Paracetamol (Acetaminophen) in Stroke 2 (PAIS 2): A double-blind, randomized, placebo-controlled clinical trial of high-dose paracetamol in patients with acute stroke and a body temperature of 36.5°C or above

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Primary objective: To assess the effect of early treatment with paracetamol in a daily dose of 6 g for three consecutive days in patients with acute stroke and a body temperature of 36.5°C or above on the occurrence of a favorable functional outcome...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Central nervous system vascular disorders
Study type	Interventional

Summary

ID

NL-OMON39031

Source
ToetsingOnline

Brief title
PAIS 2

Condition

- Central nervous system vascular disorders

Synonym
Stroke (cerebral infarction and intracerebral hemorrhage)

Research involving

Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: acetaminophen, acute stroke, body temperature, cerebral infarction, functional outcome, inflammation, intracerebral hemorrhage

Outcome measures

Primary outcome

The primary outcome measure is the score on the modified Rankin Scale (mRS).

Secondary outcome

The secondary outcomes will be poor outcome defined as mRS>2 at 3 months; score

on the Barthel index and EQ5D score at 3 months; and body temperature 24 hours

after start of treatment.

Study description

Background summary

In patients with acute stroke, increased body temperature is related to poor functional outcome. In the Copenhagen study, the risk of poor outcome doubled with every degree Celsius increase in body temperature. Animal studies have suggested that a rise in temperature results in increased ischemic damage through increased cerebral metabolic demands, increased blood-brain barrier permeability, acidosis, and an increased release of excitatory amino acids. In the Paracetamol (Acetaminophen) in Stroke (PAIS) trial, a double blind, placebo-controlled randomized clinical trial of 1400 patients with acute stroke, more paracetamol-treated patients than placebo-treated patients showed improvement on the modified Rankin scale (mRS), yet the difference was not statistically significant (adjusted Odds Ratio (aOR) 1.21; 95% Confidence Interval (CI): 0.97-1.51). In the 661 patients with a baseline body temperature of 36.5°C or above, paracetamol yielded a larger decrease in temperature than in those with a baseline temperature lower than 36.5°C, and increased the odds

of improvement (aOR, 1.31; 95% CI: 1.01-1.68).

Study objective

Primary objective:
To assess the effect of early treatment with paracetamol in a daily dose of 6 g for three consecutive days in patients with acute stroke and a body temperature of 36.5°C or above on the occurrence of a favorable functional outcome.

Secondary objectives:
1. To investigate the association between body temperature in the first 12-36 hours after acute stroke and serum inflammation markers.
2. To investigate the relationship between paracetamol in a daily dose of 6 g for three days and an inflammatory response in stroke.

Study design

PAIS 2 is a multicenter, randomized, double-blind placebo-controlled clinical trial.

Intervention

About fifty percent of the patients receive 6 gram paracetamol a day for 3 days, the rest receive placebo.

Study burden and risks

In two pilot trials, and in the PAIS trial, paracetamol in a dose of 6 g/day was neither associated with hepatotoxicity nor with other side effects. In the PAIS trial the number of serious adverse events was similar in both treatment groups. Paracetamol has only a small effect on body temperature. Yet, when treatment will be proven effective, a simple, safe and inexpensive therapy will be available for many patients with acute stroke.

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

- clinical diagnosis of ischemic stroke or intracerebral hemorrhage, confirmed by CT or MRI scan within 24 hours after inclusion in the study
- a measurable deficit on the National Institutes of Health Stroke Scale (NIHSS)
- the possibility to start treatment within 12 hours of symptom onset (for patients who noticed symptoms when awaking from sleep, the time last seen well is taken as the time of onset of symptoms)
- a body temperature of 36.5°C or higher
- age of 18 years or older
- signed informed consent

Exclusion criteria

- a history of liver disease or alcohol abuse
- liver enzymes (ASAT, ALAT, AP or gamma-GT) increased above twice the upper limit of normal values
- allergy to paracetamol
- death appearing imminent at the time of inclusion
- any pre-stroke impairment that has led to dependency (modified Rankin scale (mRS)>2) and therefore interferes with the assessment of functional outcome.

Study design

Design

Study phase:	3
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):	01-05-2011
Enrollment:	1500
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	eigen bereiding
Generic name:	acetaminophen
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	28-09-2010
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	04-02-2011
Application type:	First submission

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-03-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	03-04-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2010-021437-30-NL
CCMO	NL32932.078.10

Study results

Date completed:	01-01-2015
Actual enrolment:	255