

Original Article

Warm saline enema and probiotics to promote feeding tolerance in preterm infants - a preliminary study

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Abstract: Feeding intolerance is associated with morbidity and mortality in preterm infants. Probiotics could improve feeding tolerance in those infants. This study aimed to examine the benefits and adverse effects of saline enema and probiotics on feeding tolerance and short-term outcomes of preterm infants. This was a retrospective study of consecutive infants (Shanghai Children's Hospital, 01/2013-06/2015). The infants were grouped as control (routine management), saline enema, probiotics, and saline enema + vprobiotics. The primary endpoint was postnatal age when achieving full enteral feeding. The secondary outcomes were postnatal age to regain birth weight, age at achieving a weight of 2500 g, complications, proportion of infants in whom feeding was withheld for any reason, age at meconium passage, and age at discharge. Compared with controls, the infants in the three treatment groups achieved full enteral feeding faster (median, 11.6 vs. 11.7, 11.3 and 14.7 days; $P = 0.022$), passed meconium significantly faster (median, 4.9, 4.9 and 4.5 vs. 8.3 days; $P < 0.001$), and regained birth weight faster (median, 7.8 vs. 6.5, 6.4 and 5.4 days, $P < 0.001$), but there were no difference among the saline enema + probiotics, saline enema, and probiotics groups. The frequencies of feeding intolerance (14.9%, 23.5% and 14.5% vs. 48.6%; $P < 0.001$) and necrotizing enterocolitis (4.5%, 5.7% and 4.2% vs. 27.0%, $P < 0.001$) were lower in the three study groups. There was no difference in sepsis ($P = 0.33$). In conclusion, saline enema and probiotics, either alone or together, had a significant positive effect on promoting feeding tolerance in preterm infants.

Keywords: Preterm infants, enteral feeding, feeding intolerance, meconium passage, saline enema, probiotics

Introduction

An appropriate nutrition plays a crucial role in the health care of preterm infants. Sufficient energy intake is essential to limit growth retardation and ensure stable metabolic homeostasis in the very early days of their lives [1]. Extrauterine growth retardation is a major problem in preterm infants [2]. Of course a number of factors affect the growth of those children (such as neurological damage, endocrine immaturity, drugs affecting metabolism, lack of sucking/swallowing coordination), but inadequate nutrition is nevertheless considered as the most important one [1, 3]. Malnutrition may lead to deficits in behavior, learning, and memory [4].

The nutritional management of preterm infants is complex. The goal of nutrition is to provide the infant with enough nutrient to allow postnatal growth to reach a weight approximately that

of a normal fetus of the same age and to maintain normal blood concentrations of nutrients [5]. The management include three stages: 1) early aggressive nutrition during the acute stage; 2) fortified human milk or preterm formula when slowly advancing toward full enteral nutrition; and 3) post-discharge stage [5].

Feeding intolerance is a state in which the infant is unable to digest enteral feeding, as shown by increased gastric residuals, abdominal distension, and/or vomiting [6]. Because of the physiological immaturity of the gastrointestinal (GI) system, GI dysmotility, perinatal intestinal hypoperfusion, infection, and GI dysbacteriosis can contribute to feeding intolerance, leading to delays in achieving full enteral feeding [6]. Feeding intolerance is closely associated with extrauterine growth retardation and poorer neurodevelopment in preterm infants [6-9].

A number of feeding strategies have been tried to prevent feeding intolerance in preterm infants, such as feeding human milk, prolonged small feeding volumes, early initiation of enteral feeding, and the use of probiotics [10]. Nevertheless, no real gain in global management was achieved. Bowel dysfunction may be the most important factor causing feeding intolerance and meconium retention has become a recognized cause of bowel dysfunction [11]. Only about 37% of premature infants pass their first stool during the first 24 h, and 32% show delayed passage beyond 48 h [12]. Meconium retention often induces abdominal distension and may result in feeding intolerance [11]. Recently, a study showed that *Lactobacillus sporogenes* supplementation (350 million CFU/day) could improve feeding tolerance [13].

Our center began to use saline enema and probiotics in order to improve the feeding tolerance of preterm infants. Therefore, the aim of the present retrospective study was to examine the benefits and adverse effects of this approach on feeding tolerance and short-term outcomes of preterm infants.

Material and methods

Patients

This was a retrospective study of consecutive infants admitted to the preterm ward of the Neonatal Department of Shanghai Children's Hospital from January 2013 to June 2015. The study was approved by the ethics committee of the Shanghai Children's Hospital. The need for individual consent was waived by the committee because of the retrospective nature of the study.

The inclusion criteria were: 1) born at gestational age < 37 weeks; and 2) did not need mechanical ventilation. Gestational age was determined by ultrasound and the last menstrual period. When discrepancies were present using these two tools, a physical examination by the neonatologist was used to determine gestational age. The exclusion criteria were: 1) congenital malformation (including gastrointestinal or other systemic malformations); 2) genetic and metabolic diseases; 3) chromosomal disease; 4) surgical operation during hospitalizing; 5) necrotizing enterocolitis (NEC); 6) admitted after 1 day of age; 7) use of prokinetic agents; or 8) discharged before regaining birth weight.

Grouping

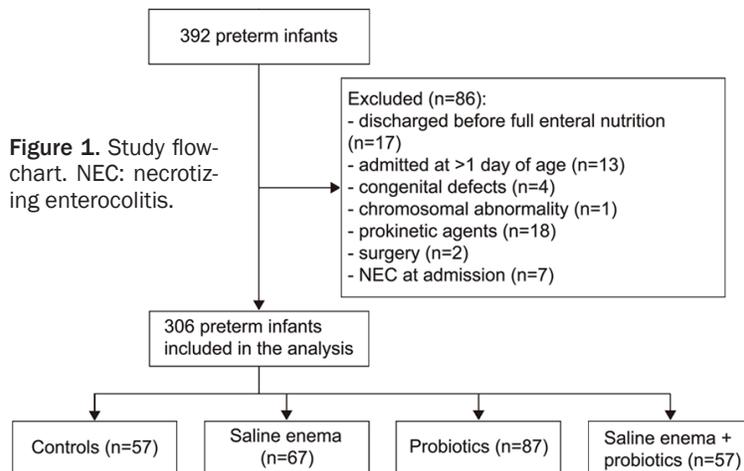
Patients were grouped according to the treatment they received during the study period: 1) control group: the infants received basic routine management; rectal stimulation was performed after 72 h without meconium passage and glycerin enema was used in cases of prolonged meconium passage failure; 2) saline enema group: saline enema was performed every morning at 7:00, using 5 ml/kg of saline (warmed at 37°C and instilled using a 6F Nelaton catheter cut to 5 cm and a syringe, with the tip placed at 1 cm above the anus) everyday within 24 h after birth until meconium passage was complete; after enema, abdominal clockwise massage was given for 2 min; 3) probiotics group: the infants were fed with a powder containing *Bifidobacterium*, *Lactobacillus acidophilus* and *Enterococcus* (Bifico, Xinyi Pharmaceutical, Shanghai, China) with a dose of 1.0×10^7 CFU/day with protein hydrolysate formula (Alfare, Nestle, Switzerland), starting on the first feed until discharge; and 4) saline enema + probiotics group: the patients received both saline enema and saline enema, as above.

All patients were managed using the same routine neonatal care by the same team. A stool occult blood test was performed once a day for a week after birth during the saline enema periods. When a complication such as rectal bleeding, positive occult blood, or aggravated medical instability was noted, saline enema was discontinued.

Nutritional approach

During the study period, the same nutrition protocol was routinely applied to all infants by the same assigned neonatologists (8 years of experience). Intravenous glucose (10-12.5%) and amino acid (started at 1 g/kg/d) infusion of 70 ml/kg/day was started immediately after birth. A percutaneous central venous catheter was placed on the first or second day after birth if the infant's birth weight was < 1500 g. Total parenteral nutrition (TPN) was started within 48 h of life, using 1.0 g/kg/d of amino acid and 0.5 g/kg/d of lipids, and this was increased at 1.0 g/kg/day up to 3 g/kg/day. Enteral feeding was started via an orogastric tube or nipple every 3 h as soon as the infants were stable. The initial feeding volume was 10 ml/kg/day. If tolerated, this volume was gradually increased by 10-20 ml/kg/day. If enteral intol-

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erance or medical instability, such as apnea, vomiting, gastric residuals, abdominal distension, abdominal tenderness, absent bowel sounds, blood in the stool, emesis, lethargy, irritability, temperature instability, sepsis, or findings of abdominal wall pneumatosis or bowel loops by X-rays, the volume was reduced or withheld. When the infants tolerated a volume of 180 ml/kg/day for at least 24 h, TPN was discontinued and fortification begun [5]. Then the percutaneous central venous catheter was removed.

Endpoints and complications

The primary endpoint was postnatal age when achieving full enteral feeding (100 kcal/kg/day). The secondary endpoints were postnatal age to regain birth weight, age at achieving a weight of 2500 g, complications, proportion of infants in whom feeding was withheld for any reason, age at meconium passage, and age at discharge. Complications and adverse events were recorded. Feeding intolerance was defined as symptoms like vomiting, gastric residuals, abdominal distension, abdominal tenderness, and impossibility to increase feeding volumes for 3 days [6, 14]. NEC as modified Bell's stage IIa or higher [15]. Sepsis was confirmed by bacterial culture of blood or of central venous catheters.

Statistical analysis

Continuous data were tested for normal distribution using the Kolmogorov-Smirnov test. Normally distributed continuous data were presented as mean \pm standard deviation and analyzed using ANOVA and the Tukey's post hoc

test. Non-normally distributed data were presented as median (range) and analyzed using the Wilcoxon test. Categorical data were presented as frequencies and analyzed using the Fisher exact test or Fisher exact test. SPSS 10.0 (SPSS Inc., Chicago, IL, USA) was used for analysis. Two-sided *P*-values < 0.05 were considered significant.

Results

Characteristics of the infants

During the study period, 392 preterm infants were admitted and 86 infants were excluded from the study: 17 infants were discharged before achieving full enteral nutrition, 13 were admitted at > 1 day of age, four had congenital defects, one had chromosomal abnormality, 18 had used prokinetic agents, two underwent surgery, and seven were diagnosed with NEC at admission. During hospital stay, 24 had missing data. Finally, 306 patients were included (187 males and 119 females) (**Figure 1**).

The infants were grouped according to the management they received. **Table 1** shows that the four groups were comparable in terms of gestational age, birth weight, and Apgar score (all *P* > 0.05).

Primary endpoint

Infants in the three treatment groups achieved full enteral feeding faster than the controls (median, 11.6, 11.7 and 11.3 vs. 14.7 days; *P* = 0.022), but there were no difference among the saline enema + probiotics, saline enema, and probiotics groups (**Table 2**).

Secondary endpoints

Infants in the three study groups passed meconium significantly faster than the control group (median, 4.9, 4.9 and 4.5 vs. 8.3 days; *P* < 0.001), but there were no difference among the saline enema + probiotics, saline enema, and probiotics groups. The patients in the control group struggled longer to regain birth weight (median, 7.8 vs. 6.5, 6.4 and 5.4 days, *P* < 0.001), but there were no difference among the saline enema + probiotics, saline enema, and probiotics groups (**Table 2**).

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Table 1. Characteristics of the infants

Variables	Controls N = 57	Saline enema N = 67	Probiotics N = 87	Saline enema + probiotics N = 95	P
Gestational age (weeks)	34.2 ± 2.0	34.2 ± 1.6	34.2 ± 1.8	34.0 ± 1.9	0.7096
Birth weight (g)	2056 ± 422	2201 ± 436	2124 ± 358	2097 ± 335	0.1766
Apgar score, 1 min	8.7 ± 1.4	8.3 ± 2.1	8.7 ± 1.6	8.8 ± 1.5	0.312
Apgar score, 5 min	9.4 ± 0.8	9.1 ± 1.3	9.3 ± 1.0	9.3 ± 1.0	0.5768

Table 2. Primary and secondary endpoints in the four groups

Variables	Controls N = 57	Saline enema N = 67	Probiotics N = 87	Saline enema + probiotics N = 95	P
Postnatal age when achieving full enteral feeding (days)	14.7 ± 10.0	11.3 ± 5.0*	11.7 ± 5.4*	11.6 ± 6.8*	0.02
Complete meconium passage (days)	7.0 ± 3.8	4.3 ± 2.1*	4.6 ± 1.4*	3.3 ± 1.4*	< 0.001
Postnatal days to regain birth weight (days)	8.7 ± 3.9	6.9 ± 2.6*	6.2 ± 2.4*	5.8 ± 2.7*	< 0.001

*P < 0.05 vs. controls.

Complications

Eleven infants developed sepsis. The pathogens in the control group were *Klebsiella pneumoniae* in one infant, *Enterococcus faecalis* in two, and *Acinetobacter baumannii* in one. In the saline enema group, one infant developed candidiasis, as well as one in the probiotics group. There was one case of *Escherichia coli* sepsis and one of *Klebsiella pneumoniae* sepsis in the probiotics group. In the saline enema + probiotics group, *Klebsiella pneumoniae* was identified in one infant and another had *Staphylococcus hominis* sepsis. There were no differences among the four groups (P = 0.3301). The frequencies of feeding intolerance (14.9%, 23.5% and 14.5% vs. 48.6%; P < 0.001) and NEC (4.5%, 5.7% and 4.2% vs. 27.0%, P < 0.001) were lower in the three study groups (Table 3).

Discussion

Feeding intolerance is associated with morbidity and mortality in preterm infants [6, 14]. It has been suggested that probiotics could improve feeding tolerance in these infants [13, 16]. Therefore, this study aimed to examine the benefits and adverse effects of saline enema and probiotics on feeding tolerance and short-term outcomes of preterm infants. The results suggest that saline enema can promote meconium evacuation and probiotics were able to establish intestinal microflora. These two approaches, either alone or together, had a significant positive effect on promoting feeding tolerance in preterm infants.

Feeding intolerance in premature infants is usually defined as the inability to digest enteral feeding, presenting gastric residual volume > 50% of the previous feeding volume, abdominal distension or emesis, or both, and the disruption of the patient's feeding plan [6, 7, 14, 17-19]. Feeding intolerance is the most common gastrointestinal problem in preterm infants and usually results in interrupted enteral nutrition [14]. Feeding intolerance is closely associated with extrauterine growth retardation and poorer neurodevelopment in preterm infants [6-9]. An increased length of time to full enteral feeding was significantly associated with poorer mental outcomes: infants who reach full enteral feeding at an earlier age appear to have a better developmental outcome despite their gestational age [20].

Although the etiology of feeding intolerance is still unclear, a number of contributing factors are known such as the immaturity of the gastrointestinal tract, delayed gastric emptying, immature digestion [18], mucoviscidosis of preterm meconium [21], hypoxic-ischemic injury, mucosal damage from free radicals [22], and stress-related factors [17]. In addition, feeding intolerance has some relation with the selected enteral nutrients [19].

Finding ways to promote and ensure early trophic feeding plays a key role in the nutrition support program in preterm infants. Promoting gastrointestinal motility in preterm infants may improve enteral feeding tolerance. Whether erythromycin can improve feeding intolerance safely and efficiently still needs to be evaluated.

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Table 3. Incidence of NEC and FI in the four groups

Variables	Controls N = 57	Saline enema N = 67	Probiotics N = 87	Saline enema + probiotics N = 95	P
FI, n (%)	27 (48.6)	10 (14.9)*	20 (23.5)*	14 (14.5)*	< 0.001
NEC, n (%)	15 (27.0)	3 (4.5)*	5 (5.7)*	4 (4.2)*	< 0.001
Sepsis, n (%)	4 (7.0)	1 (2.1)	2 (3.9)	1 (1.8)	0.3301

*P < 0.05 vs. controls. FI: feeding intolerance; NEC: necrotizing enterocolitis.

ed through large sample randomized controlled trials [23]. Cisapride is no longer used because of its adverse effect on the cardiovascular system (fatal arrhythmia) [24, 25]. Therefore, seeking safe and effective ways to improve premature infant gastrointestinal function is particularly important. Shim et al. [11] used glycerin enema to promote early discharge of meconium, through which very-low-birth-weight infants reached full enteral nutrition earlier, and with a reduced occurrence of sepsis.

The induction of early meconium evacuation using warm saline enema at our center was found to be effective at promoting feeding tolerance and its adoption was found to result in a shortening of the time required to achieve full enteral feeding in preterm infants. It was also found that induction of meconium passage can also reduce the incidence of feeding intolerance. A possible explanation is that warm saline enema dilutes the meconium and promotes intestinal peristalsis, thus accelerating meconium passage. Probiotics also seem to have similar effect on meconium passage. Although glycerin has been used to enhance meconium passage for a long time, it may lead to hyperosmolality and damage to bowel epithelial cells. For this reason, we selected warm saline as it is isotonic, inexpensive, and easy to obtain. During the study period, no complication related to the administration of warm saline enema was observed and no difficulties were reported during the procedure.

The intestinal microbiological flora is an important factor in the host-defense mechanism against bacterial infections [16]. Colonization of the intestine by pathogenic microorganisms may serve as a predisposing factor in the development of NEC [16]. A severe clinical manifestation of feeding intolerance may be an early sign of NEC [16]. A randomized controlled trial showed that infants fed with a supplement of *Bifidobacterium brevis* had higher rates of fecal *Bifidobacterium* colonization at 2 weeks of

age, improved weight gain, and better feeding tolerance [26]. Recently, a study showed that *Lactobacillus sporogenes* supplementation at 350 million CFU/day could improve feeding tolerance [13]. In the present study, the selected probiotics was Bifico, which contains fecal streptococci, *Lactobacillus acidophilus*, and *Bifidobacterium*. In the present study, compared with the control group, the patients who were fed probiotics achieved full enteral feeding earlier, and it seemed that less NEC or feeding intolerance happened in those two groups of patients, as supported by previous studies [26, 27].

Feeding challenges place vulnerable premature infants at risk of prolonged hospital stay and readmission after discharge. The earlier they achieved full enteral feeding, the shorter TPN they need, which means less associated complications such as endogenous sepsis, cholestasis, hepatic function lesion, and extrauterine growth retardation [5, 28]. Therefore, besides NEC and feeding intolerance, complications were also examined. In the present series, eight infants developed bacterial infection and one developed sepsis, but there were no differences among the four groups.

Certainly, this study has some limitations. It was a retrospective study, with all the inherent limitations. The sample size was small and from a single center. Despite promising results, additional studies are still necessary to improve the nutritional management of preterm infants.

Taken together, these results suggest that promoting meconium evacuation by using warm saline enema and establishing normal intestinal microflora contributed to earlier full enteral feeding, regained birth weight earlier, and could significantly reduce the frequency of feeding intolerance and NEC in preterm infants. The induction of meconium evacuation and establishing normal intestinal microflora had a significant positive effect on feeding tolerance in preterm infants.

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Disclosure of conflict of interest

None.

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