocol will be promptly disseminated to relevant parties via email or other means. Any modifications will also be reflected in the trial registry.

Data registered in the clinical trial data management system do not contain personal information. After the completion of all planned analyses, the findings of the trial will be presented at relevant scientific meetings and disseminated through publications in peer-reviewed journals. Following the completion of all ancillary analyses by the trial group, the data sets analysed during the current study and statistical
DISCUSSION

This multicentre, pragmatic, single-blind, stepped-wedge cluster RCT will investigate the efficacy of restricted oxygen administration until 12 hours after ROSC and examine whether the neurological functions would recover more in patients treated with 94%-95% of target SpO₂ than in those treated with 98%-100% of target SpO₂.

One rationale for restricted oxygen therapy is based on the observation that supraphysiological arterial oxygen in the early phase after ROSC is associated with unfavourable clinical outcomes among patients with PCAS. Therefore, titrating the amount of oxygen delivered to patients with PCAS should ideally follow serial PaO₂ measurements to avoid hyperoxia. However, continuous SpO₂ monitoring is more pragmatic and common practice in the ICU than frequent collection of arterial blood samples; therefore, the present study uses SpO₂ instead of PaO₂ as a target for oxygen titration. In addition, the target SpO₂ range is recommended and has been revised without high-quality evidence in the American Heart Association guidelines; in this trial, the target SpO₂ range for restricted oxygen treatment is set at 94%-95% considering patient safety.

In this study, the duration of oxygen restriction is 12 hours because a considerable number of studies have shown adverse effects of hyperoxia during the first 4-24 hours after ROSC, whereas other studies have reported that hyperoxia within 1-2 hours after ROSC was not associated with decreased neurological functions. Although the study protocol mandates treating physicians to restrict (or liberally adjust) the amount of oxygen administered only 12 hours after ROSC, restricted oxygen therapy can linger thereafter based on the decision of the treating physicians. Therefore, it should be noted that the restriction duration would be prolonged for >12 hours.

There are several limitations of this study in the context of its design. First, the treating physicians are not blinded to the study intervention. To adjust the amount of oxygen to a predefined target SpO₂, healthcare providers need to know the intervention assigned. Second, the difference in target SpO₂ between the two interventions is only 4%-5% (94%-95% vs 98%-100%). Similar cohorts may have eventually been generated. Third, a stepped-wedge cluster randomised design cannot adapt to a significant change in non-study-related treatments during the study period. When a novel treatment for PCAS is reported, the DSMC will discuss the continuation of the trial based on the absolute effect of such treatments on patients with PCAS. Fourth, as this study targets patients with both out-of-hospital and in-hospital cardiac arrest, confounding effects between them will exist. Finally, although the sample size has been calculated with a 10% absolute difference in outcome based on previous studies, smaller effects of restricted oxygen treatment cannot be validated.

TRIAL STATUS

The trial protocol V.1 was approved on 10 February 2022 (approval number: 20211106), with the approval process initiated in 2021. The latest protocol is V.6.0, which was approved on 28 February 2023, after minor revisions regarding the addition of participating hospitals, clarification on the statements of exclusion criteria and modification of the study period due to the lower-than-expected enrolment of patients. The first participant was recruited on 5 June 2022, in 1 of the 38 participating hospitals; subsequently, 1 more hospital joined the trial. The trial is ongoing, and approximately 150 patients had been enrolled as of the end of February 2023. The estimated primary completion date is 31 August 2025.
Contributors
RY, KY, AE, KH, YS and RT conceived and designed the trial. RY drafted the manuscript. YS and RT drafted the statistical plan. RY, KY, AE, YS and RT calculated the sample size and developed the statistical model. JS supervised the trial planning. KY, AE, KH, TY, KS, KShinada, YK, YFujinami, YT, KM, TW, YT, MN, JN, WT, KI, KYo, YFujita, HN, HT, KShinada, TS, SF, UN, MN, EH, AT, HS, HT, SI, HK, JH, TT and YF discussed the trial plan, included patients calculated the sample size and developed the statistical model. JS supervised the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

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Competing interests
None declared.

Patient and public involvement
Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

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