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SHORT COMMUNICATION

Lactase for infantile colic: A systematic review of randomized clinical trials

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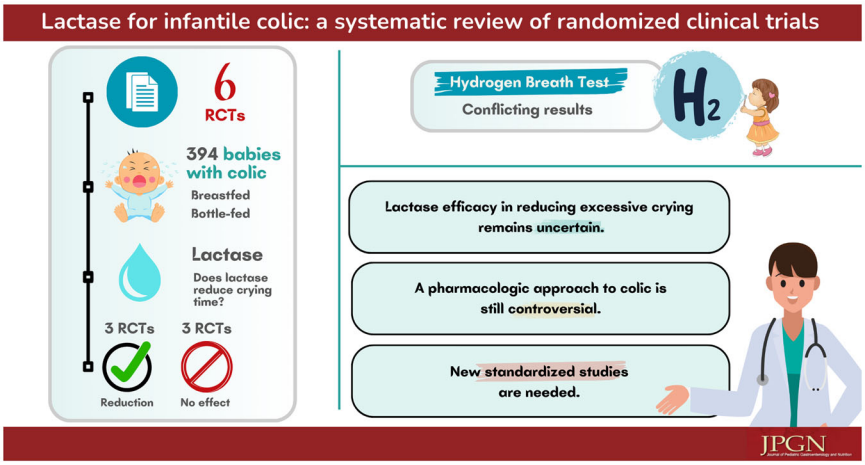
Abstract

Infantile colic is excessive crying for no apparent reason in an otherwise healthy infant. Although its physiopathology is not completely understood, therapies usually target gastrointestinal symptoms. This systematic review of randomized controlled trials (RCTs) analyzes the efficacy of lactase supplementation in infantile colic. PubMed, Embase, and Cochrane were searched for RCTs evaluating lactase supplementation in infants up to 6 months old with infantile colic. Out of six RCTs including 394 patients, three reported a significantly shorter crying time in the lactase group than in the placebo group, while the other three found no significant difference between groups. Of the two studies that performed the hydrogen breath test, only one reported a significant reduction in exhaled hydrogen levels. The pharmacological approach to infantile colic remains debatable, and new studies with standardized diagnostic criteria and outcomes are required to guide lactase supplementation in clinical practice.



KEYWORDS

children, crying, enzyme supplementation, hydrogen breath test, infant

1 | INTRODUCTION

Infantile colic is the unexplained crying and fussing in an otherwise healthy infant and has been understood as a challenging behavioral event.[1] There is no universal definition for infantile colic, but the most commonly used criteria, such as Rome IV,[2,3] Wessel's, and Modified Wessel[4] (Figure 1) apply the same rationale, that is, excessive crying without an apparent reason in an otherwise healthy baby.

The definitive cause of infantile colic is unknown.[5] It may be related to the immaturity of the gut-brain axis and intestinal microbiome or behavioral-related causes, such as parental anxiety and child temperament.[6,7] It is often attributed to digestive conditions leading to abdominal pain or discomfort[5–9] and more gas production, which could theoretically be associated with hydrogen content in their breath.[10–12] Despite its unclear origin, therapeutic interventions such as dietary modifications, probiotics, parental education, positioning, and enzyme replacement aim at gastrointestinal conditions, without consensus on the most appropriate approach.[2,13,14]

Lactase is the enzyme responsible for the digestion of lactose into galactose and glucose, and its supplementation has been administered as an attempt to relieve symptoms. Although lactase may improve gastrointestinal symptoms of infants, there is no consensus on its role in infantile colic. Therefore, we performed a systematic review to assess the efficacy of lactase supplementation for infantile colic.

What is Known

- Infantile colic is the excessive, difficult-to-soothe, poorly understood crying in an otherwise healthy infant.
- Multiple etiologies have been proposed, but the precise origin of infantile colic remains obscure.
- Management of infantile colic includes dietary modifications, probiotics, parental education, positioning, and enzyme replacement, with no consensus on the ideal approach.

What is New

- Despite new evidence suggesting the role of lactase supplementation in infantile colic, its efficacy in reducing excessive crying remains uncertain.
- Hydrogen breath testing in colicky infants showed conflicting results after lactase supplementation.

2 | METHODS

2.1 | Eligibility

We restricted inclusion to the following criteria: (1) randomized controlled trials (RCTs); (2) comparing lactase with placebo; (3) in infants younger than 6 months with infant colic. We included studies using Wessel's criteria, modified Wessel's criteria, or Rome IV criteria. Studies that used the same diagnostic rationale, that is, excessive crying with no apparent reason in an otherwise healthy baby, were also included. We excluded studies with children older than 6 months or with conditions that could clearly explain the crying, conference abstracts, letters to the editor, and incomplete reports. There were no restrictions on publication date or language.

The primary outcomes of interest were (1) duration of crying per day and (2) breath hydrogen analysis. Parental satisfaction, duration of sleep, and lactase adverse effects were also assessed in individual studies. All identified articles were systematically assessed using the inclusion and exclusion criteria.

2.2 | Search strategy and data extraction

This review followed the *Cochrane Handbook for Systematic Reviews of Interventions*[15] recommendations and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2020 statement guidelines.[16] PubMed, Cochrane Library, and Embase databases were systematically searched from inception to April 2023, using the following search strategy: (colic OR cry OR crying) AND (lactase OR galactosidase). We performed a backward snowballing search to confirm that all eligible trials were selected. This study was registered in the International Prospective Register of Systematic Reviews (PROSPERO), registration number CRD42023462168.

Studies were evaluated based on the cited criteria by two authors independently. Disagreements were resolved through consensus, eventually with a third author. Data were extracted by two authors independently, as follows: publication year, trial design, sample size, age, sex, intervention, treatment duration, outcomes, results, and conclusions.

2.3 | Quality assessment

The risk of bias and quality assessment of individual studies were analyzed by two authors independently, using Cochrane Collaboration's tool for assessing the risk of bias in randomized studies (RoB-2).[17]

3 | RESULTS

The initial search yielded 149 studies (Supporting Information S1: Figure). After the removal of duplicate reports and unrelated studies, eight studies were reviewed in full to assess for inclusion and exclusion

criteria. One study was excluded because the control group was probiotics, rather than placebo; another study was excluded due to publication as a letter to the editor. We included six studies, of which four were crossover trials.[18–21]

3.1 | Study characteristics

Table 1 summarizes the main characteristics of the six selected RCTs. A total of 394 patients were included. Three RCTs used Wessel's criteria to define infant colic[18,19,22]; one used a modified Wessel's[20]; one used Rome IV[23]; and one used the excessive crying rationale.[21] Age ranged from 0 to 6 months, and follow-up varied from 4 to 28 days. Four RCTs included patients who were both breastfed and bottle-fed,[18,21–23] while in two, they were exclusively breastfed[20] or bottle-fed.[19] The hydrogen breath test was performed in two studies,[18,20] comprising 17.4% of patients. As shown in Supporting Information S1: Figure, there is no evidence of publication bias.

3.2 | Outcomes

Table 2 presents a summary of the design, outcomes and risk of bias of the six included RCTs.

3.3 | Crying time

All six studies included in this systematic review assessed the duration of crying after lactase supplementation. Three of them[18,22,23] reported significantly less crying time in the lactase group compared with the placebo group, as displayed in Table 2.

3.4 | Hydrogen breath test

Two studies measured breath hydrogen with conflicting results.[18,20] Kanabar et al. showed a significant reduction in the hydrogen breath test in the lactase group, while Miller et al. found no significant difference between the groups (Table 2).

Wessel's Criteria ("Rule of threes")

- Paroxysms of irritability, fussing or crying lasting ≥3 hours/day on ≥3 days/week in any 1 week in an otherwise healthy baby aged 2 weeks to 4 months.
- Severe colic paroxysms must persist for > 3 weeks.

Modified Wessel's Criteria

- Crying for ≥3 hours/day on at least 3 days in any 1 week at different age stages during the first 12 weeks of life

Rome IV Criteria

Clinical purposes

Diagnostic Criteria for Infant Colic must include all of the following:

- An infant under 5 months of age when the symptoms start and stop;
- Recurrent and prolonged periods of infant crying, fussing, or irritability reported by caregivers (without obvious cause and cannot be prevented or resolved by caregivers);
- No evidence of failure to thrive, fever, or illness.

Clinical research purposes

Diagnostic Criteria for Infant Colic must include the following:

- All of the criteria mentioned above
- Caregiver reports of infant crying ≥ 3hours/day during ≥3 days in 7 days in a telephone or face-to-face screening interview with a researcher or clinician
- Total 24-hour crying plus fussing in the selected group of infants is confirmed to be 3 hours

FIGURE 1 Criteria for infantile colic diagnosis.[2,4]

TABLE 1 Characteristics of studies included in systematic review.

	Type of study	Infant colic criteria	Number of patients	Follow-up (day)	Gender (M/F)	Age	Type of feeding	Lactase administration	Lactase brand and dose	Hydrogen breath test
Narang 2022	RCT	Rome IV	162	28	99/63	0–5 months	BM/FM	Mixed with BM/FM 30 min BF	5 drops (0.2 mL), 600 FCC/mL, 4x a day	No
Ahmed 2018	RCT	Wessel's	148[b]	14	50/54[c]	0–6 months	BM/FM	Given immediately BF	BM: 5 drops FM: 1 drop to the ounce	No
Kanabar 2001	RCT, crossover	Wessel's	46	25	NA	3–13 weeks	BM/FM	Mixed with BM, given at the end of feed/mixed with FM, refrigerated for 4 h BF	BM: 4 drops in fore-milk expressed FM: 2 drops/feed	Yes
Kearney 1998	RCT, crossover	Wessel's	13	14	9/4	53.5 days (mean)	FM	Mixed with FM, refrigerated for 24 h BF	LactAid 3 drops	No
Miller 1990	RCT, crossover	Modified Wessel's	15	23	5/10	6.5 weeks (mean)	BM	Given directly into the mouth within 5 min of feeding	LactAid 6 drops (2000 NLU) 0.63 g/feeding (median)	Yes
Stahlberg 1986	RCT, crossover	Excessive crying[a]	10	4	NA	11.9 weeks (mean)	BM/FM	Pre-mixed with BM/FM formulations, maintained frozen	Maxilact dosing not reported	No

Abbreviations: BF, before feeding; BM, breastmilk; F, female; FM, Formula; M, male; NA, not available; NLU, neutral lactase units; RCT, randomized controlled trial.
[a]Authors used diagnostic criteria rationale; [b]randomized group (before a loss to follow-up); [c]analyzed participants (after loss to follow-up).

TABLE 2 Studies design and outcomes.

Study	Design	Lactase brand and dose	Effect on crying or fussing	HBT	Parental satisfaction	Adverse effects	RoB
Narang 2022 India	RCT, DB 4 weeks of follow-up	Yamoo 5 drops (0.2 mL), 600 FCC units/mL, 4x a day, after BM or FM.	Reduction of 79.1 min/day ($p < 0.001$)	NR	Assessed by Likert-scale Lactase group: Reports of improved behavior, alertness, comfort, and oral fluid intake.	Mild symptoms[b]	Low
Ahmed 2018 Pakistan	RCT, DB 2 weeks of follow-up	Colibid 5 drops before BM or 1 drop/ounce to FM	Infants with reduced crying time: LG: 86.5% PG: 60% ($p = 0.002$)[a]	NR	NR	NR	Low
Kanabar 2001 Ireland	RCT, DB crossover: 10 days period (wash-out: 5 days)	Brand not reported[c] 2 drops to FM (refrigerated) or 4 drops to expressed BM	Crying median duration: LG: 520.0 min PG: 872.5 min ($p = 0.0052$)[a]	LG = 6.0ppm PG = 9.5ppm ($p < 0.0007$)	NR	NR	Low
Kearney 1998 Ireland	RCT, DB Crossover: 1 week period (wash-out: 2 days)	Lactaid 3 drops to FM	Reduction of crying: 1.14 h/day (95% CI 0.23–2.05)	NR	NR	NR	Low
Miller 1990 Australia	RCT, DB crossover: Two periods of 1-week (no wash-out)	Lactaid 6 drops (2000 NLU) before BM	Mean (±SE) daily duration of crying and fussing: LG: 225 (±22) min. PG: 185 (±25) min. Not significant	Highest mean (±SE) breath H2 value: LG: 35 (±6) ppm PG: 33 (±6) ppm Not significant	NR	NR	Low
Stahlberg 1986 Finland	RCT, DB crossover Four periods of 1-week (no wash-out), four milk preparations: (1) BM; (2) BML (3) FM; (4) FML	Maxilact LX 500 Dose not reported	No difference in days with colic at the end of 4-wk between "Lactose containing" versus "Lactase treated" preparations ($p > 0.05$)	NR	NR	NR	Low

Abbreviations: BM, breastmilk; BML, breastmilk with lactase; DB, double-blind; FCC, food chemical codex units; FM, formula milk; FML, formula milk with lactase; HBT, hydrogen breath test; LG, lactase group; min, minutes; NR, not reported; PG, placebo group; RCT, randomized controlled trial; RoB, risk of bias; SD, standard deviation; SE, standard error.

[a]Per protocol analysis (complaints); [b]Vomiting, regurgitation, constipation, self-limited diarrhea; [c](beta-galactosidase derived from *Aspergillus*).

3.5 | Parental satisfaction

Narang et al. assessed parental satisfaction after the intervention. Parents reported improved behavior, alertness, comfort, and oral fluid intake in the lactase group, with better parental perception of their child. No other study reported the outcome of parental satisfaction (Table 2).

3.6 | Adverse effects

As highlighted in Table 2, the only RCT to analyze the adverse effects of lactase supplementation showed that the treatment was well tolerated and symptoms were mild and self-limited.[23]

4 | DISCUSSION

In this systematic review of six RCTs and 394 patients, we assessed the efficacy of lactase supplementation in infants with excessive crying (i.e., infantile colic). The main outcomes were a reduction in infant crying time and a hydrogen breath test. The efficacy of lactase supplementation was inconclusive, and only half of the included studies showed benefits in crying time reduction.[18,22,23] Only one of the two studies that assessed hydrogen breath test results showed a significant reduction in exhaled hydrogen levels.[18]

The discrepancies in study outcomes can be attributed to variations in study design, small sample sizes, and the diverse lactase formulations, dosages, and administration methods employed. These factors were subjectively determined based on clinical experience and lack of standardization in the literature. Miller et al.[20] administered yeast-derived lactase orally within 5 min of feeding and observed a lack of response, possibly attributable to nonadherence to treatment. Yeast-derived lactase drops loses its stability at acidic gastric pH, whereas lactase derived from fungi maintains its function at a pH of 4.4.[19] Two other studies[19,21] employed preincubation, but similarly yielded no evidence of the effectiveness of lactase in reducing crying. Both studies had a small sample size and a significant proportion of participants were noncompliant, potentially influencing results.

In contrast, three other studies[18,22,23] reported efficacy when preincubating formula or breastmilk with lactase, including formulations derived from yeast. This may be attributed to the stability of the lactase formulation in the neutral pH of formula or pre-extracted breastmilk, and adherence to treatment. Notably, the two most recent studies had larger sample sizes and more robust designs, which could contribute to the outcomes reported. The optimal method of lactase administration remains debatable. These variations in results highlight a potential role of different lactase administration methods but also suggest that additional factors such as gastric pH, origin of lactase (yeast or fungal), and prior incubation with milk may influence the efficacy of lactase in managing infant colic.[18–20]

Interestingly, studies demonstrating the efficacy of lactase were the most recent ones, conducted in low-income countries (Pakistan and India), while others originated from European countries and Australia. This geographical diversity may explain variations in lactase efficacy attributable to ethnicity, genetic polymorphisms, and different microbiota among different populations. In addition, during the past three decades, the industry has made changes in lactase manufacture technology and maybe formulation, concentration, and pharmacodynamics that could contribute to this generational difference.

The reduction in crying time in some studies may be attributed to the natural progression of infantile colic, as this condition is recognized to spontaneously improve over time. Four of the six included studies were crossover trials.[18–21] Crossover trials are designed to investigate longstanding conditions. Given that infantile colic is a short-term condition, employing a crossover design may lead to misinterpretation of results.

Assessing breath hydrogen levels in infants is controversial. It is unknown whether paroxysmal episodes of pain and discomfort are linked to an increased production of colonic gas and intestinal distention or a transient lactose intolerance.[24,25] Herein, the included studies also examined breath hydrogen levels, retrieving inconsistent findings.[18,20] Miller et al. did not observe a significant difference between groups, and they proposed that probably lactase degradation in the stomach before reaching the small intestine may influence its effectiveness.

Lactose plays a crucial role as an energy source in early life.[26,27] As an essential disaccharide, it contributes to maintaining gut balance in infants and improves bowel movement frequency, reducing stool consistency through its osmotic effect.[28] Lactose also has a bifidogenic effect, which contributes to developing a healthier intestinal microbiota.[29] Neonates have sufficient lactase activity to meet the demands of milk-feeding,[24] and a decrease in this activity is not expected until around the age of 5 years.[30] Persistently attempting to reduce the lactose load may lead to undesirable consequences, and any intervention should be careful and rationale.

Infantile colic is challenging for caregivers. Quality of life is a main goal in clinical practice, and treatment must focus not only on the condition itself but also on its implication on mental health, family relationships, and parent–infant bonding. For instance, infantile colic is associated with maternal depression.[31] Therefore, parental satisfaction is an important, although

subjective, sign of treatment efficacy. Only one[23] of the studies assessed parental satisfaction, using a Likert scale. In that study, parents seemed happier with their children after 4 weeks of treatment.

Only one study assessed the adverse effects of enzyme supplementation[23] and found that lactase was generally well-tolerated, with mild and self-limited adverse effects. Even so, introducing lactase into a child's diet may increase financial costs and, hypothetically, have subsequent implications on intestinal microbiota composition. It may also interfere with parents' self-assessment of their ability to care for their child and make it more difficult for them to accept efficient methods to manage crying, such as reassurance, soothing techniques, and parental education.[32]

Due to the high burden of crying in pediatric care, with an impact on healthcare costs and family well-being, and the absence of evidence for effective interventions, further studies are warranted to address this unmet need in patients with infantile colic. Most studies included in this systematic review had a small number of participants and a short period of follow-up, which raises concerns about the reliability of results and the applicability of lactase in clinical practice. Well-designed RCTs, with larger sample sizes, longer follow-ups, standardized lactase administration, and diagnostic criteria, are needed to provide more definitive results to help understand the relevance of lactase as a treatment for infantile colic. Further investigations of the optimal dosage, duration of lactase supplementation, financial cost-effectiveness, and parental satisfaction are also crucial.

Our systematic review has limitations. We were unable to perform a meta-analysis due to a heterogeneous assessment of outcomes between groups. In addition, most of the studies were crossover trials, and some did not report data before the washout and crossover period. Moreover, the diagnostic criteria differed between the studies, which reflects the historical evolution of the definition and understanding of infantile colic.

In conclusion, there is controversial evidence about the efficacy of lactase supplementation in the treatment of infantile colic. Management should be individualized, including, at the very least, parental education and supportive care. Adequately powered RCTs, with standardized inclusion criteria and endpoints, are warranted to conclusively evaluate the role of lactase in the management of infantile colic.

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CONFLICT OF INTEREST STATEMENT
The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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