ORIGINAL ARTICLE

The effect of symbiotic in the treatment of infantile colic: A double-blind, randomized, placebo-controlled clinical trial

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Background: This study aims to evaluate the effect of symbiotic (Pedilact) on the treatment of infantile colic. **Materials and Methods:** In this randomized clinical trial in Zanjan, Iran, 76 infants with infantile colic were assigned to two groups of 38 cases using block randomization. The intervention group received 5 drops of Pedilact, a symbiotic containing *Lactobacillus reuteri* and simethicone (20 mg twice daily), and the control group received placebo in addition to simethicone for 4 weeks. Daily crying time, number of crying attacks per day, and sleep duration were recorded on days 1, 7, 14, 21, and 28, and the results were compared. **Results:** Thirty-three infants in the intervention group and 35 infants in the control group were enrolled. There was no significant difference between the two groups in terms of age, gender, gestational age, maternal age, type of delivery, type of feeding, and weight at the beginning and the end of the study (all $P > 0.05$). Daily crying time in the control and intervention groups decreased from 240 and 210 min/day, respectively, to 0 min/day in both the groups. Daily crying attacks decreased from 5 and 4/day in the control and intervention groups, respectively, to 0/day. Sleep duration in both the groups increased from 720 to 840 and 930 min/day in the control and intervention groups, respectively, but the changes were not significant ($P = 0.56$, $P = 0.52$, and $P = 0.13$, respectively). **Conclusion:** We did not find a significant improvement in colic symptoms in infants receiving symbiotic compared to placebo.

Key words: Clinical trial, infantile colic, probiotic, symbiotic

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INTRODUCTION

Infantile colic is a common condition in infancy with many adverse impacts on family.[1] It usually presents by unpreventable, paroxysmal, inconsolable, and prolonged crying of the healthy infant (described by the new ROME IV criteria).[2] It is seen in approximately 10%–40% of infants and it can be considered when other causes have been ruled out.[3] The etiology of infantile colic is not yet completely known; theories such as altered intestinal microflora, food hypersensitivity as well as maternal smoking and emotional problems have been proposed.[3] There is still no consensus on colic management, although dietary and behavioral interventions are recommended.[4] Dicyclomine and cimetropium can reduce crying but are not recommended because of their side effects.[1] Proton-pump inhibitors are not effective and may increase the risk of infection.[1] Simethicone is practically used in infantile colic although its pharmacological role is unknown.

Some studies have shown that colicky infants had altered intestinal microflora with low amount of lactobacilli.[5] It was proposed that changes in intestinal flora can affect pain pathways in the brain,[6] therefore, it could be hypothesized that lactobacilli could help to relieve and prevent colicky pain.[4,7,8] Probiotics are "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host."[9] It

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has been suggested that probiotics such as *Lactobacillus reuteri* inhibit gas-forming coliforms and reduce intestinal inflammation.[8] In studies conducted in Iran and other countries, the administration of symbiotic has been associated with conflicting results.[7,10-12] Thus, to evaluate the efficacy of symbiotic administration on Iranian infants with colic, we designed this double-blind placebo-controlled clinical trial in our area.

MATERIALS AND METHODS

In the present double-blind, parallel, randomized clinical trial study (allocation ratio 1:1), the effect of symbiotics in the treatment of infants with colic was investigated. This project was approved by the Institutional Ethics Committee (IR.ZUMS.REC.1393.105), and registered on IRCT (IRCT20131217015835N8).

The sample size was calculated by the following formula and based on a previous study:[13]

$$n = \frac{\left[Z_{1-\frac{\alpha}{2}} + Z_{1-\beta}\right]^2 \left[P_1(1-P_1) + P_2(1-P_2)\right]}{(P_1 - P_2)^2}$$

With a statistical power of 80% and assuming an error of the first type of 0.05, the efficacy was assumed 50% reduction of crying time (P1 = 10% in the control group and P2 = 40% in the intervention group), and the number of samples was calculated as 38 patients in the intervention and placebo groups.

Infants <3 months old, who had colic according to Wessell's criteria,[14] were recruited from January 2015 to May 2016. Recruitment was made in Zanjan, Iran, from the busiest referral centers which consisted of the community-oriented medical education (COME) clinics (health clinics with the supervision of faculty members in the city center), hospital outpatient clinics, and emergency department of hospital (the sole referral and academic hospital with pediatric wards and subspecialties in the province).

Inclusion and exclusion criteria

Inclusion criteria for enrollment consisted of (1) age <3 months or 13 weeks, (2) gestational age more than 36 weeks, (3) birth weight more than 2500 g, (4) weight gain more than 100 g/week, and (5) the feeding pattern of the infants could be exclusively breastfed and/or formula fed.[15]

Exclusion criteria consisted of (1) any developmental disorders or specific underlying disease, such as digestive or nutritional problems including allergies to cow's milk protein; (2) infants of mothers taking probiotics; (3) infants taking any antibiotics and/or probiotics including formulas containing probiotics; and (4) infants on cow's milk.

Parents were informed about the study protocol, possible risks, and benefits of the study. Written informed consent was obtained from the parents.

Randomization

Individuals were assigned for the intervention and control groups based on the block randomization method by an independent statistician using a random number table (each block size was 4, and 20 blocks were randomly chosen from 6 possible blocks).

All participants and investigators were blinded about treatment allocation throughout the study including outcome measurement. A hospital cooperator assigned an identification number to participants and distributed the treatment product according to the randomization schedule. The patients' mothers knew that they may take medicines besides simethicone, but instead of the name of symbiotic, we used codes. The outcomes were evaluated according to the codes.

Treatment protocol

Both the groups received simethicone 20 mg twice daily for 4 weeks. Simethicone was provided by Tolid Daru Pharmaceutical Company (Dimetin 40 mg/ml oral drop). The treatment included daily administration of 5 drops of Pedilact (equivalent to 10^9 CFU) in an oil suspension for 4 weeks. Pedilact is a symbiotic preparation composed of three probiotics of *Bifidobacterium infantis*, *Lactobacillus rhamnosus*, and *L. reuteri* (10^9 CFU), as well as the prebiotic of fructooligosaccharide, and was produced by the Research Department of Zist Takhmir Company, Iran.

The control group received 5 drops of placebo daily for 1 month. The placebo was made by the same company and had all the ingredients in Pedilact drops except bacteria and prebiotics, was lactose based in the same oil suspension, and was prepared completely similar to Pedilact drops with the same taste, color, appearance, and package. Both Pedilact and placebo were labeled with only the randomization number and code. Caring for an infant with colic was taught equally to both the groups.

Outcome measures

The primary outcome was reducing the crying time to <3 h/day at the end of the study. The outcomes and compliance of drug were assessed by a telephone verbal interview each week. The duration of crying was asked and recorded weekly from the parents. The compliance of the drugs was ensured. The secondary outcome was defined as the number of infants whose crying duration was reduced to 50% of the baseline.

Demographic information including age, sex, maternal age, and possible confounding factors including passive

smoking, feeding type, family history of atopy, use of antibiotics or probiotics, and type of delivery were recorded.

The participants were examined and weighed at the beginning of the study and at day 28 after the intervention. The outcomes of the study (crying duration, frequency of colicky cries per day, and the duration of sleep), patient tolerance, and drug side effects were asked by phone on the 7th, 14th, and 21st days and recorded in the questionnaire.

Data analysis

Data were analyzed by SPSS version 16.0 software (SPSS Inc. Chicago, IL). Data were presented as number, percentage, mean, standard deviation, median, and interquartile range (if the quantitative data were not normally distributed). Qualitative variables were analyzed by Chi-square test and quantitative variables were analyzed by Mann–Whitney and Friedman tests. *P* values were calculated and a statistically significant level was considered <0.05.

RESULTS

Thirty-eight patients were randomly assigned in each group from January 2015 to May 2016. Out of 76 infants studied, 2 were collected from the emergency department and 55 from outpatient clinics of Mousavi Hospital, and 19 from the COME clinic. During the 1st and 2nd weeks of the study, three patients in the intervention group and two patients in the placebo group, during the 3rd week, one patient in the intervention group and one in the placebo group, and during the 4th week, one patient in the intervention group were excluded from the study due to lack of cooperation. At the end of the study, 33 infants were in the intervention group and 35 infants in the placebo group. Figure 1 shows the study chart. During the study, no side effects were reported in the participants.

The demographic data of the studied infants are summarized in Table 1. As shown in Tables 1 and 2, by using MannWhitney test, there was no significant difference between the two groups in terms of age ($P = 0.19$), gestational age ($P = 0.45$), birth weight ($P = 0.21$), age of colic onset ($P > 0.999$), and maternal age ($P = 0.95$). Infant weight at the beginning and the end of the study did not differ between the two groups ($P = 0.52$ and $P = 0.92$, respectively). Chi-square test did not show a significant difference between the two groups in terms of delivery type ($P = 0.80$), sex ($P = 0.36$), family history of atopy ($P = 0.33$), and passive smoking ($P = 0.45$) and type of feeding ($P = 0.74$). During the study, the type of feeding did not change in the study groups.

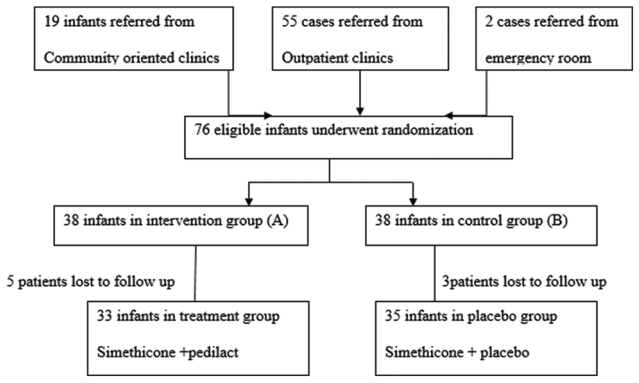

Figure 1: Flow diagram of the study design

As shown in Table 3, we did not find a significant decrease in the crying time and episodes of crying between the two groups based on the results of Mann–Whitney test. Moreover, sleep duration did not increase significantly at the end of the study comparing the intervention and placebo groups ($P = 0.13$).

It should be noticed that in both the intervention and control groups, the number and duration of colicky crying decreased during the 1st, 2nd, 3rd, and 4th weeks, and these differences in both the groups were significant ($P < 0001$). Furthermore, comparing the beginning and the end of the study, the duration of sleep finally increased significantly in each group ($P < 0.001$).

In the present study, the secondary outcome was defined as the number of infants whose crying duration was reduced to 50% on days 7, 14, 21, and 28. According to Table 4, there was no significant difference between the two groups in the secondary outcomes on days 7, 14, 21, and 28 ($P = 0.16$, $P = 0.21$, $P = 0.12$, and $P = 0.07$, respectively).

DISCUSSION

In this study, 66 infants out of 76 infants with colic were evaluated in two intervention and control groups. In the

Table 1: Demographic and baseline characteristics of patients in case and control groups

Variable (qualitative)	Probiotic, *n* (%)	Placebo, *n* (%)	*P*
Sex			
Female	19 (50)	23 (60.5)	0.36
Male	19 (50)	15 (39.5)	
Family history of atopy			
Yes	4 (10.5)	7 (18.4)	0.33
No	34 (89.5)	31 (81.6)	
Type of delivery			
Vaginal delivery	26 (68.4)	27 (71.1)	0.80
Cesarean section	12 (31.6)	11 (28.9)	
Passive smoker			0.45
Yes	10 (26.3)	13 (34.2)	
No	28 (73.7)	25 (65.8)	
Type of feeding			
Breastfeeding	20 (52.6)	23 (60.5)	0.74
Artificial feeding	13 (34.2)	10 (26.3)	
Mixed	5 (13.2)	5 (13.2)	

Table 2: Baseline characteristics of patients in case and control groups

Variable (quantitative)	Median (IQR)		*P*
	Probiotic	Placebo	
Age (week)	7 (4)	7 (5.25)	0.19
Birth weight (kg)	3.165 (0.555)	3.030 (0.612)	0.21
Gestational age (week)	38 (1)	38 (1)	0.45
Age of colic onset (week)	2 (2)	2 (2.25)	>0.999
Maternal age	26 (6.5)	27 (9)	0.95
Infant weight at the beginning of the study (kg)	4.850 (1.062)	5.000 (1.200)	0.52
Infant weight at the end of the study (kg)	5.600 (0.700)	5.600 (1.100)	0.92

IQR=Interquartile range

Table 3: Main outcomes after intervention in both groups

Variables	Median (IQR)		P#
	Intervention	Placebo	
Crying time minutes per day			
Day 0	240 (180)	210 (97.5)	0.17
Day 7	150 (90)	120 (150)	0.96
Day14	60 (220)	90 (172.5)	0.97
Day 21	37.5 (135)	30 (150)	0.79
Day 28	0 (75)	0 (150)	0.56
P##	<0.001	<0.001	
Number of colicky episodes per day			
Day 0	4 (3.25)	5 (6)	0.04
Day 7	2 (2)	3 (3)	0.02
Day14	1 (2)	3 (4)	0.72
Day 21	1 (3)	1.5 (4.75)	0.38
Day 28	0 (2.5)	0 (3)	0.52
P##	<0.001	<0.001	
Sleep duration minutes per day			
Day 0	720 (900)	720 (480)	0.57
Day 7	810 (300)	840 (420)	0.74
Day14	840 (340)	750 (390)	0.42
Day 21	930 (360)	825 (360)	0.30
Day 28	930 (330)	840 (360)	0.13
P##	<0.001	<0.001	

#Mann-Whitney test; ##Friedman test. IQR = Interquartile range

Table 4: Number of infants with decreased crying during the study in both groups

	Intervention (%)	Placebo (%)	*P*
Number of infants with crying <3 h	28 (84.8)	27 (77.1)	0.42
Number of infants with >50% decrease in crying time in day 7	18 (51.4)	13 (35.1)	0.16
Number of infants with >50% decrease in crying time in day 14	24 (68.6)	20 (54.1)	0.21
Number of infants with >50% decrease in crying time in day 21	29 (85.3)	25 (69.4)	0.12
Number of infants with >50% decrease in crying time in day 28	30 (91)	26 (74.2)	0.07

intervention group, the mean duration of infant crying decreased from 298.7 (149.6) min on the 1st day to 47 (80.1) min on the 28th day. Moreover, in the placebo group, it decreased from 262.1 (123.5) min to 81 (134.3) min at the end of the study. The number of crying episodes in the intervention group decreased from 4.6 (2.3) to 1 (1.5) and in the control group from 6.3 (3.8) to 1.6 (2.3) at the end of the study. Sleep duration in the intervention and control groups on the 1st day was 732.9 (213.6) and 712.1 (257.6) min, respectively, which increased to 912.8 (195.6) in the probiotic group and 842.6 (198.4) min in the control group on the 28th day.

Our study showed that symbiotic preparation did not significantly decrease the crying time or the episodes of crying between the intervention and control groups. Moreover, sleep duration did not increase significantly in the intervention group. Our findings are similar to some studies.[5,16,17]

In the randomized double-blind controlled clinical trial of Partty in Finland on 34 colicky infants aged 16 weeks, there was no significant decrease in crying time between the two groups after ingestion of *L. rhamnosus* GG which is similar to our study.[5]

In the study of Sung in Australia on 167 infants with colic, the mean daily crying time decreased in both the groups after 1 month, the crying time in the probiotic group was 49 min more than the placebo group, but the number of cry and sleep duration did not differ in both the groups.[15]

In a randomized clinical trial by Dorreh, on 84 breastfed infants and formula-fed infants <13 weeks, the crying time and the number of crying attacks did not show any significant changes which is similar to our study. It is noteworthy to point out that they used the same synbiotic as our study.[16]

However, some studies show different results. In a study by Savino in Italy on 83 infants comparing the effect of *L. reuteri* and simethicone on colicky infants, crying time decreased significantly in infants taking probiotics at the end of the 1st week.[18] In another study of Savino evaluating the efficacy of *L. reuteri* and Vitamin D in colicky infants, in the treatment group, the use of pain-relieving agents was significantly lower than the control group, but this study was not double blinded and it was taken in a small population.[10] In a meta-analysis by Szajewska, it was concluded that the use of *L. reuteri* diminished crying time in breastfed infants.[8] In another meta-analysis by Xu, from 6 trials including 423 infants, the use of *L. reuteri* decreased significantly the crying time at the 2nd and 3rd weeks, but treatment effectiveness was not seen at the 4th week. This probiotic effect may be overlapped with physiologic gradual improvement of colic symptoms.[19] A systematic review by

Radoslaw showed that *L. reuteri* can reduce crying time in only breastfed infants and it can be used in the treatment of colic, but the role of other probiotics is still undefined.[4] In some other randomized, double-blind, placebo-controlled trials, the crying time decreased significantly in infants receiving probiotic mixture.[7,20]

Perry's meta-analysis on colicky infants showed that the most common probiotic used was *L. reuteri* DSM17398. Although most of the studies found probiotics to be effective, there was low confidence on most of the results of reviews.[21]

The systematic review by Anabrees *et al*. showed that probiotic could decrease the episodes of crying, but due to small sample sizes in most studies, a multicenter randomized clinical trial with large sample sizes was recommended.[22]

It seems that infantile colic is affected by multiple factors such as feeding type, cow's milk allergy, bowel movements, and environmental background.

The varieties in the results of different studies may be due to differences in study methods, infant feeding type, age at study onset, sample size, and racial differences. Moreover, the type and dosage of used probiotic may influence the final results.[19] Age is an important factor in decreasing colic pain. It should be noted that colic improves spontaneously over time and heals in 3–4 months. Because colic improves with age, the infant's age at the beginning of the study can affect the final results. In our study, the median age of infants (7 [4] weeks for intervention and 7 [5.25] weeks for the placebo group) was higher than studies with different results (33.5 days and 35.2 days for the probiotic and placebo groups)[19] and was similar to studies with the same results.[16,17]

Behavioral measures to soothe a colicky baby, including using a pacifier and five relaxation maneuvers (swaddling, shushing, stomach position, swinging, and sucking), can play an important role in reducing the baby's cries. The different abilities of parents in calming and care of infants may influence the results. In this study as well as in Dorreh's study,[16] behavioral measures have been matched in the two groups and the results of these two studies are similar. However, in other studies, relaxation maneuvers had not been taken into consideration in both the groups.

Most studies that have different results have been performed in infants who are exclusively breastfed. In our study, Dorreh's study,[16] and Sung's study,[15] the infants were both breastfed and formula fed.

In some studies, parents recorded the duration of their infant's crying on a daily basis.[12] However, in the present study and Dorreh's study,[17] the duration of crying was asked weekly from the parents. The average crying time asked on a daily basis may be different from weekly statements. The study's results depend fully on parents' reports which can be affected by confounding factors such as maternal mental conditions, education, and cultural differences.[19] These two issues should be considered in the reliability of mothers' statements.

This study has some limitations. The different levels of education of parents, especially mothers, were not evaluated. Because our data collection was dependent on the mother's interview, it was better to use video recording system for better analysis. Furthermore, the rank of colicky infants had not been taken into consideration. Of course, parents who have an older child will usually be more familiar and less worried with baby care. Moreover, gut microbial flora was not evaluated after our intervention in this study. Hence, we cannot detect the definite role of different strains of probiotics.

CONCLUSION

Our findings did not show any significant differences in crying time, crying frequency, and sleep duration in colicky infants receiving probiotics compared to the control group.

Multicenter clinical trials considering more confounding factors (calming maneuvers, maternal education level and mental condition, allergy history, birth rank, type of infant feeding, and age of enrolment) with the use of video recording are recommended for better evaluation of probiotics effects on infantile colic.

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Conflicts of interest

There are no conflicts of interest.

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