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Live Probiotic Culture Supplementation in the Treatment of Infantile Colic: A Review of Literature

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Abstract

Probiotics are viable microorganisms that can exert potential benefit to health. They have been administered in several clinical conditions with conflicting results. Infantile colic is a recurring condition in the first months of life, defined by Rome III criteria such as paroxysms of irritability, fussing or crying that start and stop without obvious cause, lasting >3 hours per day and occurring >3 days each week and without a failure to thrive. Laboratory tests and radiological examinations are unnecessary if the infant is gaining weight normally and has a normal physical examination. Despite the fact that these symptoms are spontaneously self-limited after the age of 3 months, infantile colic may lead to a significant parental strife. Currently aetiopathogenesis is not yet understood but different treatments have been proposed to mitigate symptoms. Several studies showed that colicky infants had an inadequate balance of *Lactobacilli* in gut microflora and probiotics have been studied as a potential therapy due to their role in the modulation of intestinal microbiota.

We performed a review of literature regarding this topic to evaluate if there was sufficient evidence to support a probiotic supplementation approach for colicky infants.

Keywords: Probiotics; Infantile colic; *Lactobacillus*; Bifidobacterium; Breast milk; Formula milk

Introduction

Probiotics are defined as an oral supplement or a food product that contains a sufficient number of viable microorganisms to alter the microflora of the host and has the potential for beneficial health effects [1]. There are a large number of studies in literature that have assessed the supplementation of probiotics in the prevention and treatment of various clinical conditions. Unfortunately not all the studies performed were well-conducted and there is considerable heterogeneity among trials.

In 2008 our research group reviewed all human trials related to probiotic therapy from 1978 to 2007 [2] and more recently a large group of authors performed an extensive clinical report reviews on the use of probiotics and prebiotics in pediatrics [3]. Data from the literature are quite conclusive regarding the use of probiotics in treatment of acute viral gastroenteritis and in prevention of antibiotic associated diarrhea. Results of randomized controlled trials in which probiotics were used to treat other diseases in pediatric population are inconclusive.

Infantile colic is a widespread clinical condition in infancy, which is observed in 10-30% of infants [4]. The first definition was made by Wessel et al. [5], but in 2006 a group of authors, the Rome Coordinating Committee, introduced this clinical entity in the childhood functional gastrointestinal disorders defining the infantile colic as "paroxysms of irritability, fussing or crying that start and stop without obvious cause, lasting >3 hours per day and occurring >3 days each week and without a failure to thrive" [6]. Symptoms can begin anytime in infancy, usually increases at 6 weeks of age and tends to generally improve by the age of 4-6 months of life. Despite several years of research, the exact etiology is still not fully understood and only less than 5% of infants have identifiable medical explanations for their crying [7]. Since the infantile colic produces appreciable distress for both parents and pediatrician, resulting in considerable medical consultation, adverse effects on maternal mental health and family quality of life, and is even a possible trigger for child abuse, several researchers tend to define an efficacious treatment for this condition.

The most common treatment strategies studied were diet modification (e.g. hypoallergenic diet for mothers of breast-fed infants or whey or casein-hydrolysed formulas for formula-fed infants), drug administration (e.g. anticholinergic medications such as dicyclomine hydrochloride, dicycloverine or cimetropium bromide and simethicone), alternative therapies like probiotics supplementation, hypertonic glucose solution, herbal remedies or even spinal manipulation and behavior modification [8-10].

The role of intestinal microbiota in aetiopathogenesis of several diseases, was the starting point for several researchers to speculate a possible application of probiotics in infantile colic therapy.

In 1994 Lehtonen et al. [11] suggested that inadequate *Lactobacilli* levels in gut microbial composition may affect intestinal fatty acid profiles and could thereby favor the development of infantile colic. *Lactobacilli* contribute to the development of local and systemic immune response and there is evidence that a low concentrations of these bacteria was present in colicky infants [12] with an inadequate balance between *Lactobacilli* strains in gut microbiota (a prevalence of *L. brevis* and *L. lactis* seemed to increase CO_2 production that can lead to meteorism and abdominal distension) [13].

Starting from this suggestive hypothesis, several studies were performed to evaluate the role of probiotics in management of infantile colic and, to our knowledge; this is the first review of literature regarding this topic.

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Materials and Methods

A literature search was conducted using PubMed, MEDLINE and EMBASE with keywords like "infantile colic", "probiotics" and "treatment".

We found only 4 published Randomized Controlled Trial (RCT) that were well-performed and designed for the specific evaluation of the role of probiotics in treatment of infantile colic; however these studies have some limitations.

Primary outcome: improvement of infantile colic

Savino et al. [14] performed a prospective randomized study to test the hypothesis that a supplementation with *Lactobacillus reuteri* 55730 improved symptoms of infantile colic. Eighty-three breast-fed colicky infants were assigned randomly to receive *L. reuteri* (10^8 cfu) orally once per day for 28 days or simethicone. All mothers were asked to follow a cow's milk-free diet. Results showed that in the probiotic group, infants had a significant reduction in daily crying already at day 7, with a persistent significant improvement at day 14, 21 and 28 compared with infants in simethicone group. An essential limitation of this study is that it was could not be conducted in a blinded manner, with a difference in dosage and time of administration of *L. reuteri* and simethicone.

For this reason the same author group performed in 2010 a randomized, double-blind, placebo controlled study to confirm the beneficial role of *L. reuteri* in colicky infants [15]. Forty-six breastfed colicky infants, defined according to Rome III criteria, aged 2 to 16 weeks at recruitment, were randomized to receive *L. reuteri DSM 17938* (a strain of *L. reuteri* ATCC 55730 without unwanted resistance traits for tetracycline and lincomycin) at a dose of 10^8 cfu or placebo. Both formulations were administered in 5 drops, once a day, 30 minutes before the feeding for 21 days. Mothers were encouraged to follow a cow's milk free diet. Results showed a significant reduction in daily crying at the end of the study among colicky infants who received the probiotic: 35 minutes/day versus 90 in placebo group. Moreover the number of infants that had crying times > 180 minutes/day was significantly lower in the probiotic group. A microbiological analysis of fecal cultures was also conducted in this study that showed a significant reduction of *Escherichia coli* and an increase of *Lactobacilli* counts in the probiotic group compared to the placebo group. The authors speculated on these findings and hypothesized that *L. reuteri* promotes gut health through a reduction of *E. coli* colonization. Even these studies have limitations: the small size of sample and the lack of an intention-to treat analyses.

The only RCT specifically designed to evaluate the role of probiotics in formula-fed colicky infants was conducted by Dupont et al. [16]. They enrolled in a prospective multi-centre, double-blind randomized trial, 66 healthy infants with colic, aged 3 weeks to 3 months. Subjects were randomly assigned to consume for 1 month an experimental formula α-lactalbumin enriched and probiotic supplemented (*Lactobacillus rhamnosus* and *Bifidobacterium infantis*) or a control probiotic-free formula. Results showed that the number of infants presenting a reduction in daily crying duration higher than 25% in the first 15 days of study did not differ between groups, but irritability and agitation without crying decreased more with the probiotic than standard formula. Authors concluded that the failure of experimental formula for an improvement in symptoms of infantile colic might be due to the limited number of infants (during the treatment period there were 16 infants drop-out) and to a flaw in the system used to measure colic. It is possible that the choice of probiotic strains could be a bias in this study.

Very recently Szajewska et al. [17] wanted to confirm the beneficial supplementation of *L. reuteri DSM 17938* in colicky infants who were exclusively or predominantly (>50%) breastfed. Mothers were not advised to follow an elimination diet. Eighty colicky infants, defined according to Rome III criteria, were randomized to receive *L. reuteri* at a dosage of 108 colony forming units (cfu) or placebo orally in 5 drops, once a day, for 21 days. The effect of treatment was evaluated at day 7, 14, 21 and 28, 1 week after the termination of intervention. Results confirmed a significant reduction of crying time in probiotic group compared to the placebo group (at the end of study 52 min/d and 120 min/d respectively). Moreover at day 28, all 40 infants in probiotic group had a reduction in the daily average crying time >50% compared with only 25 infants in placebo group. Authors also demonstrated, throughout the study period, a significant reduction in the parental perception of colic severity and an improvement of parental/family quality of life in parents of probiotic group infants compared to the placebo group. A limitation of this study is that authors did not use an objective way to assess the duration of crying in infants, instead trusting in the parents' report.

In our research of literature we identified two additional studies where the protocols seemed to be well designed. Unfortunately, as of this review, these studies have not been published and we can report only on the data from an abstract presented in a congress.

The first of these, performed in 2010 by Kazmin et al. [18] was a randomized, double blind placebo-controlled trial in which 100 breastfed colicky infants, defined with Rome III criteria, received once-daily supplementation of *L. reuteri* or placebo for 21 days in a double blind fashion. Results were not presented in this congress and authors declared that these were in progress. The second study, conducted by Chau et al. [19] in 2012, was a randomized, double-blind, placebo controlled study, in which 100 infants diagnosed with either colic symptoms (according to Rome III criteria), fussy-gassy or gastroesophageal reflux (with or without esophagitis) were enrolled to receive *L. reuteri* (10^8 cfu) or placebo 30 minutes following breast-feeding once daily for 21 days. Also these results were in progress, but both these studies seemed well-conducted and data from them could help to clarify if supplementation of *L. reuteri* could become an effective and efficacious treatment for infantile colic.

Primary outcome: safety and tolerance of probiotics in formulas

There also have been studies published in the literature that have evaluated the role of probiotics in the treatment of infantile colic as a secondary outcome in which limitations were significant: small number of subjects enrolled, lack of accepted and well-defined criteria for diagnosis of symptoms and an ample heterogeneity of probiotic strains used.

One of these studies was conducted by Menthula et al. [20], in which authors supplemented colicky (9) and non-colicky infants (9) with randomly provided capsules contained a mixture of probiotic strains (*Lactobacillus rhamnosus* GG, *Lactobacillus rhamnosus* LC705, *Bifidobacterium breve* Bbi99, and *Propionibacterium freudenreichii* ssp. *shermanii* JS) or placebo suspended in water or breast milk once a day for 2 weeks. Authors did not find any significant difference in total crying time between groups of colicky infants supplemented or not.

Results from this study were limited by the very small sample size and because of this statistical tests were not reported.

In another study Weizman and Alsheikh [21], created to test safety and tolerance of two formulas in full-term healthy infants, 59 subjects, aged 3-65 days, were randomized to receive formula supplemented with probiotic strains (*Bifidobacterium lactis* and *Lactobacillus reuteri*) or a probiotics-free formula. Apart from the primary outcomes of this study (safety and tolerance of new formulas and normal growth parameters) the authors did not find significant differences between the two formulas regarding number of bowel movements, crying and restlessness scores, number of severe crying episodes and number of night awakenings.

Saavedra et al. [22] conducted a similar study in which healthy infants, aged 3-24 months, were assigned to receive a standard milk-based formula containing 10^7 cfu of *Bifidobacterium lactis* and *Streptococcus thermophilus*, or a formula containing 10^6 cfu of the same strains or unsupplemented formula. The final study population was composed of 118 infants that were randomized to consume the three formulas for 210 ± 127 days. Regarding the clinical outcomes, authors did not report any significant differences between groups in frequency of reporting loose stools, fever and vomiting, or discomfort passing bowel movements, while the colic or irritability results showed a significant lower frequency of reporting symptoms in both supplemented groups. An important limitation of this study was, primarily, the lack of defined criteria for infantile colic; moreover the advanced age of enrolled infants (more than 3 months) was very near the period of life when infantile colic tends to improve spontaneously.

Chouraqui et al. [23] in a prospective, controlled, double-blind, randomized trial, enrolled 227 healthy full-term formula-fed infants to assume either a control formula or three different study formulas containing *Bifidobacterium longum BL999* plus *Lactobacillus rhamnosus LPR* (group 1), or these probiotic strains plus galactooligosaccharide and short-chain fructooligosaccharide (GOS/SCFOS) (group 2) or *B longum* plus *Lactobacillus paracasei ST11* plus GOS/SCFOS (group 3). Regarding clinical outcomes, the authors demonstrated, during the treatment period (2-16 weeks of age), that liquid stools occurred more frequently in group 3 than other two groups and control group, but the frequency with which flatulence, colic, spitting up and vomiting occurred were not significantly different between the control and study groups. Even in this study there is no clear definition of infantile colic.

We observed the same limitation in the randomized double blinded controlled study of Olivares et al. [24]. These authors enrolled 126 formula-fed infants of 1 month of age randomly assigned to assume formula supplemented with *L. fermentum* CECT5716 or probiotic-free formula until the age of 6 months. Regarding clinical outcomes, the authors did not find significant differences in the incidence of infantile colic, spitting up or constipation in both groups. The only difference was a threefold greater incidence of diarrhea in infants of the control group versus the probiotic group.

An interesting systematic review of studies in which synbiotics, prebiotics and probiotics were added to infant formula to promote development and growth of infants was recently performed by Mugambi et al. [25]. Data from these studies confirmed the insufficient role of probiotic supplementation to reduce incidence of diarrhea, colic, spitting up, regurgitation, crying, restlessness or vomiting. All of these studies noted an improvement in infantile colic but only as a secondary outcome, thus reducing the reliability of results.

Results and Discussion

The exact mechanisms by which a probiotic might exert its actions have yet to be elucidated. *L. reuteri* was the strain primarily studied and yielded the best results in the treatment of infantile colic. The effect of this probiotic strain on gut motility and function, colonic sensory nerves, colon contractile activity, pain perception, and anti-inflammatory properties, could be possible explanations [26-31]. Moreover, given that some data suggest that infantile colic may represent the first clinical symptoms of food hypersensitivity, *L. reuteri*, thanks to its demonstrated features of modulation and stimulation of immune response, may play a role in treatment of such clinical entity.

Based on results of studies analyzed in this review, it is clear that it is necessary, in future studies, to perform trials specifically designed to assess the role of probiotic supplementation for treatment of infantile colic and try to reduce the confounding responses where this outcome is secondary. These studies will be need to be randomized, double-blind and placebo-controlled to limit any possible bias. Moreover there is a necessity to restrict the heterogeneity of probiotic strains, the dosage and the treatment period proposed, and more important, it is essential that symptoms are defined based on universally accepted criteria.

Certainly further research is needed to confirm the role of probiotics in the management of infantile colic, but considering the results from these studies and the lack of effective therapy for this clinical entity, a supplementation with *L. reuteri DSM 17938* can still be considered, given the generally safe profile of probiotics.

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