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Revisión

Probiotics in the treatment of infantile colic: a meta-analysis of randomized controlled trials

Probióticos en el tratamiento del cólico infantil: un metaanálisis de ensayos controlados aleatorios

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Abstract

Introduction: infantile colic has always been a problem for caregivers, and research on probiotics in treating and preventing infant colic is still controversial.

Material and methods: trials were performed before November 2021 and retrieved from the PubMed, Web of Science, The Cochrane Library, Medline, and Google Scholar databases. Data extraction and quality evaluation of the trials were performed independently by two investigators. A meta-analysis was performed using Review Manager 5.3. It includes nine randomized controlled trials in 587 infants with colic.

Results: eight of these experiments described probiotics for the prevention and treatment of intestinal colic in infants, with 228 in the probiotics group and 227 in the placebo group, with a total effective rate (RR = 1.88, 95 % CI: 1.61 to 2.19, $p < 0.00001$).

Conclusion: probiotics may improve therapeutic and preventive effects, especially within four weeks of probiotic treatment.

Keywords:

Infantile colic. Probiotic. Placebo. Treatment. Meta-analysis.

Resumen

Introducción: el cólico infantil siempre ha sido un problema para los cuidadores y la investigación sobre los probióticos para tratar y prevenir el cólico infantil sigue siendo controvertida.

Material y métodos: los ensayos se realizaron antes de noviembre de 2021 y se recuperaron de las bases de datos PubMed, Web of Science, The Cochrane Library, Medline y Google Scholar. Dos investigadores realizaron de forma independiente la extracción de datos y la evaluación de la calidad de los ensayos. Se realizó un metaanálisis utilizando Review Manager 5.3. Incluye nueve ensayos controlados aleatorios en 587 lactantes con cólicos.

Resultados: ocho de estos experimentos describieron probióticos para la prevención y el tratamiento del cólico intestinal en lactantes, con 228 en el grupo de probióticos y 227 en el grupo de placebo, con una tasa efectiva total (RR = 1,88, IC del 95 %: 1,61 a 2,19, $p < 0,00001$).

Conclusión: los probióticos pueden mejorar los efectos terapéuticos y preventivos, especialmente dentro de las cuatro semanas posteriores al tratamiento con los mismos.

Palabras clave:

Cólico infantil. Probiótico. Placebo. Tratamiento. Metaanálisis.

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INTRODUCTION

Infantile colic is a behavioral syndrome that manifests as irritable or crying behaviors that are difficult to soothe in healthy babies. It appears for more than three hours a day, lasts for more than three days per week, and lasts for more than three weeks (1). It usually occurs within three months of birth, but approximately 10 % of cases occur after 4-5 months. However, as neurophysiological development occurs, the symptoms of infantile colic will gradually improve, and the symptoms among infants aged three to four months will disappear on their own. In addition, infantile colic can increase the occurrence of psychological distress and depression in caregivers, hinder the development of heathy mother-to-child relationships, and cause infants to suffer accidental injuries and impaired family function (2).

The pathogenesis of infantile colic is unclear. Gastrointestinal motility, lactose intolerance, and psychosocial factors may be involved in the occurrence of infantile colic, but there is no firm evidence (3). Current treatments for infantile colic include dietary adjustments, pharmacological and behavioral interventions, and complementary and alternative therapies, but none of these treatments are effective (4). However, probiotics are viable, nonpathogenic microorganisms that can potentially positively affect a child's body by balancing the intestinal flora. Several beneficial effects of probiotics on the host intestinal mucosal defense system have been identified. These include blocking pathogenic bacterial effects by producing bactericidal substances and competing with pathogens and toxins for adherence to the intestinal epithelium (5-7). The results of research on the treatment and prevention of colic in infants remain controversial. Therefore, this meta-analysis aimed to systematically evaluate the effectiveness of probiotics in preventing and treating infantile colic, to provide evidence-based medical support for clinical practice.

METHODS

DATA SOURCES AND LITERATURE SEARCH

We followed the guidelines of the meta-analysis of observation studies in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). A comprehensive computer search of PubMed, Web of Science, The Cochrane Library, Medline, and Google Scholar databases, collection of published studies on the prevention and treatment of infantile colic as of 2021-11, was performed. Search terms included (probiotic or probiotics or probiotic bacteria) AND (colic or infantile colic or intestinal colic) AND (infant or kid or child and pedia) AND (prevention or treatment or excessive crying or duration of crying or crying time or maternal mental health). The literature was retrieved using the reference backtracking method to avoid missing relevant research as much as possible.

STUDY SELECTION

Inclusion criteria were: a) published randomized controlled study (randomized controlled trials [RCTs]); b) assessed association between probiotics and colic in infants; and c) the experimental group was treated with probiotics, and the control group was treated with placebo. In the data, the titles and abstracts of the searched papers were independently screened by two reviewers, and articles that did not meet the above inclusion criteria were excluded. The third person resolved the differences and contradictions between them. The main data extracted include the first author's last name, year of publication, country of study, indication, sample size, interventions, treatment strategy, duration, and outcomes. The overall details of risk of bias were shown (Figs. 1 and 2). Papers selected for retrieval were assessed by two independent reviewers for methodological validity prior to inclusion in the review using standardized critical appraisal instru-

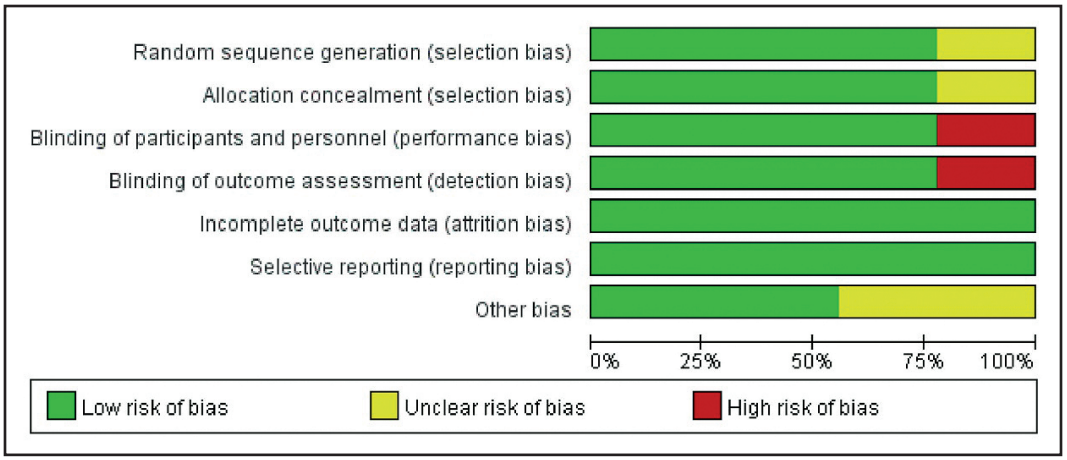

Figure 1.
Risk of bias.

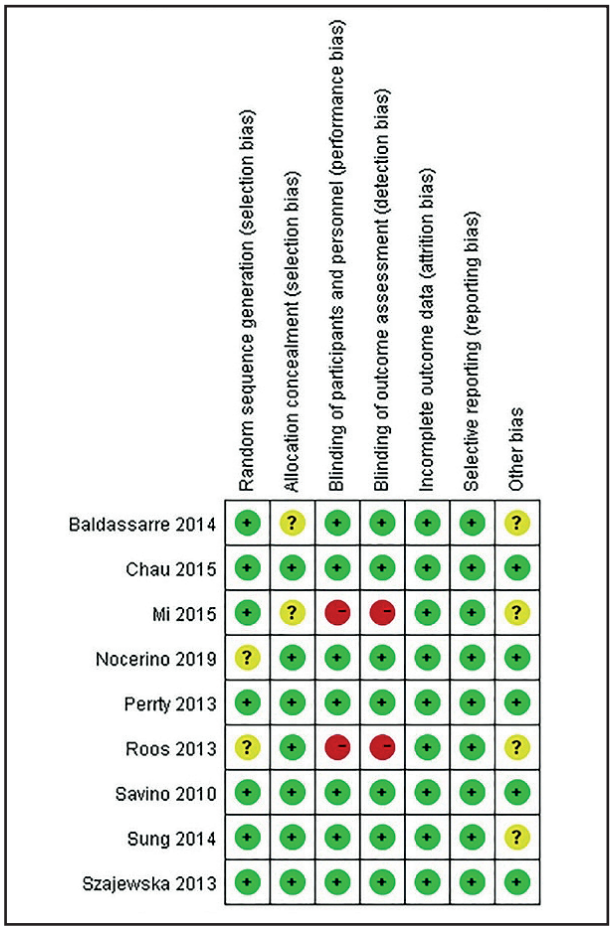

Figure 2.
Risk of bias summary.

ments for RCTs available through The Cochrane Collaboration. Five trials were categorized as being at low risk of bias, three as being at unclear risk of bias and two as being at high risk of bias. All quality measures recorded, and data extracted for meta-analysis, occurred within Review Manager 5.3.

STATISTICAL ANALYSES

Meta-analysis was performed using Review Manager 5.3. The effect of counting data was RR value and 95 % confidence interval (CI). It was estimated by the Cochran Q test and I^2 statistic. Q statistic was considered as significant when the p value was less than 0.10, and the I^2 index was used to quantify the extent of statistical heterogeneity. If $I^2 < 50$ %, $p > 0.05$, it is considered that there is no heterogeneity, and a fixed effect model is used; if $I^2 > 50$ %, $p \leq 0.05$, it is considered that there is heterogeneity, and a random effect model is used for analysis. However, there is heterogeneity between the results of each study, $I^2 > 50$ %, $p \leq 0.05$; the source of heterogeneity needs to be explored, and sensitivity analysis is necessary if necessary. The publication bias was tested using the Begg method, with a test level of $p < 0.05$.

RESULTS

STUDY CHARACTERISTICS

As shown in figure 3, by searching the database, 894 related studies were screened. After reading the title and abstract, 873 studies were excluded. Of the remaining 21 studies, three studies are no quantitative assessment, two studies are no out-

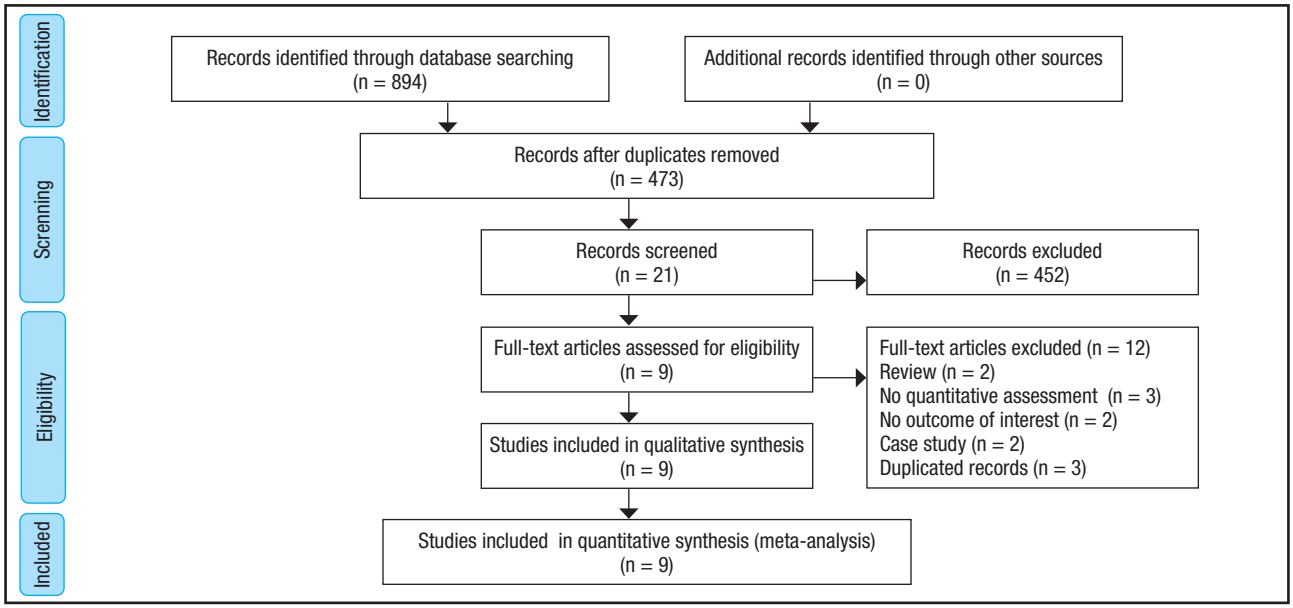

Figure 3.
PRISMA flow diagram of the search result of the meta-analysis.

come of interest, two studies are review, two studies are case study, and three studies are duplicated records, therefore excluded. Finally, the meta-analysis includes nine RCTs between 2010 and 2020 (8-16), and a total of 587 infant patients. Table I summarizes the characteristics of the studies included. Three studies were conducted in Italy (8,14,16) and one in Poland (9), Sweden (10), Australia (11), China (12), Canada (13) and Finland (15), respectively. All included studies provided probiotic species and application metrics, and most provided number of responders.

PRIMARY END POINT

Associations between whole infant colic and the probiotic treatment and prevention

As shown in figure 4, of the nine studies included, eight (8-10,12-16) examined the effectiveness of placebo and probiotics in the treatment and prevention of infantile colic. There was statistical heterogeneity between studies (I^2 = 62 %, p = 0.01), and the analysis was performed using a random effects model. The combined effect size (relative risk [RR] = 1.88, 95 % CI: 1.61 to 2.19, p < 0.00001). The results of the analysis suggest that probiotics are generally beneficial for the treatment and prevention of intestinal colic in infants.

Treatment of infantile colic with probiotics in one month

As shown in figure 5, four of the nine studies included (8,9,12,13) examined the effects of probiotics on infant colic at seven days (RR = 2.47, 95 % CI: 1.40 to 4.36 , p = 0.002); four studies (8,9,12,13) examined the effects of probiotics on infant colic at 14 days (RR = 3.43, 95 % CI: 1.30 to 9.01, p = 0.01); five studies (8-10,12,13) examined the effects of probiotics on infant colic at 21 days (RR = 2.42, 95 % CI: 1.35 to 4.35, p = 0.003); and three studies (9,12,14) examined the effect of probiotics on infant colic at 28 days (RR = 2.48, 95 % CI: 1.28 to 4.80, p = 0.007). The results of the comprehensive analysis suggest that probiotics are more effective than a placebo in treating intestinal colic in infants within seven, 14, 21, and 28 days.

SUBGROUP ANALYSES AND SENSITIVITY ANALYSES

Figure 6 shows the results of a subgroup analysis of the effectiveness of probiotics for treating and preventing intestinal colic in infants. The subgroup analysis examined groups by treatment method. Six studies (8-10,12-14) examined the effects of probiotics on infant colic (RR = 2.08, 95 % CI: 1.45 to 2.98, p < 0.001). There was statistical heterogeneity (I^2 = 74 %, p = 0.002). Two studies (15,16) examined the effect of probiotics on the prevention of intestinal colic in infants (RR = 1.48, 95 % CI: 1.11 to 1.99, p = 0.008), and there was no statistical heterogeneity between studies (I^2 = 0 %, p = 0.84). The results of the subgroup analysis show that probiotics are effective not only in treating infantile colic, but also in preventing infantile colic. Because there was substantial heterogeneity among the studies that examined treatment, a sensitivity analysis was performed on the treatment group. As shown in figure 7, the overall sensitivity analysis results are stable, and the main sources of heterogeneity are the studies by Mi et al. (12) and Chau et al. (13). After excluding the two studies, the combined effect size reduced the heterogeneity (I^2 = 24 %, p = 0.26). However, after excluding any other literature, the heterogeneity did not change significantly.

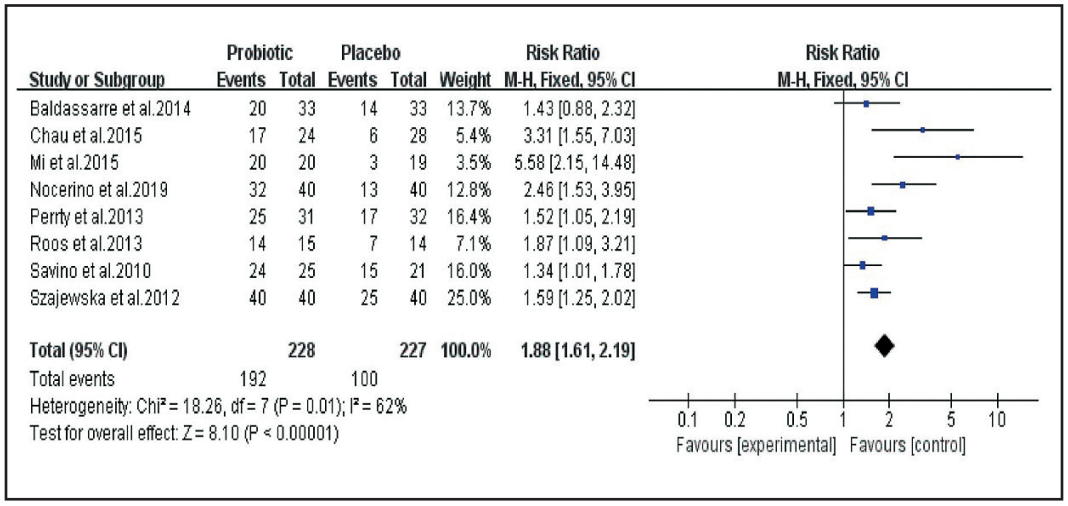

Figure 4.

Total effectiveness of probiotics in preventing and treating infantile colic.

Table I. Characteristics of included studies for the analysis of efficacy

Study	Year	Location	Indication	Sample size (B/G)		Duration of intervention	Intervention	Treatment strategy	Outcomes
				Probiotic	Placebo				
Savino et al. (8)	2010	Italy	Therapy	14/11	15/10	21 days	*L. reuteri* DSM 17938 in a mixture of sunflower oil and medium-chain triglyceride oil	*L. reuteri* at a dose of 10^8 CFU/day for 21 days	Decrease in daily average crying time of < 50 %; infants intestinal microflora; safety
Szajewska et al. (9)	2013	Poland	Therapy	24/16	22/18	28 days	*L. reuteri* DSM 17938	*L. reuteri* at a dose of 10^8 CFU/day for 21 days	Decrease in daily average crying time of < 50 %; parental perceptions of colic severity; family quality of life; safety
Roos et al. (10)	2013	Sweden	Therapy	9/6	7/7	21 days	*L. reuteri* DSM 17938	*L. reuteri* at a dose of 10^8 CFU/day for 21 days	Decrease in daily average crying time of < 50 %; gut microbiota
Sung et al. (11)	2014	Australia	Therapy	37/48	48/34	6 months	*L. reuteri* DSM 17938 an oil suspension	*L. reuteri* at a dose of 0.2×10^8 CFU/day for 1 month	Crying time; parental maternal depression
Mi et al. (12)	2015	China	Therapy	14/7	11/10	28 days	An oil based suspension containing *L. reuteri* DSM 17938	*L. reuteri* at a dose of 10^8 CFU/day for 21 days	Decrease in daily average crying time of < 50 %; parental maternal depression
Chau et al. (13)	2015	Canada	Therapy	14/13	14/14	21 days	10^8 CFU/5 drops of *L. reuteri* DSM 17938 suspended in sunflower oil, medium-chain triglyceride oil, and silicon dioxide	*L. reuteri* at a dose of 10^8 CFU/day for 21 days	Decrease in daily average crying time of < 50 %; safety
Nocerino et al. (14)	2020	Italy	Therapy	22/18	21/19	28 days	lactis BB-12®, DSM 15954 in oil maltodextrin suspension	lactis BB-12® at a dose of 10^9 CFU/day for 28 days	Decrease in daily average crying time of < 50 %; gut microbiota structure and butyrate, beta-defensin-2 (HBD-2), cathelicidin (LL-37), secretory IgA (sIgA) and fecal calprotectin levels were assessed
Perrty et al. (15)	2013	Finland	Prophylaxis	16/15	23/8	2 months	*Lactobacillus rhamnosus* GG (ATCC 53103)	*Lactobacillus rhamnosus* GG (ATCC 53103) 1×10^9 CFU/day in 1 dose from day 1 to day 30 and 1×10^9 CFU twice daily from day 31 to day 60	Decrease in daily average crying time of < 50 %; frequency of stools, consistency of stools

(Continues on next page)

Table I (Cont.). Characteristics of included studies for the analysis of efficacy

Study	Year	Location	Indication	Sample size (B/G)		Duration of intervention	Intervention	Treatment strategy	Outcomes
				Probiotic	Placebo				
Baldassarre et al. (16)	2014	Italy	Prophylaxis	33*	33*	36 weeks gestation to 4 weeks postnatally	High concentration, multi-strain probiotic supplement	900 billion viable lyophilised bacteria of *4 different strains of lactobacilli (L. paracasei* DSM 24733, *L. planetarium* DSM 24730, *L. acidophilus* DSM 24735 and *L. delbrueckii subspbulgaricus* DSM 24734), 3 strains of bifidobacterial (B longum DSM24736, BB breve DSM24732 and B infantis DSM24737) and 1 strain of *Streptococcus thermophilus* DSM 24731	Decrease in daily average crying time of < 50 %; analysis of breast milk for cytokine patterns, secretory IgA in breast milk and stools, fecal lactoferrin

**No specific number of boys and girls reported.*

SECONDARY END POINTS

Impact on parent mental health

Figure 8 shows that two studies (11,12) examined the effects of probiotics on the mental health of pregnant women after treatment and prevention of infant colic (WMD = -1.43, 95 % CI: -2.76 to -0.10, p = 0.04). There was no statistical heterogeneity between the studies (I^2 = 0 %, p = 0.32). The analysis shows that probiotics can make parents feel happy by affecting the baby's intestinal colic.

PUBLICATION BIAS AND SENSITIVITY ANALYSIS

Although the scatter of the funnel plot is slightly asymmetric (Fig. 9), the publication bias was detected by the Begg method. The results showed that the Begg method of the included study was p = 0.063, and there was no evidence of publication bias in the included study.

DISCUSSION

To the best of our knowledge, this is the first meta-analysis examining the effectiveness of probiotics in the treatment and prevention of infantile colic. The results of the meta-analysis show that probiotics are significantly more effective in treating intestinal colic in infants than placebo. Subgroup analysis revealed that probiotics were superior to placebo not only in the treatment of infant colic, but also in prevention. In addition, the use of probiotics to relieve intestinal colic in infants can lead to reduced psychological stress among parents; the results of this study were not found in similar studies.

Infantile colic affects a large proportion of infants. Infants may exhibit symptoms such as uncomfortable crying, painful expressions, high-pitched crying, and curled legs (17). These symptoms are enough to make researchers realize that these infants are in pain. However, in more than 90 % of cases of intestinal colic in infants, the intestinal colic does not need to be treated, but rather, caregivers need to be helped through the challenging period of child growth and development (18). In general, if the symptoms of infantile colic can be relieved and the attention of the caregiver can be appropriately shifted, then infantile colic is not a threat to the baby's body (19). Conversely, an incorrect diagnosis and inappropriate treatment can physically and emotionally harm babies and caregivers unnecessarily (20). Clinicians need to assess caregivers' vulnerabilities, such as depression and lack of social support, and provide sustainable help to the family (21). If attempts to intervene in the baby's intestinal colic are unsuccessful, then it is likely that the caregiver's anxiety and frustration will be increased, eventually impairing the caregiver's ability to comfort the baby and making him/her doubt his/her ability as a caregiver (22).

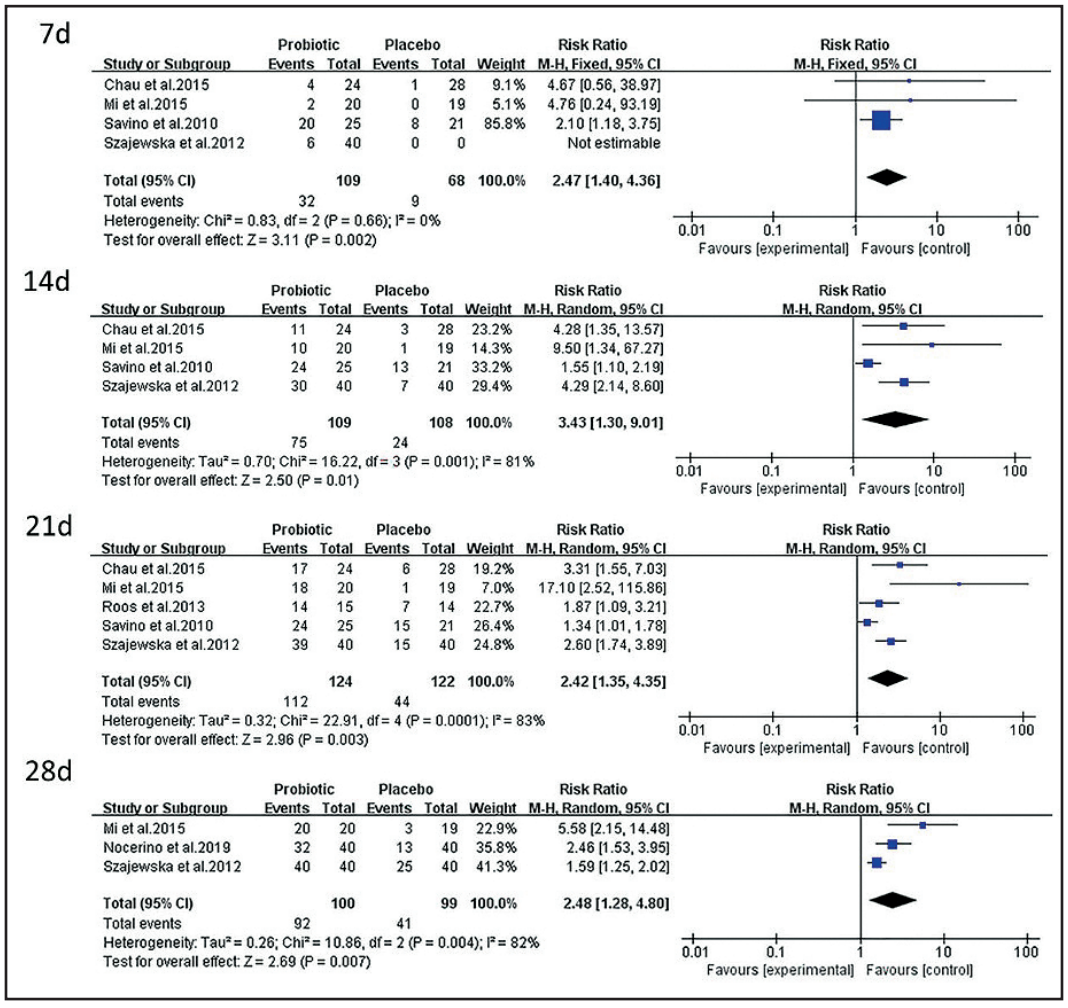

Figure 5.

Effectiveness rate comparison of 7, 14, 21 and 28 days in probiotic groups and the placebo group.

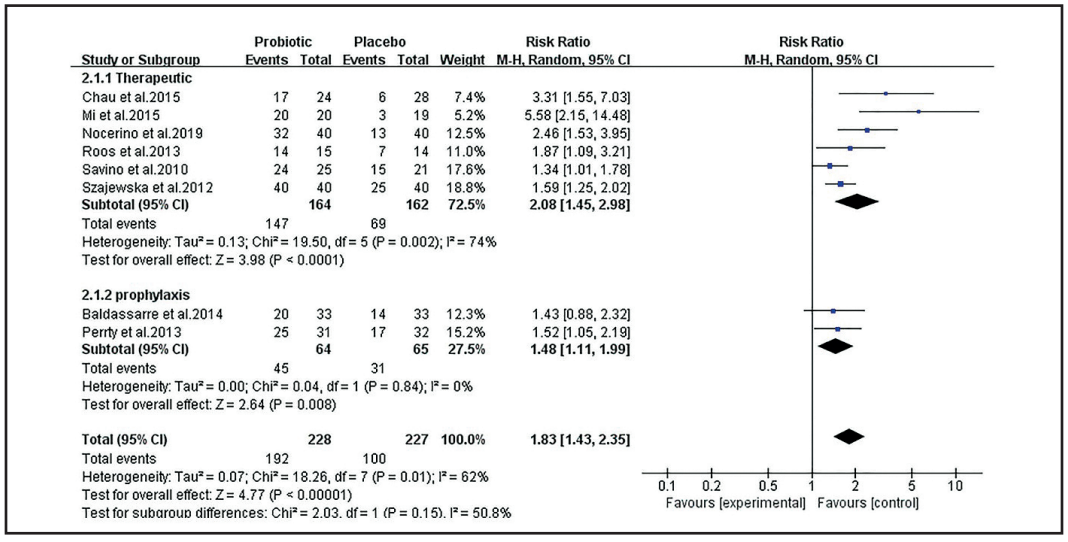

Figure 6.

Subgroup analysis of treatment and prevention groups.

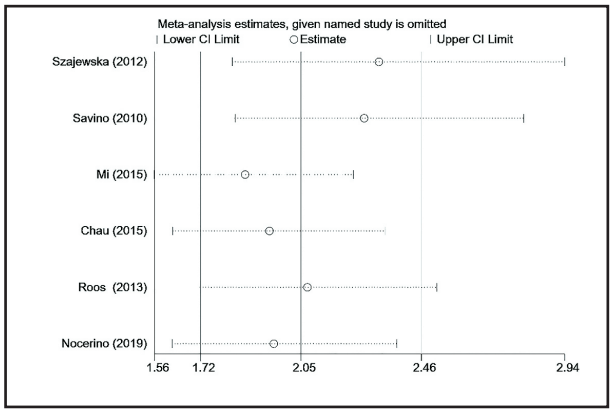

Figure 7.

Sensitivity analysis.

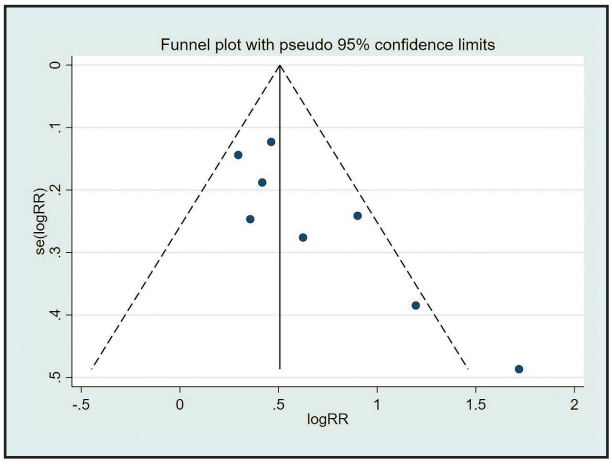

Figure 9.

Funnel diagram of effective probiotics for preventing and treating infantile colic.

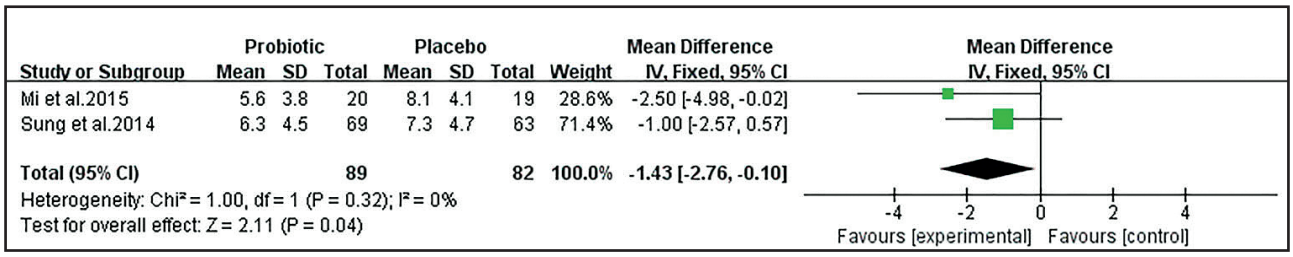

Figure 8.

Compared with the placebo group, the probiotic group can benefit parents' mental health.

In our meta-analysis, eight RCTs produced relatively stable results: probiotics can be used to treat and prevent infantile colic, even at seven, 14, 21, and 28 days. A sensitivity analysis revealed that the studies by Mi et al. (12) and Chau et al. (13) affected the stability of the results. Based on the above analysis, we reached a comprehensive conclusion that probiotics can effectively treat and prevent infantile colic, suggesting that probiotics can play an active role in the treatment and prevention of infantile colic. Gerasimov et al. (23) studied the auxiliary application of *Lacticaseibacillus rhamnosus (L. rhamnosus)* 19070-2 and *Lactobacillus reuteri (L. reuteri)* 12246 in 84 infants with colic. The mean change in cry and fuss time from day 0 to day 28 was 163 ± 99 minutes in the probiotic group and 116 ± 94 minutes in the control group ($p = 0.019$). The findings confirm that *Lactobacilli* can be used to decrease cry and fuss time and to provide dietary support in exclusively breastfed infants with colic. Indrio et al. (24) studied 238 infants who received *L. reuteri* DSM 17938 probiotics for three months. At three months of age, infants in the probiotic group showed a lower mean duration of crying time (38 *vs* 71 minutes; $p < 0.01$), confirming that the use of this probiotic can prevent the incidence of gastrointestinal disorders in infants. In addition, the probiotic strains studied in this paper mainly include *Lactobacillus* (*L. reuteri* DSM17938) and *Bifidobacterium* (*B. lactis* Bb-12), which are currently the best studied probiotics. Some lactobacilli and *Bifidobacterium* strains have proven to be most effective if treatment is introduced early (25). In a study by Chau et al. (13), infants took a daily dose of *L. reuteri* (1×10^8 colony forming units). By 21 days, total average crying and fussing times throughout the study were significantly shorter among infants with colic in the probiotic group compared with infants in the placebo group (29 ± 13 hours *vs* 37 ± 13 hours, $p = 0.028$). Infants given *L. reuteri* DSM 17938 showed a significant reduction in daily crying and fussing times at the end of treatment period compared with those receiving placebo (64 minutes/day *vs* 87 minutes/day, $p = 0.045$). On day 21, a significantly higher proportion of infants in the *L. reuteri* DSM 17938 group responded to treatment with a ≥ 50 % crying time reduction compared with infants given placebo (17 *vs* 6, $p = 0.035$). The results of the study by Nocerino et al. (14) showed that infants treated with lactis BB-12 at a dose of 10^9 CFU/day for 28 days from week 2 had a higher rate of ≥ 50 % reduction in mean daily crying time. After treatment was stopped, no infants relapsed. Mean crying times were reduced in both groups, but the effect was higher in the BB-12 group (-4.7 ± 3.4 *vs* -2.3 ± 2.2, $p < 0.05$). Average daily stool frequency was reduced in both groups, but the effect was significantly higher in the BB-12 group; stool consistency was

similar in both groups. *Bifidobacterium* abundance (significantly associated with reduced crying time), butyrate and increased levels of HBD-2, LL-37, sIgA in the BB-12 group were associated with decreased fecal calcin levels.

Although this study has formulated strict inclusion and exclusion criteria, it still has the following limitations: a) statistical heterogeneity has been detected in the current study (heterogeneity may be due to different probiotic types and different sample sizes); b) some studies did not explain randomization methods, distribution methods, and statistical analysis methods; c) due to language restrictions, only English literature was included, and literature in other languages was excluded; d) the quality of different studies varies, which may lead to bias; and e) different research treatments are different.

The differences in treatments may directly lead to the degree of colic in infants and affect the prognosis. Nowadays, the international community has been working to find a specific probiotic strain with good effect and good safety to better treat infant patients, but it seems to be cautious about probiotics treatment and prevention of infant colic. Therefore, in the future, more rigorous multi-center randomized double-blind controlled trials will further clarify the significance of probiotics in preventing and treating colic in infants.

CONCLUSION

In summary, the meta-analysis has extensively evaluated the existing data, and the results show that probiotics have a certain positive effect on infant colic. Probiotics may improve therapeutic and preventive effects, especially within four weeks of probiotic treatment. However, the conclusions of this study are limited by the heterogeneity of the included randomized controlled trials and require careful consideration. Therefore, we must comprehensively consider the situation of the baby and provide the most appropriate treatment plan under the premise of respecting the wishes of the guardian, improving the treatment effects for the baby, and improving the quality of family life.

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