Ghrelin treatment of comatose patients after cardiac arrest:
A phase 2 clinical trial to estimate safety and efficacy of ghrelin to promote cerebral recovery

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Primary objective: We aim to measure safety and efficacy of intravenous treatment with acyl-ghrelin to promote cerebral recovery in comatose patients after cardiac arrest. Safety will be monitored throughout hospitalization and during follow-up...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Heart failures
Study type	Interventional

Summary

ID

NL-OMON46402

Source
ToetsingOnline

Brief title
Ghrelin in Coma

Condition

- Heart failures
- Cranial nerve disorders (excl neoplasms)

Synonym
Cerebral recovery

Research involving
Human

Sponsors and support

Primary sponsor: Universiteit Twente
Source(s) of monetary or material Support: ZonMW

Intervention

Keyword: Cardiac arrest, Cerebral recovery, Coma, Ghrelin

Outcome measures

Primary outcome

The primary outcome measure will be functional outcome as expressed as the score of the cerebral performance category (CPC) at 6 months.

Secondary outcome

Secondary study parameters/endpoints

Secondary outcomes include case fatality at one week and 6 months, time to awaken (time interval between resuscitation and GCS score of 14), EMV score and estimated CPC score at 1 week, CPC score at 3 and 12 months, and cognitive functioning at 12 months

Cardiovascular secondary outcome measures are

* Mean arterial blood pressure day 1-7 (mean, highest, lowest)

* Heart rate day 1-7 (mean, highest, lowest)

* Arrhythmia day 1-7: yes / no. If yes: type of arrhythmia

* Cumulative dose of vasopressive medication day 1-7

* Cumulative dose of inotropic medication day 1-7

* Sequential Organ Failure Assessment score day 1-7

* Kidney function day expressed as GFR day 1-7

* CVVH day 1-7: yes / no

* Assist devices day 1-7: yes / no

* Biomarkers: troponine and CK / CK-MB ratio at day 0, 1, 2 or 3

These are collected in the context of current care.

Other study parameters (if applicable)

We assume that potential effects of ghrelin are mediated by mild neuronal activation, preventing ill-fated neuronal inactivity. This is based on studies under experimental in vitro and in vivo conditions. To study effects of ghrelin on neuronal activity, we consider brain activity as measured by the EEG. Continuous EEG measurements during day 0-3 after cardiac arrest are performed in all participating hospitals in the context of current care. The following EEG measures will be extracted and studied in relation to ghrelin treatment: the temporal brain symmetry index (tBSI), the cerebral recovery index (CRI) and EEG background continuity. All three measures strongly represent restoration of brain activity after an hypoxic insult and are strongly related to clinical recovery.

Study description

Background summary

Comatose patients after cardiac arrest have an insecure prognosis
Anoxic brain damage after cardiac arrest is one of the most common causes of coma worldwide. In the Netherlands alone, approximately 5000 patients are admitted, yearly. Epidemiologic studies have predicted a rising incidence, because of an increasing prevalence of cardiovascular risk factors and the aging population. Postanoxic encephalopathy is the most common cause of death

in patients that survive cardiac arrest to hospital admission. As opposed to increased survival of cardiopulmonary resuscitation, outcome of postanoxic coma has improved only little over the past years. Despite treatment on an intensive care unit, approximately half of all comatose patients never regain consciousness as a result of severe hypoxic-ischemic brain damage.1,21,2 In the other half, there is a large probability of lasting brain damage with functional and cognitive impairments. There is limited knowledge of the pathophysiology of brain damage in postanoxic coma and hardly any insight into the severity of brain damage in individual patients.

Treatments are not available

Effective treatments to improve brain recovery in postanoxic coma are unavailable. Over the past years, there has been no substantial scientific progress. The only general treatment of presumed benefit is has been cooling the brain to 32°C. This was based on evidence from two small trials in 2002. However, , although its gainthe benefit of cooling has become uncertain since the recent large Targeted Temperature Management trial, where cooling to 32°C was associated with the same outcome as cooling to 36°Cand mechanisms of action are unclear.33 Currently, most experts believe that prevention of hyperthermia (fever) is more important than induction of hypothermia. An important rationale behind all studied, but ineffective, neuroprotective strategies, including hypothermia, has been prevention of secondary damage by inhibition of neuronal activation. The presumption is that this should preserve the remaining energy in order to maintain basic cellular processes. However, we observed that hypoxia causes wide spread inhibition of neuronal activity in itself.44 We established that insufficient neuronal activity during more than 24 hours is an independent predictor of absence of recovery to physiological activity patterns in vitro55 and in patients with postanoxic coma.6,76,7 This association was unrelated to the duration of the initial circulatory arrest or to the actual oxygen level. This suggests that, after the initial insult, it is not only the lack of energy, but also lack of neuronal activity, which may lead to secondary irreversible damage or recovery. None of the previously tested neuroprotective modalities by inhibition of activation were of proven benefit.88

Ghrelin was effective in animal models

Contrary to previous attempts, we now propose a treatment modality with mild neuronal activation. We found a massive increase of physiological neuronal activity and formation of new synapses by mild neuronal activation with Ghrelin in vitro.99 Furthermore, Ghrelin prevented apoptosis in living rats after cardiac arrest, with improved neurological recovery.1010 In more than ten rat studies on focal cerebral ischemia and reperfusion (mainly by intraluminal vessel occlusion), ghrelin improved neuronal survival and functional recovery without exception, where in most studies it was assumed that ghrelin prevented apoptosis.1111

Ghrelin is a naturally occurring hormone and mildly excitatory neurotransmitter. The presumed mechanism of action is slowing down of

apoptosis.12*1512*15 Since hypoxia induced neuronal inactivity was independently associated with progression towards irreversible damage, both in vitro1616 and in patients,6,76,7 we assume that the beneficial effects of ghrelin are mediated by mild neuronal activation, preventing ill-fated neuronal inactivity.55 This is perpendicular to the classical view of neuroprotection by inhibition, which is currently applied in all comatose patients after cardiac arrest.

Ghrelin seems safe

Ghrelin has been tested in over one hundred 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.17

Ghrelin has been administered as an infusion or a bolus in a variety of doses to at least 1850 study participants, including healthy participants and patients with obesity, prior gastrectomy, cancer, pituitary disease, diabetes mellitus, eating disorders, cardiovascular disease and neurodegenerative disease (for reviews please see17,18). Taken together: there is strong evidence that ghrelin stimulates appetite and increases circulating GH, ACTH, cortisol, prolactin, and glucose in various patient populations. There is a paucity of evidence regarding the effects of ghrelin on LH, FSH, TSH, insulin, lipolysis, body composition, cardiac function, pulmonary function, the vasculature, and sleep (review17).

At the doses evaluated in the 66 published studies with adverse event reporting, ghrelin demonstrated an excellent short-term safety profile with few adverse effects.17 Serious adverse events such as pneumonia, enteritis, and lung cancer were extremely rare and difficult to attribute biologically to ghrelin administration. Most of the severe adverse events derived from 1 study of ghrelin v.s placebo administration in severely ill patients with pulmonary cachexia, a group that is vulnerable to developing additional medical problems.19 Mild adverse events occurred in approximately 20% of participants receiving ghrelin. The most common effect was transient flushing, which occurred in 10% of volunteers, but resulted in discontinuation of study medication in only 3 of the 939 participants in whom adverse event collection was reported.20*22 There was no difference in the percentage of participants experiencing flushing between bolus and infusion routes of administration. Larger ghrelin doses may increase the risk of flushing, as indicated by the higher rate of flushing in the 2 ghrelin bolus studies that employed the largest tested dose (10*g/kg/dose). The most common gastrointestinal side effect was gastric rumbles, which occurred in 22 participants (2.3%) and was never severe enough to lead to ghrelin discontinuation. Gastrointestinal side effects and increased thirst were more common in volunteers who received continuous ghrelin infusions, perhaps due to the longer duration of exposure to ghrelin. Few participants developed neurocognitive effects including somnolence, fatigue, vertigo, or change in mood (26 subjects, 2.8%). These effects were more common in subjects who received ghrelin bolus, potentially

due to the rapid ghrelin delivery.17 For more details please see investigators brochure.

First effective neuroprotective treatment in cerebral ischemia?
We propose to estimate study the effect of ghrelin on neurological recovery of comatose patients after cardiac arrest based on the large probability of a poor outcome in this patient group, lack of effective treatments to promote brain recovery, consistent beneficial effects of ghrelin under experimental in vitro and in vivo conditions, and substantial evidence of safety.

If mild stimulation of neurons with Ghrelin provides clinically relevant improvement of recovery after hypoxic-ischemic brain damage in postanoxic coma, this will be the first identified effective treatment. This will be of large relevance for patients, families, and society given the high incidence and large impact of the disease, and the large probability of a poor outcome without adjunctive treatment. Apart from the evident potential clinical value, the first effective neuroprotective treatment in hypoxic-ischemic brain damage will be of conceptual value, and may be translated to other patients with cerebral ischemia, such as patients with ischemic stroke.

We know of no patents or other initiatives aiming at testing effects of ghrelin or other modalities based on neuronal activation in postanoxic coma.

Study objective

Primary objective:
We aim to measure safety and efficacy of intravenous treatment with acyl-ghrelin to promote cerebral recovery in comatose patients after cardiac arrest. Safety will be monitored throughout hospitalization and during follow-up using all AEs reported, and by interim analyses by an independent DSMB. Efficacy will be measured by the primary outcome measure, i.e. functional recovery as measured by the Cerebral Performance Category (CPC) scale at six months after cardiac arrest.

Secondary objective:
1. Case fatality
2. Time to awaken (time interval between resuscitation and Glasgow Coma Scale (GCS) score of 14)
3. Long term outcome: CPC and cognitive functioning at 12 months
4. Cardiovascular measures:
Mean arterial blood pressure day 1-7 (mean, highest, lowest)
Heart rate day 1-7 (mean, highest, lowest)
Arrhythmia day 1-7: yes / no. If yes: type of arrhythmia
Cumulative dose of vasopressive medication day 1-7
Cumulative dose of inotropic medication day 1-7
Sequential Organ Failure Assessment score day 1-7
Kidney function day expressed as GFR day 1-7

CVVH day 1-7: yes / no
Assist devices day 1-7: yes / no
5. Biomarkers:
Cardiac: troponine and CK / CK-MB ratio at day 0, 1, 2 or 3
Neurological: NSE day 1, 2, 3
Endocrinological: cortisol, growth hormone, prolactine, ACTH, IGF-1 day 1, 2, 3
6. Gastro-intestinal: gastric residual volume (day 1-7, during ICU admission)

Study design

This will be a phase 2 multicenter, double blind, placebo controlled randomized clinical trial.

Intervention

Intravenous treatment with acylated ghrelin 600 micro gram twice daily for 1 week vs. placebo (the highest tested and safe dosage regime in human subjects). 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.

Study burden and risks

Risk analysis is described in chapter 11 of the study protocol.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

* Age *18 years
* Out of hospital cardiac arrest
* Successful cardiopulmonary resuscitation
* Return of spontaneous circulation *12 hours ago
* GCS score on admission * 8 or suspected coma in patients who are sedated
* Admission to intensive care unit
* Hemodynamic and respiratory stability as determined by the treating intensive care physician, with the minimum requirement of mean arterial pressure > 65 mmHg. Treatment with inotropes, vasopressors or IABP is allowed.

Exclusion criteria

* Age <18 years
* A known progressive neurological disease
* Expected death within 48 hours

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel

Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	18-01-2019
Enrollment:	160
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Ghrelin
Generic name:	acyl-ghreline

Ethics review

Approved WMO Date:	19-11-2018
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	12-12-2018
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2018-000005-23-NL
CCMO	NL64594.044.18