Efficacy of Milk Fortified with a Probiotic *Bifidobacterium lactis* HN019 (DR-10™) and Prebiotic Galacto-oligosaccharides in Prevention of Morbidity – A Community Based Double Masked Randomized Trial

S. Sazawal[1,2], U. Dhingra[2], A. Sarkar[1], P. Dhingra[1], S. Deb[1], D. Marwah[1], V.P. Menon[1] and R.E. Black[2]

[1]Center for Micronutrient Research, Annamalai University India [2]Department of International Health, Bloomberg School of Public Health, Johns Hopkins University, Baltimore U.S.A.

Summary

Although there is increasing evidence demonstrating the beneficial effects of prebiotic and probiotic therapeutic effects on the gut, data from controlled clinical trials of adequate size evaluating preventive effects of probiotics on and beyond the gut are lacking. This double blind randomized controlled trial evaluated the efficacy of combined prebiotic and probiotic delivery via fortified milk in preventing diarrhea and other invasive bacterial and viral infections among preschool children. There was a significant reduction in incidence and prevalence of bloody diarrhea, febrile illness, days with severe illness, and a 10% reduction in diarrhea and days with ear discharge both of which were statistically non significant

Introduction

Diarrhea and pneumonia continue to be important causes of childhood morbidity and mortality in preschool children in developing countries. Interventions that can affect these morbidities would have important implications for child health and survival. In recent years there has been increasing evidence for the role of probiotics in treatment of diarrhea and suggestions for their role in prevention. Probiotics increase immu-

nity by increasing the production of γ interferon (1). However studies show that it is imperative that colonization must occur before benefits of probiotics can be realized (2). A meta-analysis of studies on healthy children aged <5 years showed that co-administration of probiotics with standard rehydration therapy reduced the stool frequency, duration, and episodes of acute diarrhea (3,4). Similarly, positive impact of probiotics administration has been reported for pneumonia and respiratory tract infections among children in hospital settings (5, 6). Another study in Finland on healthy children aged 1-5 yrs showed significant reduction in both respiratory and gastrointestinal symptoms, absences from day care because of illness, episodes of respiratory tract infections, and course of antibiotics (7). Most of these studies have been limited to children on antibiotic treatment in hospital settings with small sample sizes and short term supplementation. Data from community based randomized clinical trials are lacking. We undertook a community based randomized controlled trial to evaluate whether long term supplementation of probiotics delivered using milk formula as a vehicle can prevent diarrheal as well as non diarrheal illnesses in preschool children.

Methods

The study was conducted in Sangam Vihar, a peri-urban population in Delhi between April 2002 to April 2004. After an initial baseline survey, children aged 1- 3 years were invited to participate, consent was sought from parents who were permanent residents in the area and whose child did not have severe malnutrition or chronic illness requiring hospitalization. A total of 634 children were enrolled and randomly allocated to either receive milk fortified with prebiotics (galacto-oligosaccharides 2.4g/day) and the probiotic *Bifidobacterium lactis* HN019 (minimum 9.6 x 10^6 cfu/day) (n=312) or the same milk without prebiotics and probiotic (control) (n = 312). The milk was provided in sachets of 32g each and children were advised to consume 2-3 sachets per day after reconstituting with boiled and cooled water. Milk sachets were delivered by a field assistant to the home each week and previous weeks compliance information and sachets were collected. The intervention was continued for 1 year. At the baseline and end study a blood sample was collected and a detailed haemogram, plasma zinc, ferritin and zinc protoporphyrin were estimated. Children were maintained under twice weekly home visitations to collect data on morbidity. All visits to the study physicians and hospitalizations were recorded. Statistical analysis was performed using SPSSPC+ (version 12.0), and STATA (version 8.0) software. For incidence of illness we used Poisson regression methods with robust standard error estimations and for prevalence logistic regression with robust standard error was used to estimate Odds ratio. Exact methods were used for estimation of P values.

Table 1: Impact of Prebiotic and Probiotic Supplementation on Childhood Morbidity

Variable	PP milk Group (N=312)	Control Group (N=312)	OR(95% CI)	P value
Gastrointestinal Effects				
Incidence of Diarrhea	334	360	0.90 (0.78,1.05)	0.18
Dysentery Episodes	120	150	0.78 (0.61,1.00)	0.04
Days of Bloody Diarrhea	246	283	0.85 (0.71,1.01)	0.05
Effects Beyond Gut				
Days with severe illness	473	550	0.84 (0.74,0.95)	0.00
Days with ear discharge	1550	1613	0.93 (0.87,1.00)	0.06
Days with temp>100 F	150	216	0.68 (0.54,0.84)	0.05
Measles	5	10	0.47 (0.13,1.56)	0.20

Abbreviations: PP milk group = Prebiotic and probiotic milk group

Results

Compliance to the feeding of milk sachets was above 80% in both groups with most children consuming at least two serves per day. The baseline characteristics of both groups were comparable for all recorded variables including age, mean SES scores, family type, water supply, literacy rate, occupation of father and mother. Supplementation with milk containing pre and probiotics resulted in a significant reduction in incidence and prevalence of dysentery (Table 1). Though there was a reduction in diarrhea episodes by 10% in the pre and probiotic supplemented group the differences were not significant. Consistent with the possibility of improved immunity, supplementation with pre and probiotic caused a significant reduction in prevalence of severe illness, fever and ear infections. There was a substantial reduction in measles and pneumonia but these findings were not statistically significant (Table 1).

Conclusions

Consumption of milk fortified with prebiotics and the probiotic *Bifidobacterium lactis* HN019 significantly reduced the incidence and prevalence of dysentery and consistent with possibility of enhancement of immune response there was a reduction in incidence of ear infections

and prevalence of severe illness, febrile illness and ear infections. Measles episodes were reduced by 53% though this reduction was not statistically significant. In addition the need for antibiotic consumption was significantly reduced in the children consuming the pre and probiotic milk. Fortified milk can therefore be an effective means of reducing the incidence and prevalence of common childhood illnesses.

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