

Clinical Efficacy Of Lactase Enzyme Supplement In Infant Colic: A Randomised Controlled Trial

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Abstract

Objectives: To determine the efficacy of lactase enzyme supplement in infant colic.

Methods: The double-blind randomised clinical trial was conducted from November 2014 to June 2017 at Kharadar General Hospital, Karachi, and comprised infants aged 0-6 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. The subjects were randomised 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. Confidentiality of active agent and placebo was maintained through drug codes. The duration of crying was recorded at baseline then after first and second weeks of intervention. The two groups were compared with level of significance set at $p < 0.05$.

Results: There were 104 subjects with 52(50%) in each of the two groups Overall, 50(48.1%) were boys. 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%) ($p < 0.05$).

Conclusion: Significant improvement was seen in the duration of crying in infants who received lactase enzyme supplement.

Keywords: Infant, Colic, Excessive crying, Lactose intolerance, Lactase. (JPMA 68: 1744; 2018)

Introduction

Infant colic or excessive crying in healthy infants is a common problem which usually occurs during the first few months of childhood. The estimated prevalence of infant colic was reported 10-30% during 3-13 weeks¹ of life in both breast-fed or formula milk babies.^{2,3} Episode of crying mostly occurs in the evenings, starting in the first weeks of life and ending at the age of 4-5 months.⁴ Wessel in 1954 defined infant colic as "a symptomatic disorder characterised by paroxysms of fussing, agitation or crying, lasting more than 3 hours a day and occurring more than 3 days a week for at least 3 weeks".⁵ Infant colic can lead to failure to thrive and, in extreme cases, can lead to dehydration and electrolyte imbalance.

The exact cause of infant colic remains unclear. Previous studies have shown that 40% babies presented with infant colic suffered from lactase enzyme deficiency,^{6,7} an intestinal enzyme that breaks down the lactose into simple sugar (galactose and glucose) in small intestine.⁸ 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 cannot 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, diarrhoea and flatulence.⁹ Previous studies have also provided the evidence that supplement of lactase enzyme can reduce the crying time in infant colic.^{10,11} Another study reported that exogenous lactase was effective in lactose intolerance and without side-effects reduced colic symptoms.¹²

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 disease, drugs, radiation, gastrointestinal(GI) surgery. Congenital lactase deficiency is a rare condition.¹³

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.¹³ Low intake of milk would cause low intake of calcium and vitamin D and has negative effect on bones and teeth development in infants.¹⁴ Therefore lactase supplements or probiotics are better options to treat lactose intolerance. A study conducted in 2010 compared the efficacy of lactase enzyme supplement and probiotic for the treatment of lactose

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intolerance and revealed that lactase supplement is better option for the treatment of lactose intolerance.¹⁵ Another study conducted in 2016 also provided the evidence that exogenous lactase was effective for the treatment of lactose intolerance with safety and excellent tolerability.¹⁶

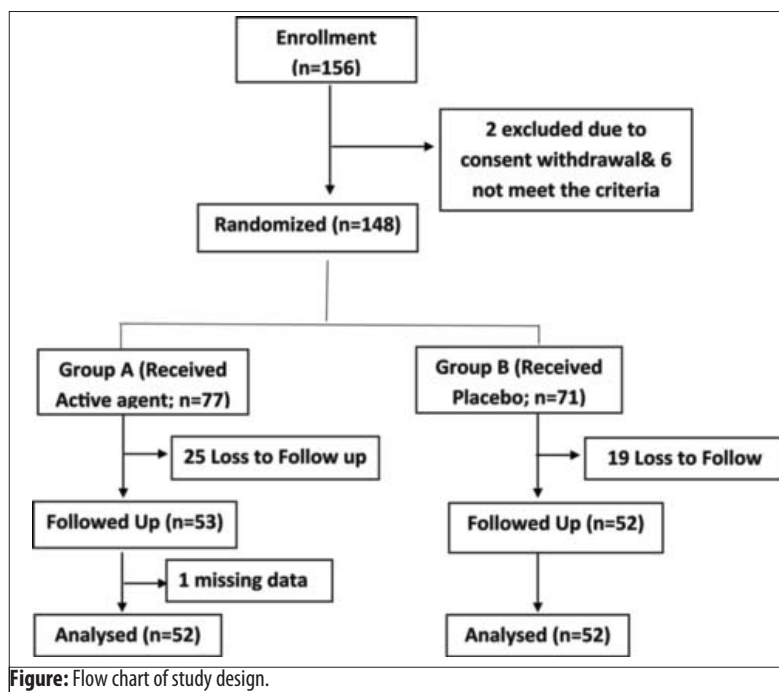
So far limited double-blind, placebo-controlled trials have been conducted on the efficacy of lactase supplements with small samples size and no study has been conducted in developing countries which may validate the role of lactase enzyme supplements in reducing the symptoms of infant colic. The current study was planned to investigate the efficacy of lactase enzyme supplements in infant colic.

Patients and Methods

The prospective, double-blind, placebo-controlled, randomised, two-arm parallel group, uni-centre trial was conducted at Kharadar General Hospital, Karachi, from November 2014 to June 2017, and comprised babies aged 0-6 months from the outpatient department (OPD). Infant colic was defined as excessive crying lasting at least 3 hours a day, on at least 3 days a week, for at least 3 weeks.⁵ Approval was obtained from the institutional review board and informed parental consent was obtained.

All the subjects were randomised consecutively into intervention group A and placebo group B (Figure). Intervention preparations were provided in bottles (drops) containing 7.5ml of either lactase enzyme (Colibid) as active agent or placebo (glycerin and potassium sorbate). Lactase preparation was labelled with Even drug code and placebo drop was labelled with Odd drug code. Coded drops were provided by the manufacturer just to prevent the investigator bias through maintaining double blindness. Group A participants received Even-coded drops whereas group B participants received Odd-coded drops. All parents were advised to ensure the use of provided drops as per the given instructions; for breast-fed babies, 5 drops of intervention preparation were given before each breast-feed for every feed, whereas for top-fed babies, one drop/ounce of the intervention preparation was given before each top-feed for every top-feed. Parents were also advised to bring back the used or empty bottle (drops) while coming for follow-up visits, just to ensure drug compliance.

During baseline visit, duration of crying was marked on pre-designed questionnaire. For the first follow-up visit,



study participants were called after one week and assessed the duration of crying, which was the outcome variable, and drug compliance and the evaluation responses were recorded on the questionnaire. Study participants were again called for second follow-up visit after two weeks of intervention and the duration of crying on the same questionnaire was recorded. Intervention outcome variable, duration of crying, was categorised as crying symptom improved or not improved. Statistical analysis was performed using SPSS16. Standard descriptive statistics were used to summarise the data. Pearson's Chi-square test was used to compare the groups against the outcome variable. $P < 0.05$ was considered statistically significant.

Results

Of the 156 babies presenting with abdominal colic, 104 (68.4%) completed the trial. Among them, 50 (48.1%) were boys. Overall mean body weight was

Table: Evaluation outcome after 1st & 2nd week of intervention (N=104).

Evaluation Outcome	Intervention received		Total	Sig. level
	Group A (Lactase)	Group B (Placebo)		
Duration of Crying after 1st week of intervention				
< 3 hours per day	45	34	79	0.012
≥ 3 hours per day	7	18	25	
Total	52	52	104	
Duration of Crying after 2nd week of intervention				
< 3 hours per day	45	31	76	0.002
≥ 3 hours per day	7	21	28	
Total	52	52	104	

4.1±1.12kg (range: 2.1-8.0kg), and the subjects were randomised into two groups of 52(50%) each.

In group A, 45(86.5%) infants showed reduced crying time, while the corresponding number in group B was 34(65.0%)($p=0.012$). At the second week follow-up, group A had 45(86.5%) infants with reduced crying time while group B had 31(60 %) ($p=0.002$)(Table).

Discussion

The main finding of the study was the significant improvement in baseline symptom of infant colic, as reduced crying time, generally in both group A and B, particularly in group A, which received lactase enzyme (Colibid) preparation as intervention. Similar findings were also reported by previous studies in which lactase preparation was given as intervention before feed and the similar results of decreased crying time as an outcome were reported.^{10-12,16} Miller et al⁹ reported contrasting results that lactase enzyme had no significant effect on the duration of crying when given to breast-fed colic babies. In the Miller study lactase was given orally after feeding, suggesting that the lactase had been inactivated in the stomach.⁹ Another study¹⁰ 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 possible causes of infant colic apart from lactose intolerance. This trial only investigated infant colic due to transient lactose intolerance caused by lactase enzyme deficiency. It was established from the previous studies that there were multiple causes of infant colic. Transient lactose intolerance was the most common cause of infant colic¹⁷ and so it was investigated in this trial. Other causes of infant colic include behavioural problem resulting from parent-infant interaction,¹⁸ infantile colic due to extreme end of normal crying¹⁹ and infant colic is just a collection of aetiologically different entities that were not easy to discern clinically.²⁰ A previous study has also reported that there was no correlation between infant colic and lactase intolerance as measured by stool potential of Hydrogen (pH) and reducing substances²¹ instead test hydrogen breath test, lactose intolerance test and genetic test to diagnose lactose intolerance.²²

Increased breath hydrogen level is an accepted indirect biomarker of hypolactasia. In previous studies hydrogen breath test was used as an indicator of lactose intolerance.^{10-12,16} This trial did not use hydrogen breath test as an indicator to assess improvement in infant colic. This trial only investigated the duration of excessive

crying at baseline presentation and then after first and second weeks of intervention. It was done because previous studies, which measured the breath hydrogen in infants with colic, produced inconsistent results.²³⁻²⁵ This trial also had a limited sample size because of financial and time constraints. Another limitation was recall bias on the part of the parents as the duration of crying was investigated through history as recalled by the mother.

The application of lactase enzyme supplement would improve infant colic due to lactose intolerance, but the supplement will have no impact on infant colic caused by reasons other than lactose intolerance. This may form the basis for further investigation and different treatment options.

Conclusion

There was generalised improvement in infant crying symptoms compared to crying time prior to intervention in both groups. Comparatively more significant reduction in crying time was observed in the intervention group. Significant proportion of infant colic patients had no benefit from the lactase supplement, which may be because of other factors of colic.

Disclaimer: Due to non-existence of RCT registration authority in Pakistan, there is no RCT trial number allotted to the study.

Conflict of Interest: None.

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