Preventive Antibiotics in Stroke Study

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To investigate whether preventive use of the antibiotic ceftriaxone improves functional health outcomes in patients with stroke by preventing infection. This will be done in a large multi-centre randomized controlled trial. Within this trial we will...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Bacterial infectious disorders
Study type	Interventional

Summary

ID

NL-OMON38262

Source
ToetsingOnline

Brief title
PASS

Condition

- Bacterial infectious disorders
- Central nervous system vascular disorders

Synonym
infection, Stroke

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: ZonMW;NHS

Intervention

Keyword: Antibiotics, Infection, Prevention, Stroke

Outcome measures

Primary outcome

The primary efficacy end point will be functional health at 3-month follow-up, as assessed by the modified Rankin scale (mRS) dichotomized as a favourable outcome (mRS 0-2) or an unfavourable outcome (mRS 3-6). The proportional odds model provides additional information from ordinal outcome data, as it takes into account improvements at any point on the mRS. Therefore, we will use this method in a secondary analysis of the primary endpoint. Beneficial effects on this outcome should be accompanied by effects on the classic endpoints in the same direction to be considered convincing.

Secondary outcome

Secondary outcomes will be death rate at discharge and at 3 months, infection rate during hospital admission, length of hospital admission, volume of post-stroke care, use of antibiotics during the 3 months follow-up, functional health using the full ordinal scoring range of the mRS, quality adjusted life years (QALYs), and costs.

Study description

Background summary

Stroke is a leading cause of death worldwide. In the Netherlands, the incidence of acute stroke is approximately 40.000 per year. This incidence is increasing because of the ageing population. The percentage of patients with poor outcome is high (50%). Associated costs after stroke are substantial with mean lifetime cost varying between 38,000 and 133,000 euro per person. Fever after stroke is a strong predictor for poor outcome. The cause of fever in stroke patients is most often lung or urinary tract infection. Infections occur in up to 50% of patients with stroke and have also been associated with poor outcome. Recent

randomized studies have shown that preventive antibiotic therapy lowers infection rate in patients after stroke. Phase III trials evaluating the effect of preventive antibiotic therapy on clinical outcome in sufficient numbers of patients with stroke have not been performed. ceftriaxone, an off-patent medicine, is an antibiotic with broad action against bacteria causing the most common infections after stroke. Recent studies have also suggested a neuroprotective effect of ceftriaxone. The administration of ceftriaxone is simple and safe, and can easily be incorporated in standard care. Therefore, preventive therapy with ceftriaxone has a great potential to effectively reduce the proportion of patients with poor outcome after acute stroke and a large randomized clinical trial is warranted.

Study objective

To investigate whether preventive use of the antibiotic ceftriaxone improves functional health outcomes in patients with stroke by preventing infection. This will be done in a large multi-centre randomized controlled trial. Within this trial we will also assess the cost-effectiveness of this preventive treatment.

Study design

We will conduct a multi-centre prospective, randomized, open-label, blinded endpoint (PROBE) trial of standard care and preventive treatment with ceftriaxone as compared to standard care without ceftriaxone. Adult patients with stroke (both ischemic and haemorrhagic) and a score >= 1 on the National Institutes of Health Stroke Scale (NIHSS) will be included. Patients will be randomly assigned to receive ceftriaxone, at a dose of 2 g given every 24 hours intravenously for 4 days, or no treatment against a background of best medical management. The primary end point will be functional health at 3-month follow-up, as assessed by the modified Rankin Scale (mRS), dichotomized as a favourable outcome (0 to 2) or an unfavourable outcome (3 to 6). Secondary outcome measures will be death rate at discharge and 3 months, infection rate during hospital admission, length of hospital admission, volume of post-stroke care, including antibiotics used during the 3 months follow-up, functional health using the full ordinal scoring range of the mRS, quality adjusted life years (QALYs) and costs. The sample size calculation based on the assumption that ceftriaxone will reduce the proportion of patients with an unfavourable outcome from 50 to 45%. A two group Chi-square test with a 0.05 two-sided significance level will have 80% power to detect the difference between a standard care proportion of 0.50 and a treatment group proportion of 0.45 (odds ratio of 0.818) when the sample size in each group is 1565. We intend to enrol a total of 3200 patients.

Intervention

The study medication will be ceftriaxone 2000 mg, intravenously, 1 times daily, for 4 days. Ceftriaxone is started within 24 hours after stroke onset. The associated direct costs of this intervention are approximately ¤50. If patients will be discharged before day 3 after admission, study medication will be stopped. If the treating physician decides to withdraw active treatment in a patient with a very poor prognosis, study medication will also be stopped. The treating physician decides whether or not to treat a patient with suspected infection with (additional) antibiotics. Recommendations will be made for the treatment of infections according to the Dutch SWAB guidelines for antibiotic policy.

Study burden and risks

After inclusion in this trial an urineanalysis will be performed in every patient, in addition to standard care. This examination is a limited burden to the patient.

After these examinations, patients will be randomized to receive either standard care with ceftriaxone through an intravenous infusion or standard care without ceftriaxone. Placement of this infusion will in a majority of cases be included in the standard care, although if not, it will form a minor burden for the patient. An intravenous infusion always gives (low) risks of infection at the place of insertion.

Risks side-effects of treatment with Ceftriaxon have been discussed before (E9). Ceftriaxon has been shown to be safe in numerous trials. Side-effects are known and will be monitored, especially the occurrence of hypersensitivity-reactions and diarrea.

When there is suspicion of an infection in patients during admission, diagnostic procedures to define the focus of infection will be performed according to a predefined algorithm. This will include a chest X-ray, a bloodsample/culture, urine-analysis and culture and if possible a sputumculture. These examinations are standard procedures in stroke-care and will therefore not form an additional burden to the patient.

After 3 months patients will be interviewed telephonically by a structured questionnaire, which will be sent to the patient one week in advance. These activities form a low burden for the patient without further risks.

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. Age><=18 yr
2. Stroke (ischemic and hemorrhagic)
3. Any measurable neurological deficit defined as NIHSS ><= 1
4. Stroke onset < 24 hours
5. Admission

Exclusion criteria

1. Symptoms and signs of infection on admission requiring antibiotic therapy
2. Use of antibiotics < 24 h before admission
3. Pregnancy
4. Hypersensitivity for cephalosporin
5. Anaphylaxis for penicillin derivates
6. Subarachnoid hemorrhage
7. Death seems imminent

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Other
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-07-2010
Enrollment:	3200
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Ceftriaxone
Generic name:	Ceftriaxone
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	23-03-2010
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-06-2012
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-09-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-09-2012
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	EUCTR2010-018421-19-NL
ISRCTN	ISRCTN66140176
CCMO	NL31551.018.10