ISRCTN17847514 https://doi.org/10.1186/ISRCTN17847514

Clinical effects of breast milk on enema-induced meconium evacuation in super premature infants and preterm infants

Submission date
26/08/2019

Recruitment status
No longer recruiting

Registration date
14/09/2019

Overall study status
Completed

Last Edited
29/04/2024

Condition category
Neonatal Diseases

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

Plain English Summary

Background and study aims
According to estimates, 15 million premature births occur every year worldwide. Delayed action of full enteral nutrition (via the digestive system) in preterm infants is closely associated with an increase in morbidity and mortality. Delayed meconium (feces composed of materials ingested during the time the infant spends in the uterus) evacuation is a recognized cause of intestinal dysfunction, which can cause delayed feeding, gastric retention, and feeding intolerance in preterm infants. Moreover, viscous meconium causes functional blockage of the intestines and abnormal gastrointestinal functions. The younger the gestational age of premature infants, the later and longer the meconium evacuation. Studies have shown that early meconium evacuation improves feeding intolerance and promotes weight gain.
Currently, the widely used strategies for inducing meconium evacuation worldwide are glass rod stimulation of the rectum, enema with formulations and oral intake of glucosamine (Gastrografin). Among them, enemas are the most commonly used approach. The formulations used for enemas include solutions (including physiological saline, glycerin, and diatrizoate) and suppositories (mainly glycerin). Glucosamine, a formulation for meconium evacuation that has emerged in recent years, is a gastrointestinal contrast agent that can be administered orally or rectally and has a hyperosmotic effect. However, the effects of glucosamine in meconium evacuation remain controversial. Glycerin solutions and glycerol suppositories have been widely used abroad as enema formulations, although a meta-analysis has suggested that the effects of glycerol solutions or glycerol suppositories in preterm infants are unclear. Saline is the most widely used formulation, but a systematic review has shown that saline does not shorten the total feeding time of preterm infants.
Because the effects of the above commonly used enema formulations are controversial, identifying a new enema formulation is necessary to increase meconium evacuation in premature infants. Studies have shown that breast milk has appropriate osmotic pressure and high safety in stimulating the digestive tract in infants. Therefore, we aimed to explore whether a breast milk-based enema might shorten the time of the last meconium evacuation and the time to achieve full enteral feeding in super premature infants and preterm infants.

Who can participate?
Super premature infants 23W ≤ gestational age <28W; Preterm infants 28W ≤ gestational age <30W

What does the study involve?
If the participants' parents voluntarily agree to their child's participation in the study, the researcher will contact them and confirm at the recruitment location. Parents of participants who meet the inclusion criteria will be required to sign an informed consent. Participants will be randomized to the intervention and control group. The control group will receive saline, and the intervention group will receive breast milk for meconium evacuation. Data collection locations are carried out at Shengjing Hospital of China Medical University. The data was obtained by standardized questionnaires and measurement.

What are the possible benefits and risks of participating?
The results of this study will help shorten the time of the last meconium evacuation and the time to achieve full enteral feeding in super premature infants and preterm infants.
The laxative process may make the participants feel uncomfortable.

Where is the study run from?
The BMEIMEPI study is being run by Shengjing Hospital of China Medical University.

When is the study starting and how long is it expected to run for?
June 2019 to October 2022 (updated 03/09/2020, previously: September 2020)

Who is funding the study?
Investigator-initiated and funded.

Who is the main contact?
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Contact information

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Scientific

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
Nil known

Study information

Scientific Title
Clinical effects of breast milk on enema-induced meconium evacuation in super premature infants and preterm infants: a randomized controlled trial

Acronym
BMEIMEPI

Study hypothesis
A breast milk-based enema will shorten the time of the last meconium evacuation and the time to achieve full enteral feeding in super premature infants and preterm infants

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 06/06/2019, Shengjing Hospital of China Medical University Medical Ethics Committee (Shengjing Hospital of China Medical University, 36 SanHao Street, Heping District, Shenyang, 110004, China; 86-24-96615-10027; wangh3@sj-hospital.org), ref:2019PS503K

Study design
A single-center randomized controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details below to request a patient information sheet

Condition
Super Premature Infants and Preterm Infants

Interventions
We will recruit 294 eligible subjects and stratify them into three groups according to gestational age. The study subjects will be assigned to the intervention group and the control group through block randomization with a 1:1 ratio. The groups will be as follows:
1. 23W ≤ gestational age <28W
2. 28W ≤gestational age <29W
3. 29W ≤ gestational age <30W
with 39, 54, and 54 infants, respectively.

Subjects in the control group will receive a saline enema, and subjects in the intervention group will receive a breast milk enema. The specific procedures will be as follows:
1. Meconium evacuation time: subjects in both the intervention group and the control group will undergo meconium evacuation twice per day at 9:00 and 21:00.
2. Preparation of materials: silicone tube [model 3.33mm (F10)], 5 ml syringe, thermostat (temperature setting 37°C), sesame oil, sterile gloves.
3. Implementation: Subjects in the treatment group and the control group will receive different enema formulations through identical methods. The nursing personnel will have consistent training in rectal injection operation to ensure identical operation procedures without causing damage to the anus and rectum, while ensuring the injection of fluids.
A. Breast milk and saline for the treatment group and the control group will be preheated to 37° C in a water bath thermostat.
B. The amount of enema fluid for the infant will be 5 ml/kg, and the required enema amount will be calculated.

C. The preheated enema solution will be extracted through a syringe (5ml) and connected to a silicone tube [4-6cm, model 3.33 mm (F10)]. The entire silicone tube will be lubricated with edible sesame oil and gently inserted 2-3cm into the rectum. A low volume solution will be injected first and then moved forward by insertion into the rectum with pushing. The movement should be performed gently. After the push is completed, the enema solution will be retained for 3 minutes in the rectum, and then the silicone tubing will be slowly withdrawn. This method will be extended until the meconium is fully evacuated.
4. If discharge is not available for 24 hours after meconium evacuation, the same procedure will be repeated once per day.

During the study period, the same feeding and parenteral nutrition schedules will be used for infants in both groups.
Intravenous amino acid infusion (1.5 g per kg) will start immediately after birth, and this infusion will increase to 3g per kg per day for the next 48 hours. Intravenous injection of lipids will start on the second day after birth with 1.5g per kg per day, and the target will be 3g per kg per day. The glucose infusion will start at 5mg per kg per min. The energy intake goal is total daily enteral nutrition and parenteral nutrition of 116-131 kcal per kg. Feeding will begin within two days after birth unless the patient has hypotensive blood pressure and must use a vasopressor. The initial milk volume will be 24 ml per kg per day, and breastfeeding will be encouraged. The daily feeding amount will be gradually increased by 20 ml per kg when the infant condition stabilizes. Feeding should be stopped when feeding intolerance appears (on the basis of a difference in the amount and nature of the residual liquid in the stomach before feeding; a residual liquid amount greater than one-half of the current feeding amount; an increase in abdominal circumference by more than two cm, on the basis of consecutive measurements twice before milk feeding; and abnormal intestinal motility; any one of these factors can be used in diagnosis of feeding intolerance).
When the daily feeding amount reaches 50-60 ml per kg, a breast milk fortifier will be added. When the amount of enteral feeding reaches 120 ml per kg per day, intravenous infusion of amino acids and lipids will be stopped. When the glucose plasma level is normal, the intravenous glucose infusion will be gradually decreased and stopped.

Intervention Type
Other

Primary outcome measure
1. Time from birth to the last meconium evacuation:
This trial will use the standard infant meconium evacuation form. Nursing personnel will be trained to correctly identify the infant’s meconium, transitional meconium, and normal feces. Detailed information on the evacuation and characteristics of each meconium will be recorded, and questionable meconium photos will be recorded and discussed in group meetings.
2. Time to achieve total enteral feeding in super premature infants and preterm infants (when the infant tolerates a volume of 180 ml/kg/day for at least 24 h or undergoes weight gain greater than 20-25 g/d in 24 h)

Secondary outcome measures
1. Stage II or III necrotizing enterocolitis (NEC, Bell standard)
2. Hospitalization days
3. Body weight at discharge
4. Duration of total parenteral nutrition
5. Cholestasis, measured 2 weeks after birth in two groups:
5.1 Serum binding bilirubin concentration > 1.0 mg/dL (17.1 mmol/L)

5.2 Serum total bilirubin < 5.0 mg/dL (85.5 mmol/L) or >20%
5.3 Total bilirubin concentration >5.0 mg/dL (85.5 mmol/L)
6. Any adverse events reported: nosocomial infection, nosocomial death, retinopathy of prematurity (ROP, any stage), chronic lung disease (CLD), requirement of ventilatory support or oxygen after a corrected gestational age of 36 weeks , intraventricular hemorrhage (IVH, grade 2 and above), bronchopulmonary dysplasia (BPD), late-onset sepsis (LOS), diarrhea, colon perforation, malabsorption, rectal bleeding, and rectal trauma

Overall study start date
20/02/2019

Overall study end date
31/10/2022

Eligibility

Participant inclusion criteria
1. Super premature infants 23W ≤ gestational age <28W and Preterm infants 28W ≤ gestational age <30W
2. Mother provides breast milk 48 hours after birth
3. Normal intestinal motility (as assessed by the team of clinical experts)
4. Parental agreement to participate in the study

Participant type(s)
Patient

Age group
Neonate

Sex
Both

Target number of participants
294

Total final enrolment
286

Participant exclusion criteria
1. Congenital digestive tract abnormalities, such as congenital gastrointestinal dysfunction
2. Congenital malformations, gastrointestinal malformations, such as rectal anal deformities
3. Abnormal hemodynamics, such aspoor intestinal motility, diarrhea, intussusception, and necrotizing enterocolitis (NEC)
4. Anorectal mucosal injury
5. Surgery within 48 hours after birth
6. Severe coagulopathy:
6.1 International standardization ratio >1.4
6.2 Partial thromboplastin time >39s
6.3 Fibrinogen <1.00g/L
6.4 Platelet count <100×109/L

7. Sepsis, symptomatic patent ductus arteriosus (PDA)
8. Neutropenia (absolute number of neutrophils <0.5×109/L)
9. Blood incompatible hemolytic disease of the newborn, requiring immediate blood exchange
10. Mother with severe disease or using medicine that is contraindicated during lactation
11. Researchers to exclude anyone that they felt would not be a good trial participant

Recruitment start date
20/09/2019

Recruitment end date
30/09/2022

Locations

Countries of recruitment
China

Study participating centre
Shengjing Hospital of China Medical University
36 SanHao Street
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Sponsor information

Organisation
Shengjing Hospital of China Medical University

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Sponsor type
Hospital/treatment centre

ROR
https://ror.org/0202bj006

Funder(s)

Funder type
Other

Funder Name
Investigator initiated and funded

Results and Publications

Publication and dissemination plan
Planned publication in a high-impact peer reviewed journal

Intention to publish date
30/11/2022

Individual participant data (IPD) sharing plan
The current data sharing plans for this study are unknown and will be available at a later date

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		26/04/2021	28/04/2021	Yes	No
Results article		01/04/2024	29/04/2024	Yes	No