PRINCESS2

ULTRAFAST HYPOTHERMIA IN CARDIAC ARREST

PRINCESS2 Trial Management Manual Version

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Contents

1. PREHOSPITAL PHASE

1.1 Screening, inclusion and randomisation

- Screen all patients with out-of-hospital cardiac arrest for eligibility of the PRINCESS2 trial after first rhythm analysis.
- Screening can be performed at the site of cardiac arrest or, if sufficient communication between the EMS units, by personnel in the second EMS vehicle on the way to the site of cardiac arrest.
- Randomise eligible patients to intervention (transnasal evaporative cooling followed by systemic cooling) or control (standard of care) after the airway is secured.
- **Important**: Note randomization number (on randomization note).

1.2 Prehospital Intervention phase

- For patients in the intervention group: start transnasal cooling as soon as possible after secured airway (endotracheal tube or laryngeal mask airway).
- If the patient achieves ROSC, check tympanic temperature.
- For patients in the intervention group: continue transnasal cooling during transportation to hospital.
- Fill in randomisation number from the randomisation note, together with relevant data in the first part of the e-CRF (follow QR-code on randomisation card or log in to RedCap). A worksheet (locally established) might be used during the resuscitation phase to facilitate documentation.
- The second part of the prehospital e-CRF is filled in according to local routines (EMS-personnel, research-nurse etc).
- **Important:** Randomisation number must be communicated to hospital staff and continue with the patient.

2. INHOSPITAL PHASE

2.1 Inhospital intervention phase

- When the patient arrives to the hospital, the randomization number (from the randomization envelope and randomization note) should follow the patient according to local routines at each site.
- Each study site will establish local routines for filling in the E-CRF. Instructions for creating a login to

REDcap and filling in the CRF is available at www.princess2.org. Data is reported after arrival to ICU, then a short daily e-CRF for the first 3 days, and finally a summary at discharge from ICU. Data on procedures should be documented in the e-CRF as close to the procedure as possible.

- For patients in the intervention group: change to inhospital trans-nasal cooling device. **Cooling should be continued during transport to the ICU, diagnostics and examinations such as CT scan or coronary angiography.**

Inform patients' close relatives about inclusion in the study as soon as practical. Written information for relatives is available in Swedish, English and German at www.princess2.org.

2.1.1 Baseline care for all patients

Sedation: Sedation is mandatory for 40 hours from randomization for all patients included in the trial. Short acting drugs and opioids should be used. The sedative should be titrated to achieve deep sedation. Richmond Agitation-Sedation Scale (RASS) of minus 4 should be targeted (no response to voice, but any movement to physical stimulation). Neuromuscular blocking drugs should not be routinely in patients undergoing TTM but may be used in case of severe shivering.

Ventilation/circulation: Targets for respiration and circulation should follow the ERC gudielines. Ventilator settings should be adjusted to normoxia (arterial saturation of 94-98 %, paO2 of 10-13 kPa) and normocapnia (pCO2 of 4,5-6 kPa), with tidal volumes of 6-8 ml/kg. Mean arterial blood pressure (MAP) should be kept >65 mmHg, and a normal lactate and urinary output >0,5 ml/kg/h should be targeted. Insufficient MAP should be treated with crystalloid fluids in case of hypovolemia, and/or with vasopressor drugs.

In patients with ST-elevation presenting on 12 lead ECG, emergent cardiac catheterization evaluation (and PCI if required) should be performed. In patients without ST-elevation, but with a high probability of acute coronary occlusion emergent cardiac catheterization should also be considered. ECMO (including ECPR) or other mechanical circulatory support such as intra-aortic balloon pump (IABP) or Impella may be used if needed, according to local guidelines.

Control of seizures: Electroencephalography (EEG) is recommended to be used to diagnose electrographic seizures in patients with clinical convulsions and to monitor treatment effects. To treat seizures after cardiac arrest, we suggest levetiracetam or sodium valproate as first-line antiepileptic drugs according to local treatment guidelines in addition to sedative drugs.

Temperature recording: Tympanic temperature should be recorded on arrival to hospital. All patients must have a systemic temperature probe placed as soon as possible after hospital arrival (e.g. esophageal or bladder). Hourly core temperatures should be recorded for the first 40 hours following ICU admission, for *all* patients included.

2.1.2 Hypothermia (intervention group)

Start systemic cooling as soon as possible after admission to ICU. Both systems for surface-cooling as well as intravascular cooling are allowed. The RhinoChill should be turned off when systemic cooling is started,

but nasal catheters should be kept in place and intermittent activation of the RhinoChill may be considered if temperature does not continue to drop via the systemic cooling method. Patients should be cooled to a target temperature of 33°C ± 0,5°C.

Target temperature (33°C ± 0,5°C) should be maintained for 24 hours, after which the patient should be rewarmed at a rate of 0,25°C per hour until the patient has reached core body temperature of 36,5°C. Fever control (see below) should be done until 72 hours from cardiac arrest.

Core body temperature should be registered every 20 minutes until the patient has reached core body temperature of 33°C ± 0,5°C.

Shivering should be assessed using the The Bedside Shivering Assessment Scale (BSAS) and treated with buspirone, magnesium, clonidine, meperidine or increased sedation or, if needed, neuromuscular blocking agents, with the goal to maintain a BSAS score of 0-1.

2.1.3 Fever control management

For both study groups, fever, defined as >37,7°C, should be avoided for 72 hours from cardiac arrest. Antipyretics and conservative measures (exposure of patient and lowering of ambient temperature) will be used primarily, and if insufficient fever control (one measurement of core body temperature >37,7°C), a systemic cooling device can be used.

2.1.4 Blood samples and examinations

- Troponin T or I according to local protocol
- NSE at arrival, at 24 hours, 48 hours and 72 hours
- Echocardiographic examinations should, if feasible, be made after 24 h and 72 hours respectively, to measure left ventricular ejection fraction (LVEF).
- EEG between 36-72 hours is mandatory unless the patient wakes up before that time. If it is not possible to perform an EEG during the specified time frame due to practical reasons, the EEG should be performed as soon as possible after 72h. SSEP is optional but recommended unless the patient wakes up before 72 hours. CT brain and/or MT brain are optional according to local protocols.

2.2 Continuous ICU-care after the intervention phase

ALL patients included in the PRINCESS2 trial should be treated for at least 72 hours from randomisation*. After 40 hours, sedation should be stopped or lowered accorded to patient status. Extubation should be attempted as early as possible. Fever control should be kept for 72 hours. Neurologic prognostication by blinded physician should be done on ALL patients (including patients more or less awake) at the earliest 72 hours and as close as possible to 72 hours from randomisation. For more information on neurological prognostication and procedures, and on withdrawal of life sustaining therapies (WLST), see separate document (Neurological prognostication manual, available at www.princess2.org)

Consent: If the patient regains consciousness, he or she should be given verbal and written information about inclusion in the study and be asked for a written consent. Each site will have a local protocol for this procedure. Information for patients and relatives is available in Swedish, English and German at www.princess2.org

*Exemptions: Participants in whom further treatment is considered unethical due to irreversible organ failure, a documented medical comorbidity, or other reasons, or participants in whom brain death is established. See separate document (Neurological prognostication manual, available at www.princess2.org)