The Effects of Probiotics on Feeding Tolerance, Bowel Habits, and Gastrointestinal Motility in Preterm Newborns

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Objective To investigate the effect of dietary supplementation with a probiotic on feeding tolerance and gastrointestinal motility in healthy formula-fed preterm infants.

Study design Thirty preterm newborns were enrolled; 10 were exclusively breast-fed, and the remaining 20 were randomly assigned in a double-blind manner to receive either *Lactobacillus reuteri* ATCC 55730 (at dose of 1×10^8 colony forming units a day) or placebo for 30 days. Clinical symptoms of gastrointestinal function (regurgitation, vomiting, inconsolable crying, and evacuation) and physiological variables (gastric electrical activity and emptying) were recorded before and after the dietary intervention.

Results Body weight gains per day were similar for the 3 groups, and no adverse events were recorded. Newborns receiving probiotics showed a significant decrease in regurgitation and mean daily crying time and a larger number of stools compared with those given placebo. Gastric emptying rate was significantly increased, and fasting antral area was significantly reduced in both the newborns receiving *L. reuteri* and breast-fed newborns compared with placebo.

Conclusions Our results suggest a useful role for *L. reuteri* supplementation in improving feeding tolerance and gut function in formula-fed preterm newborns. *(J Pediatr 2008;152:801-6)*

The rationale for supplementing a formula-fed infant with probiotics is based on efforts to obtain the bifidogenic effect of breast-feeding. The larger number of bifidobacteria in the intestine of breast-fed infants has been associated with better health compared with formula-fed infants.[1] A growing number of studies involving formulas supplemented with probiotics and prebiotics have demonstrated that they can affect health outcome in both formula-fed and breast-fed infants.[2] The use of probiotics to promote food tolerance has also been proposed in preterm newborns.[3] However, to the best of our knowledge, the links between nutritional, clinical, and functional gastrointestinal variables, such as gastric electrical activity and motility, are lacking.

The intestinal microflora participates in the development and maintenance of gut sensory and motor functions by the release of bacterial substances, fermentation products and intestinal neuroendocrine factors, and through the effects of mediators released by the gastrointestinal immune system.[4,5] The end-products of colonic microflora fermentation (ie, the short-chain fatty acids [SCFAs] butyrate, acetate and propionate) may affect local and distant motor events via direct[4] and indirect (nervous) pathways, although the latter is still controversial.[5] The intestinal microflora is also essential for the normal development of the gut-associated lymphoid tissue.[6] Mediators released by immune cells are known to modulate various digestive functions, many of which involve the enteric nervous system,[7,8] the enteric smooth muscles, and interstitial cells of Cajal (ICC).[9]

Cutaneous electrogastrography (EGG)[10] is a reliable method for recording gastrointestinal motility. EGG studies in newborns[11-14] have demonstrated the absence of normal slow waves at birth and a maturation process that may or may not be modulated by enteral feeding. Normal gastric electrical activity and gastric emptying is detectable from 34 weeks gestational age, after which the pattern is similar to that of full-term

ANOVA	Analysis of variance	ICC	Interstitial cells of Cajal
DF	Dominant frequency	*L. reuteri*	*Lactobacillus reuteri* (ATCC 55730)
DFIC	Instability coefficient	NEC	Necrotizing enterocolitis
EGG	Cutaneous electrogastrography	SCFA	Short-chain fatty acid
GE	Gastric emptying		

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infants. Gastric emptying (GE) can be assessed by ultrasonography, a noninvasive technique particularly suitable for young patients.[15] We hypothesized that giving the probiotic *Lactobacillus reuteri* (ATCC 55730) (*L. reuteri*) to a preterm, formula-fed infant would improve feeding intolerance, bowel habit, and gastrointestinal motility patterns.

METHODS

Subjects and Protocol

The study was performed in the Neonatology Section of the Department of Pediatrics at the University of Bari. Between January and September 2006, 30 healthy appropriate for gestational age preterm infants, with normal Apgar scores, were enrolled on days 3 to 5 of life in this double-blind, controlled study. Newborns with respiratory distress, congenital malformation, inborn errors of metabolism, or proven sepsis or infection were excluded. Ten newborns were exclusively breast-fed, and the remaining 20 were randomly assigned to receive either *L. reuteri* at dose of 1×10^8 colony forming units (CFU) per day, delivered in an oil formulation (BioGaia AB, Sweden; 5 drops per day) or an indistinguishable placebo formulation for 30 days. The 20 randomized preterm newborns were all exclusively bottle-fed with the same standard formula throughout the intervention period. The daily formula intake was approximately 30 mL/kg/d at baseline and 180 mL/kg/d at the end of the study. The intake of breast milk in the breast-fed babies was calculated as the increase in the infant's weight after feeding. Written informed consent was obtained from the parents, and the institutional ethics committee at the Policlinico Università di Bari approved the study.

Symptom Evaluation

During hospital stay, the number of episodes per day of regurgitation (defined as the passage of refluxed gastric contents into the oral pharynx), vomiting (defined as the expulsion of the refluxed gastric contents from the mouth, i.e. feeding tolerance), inconsolable crying episodes (minutes per day as already described in literature[16]), and the number of evacuations per day (bowel habits) were recorded by the nurses. On discharge from the ward, parents were given written information about the study and were asked to record the same symptoms and any observations of adverse effects, by means of a structured diary. To aid the uniform documentation of crying times and to confirm that the infants were given the study products correctly, one of the investigators was always available by telephone to help parents.

Assessment of Gastric Electrical Activity

Gastric electrical activity was recorded on day 4 (time 0) and day 35 after birth. After overnight fasting, the EGG recordings were performed with portable equipment before and 120 minutes after a meal. Two silver-silver chloride bipolar electrodes (Clear Trace, ConMed, Utica, NY) were placed on the cleaned abdominal surface overlying the antropyloric axis to obtain the best signal-noise ratio. The reference electrode was placed to form an equilateral triangle.[14] Electrogastrography was performed with a portable EGG recorder (UPS 2020, Medical Management Systems, MMS, The Netherlands). All recordings were made at a sampling frequency of 1 Hz and the internal high- and low-pass filters were set at 1.8 and 16 cycles/min, respectively. After recording, the electrogastrogram data were fed into a personal computer and analyzed by means of the built-in software. In addition to the analysis available with the UPS 2020, we used Redtech GiPC software to perform further EGG data filtering and analysis. The following variables were evaluated for each subject:

Mean frequency of the EGG. The dominant frequency (DF) of the gastric peak was determined by the absolute peak value, and the mean frequency/power was computed by averaging the individual spectra.

Instability coefficient. This specifies the stability of the gastric electrical peak visible on the running spectra plot. It was calculated as the percentage ratio of the frequency standard deviation to the mean gastric frequency (DFIC).

The percentage of DF in the ranges defined as normal, bradygastric and tachygastric. A rhythmic gastric electrical activity ranging from 2.0 to 4.0 cycles/min was considered normal. Tachygastria was considered to be present when the running spectra had a dominant peak in the range 4.0-9.0 cycles/min, and bradygastria when the dominant peak was <2.0 cycles/min.

The power ratio. Because the absolute values of EGG power are influenced by several factors, (skin conductance, distance between the electrodes and the wall of the stomach, variable shape of the stomach, etc.), the EGG power can only be evaluated as the relative changes observed. The power ratio is the ratio of postprandial to fasting EGG power values.

The EGG signal was visually inspected to verify that no artifacts were present in any recording period. Periods containing these motion artifacts were deleted before computer analysis. EGG variables were obtained by means of running spectral analysis. This is currently the method most commonly used to analyze the EGG, and since Van der Schee et al[17] introduced the running spectral analysis in EGG, it has also been possible to analyze the frequency and amplitude changes over time. With this procedure, using a fast Fourier transform (FFT) the frequency components of 256 sec epochs of EGG signal are calculated, overlapped by 75%, and displayed as a 3-dimensional frequency plot.

Assessment of Gastric Emptying

Gastric emptying was recorded on day 4 (time 0) and day 35 after birth. The ultrasound gastric emptying examinations were always performed by the same investigator using a real-time apparatus (Image Point HX; Hewlett Packard

Table I. Clinical characteristics in preterm newborns before the start of the study

	Formula + LR (n = 10)	Breast milk (n = 10)	Formula + placebo (n = 10)
Gestational age (wks)	34 ± 1.1	34 ± 1.3	34 ± 1.1*
Sex (male/female)	5/5	4/6	5/5
Birth weight (g)	1890 ± 432	1920 ± 491	1850 ± 342*
Apgar score	8 [2]	8 [2]	8 [1]†

Values are given as mean ± SD apart from Apgar score expressed as Median and [Range]. Continuous variables were tested with one way ANOVA whereas discrete ones were tested with Kruskal-Wallis ANOVA on ranks.
*One-way ANOVA, $P > .05$.
†Kruskal-Wallis ANOVA on ranks, $P > .05$.

Table II. Baseline physiological characteristics in the preterm newborns

Time 0 (day 4)	Formula + LR (n = 10)	Breast milk (n = 10)	Formula + placebo (n = 10)
EGG data			
Preprandial EGG			
Dominant frequency (cpm)	3.1 ± 0.3	2.8 ± 0.5	3.0 ± 0.5
Instability coeff. of DF %	47.5 ± 6.0	44.4 ± 8.0	43.3 ± 11.0
Bradygastria %	22.2 ± 5.4	31.1 ± 11.1	23.1 ± 8.7
Normal slow wave %	59.4 ± 7.2	57.8 ± 7.0	61.6 ± 8.6
Tachygastria %	18.4 ± 7.3	10.7 ± 8.3	15.3 ± 10.4
Postprandial EGG			
Dominant frequency (cpm)	3.4 ± 0.3	3.1 ± 0.4	3.2 ± 0.8
Instability coeff. of DF %	51.5 ± 14.8	39.8 ± 7.2	47. ± 16.2
Bradygastria %	16.1 ± 9.5	19.6 ± 8.2	27.0 ± 6.4
Normal slow wave %	60.4 ± 10.6	66.5 ± 10.7	54.6 ± 12.9
Tachygastria %	22.1 ± 9.0	13.90 ± 9.0	17.5 ± 10.5
Power ratio	1.4 ± 0.8	1.5 ± 0.8	1.4 ± 0.5
GE data			
Fasting antral area (cm^2)	0.7 ± 0.2	0.6 ± 0.1	0.5 ± 0.2
Gastric emptying rate (%)	60.9 ± 9.7	66.8 ± 12.8	67.9 ± 7.3

Values are given as mean ± SD. Analysis of the data: 1-way ANOVA, $P > .05$.

Company, Palo Alto, Calif) equipped with a 3.5 MHz linear probe. The probe was positioned at the level of the transpyloric plane for simultaneous visualization of the antrum, superior mesenteric vein, and the aorta. The antral measurements were always taken from the outer profile of the wall. Because the cross-section of the gastric antrum, corresponding to the sagittal plane passing through the superior mesenteric vein is elliptical in shape, its area can be calculated by measuring the longitudinal (L) and anteroposterior (AP) diameters and applying the formula $\pi L \times AP/4$.[15] During the same EGG recording session, antral measurements were made before and immediately after the end of the test meal (time 0), and at regular 30-minute intervals up to 180 minutes after the meal. In each patient, the gastric emptying rate was expressed as percent reduction in antral cross sectional area from time 0 to 120 minutes after meal ingestion.[18]

Data Analysis

For clinical variables, the mean values per day recorded over the last 7 days of the treatment period were calculated. The data were analyzed first by use of simple descriptive statistics of centrality and dispersion. All data were expressed as mean ± SD, and parametric or nonparametric statistical tests were performed as appropriate (continuous or discrete variables, respectively). The differences in scores, minutes, and number of episodes/day among the groups were determined by Kruskal-Wallis analysis of variance (ANOVA) on Ranks and Dunn's test for multiple comparisons, and the differences in anthropometrical, EGG, and GE variables were determined by the 1-way ANOVA and Tukey test for multiple comparisons. All the differences were considered significant at a 5% level. The software package used for the statistical analysis was STATA (STATA version 4.0 Statistical Software; Stata Corporation, College Station, Texas).

RESULTS

Demographic data of all the newborns before the start of the study are shown in Table I. At baseline (day 4), EGG and gastric emptying were similar in the 3 groups (Table II).

The newborns receiving breast milk and those receiving *L. reuteri* had a significant decrease in the number of episodes of regurgitation, and a significantly reduced mean crying daily time compared with those given placebo, expressed as the mean values per day recorded over the last 7 days of the treatment (Table III). Moreover, the newborns receiving breast milk or *L. reuteri* had a larger number of stools at the

Table III. Feeding tolerance characteristics and bowel habits in preterm newborns fed formula with placebo, formula with *L. reuteri*, or breast milk

	Formula + LR (n = 10)	Breast milk (n = 10)	Formula + placebo (n = 10)
Daily amount of feeding (mL)	650 ± 50	600 ± 75	600 ± 60
Weight gain/day (g)	28 ± 7.0	30 ± 9.1	25 ± 8.1
Regurgitation (No. of episodes/d)	2.1 ± 0.9*	1.6 ± 0.3†	4.2 ± 1.1*†
Vomiting (No. of episodes/d)	0	0	0.01 ± 0.04
Crying time (min/d)	32 ± 6‡	66 ± 11§	88 ± 16‡§
Evacuations (No. of episodes/d)	3.7 ± 0.5‖	4.8 ± 0.2¶	2.1 ± 0.4‖¶
Side effects (No. reported)	0	0	0

LR, L. reuteri.

Clinical data are shown as the daily mean ± SD over the last 7 days of treatment. Continuous variables were tested with 1-way ANOVA, whereas discrete variables were tested with Kruskal-Wallis ANOVA on Ranks.

*Formula + LR versus formula + placebo, $P < .01$, Kruskal-Wallis test, $P = .01$; multiple comparisons procedure (Dunn's test).

†Breast milk vs formula + placebo, $P < .01$, Kruskal-Wallis test, $P = .01$; multiple comparisons procedure (Dunn's test).

‡Formula + LR versus formula + placebo, $P < .01$, Kruskal-Wallis test, $P = .01$; multiple comparisons procedure (Dunn's test).

§Breast milk versus formula + placebo $P < .05$, Kruskal-Wallis test, $P = .01$; multiple comparisons procedure (Dunn's test).

‖Formula + LR versus formula + placebo $P < .05$, Kruskal-Wallis test, $P = .01$; multiple comparisons procedure (Dunn's test).

¶Breast milk versus formula + placebo $P < .05$, Kruskal-Wallis test, $P = .01$; multiple comparisons procedure (Dunn's test).

end of intervention diet compared with those on placebo (Table III). Only 1 episode of vomiting was recorded in the placebo group. No difference was seen in daily body weight gain, and there were no adverse events reported related to the trial (Table III).

None of the EGG variables showed any differences in newborns receiving breast milk or formula feeding, with or without the probiotic strain. Significant differences, however, in the gastric emptying rate and fasting antral area were detected. In particular, the fasting antral area was significantly smaller, and the gastric emptying rate was significantly faster in the newborns receiving *L. reuteri* compared with formula with placebo, and the *L. reuteri* supplemented babies had a motility pattern resembling that of newborns fed with breast milk (Figure).

DISCUSSION

This pilot study demonstrates the potential beneficial effects of probiotics on clinical and physiological variables related to gut function. In particular, it shows that oral supplementation with *L. reuteri* improves feeding tolerance and bowel habits and reduces crying time in preterm newborns. Gastric motility was improved in the infants given formula supplemented with *L. reuteri* as shown by the increased gastric emptying rate and the reduced fasting antral area. These findings were similar to those reported in the newborns fed with breast-milk. None of the newborns receiving *L. reuteri* had adverse growth or behavioral effects, consistent with the earlier demonstration of the safety and tolerance of this probiotic in full-term infants.[19]

Gastrointestinal motility can be evaluated by measuring gastric electrical activity (a measure of stomach wall movements) and gastric emptying time. There are several studies on gastrointestinal motility in neonates that looked at the electrical and mechanical activity of the gut. EGG studies have demonstrated that gastric electrical signals are similar in preterm and term newborns.[12,13] Gastrointestinal motility in

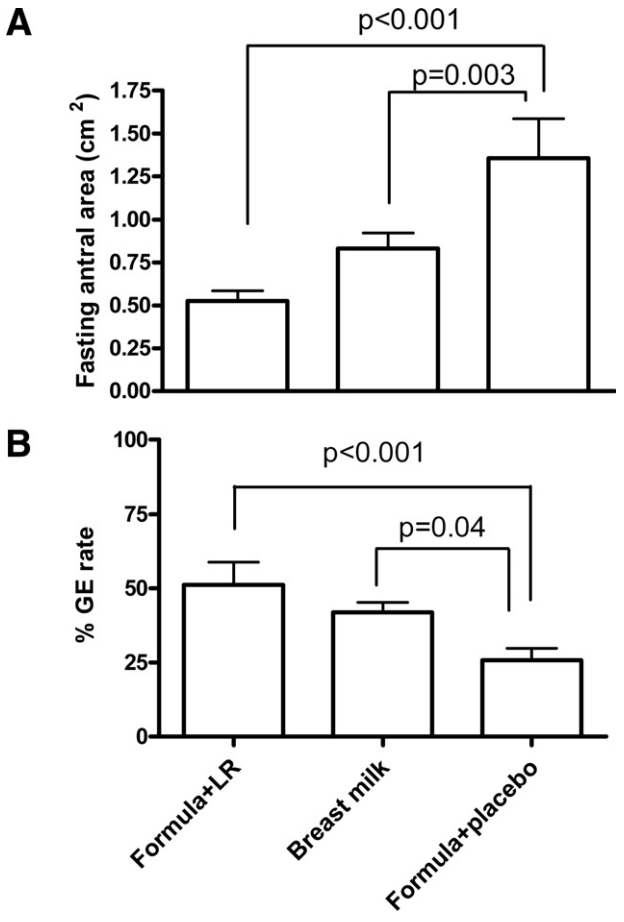

Figure. Gastric emptying variables recorded from 3 groups at end of intervention diet. **A,** Significant differences in fasting antral area among groups were detected by use of 1-way ANOVA testing ($P < .001$). Multiple comparisons (Tukey Test): Formula + *L. reuteri* versus formula + placebo, $P < .001$; breast milk versus formula + placebo ($P = .003$). **B,** Significant differences in gastric emptying rate among groups were detected by use of 1-way ANOVA testing ($P < .001$). Multiple comparisons (Tukey Test): Formula + *L. reuteri* versus formula + placebo $P < .001$; breast milk versus formula + placebo ($P = .04$).

preterm infants, recorded by means of cutaneous EGG and ultrasonography, show a clear pattern of maturation.[14] An abnormal EGG pattern and delayed gastric emptying time are evident in preterm infants of 28 to 32 weeks of age. The 3-cycle/min activity becomes dominant at approximately 32 to 36 weeks of gestational age, and by that time, the gastric emptying time is similar to that of full-term infants. Although enteral feeding is important for the development of gastrointestinal motility, gastric electrical activity, and emptying show an intrinsic maturation pattern depending on the gestational age. Such data on the development of gastric slow waves and effects of feeding in preterm and full-term infants have been recently reported by Chen.[20] Our study confirms a stable and normal EGG activity in older preterm newborns. Before the start of the intervention diet, preprandial EGG data did not differ in the 3 groups of preterm newborns, and the same was true for postprandial EGG variables. At the end of the study, no differences were seen in the EGG variables among the 3 groups. We chose newborns of 34 weeks gestational age because at this age the motility pattern is fully developed. In this way, the only factor that could modify the motility pattern was the addition of the probiotic to the formula.

An increased gastric emptying rate and reduced fasting antral areas were seen in formula-fed preterms supplemented with *L. reuteri* and babies fed with breast milk. The clinical counterpart of such a reduction in gastric antral area may be the reduced episodes of regurgitation. In fact, in adult functional dyspeptic patients, gastrointestinal symptoms have been related to impaired accommodation and antral dysfunction. Fundic relaxation is markedly impaired in functional dyspepsia when an antral distension is induced by an intragastric air-filled bag. As a result antral and fundic dysfunctions interact to produce dyspeptic symptoms.[21] Because only 1 episode of vomiting was observed (in the newborns fed with formula with placebo), no clinical conclusions could be made. However, this may be indicative of reduced gastric residual in the breast-milk and formula-fed with *L. reuteri* newborns compared with those given placebo. Interestingly, recent data on infants with cow's milk allergy showed a close link between gastrointestinal symptoms, gastroesophageal reflux, and gastric emptying time.[22] Moreover, an increased gastric residual is considered to be a risk factor for the onset of necrotizing enterocolitis (NEC). Most probably the underlying mechanism of probiotic in reducing NEC[23] could be related to a reduction of gastric residual. It is possible that probiotic intervention on premature infants with lower gestational ages could have a stronger effect either on motility maturation or feeding tolerance. The action of probiotic on upper gastrointestinal motility might be explained by several pathophysiological pathways. The volume and chemical characteristics of meals are supposed to generate vagal afferent signals that mediate gastric emptying.[24] Fiber content (soluble and insoluble fibers) has been associated with a significant increase in gastric antrum motility, monitored by manometry, compared with fiber-free and insoluble-fiber diets.[25] Indirect effects on intestinal motility may be mediated by bacterial metabolites such as SCFAs which have metabolic effects on blood lipids and carbohydrates.[26] SCFAs seem to stimulate smooth muscle modulating cellular calcium influx in a canine in vitro model.[27] In the large intestine they inhibit peristaltic activity and may stimulate tonic activity. Through a humoral pathway involving polypeptide YY, ileal and colonic SCFAs modify upper motility by inducing relaxation of the proximal stomach, lower esophageal sphincter, and reducing gastric emptying.[7] The role of SCFA might be to coregulate the motility of the upper intestine.

Cross-talk between digestive motor activities and immune-related mechanisms has become progressively better understood. This interaction may involve the enteric nervous system, enteric smooth muscle, and ICC. This may highlight a potential role of the probiotic not only in health but also in disease, particularly in infectious diseases. Enteric neuronal dysfunction can involve cellular and/or humoral mechanisms and may or may not result in neuronal loose.[28] In animal models of postinfectious enteric muscle dysfunction, a persistent dysfunction of the neuromuscular tissue is maintained by the production of TGF-β and prostaglandin E_2 by the intestinal muscle layers themselves. The ICC network can also be damaged by inflammation, and such alterations may explain motor abnormalities as supported by Wang et al.[29] The restoration of muscle function after gastrointestinal infection was improved by the administration of probiotics and, potentially, the mechanism involved the modulation of multiple proteins and other components of excitation-contraction coupling.[30]

Our study addresses the motility of the hindgut by use of the measures of inconsolable crying time and number of evacuations, both of which were significantly improved in newborns fed with *L. reuteri*. Savino et al[16] recently reported significant reductions in crying time in breast-fed, colicky newborns in response to supplementation with *L. reuteri* compared with simethicone-treated control subjects. Several possible links between these symptoms and physiological variables, such as changes in intestinal flora, improved mucosal barrier, and antiinflammation were suggested by the authors. Our data support and confirm these findings and, furthermore, provide a mechanistic explanation of the phenomenon through an improved motility of the whole intestine.

In conclusion, our results suggest a useful role for *L. reuteri* supplementation in ameliorating feeding tolerance and improving gut function in newborns. The physiological mechanisms underlying these effects involve changes in gastrointestinal motility, which is improved in both the upper and lower gut. Further understanding and elucidation of the mechanisms underlying the beneficial effects of *L. reuteri* on gastrointestinal symptoms and motility should provide new regimens for prevention and treatment of illness in the preterm infants.

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