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Lactobacillus reuteri DSM 17938 Improves Feeding Intolerance in Preterm Infants

Risma K. Kaban,[1] **Wardhana**,[1] **Badriul Hegar**,[1] **Rinawati Rohsiswatmo**,[1] **Setyo Handryastuti**,[1] **Novie Amelia**,[1] **Dina Muktiarti**,[1] **Flavia Indrio**,[2] **and Yvan Vandenplas**[3]

[1]Department of Pediatric Health, Faculty of Medicine, Universitas Indonesia–Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia
[2]Department of Paediatrics, University of Bari, Bari, Italy
[3]KidZ Health Castle, UZ Brussel, Vrije Universiteit Brussel, Brussels, Belgium

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Correspondence to
Yvan Vandenplas
KidZ Health Castle, UZ Brussel, Vrije Universiteit Brussel, laarbeeklaan 101, 1090 Brussels, Belgium.
E-mail: yvan.vandenplas@uzbrussel.be

ORCID iDs
Risma K. Kaban
https://orcid.org/0000-0003-0345-0077
Wardhana
https://orcid.org/0000-0001-9499-0655
Badriul Hegar
https://orcid.org/0000-0002-5924-1664
Rinawati Rohsiswatmo
https://orcid.org/0000-0003-3467-4751
Setyo Handryastuti
https://orcid.org/0000-0001-6968-9780
Novie Amelia
https://orcid.org/0000-0001-6147-4179
Dina Muktiarti
https://orcid.org/0000-0002-0828-3354

ABSTRACT

Purpose: Feeding tolerance is extremely important in preterm infants. This study aimed to evaluate whether preterm infants receiving *Lactobacillus reuteri* DSM 17938 would develop fewer symptoms of feeding intolerance. Secondary outcomes were duration of parenteral nutrition, time to reach full feeding, length of hospital stay, sepsis, necrotizing enterocolitis (NEC), diarrhea, and mortality.
Methods: This double-blind randomized controlled trial of *L. reuteri* DSM 17938 versus placebo included 94 neonates with a gestational age of 28–34 weeks and birth weight of 1,000–1,800 g.
Results: Feeding intolerance (vomiting and/or distension) was less common in the probiotic group than in the placebo group (8.5% vs. 25.5%; relative risk, 0.33; 95% confidence interval, 0.12–0.96; p=0.03). No significant intergroup differences were found in proven sepsis, time to reach full feeding, length of hospital stay, or diarrhea. The prevalence of NEC (stages 2 and 3) was 6.4% in the placebo group vs. 0% in the probiotic group (relative risk, 1.07; 95% confidence interval, 0.99–1.15; p=0.24). Mortality rates were 2.1% in the probiotic group and 8.5% in the placebo group, p=0.36).
Conclusion: The administration of *L. reuteri* DSM 17938 to preterm infants was safe and significantly reduced feeding intolerance. No significant differences were found in any other secondary outcomes.

Keywords: *Lactobacillus reuteri*; Preterm; Feeding intolerance

INTRODUCTION

Probiotics are beneficial for commensal bacterial colonization and suppression of pathogenic bacterial colonization in the gastrointestinal tract. Probiotics increase the immunoglobulin A (IgA) response of the mucosal lining of the gastrointestinal tract, which reportedly improves the tolerance of enteral nutrition and regulates the immune responses [1-4]. The most commonly used probiotics are *Lactobacilli* and *Bifidobacterium* [5-9]. The administration

Flavia Indrio
https://orcid.org/0000-0002-0606-1360
Yvan Vandenplas
https://orcid.org/0000-0002-1862-8651

Conflict of Interest

FI has participated as a clinical investigator and/or advisory board member and/or consultant and/or speaker for Abbott, Biogaia, Danone, and Nestle Nutrition Institute. YV has participated as a clinical investigator and/or advisory board member and/or consultant and/or speaker for Abbott Nutrition, Biocodex, Danone, Nestle Health Science, Nestle Nutrition Institute, Nutricia, Mead Johnson, Phacobel, and United Pharmaceuticals.

of *Lactobacillus reuteri* DSM 17938 has been suggested to decrease feeding intolerance and sepsis and shortening hospital length of stay [10-14]. It is unclear whether *L. reuteri* decreases the incidence and severity of necrotizing enterocolitis (NEC) [10-12,15-17]. *L. reuteri* DSM 17938 is often chosen due to its safe and easy administration through a suspension given orally or through an orogastric tube. Adverse events rarely occur with the administration of *L. reuteri* DSM 17938 [16-20]. However, the administration of *L. reuteri* DSM 17938 in preterm infants has not been sufficiently studied. Kaban [21] showed that counts of commensal bacteria in the gastrointestinal tract in preterm infants were very low compared to those of pathogenic bacteria.

The aim of the study was to evaluate the effect of *L. reuteri* DSM 17938 on feeding intolerance in preterm infants.

MATERIALS AND METHODS

This double-blind randomized controlled clinical trial compared the oral administration of *L. reuteri* DSM 17938 or placebo to neonates with a gestational age of 28–34 weeks and a birth weight of 1,000–1,800 g in a stable condition allowing the administration of oral and enteral nutrition and was conducted at the Neonatology Unit, Department of Pediatric Health of the Dr. Cipto Mangunkusumo Hospital from January to October 2017. The exclusion criteria were absolute contraindications for feeding such as lower gastrointestinal tract obstruction, massive gastrointestinal tract bleeding, NEC, sepsis and shock, and refusal of the infants' parents to participate in the study. Dropout criteria were parents requesting discharge against medical advice and refusing participation after the intervention was started.

The study subjects were recruited through consecutive sampling by including every infant who fulfilled the inclusion criteria and met none of the exclusion criteria. The infants were then followed until discharge or the incidence of severe complications such as sepsis, NEC, or death. A total of 94 infants were needed (47 each in a probiotic group and a placebo group).

Subjects were allocated to the groups by a third party using a simple alternating randomization technique. The probiotic used in this study was *L. reuteri* DSM 17938 (Interlac) suspension. The dose administered was five drops per day, equivalent to 10^8 colony-forming units/day, the recommended dose. The placebo contains a mixture of pharmaceutical-grade medium-chain triglycerides and sunflower oil together with pharmaceutical-grade silicon dioxide to give the product the correct rheological properties.

The probiotic or placebo was given as soon as the neonate reached a stable condition i.e. could be orally or enterally fed breast milk and/or formula at least 40–50 mL/kg body weight. Subjects with a suspected infection (signs including lethargy, respiratory distress in need of mechanic ventilation) but normal septic screening laboratory values (complete blood count, peripheral blood count, C-reactive protein, immature-to-total ratio, and blood culture) were included in the study. The probiotic or placebo was administered as soon as the infant had two sequential feedings of 40–50 mL/kg body weight. The intervention was given for the duration of at least 7 days or until the subject was discharged, experienced NEC, or died. Feeding was started at 10–20 mL/kg depending on the subject's gestational age, and increased by 10–30 mL/kg each day according to the subject's clinical condition and tolerance [22]. Feeding intolerance was defined as the difficulty in ingesting or digesting milk that disrupts the enteral feeding plan due to the manifestation of clinical symptoms [23]. If

feeding intolerance was present i.e. abdominal distension (increase in abdominal girth by 2 cm or more between feedings) and/or vomiting, the feeding was stopped or delayed until the tolerance improved. If a feeding contraindication was present, the probiotic or placebo administration was temporarily stopped. Feeding intolerance was the primary outcome. The secondary outcomes were differences between probiotics and placebo in duration of total parenteral nutrition (TPN), number of days needed to reach full enteral feeding, length of stay, sepsis, diarrhea, and NEC incidence and severity.

This study obtained ethical approval from the Ethics Committee of the Faculty of Medicine, Universitas Indonesia (Number 43.UN2.F1/ETIK/2017) as well as a study permit from Dr. Cipto Mangunkusumo Hospital.

The data analysis was conducted using the statistical program using IBM SPSS Statistics for Windows, Version 20.0 (IBM Co., Armonk, NY, USA). This study compared methods between categorical calculation scales as well as categoric-numerical unpaired groups. A bivariate analysis was conducted to analyze subject characteristics with NEC incidents. Two unpaired groups with normal distributions were analyzed with parametric methods (unpaired t-tests), while two unpaired groups without normal distributions were analyzed using a non-parametric method (Mann-Whitney U-test). *p*-values less than 0.05 were considered statistically significant. An intention-to-treat analysis was performed.

RESULTS

This study was performed between January and October 2017. A total of 105 infants were initially included; of them, 11 were excluded (3 refused to participate, 1 had a congenital anomaly, and 7 died before the probiotic or placebo could be administered). A total of 94 subjects fulfilled the inclusion criteria and were allocated in one of the study groups. No subjects dropped out.

There were no significant intergroup differences in subject characteristics at inclusion (**Table 1**). The majority of the subjects of both treatment groups were of moderately preterm gestational age (median gestational age, 33 weeks; range, 28–34 weeks). Ninety percent (85/94) received TPN; the TPN duration was less than or equal to 7 days in 36.5% (31/85) and more than 7 days in 63.5% (54/85). Nutritional intake consisted of predominantly breast milk in 9 (19.1%) subjects in the *L. reuteri* group and 10 (21.3%) in the placebo group. Feeding was predominantly formula in 38 (80.9%) subjects in the *L. reuteri* group and in 37 (78.7%) infants

Table 1. Patient demographics (n=94)

Variable	*L. reuteri* (n=47)	Placebo (n=47)	*p*-value
Sex			0.02
Male	28 (59.6)	17 (36.2)	
Female	19 (40.4)	30 (63.8)	
Gestational age			0.66
Moderately preterm	33 (70.2)	31 (66.0)	
Very preterm	14 (29.8)	16 (34.0)	
Birth weight			0.84
Very low birth weight	20 (42.6)	21 (44.7)	
Low birth weight	27 (57.4)	26 (55.3)	

Values are presented as number (%).
Moderately preterm: 32–33 weeks, 6 days of gestational age; very preterm: 28–31 weeks, 6 days of gestational age; very low birth weight: 1,000 to <1,500 g; low birth weight: 1,500–1,800 g.

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in the placebo group (p=0.80). The clinical characteristics and maternal risk factors are listed in **Tables 2** and **3**.

The incidence of feeding intolerance differed significantly between the two study groups. Feeding intolerance in the form of vomiting and/or abdominal distension was reported in 4 (8.5%) subjects in the *L. reuteri* group and 12 (25.5%) subjects in the placebo group (relative risk [RR], 0.33; 95% confidence interval [CI], 0.12–0.96; p=0.03) (**Table 4**). However, TPN duration and number of days needed to reach full enteral feeding did not different between groups. Total and partial parenteral nutrition are often needed in patients with low birth weight or an unstable clinical condition. In this study, the median duration of parenteral nutrition was 8 days in the *L. reuteri* group versus 9 days in the placebo group (p=0.52). The median length of stay was 27 days (range, 8–72 days) for the *L. reuteri* group and 27 days (range, 11–73 days) in the placebo group (p=0.28). Subjects who were discharged in the second week of care were those of an older gestational age (>32 weeks) and had a higher birth weight (>1,500 g).

Data on secondary outcomes are presented in **Table 5**. One subject (2.1%) of the *L. reuteri* group and 2 subjects (4.3%) of the placebo group developed diarrhea (p=1.00). There was a trend, but without a statistically significant difference, between the *L. reuteri* and placebo group in NEC incidence and death. Three (6.4%) subjects of the placebo group and zero

Table 2. Clinical characteristics of risk factors for NEC (n=94)

Risk factors for NEC	*Lactobacillus reuteri* group (n=47)	Placebo group (n=47)	*p*-value
Gestational age (wk)	33 (28–34)	33 (28–34)	0.75
Birth weight (g)	1,520 (1,035–1,800)	1,605 (1,060–1,800)	0.73
Cesarean section	39 (83.0)	40 (85.1)	0.78
Steroid administration	35 (74.5)	35 (74.5)	1.00
Length of steroid administration (d)	2 (0–4)	2 (0–2)	0.16
Asphyxia	38 (80.9)	42 (89.4)	0.25
Patent ductus arteriosus	2 (4.3)	3 (6.4)	1.00
APGAR score, 1 min	7 (5–9)	7 (3–9)	0.72
APGAR score, 5 min	9 (6–10)	9 (5–10)	0.34
Nutrition			
Age at first feeding (d)	2 (0–12)	1 (0–14)	0.79
Predominant breast milk	9 (19.1)	10 (21.3)	0.80
Predominant preterm formula milk	38 (80.9)	37 (78.7)	-
Duration of total parenteral nutrition (d)	8 (0–35)	9 (0–69)	0.52
Time to reach full feeding (d)	6 (0–25)	7 (0–63)	0.82
Age at intervention (d)	3 (0–18)	4 (0–21)	0.71
Duration of intervention (d)	21 (8–53)	21 (7–66)	0.78

Values are presented as mean (range) or number (%).
NEC: necrotizing colitis.

Table 3. Clinical characteristics of maternal risk factors for NEC (n=94)

Maternal risk factors	*Lactobacillus reuteri* group (n=47)	Placebo group (n=47)	*p*-value
Maternal risk factor			
Premature rupture of membranes	20 (42.6)	19 (40.4)	0.83
Oligohydramnios	2 (4.3)	4 (8.5)	0.68
Urinary tract infection	3 (6.4)	3 (6.4)	1.00
Intrauterine infection	2 (4.3)	3 (6.4)	1.00
Hypertension	1 (2.1)	4 (8.5)	0.36
Severe preeclampsia	12 (25.5)	10 (21.3)	0.63
Placenta previa	1 (2.1)	1 (2.1)	1.00
Cardiological anomaly	2 (4.3)	1 (2.1)	1.00

Values are presented as number (%).
NEC: necrotizing colitis.

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Table 4. Primary outcome comparison of feeding intolerance between subjects receiving *Lactobacillus reuteri* DSM 17938 or placebo (n=94)

Feeding intolerance	*Lactobacillus reuteri* DSM 17938 (n=47)	Placebo (n=47)	*p*-value	RR (95% CI)
Feeding intolerance	4 (8.5)	12 (25.5)	0.03	0.33 (0.12–0.96)
Vomiting	1 (2.1)	6 (12.8)	0.11	-
Abdominal distension	3 (6.4)	7 (14.9)	0.18	-

Values are presented as number (%).
RR: relative risk, CI: confidence interval.

Table 5. Secondary outcomes (n=94)

Variable	*Lactobacillus reuteri* DSM 17938	Placebo	*p*-value	RR (95% CI)
Total NEC (stage 2 and 3)	0 (0)	3 (6.4)	0.24	1.07 (0.99–1.15)
Age at onset (d)	-	18 (10–46)		
Proven sepsis	1 (2.1)	3 (6.4)	0.62	-
Length of stay (d)	27 (8–72)	27 (11–73)	0.28	-
Diarrhea	1 (2.1)	2 (4.3)	1.00	-
Death	1 (2.1)	4 (8.5)	0.36	-
Age at death (d)	31	51 (21–62)		-

Values are presented as number (%) or mean (range).
RR: relative risk, CI: confidence interval, NEC: necrotizing colitis.

subjects of the *L. reuteri* group experienced NEC (RR, 1.07; 95% CI, 0.99–1.15; *p*=0.24). There were no significant differences in the incidence of proven sepsis (6.4% in the placebo group vs. 2.1% in the *L. reuteri* group; *p*=0.62). In the placebo group, the etiology based on blood culture findings included 3 gram-positive bacteria (*Staphylococcus epidermidis*, methicillin-resistant *S. epidermidis*, and *Staphylococcus aureus*) and one gram-negative bacteria (*Klebsiella pneumoniae*). In the probiotic group, the sepsis was caused by *S. aureus*. NEC was diagnosed according Modified Bell staging (stage 2 and 3) diagnostic criteria [24,25]. Three (6.4%) cases of NEC occurred in the placebo group versus none in the *L. reuteri* group (RR, 1.07; 95% CI, 0.99–1.15; p=0.24). The mortality rate did not differ significantly between groups. One (2.1%) subject in the *L. reuteri* group and 4 (8.5%) subjects in the placebo group died (*p*=0.36). Two (4.2%) subjects from the placebo group had a cause of death related to NEC.

DISCUSSION

The incidence of feeding intolerance defined as vomiting or abdominal distension was higher in the placebo group (25.5%) than in the *L. reuteri* group (8.5%) (RR, 0.33; 95% CI, 0.12–0.96; *p*=0.03). Our findings confirm those of previous reports. Rojas et al. [12] reported a feeding intolerance incidence of 7% in a *L. reuteri* group versus 10.6% in a placebo group. According to recent data from Sweden, *L. reuteri* DSM 17938 did not reduce time to reach full enteral feeds in extremely low birth weight infants [26]. The results of this trial provides additional information about the effect of probiotics on feeding tolerance. The *L. reuteri*–supplemented infants, however, had a better cranial growth rate during the first month of life [26].

A prospective study with a large sample size reported that infants who were exclusively breastfed had a 6–10 times lower risk of developing NEC than those who received standard formula; the risk was 3 times lower than that of those who were given a mix of breast milk and standard formula [27]. Oncel et al. [15] reported that the incidence of NEC did not differ significantly between an *L. reuteri* group and a placebo group (RR, 1.26; 95% CI, 0.48–3.27). Shadkam et al. [10] reported that the incidence of NEC was lower in an *L. reuteri* group than in

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a placebo group (6.7% vs. 36.7%; p=0.005). A meta-analysis conducted by AlFaleh et al. [16] and van den Akker et al. [28] showed that probiotics may decrease the incidence of NEC (RR, 0.43; 95% CI, 0.33–0.56) and prevent mortality (RR, 0.56; 95% CI, 0.52–0.81). Wang et al. [29] conducted a meta-analysis of 20 randomized controlled trials (RCTs) and reported that probiotics significantly reduce the occurrence of NEC (RR, 0.22; 95% CI, 0.24–0.46; p<0.00001) and mortality rate (RR, 0.56; 95% CI, 0.43–0.73; p<0.001). Hunter et al. [17] reported that *L. reuteri* DSM 17938 significantly reduced NEC (2.5% vs. 15.1%; p=0.047) and delayed the onset of sepsis. However, a study by Escribano et al. [30] found an increased risk of NEC due to the routine administration of *L. acidophilus* and *B. bifidum* in extremely preterm infants.

In our study, the occurrence of proven sepsis was 6.4% in the placebo group vs. 2.1% in the *L. reuteri* group (p=0.62). Sepsis was not caused by *L. reuteri* in any of the infants. Rojas et al. [12] reported that 9.1% of the infants in the *L. reuteri* group had a positive blood culture versus 10.6% in the placebo group (RR, 0.86; 95% CI, 0.56–1.33; p=0.51). Romeo et al. [31] reported that the occurrence of delayed-onset sepsis was lower in a group receiving *L. reuteri* (1.2%) than in a placebo group (3.6%). Comparable findings were reported by Oncel et al. [15]. In the probiotic groups, no positive culture was related to *L. reuteri* intake.

The results of this study are in line with a previous study by Rojas et al. [12] reporting a nonsignificant difference in mortality rate between the probiotic and placebo groups (RR, 0.87; 95% CI, 0.63–1.19; p=0.376) and by Oncel et al. [15] showing a mortality rate of 10% in the probiotic group compared to 13.5% in the placebo group (RR, 1.4; 95% CI, 0.76–2.59; p=0.27). Shadkam et al. [10] reported a mortality rate in the probiotic group of 3.3% compared to 6.7% in the placebo group (p=0.5).

Hunter et al. [17] reported that no adverse effects of *L. reuteri* in 311 infants with birth weights less than 1,000 g. A systematic review by Shlomai et al. [32] analyzed results of 25 RCTs of 5,000 preterm infants and reported that adverse effects of probiotics rarely occurred. Several studies have reported infections occurring due to organisms present in probiotics, including fungemia in 33 cases reportedly due to Saccharomyces cerevisiae and/or Saccharomyces boulardii [19]. Cases were reported of sepsis due to Lactobacillus including *L. acidophilus*, *L. casei*, *L. GG*, *S. boulardii*, *Bacillus subtilis*, and *Bifidobacterium breve* [19,20].

A systematic review of eight studies (6 RCTs, 2 non-RCTs) reported several outcomes related to *L. reuteri* DSM 17938 supplementation in preterm infants including time to full feeds, duration of hospitalization, late-onset sepsis, and NEC risk. Based on the study by Athalye et al. [11], *L. reuteri* supplementation may reduce the risk of NEC and late-onset sepsis in preterm infants. Another study by Indrio et al. [33] reported the outcomes of *L. reuteri* DSM 17938 in preterm infants including feeding intolerance, weight gain, time to full enteral feeding, length of hospital stay, and days of antibiotic treatment. They concluded that *L. reuteri* DSM 17938 effectively prevents feeding intolerance in preterm infants.

About 20% of the infants included in our study were predominantly breastfed. Breastfeeding contains IgA, which influences the development of the intestinal immune system and the overall composition of the GI microbiota [34]. However, we did not collect data relevant to these aspects.

This is the first study conducted in Indonesia to support the use of probiotics in premature neonates. The study was conducted on the basis of data in a previous study which

found the number of commensal bacteria (*Lactobacillus* sp and *Bifidobacterium* sp) in the digestive tract of premature infants was very low compared to the number of pathogenic bacteria (*K. pneumoniae* and *Acinetobacter* sp) in the neonatology ward of Dr. Hospital Cipto Mangunkusumo, Jakarta [21].

In conclusion, the incidence of feeding intolerance in preterm infants of gestational age 28–34 weeks and birth weight of 1,000–1,800 g was found to be lower in the *L. reuteri* DSM 17938 group than in the placebo group (8.5% vs. 25.5%; p=0.33). The incidence of NEC in these infants was higher in the placebo group (6.4%) than in the *L. reuteri* group (0%; NS). Proven sepsis, length of time to reach full feeding, length of hospital stay, diarrhea, and mortality did not differ significantly between the groups.

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