Arginine and nitric oxide (NO) metabolism in sepsis: L-Citrulline enteral supplementation for the normalisation of the Arginine-NO metabolism.

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Primary Objective: To study stimulating effects of prolonged (8h) enteral L-citrulline supplementation on the normalisation of the Arginine-NO metabolism.Secondary Objective: To study stimulating effects of prolonged (8h) enteral L-citrulline...

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

Summary

ID

NL-OMON37149

Source
ToetsingOnline

Brief title
L-citrulline supplementation during sepsis

Condition

- Other condition
- Ancillary infectious topics

Synonym
blood born infection, sepsis

Health condition

Alle vormen van sepsis of septische shock

Research involving
Human

Sponsors and support

Primary sponsor: Algemene Heelkunde
Source(s) of monetary or material Support: VENI vernieuwingsimpuls

Intervention

Keyword: arginine, L-citrulline, microcirculation, sepsis

Outcome measures

Primary outcome

Primary study endpoints are the imporvement of the citrulline plasma concentrations and the arginine-NO metabolism, which will be determined in blood samples. To determine the NO production we will measure the Nitrosyl-Hb in whole blood.

Secondary outcome

Secundary study parameters are the microcirculation, using gastric tonometry, which measures the pCO2 of the stomach, and the microcirculation. Sidestream Darkfiled Imaging (SDF) is used to investigate the microvasculature directly sublingual, as an indication for organ vascularisation. Organ function scores will also be evaluated.

Study description

Background summary

Sepsis can be defined as an overwhelming systemic response to an infection leading to
disturbed organ function, i.e. multiple organ dysfunction or failure (MOF).
Mortality rates of patients with sepsis vary from 40-70% and are determined by

the degree of organ failure.
During sepsis NO synthesis is compromised and contributes to impaired microcirculation and organ disfunction. The cause for this compromised NO production seems to be an impaired arginine metabolism, as plasma arginine levels are reduced in sepsis.
Our recent data showed for the first time that arginine de novo synthesis (citrulline converted back into arginine) cannot compensate these decreased arginine levels in patients with severe sepsis, with decreased citrulline plasma concentrations as underlying cause.
Therefore, reduced arginine de novo synthesis, through a decreased NO production, may lead to a
decreased organ perfusion. Several mechanism may cause a reduced arginine synthesis. Improving specifically the arginine de novo synthesis (supplementation of L-citrulline) may thus be a possibility to improve NO synthesis (by either enzyme), and may subsequently improve organ perfusion. since the citrulline plasma concentrations are decreased in these patients during sepsis, suppletion is the only option to normalise these concentrations.

Study objective

Primary Objective: To study stimulating effects of prolonged (8h) enteral L-citrulline supplementation on the normalisation of the Arginine-NO metabolism.

Secondary Objective: To study stimulating effects of prolonged (8h) enteral L-citrulline supplementation on the microcirculation, systemic hemodynamics, and organ function and disease severity scores.

Research questions:
1. What are the effects of prolonged (8h) L-citrulline supplementation on whole body arginine de novo nitric oxide metabolism in septic patients, after normalization of the citrulline levels?
2. Can prolonged L-citrulline supplementation improve microcirculation, vascular reactivity and permeability in sepsis?
3. Does this prolonged L-citrulline supplementation subsequently result in improved organ function and disease score?

Hypothesis
NO synthesis is compromised during sepsis through lack of arginine de novo synthesis and may thereby contribute to impaired microcirculation and organ dysfunction. Supplementation of L-citrulline in septic patients will normalize the plasma citrulline concentrations and increase the NO production without increased arginase activity and will improve organ function, vascular permeability and microcirculation.

Study design

Open label supplementation study.
Duration: 2-year period
Setting: Intensive Care Units Maastricht University Medical Center (MUMC+)

The experimental phase is conducted in 24 patients with severe sepsis or septic shock to study the effect of 8h enteral L-citrulline supplementation on the normalisation of the plasma citrulline concentrations and the whole body nitric oxide (NO) production, whole body arginine de novo metabolism, arginase activity and microcirculation.
The L-citrulline dose (1.8 micromol.kg-1.min-1) will be based on:
1) the dosage used in the arginine clinical suppletion study
2) The dosage used in the previous pig studies,
2) a comparable increase in plasma citrulline with immunonutrition.
The experiment involves 8 hours and is designed as an open label feeding supplementation study. L
-alanine (3.6 micromol.kg-1.min-1; isocaloric) is used as an alternative suppleted amino acid during the study, based on our experience in healthy subjects on the metabolic ward and in the pig studies in our lab. An alternative suppletion is chosen to maintain equal isocaloric energy intake during the experiment.
During the study period, metabolism is measured at 2 time points (T0 (=baseline), T8h), using a 2 x 2h stable isotopes protocol. Organ function is monitored at regular intervals and microcirculation are performed during the study period.

Intervention

The experiment involves 8 hours during which L-citrulline-HCl (dose 1.8 micromol.kg-1.min-1) is supplemented enteral continuously (duodenal gauge) together with the standard enteral nutrition provided through an enteral canula. L-alanine-HCl (isocaloric dose: 3.6 micromol.kg-1.min-1) is used as an alternative amino acid during the study.

Study burden and risks

In general, no side effects were observed regarding hemodynamics, and plasma electrolytes with L-arginine infusion (MEC 03-139). These side effects are also not expected from the L-citrulline supplementation. L-alanine is an amino acid, which showed no side effects in previous patient (MEC 02-010) and animal studies. Blood sampling is limited as much as possible by combining the blood sampling in the protocol with the routine blood sampling for patient care. During the study 10-ml blood samples are taken at regular intervals for additional laboratory analyses (115 ml in total). These samples are drawn from an indwelling arterial line already in place for standard treatment purposes. The gastric tonometry catheter will replace the normal gastric catheter in the

patients. During standard endoscopic placement of a jejunal feeding tube, microscopic images of the intestinal villi will be recorded. All other measurements are non-invasive and are harmless.
Clinical side effects will be controlled intensively during the study, by continuous hemodynamic observation. Changes in the patient*s profile are treated according to standard ICU practice. The protocol will not interfere with the patient care and treatment; when necessary due to surgical need or other care, measurements will be postponed. No benefits are to be expected for the individual patient in this studie.

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

1. Written informed consent from close relative

2. Age > 18 years
3. patient meets the general criteria for severe sepsis or septic shock, diagnosed less than 48 h prior to study inclusion. (according to Levy and Fink et al. Intensive care med 29: 530-538. 2003)
4. Patient must be relatively hemodynamically stable, defined as stable blood pressure (variation in mean arterial pressure < 15 mm Hg), during 2 h without necessity of increasing the vasopressor dose, inotropic support or rate of fluid administration.
5. Systemic arterial catheter in place with continous pressure monitoring.
6. Patients in whom the clinician is prepared to provide full life support during duration of the study.

Exclusion criteria

1. Shock due to any cause other than sepsis (e.g drug reaction or drug overdose, pulmonary embolus, burn injury etc.)
2. prolonged or high dose corticosteroid use
3. chronic pancreatitis
5. insulin-dependent diabetes mellitus
6. metastases, haematological malignancies or chemotherapy
7. patients on dialysis (CVVH or other)
8. pre-existent renal failure (on dialysis)

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	24-11-2011
Enrollment:	48

Type:	Actual

Ethics review

Approved WMO Date:	20-06-2011
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

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
ClinicalTrials.gov	NCT00628381
CCMO	NL20674.000.10