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“Does Lactobacillus reuteri DSM 17938 reduce daily crying times in infants with colic?”

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements for

The Degree of Master of Science

In

Health Sciences- Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

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ABSTRACT

Objective: The objective of this selective EBM review is to determine whether or not “Does Lactobacillus reuteri DSM 17938 reduce daily crying times in infants with colic?”

Study Design: Review of all English language primary studies published in 2010, 2013, 2015.

Data Sources: Three randomized, double blind, placebo controlled clinical trials found using PubMed.

Outcomes Measured: Daily average crying times were measured by parents who documented these in a journal.

Results: In all three randomized control studies by Chaeu et al. (2015), Savino et al, (2010), and Szajewska et al. (2013), they found that infants with colic given Lactobacillus reuteri DSM 17938 had reduced daily crying times as documented by the parents compared to the infants with colic given a placebo that looked and tasted the same.

Conclusion: All three randomized control trials included in this review indicate that Lactobacillus reuteri DSM 17938 reduces the daily crying times in infants with colic.

Keywords: infantile colic, Lactobacillus reuteri DSM 17938, reduced cry times.

Introduction

Colic is a benign self-limited condition that resolves within a couple of months and has no standard definition. Clinically, it can be defined by the Wessel's criteria as crying for no apparent reason for ≥ 3 hours per day and occurs on ≥ 3 days per week in healthy infants < 3 months of age.¹ This paper evaluates three randomized, double-blind, placebo-controlled trials to determine the efficacy of *Lactobacillus reuteri* DSM 17938 for improving average crying times for infants with colic.

There are no clearly defined estimates for the prevalence of colic due to provider differences in diagnostic criteria, populations, and family perceptions. Estimates of the prevalence of colic in infants range from approximately 8 to 40 percent.¹ The exact total healthcare cost for infantile colic has not been identified either due to the challenges of properly diagnosing colic.¹ Furthermore, it is unknown the exact estimate of healthcare costs to treat colic due to the differences as well.¹

The etiology of infantile colic is unknown; however, it is thought to be due to gastrointestinal, biologic, and psychosocial reasons. Gastrointestinal reasons include faulty feeding techniques, cow's milk protein intolerance, lactose intolerance, gastrointestinal immaturity, intestinal hypermobility, and alterations in fecal micro flora. Biologic reasons include immature motor regulation, increased serotonin, maternal smoking during pregnancy and post-partum, and early form of migraines. Psychosocial reasons include temperament, hypersensitivity, and parental variables.¹

Current treatment methods differ widely. These treatments are mostly trying to control the infants' comfort levels and to help with the parents' quality of life. There is no current cure for infantile colic. About 80-90% of infants with colic have complete resolving of symptoms by

four months of age.¹ Treatment methods include soothing techniques including pacifiers, taking the infant for a car ride, rocking, warm baths, and changing feeding techniques. Many parents are encouraged to also change from milk-based formula to extensive hydrolysate formula, soy protein formula, lactose-free formula, herbal teas, or fiber-enriched formula. These treatments have not shown to provide great improvement in the infants' symptoms. Also, parental support and education is offered to help the parents care for their child and decrease the stress brought on by an infant with colic. It is thought that the cause of colic stems from gastrointestinal disturbances; therefore, the *Lactobacillus reuteri* DSM 17938 addresses this problem.¹

Objective

The objective of this selective EBM review is to determine whether or not “Does *Lactobacillus reuteri* DSM 17938 reduce daily crying times in infants with colic?”

Methods

This investigation looks at three randomized, double blind, placebo controlled clinical trials. In order to participate in the studies the infants had to be < 6 months of age and diagnosed with infantile colic by the Wessel's criteria. All studies included *Lactobacillus reuteri* DSM 17938 as intervention therapy. In all studies, the comparison group's therapy was a placebo identical in appearance and taste. The main outcome looked at for the purpose of this paper was reduction in average crying times.

The author performed searches using the PubMed databases using the key words of infantile colic, *Lactobacillus reuteri* DSM 17938, and reduced cry times. All searches performed were set for English language. All articles searched were published in peer-reviewed journals after the year 2010 and were selected based on relevance and importance of outcome to the patient. Inclusion criteria for the purpose of this paper included randomized, double blind

controlled studies that included POEMs and exclusively breastfed infants. Exclusion criteria included previous Cochrane reviews, previous student published systematic reviews, and infants > 6 months. All studies used similar statistics such as *p*-value, NNT, RBI, ABI to evaluate the outcomes. The demographics of the studies are included and outlined below in Table 1.

1. Table 1 - Demographics & Characteristics of included studies

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W /D	Interventions
Chau, 2015 (1)	Double blind RCT	52	3 weeks-6 months	-diagnoses with colic by Wessel criteria -age 3 weeks to 6 months -exclusively breastfed - term delivery (>37wks) - 5 minute APGAR score ≥ 7 -birth weight ≥ 2500 g	-a major medical problem or acute illness, including gastro esophageal reflux -history of ABX tx before or during the study - history of probiotic or <i>L reuteri</i> supplementation -history of any allergies to any of the ingredients of the probiotic -concurrent participation in another clinical trial	0	<i>Lactobacillus reuteri</i> DSM 17938, 5 drops orally once daily for 21 days
Savino, 2010 (2)	Double blind RCT	50	2-16 weeks	- recruited from general pediatricians and outpatients at the Department of Pediatrics, University of Turin between March 2008 and August 2009 -exclusively breastfeed -mothers avoided cow's milk in their diet,	-clinical evidence of chronic illness or GI disorders -intake of probiotics and/or antibiotics in the week preceding recruitment -formula feeding no acid blockers used	4	<i>Lactobacillus reuteri</i> DSM 17938, 5 drops orally once daily, 30 minutes before feeding, for 21 days
Szajewska, 2013 (3)	Double blind RCT	80	16-81 days	-full term infants aged < 5 months - diagnosed with colic by Wessel's criteria -exclusively or predominately breastfed	-acute or chronic illness -gastrointestinal disorders -use of any ABX and/or probiotics pharmaceutical products within 7 days prior to the study	0	<i>Lactobacillus reuteri</i> DSM 17938, 5 drops orally once daily for 21 days

Outcomes

All the studies measured the reduction in the duration of average crying and fussing times. Parents were instructed to keep a diary to record frequency of colic episodes, daily crying times, feeding schedule, stool frequency, stool characteristics, and any adverse events experienced.

Results

All three articles reviewed were randomized double blind, placebo controlled studies, and they all assessed the efficacy of *Lactobacillus reuteri* DSM 17938 in reducing the crying times of infants diagnosed with colic. All three used a placebo that was similar in appearance and taste to the *Lactobacillus reuteri* DSM 17938. Furthermore, all three studies randomized their sample population and matched them to the experimental and control groups.

Chau et al. had 55 eligible infants enrolled in the study based on inclusion and exclusion criteria as in Table 1. There were 27 assigned to receive placebo while 28 were assigned to receive *L. reuteri*. They had three participants from the *L. reuteri* group withdrawn from the trial and not included in the analysis.² No adverse reactions were reported in the treatment or placebo group. At the end of the treatment period (day 21), the *L. reuteri* group exhibited a significantly greater reduction in daily crying and fussing time. The average daily crying times for the treatment group was 60 minutes (IQR 64) compared to the placebo group being 102 minutes (IQR: 87). *P*-value was .045, which is statistically significant.²

Table 2: Primary outcome: duration of crying and/or fussing times in the placebo and *L reuteri* DSM 17938 groups

	Placebo (n=28)	<i>L reuteri</i> (n=24)	Median difference (95% CI)	P-value
Baseline	122 (163-88)	131 (149-84)	9 (-29 to 46)	.804
Day 7	120 (149-91)	90 (129-53)	-30 (-65 to 5)	.032
Day 14	103 (140-78)	75 (103-54)	-28 (-55 to 0)	.018
Day 21	102 (148-61)	60 (99-35)	-42 (-74 to -10)	.045

Szajewska et al. had 80 infants enrolled in the study based on inclusion and exclusion criteria as in Table 1. There were 40 infants assigned to receive placebo while 40 were assigned to receive *L. reuteri*. There were no participants that were withdrawn. No adverse reactions were reported in the treatment or placebo group.³ At the end of the treatment period (day 28), the *L. reuteri* group exhibited a significantly greater reduction in daily crying and fussing time. The average daily crying times for the treatment group was 52 minutes (IQR: 30) compared to the placebo group being 120 minutes (IQR: 38). *P*-value was <.0001 which is statistically significant.³

Table 3: Primary outcome: duration of crying and/or fussing times in the placebo and *L reuteri* DSM 17938 groups

	Probiotic group (n=40)	Placebo group (n=40)	Median difference (95% CI)	P- value
Baseline	240 (210-270)	240 (203-278)	0.0 (-30 to 30)	.8
Day 7	180 (149-180)	180 (150-210)	0.0 (-60 to 0)	.002
Day 14	105 (101-120)	150 (120-180)	-45 (-75 to -30)	<.0001
Day 21	75 (60-90)	128 (116-150)	-53 (-83 to -45)	<.0001
Day 28	52 (45-75)	120 (90-128)	-68 (-75 to -60)	<.0001

Savino et al. had 50 infants in the study based on inclusion and exclusion criteria as Table 1. Four patients were withdrawn from the placebo group analysis due to fever, failure to complete the diary, or GERD. There were 21 assigned to receive placebo while 25 were assigned to receive *L reuteri*.⁴ There were no withdrawals due to adverse effects related to the trial. Adverse events reported during the study were rhinitis, eczema, fever, otalgia, and gastroesophageal reflux. At the end of the treatment period (day 21), the *L reuteri* group exhibited a significantly greater reduction in daily crying and fussing time. The average daily crying times for the treatment group was 35 minutes (IQR: 85) compared to the placebo group being 90 minutes (IQR: 148). *P*-value was .022 which is statistically significant.⁴

Table 4: Primary outcome: duration of crying and/or fussing times in the placebo and *L reuteri* DSM 17938 groups

	L reuteri group (n=25), Median (IQR)	Placebo group (n=21), Median (IQR)	P- value
Baseline	370 (120)	300 (150)	.127
Day 7	95 (85)	185 (149)	.082
Day 14	60 (70)	150 (145)	.099
Day 21	35 (85)	90(148)	.022

Discussion

All studies were very similar in patient population, sample size, inclusion criteria, exclusion criteria, sample size, methods, and results. They all had the same general outcomes as well. The only difference is Savino et al addresses bacteria in the stools. They took stool samples throughout the trial to evaluate the bacteria concentrations such as *E. coli*.⁴

Currently, Lactobacillus is mostly offered over the counter for infants and children. It is available as drops, capsules, caplets, granules, powder, tablets, chewable tablets, and wafers. It is

also available as an intramuscular injection.⁵ Gerber Soothe colic drops, which are *L. reuteri* drops, cost about \$24.99 on average.⁶ These drops are marketed to help improve good bacteria in an infant's digestive system, which helps to promote digestive comfort. Parents have complained of excess flatulence and bloating while the infant is taking these probiotic drops. It is recommended to use caution with patients who are immunocompromised because it is a live bacterium. Because probiotics are classified as dietary supplements, there are no safety reviews and approved indications by the FDA. Furthermore, there are currently no black box warnings or known drug interactions.⁵

One limitation for these studies was sample size. The sample sizes were 50, 52, and 80.^{2,3,4} Another limitation was the parents' accuracy in documenting the daily average crying times, and all the studies discussed this limitation. The parents' perceptions of the crying times vary, and the time that the parents document the crying times could change the accuracy of the crying times documented. One study was concerned parents would wait until the day of the infant's appointment to document all the crying times.³ Compliance was also not assessed in two studies. It is hard to definitely classify crying times when it is based on many different parents' perceptions versus crying times determined by a single person.

Conclusion

After reviewing these three studies, evidence strongly suggests that *Lactobacillus reuteri* DSM 17938 does reduce daily crying times in infants with colic. The studies followed the participants for an appropriate amount of time, and although the sample sizes were relatively smaller in each study, the results found were still considered statistically significant. The limitation with these studies is there was no objective way to measure crying times. The studies had to rely on the parents to document the crying times daily in a diary. One way to fix this

limitation would be to have voice-activated recorders to measure the crying times. One area of thought for further research about infantile colic was discussed by Savino et al. They checked stool samples. They determined that there was an increase in the probiotic in the stool and a decrease in *E.coli*.² *E. coli* has been found to be in higher concentrations in the stool of those infants with colic than those infants without colic.² There should be a further study to determine if *E. coli* decreasing in the stool decreases the crying times in the infants as well. This would also provide a more objective way to determine if infantile colic is due to gastrointestinal symptoms. Also, future study is warranted to determine if infantile colic predisposes infants to have recurrent abdominal pain, allergic diseases, or psychological disorders later in life. This study could be used to determine if probiotics are recommended to these infants later in life as well.

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