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The administration of probiotic to premature babies to prevent infection, severe intestinal complication (i.e. necrotising enterocolitis) and death

Submission date
17/09/2009

Registration date
24/09/2009

Last Edited
07/09/2016

Recruitment status
No longer recruiting

Overall study status
Completed

Condition category
Neonatal Diseases

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

Plain English summary of protocol

Background and study aims
Babies born prematurely are at increased risk of episodes of bacterial infection, which can lead to longer hospital stay, long-term complications, and may be fatal. This is largely because preterm babies have immature defences against infection. An important way in which the body is protected is through the 'friendly bacteria' that normally thrive in our gut and promote its health. At birth there are few organisms in the gut and healthy babies who are nursed with their mothers quickly become colonised with their 'friendly' bacteria. Preterm babies who are separated from their mother at birth are more likely to become colonised with bacteria in the environment of the Neonatal Intensive Care Unit that may cause disease. We think that if we begin to give babies a few drops of liquid containing 'friendly bacteria' (probiotic) daily starting soon after birth that these bacteria will multiply in the intestine, improve the general health of the intestine and reduce the chance of potentially pathogenic (harmful) organisms becoming established. This should reduce the possibility of infection caused by organisms invading the bloodstream from the gut, and of severe complications such as necrotising enterocolitis, a serious condition of the gut. There is some evidence for the beneficial effects of probiotics but they have not been adequately tested in a study involving more than one hospital and including the babies at greatest risk. Probiotics do seem to be safe, but again more data are needed. The study will test whether a simple product containing a single probiotic bacterium prevents bloodstream infections and necrotising enterocolitis in preterm babies.

Who can participate?
Babies less than 48 hours old, who were born before 31 completed weeks of gestation

What does the study involve?
Babies are randomly allocated to be fed either the probiotic or a placebo (inactive substance). We then measure the following in both groups: episodes of infection, episodes of necrotising enterocolitis, deaths, growth, use of antibiotics, and length of hospital stay.

What are the possible benefits and risks of participating?
Not provided at time of registration

Where is the study run from?
Barts and the London School of Medicine and Dentistry (UK)

When is the study starting and how long is it expected to run for?
December 2009 to August 2013

Who is funding the study?
NIHR Health Technology Assessment Programme - HTA (UK)

Who is the main contact?
Prof. Kate Costeloe
kate.costeloe@homerton.nhs.uk

Contact information

Type(s)
Scientific

Contact name
Prof Kate Costeloe

Contact details
Barts and the London School of Medicine and Dentistry
Neonatal Unit
Homerton University Hospital
Homerton Row
London
United Kingdom
E9 6SR
-
kate.costeloe@homerton.nhs.uk

Additional identifiers

Clinical Trials Information System (CTIS)
2006-003445-17

Protocol serial number
HTA 05/501/04; BBG001 v 2

Study information

Scientific Title
The probiotic Bifidobacterium breve strain BBG-001 administered early to preterm infants to prevent infection, necrotising enterocolitis and death: a double-blind randomised placebo-controlled trial

Acronym
PiPS

Study objectives
Does early enteral administration to preterm infants, of the probiotic Bifidobacterium breve strain BBG started soon after birth, reduce the number of cases of:
1. Late onset (after 72 hours) blood stream infection
2. Necrotising enterocolitis (NEC), a serious condition of the gut
3. Death

More details can be found at: http://www.nets.nihr.ac.uk/projects/hta/0550104
Protocol can be found at: http://www.nets.nihr.ac.uk/__data/assets/pdf_file/0012/51213/PRO-05-501-04.pdf

Ethics approval required
Old ethics approval format

Ethics approval(s)
Oxfordshire REC A, 12/05/2009, ref: 09/H0604/30

Study design
Multi-centre double-blind placebo-controlled randomised trial

Primary study design
Interventional

Study type(s)
Prevention

Health condition(s) or problem(s) studied
Blood stream infection and necrotising enterocolitis in preterm infants

Interventions
The investigational product to be tested is Bifidobacterium breve strain BBG (B breve BBG). The product is supplied freeze dried with corn starch; the placebo is corn starch alone. Both products are manufactured in identical foil sachets each containing 1 gram of product.

The freeze dried powder is suspended, the starch allowed to settle and the supernatant administered to the baby. In order that the active product and placebo cannot be distinguished both are suspended in 3 ml 1/8 strength (1 scoop to 240 ml sterile water) of the elemental infant formula Neocate® and allowed to settle for 30 minutes. 1 ml of supernatant is withdrawn to be given to the baby; for the active product this contains 2.7 +/-0.5 X 10^9 colony forming organisms. The products are administered via a naso-gastric or oro-gastric tube or, for babies no longer tube fed, directly into the mouth using a syringe.

The intervention will be given once daily starting as soon as possible after randomisation and continuing until 36 completed weeks of post-menstrual age (36 weeks + 0 days) or death or discharge from hospital if sooner.

1,300 babies will be recruited over 30 months. The trial will have ended when the last recruited baby is discharged from hospital or dies.

Intervention Type
Biological/Vaccine

Primary outcome(s)
1. Any baby with an episode of blood stream infection, with any organism other than a skin commensal, diagnosed on a sample of blood drawn more than 72 hours after birth and before death or discharge from hospital. Skin commensals include coagulase negative staphylococci (CoNS) and Corynebacteria.
2. Necrotising enterocolitis, Bell stage II or III. Duration of follow-up: until discharge from hospital or death.
3. Death before discharge from hospital

Key secondary outcome(s))
1. Number of babies with the composite outcome of any or a combination of the 3 primary outcomes.

Microbiological outcomes:
Outcomes 2 to 7 are for samples taken more than 72 hours after birth and before death or discharge home:
2. Number of babies with any positive blood culture with an organism recognised as a skin commensal e.g. CoNS or Corynebacteria
3. Number of babies with blood cultures taken
4. Number of blood cultures taken per baby
5. Number of babies with episodes of blood stream infection with organisms other than skin commensals by organism: e.g. E.Coli, Klebsiella spp, fungi, and by antibiotic resistance types: specifically methicillin-resistant Staphylococcus aureus (MRSA), vancomycin resistant enterococci (VRE) and extended spectrum betalactamase producing Gram negative bacteria (ESBL)
6. Number of babies with isolates of organisms other than skin commensals from a normally sterile site other than blood: e.g. CSF, supra-pubic aspiration of urine, pleural cavity etc.
7. Number of babies with a positive culture of B breve BBG from any normally sterile site

Also:
8. Total duration of days of antibiotics and/or anti-fungals administered per baby after 72 hours and until death or discharge from hospital for treatment of suspected or proven sepsis i.e. excluding prophylactic use
9. The number of babies colonised with the administered probiotic strain defined by the isolation of B breve BBG from stool samples at 2 weeks post-natal and at 36 weeks post-menstrual age
10. Stool flora: the number of babies colonised with MRSA, VRE or extended spectrum betalactamase producing Gram negative bacteria (ESBL) at 2 weeks post-natal and at 36 weeks post-menstrual age

Nutritional and gastroenterological outcomes:
11. Age at achieving full enteral nutrition (defined as 150 ml/kg/day for 1 day)
12. Change of weight Z score from birth to 36 weeks post-menstrual age or discharge from hospital if sooner

Other clinical outcomes:
13. Broncho-pulmonary dysplasia. Duration of follow-up: until discharge from hospital or death.
14. Hydrocephalus and/or intraparenchymal cysts confirmed by cerebral ultrasound scan

performed during the baby's in-patient stay
15. Worst stage of retinopathy of prematurity in either eye at discharge or death
16. Length of stay in intensive, high dependency and special care (British Association of Perinatal Medicine (BAPM) 2001: definitions)

Completion date
31/08/2013

Eligibility

Key inclusion criteria
1. Both males and females, born before 31 completed weeks of gestation, i.e. up to and including 30 weeks + 6 days by the best estimate of Expected Date of Delivery (usually by first trimester antenatal ultrasound, alternatively calculated from the first day of the last menstrual period [LMP])
2. Less than 48 hours old
3. With written informed parental consent
4. Babies already on antibiotics for suspected or proven infection are eligible for recruitment to the study

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Neonate

Sex
All

Key exclusion criteria
1. A lethal congenital abnormality known at trial entry
2. Any known gastrointestinal malformation
3. No realistic prospect of survival

Date of first enrolment
01/12/2009

Date of final enrolment
31/08/2013

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Barts and the London School of Medicine and Dentistry
London
United Kingdom
E9 6SR

Sponsor information

Organisation
Queen Mary, University of London (UK)

ROR
https://ror.org/026zzn846

Funder(s)

Funder type
Government

Funder Name
Health Technology Assessment Programme

Alternative Name(s)
NIHR Health Technology Assessment Programme, Health Technology Assessment (HTA), HTA

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	13/02/2016		Yes	No
Results article	results	01/08/2016		Yes	No
HRA research summary			28/06/2023	No	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Study website	Study website	11/11/2025	11/11/2025	No	Yes