Effect of procalcitonin-guided decision making on duration of antibiotic therapy in suspected early-onset neonatal sepsis: multicenter prospective randomized intervention study

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1. To decrease the proportion of infants treated with antibiotics for > 48 - 72 hours with possible or unlikely infection, with unchanged outcome. 2. To reduce the duration of antibiotic therapy

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

Summary

ID

NL-OMON39201

Source
ToetsingOnline

Brief title
NeoPInS

Condition

- Bacterial infectious disorders

Synonym
infection in newborns

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Brahms,de firma Brahms financiert de procalcitonine bepalingen

Intervention

Keyword: neonatal infection, procalcitonin

Outcome measures

Primary outcome

* The proportion of infants with a recurrence of infection requiring additional

courses of antibiotic therapy in the first month of life, within 72 hours

after ending antibiotic therapy (safety of study intervention)

* The absolute reduction of the duration of antibiotic therapy

Secondary outcome

* Mortality

* Duration of hospitalization

Study description

Background summary

Neonatal infections are important causes of morbidity and mortalitiy in the neonatal period. The diagnosis of neonatal infections is difficult, because clinical symptoms are often non specific and can be absent when the neonate has become infected just before birth. Current laboratory tests have low positive and negative predictive values. And cultures take 3 or more days for their outcome. A relatively new marker for infections in blood is procalcitonin (PCT). Multiple observational studies in neonates have been performed on the use of PCT as a parameter for bacterial infection in neonates. Compared to the conventional marker in blood for infection, CRP, sensitivity and specificity of PCT are higher in neonatal infection. Pitfall in the use of PCT during the

first days of life is the use of age-specific reference values in these neonates. The value of PCT as a marker for bacterial infection in neonates is complicated by a physiological increase of PCT during the first 3 days of life. After a peak value that is reached after 18-30 hours, PCT decreases and normalizes to reference values comparable to adults after 42-48 hours.

Based on data generated by a pilot single center intervention study in Switzerland on the use of PCT in neonatal infection, it was concluded that 1. PCT analysis is feasible in newborn infants 2. serial PCT determinations allowed to significantly reduce the duration of empiric antibiotic therapy in term and near-term infants with suspected early-onset sepsis, 3. the age-dependent PCT nomogram with a maximal threshold value of 10 ng/ml seemed to be reasonable, and 4. a multi-center study will be required to test the reliability of a PCT-based strategy in a larger cohort of neonates

To shorten the duration of administration of empiric parenteral antibiotics is important. Because of the high risk of not treating neonates with a bacterial infection, all neonates with any suspicion of infection are being treated for 7 days. Because the treatment consists of intravenously administered antibiotics, this means admission to the hospital for the neonate with separation of mother and child during these important first days of life. Furthermore is antibiotica-resitance caused by too much antibiotica prescription.

Study objective

1. To decrease the proportion of infants treated with antibiotics for > 48 - 72 hours with possible or unlikely infection, with unchanged outcome.
2. To reduce the duration of antibiotic therapy

Study design

A multi-center, prospective, open, randomized controlled intervention study in which serial PCT measurements will guide the treatment with intravenously administered antibiotics of neonates suspected of early-onset neonatal infection. Based on data of a pilot study in 120 neonates (60 neonates the PCT intervention arm and 60 neonates in the control arm) a poweranalysis has been performed. To answer the objectives of this study, with a power assumption of 80% and a duration of hospitalization in the pilot study of 5,4 days, 400 neonates should be enrolled.

Randomization:
Randomization will be to either a standard treatment based on conventional laboratory parameters (standard group) or to PCT-guided treatment (PCT group) blocked by center: Randomization by drawing group assignment cards in opaque sealed envelopes.

Laboratory parameters:
In both groups at t = 0 hours (= start antibiotics), t = 18-36 hours , t = 36-72 hours en 72-120 hours CRP and hematology screen will be done. In the PCT-group will be done an additional puncture at t = 12.
Based on riskfactors, clinical symptoms and results from conventional laboratory parameters, patients will be divided into 3 risk classification categories: 4. low risk (infection unlikely), 3. Intermediate risk (infection possible), 2. High risk (infection probable). 1. infection proven
The duration of antibiotic therapy in the standard group is based on the attending physician*s assessment of the probability of infection during hospitalisation: in category 1/2 patients, antibiotics are given for 7 - 21 days, in category 3 patients for 5 - 7 days and in category 4 patients for 2 - 3 days. In the PCT group, if infection is considered to be at low or intermediate risk, antibiotic therapy is discontinued when two consecutive PCT values are within the normal range. Antibiotic therapy can be continued despite fulfilled PCT criteria at the discretion of the attending physician.

Intervention

The duration of antibiotic therapy in the standard group is based on the attending physician*s assessment of the risk classification during hospitalisation: in category 1/2 patients, antibiotics are given for 7 - 21 days, in category 3 patients for 5 - 7 days and in category 4 patients for 2 - 3 days. In the PCT group, if infection is considered to be at low or intermediate risk, antibiotic therapy is discontinued when two consecutive PCT values are within the normal range. Antibiotic therapy can be continued despite fulfilled PCT criteria at the discretion of the attending physician.

Study burden and risks

The burden is minimal, because only one extra time point for blood drawing will be done, only in the PCT-group. For the other time points no additional diagnostic procedures are needed. The additional burden consists of a couple of extra blood drops during routine bloodsampling.

The estimated risk is low. There is a low risk on discontinuing antibiotic treatment too early, resulting in the development of a neonatal infection with its morbidity and mortality.

A pilot study with 120 neonates has been perfomed in Switserland (see the manuscipt that is in press in the scientific journal Neonatology, in the Research protocol, Appendix III). Based on follow-up data of this pilot study no mortality was observed. In two children antibiotic treatment was restarted. In one neonate because of respiratory insufficiency, this neonate was born at a gestational age of 35 6/7 weeks with a clinical surfactant deficiency that explains the respiratory insufficiency. The other neonate was restarted on

antibiotic treatment because of Ecoli found in tracheal aspirate. This study used the same age-dependent reference range values for procalcitonin as the current study will use.

Safety will be garanteed by the standard Dutch health system. This system is applicable for all neonates, as infection can also become apparent after the first three days of life. Parents and their neonates have 24 hours a day, 7 days a week access to medical help by their pediatricians. In addition, during the first week of life a nurse is assisting the mother and her baby at home. These nurses check basic medical parameters (temperature, heartrate, respiratory frequency, weight) on a daily basis and are trained in the observation of baby's to detect symptoms and signs of infection. Again, each and every neonate can develop an infection, also after the first 3 days of life.

To make parents of studyparticipants extra aware of the symptoms and signs of an infection and to facilitate seeking medical help even more, parents will receive, in addition to the routinely given oral information, a card upon discharge. This card will state when parents should contact a physician and how they can do that (Researchprotocol Appendix II).

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Children (2-11 years)

Inclusion criteria

Gestational age 34 weeks or more; 3 or less days old; suspected infection requiring empiric antibiotic therapy; parental informed consent

Exclusion criteria

Surgery before or during the study; severe malformations

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	13-04-2010
Enrollment:	1150
Type:	Actual

Ethics review

Approved WMO
Date: 17-11-2009

Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	07-04-2010
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	19-05-2010
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	09-06-2010
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	04-05-2011
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	17-08-2011
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	22-12-2011
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	21-03-2012
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO Date:	05-06-2012
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	25-09-2012
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	15-02-2013
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	18-04-2013
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	30-01-2014
Application type:	Amendment
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	NCT00854932
CCMO	NL29250.000.09

Study results

Date completed: 14-02-2016

Actual enrolment: 1071

Summary results

Trial is onging in other countries