Early high-dose vitamin C in post-cardiac arrest syndrome.

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Objectives:- To determine whether an early high dose i.v. vitamin C can improve organ function, especially neurological outcome, in patients after cardiac arrest- To explore the optimal dosing regimen for high dose i.v. vitamin C- To investigate in...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON55399

Source
ToetsingOnline

Brief title
Vitamin C post cardiac arrest.

Condition

- Other condition
- Coronary artery disorders

Synonym
organ dysfunction after cardiopulmonary resusciation, Post cardiac arrest syndrome

Health condition

na reanimatie

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: ZonMW programma drug rediscovery

Intervention

Keyword: antioxidants, cardiac arrest, resuscitation, Vitamin C

Outcome measures

Primary outcome

We will determine organ failure at 96 hours measured by the delta (Δ) Sequential Organ Failure Assessment (SOFA) score. ΔSOFA score is defined as the difference between SOFA admission and SOFA at 96 hour. Death at 96-hours will be counted as the maximum SOFA score (24 points).

Secondary outcome

As secondary outcomes we will investigate: neurological outcome (Maximal Glasgow Coma Score at 96-h and at the end of ICU-stay; Cerebral Performance Categories scale, Modified Rankin Scale at 30 and 180 days; HUI-3 questionnaire at 180 days; neuron-specific enolase day 1, 2 and 3); clinical parameters (IC- and hospital stay, 30-day and 90-day mortality), organ injury (myocardial injury measured by troponin and CK-MB (maximum day 1), lung injury score, ventilation time, renal function, need of renal replacement therapy, IC-acquired weakness (Medical Research Council score), delirium (CAM-ICU score), MitoPO2, oxidative stress parameters (F2-isoprostanes and oxidation reduction potential (ORP)), anti-oxidant capacity (AOC) and vitamin C plasma concentrations.

In vitro experiments:

To determine the different effect of vitamin C or placebo on the underlying oxidative pathways we will investigate how plasma obtained from the trial patients affects cultured human systemic microvascular endothelial cells with regard to endothelial cell viability, ROS production intracellular vitamin C concentrations, NADPH-oxidase expression, p47Phox expression, endothelial barrier function and mitochondrial respiratory chain function.

Study description

Background summary

Only half of the patients suffering from cardiac arrest arrive at the hospital alive. Of these survivors, 50% will still die or remain severely disabled. During cardiac arrest ischemia causes damge to the vital organs, especially the brain. When with return of spontaneous circulation oxygen is re-offered to the ischemic organs, massive amounts of reactive oxygen species (ROS) are produced. These ROS can increase the damage to the myocardium and brain (reperfusion injury). Vitamin C is the primary circulating antioxidant. It can scavenge free radical and reduce the production of ROS. In a recent study we demonstrated that vitamin C plasma levels are deficient in ~60% of the patients after cardiac arrest, probably due to massive consumption. These deficient levels reduce the protection against oxidative stress. Patients with decreased vitamin C levels had more organ dysfunction and a worse survival. Vitamin C deficiency will often remain unnoticed, because this complicated and expensive laboratory measurement will not be routinely available. The antioxidative effect of vitamin C is much more potent if it is administered intravenously in a higher, supraphysiological dose (>= 3 gr per day). Its strong antioxidative effect may reduce damage to brain, heart and other organs. Beneficial effects of high dose i.v. vitamin C after cardiac arrest have been demonstrated in preclinical studies, but not in patients.

Study objective

Objectives:
- To determine whether an early high dose i.v. vitamin C can improve organ function, especially neurological outcome, in patients after cardiac arrest
- To explore the optimal dosing regimen for high dose i.v. vitamin C

- To investigate in vitro the difference in effect of plasma obtained from post cardiac arrest patients treated with placebo, 3 gr/day or 10 gr/day vitamin C on endothelial cell viability and underlying oxidative pathways.

Study design

In this multicentre, placebo controlled double-blind randomized clinical trial patients will be recruited from the Intensive Care Units of: VU University Medical Centre, Noordwest Ziekenhuisgroep, Gelderse Vallei Hospital, Franciscus Gasthuis & Vlietland, Tergooiziekenhuizen, the Amphia Hospital, the Erasmus Medical Centre, OLVG Oost and the Maasstad Hospital.

Intervention

As soon as possible (ultimately < 5 hours after ROSC) after their arrival at the Emergency Department, patients will be randomly allocated to one of 3 treatment groups of 120 (90 evaluable) patients each and vitamin C or placebo will be started for 96 hours.
Group 1 will be treated with placebo, group 2 with 2 times a day a bolus of 1.5 gr vitamin C and group 3 with 2 times a day a bolus of 5 gr vitamin C. After these 4 days the overwhelming oxidative stress and associated organ damage will have settled down and vitamin C levels will be restored. Vitamin C administration will then be lowered to standard nutritional dose to allow the physiological signaling and repair function of low concentrations of ROS. All patients will receive thiamine 200 mg q 12 hourly for 4 days to limit the conversion of vitamin C to oxalate.

Study burden and risks

A total of 100 ml blood will be taken during a period of four days from an arterial line which is routinely present for monitoring. The patient will not notice the blood sampling. He/she will notice the collection of urine samples, because all patients have a bladder catheter.

The risk of potential side effects of high dose vitamin C is very small. There is a small risk of formation of oxalate crystals in the urine. Formation of kidney stones of oxalate crystals has only been observed after prolonged intake of high dose vitamin C. In addition, renal function of all patients at our ICU is monitored routinely by daily determination of serum creatinine, estimated Glomerular Filtration Rate (eGFR) and fluid balance. Diuresis is monitored hourly. When indicated, an urine sediment analysis or echography of the kidneys will be carried out. Vitamin C can exert pro-oxidatieve effects. Pro-oxidative effects are mostly observed at low dose vitamin C and in patients with hemochromatosis. In this study patients will receive high doses and patients with hemochromatosis will be excluded. Therefore, we will expect less oxidative stress. Sometimes high-dose i.v. vitamin C can lead to factitious hyperglycemia

when measured with point-of-care devices, mostly at dosages much higher than used in our study. We will measure blood glucoses during the period of vitamin C administration by blood gas analysis or in the central laboratory.

Contacts

Public
Vrije Universiteit Medisch Centrum

De Boelelaan 1117
Amsterdam 1081 HV
NL
Scientific
Vrije Universiteit Medisch Centrum

De Boelelaan 1117
Amsterdam 1081 HV
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Patients admitted to the Intensive Care after out-of-hospital cardiac arrest with return of spontaneous circulation, ventricular fibrillation or ventricular tachycardia as first registered cardiac rhythm and EMV-score <=8.

Exclusion criteria

Patients with pre-existent terminal renal insufficiency (i.e. receiving renal replacement therapy (RRT)), known glucose 6-phosphate dehydrogenase deficiency (risk of hemolysis), history of urolithiasis, oxalate nephropathy, hemochromatosis or treatment limitations will be excluded.

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:	Recruiting
Start date (anticipated):	21-10-2019
Enrollment:	360
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Vitamin C
Generic name:	Ascorbic acid
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	08-06-2018
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-04-2019
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-07-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-07-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-10-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-11-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-11-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-07-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-08-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	07-12-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-02-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-04-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-04-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-09-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-09-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2017-004318-25-NL
ClinicalTrials.gov	NCT03509662
CCMO	NL63681.029.18