Lactobacillus reuteri DSM 17938 for the Management of Infantile Colic in Breastfed Infants: A Randomized, Double-Blind, Placebo-Controlled Trial

Hania Szajewska, MD[1], Ewa Gyrczuk, MD[2], and Andrea Horvath, MD[1]

Objective To determine whether administration of *Lactobacillus reuteri* (*L reuteri*) DSM 17938 is beneficial in breastfed infants with infantile colic.

Study design Eighty infants aged <5 months with infantile colic (defined as crying episodes lasting 3 or more hours per day and occurring at least 3 days per week within 7 days prior to enrollment), who were exclusively or predominantly (>50%) breastfed were randomly assigned to receive *L reuteri* DSM 17938 (10^8 colony-forming units) (n = 40) or an identically appearing and tasting placebo (n = 40), both orally, in 5 drops, 1 time daily, for 21 days. The primary outcome measures were the treatment success, defined as the percentage of children achieving a reduction in the daily average crying time ≥50%, and the duration of crying (minutes per day) at 7, 14, 21, and 28 days after randomization.

Results The rate of responders to treatment was significantly higher in the probiotic group compared with the placebo group at day 7 (P = .026), at day 14 (relative risk (RR) 4.3, 95% CI 2.3-8.7), at day 21 (RR 2.7, 95% CI 1.85-4.1), and at day 28 (RR 2.5, 95% CI 1.8-3.75). In addition, throughout the study period, the median crying time was significantly reduced in the probiotic group compared with the control group.

Conclusion Exclusively or predominantly breastfed infants with infantile colic benefit from the administration of *L reuteri* DSM 17938 compared with placebo. *(J Pediatr 2013;162:257-62)*.

The criteria for infantile colic includes all of the following in infants from birth to 4 months of age: paroxysms of irritability, fussing, or crying that start and stop without obvious cause; episodes lasting 3 or more hours per day and occurring at least 3 days per week for at least 1 week; and no failure to thrive.[1] The crying typically peaks at approximately 6 weeks of life and ends around the fourth month. Possible causes of colic include painful intestinal contractions, lactose intolerance, food hypersensitivity, altered gut microbiota, gas, parental misinterpretation of the normal crying pattern, or various combinations of the above.[2] A number of therapies have been tried, including use of hydrolyzed formulas, sucrose, herbal teas, soy formula, lactose-reduced formula, and fiber-enriched formulas, increased carrying, music, vibration or massage, and spinal manipulation; however, none has been proven to be effective.[3] It has been suggested that colic in infancy increases the susceptibility to recurrent abdominal pain, allergic diseases, and psychological disorders in childhood.[4] Recent evidence suggests that probiotics might offer some benefit. First, an open randomized controlled trial (RCT) performed in 83 breastfed infants documented that compared with simethicone, administration of *Lactobacillus reuteri* (*L reuteri*) ATCC 55730 may reduce the crying time.[5] However, it was considered that methodological limitations of the study, including no allocation concealment, no blinding, and no intention-to-treat analysis, as well as the lack of a true placebo group, might invalidate the results. Furthermore, the *L reuteri* ATCC 55730 strain was found to carry potentially transferable resistance traits for tetracycline and lincomycin and was replaced by a new strain, *L reuteri* DSM 17938, with no unwanted plasmid-borne resistances.[6] More recently, Savino et al[7] showed in a double-blind, RCT that compared with placebo, *L reuteri* DSM 17938 administered to 46 breastfed infants improved symptoms of infantile colic.

There is no consensus regarding the use of *L reuteri* DSM 17938 for the management of infantile colic.[8] The importance of repeat studies in different populations and by independent investigators before firm conclusions can be drawn has been highlighted in the literature.[9] Thus, we undertook this clinical study to compare the effectiveness of *L reuteri* DSM 17938 with placebo in the treatment of breastfed infants with infantile colic in a double-blind, RCT.

Methods

The standards from the guidelines of the Consolidated Standards of Reporting Trials (CONSORT) were followed for this RCT. The trial was registered at

L reuteri	*Lactobacillus reuteri*
RCT	Randomized controlled trial
RR	Relative risk
VAS	Visual analog scale

From the Departments of [1]Pediatrics and [2]Family Medicine, The Medical University of Warsaw, Warsaw, Poland

Funded by the Medical University of Warsaw, which received a donation from the manufacturer of *L reuteri* DSM 17938, BioGaia AB, Lund, Sweden. The manufacturer had no role in the conception, design, or conduct of the study, or in the analysis or interpretation of the data. The authors declare no conflict of interest.

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ClinicalTrials.gov (NCT01046617). All infants were eligible for recruitment after written informed consent was obtained from their parents. The study was approved by the Ethics Committee of the Medical University of Warsaw.

The study was carried out between January 2010 and December 2011 in a family primary care practice in Warsaw, Poland. To be eligible for entry, participants had to be full-term infants aged <5 months with infantile colic (defined as crying episodes lasting 3 or more hours per day and occurring at least 3 days per week within 7 days prior to enrollment), who were exclusively or predominantly (>50%) breastfed. Exclusion criteria included acute or chronic illness, gastrointestinal disorders, or use of any antibiotics and/or probiotic pharmaceutical products within 7 days prior to the study.

Investigators at the Medical University of Warsaw used computers to generate independent allocation sequences and a randomization list (StatsDirect statistical software; StatsDirect Ltd, Altrincham, Cheshire, United Kingdom). To avoid disproportionate numbers of patients in each group, randomization was performed in blocks of 6 subjects (3 receiving the probiotic product and 3 receiving the placebo). To ensure allocation concealment, an independent person prepared the randomization schedule and oversaw the packaging and labeling of the study products. All study personnel, parents, and guardians were unaware of the group assignments. Randomization codes were secured until all data were analyzed.

All participants and investigators were blinded throughout the study. Both study products, *L reuteri* DSM 17938 and the placebo, were manufactured and supplied by BioGaia AB (Lund, Sweden) as a fluid in identical bottles and kept refrigerated until use. The manufacturer had no role in the conception, design, or conduct of the study, or in the analysis or interpretation of the data. The unblinding was done when all data were analyzed.

All infants were eligible for screening. If an infant appeared to meet the criteria for enrollment and caregivers expressed interest in the study, caregivers were asked to record symptoms of colic for 1 week. Children fulfilling the inclusion criteria were asked to participate in the study. Eligible infants were randomly assigned to receive either *L reuteri* DSM 17938, administered orally at a dose of 10^8 colony-forming units, or placebo. The placebo consisted of an identical formulation in all respects except that the live probiotic bacteria were excluded. Both the active treatment and placebo were taken orally, in 5 drops, 1 time daily, for 21 days. Parents were given a diary and were asked to record the times of administration of study products, the daily duration of crying time, parental perceptions of colic severity, and family quality of life, as well as any adverse events. The visits after the enrollment were scheduled for 7, 14, 21, and 28 days after the initiation of the administration of study products. The end of the treatment visit was scheduled for day 28 to evaluate the effect of the intervention 1 week after its termination. At that visit, diaries and unused study products were returned. However, no specific measures to assess compliance were taken. The same study physician (E.G.) examined all study infants at all visits. Parents were encouraged to contact the same physician whenever needed. Parents were also encouraged to keep their infants in the study for follow-up visits even in cases of discontinuation of the study products. Only the study physician was in contact with the parents. The analyses of the diaries were done independently, first by the study physician (E.G.), and then by 2 other investigators. All members of the study team interpreting the diaries were blinded from treatment allocation.

The primary outcome measures were: (1) the treatment success (defined as the percentage of children achieving a reduction in the daily average crying time ≥50% during the study); and (2) the duration of crying (minutes per day). The secondary outcome measures were as follows: a reduction in the daily average crying time, from baseline until the end of the treatment period (day 21), to <3 h/d (the cutoff value proposed by Wessel et al[3]); persistence of infantile colic after the intervention; parental perceptions of colic severity; and parental/family quality of life. To assess the 2 latter outcomes, a 10-cm visual analog scale (VAS) was used. The possible scores ranged from 0 to 10. For the parent's perception of colic severity, 0 indicated no pain and 10 indicated the worst pain. For the parental/family quality of life, 0 indicated no effect and 10 indicated a very good effect.[10] Parents were instructed how to use the VAS scale prior to the study. In addition, adverse effects (ie, vomiting, constipation, and other symptoms spontaneously reported) were recorded by the caregivers.

We estimated that with 33 infants per group, we would be able to detect an absolute increase of 35% in the rate of treatment success from 15% in the control group to 50% in the intervention group with 80% power ($\alpha = 0.05$). In total, we planned to enroll 80 infants to account for possible 20% follow-up losses.

Statistical Analyses

The statistical analyses were conducted with the computer software StatsDirect v. 2.7.8. The Student *t* test was used to compare mean values of continuous variables approximating a normal distribution. For non-normally distributed variables, the Mann–Whitney U test was used. The χ^2 test or Fisher exact test was used, as appropriate, to compare percentages. The same computer software was used to calculate the relative risk (RR), number needed to treat, and median difference, all with a 95% CI. The difference between study groups was considered significant when the *P* value was <.05, when the 95% CI for RR did not include 1.0, or when the 95% CI for mean difference did not include 0. All statistical tests were two tailed and performed at the 5% level of significance. All analyses were conducted on an intention-to-treat basis, including all patients in the groups to which they were randomized for whom outcomes were available.

Results

The Figure is a flow diagram showing the subjects' progression through the study. The intention-to-treat population included 80 infants—40 were assigned to the

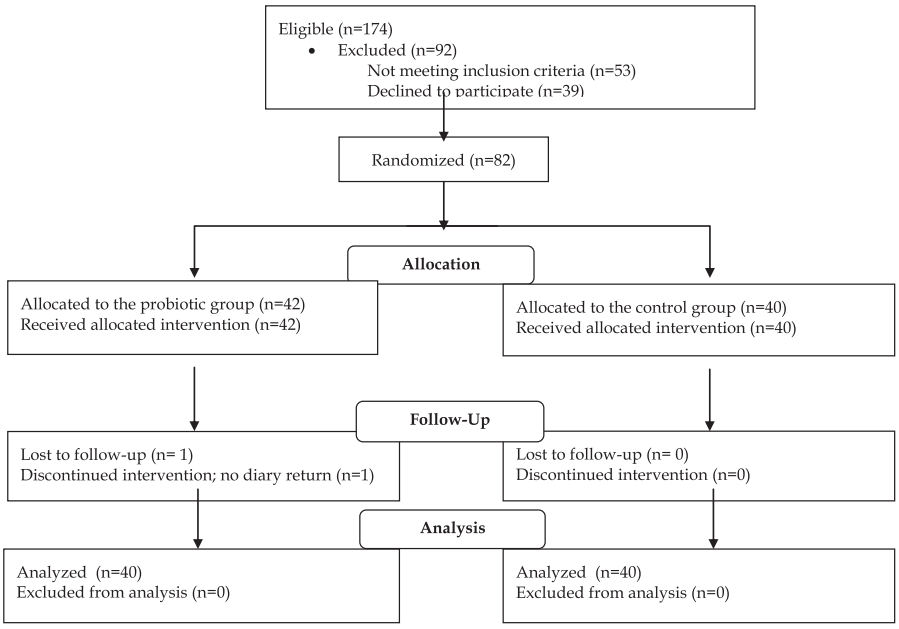

Figure. Flow diagram of the subjects' progression through the study.

probiotic group and 40 were assigned to the placebo group. Baseline demographic and clinical characteristics did not differ between the 2 groups, except for a family history of allergy that was higher in the probiotic group compared with the placebo group (21/40 vs 7/40 infants) (**Table I**).

The treatment success rate was significantly higher in the probiotic group than in the placebo group at all points after randomization. Throughout the study period, the crying time was significantly reduced in the probiotic group compared with the placebo group (**Table II**).

The secondary outcome measures are summarized in **Table III**. Throughout the study period, there was a significant reduction in the parental perception of colic severity for parents of infants in the probiotic group compared with the placebo group. In addition, VAS scores indicated improved parental/family quality of life throughout the study for parents and families of infants in the probiotic group compared with the placebo group. No adverse events associated with the probiotic therapy or with the use of the placebo were reported.

Discussion

Administration of *L reuteri* DSM 17938 at a dose 10^8 colony-forming units to exclusively or predominantly breastfed infants is superior to placebo for the management of infantile colic. The use of *L reuteri* was associated with the treatment success and reduced crying times at 1, 2, 3, and 4 weeks after randomization. No adverse events were recorded during the treatment.

In principle, our findings are consistent with the findings of a previous smaller trial by Savino et al,[7] which used the same strain of *L reuteri* DSM 17938, despite some minor differences in the study populations. Compared with Savino et al, who included only exclusively breastfed infants whose mothers were on a cow's milk protein elimination diet, we additionally included predominantly (>50%) breastfed infants. In our study, mothers were not advised to follow an elimination diet.

In both studies, treatment success (similarly defined in both studies as a 50% reduction in the crying time compared with baseline) was more likely in the probiotic group compared with the placebo group. Also, in both studies, median crying times were significantly shorter in the probiotic group than in the placebo group.

Compared with the previous trial, the effect size was larger in our study. One may hypothesize that 1 difference in the study populations, ie, the higher percentage of infants with a family history of allergy in our probiotic group, may have contributed to the differences in the findings. The results of some previous trials indicate that *L reuteri* may have an effect on the immune system and allergic symptoms in children.[11]

In our study, the response to the active (probiotic) intervention was impressive. The same applies to the previous study by Savino et al.[7] However, one should recognize that the response to the active intervention consists of at least 2 elements: the effect of the active treatment and the placebo effect.[12] Previous studies have shown that placebo response rates in trials on infantile colic could range from 5% to 83%.[13] Fifteen of 40 (37.5%) of the infants responded to placebo at day 21 after randomization (it was as high as 71% in the study by Savino et al) and 25 of 40 (62.5%) responded to the placebo at day 28 (not assessed by Savino et al). Although

Table I. Baseline characteristics

Characteristic	Probiotic group (n = 40)	Placebo group (n = 40)
Boys/girls, n	26/14	22/18
Birth weight, g, mean ± SD	3796.5 ± 329.7	3739.4 ± 314.6
Age at entry, days, mean ± SD (median; range)	34.3 ± 12.5 (33; 16-81)	38.1 ± 11.7 (35.5; 17-69)
Vaginal/cesarean delivery, n	35/5	33/7
Family history of allergy, n	21	7
Exclusive/partial breastfeeding (at inclusion), n	36/4	33/7

a direct placebo effect in young infants may be disputable, an indirect placebo effect (for example, via more relaxed caregivers) seems possible. Other factors contributing to the placebo effect include the natural history (infantile colic peaks at some point and then subsides) and the regression to the mean (subjects are enrolled when most symptomatic and inevitably improve with time owing to the natural variation in symptom severity and irrespective of trial participation).[14,15] Taken together, these considerations should be seen as reasons for caution when interpreting the findings. The true effect of an active treatment is likely to be lower, although still good.

The exact mechanisms by which *L reuteri* might exert its actions have yet to be elucidated. One possible explanation is that this beneficial effect is due to the effect of *L reuteri* on gut motility and function, colonic sensory nerves, colon contractile activity, and pain perception,[16-18] although this has been documented only in preterm infants.[19] Additional mechanisms include anti-inflammatory effects documented both in vitro[20] and in vivo[21] or interaction with altered gut microbiota. Compared with healthy infants, a reduced count of intestinal lactobacilli and increased concentration of coliforms were observed in colicky infants in 1 study.[22] Finally, some data suggest that infantile colic may represent the first clinical symptom of food hypersensitivity. In this case, stimulation or modulation of immune responses by *L reuteri* may play a role.

A number of other RCTs have reported on colic and/or irritability and have used various probiotics for treatment[23-25]; some of these studies have documented lower frequencies of these outcomes in the probiotic group compared with the control group.[25] However, in none of these trials did the study population consist of infants with colic defined according to widely accepted criteria.

Strengths of our study are the adequate sample size, the adequate methods for the generation of the allocation sequence and allocation concealment, proper blinding maintained throughout selection, treatment, data management and data analyses, and no losses to follow-up. We also used a generally accepted definition of colic. Infants were recruited at a similar, early age. Age at recruitment is important considering the natural history of colic and the self-limiting nature of the symptoms with time.

A limitation of the study is that we did not use an objective way to assess the duration of crying in infants. Thus, we fully relied on parents' reports on the duration of crying recorded in the diaries. The precision and validity of such reporting may be questioned. Well-known problems with paper diaries include poor adherence and retrospective or just before a visit recording.[26] Our intention was to assess the crying time. However, symptoms such as irritability and fussing might have been difficult to isolate. In addition, the design of our study did not allow for a better description of the crying (eg, food related? typical afternoon crying?). Another important limitation of the study is that we did not assess compliance. However, the study population was cared for by the investigator (E.G.), who is a well-known family physician and primary care pediatrician, with a good reputation and the trust of patients.

In summary, exclusively or predominantly breastfed infants with infantile colic benefit from treatment with

Table II. Primary outcomes

Outcome	Probiotic group (n = 40)	Placebo group (n = 40)	RR (95% CI)	NNT (95% CI)	*P* value*
Treatment success (reduction in the daily average crying time ≥50%)					
Day 7	6	0	-	7 (4-19)	.026
Day 14	30	7	4.3 (2.3-8.7)	2 (2-3)	<.001
Day 21	39	15	2.6 (1.8-4.0)	2 (2-3)	<.001
Day 28†	40	25	1.6 (1.3-2.1)	3 (2-5)	<.001
			Median difference (95% CI)		
Duration of crying (min/d) (median, IQR)					
Baseline	240 (210-270)	240 (203-278)	0.0 (−30 to 30)	N/A	.8
Day 7	180 (149-180)	180 (150-210)	0.0 (−60 to 0)	N/A	.002
Day 14	105 (101-120)	150 (120-180)	−45 (−75 to −30)	N/A	<.0001
Day 21	75 (60-90)	128 (116-150)	−53 (−83 to −45)	N/A	<.0001
Day 28†	52 (45-75)	120 (90-128)	−68 (−75 to −60)	N/A	<.0001

N/A, not applicable; *NNT*, number needed to treat.
*Fisher exact test or χ^2, or Mann–Whitney test, as appropriate.
†Follow-up visit 1 week after the termination of the intervention.

Table III. Secondary outcomes

Outcome	Probiotic group (n = 40)	Placebo group (n = 40)	RR (95% CI)	*P* value*
Reduction in the daily average crying time on day 21 (<3 h/d)	40/40	34/40	1.18 (1.03-1.4)	.03
Reduction in the daily average crying time on day 28 (<3 h/d)	40/40	38/40	1.05 (0.9-1.18)	.5
			Median difference (95% CI)	
Parental perception of severity (VAS; 0–no pain; 10–severe pain), median (IQR)				
Baseline	8.4 (7.7-8.7)	8 (7.5-8.4)	0.4 (−0.5 to 9)	.054
Day 7	3.2 (2.6-4.0)	5.5 (5.0-6.2)	−2.4 (−3.0 to −1.9)	<.0001
Day 21	2.2 (2.0-2.6)	5.0 (4.4-5.2)	−2.8 (−3.1 to −2.8)	<.0001
Day 28†	2.1 (2.0-2.2)	5.1 (4.2-5.2)	−3.0 (−3.1 to −2.9)	<.0001
Family quality of life (VAS; 0–no effect; 10–very good effect), median (range)				
Day 7	8.0 (7.5-8.2)	5.1 (4.9-6.1)	2.9 (1.9-3.0)	<.0001
Day 21	8.5 (8.0-8.6)	5.1 (5.0-5.6)	3.4 (3.0-3.4)	<.0001
Day 28†	8.7 (8.3-9.0)	5.3 (5.1-6.1)	3.5 (3.2-3.8)	<.0001

VAS: where score ranges from 0 to 10.
*Fisher exact test or chi-square test, or Mann–Whitney test, as appropriate.
†Follow-up visit 1 week after the termination of the intervention.

L reuteri DSM 17938 compared with placebo. The necessity of treating this self-limiting condition may be questioned. However, if one wants to modify the natural history of infantile colic, the use of *L reuteri* DSM 17938 could be discussed with caregivers. The lack of effective therapy for infantile colic and the generally good safety profile of probiotics in otherwise healthy populations are in favor of such treatment. Future studies should clarify the role of *L reuteri* DSM 17938 in the management of infantile colic in formula-fed infants. ■

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Reprint requests: Hania Szajewska, MD, Department of Pediatrics, The Medical University of Warsaw, 01-184 Warsaw, Dzialdowska 1, Poland. E-mail: hania@ipgate.pl

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