# 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

Published: 28-09-2010 Last updated: 04-05-2024

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

## **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**

#### **Public**

Erasmus MC, Universitair Medisch Centrum Rotterdam

Dr. Molewaterplein 50 Rotterdam 3015 GE NI

#### Scientific

Erasmus MC, Universitair Medisch Centrum Rotterdam

3 - Paracetamol (Acetaminophen) in Stroke 2 (PAIS 2): A double-blind, randomized, pl ... 8-05-2025

Dr. Molewaterplein 50 Rotterdam 3015 GE NI

## **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