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LETTER TO THE EDITOR

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.[3]

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

(hazard ratio with a point estimate in favour of 36° C of 1.06 (95% confidence interval 0.89-1.28; p=0.51)) or neurological function at 6 months after the arrest, measured with the Cerebral Performance Category and the modified Rankin Scale.

In TTM2, an international, multicentre, parallel group, non-commercial, randomised, superiority trial a target temperature of 33° C will be compared with normothermia with early treatment of fever (37.8° C) *(table 1)*. Patients eligible for inclusion will be unconscious adult patients with OHCA of a presumed cardiac cause with stable ROSC. Randomisation will be performed via web-based application using permuted blocks with varying sizes, stratified by site. Due to the nature of the intervention, health care staff will not be blinded to the intervention. However, the personnel who will assess outcomes will be blinded to temperature allocation, as will those who perform prognostication. The intervention period will commence at the time of randomisation. Rapid cooling (within 4 hours) in the hypothermia group will be achieved by means of cold fluids and state-of-the-art cooling devices (intravascular/body surface/nasal/oesophageal). A closed loop system will be used to maintain the target temperature for 24 hours. After these 28 hours the patients will be rewarmed slowly during 12 hours. In the normothermia arm the aim will be early treatment of fever (37.8° C) using pharmacological measures and physical cooling when needed. For patients who develop a temperature of 37.8° C, a cooling device will be used and set at 37.5° C. All patients will be sedated, mechanically ventilated and haemodynamically supported throughout the intervention period of 40 hours. Patients who remain unconscious will be assessed according to a conservative protocol based on the European Resuscitation Council recommendations for neurological prognostication after cardiac arrest.[10] Follow-up will be performed at 6 and 24 months after cardiac arrest. The main results of the trial will be published following the 6-month follow-up. For the Netherlands, deferred consent will be possible, enabling inclusion in the study within 180 minutes after ROSC. Michael Kuiper is the national coordinator for this study (see www.ttm2trial.org, for contact with national coordinator : mi.kuiper@wxs.nl)

TAME Cardiac Arrest Trial: mild hypercapnia or normocapnia

After ROSC, cerebral hypoperfusion continues, probably leading to ongoing cerebral damage. Cerebral vasoconstriction and cerebral hypoxia have been demonstrated, using technologies that include positron emission tomography, ultrasound, jugular bulb oxygen saturation and cerebral oximetry. A likely mechanism responsible for sustained early cerebral hypoperfusion relates to impaired cerebrovascular autoregulation. Such impaired cerebral autoregulation may make even a normal arterial carbon dioxide tension (PaCO2) insufficient to achieve and maintain adequate cerebral perfusion and, consequently, cerebral oxygenation. PaCO2 is the major determinant of cerebral blood flow and an increased PaCO2 (hypercapnia) markedly increases cerebral blood flow.[11] Moreover, arterial carbon dioxide is modifiable and, as such, is a potential therapeutic target.

A positive effect of mild hypercapnia, aiming at a PaCO2 of 50-55 mmHg (6.65-7.31 kPa), was found in a prospective double crossover physiological clinical study and randomised, controlled, parallel group, multicentre, phase II trial.[12,13] In both studies the control group was ventilated aiming at normocapnia defined as a PaCO2 of 35-45 mmHg (4.65-5.98 kPa). A positive effect on regional cerebral tissue oxygen saturation (SctO2) assessed by near infrared spectroscopy was seen *(figure 1)*. The phase II study included 86 adult patients admitted to an ICU (in New Zealand or Australia) after cardiac arrest.[12] Both in-hospital and out-of-hospital cardiac arrest patients were included. The primary endpoint in this study was

Table 1. Details of studies

	TTM2	TAME	Grhelin	VITaCCA	TELSTAR
Design	Phase III, multicentre, international RCT	Phase III, multi-centre, parallel-group internati-onal RCT	Phase II, multicentre, placebo-controlled RCT	Phase II, multicentre, placebo controlled RCT	Multicentre RCT
Comparison	Target temperature 33°C for 24 hours vs. early tre-atment of fever (>37.8°C)	Mild hypercapnia (PaCO2 50-55 mmHg) vs. nor-mocapnia (PaCO2 35-45 mmHg) for 24 hours	Acylated ghrelin 10 µg/kg, twice daily for 1 week vs. placebo	vitamin C 40 or 125 mg /kg/day or placebo for 4 days	Intensive treatment vs. no treatment for status epilepticus.
Inclusion criteria	Adults after OHCA with presumed cardiac cause and stable ROSC	Adults after OHCA with presumed cardiac cause and stable ROSC	Adult, comatose patients after CA and successful CPR.	Adult after CA with VF or VT as first rhythm and EMV score ≤8	Adults after CA with SE on EEG recording
Primary endpoint	All-cause mortality after 180 days	Favourable neurological outcome after 6 months	Functional outcome after 6 months	Delta SOFA score	Neurological outcome after 3 months
No. of patients	1900	1700	408	270	172
Financial	Limited compensation for each included patient	Limited compensation for each included patient	No financial compen-sation	Limited compensation for each included patient	No financial compen-sation

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

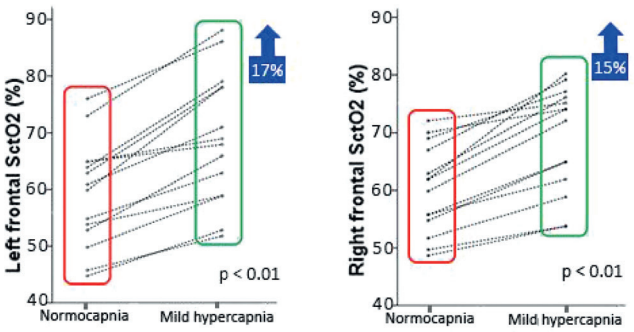

Figure 1. Changes in cerebral tissue oxygen saturation (SctO2) values induced by mild hypercapnia

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. Adult patients admitted to an ICU after out-of-hospital cardiac arrest due to a cardiac cause will be included. The aim is

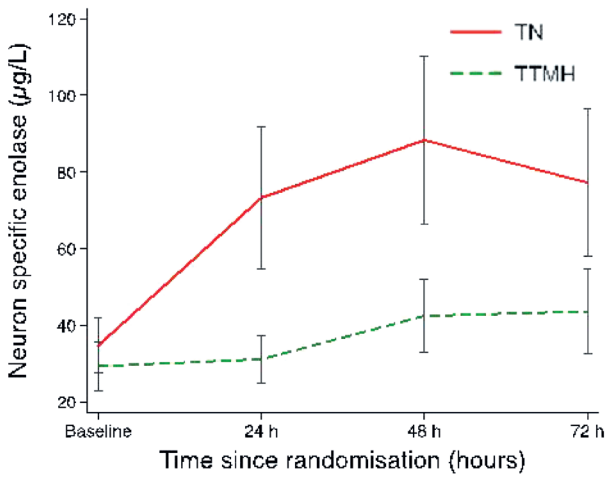

Figure 2. Baseline, 24 hour, 48 hour, and 72 hour neuron specific enolase levels for patients allocated to targeted therapeutic mild hypercapnia (TTMH) and standard care (TN). Values are reported as mean (SE)

to include 1700 patients, a deferred consent procedure will be used in which the legal representative is asked as soon as possible. Neurological prognostication in patients who do not wake up and follow-up for all patients are similar as described in the TTM2 study. For the Netherlands, Janneke Horn will be the national coordinator (j.horn@amc.uva.nl)

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.[14] In a state of the art *in vivo* rat model of cardiac arrest, ghrelin improved functional neurological recovery and reduced histopathological damage.[15] The presumed mechanism of action is a reduction of apoptosis.[16-18] Since hypoxia-induced neuronal inactivity was independently associated with progression towards irreversible damage, both *in vitro*[19] and in patients,[20,21] we assume that the beneficial effects of ghrelin are mediated by mild neuronal activation, preventing ill-fated neuronal inactivity.[22] 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.[23] 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.[24] 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.[25] Vitamin C levels were inversely associated with severity of organ failure, quantified by the SOFA (Sequential Organ Failure Assessment) score and with mortality.[25] 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[26] and recover endogenous vasopressor synthesis.[27] 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[28] and reduced ischaemia/reperfusion injury after clamping of individual organs, such as the kidney,[29] brain,[30] liver[31] and lungs.[32] 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.[33,34] 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.[35]

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.[36,37] 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 in these studies. If you want to be part of this exciting movement, do not hesitate to contact one of the study coordinators and join!

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