Towards improved outcome after cardiac arrest: new studies coming up

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Abstract
Patients admitted to an intensive care unit after cardiac arrest often suffer from severe brain injury. This injury worsens further after restoration of circulation due to the cascade of reactions in the brain. Neuroprotective therapies aim to diminish this secondary brain injury, thereby targeting at a better outcome. Several new large international studies will start soon, next to two smaller national phase II studies. In this paper we describe the new studies and invite Dutch intensive care units to join.

Introduction
The outcome of patients after out-of-hospital cardiac arrest (OHCA) has improved in the last decades in the Netherlands.[1] Whereas in 2000, 10% of these patients survived, the more recent figures report a survival of over 20%. The widespread introduction of automatic external defibrillators (AEDs) and increased training of lay people has certainly added to this increased survival rate. [2] Otherwise, the outcome of the patients who are admitted to an intensive care unit (ICU) after successful cardiopulmonary resuscitation (CPR) has not changed significantly. About 50% of patients survive after ICU treatment and 90% of these patients recover sufficiently so they can live at home. In these good outcome patients, cognitive deficits have been described in the last decade.[3] This has been recognised as an important problem leading to, for example, a decreased return to work.[4] Surprisingly, similar cognitive defects as seen in OHCA patients were found in age and gender matched patients who suffered a myocardial infarction, but no cardiac arrest.[5]

The majority of patients with a poor outcome die, mainly after withdrawal of life-supporting treatment in the ICU. In the Netherlands the number of patients that remain in a vegetative state is negligible and only a very small group needs nursing home care. Current ICU treatment of patients after cardiac arrest consists of target temperature management (TTM) and general supportive care.[5] This limits the development of secondary injury which continues to increase for several hours to days.[6] Specific treatments to diminish the brain injury by interrupting the chemical cascade that starts after cardiac arrest, such as noble gases, erythropoietin and calcium antagonists, have so far not proved to be effective.[7] The disappointing results of promising neuroprotective drugs in patients with ischaemic stroke finally led to a cessation of this type of study. But times are changing. Several initiatives to diminish brain injury and improve the outcome of patients who are admitted to an ICU after cardiac arrest will start soon. These include two large international randomised controlled trials and two Dutch phase II studies. The ICUs of the Netherlands can collaborate in these studies and in that way contribute substantially to a better outcome for this large group of ICU patients. In this paper we describe the new studies coming up.

Target Temperature Management-2 trial
The TTM2 trial is a continuation of the collaboration that resulted in the previous Target Temperature Management after out-of-hospital cardiac arrest trial (hereafter: TTM1).[8] With its planned size, TTM2 will supersede the TTM1 trial as the largest trial on temperature management as a post-cardiac arrest intervention. The TTM1 trial was a multicentre, multinational, outcome assessor-blinded, parallel group, randomised clinical trial comparing two strict target temperature regimens of 33° C and 36° C in adult patients, who had sustained return of spontaneous circulation (ROSC) and were unconscious after OHCA.[9] The trial did not demonstrate any difference in survival
Table 1. Details of studies

<table>
<thead>
<tr>
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<th>TTM2</th>
<th>TAME</th>
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<tr>
<td><strong>Design</strong></td>
<td>Phase III, multicentre, international RCT</td>
<td>Phase III, multi-centre, parallel-group international RCT</td>
<td>Phase II, multi-centre, placebo-controlled RCT</td>
<td>Phase II, multi-centre, placebo controlled RCT</td>
<td>Multicentre RCT</td>
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<tr>
<td><strong>Comparison</strong></td>
<td>Target temperature 33°C for 24 hours vs. early treatment of fever (≥37.8°C)</td>
<td>Mild hypercapnia (PaCO2 50-55 mmHg) vs. normocapnia (PaCO2 35-45 mmHg) for 24 hours</td>
<td>Acylated ghrelin 10 µg/kg, twice daily for 1 week vs. placebo</td>
<td>vitamin C 40 or 125 mg/kg/day or placebo for 4 days</td>
<td>Intensive treatment vs. no treatment for status epilepticus.</td>
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<tr>
<td><strong>Inclusion criteria</strong></td>
<td>Adults after OHCA with presumed cardiac cause and stable ROSC</td>
<td>Adults after OHCA with presumed cardiac cause and stable ROSC</td>
<td>Adult, comatose patients after CA and successful CPR.</td>
<td>Adult after CA with VF or VT as first rhythm and EMV score ≤8</td>
<td>Adults after CA with SE on EEG recording</td>
</tr>
<tr>
<td><strong>Primary endpoint</strong></td>
<td>All-cause mortality after 180 days</td>
<td>Favourable neurological outcome after 6 months</td>
<td>Functional outcome after 6 months</td>
<td>Delta SOFA score</td>
<td>Neurological outcome after 3 months</td>
</tr>
<tr>
<td><strong>No. of patients</strong></td>
<td>1900</td>
<td>1700</td>
<td>408</td>
<td>270</td>
<td>172</td>
</tr>
<tr>
<td><strong>Financial</strong></td>
<td>Limited compensation for each included patient</td>
<td>Limited compensation for each included patient</td>
<td>No financial compensation</td>
<td>Limited compensation for each included patient</td>
<td>No financial compensation</td>
</tr>
</tbody>
</table>

CA = cardiac arrest; CPR = cardiopulmonary resuscitation; EEG = electroencephalography; EMV = eye motor verbal; OHCA = out-of-hospital cardiac arrest; RCT = randomised controlled trial; ROSC = return of spontaneous circulation; SE = status epilepticus; VF = ventricular fibrillation; VT = ventricular tachycardia
Improved outcome after cardiac arrest

Neuron specific enolase (NSE) serum levels. NSE is a biomarker of neuronal injury that is released into the bloodstream after cerebral injury. Without differences in ventilation, temperature, or sedation management, a significantly attenuated NSE release was seen in the mild hypercapnia group compared with standard care (figure 2). For neurological outcome, used as a secondary endpoint in this study, a favourable effect of mild hypercapnia was also found. The TAME Cardiac Arrest Trial will be a phase III multi-centre randomised controlled trial investigating the effectiveness of targeted mild hypercapnia during the first 24 hours on neurological outcome after 6 months compared with standard care (targeted normocapnia). A favourable neurological outcome is defined as a score of five or higher on the extended Glasgow Outcome Scale. The protocol has been registered in the Australian New Zealand Clinical Trials Registry, Number: ACTRN12617000036314p and is funded by a Project Grant from the Australian National Health and Medical Research Council (NHMRC) – Project Grant ID APP1119855.

Ghrelin trial

Ghrelin is a naturally occurring hormone and mildly excitatory neurotransmitter. Ghrelin induced an increase of physiological neuronal activity and formation of new synapses in in vitro models of postanoxic encephalopathy. In a state of the art in vivo rat model of cardiac arrest, ghrelin improved functional neurological recovery and reduced histopathological damage. The presumed mechanism of action is a reduction of apoptosis. Since hypoxia-induced neuronal inactivity was independently associated with progression towards irreversible damage, both in vitro and in patients, we assume that the beneficial effects of ghrelin are mediated by mild neuronal activation, preventing ill-fated neuronal inactivity. This is perpendicular to the classical view of neuroprotection by inhibition. The aim of the Ghrelin trial is to test intravenous ghrelin treatment for safety and efficacy, hypothesising that ghrelin will improve the neurological outcome of comatose patients with post-anoxic encephalopathy after cardiac arrest.

The trial is designed as a phase II multicentre, double-blind, placebo-controlled randomised clinical trial. The intervention will be intravenous acylated ghrelin 10 µg/kg twice daily for 1 week versus placebo. A total of 408 adult, comatose patients after cardiac arrest and successful CPR will be included within 12 hours. The primary outcome measure will be functional outcome as expressed by the Cerebral Performance Category score at 6 months. Secondary outcomes include time to awaken and cognitive functioning at 12 months, and changes of the EEG pattern during treatment. The latter outcome measure is chosen to substantiate the translational assumption that an eventual effect is mediated by ghrelin influencing brain activation patterns.

Ghrelin has been tested in over 100 human studies, including studies in healthy volunteers and patients with cardiopulmonary diseases, neuro-endocrine diseases, psychiatric diseases, and neurodegenerative diseases. Serious adverse events (pneumonia, enteritis, lung cancer) were extremely rare and difficult to attribute to ghrelin administration. In this trial, a treatment duration of one week is chosen because (i) ill-fated neuronal inactivity is mainly observed in the acute phase (first days) after cardiac arrest and (ii) previous phase 0 and 1 studies have proven safety with a treatment duration of one week. The trial is projected to start on the intensive care units of Radboudumc, Rijnstate Hospital and Medisch Spectrum Twente on 1 January 2018. The trial is supported by ZonMw and Hersenstichting (Netherlands Brain Foundation). There is
no financial benefit for participants. Jeannette Hofmeijer is the principal investigator of this project (JHofmeijer@rijnstate.nl).

**VITaCCA trial: Early high-dose vitamin C in post-cardiac arrest syndrome**

Injury to the brain and other organs does not only occur during the period of ischaemia, but also after recovery of the circulation when an overwhelming amount of reactive oxygen species generated at reperfusion of the ischaemic organs leads to endothelial dysfunction with cerebral and cardiovascular damage. This massive oxidative stress can rapidly decrease plasma levels of vitamin C, our primary circulating antioxidant, due to consumption of its body stores.

In a recent study we showed that about 60% of the patients had deficient plasma concentrations of vitamin C at day 3 after cardiac arrest. Vitamin C levels were inversely associated with severity of organ failure, quantified by the SOFA (Sequential Organ Failure Assessment) score and with mortality. Vitamin C deficiency in post cardiac arrest patients will mostly remain undetected, because the measurement of vitamin C levels is laborious and expensive and therefore not available for daily practice. Correction of vitamin C deficiency may simply prevent scurvy, but supraphysiological vitamin C levels can also modulate numerous enzyme reactions, directly scavenge reactive oxygen species and recover endogenous vasopressor synthesis. Vitamin C may therefore reduce reperfusion damage to ischaemic organs and could thereby be a cheap, safe and simple therapy to improve outcome after cardiac arrest.

Preclinical studies with high-dose intravenous vitamin C showed improved survival after cardiac arrest and reduced ischaemia/reperfusion injury after clamping of individual organs, such as the kidney, brain, liver and lungs. In clinical studies in critically ill patients, high-dose iv vitamin C reduced pulmonary morbidity (combined endpoint of ARDS and nosocomial pneumonia), organ dysfunction and mortality and no significant adverse events were reported. Dosages varied from 3 up to 126 gram per day. So, the optimal dosing regimen remains to be determined. None of the clinical studies investigated the effect in patients after cardiac arrest.

The aim of the Vitamin C after Cardiac Arrest (VITaCCA) study is to determine the effect of two different high dosages of intravenous vitamin C (40 and 125 mg/kg/day) during the very early phase of reperfusion after cardiac arrest on organ damage, especially cerebral injury. In this phase II multicentre, randomised controlled trial 270 patients admitted after cardiac arrest with ventricular fibrillation or tachycardia as first registered cardiac rhythm and EMV score ≤8 will be included. The patients will be randomly allocated to intravenous treatment with 40 or 125 mg vitamin C/kg/day or placebo for 4 days. Primary outcome will be the delta SOFA score, secondary outcomes will be neurological outcome, cardiac injury and survival.

A grant application to obtain the necessary funding to perform this trial has been submitted to ZonMW. If this ZonMW grant is awarded the plan is to start the trial in 2018 in collaboration with Gelderse Vallei Hospital, Erasmus Medical Centre, Noordwest Ziekenhuisgroep, Franciscus Gasthuis & Vlietland, Tergooiziekenhuizen and the Amphia Hospital. The study was designed by Heleen Oudemans-van Straaten, and will be coordinated by Angelique Spoelstra-de Man and Paul Elbers (for contact: am.spoelstra@vumc.nl).

**Treatment of Electroencephalographic Status epilepticus After CPR: TELSTAR trial**

This study is already ongoing. Electroencephalographic status epilepticus is described in 9–35% of patients with postanoxic encephalopathy after cardiac arrest and is associated with case fatality rates of 90–100%. It is unclear whether electrographic seizure patterns in these patients represent a condition to be treated with antiepileptic drugs to improve outcome, or an expression of severe ischaemic damage, in which treatment with antiepileptic drugs would be futile. The aim of the TELSTAR trial is to estimate the effect of medical treatment of electrographic status epilepticus on neurological outcome of comatose patients with postanoxic encephalopathy after cardiac arrest. TELSTAR is a multicentre clinical trial with randomised treatment allocation, open label treatment and blinded endpoint evaluation (PROBE design; NCT02056236). The intervention contrast is intensive medical treatment versus no treatment of electrographic status epilepticus. The study population consists of adult patients with postanoxic encephalopathy after cardiac arrest with electrographic status epilepticus on continuous EEG. Treatment is based on the recommendations for the treatment of status epilepticus by the Netherlands Society of Neurology (NVN) and includes all incremental steps, including possible treatment with barbiturates. Treatment should be initiated within three hours after detection on continuous EEG. The objective of the treatment is to suppress all epileptiform activity on the EEG. If status epilepticus returns after tapering medication after 24 hours of treatment, the intensive treatment is repeated. If the status returns after 2 x 24 hours of treatment, it may be considered refractory. The primary outcome measure is neurological outcome defined as the Cerebral Performance Category score at 3 months. TELSTAR is funded by the Dutch Epilepsy Foundation and started on 1 April 2014. Currently, (1 August 2017) 90 of the intended 172 have been included in seven out of nine participating centres in the Netherlands and Belgium (for details see www.telstartrial.nl). Active centres are participating in publications. There is no financial benefit. The TELSTAR study is coordinated by Barry Ruijter, Jeannette Hofmeijer is the principle investigator (JHofmeijer@rijnstate.nl).

**Discussion**

As described above, therapeutic strategies aiming at neuroprotection are hot. Recently, results of several phase
II studies have been published and many animal studies are reported. Strategies used for neuroprotection are diverse, representing the impressive cascade of cellular reactions in the brain that occur after circulatory arrest. Whether a single therapeutic intervention will be successful or a combination of, for example, temperature management, optimal CO2 ventilation and drugs will be the answer in the end, remains to be seen.

For phase III studies investigating effectiveness on clinically relevant outcomes large groups of patients are needed. Ideally, an effective treatment works at two levels. First it should diminish the number of patients with a poor outcome. Poor outcome after cardiac arrest is usually defined as death, persistent vegetative state, or severe disability. In daily clinical care, the majority of this group dies, often after withdrawal of life-supporting treatment. This can be expected for about 50% of the study population. Furthermore, an effective treatment should reduce cognitive disturbances in the patients who survive. As the cognitive symptoms in this population are diverse, subtle changes should be sought, also necessitating a substantial number of patients available for long-term follow-up. This follow-up period should be at least 6 months to allow for spontaneous recovery, which is normally seen in patients with brain injury.

The TTM2 and TAME study coordinators have decided to enable co-enrolment. Patients admitted after OHCA can be included in both studies simultaneously. Data collection in both studies is also similar wherever possible, facilitating data collection in the daily clinical situation.

With approximately 5500 patients admitted to an ICU in the Netherlands every week, we can become an important country included in both studies simultaneously. Data collection with brain injury.

References