Annals of Neonatology

OPEN ACCESS
ISSN: 2636-3596

Original Article

The Effect of Oral Lactase Enzyme on Infantile Colic in The First 4 Months of Life: A Prospective Case Control Study

Asmaa M. Ahmed*; Abd El-Maggid M. Bayomi; Mohammed M. Syed Younis
DOI: 10.21608/anj.2023.246124.1078
***Correspondence** Pediatric Department, Faculty of Medicine, Al-Azhar University, Assiut, Egypt
Email: asmaali88@gmail.com

Abstract

Background: Common problem that usually happens during the first few months of childhood. The estimated prevalence of infant colic was reported 10-30% during 3-13weeks of life in both breast-fed or formula milk babies.

Objective: To determine the efficacy of lactase enzyme supplement in infant colic in the first 4 months of life.

Patients and Methods: This prospective study attended at pediatric clinic at Sohag Teaching Hospital include 200 infants subdivided into 2 groups: Group A (100 cases): infants in this group treated by lactase enzyme LACTASE ENZYME SUPPLEMENT as 5 oral drops before maternal milk or 2 oral drops for every 20 cm of milk formula twice daily. Group B (100 cases): infants in this group are treated by the ordinary treatment of colics (placebo) in the form of abdominal massage and anti colics (e.g.: Simethicone, Dimethicone).

Results: All infants in group A and group B reported normal abdominal US. RegardingX-ray in erect position, at group (A), 83% infants had gaseous distension, and 17% of them had marked gaseous distension. While at group (B), 88% infantshad gaseous distension, and 12% of them had marked gaseous distension. There was no statistically marked difference between the two groups ($p>0.05$).

Conclusion: We conclude that oral lactase drops may result in significant symptomatic relief in infantile colic in terms of reducing the crying and number of colic days.

Key words: Infantile colic, oral lactase

Introduction

The infantile colic is a benign, self-limited process in which a healthy infant has attacks of continous crying. The gold standard diagnostic criteria known as the "rule of three" is crying more than three hours per day, more than three days per week, for longer than three weeks **[1].**

Symptoms usually resolve by 3 to 6 months of age. Colics affect around 10% to 40% of infants worldwide **[2]**.

Mostly peaks at about six weeks of age, and could be associated with significant parental guilty sensation, and frequent physician visits. Colic was associated with postpartum depression and shaken baby syndrome **[3]**.

Parents usually report that attacks occur in the evening and are unprovoked. The incidence has no difference between sexes, and there is no correlation with type of feeding (breast vs. bottle), gestational age (full term vs. preterm), socioeconomic status, or season of the year **[4]**.

Although decades of research, the cause of infantile colic is unknown. Suggested causes include disturbances in fecal microflora, cow's milk protein and lactose intlerence, GIT immaturity or inflammation, high serotonin secretion, poor feeding habits, and smoking mothers or nicotine replacement therapy **[5]**.

It is believed that in early life, babies have immature digestive system and their gut does not produce sufficient quantity of lactase enzyme which was needed to digest the lactose. So the undigested lactose can't get absorbed by the small intestine and enters into the colon where it is fermented by bacteria and produces lactic acid and hydrogen gas.

These end-products cause lactose intolerance which is characterised by abdominal pain, distention, bloating, diarrhea and flatulence **[6]**.

Previous studies have also provided the evidence that supplement of lactase enzyme can reduce the crying time in infant colic **[7]**.

Other study reported that exogenous lactase supplement was effective in

lactose intolerance and reduced colic symptoms without side effects **[8]**.

Lactase enzyme deficiency is prevalent throughout the world. The most common cause of lactase deficiency is lactase non-persistence, a condition in which lactase activity decreases during infancy. Secondary lactase deficiency is due to small intestinal infectious enteritis, coeliac disease, inflammatory bowel disorder, drugs, radiation& gastrointestinal (GI) surgery. Congenital lactase deficiency is a rare condition **[9]**.

Currently the treatment options for lactose intolerance include lactose-reduced diet, limiting the consumption of milk or using low-lactose milk, and using supplemental lactase or probiotics **[9]**.

Low intake of milk would cause low intake of calcium and vitamin D and has negative effect on bones and teeth development in infants **[10]**.

Although lactase supplements and probiotics are good options to treat lactose intolerance. A study conducted in 2010 compared the efficacy of lactase enzyme supplement and probiotic for the treatment of lactose intolerance and revealed that lactase supplement is better option for the treatment of lactose intolerance **[11]**.

Aim of the study

We aimed to determine the efficacy of lactase enzyme supplement in infant colic in the first 4 months of life.

Patients and Methods

Study design: Prospective correlation hospital based study.

Study setting: This study was carried out at Pediatric clinic at Sohag Teaching Hospital during the period from January 2022 to January 2023.

Study population: This study included 200 infants subdivided into 2 groups: Group A (100 cases): infants in this group treated by LACTASE ENZYME SUPPLEMENT as 5 oral drops before maternal milk or 2 oral drops for every 20 cm of milk formula twice daily. Group B (100 cases)*:* infants in this group are treated by the ordinary treatment of colics (placebo) in the form of abdominal

massage and anti colics (e.g: Simethicone, Dimethicone).

Inclusion criteria: This study included infants 0-4 months of age with abdominal colics lasting for 3 hours or more for 3 days or more and don't improve with usual treatment with free abdominal US.

Exclusion Criteria*:* Chronic constipation, congenital megacolon, intestinal obstruction.

Research Methodology:

Selection Method: Randomized.

Clinical Examination: History taken at pediatric clinic: infants aged 0-4 months with infant colic, excessive crying lasting at least 3 hours a day on at least 3 days a week for at least 3 weeks. whose history was compatible with colic and who were otherwise well.

Ex: inspection of abdominal distention , palpation to exclude any organomegally, percussion to detect gaseous distension ,auscultation to her the loud intestinal sounds.

Investigations: Abdominal Ultrasonography (US), X-ray abdomen erect position.

Monitoring and follow-up: Parents were instructed to record 24hrs diaries of infant crying and other behavior based on the criteria laid by Barr et al. for 28 consecutive days following enrolment [19]. The crying duration was recorded to an accuracy of 5 min using the 'Time rulers' in the diary card as recommended by Barr et al. Parents were also instructed to record stool criteria and frequency and any solicited (vomiting/milk regurgitation, diarrhea and constipation) or unsolicited adverse events (AEs) detected on each day of the study. Enrolled infants were called for follow-up visits on 1, 2, 3 and 4 months. Symptom diary and infant's weight were checked at every visit. All bottles were collected from parents at the end of the study.

Study outcomes

The primary outcomes of the study were: duration of crying or fussing (that starts and stop without obvious cause) in

minutes/days during 4 months of use of drug/placebo and number of days with colic (that lasts > 3 h/day).

The secondary outcomes included occurrence of AEs (e.g. milk regurgitation, vomiting, diarrhea, constipation). AEs such as illness signs, or symptoms which occurred or got worse during the course of the study were assessed through parental meetings after examination of their daily records maintained in the dairy.

Ethics Approval

Parental consent was obtained after full explanation of the purpose and nature of the trial. (β-galactosidase (lactase) has been commercially produced from the yeast Kluyveromyces lactis and is available as LACTASE ENZYME SUPPLEMENT, an over-the-counter preparation. We obtained both LACTASE ENZYME SUPPLEMENT and placebo preparations from the manufacturers).

The study was approved by the hospital ethics committee of Faculty of Medicine AL- Azhar University (Assiut)

The privacy of all data collected had been assured.

Statistical analysis:

Data was collected, coded then entered as a spread sheet using Microsoft Excel 2016 for Windows, of the Microsoft Office bundle; 2016 of Microsoft Corporation, United States. Data was analyzed using IBM Statistical Package for Social Sciences software (SPSS)- (IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp). The Kolmogorov--Smirnov test was used to verify the normality of distribution. Continuous data was expressed as mean ± standard deviation, median & IQR while categorical data as numbers and percentage. A statistical value <0.05 was considered as significant.

Analytic statistics: Chi-square test; used to study the association between two qualitative variables. Student T-test: For normally distributed quantitative variables, to compare between two studied groups Mann Whitney test: For abnormally distributed quantitative

variables, to compare between two studied groups. Repeated ANOVA test: was used for continuous data to test for significant difference between more than two dependent parametric data along different time points.

Results

There was no statistically significant difference between the three studied groups regarding gender and postnatal age (p>0.05). On the other hand, there was statistically significant difference between the three studied groups regarding weight (p= 0.013) as weight in salbutamol was significantly lower compared to control group (Table 1).

In table (2) there was statistically significant difference between the three studied groups regarding maternal history during pregnancy (p= 0.046). On the other hand, there was no statistically significant difference between the three studied groups regarding type of delivery and gestational age (p>0.05).

No gross congenital anomalies were observed in the three studied groups. Normal cardiac and abdominal examination was reported in the three studied groups. There was no statistically significant difference between the three studied groups regarding cyanosis (p>0.05) This table shows: The mean TTN score in control group was 2.38± 1.19, 2.36± 1.06 in adrenaline group and 2.34± 1.06 in salbutamol group. There was no statistically significant difference between the three studied groups regarding TTN score (p>0.05) (Table 4).

In table (5): There was no statistically significant difference between the three groups regarding oxygen saturation (p>0.05). Regarding respiratory rate, there was significant decrease in respiratory rate after treatment compared to before treatment in control group (p<0.001), adrenaline group (p<0.001) and salbutamol group (p<0.001). on the other hand, salbutamol group showed significant lower respiratory rate after treatment compared to control group.

Table (1): Demographic characteristics among the studied groups.

Item		Group (A) (No. = 100)		Group (B) (No. = 100)		Test value	P-value
		No.	%	No.	%		
Sex	**Male**	81	81.0%	71	71.0%	X^2= 2.74	0.098
	Female	19	19.0%	29	29.0%		
Post-natal age (days)	**Mean± SD**	16.03± 4.75		15.43± 6.33		T= 0.758	0.449
	Range	6.0 - 27.0		4.0 - 30.0			

p≤0.05 is considered statistically significant, p≤0.01 is considered high statistically significant, SD= standard deviation, * X2: Chi- Square test and T: Student T test

Table (2): Comparison between the studied groups regarding gestational age.

Item		Group (A) (No. = 100)	Group (B) (No. = 100)	Test value	P-value
Gestational age (weeks)	**Mean± SD**	37.17± 1.30	37.44± 0.78	Z = MWU 1.819	0.069
	Median	37.0	37.0		
	Range	35.0 - 40.0	36.0 - 39.0		

p≤0.05 is considered statistically significant, p≤0.01 is considered high statistically significant, SD= standard deviation, * Mann-Whitney U test

Table (3): Comparison between the studied groups regarding weight at different follow-up periods

Weight	Group (A) (No. = 100)				Group (B) (No. = 100)				Student T test	
	Mean	± SD	Range		Mean	± SD	Range		Test value	P-value
At birth	3.11	0.55	2.10	4.20	3.06	0.51	1.90	4.10	0.666	0.506
After 1 month	3.94	0.55	3.00	5.00	3.74	0.50	2.70	4.90	2.639	0.009
After 2 months	4.83	0.57	3.80	5.80	4.40	0.50	3.40	5.60	5.73	**<0.001**
After 3 months	5.73	0.58	4.60	6.90	5.09	0.50	4.00	6.20	8.401	**<0.001**
After 4 months	6.53	0.58	5.50	7.90	5.80	0.54	4.60	7.00	9.247	**<0.001**
p- value for within groups, time effect*	**<0.001**				**<0.001**					

p≤0.05 is considered statistically significant, p≤0.051 is considered highly statistically significant, SD: standard deviation, *Comparison inside the same group in different period by Repeated ANOVA test

Table (4): Comparison between the studied groups regarding height at different follow-up periods

Height	Group (A) (No. = 100)				Group (B) (No. = 100)				Student T test	
	Mean	± SD	Range		Mean	± SD	Range		Test value	P-value
At birth	50.50	1.10	48.50	52.30	50.24	1.09	48.00	52.50	1.708	0.089
After 1 month	51.84	.98	50.00	53.50	51.73	.96	50.00	53.80	0.745	0.457
After 2 months	53.14	.89	51.30	54.60	53.20	.84	51.50	55.00	0.546	0.586
After 3 months	54.51	.87	52.80	56.00	54.70	.80	53.00	56.40	1.637	0.103
After 4 months	55.93	.81	54.00	57.20	56.28	.61	54.80	57.50	3.408	**0.001**
p- value for within groups, time effect*	**<0.001**				**<0.001**					

p≤0.05 is considered statistically significant, p≤0.051 is considered highly statistically significant, SD: standard deviation, *Comparison inside the same group in different period by Repeated ANOVA test

Table (5): Comparison between the studied groups regarding head circumference at different follow-up periods

Head circumference	Group (A) (No. = 100)				Group (B) (No. = 100)				Student T test	
	Mean	± SD	Range		Mean	± SD	Range		Test value	P-value
At birth	35.50	0.48	34.70	36.30	35.45	0.44	34.70	36.30	0.784	0.434
After 4 months	39.05	0.67	37.00	40.20	39.17	0.68	37.70	40.60	1.323	0.187
p- value for within groups, time effect*	**<0.001**				**<0.001**					

p≤0.05 is considered statistically significant, p≤0.051 is considered highly statistically significant, SD: standard deviation, *Comparison inside the same group in different period by Paired- Sample T test

Table (6): Comparison between the two studied groups regarding colics at different follow up periods.

Colics		Group (A) (No. = 100)		Group (B) (No. = 100)		P-value
		No.	%	No.	%	
At birth	**Most of day**	100	100.0%	100	100.0%	-
After 1 month	**got better**	0	0.0%	27	27.0%	**<0.001**
	highly better	100	100.0%	0	0.0%	
	mildly improved	0	0.0%	73	73.0%	
After 2 months	**Better**	0	0.0%	27	27.0%	**<0.001**
	Fine improvement	0	0.0%	73	73.0%	
	Mild colics	100	100.0%	0	0.0%	
After 3 months	**Scattered attacks**	0	0.0%	100	100.0%	**<0.001**
	Sometime	100	100.0%	0	0.0%	
After 4 months	**Almost no colics**	100	100.0%	0	0.0%	**<0.001**
	Got better	0	0.0%	27	27.0%	

p≤0.05 is considered statistically significant, p≤0.01 is considered high statistically significant, SD= standard deviation, * Chi- Square test and Mann-Whitney U test

Table (7): Comparison between the two studied groups regarding crying time at different follow up periods.

Crying time		Group (A) (No. = 100)		Group (B) (No. = 100)		P-value*
		No.	%	No.	%	
At birth	**No**	0	0.0%	3	3.0%	0.081
	Most of day	100	100.0%	97	97.0%	
After 1 month	**Got better**	100	100.0%	0	0.0%	**<0.001**
	Mild progress	0	0.0%	27	27.0%	
	No obvious progress	0	0.0%	73	73.0%	
After 2 months	**Good progress**	0	0.0%	73	73.0%	**<0.001**
	Marked progress	100	100.0%	27	27.0%	
After 3 months	**Almost no cry**	100	100.0%	0	0.0%	**<0.001**
	Minimal times	0	0.0%	100	100.0%	
After 4 months	**Almost no cry**	0	0.0%	100	100.0%	**<0.001**
	Calm baby	100	100.0%	0	0.0%	

p≤0.05 is considered statistically significant, p≤0.01 is considered high statistically significant,
* Chi- Square test

Table (8): Comparison between the two studied groups regarding diarrhea & constipation.

		Group (A) (No. = 100)		Group (B) (No. = 100)		Test value	P-value*
		No.	%	No.	%		
Diarrhea	**Yes**	0	0.0%	0	0.0%	-	-
	No	100	100.0%	100	100.0%		
Constipation	**No**	0	0.0%	3	3.0%	3.46	0.326
	Mild	58	58.0%	59	59.0%		
	Moderate	35	35.0%	30	30.0%		
	Severe	7	7.0%	8	8.0%		

p≤0.05 is considered statistically significant, p≤0.01 is considered high statistically significant,

* Chi- Square test

Table (9): Comparison between the two studied groups regarding abdominal distension.

Item		Group (A) (No. = 100)		Group (B) (No. = 100)		Test value	P-value*
		No.	%	No.	%		
Organomegaly	**Yes**	0	0.0%	0	0.0%	-	-
	No	100	100.0%	100	100.0%		
Abdominal distension	**No**	0	0.0%	3	3.0%	15.79	**0.001**
	Mild	34	34.0%	56	56.0%		
	Mild to moderate	59	59.0%	33	33.0%		
	Marked	7	7.0%	8	8.0%		

p≤0.05 is considered statistically significant, p≤0.01 is considered high statistically significant,

* Chi- Square test

Table (10): Comparison between the two studied groups regarding radiological findings.

Item		Group (A) (No. = 100)		Group (B) (No. = 100)		Test value	P-value*
		No.	%	No.	%		
Abdominal US	**Abnormal**	0	0.0%	0	0.0%	-	-
	Normal	100	100.0%	100	100.0%		
Abdominal X-ray erect	**Gaseous distension**	83	83.0%	88	88.0%	1.01	0.315
	Marked gaseous distension	17	17.0%	12	12.0%		

p≤0.05 is considered statistically significant, p≤0.01 is considered high statistically significant,
* Chi- Square test

Discussion

The infantile colics are unexplained and inconsolable crying attacks without any known cause in other healthy infants is a common problem. It may result in parental upset, child abuse and early breast-feeding stoppage. Nowadays, there is no well-established cure of infantile colics. Systematic feedbacks are available on pharmacological treatment, parent training techniques, modification of dietary habits and probiotics in cessation on infantile colic. Most treatment strategies have failed to document marked improvement [12,13].

The use of complementary and alternative medicine (CAM) is increasing in various conditions such as cardiovascular disease, diabetes, and infantile colic where there is no definite 'cure'. CAM strategies in infantile colic include spinal manipulations, herbal medicine and pain-relieving agents, and acupuncture [14].

The effectiveness and safety of parent training program for managing infantile colic is also in-conclusive [15].

There is no obvious evidence that probiotics such as Lactobacillus, Bifidobacterium, and Streptococcus are more effective than placebo at preventing infantile colic however daily crying time appeared to reduce with probiotic use compared to placebo in babies with infantile colic. Infantile colic has been postulated to be caused due to painful intestinal contractions, lactose

intolerance, altered gut microbiota, aerophagy, food hypersensitivity and behavioral factors [16].

Low-grade systemic inflammation is configured by high systemic and gut inflammatory biomarkers with abnormal gut microbial composition was documented to be associated with infantile colics. Transient lactose intolerance has considered an immediate cause of infantile colic. Researches are still ongoing to detect the role of lactase supplement in infantile colics [17].

Lactase is present on the brush border of the small intestine that hydrolyzes lactose to glucose and galactose. The undigested lactose produces lactic acid and hydrogen in infants, that could cause bloating & diarrhea; So because of, the only diet for infants below 6 months is milk, lactase enzyme supplements with milk may have the effect to control these colic symptoms [18].

This study aimed to the efficacy of lactase enzyme supplement in infant colic in the first 4 months of life. This prospective study was attended at pediatric clinic at Sohag Teaching Hospital include 200 infants subdivided into 2 groups: Group A (100 cases): infants in this group treated by lactase enzyme LACTASE ENZYME SUPPLEMENT as 5 oral drops before maternal milk or 2 oral drops for every 20 cm of milk formula twice daily. Group B (100 cases): infants in this group are treated by the ordinary treatment of colic (placebo) in the form of abdominal massage and anti-colic (e.g.: Simethicone, Dimethicone).

Our results revealed that comparison between the two studied groups regarding demographic data. There was statistically no significant difference between the two groups regarding age ($p>0.05$). 81% infants were males and 19% were females in group (A) while 71% cases were males and 29% were females in group (B) with no statistically significant difference between the two groups regarding sex ($p>0.05$).

In the same context with our results, (Narang et al.) investigated one hundred

sixty-two clinically healthy infants aged < 5 months age [mean (SD)=63.5 (30.5) days] fulfilling the Rome-IV diagnostic criteria for infantile colic were enrolled. Eligible children were randomly chosen to receive 5 drops of lactase supplement (600 FCC units/mL) (n=80) or placebo (n=82) mixed with breast milk or formula feed four times a day for a duration of 4 weeks and found that age was comparable between both groups a total of 162 children (99 boys and 63 girls) were included in the study. [(19)]

Our findings showed that, weight was measured at birth and 1, 2, 3 and 4 months after birth. The mean weight in group (A) was 3.11± 0.55 SD at birth, increased to 3.94± 0.55 SD at 1st month, and increased to 4.83± 0.57 SD at 2nd months, and to 5.73± 0.58 SD at 3rd months, finally to 6.53± 0.58 SD at 4th months follow-up. While, in group (B) mean weight was 3.06± 0.51 SD at birth, increased to 3.74± 0.50 SD at 1st month, and increased to 4.40± 0.50 SD at 2nd months and to 5.09± 0.50 SD at 3rd months, finally to 5.80± 0.54 SD at 4th months follow-up. There was a significant increase in terms of weight between at birth and (at 1, 2, 3 and 4 months after birth follow-up) measurements (P<0.001) in both groups. This came line with (Narang et al.) who found no difference in weight at baseline [19].

Our study stated that height was measured at birth and 1, 2, 3 and 4 months after birth. The mean height in group (A) was 50.50± 1.10 SD at birth, increased to 51.84±0.98 SD at 1st month, and increased to 53.14± 0.89 SD at 2nd months, and to 54.51±0.87 SD at 3rd months, finally to 55.93± 0.81SD at 4th months follow-up. While, in group (B) mean height was 50.24± 1.09 SD at birth, increased to 51.73± 0.96 SD at 1st month, and increased to 53.20± 0.84 SD at 2nd months and to 54.70± 0.80 SD at 3rd months, finally to 56.28± 0.61SD at 4th months follow-up. There was significant increase height after 4 months in group (B) compared to group (A); otherwise, there was no significant difference. Also, there

was highly significance difference (P<0.001) between weight between at birth and other times (at 1, 2, 3 and 4 months after birth follow-up) in each group. This came line with (Narang et al.) who found no difference in weight at baseline [19].

In (Shah et al.) found that when adjusted for BMI status, both the normal weight patients with Lactose intolerance had significantly lower 25 (OH)D levels compared to the normal-weight controls [20].

Also, infant lactose intolerant, getting the right number of important vitamins and minerals can prove difficult. This may lead to unhealthy weight loss and affect height [21].

At birth, all infants in both groups had colic most of day, after 1 month, group A showed significant improvement after 1, 2, 3 and 4 months compared to group B (p<0.001). In the present study at birth, all infants in both groups had colic most of day, after 1 month, group A showed significant improvement after 1, 2, 3 and 4 months compared to group B (p<0.001). At birth, all infants in group A and 97% infants in group B were crying most of days had colic most of day, after 1 month, group A showed significant improvement after 1, 2, 3 and 4 months compared to group B (p<0.001). Our results supported by a study done by (Ahmed et al.) studied Clinical efficacy of lactase enzyme supplement in Colic on 104 subjects. The subjects were randomized into intervention group A which received lactase enzyme Colibid, and placebo group B. Five drops of intervention preparation were received by all the infants before each feed for two weeks and stated that at baseline, all (100%) the subjects had infant colic or excessive crying. After two-week intervention, significant improvement was seen in the duration of crying in group A 45 (86.5%) compared to group B 31(59.6%) (p<0.05). They concluded a significant improvement was seen in the duration of crying in infants who received lactase enzyme supplement [22].

The same with our results, (Narang et al.) showed a progressive decrease from 1st to 4th week in both the groups but was markedly less in infants receiving lactase in comparison to infants receiving placebo, at the end of every week of assessment. Considering crying and irritation duration for all 4 weeks of study, the mean (SD) duration of crying was 155.1 (101.4) min despite in case of placebo group it was 234.1 (127.1) min. they also observed infants receiving lactase had a mean reduction in crying or fussing time by 35.1–52.2 min/day. The reduction in crying or fussing duration was higher during 3rd and 4th week of intervention [19].

Additionally, earlier studies reported decreased crying duration when lactase preparation was administered as an intervention. A randomized, double-blind, cross- over trial of lactase and placebo drops added to milk formula of 13 infants with infantile colic showed significant reduction in crying time [22].

A double blind randomized placebo controlled crossover study in 53 infants with colic resulted in marked control in both crying time and breath hydrogen with pre incubation of feed with lactase [23].

Although, previous study had showed that lactase had no obvious effect on crying duration when given orally after feeds. It was thought that lactase got inactivated in the stomach when given after feeds. In contrast, lactase showed improvement in other children when given with food [6].

Another study reported that lactase given before feeding resulted in a significant reduction in crying times in babies with infant colic. Significant numbers of study infants (13%) did not benefit from lactase enzyme (Colibid) preparation. Possible explanation for this, was the other known causes of infant colic otherwise lactose intolerance. This trial only observed infant colic due to transient lactose intolerance caused by lactase enzyme deficiency. It was known from the

previous studies that there were numerous causes of infant colic [22].

The etiology & pathogenesis of infantile colic remains unknown and is moslyt multifactorial. Although this is common condition, there is a general paucity of evidence investigating this field. Theories thought to be relating multiple infantile colic factors can be classified as gastrointestinal or non-gastrointestinal. The gastrointestinal causes include lactose intolerance, altered gut micro-organisms, increased motilin receptors or cow milk hypertensives. The non-gastrointestinal causes include behavior causes or altered child-parent interaction [19].

As most of infants in this study showed decrease of crying duration after administration of lactase drops, lactose intolerance may be a factor of causation of infantile colic. The aggressivness of symptoms after lactose ingestion depends on the dose of lactose, lactase expression, intestinal flora state, and reactivity of gastrointestinal tract [9].

The ability of colonic microbes to process lactose can adapt to increase influx of lactose to the colonic lumen. Colonic adaptation occurs mostly in lactase deficient infants and it may be responsible for the increased tolerance to lactose after a lactose-feeding period. Spontaneous recovery of colic by 5–6 months in infants who continue on milk diet alone also may be related to adaptation of colonic microbes to continuing lactose stimulation of gut. However, there may be sub group of lactose deficient infants where colonic adaptation not occur to a desired level and their lactase level further depletes [24].

Infantile colic can also be considered as a behavioral problem. It may result into inadequate parental reactions, or parental distress or depression. This may also affect the parent–child relationship [25].

In our study, none of infants in group A and group B complained from diarrhea. At group (A), 58% infants had mild constipation, 35% of them had moderate constipation and 7% of them had severe

constipation. While at group (B), 3% infants had no constipation, 59% infants had mild constipation, 30% of them had moderate constipation and 8% of them had severe constipation. There were no statistically marked differences between the two groups (p>0.05). These findings came with line with, (Narang et al) study Narang and Shah [19].

In our study, abdominal distension was statistically significant differences between the two groups (p=0.001). All infants in group A and group B reported normal abdominal US. Regarding X-ray in erect position, at group (A), 83% infants had gaseous distension, and 17% of them had marked gaseous distension.

While at group (B), 88% infants had gaseous distension, and 12% of them had marked gaseous distension. There were no statistically marked differences between the two groups (p>0.05). In this context, lactase becomes a diagnostic agent. Where it works, lactose intolerance can be assumed to be the cause of the infant's symptoms, and lactase can logically be recommended for use for a period of around 3 months. In infants who do not benefit, a negative result with lactase indicates a different aetiology and may form the basis for further investigation and different treatment decisions. This model lends itself to a simple treatment algorithm for infant colic as follows:

Treat infant with lactase. If positive response, continue for as long as the symptoms of colic persist. If negative, switch to low-allergenicity feed. If positive response to low-allergen feed, continue low-allergen feed until weaning. If negative, further investigation may be required, i.e. screen for low-level infection, metabolic error, possible child abuse, etc. Our study was designed to screen the efficacy of lactose load reduction in infant colic at the primary health care level.

Finally, making additions to a feed and then incubating could theoretically increase the risk of microbial contamination. However, the clear instructions for use with lactase (i.e.

incubate in a fridge, then warm before feeding) minimize the potential risk.

Conclusions

We concluded that oral lactase drops may result in significant symptomatic relief in infantile colic in terms of reducing the crying and number of colic days.

Acknowledgements

The study group is grateful to the NICU team who supported this work

Author's contributions

All authors contributed equally in this work. The authors have read and approved the manuscript.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

Funding

The manuscript was funded by the authors.

Author's details

Pediatric department, faculty of Medicine, Al-Azhar university, Assiut, Egypt

Date received: 18th September 2023, accepted 26th November 2023

References

1. Wessel MA, Cobb JC, Jackson EB, Harris GS, Detwiler AC. Paroxysmal fussing in infancy, sometimes called" colic". Pediatrics. 1954; 14(5):421-35.
2. Lucassen PL, Assendelft WJ, Gubbels JW, van Eijk JT, Douwes AC. Infantile colic: crying time reduction with a whey hydrolysate: a double-blind, randomized, placebo-controlled trial. Pediatrics. 2000; 106(6):1349-54.
3. Radesky JS, Zuckerman B, Silverstein M, Rivara FP, Barr M, Taylor JA, Lengua LJ, Barr RG. Inconsolable infant crying and maternal postpartum depressive symptoms. Pediatrics. 2013; 131(6):e1857-64.
4. Ali AM. Helicobacter pylori and infantile colic. Archives of pediatrics & adolescent medicine. 2012; 166(7):648-50.
5. Ali AM, Mohamed MA. Irritable bowel syndrome in children; is there an association with infantile colic in infants. Am Assoc Sci Technol. 2014;1(2):56-61.
6. Swagerty Jr DL, Walling AD, Klein RM. Lactose intolerance. American family physician. 2002; 65(9):1845-51.
7. Kearney, Malone, Hayes, Hyland. A trial of lactase in the management of infant colic. Journal of Human Nutrition and Dietetics. 1998; 11(4):281-5.
8. Montalto M, Nucera G, Santoro L, Curigliano V, Vastola M, Covino M, Cuoco L, Manna R, Gasbarrini A, Gasbarrini G.

Effect of exogenous β-galactosidase in patients with lactose malabsorption and intolerance: a crossover double-blind placebo-controlled study. European journal of clinical nutrition. 2005; 59(4):489-93.

9. Misselwitz B, Pohl D, Frühauf H, Fried M, Vavricka SR, Fox M. Lactose malabsorption and intolerance: pathogenesis, diagnosis and treatment. United European gastroenterology journal. 2013; 1(3):151-9.
10. Segal E, Tamir A, Ish-Shalom S. Compliance of osteoporotic patients with different treatment regimens. Imaj-Ramat Gan-. 2003; 5(12):859-62.
11. Ojetti V, Gigante G, Gabrielli M, Ainora ME, Mannocci A, Lauritano EC, Gasbarrini G, Gasbarrini A. The effect of oral supplementation with. European review for medical and pharmacological sciences. 2010;14:163-70.
12. Johnson JD, Cocker K, Chang E. Infantile colic: recognition and treatment. American family physician. 2015; 92(7):577-82.
13. Khan A. An infant with inconsolable crying. The American Journal of Emergency Medicine. 2022; 55:227-e5.
14. Oflu A, Bukulmez A, Gorel O, Acar B, Can Y, Ilgaz NC, Yenioglu I, Uygun S, Sulecik S. Complementary and alternative medicine experiences of mothers in the treatment of infantile colic. Sudanese Journal of Paediatrics. 2020;20(1):49.
15. Gordon M, Gohil J, Banks SS. Parent training programmes for managing infantile colic. Cochrane Database of Systematic Reviews. 2019(12).
16. Ong TG, Gordon M, Banks SS, Thomas MR, Akobeng AK. Probiotics to prevent infantile colic. Cochrane Database of Systematic Reviews. 2019(3).
17. Sung V. Infantile colic. Australian prescriber. 2018 Aug;41(4):105.
18. Cohen-Silver J, Ratnapalan S. Management of infantile colic: a review. Clinical pediatrics. 2009; 48(1):14-7.
19. Narang M, Shah D. Oral lactase for infantile colic: a randomized double-blind placebo-controlled trial. BMC pediatrics. 2022; 22(1):1-8.
20. Setty-Shah N, Maranda L, Candela N, Fong J, Dahod I, Rogol AD, Nwosu BU. Lactose intolerance: lack of evidence for short stature or vitamin D deficiency in prepubertal children. PLoS One. 2013; 8(10):e78653.
21. Facioni MS, Raspini B, Pivari F, Dogliotti E, Cena H. Nutritional management of lactose intolerance: the importance of diet and food labelling. Journal of translational medicine. 2020; 18:1-9.

22. Ahmed M, Billoo AG, Iqbal K, Memon A. Clinical efficacy of lactase enzyme supplement in infant colic: a randomised controlled trial. J Pak Med Assoc. 2018; 68(12):1744-7.
23. Kanabar D, Randhawa M, Clayton P. Improvement of symptoms in infant colic following reduction of lactose load with lactase. Journal of Human Nutrition and Dietetics. 2001; 14(5):359-63.
24. Forsgård RA. Lactose digestion in humans: intestinal lactase appears to be constitutive whereas the colonic microbiome is adaptable. The American journal of clinical nutrition. 2019; 110(2):273-9.
25. Akman I, Kuşçu K, Özdemir N, Yurdakul Z, Solakoglu M, Orhan L, Karabekiroglu A, Özek E. Mothers' postpartum psychological adjustment and infantile colic. Archives of Disease in Childhood. 2006; 91(5):417-9.

Citation: Ahmed, A., Bayomi, A. E., Syed Younis, M. The Effect of Oral Lactase Enzyme on Infantile Colic in The First 4 Months of Life: A Prospective Case Control Study. *Annals of Neonatology*, 2024; 6(1): 93-112. doi: 10.21608/anj.2023.246124.1078