ORIGINAL RESEARCH

A study to compare the effectiveness of two commercial preparations containing probiotics, prebiotics combination versus Simethicone, Dill oil, Fennel oil combination in managing infantile colic: An open label randomized controlled trial

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ABSTRACT
Probiotics positive effects on disorders like constipation, protection from infection, necrotizing enterocolitis, diarrhea, as well as capacity to modulate immuneresponces have been demonstrated earlier without any side effects. Lactobacilli are classified as"generally regarded as safe" category by WHO. Also, FDA (Food and drug administration) has approved use of Lactobacilli and Bifidobacteria in infants. We divided the study infants into group A (Probiotics and Prebiotics combination) and group B (Simethicone, Dill oil and Fennel oil combination). Number in each block (block size) was calculated using the formula-2n (where and is number of groups). So, we got block size-4. As the total sample size was 96(we recruited 76), number of total blocks-19 for the recruited sample. All possible allocation sequence were assigned to numbers 1 to 6 For ex, ABAB-1, AABB-2, ABBA-3. In our study there is significant increase in night time sleep at the end of study (mean 6.539 and 5.816 with p=0.011) in Probiotics, Prebiotics combination group. Daytime sleep was similar in both groups; however, Simethicone, Dill oil, Fennel oil combination group shows less daytime sleep on day7 which is statistically significant. The increase in nighttime sleep may be due to decrease in mean crying time and less crying episodes from day3 onwards in Probiotic, Prebiotic combination group.

Key words: Probiotics, simethicone, infantile colic

INTRODUCTION

Presently, there is no definite treatment for infantile colic and usual treatment with Simethicone (doubtful benefits),Herbal medication (potential risks of contamination with bacteria, toxins, unlabeled ingredients like alcohol),Manipulative therapies (safety and inconclusive efficacy),drug like Dicyclomine (rare serious side effects of-apnea, seizure, syncope)has not shown suitable evidence to relieve infantile colic. Only Parental support and education is the mainstay of management.[1,2]

Recently, there is lot of interest in the role of probiotics in infantile colic. Oral supplementation of probiotic i.e. Lactobacillus has shown to improve symptoms and decrease duration of crying. Probiotics positive effects on disorders like constipation, protection from infection, necrotizing enterocolitis, diarrhea, as well as capacity to modulate immuneresponces have been demonstrated earlier

without any side effects. Lactobacilli are classified as"generally regarded as safe" category by WHO. Also, FDA (Food and drug administration) has approved use of Lactobacilli and Bifidobacteria in infants.[3]

As probiotics and prebiotics studies need additional research from clinical observation to microbiological analysis to confirm beneficial effects, we plan to do the study using probiotics and prebiotic in infantile colic and compare with Simethicone which is widely used for colic.[4]

METHODOLOGY

STUDY POPULATION: Babies of 2 weeks to 5 months of age fulfilling the Modified Wessel'scriteria i.e. crying for more than 3 hours a day for more than 3 days a week.

INCLUSION CRITERIA

1. Term babies from 2 weeks-5months who fulfill (Modified Wessel's) criteria of crying for more than 3 hours a day for at least 3 days in a week.
2. Exclusively breastfeeding babies.

EXCLUSION CRITERIA

1. H/o birth asphyxia or abnormal neurological examination.
2. Organic cause for cry.
3. Abnormality preventing enteral feeding.
4. Easily consolable cries like hunger cries, nappy change cries.
5. On prolonged medication like Anticonvulsants, Levothyroxine etc.
6. Probiotic or antibiotic use within 7 days.

STUDY DESIGN: An open labeled randomized control study

- Informed consent was taken for those who fulfilled Modified Wessel's criteria of cryingfor more than 3 hours a day for at least 3 days in a week.
- Babies were randomized into 2 groups according to computer generated block randomization by an independent statistician:

We divided the study infants into group A (Probiotics and Prebiotics combination) and group B (Simethicone, Dill oil and Fennel oil combination). Number in each block (block size) was calculated using the formula-2n (where and is number of groups). So, we got block size-4. As the total sample size was 96(we recruited 76), number of total blocks-19 for the recruited sample. All possible allocation sequence were assigned to numbers 1 to 6 For ex, ABAB-1, AABB-2, ABBA-3.

Then computer generated random numbers were taken. The last digit of each number wastaken to give the corresponding allocation sequence to the particular block. If last number was 0 or >6 then the previous number was took for the same. For ex 3292 last digit 2 was taken and the block was given the Sequence AABB. 8018-as the last digit was >6, previous number was taken which is 1 here. So, the block was given the sequence of ABAB.

This allocation sequence was kept hidden and according to the randomization separate chit is picked with each case and treatment was given. The primary investigator was not aware of the allocation sequence.

After randomization if the child gets group A, then child was given preparation A containing Probiotics and Prebiotics combination. If child belong to group B then was given preparation B containing Simethicone, Dill oil and Fennel oil combination.

- Preparation A, one tenth (1/10th) sachet per day for 10 days Each sachet contains

(Lactobacillus acidophilus in a dose of 1.25 x 109CFU, *B.longum*1.25 x108CFU, *B.bifidum*1.25 x108CFU, *B.lactis* 1x109CFU and Prebiotic Inulin 25mg, alsoCarbohydrate 0.791gm, Fat 0.008gm, Protein 0.005gm)

- Preparation B was given as 20mg twice a day (13drops/dose) for 10 days
  (1ml ≈25 drops=40 mg Simethicone,
  0.005ml Dill Oil B.P, 0.0007ml Fennel Oil USP-NF)
- Parents were told by the doctor to mix products immediately before administration to infant with 10ml of breast milk and to be given by spoon twice a day for preparation B, once daily for preparation A.
- It was explained to the parents that the questionnaire needs to be filled on particular days for the initial 10 days and the filled form returned.
- Questionnaire to parents included details of sleep, feeding and crying episodes of the baby. Parents were instructed to exclude easily consolable cries like hunger cries, nappy change cries.
- Normal sleep pattern was taken as

Total-13hr (till 2month), 12hr (2 to 5 month).
Night-8hr30min (till 2month), 9hr (2 to 5 month).
Daytime-5hr 45min (till 2month), 3hr (2 to 5 month).

- Feeding pattern was considered adequate if infant feeds at least 8 times a day.
- Infants were clinically examined by doctor before and after treatment completion and in between if required. Birth history, anthropometry and detailed systemic and general examination were done on each visit. The parents were asked about adverse events during each visit.
- On days 1, 3, 7 and 10 the study doctor had send a mobile text message to families to remind them to fill the questionnaire about infants crying time and episodes.
- The doctor called families on day 11, to remind them to

a) Stop administration of the study product.
b) To return the filled questionnaire.

- In addition to the questionarre for parents, the doctor assessed the quality of life using validated PedsQL™ Family Impact Moduleat the time of recruitment of the study and after 10 days.
- The study ended after 10 days.
- At the end of the study the following outcomes were analyzed in both groups Primary outcome

1. Mean and % reduction in crying time per day Secondary outcomes.
2. Decrease in number of crying episodes per day.
3. Scores on standardized measure of Parent quality of life.
4. Scores on standardized measure of family functioning.
5. Duration of sleep in each group.
6. Feeding pattern in each group.
7. Episodes of vomiting of feeds in both groups.
8. Number and nature of stools in each group.

RESULTS

Table 1: Crying time per day (in minutes) between two groups after medical intervention

Variable	Group	Mean (% of baseline)	SD	t-value	p-value
Cry before medical intervention	A	264.11	55.945	0.313	0.755
	B	260.26	50.883		
Cry day1	A	216.18(82%)	34.649	0.445	0.658
	B	220.32(85%)	45.606		
Cry day3	A	202.76(77%)	25.247	2.291	0.025
	B	220.92(85%)	41.835		
Cry day7	A	188.89(72%)	37.217	3.105	0.003
	B	214.76(83%)	35.386		
Cry day10	A	169.34(64%)	30.228	5.196	0.000
	B	210.39(81%)	38.192		

Crying time was significantly lesser in group A (Probiotic, Prebiotic combination) compared to group B (Simethicone, Dill oil, Fennel oil combination) on day 3 onwards. (p<0.05).

Table 2: Crying episodes between two groups on day 1 of intervention

Crying episodes	Group A (No of infants)	Group B (No of infants)	Chi-square value	p value
6	6(15.7%)	6(15.7%)	9.6	0.085
7	22(57.8%)	13(34.2%)		
8	7(18.4%)	13(13.42%)		
9	1(2.6%)	6(15.7%)		
10	1(2.6%)	0(0%)		
11	1(2.6%)	0(0%)		

Crying episodes per day had no significant difference between group A compared to group B on day 1 of intervention (p>0.05).

Table 3: Crying episodes between two groups on day 3 of intervention

Crying episodes	Group A (No of infants)	Group B (No of infants)	Chi-square value	p value
5	2(5.2%)	0(0%)	14.2	0.007
6	12(31.5%)	7(18.4%)		
7	18((47.3%)	13(34.2%)		
8	2(5.2%)	15(39.4%)		
9	4(10.5%)	3((7.8%)		

Crying episodes per day was significantly lesser in group A (Probiotic, Prebiotic combination) compared to group B (Simethicone, Dill oil, Fennel oil combination) on day 3. (p<0.05)

Table 4: Crying episodes between two groups on day 7 of intervention

Crying episodes	Group A (No of infants)	Group B (No of infants)	Chi-square value	p value
5	4(10.5%)	0(0%)	15.5	0.008
6	19(50%)	9(23.6%)		
7	11(28.9%)	13(34.2%)		
8	4(14.2%)	13(34.2%)		

9	0(0%)	2(5.2%)		
10	0(0%)	1(2.6%)		

Crying episodes per day was significantly lesser in group A compared to group B on day 7. (p<0.05).

Table 5: Crying episode between two groups on day 10 of intervention

Crying episodes	Group A (No of infants)	Group B (No of infants)	Chi-square value	p value
4	3(7.8%)	0(0%)	24.957	0.000
5	10(26.3%)	0(0%)		
6	16(42.1%)	11(28.9%)		
7	7(18.4%)	13(34.2%)		
8	2(5.2%)	11(28.9%)		
9	0(0%)	3(7.8%)		

Crying episodes per day was significantly lesser in group A compared to group B on day 10. (p<0.05).

Table 6: Daytime sleep (in hours) between two groups after medical intervention

Variable	Group	Mean(Hours)	SD	t-value	p-value
Sleep before medical intervention	A	6.53	1.330	0.261	0.795
	B	6.61	1.306		
Sleep day1	A	6.184	1.2704	1.025	0.309
	B	5.908	1.0708		
Sleep day3	A	5.829	1.4854	0.178	0.859
	B	5.882	1.0618		
Sleep day7	A	6.382	1.2161	2.530	0.014
	B	5.750	0.9426		
Sleep day10	A	6.421	1.2762	1.261	0.211
	B	6.079	1.0813		

Daytime sleep was similar in both groups; however group B showed less daytime sleep on day 7 which is statistically significant. p – 0.014 (<0.05)

Table 7: Night time sleep (in hours) between two groups after medical intervention

Variable	Group	Mean(Hours)	SD	t-value	p-value
Sleep before medical intervention	A	5.63	1.683	0.401	0.690
	B	5.76	1.125		
Sleep night1	A	6.05	1.610	0.156	0.876
	B	6.11	1.311		
Sleep night3	A	6.184	1.4210	0.629	0.531
	B	5.987	1.3126		
Sleep night7	A	6.039	1.4813	0.666	0.507
	B	5.829	1.2643		
Sleep night10	A	6.539	1.3017	2.612	0.011
	B	5.816	1.1054		

Nighttime sleep was significantly higher in group A compared to group B on day 10 (p<0.05).

Discussion

In our study there is significant increase in night time sleep at the end of study (mean 6.539 and 5.816 with p=0.011) in Probiotics, Prebiotics combination group. Daytime sleep was similar in both groups; however Simethicone, Dill oil, Fennel oil combination group shows less daytime sleep on day7 which is statistically significant. The increase in nighttime sleep may be due to decrease in mean crying time and less crying episodes from day3 onwards in Probiotic, Prebiotic combination group.

Sung V *et al*., has done double blind randomized placebo-controlled trial using probiotic Lactobacillus reuteri DSM 17938 and placebo in 167 colicky infants from August 2011 to August 2012. The study was analyzed at 1 month and 6 month post intervention, concluded that there was no statistically significant difference in sleep hours.[5]

In our study there is no significant difference in

number and type of motion, vomiting per day between 2 groups. These results consistent with previous studies. Additionally, in our study we also found that there is no significant difference in number of feeds per day after 10 days of treatment.

Savino F *et al*., has done a double-blind randomized placebo-controlled trial in 2010 in Fifty exclusively breastfed colicky infants to test the efficacy of Lactobacillus reuteri DSM 17 938 (108 colony-forming units) or placebo daily for 21 days. Study concluded that there were no differences in weight gain, stool frequency, or incidence of constipation or regurgitation between groups at the end of study.[6]

Pärtty A *et al*., has done randomized controlled trial between June 2008 and May 2011, in which 94 infants who were recruited between days of life 1 and 3 in Finland to evaluate the impact of early prebiotic and probiotic intervention on preterm infants crying, stool frequency-consistency, growthand microbiological programming comparing with placebo. The frequency of stools (>3stools/d) tended to be higher in the prebiotic than in the probiotic and placebo groups at the age of 1 month (71% vs 50% vs 57%, respectively; P= .08), but there was no difference between the groups in consistency of stool.[7,8]

CONCLUSION

Probiotics and prebiotics combination shows significant improvement in nighttime sleep compared to Simethicone,Dill oil and Fennel oil combinationfrom baseline (day 10 mean 6.5hrs, 5.8hrs p value 0.011 from baseline 5.6 and 5.7 hrs). Daytime sleep is same in Probiotics, Prebiotics combination group at the end of study from baseline but is reduced in Simethicone, Dill oil, Fennel oil group. Difference in daytime sleep between 2 groups shows inconsistent results. These changes probably related to decrease in mean crying time and natural history of sleep pattern in infants wherein nighttime sleep hours gradually increases and daytime decreases as child grows.

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