

Probiotics versus placebo in infantile colic symptoms: A randomized control trial

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Aim: The aim of the study was to estimate the relative improvement in infantile colic symptoms on giving probiotics versus placebo. **Background:** Continued crying mostly inconsolable crying is a source of anxiety and distress for the parents, and task for the doctor. Despite having many treatment modalities available, there is no gold standard treatment option available for colicky infants. **Study Design:** A randomized, single blind, and placebo-controlled trial was conducted involving 80 infants between 1 week to 6 months of age with infantile colic, according to modified ROME 4 criteria, who was randomized and divided into two groups and received Multistrain probiotic or probiotic for 7 days. Daily crying time and changes on face scale was compared on enrollment and follow-up and adverse effects were documented. **Results:** Total average crying time per day in this study (from baseline to 7 days) reduced significantly statistically in both group (237 ± 81 min vs. 268 ± 64 min; $P = 0.001$). Effect on pain scale was reduced significantly statistically in both the group ($P = 0.0001$). Effect on consistency of stool and number of bowel movements was improved significantly statistically in both group ($P = 0.0001$). **Conclusion:** Administration of multistrain probiotic significantly improved colic symptoms by reducing duration of cry and fussing times in infants with colic. **Clinical Significance:** Probiotic usage is a good option for the clinician as efficacious treatment to infantile colic though parental reassurance is the mainstay of the treatment.

KEY WORDS: Gut-brain axis, Infantile colic, Probiotic

INTRODUCTION

Crying is good signal that child is in need but a poor signal of what the child needs. Continued crying mostly inconsolable crying is a source of anxiety and distress for the parents, and task for the doctor. Infant colic is a diagnosis of exclusion in early infancy. It is a benign self-limiting process which leads to significant parental frustrations well as repeated physician visits. Finding an effective strategy for treating infantile colic can improve the quality of family life.^[1]

For research purposes, to make a diagnosis of infant colic it must include a crying time of three or more hours in a day during 3 or more days in 7 days in a telephonic or face-to-face interview with a researcher or clinician.^[2]

Despite having many treatment modalities available, there is no gold standard treatment option available for colicky infants. The management technique which is presently proposed is support and reassurance to the parents. Probiotics are live microorganisms when given in adequate amounts, give health benefits to the host. Recent growing evidence shows that supplementation with probiotics can change intestinal bacterial patterns by helping the colonization of beneficial bacteria.^[3]

Lactobacillus species have been the most widely studied probiotic agents in children and adults. Research on Lactobacillus species has increased over the past 20 years. Probiotics has important role in the gut microbiota-brain axis. Probiotics is

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anti-inflammatory and exerts immunoregulatory effects. An anti-inflammatory action of *Lactobacillus* has been studied in animals which show reduction in the intestinal mucosal levels of pro-inflammatory cytokines such as interleukin-8 (IL-8), IL-1 α , interferon- α , and TNF-alpha in newborn rats with LPS-induced small intestinal and ileum inflammation. *Lactobacillus* increases both muscle electric motility complex frequency and velocity. It also increases the production of SCFA that alters gut motility. They also secrete antimicrobial substances and downregulating pain as well as by stabilizing gut microbiota. *Lactobacillus reuteri* has a antimicrobial activity. It reduces pain perception by the use of transient receptor potential vanilloid 1 channel. It has an influence on the activity of potassium dependent calcium channel channels intermediate conductance enteric neurons and it also act as a inhibitor of colon contractility.^[4,5]

Even though much of research work is done on probiotic supplementation apart from exclusively breast feeding, one should always think of also proper counseling as an important part of management. It has been thought that suggested that misjudging and misinterpretation of result in compromised infants by the caregiver which leads to unsatisfied and irritable infant. Behavioral changes in the parents are a initial management because of no side effects and is cost-effective. Proper counseling is very important in the management of infantile colic technique such as feeding, swaying, and massaging is very important. Proper parents education is also very important in the management of the colicky babies.

Although some studies are available from Iran and Italy, there is dearth of Indian studies.

MATERIALS AND METHODS

A total of 80 infants in the age group 1 week to 6 months were included in the study. The subjects who will visit the outpatient department will be consecutively enrolled from November 1, 2019, to October 31, 2020. The study protocol was explained to parents and their written consent to participate voluntarily will be obtained on study pro forma. Detailed history was documented in predesigned pro forma. 40 cases were be treated with probiotic for infantile colic and remaining 40 cases with a placebo [Figure 1]. Both the groups are comparable.

- Group A - PROBIOTICS GROUP
- Group B - PLACEBO GROUP

Inclusion Criteria was (a) born at term (born after 37 weeks), (b) aged between 1 week to 6 months, (c) exclusively breastfed or exclusive top fed either by cow milk or powder milk during the course of study period, (d) with a diagnosis of infantile colic (defined as crying episodes lasting 3 or more hours in a day and occurring at least 3 days per week, within 7 days prior to enrolment).

Exclusion criteria were (a) any major acute or chronic diseases, (b) gastrointestinal diseases and frequent regurgitation of feeds, (c) use of antibiotics the week before

or during randomization, (d) gastrointestinal malformations, (e) neurological abnormalities, (f) psychosocially deprived babies, and (g) severe acute malnutrition babies.

Infants will be divided into two groups, probiotic and placebo group. All infants enrolled be randomized to receive, either probiotics or placebo. Randomization was done by software method. Detailed history was taken from parents and diagnosis of infantile colic will be made according to the standard definition. Pre-test scoring of pain by smile pain scoring system will be done on study pro forma. Basic investigations were advised that is required on individual cases such as complete blood count, stool and urine routine-microscopy, ultrasonography abdomen to exclude the infants according to exclusion criteria.

Parents in the probiotic group were requested to administer their infants five drops of probiotics (Strain of Probiotic: *Streptococcus faecalis*, *Clostridium butyricum*, *Bacillus mesentericus*, and Lactic acid bacillus) twice a day morning and evening, for 7 days directly in the mouth and same drops of placebo was advised to the placebo group. Parental compliance was also be studied by a diary in the follow-up visits. No dietary restrictions during breastfeeding will be recommended. Parents were advised not to use any commercial products which contain probiotics. Parents were told not to apply any methods to improve colicky pain. On enrolment (day 0), a pediatric medical examination and detailed history will be taken along with the filling of predesigned pro forma. A diary to record events such as a feeding timing, daily episodes of fussing/crying, amount of time of excessive crying per day and stool consistency will be asked and on follow-up was asked to produce that diary. Parents were given and taught to use the smile pain scoring system to show the improvement [Figure 2]. Parents were also be asked to keep a record of sleep awake pattern, duration of crying, time of crying, response to probiotic/placebo, the time of use of the probiotics, and any adverse events if present.

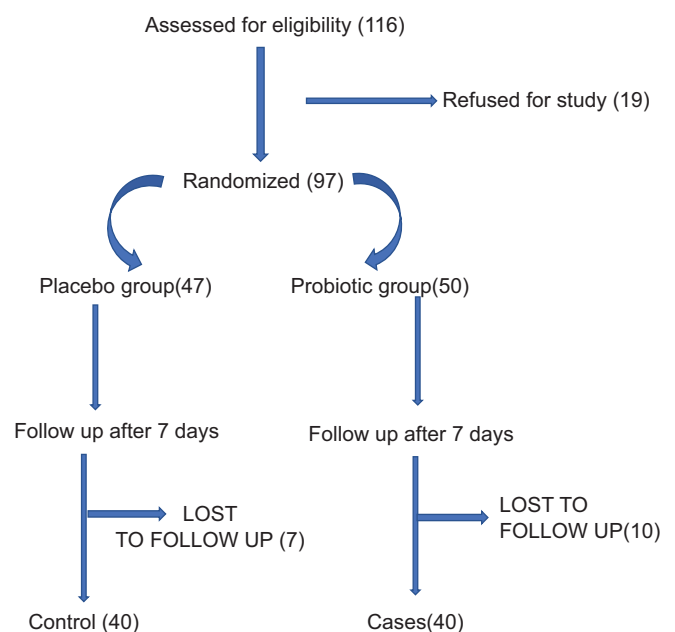


Figure 1: Study flowchart

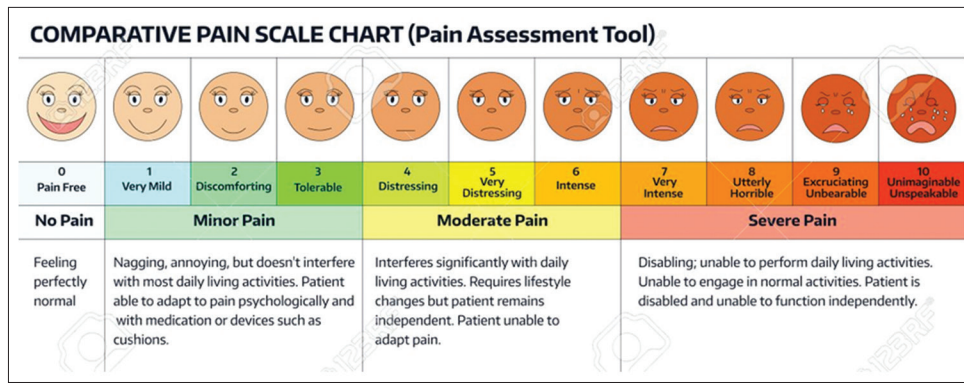


Figure 2: Comparative face pain scale

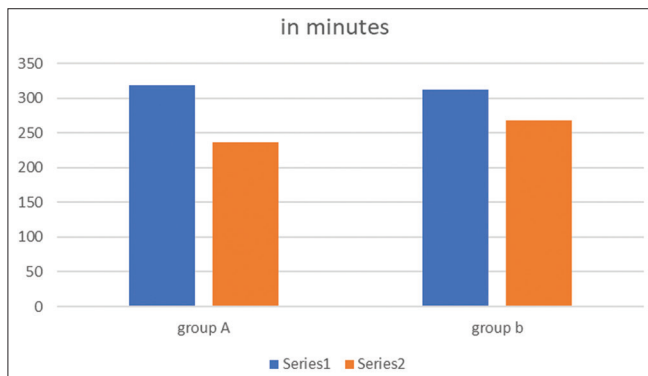


Figure 3: Comparing the effect on average duration of cry per day in probiotic vs placebo

Table 1: Comparing the effect on average duration of cry per day in probiotic versus placebo

	Baseline	After 7 days	P-value
Group A	319±97	237±81	0.0001
Group B	312±65	268±64	0.0001

Table 2: Comparing the effect on pain scale in probiotic versus placebo

	Baseline	After 7 days	P-value	T-value
Probiotic group a	4.70 ± 0.99 SD	3.83 ± 0.96 SD	0.0001	
Group B	5.00 ± 0.75 SD	4.13 ± 0.79 SD	0.0001	1.52

Follow-up visits will be scheduled on 7th day. A detailed interview was taken to assess the improvement of symptoms or any documented side effects on predesigned pro forma will be filled. If there is a failure to visit at 7th day, then by 10th day telephonic interview was taken and improvement will be assessed. Parents can also use personalized social media (WhatsApp) to show their babies improvement in symptoms.

Statistical Analysis

Data entry, clearing, and computing will be done and followed by analysis using SPSS (Statistical Package for the Social Science) version 22. Appropriate statistical test - Independent Student *t*-test will be applied and result will be tabulated as percentages along with graphical representations.

Sample Size Calculations

Sample size was calculated using software power and a sample size (PS2) calculations. Independent student *t*-test was applied with alpha error of 0.05 and delta of 20 and probability (power) of 0.7 and standard deviation (sigma) of 35.

RESULTS

There were 65% males and 35% females in Group A and 37% females and 63% males in Group B. There were 80% patients in Group A and 77% patients in Group B from urban and 20% patients in Group A and 23% patients in Group B. Maximum

number of patients were of age 3 month and majority was of age group of 1 month to 3 months. Majority of patients were exclusively breast fed. Majority of parents used swaying and feeding strategy. Few parents used strategies such as massage, sugar solution, pan leaves, and ginger paste application chest. Majority of parents did not report any side effects (92%). Few parents complained of constipation after 7 days at follow-up (2%) and few rashes (1%). There was insignificant change (*P*-value -0.35) in both the group so group was comparable. Duration of cry per day reduced significantly statistically in both group (*P* = 0.062) [Table 1 and Figure 3]. Effect on pain scale was reduced significantly statistically in both the group (*P* = 0.0001) [Table 2 and Figure 4]. Effect on consistency of stool was improved significantly statistically in both group (*P* = 0.0001). There was significant change statistically in number of bowel movements per day in both group (*P* = 0.0001).

DISCUSSION

In a study by Dorreh *et al.* in year 2017^[6] conducted a study in 84 infants of age <3 months and found there was no significant difference in the gender distribution in both the group cumulative (p-value -0.015). In our study, there were 65% males and 35% females in Group A and 37% females and 63% males in Group B. Vijayalakshmi *et al.* in year 2017^[7] conducted a study involving 50 breastfed babies aged 30–180 days with infantile colic which correlates with our study that it is more common in

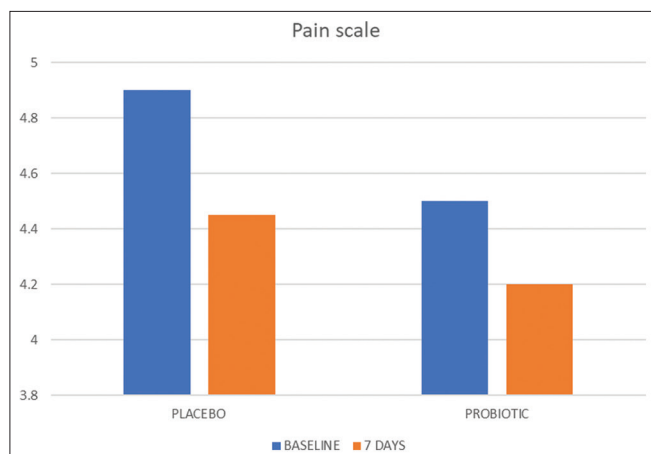


Figure 4: Comparing the effect on pain scale in probiotic vs placebo

early infancy. In our study, maximum number of patients was of age 3 months and majority was of age group of 1–3 months. This shows that infantile colic is more common in the early infancy. Paetty *et al.* in year 2018^[8] conducted a study and reviews a meta-analysis of 345 infants and found that majority of babies were exclusively breast fed and was more effective in them and not formula fed. This may be due to different composition of gut in the breastfed and formula fed babies. In our study, majority of babies were exclusively breast fed (51%). 25% of babies were having mixed feeding. About 23% of babies were top fed.

Savino *et al.* in year 2014^[9] conducted a study and found that parents used different strategies such as herbal supplements, swaying, feeding, use of different pharmacological medication but none of them is advised for usage though there was some improvement in the colicky symptoms though they were not significant. In our study we found that majority of parents used swaying and feeding strategy. Few parents used strategies such as massage, sugar solution, pan leaves, and ginger paste application chest.

Chau in year 2015^[10] conducted a study in 52 infants and found that in infants who received probiotics for 7 days did not reported in side effects and was well tolerated and no serious adverse effects was seen. In our study, majority of parents did not reported any side effects (92%). Few parents complained of constipation after 7 days at follow up (2%) and few rashes (1%). This shows that probiotic is relatively safe for usage.

Anabrees *et al.* in 2013^[11] in his study of 209 infants found a significant shorter duration of crying time after 7 days of probiotic usage. The treatment was stabilized after 3 weeks of usage. Probiotic decreased crying times by 1 h [mean difference-56.03 min; 95% CI]. However, there was less number of babies enrolled despite the condition being common in urban areas. In our study, there was insignificant change (P -value=0.35) in both the group so group was comparable. Duration of cry per day reduced significantly statistically in both group ($P = 0.062$). Effect on consistency of stool was improved significantly statistically in both group ($P = 0.0001$).

In a study by Baldassarre *et al.* in year 2018^[12] of 62 infants who were randomized found that there was no changes in

consistency of stool with a P value (0.13) and therefore was not significant statistically. There was score of 14 in placebo group and nine in probiotic group after 7 days of their usage. There was significant change statistically in number of bowel movements per day in both groups ($P = 0.0001$). There were no significant changes in the average total movements of bowel per day as there was P value of 0.35. There was mean of 3.8 in placebo group and 2.9 in probiotic group.

CONCLUSION

In our study, we found that there was decrease in duration of cry after probiotics usage for 7 days in probiotic group though it was not significant statistically. Probiotics also decreased the parameters on facial pain scale but it also had significant change in the consistency and frequency of stools after the probiotics and placebo usage. Of the limitation of this study which can be noted is that is probable that in some cases in both the groups due to excessive crying in the infants, the parent may have used other methods or drugs as intervention. It is also recommended that some further studies should be carried out as the sample size of the study was less. Third limitation was that this study was not double or triple blind so effect of biases can be there in our study.

CLINICAL SIGNIFICANCE

It is a test for medical professionals to diagnose this condition and rule out other pathological condition. If any treatment is considered to be important for support to the baby and parents, it is advisable to consider the options in which there are more benefits and less side effects. Babies which are feeding on formula can also be managed using hydrolyzed feeds and less thick feeds. Probiotic usage is a good option for the clinician as efficacious treatment to infantile colic though parental reassurance is the mainstay of the treatment and despite all the treatments methods, support of the parents by family members remains the most important thing in the infantile colic management. Hence, the clinical acumen lies in the hands of clinician what treatment they want to go forward.

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