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A novel human milk fortifier derived from donkey milk for the nutrition of preterm or low-weight newborns

Submission date
01/05/2017

Recruitment status
No longer recruiting

Registration date
10/05/2017

Overall study status
Completed

Last Edited
07/07/2025

Condition category
Neonatal Diseases

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

Plain English summary of protocol

Background and study aims
Fortification of human milk is a standard practice in Neonatal Intensive Care Units for feeding very low birth weight infants (VLBWI). However, preterm infants often still experience suboptimal (low) growth and feeding intolerance. New fortification strategies and different commercially available fortifiers have been developed over the years, and are being constantly improved. Commercially available fortifiers are a blend of ingredients from different sources, including plant oils and cow's milk proteins, and contain different levels of nutrients to human milk. Donkey milk has been recently suggested as a valid alternative for children allergic to cow's milk due to its similarity to human milk. Donkey milk could therefore be a suitable ingredient for developing a new human milk fortifier for very low birth weight infants and preterm newborns. The aim of the study is to assess feeding tolerance, growth and short- and long-term outcomes in preterm infants fed with a new fortifier and protein supplement made from donkey milk, in comparison to infants fed with a traditional fortifier and protein supplement made from cow's milk.

Who can participate?
Very low birth weight/preterm infants (gestational age less than 32 weeks, or birthweight less than 1500 g)

What does the study involve?
Newborns are randomly allocated to be fed with a fortifier and protein supplement made from either cow's milk or donkey milk for a minimum of 21 days (if necessary, fortification is continued after this period using the same type of product). Feeding tolerance, growth and short-term outcomes are assessed at the start of the study and at 7, 14 and 21 days, and long-term outcomes are assessed at 6, 12 and 18 months.

What are the possible benefits and risks of participating?
This is the first study in which a protein concentrate made from donkey milk is given to preterm

newborns. This could improve feeding tolerance and growth. Participation in the study will not involve any health risk to infants. Standard clinical practices will be applied. The only difference will be the kind of fortification used.

Where is the study run from?
University of Turin (Italy)

When is the study starting and how long is it expected to run for?
January 2014 to January 2018

Who is funding the study?
1. Compagnia di San Paolo (Italy)
2. Regione Piemonte (Italy)

Who is the main contact?
1. Dr Alessandra Coscia (scientific)
2. Prof. Enrico Bertino (public)
3. Dr Francesco Cresi (scientific)
4. Dr Laura Cavallarin (scientific)

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Additional identifiers

Protocol serial number
P/001-2017

Study information

Scientific Title
Randomized controlled clinical trial in single-blind to evaluate the nutritional adequacy of a novel human milk fortifier derived from donkey milk for the nutrition of preterm or low-weight newborns

Acronym
Fortilat-Study

Study objectives
Feeding Very Low Birthweight newborns according to ADJ fortification principles, with human milk fortified by a protein supplement and a multi-component supplement (both derived from donkey milk), will improve the nutritional tolerance and the clinical, metabolic, neurological and auxological outcome at short- and long-term.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Ethics Committee of Città della Salute e della Scienza di Torino Board Affiliation: Città della Salute e della Scienza di Torino, 11/03/2014, ref: 0025847

Study design
Single-center single-blind randomized controlled clinical trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Enteral nutrition in very low birthweight infants

Interventions
Starting from the first fortifier administration, i.e., after reaching an enteral feeding ≥ 80ml/kg /d, newborns included in the trial will be randomized 1:1 by a software-generated list to the following groups:
Group 1: ADJ Fortification with multi-component fortifier (FM85 Nestlè) and protein concentrate (Protifar Nutricia) derived from bovine milk for a minimum of 21 days (if necessary, fortification will be continued after this period using the same type of product)
Group 2: ADJ Fortification with multi-component fortifier and protein concentrate derived from donkey milk (not commercially available, prepared according to cGMP criteria) for a minimum of 21 days (if necessary, fortification will be continued after this period using the same type of product).

The experimental products were produced by ultrafiltration of pasteurized donkey milk in a pilot stainless steel plant by using polyacrylonitrile membrane. Retentate from the ultrafiltration processes were then pasteurized and aseptically lyophylized and packed, and underwent to the required analyses to ensure compliance to the Regione Piemonte legislation. The products are stored at -80°C until used.

A nutrition protocol following the criteria of ADJ fortification has been established to ensure that fortification advancement is consistent for all study participants. Since the protein concentration and energy content of the bovine milk based products differ from the donkey milk based products, the amounts of powder required to obtain the same level of fortification are different depending on the product in use. Advancing of enteral feeds is strictly regulated according to the feeding protocol adopted in the NICU, based on the evaluation of signs of feeding intolerance. The criteria for hospital discharge are uniform, i.e., satisfactory weight gain while receiving full oral feeding, maintenance of adequate thermal stability and resolution of acute medical conditions.

Sample size
The sample size has been determined based on the occurrence of primary endpoint (at least one episode of interruption of enteral feeding longer than 8 hours). Based on the data available in the NICU from the population of VLBWI or preterm infants, about 45% of infants present at least one interruption of enteral feeding longer than 8 hours. In the hypothesis that the use of a better tolerated fortifier causes a 25% reduction in the frequency of the primary endpoint, and setting the risk of type I errors and the power at the usual 5 and 80%, 62 newborns per group have been considered as required.

Statistical analysis
At the end of the recruitment, the occurrence of the primary endpoint will be evaluated on the

intention-to-treat population (all randomized infants). The comparison between the two study groups will be performed with the exact Fisher test. For secondary endpoints, the comparison will be made using appropriate generalized linear models. The difference between the treatments concerning the variation of the anthropometric indices, expressed as SDS (standard deviation score) will be performed with a repeated measures model.

Intervention Type
Supplement

Primary outcome(s)
Occurrence of at least one episode of alimentary intolerance, defined as the necessity to interrupt enteral feeding for more than 8 consecutive hours during the study period from T0 to T3 (day 21)

Key secondary outcome(s))
1. Short-term outcome measures:
1.1. Number of alimentary intolerance episodes, measured using clinical protocol focused on feeding tolerance every day during observational period (T0-T3)
1.2. Number of feeding interruption episodes (even for periods shorter than 8 hours) , measured using clinical protocol focused on feeding tolerance every day during observational period (T0-T3)
1.3. Total hours of enteral feeding interruption, measured using clinical protocol focused on feeding tolerance every day during observational period (T0-T3)
1.4. Time required to reach full enteral feeding (150 ml/kg/d of enteral feeding), measured using evaluation of clinical records at discharge
1.5. Variation of anthropometric indices (weight, length and cranial circumference), measured using weight, length, cranial circumference scale during the study period and at 40 ± 1 weeks of postmenstrual age
1.6. Hospitalization duration, measured using evaluation of clinical records at discharge

2. Clinical indices, measured using clinical evaluation at discharge:
2.1. Necrotizing enterocolitis (NEC), classified following Bell stages
2.2. Suspected or diagnosed sepsis
2.3. Death

3. Analytical parameters, measured using specific tests conducted in laboratory analysis:
3.1. Calcium, phosphorus, alkaline phosphatase, BUN, creatinine and albumin, measured at T0, T1, T2 and T3
3.2. Amino acid profile in plasma and urine, measured at T0 and T3
3.3. Indices of metabolic acidosis (pH, BE, bicarbonates), measured at T0, T1, T2 and T3

4. Gastic emptying time, assessed using echography at T3 in patients with GERD symptoms
5. Gastroesophageal reflux, assessed using pH-impedance monitoring at T3 in patients with GERD symptoms
6. Urinary metabolomic profile, measured using NMR metabolomics at T0 and T3
7. Faecal analysis (calprotectin), measured using specific tests conducted in laboratory analysis at T0 and T3
8. Occurrence of other pathological events, measured using clinical evaluation during the study period from T0 to T3

9. Long-term outcome measures:
9.1. Auxological outcome (weight, length, cranial circumference), measured using weight, length, cranial circumference scale at 6, 12 and 18 months
9.2. Neuroevolutionary outcome, tested according to Griffiths scale at 18 months

T0: before starting the fortification
T1: day 7 after beginning the fortification (if level 3 of ADJ fortification) or as soon as level 3 is reached
T2: day 14 since beginning of fortification
T3: day 21 since beginning of fortification

Completion date
01/01/2018

Eligibility

Key inclusion criteria
1. Gestational age < 32 weeks, or birthweight < 1500 grams
2. Feeding with human milk (fresh or donor) > 80% of the total
3. Enteral feeding ≥80ml/kg/d of human milk reached within the first 4 weeks of life
4. Informed consent by a parent

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Neonate

Sex
All

Key exclusion criteria
1. Severe gastrointestinal pathologies (diagnosed or suspect necrotizing enterocolitis, colostomy, intestinal obstruction, symptoms of peritonitis, presence of blood in the feces)
2. Chromosomal abnormalities or major malformations
3. Hereditary metabolic pathologies
4. Intravascular disseminated coagulation (IDC), shock
5. Patent Ductus Arteriosus (PDA) requiring medical care or surgery
6. Severe renal insufficiency (serum creatinine > 2 mg/dl)

Date of first enrolment
27/11/2014

Date of final enrolment
22/12/2016

Locations

Countries of recruitment
Italy

Study participating centre
Neonatology and Neonatal Intensive Care Unit, Città della Salute e della Scienza di Torino, Ospedale S. Anna, Department of Public Health and Pediatrics, University of Turin
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Sponsor information

Organisation
SC Neonatologia, University of Turin

ROR
https://ror.org/048tbm396

Funder(s)

Funder type
Research organisation

Funder Name
Compagnia di San Paolo

Alternative Name(s)
San Paolo Company, San Paolo Company Foundation, Compagnia San Paolo, Fondazione Compagnia di San Paolo, CSP, FCSP

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
Italy

Funder Name
Regione Piemonte (FORTILAT project - Call "Poli di Innovazione", Por-Fesr 2007-2013 Program)

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request from Dr Chiara Peila (chiara.peila@gmail.com).

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	01/01/2019		Yes	No
Results article	follow results at 18 months	03/12/2020	14/06/2023	Yes	No
Results article	gastroesophageal reflux additional results	18/07/2020	14/06/2023	Yes	No
Results article	metabolomic profile results	27/07/2020	14/06/2023	Yes	No
Results article	neurodevelopmental outcome at 18 months	11/12/2020	14/06/2023	Yes	No
Results article	Effects on gastroesophageal reflux	18/07/2020	07/07/2025	Yes	No
Protocol article	protocol	09/01/2018		Yes	No
Participant information sheet		08/05/2017	01/04/2019	No	Yes
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes