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Slow initial beeta-lactam infusion, and high-dose paracetamol to improve the prognosis of childhood bacterial meningitis, especially of pneumococcal meningitis

Submission date
22/08/2005

Recruitment status
No longer recruiting

Registration date
04/10/2005

Overall study status
Completed

Last Edited
19/10/2011

Condition category
Infections and Infestations

[_] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol
Not provided at time of registration

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers

Study information

Scientific Title

Acronym
BOL/INFLU-PARA/PLA

Study objectives
1. Can the prognosis of childhood Bacterial Meningitis (BM) be improved by instituting beeta-lactam such as cefotaxime with a slow infusion, instead of giving traditionally large doses intermittently from the early beginning?
2. Can the prognosis be further improved by large doses of paracetamol?
3. To which extent is the prognosis of BM affected by the host response and Cerebrospinal Fluid (CSF) genome count and serotype, paying special attention to Streptococcus pneumoniae?

Please note that as of 22nd January 2008 an update has been performed on this trial record. Any changes to the trial record can be found under the date 22/01/2008 in the specific section.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Added as of 22/01/2008:
Approval of the protocol: June 2005
Approval of the amended protocol: 21 December 2007

The data Safety and Monitoring Board is formed by Dr Heinz-J. Schmitt, Professor of Pediatric Infectious Diseases at Johannes Gutenberg University, Mainz, and two clinical statisticians, Dr R¨¹diger von Kries, Professor of Pediatrics and Chief of the Department of Pediatric and Adolescent Epidemiology, Ludwig Maximilian University, Munich, and Dr Jean Baptiste du Prel, Johannes Gutenberg University, Mainz. The Board's responsibility is to follow-up the study from the ethical and scientific points of view, and it has an access to the treatment codes at any time. If an indisputable significance between groups is met before the study ends, the team interrupts the trial for ethical reasons.

After the first 50 - 100 enrolled patients, the Board will check the accuracy of the study. Thereafter, the situation is checked every six months.

Study design
Randomised controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)

Hospital

Study type(s)
Treatment

Participant information sheet

Health condition(s) or problem(s) studied
Childhood bacterial meningitis

Interventions
All children will receive cefotaxime 250 mg/kg/day for seven days, except salmonella meningitis for which antimicrobial treatment should last for 14 days or more. Regardless of etiology, the children are randomised in a double-blind fashion in two groups for the first 24 hours: 50% receive cefotaxime in two 12-hour infusions, the other 50% getting cefotaxime in four boluses.

Added as of 22/01/2008:
In addition to the intervention of cefotaxime bolus versus cefotaxime infusions:
During the first 48 hours, 50% of the patients are randomised to receive high dose paracetamol (first dose 30 mg/kg, then 20 mg/kg every six hours for 42 hours) and the other 50% an oral placebo.

Thus the four treatment alternatives are:
1. Cefotaxime boluses + oral high dose paracetamol
2. Cefotaxime boluses + oral placebo
3. Cefotaxime infusions + oral high dose paracetamol
4. Cefotaxime infusions + oral placebo

Analysis plan:
Analysis by intention to treat will include all children in whom bacterial meningitis was suggested and a study medication was instituted. The patients in whom meningitis was confirmed (greater than or equal to 1 diagnostic criterium fulfilled) will be analysed per protocol.

Chi square test is used to test potential differences in the primary endpoints comparing the groups of infusion versus bolus dosing, and those receiving versus not receiving paracetamol. The secondary endpoints are examined similarly.

Intervention Type
Drug

Phase
Not Specified

Drug/device/biological/vaccine name(s)
Cefotaxime, paracetamol

Primary outcome measure
Current primary endpoints as of 22/01/2008:
1. Death (measuring the exact time from institution of antimicrobial) OR severe neurological

sequelae (blindness, quadriplegia, hydrocephalus requiring a shunt, or severe psychomotor retardation) at discharge
2. Profound hearing loss (more than 80 dB in both ears) at discharge

Previous primary endpoints:
1. Death (measuring the exact time from institution of antimicrobial)
2. Severe neurological sequelae (blindness, quadriplegia, hydrocephalus requiring a shunt, or severe psychomotor retardation)
3. Profound hearing loss (more than 80 dB in both ears), as found at discharge from hospital and dismal outcome denotes death, severe neurological sequelae and/or profound hearing loss.

Because severe neurological sequelae and death may form a continuum, their combination is taken as a composite endpoint. Various patient characteristics are taken into account as covariates, those being essentially the age, etiology (pneumococcus, Hib, meningococcus, other agents, and unidentified etiology), blood hemoglobin level, potential HIV- and/or malaria-infection, and the presenting status. This is graded by Glasgow Coma Scale (adjusted for age), the Blantyre Coma Scale, and the Herson-Todd Score. Also blood hemoglobin concentration will be related to the outcome, which is assessed with the modified Glasgow Outcome Scale.

Secondary outcome measures
Current secondary endpoints as of 22/01/2008:
1. Death or any audiological or any neurological sequelae: any neurological sequelae are, in addition to severe neurological sequelae : hemiparesis, monoparesis moderate psychomotor retardation, or ataxia. Psychomotor retardation is graded by (according to the Denver-II developmental screening test). Hearing is deemed impaired if a threshold of 40 dB remains unrecognized by the better ear, the cut-off levels for moderate and severe hearing impairment being 60 dB and 80 dB, respectively
2. Glasgow Outcome Scale
3. Potential differences in the indices of inflammation such as serum C-reactive protein (CRP) will also be examined

Previous secondary endpoints:
The secondary endpoints comprise any audiological or neurological sequelae (according to the Denver-II developmental screening test). Hearing is deemed impaired if a threshold of 40 dB is not recognized by the better ear. The cut-off levels for moderate and severe hearing impairment are 60 dB and 80 dB, respectively. Potential differences in the indices of inflammation such as serum C-Reactive Protein (CRP) will also be examined.

Overall study start date
27/06/2005

Completion date
30/12/2008

Eligibility

Key inclusion criteria
[Added as of 22/01/2008: All children aged at least 2 months with suspected or confirmed bacterial meningitis.]

Diagnosis:
BM is defined as a case with:
1. Positive CSF culture, or
2. Symptoms and signs compatible with bacterial meningitis, and positive blood culture, or
3. Symptoms and signs compatible with bacterial meningitis, and at least two of the following criteria:
3.1. CSF pleocytosis more than or equal to 100 cells/mm^3
3.2. A positive Gram-stain result
3.3. Positive latex agglutination test
3.4. Serum C-Reactive Protein (CRP) more than or equal to 40 mg/l, or
4. Symptoms and signs compatible with bacterial meningitis, and positive CSF antigen detection by Polymerase Chain Reaction (PCR)

Participant type(s)
Patient

Age group
Child

Lower age limit
2 Months

Sex
Both

Target number of participants
750 (No. of patients enrolled 05/10/07: 600)

Key exclusion criteria
The exclusion criteria comprise the age less than two months, trauma, or relevant underlying illness such as intracranial shunt, previous neurological disease (cerebral palsy, Down's syndrome, meningitis), previous hearing impairment if known, and immunosuppression, except Human Immunodeficiency Virus (HIV) infection.

Date of first enrolment
27/06/2005

Date of final enrolment
30/12/2008

Locations

Countries of recruitment
Angola

Finland

Study participating centre

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Sponsor information

Organisation
Luanda Hospital (Angola)

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Sponsor type
Hospital/treatment centre

Funder(s)

Funder type
Research organisation

Funder Name
The Pediatric Research Foundation (Finland)

Funder Name
Sigrid Juselius Foundation (Finland)

Funder Name
Helsinki University Central Hospital Research (Finland)

Results and Publications

Publication and dissemination plan
Not provided at time of registration

Intention to publish date

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	01/08/2011		Yes	No