Lactobacillus GG and Acute Diarrhoea in Young Children in the Tropics

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Summary

A prospective, placebo controlled, triple blind clinical trial was undertaken in Thailand to determine the effect of *Lactobacillus GG* on recovery from acute diarrhoea in children. Thirty-nine children (mean age = 8 months) were enrolled and following rehydration received either oral *Lactobacillus GG* ($n = 20$) as a freeze-dried preparation or placebo ($n = 19$) twice daily for 2 days. The clinical characteristics of the study groups were similar. There was no significant difference overall in clinical response detected between the study groups. When only those with acute non-bloody diarrhoea ($n = 26$) were considered, the mean duration of diarrhoea was significantly shorter in the lactobacillus group (1.9 days) than in the placebo group (3.3 days) ($P < 0.055$). Stool frequency was less on the second day in the lactobacillus group ($P < 0.05$). The results suggest that *Lactobacillus GG* accelerates recovery from acute watery diarrhoea in young children in a tropical setting.

Introduction

Diarrhoeal disease continues to be a major cause of morbidity and mortality among infants and young children in developing countries. The widespread use of oral rehydration solution (ORS) has been important in reducing the risk of dehydration, but it neither shortens the duration of diarrhoea nor provides any significant nutritional value. There has been a recent shift in emphasis in the nutritional strategies used to promote recovery from diarrhoea.[1] Following rehydration, early feeding with mixed milk feeds, yogurt, or traditional fermented foods have been shown to improve outcome as well as to provide nutrients.[2–5] The continuation of breastfeeding remains important.[6]

Another approach to promote recovery, which partly may explain the effect of fermented foods, is to colonize the gut with non-pathogenic bacteria that may replace the pathogens. *Lactobacillus casei* strain GG (*Lactobacillus GG*) is a human isolate of lactobacillus that can colonize the bowel,[7] and demonstrates both antimicrobial[8] and immunostimulatory[9] activity in the gut. A study of Finnish children with gastroenteritis, predominantly due to rotavirus, suggested that *Lactobacillus GG* had a significant effect in shortening the course of acute diarrhoea.[10] However, no study has investigated whether *Lactobacillus GG* could accelerate recovery from acute diarrhoea in a tropical country.

Methods

Patients and study design

The study was conducted in the diarrhoea ward of Bangkok Children's Hospital, Thailand, over a 6-week period between July and mid-August, 1993. Study subjects included 39 children, aged between 1 and 24 months, consecutively admitted with acute diarrhoea, defined as diarrhoea of less than 14 days duration, and with more than three watery stools during the previous 24 hours. A prospective, block randomized, placebo controlled, triple blind clinical trial using *Lactobacillus GG* strain *v.* placebo was undertaken. *Lactobacillus GG* in freeze-dried powder form and a visually identical placebo (microcrystalline cellulose) were obtained from Scientific Hospital Supplies, Liverpool, UK. Exclusively breastfed children were not included so as not to interrupt this feeding pattern in any way, though no such children

Acknowledgements

The authors would like to thank the nursing staff of the diarrhoea ward at the Bangkok's Children Hospital for their assistance throughout the study. We are also grateful to Scientific Hospital Supplies, UK, for providing the *Lactobacillus GG* freeze-dried preparation. This study was carried out as part of the Master in Tropical Paediatrics degree (Dr A. R. Pant) from the Liverpool School of Tropical Medicine, U.K.

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were admitted over the time of study. Children with septicaemia were also excluded.

On admission, each patient was weighed and examined clinically, assessing degree of dehydration according to a standard WHO protocol.[11] Those with mild to moderate dehydration were given WHO–ORS while those with severe dehydration received intravenous fluid therapy, according to the usual protocol of Bangkok Children's Hospital. After the initial rehydration period (6 hours), children received either *Lactobacillus GG* (10^{10}–10^{11} colony-forming units) as a freeze-dried preparation or a placebo mixed in 10 ml of ORS and given orally. Both *Lactobacillus GG* and placebo had the same appearance and texture. No problems were encountered with either preparation on the ward or with administering the treatment to the child. Treatment was continued at 12-hourly intervals for 2 days (i.e. four doses), in addition to the usual diet of a mixed milk feed.

Data collection

Data collected included age, sex, duration, and frequency of both diarrhoea and vomiting, character of the stool (classified as watery with or without blood) and any treatment prior to admission, including antibiotics or anti-diarrhoeal medication. Weight and axillary temperature were recorded daily. As per the routine at the hospital, blood was taken on admission for haematocrit and electrolytes.

Fluid intake, episodes of vomiting, frequency of diarrhoea, and character of stool (watery, loose, or formed) were recorded over the next 48 hours. Stool volume was measured in boys only using preweighed absorbent pads and the application of a urinary bag to avoid mixing. Each child was followed until discharge and duration of diarrhoea was recorded as the time from admission until the time of the last watery stool. It was not possible to follow patients beyond hospital discharge.

Stool samples collected on admission and at 48 hours were examined for ova, cysts, parasites, and cryptosporidium. A portion of each sample was stored at 4°C and transported to Liverpool within 60 days of collection in a sealed ice pack for viral analysis at the Department of Medical Microbiology, University of Liverpool.

Statistics

The statistical analysis was carried out blindly, and the code was only broken once all the results and tables had been prepared. Students *t*-test was used for comparison of means of continuous variables. Discrete variables were analysed using chi-squared test and Fischer's exact test when appropriate.

Results

A total of 39 children were enrolled in the study. Twenty received *Lactobacillus GG* and 19 received the placebo. The patient characteristics on admission were similar for each group and are summarized in Table 1. All stools were negative for parasitic ova, cysts, and cryptosporidium. A virus was identified in eight cases (21 per cent) using electron microscopy: three patients in the lactobacillus group (two rotavirus and one astrovirus); and five with rotavirus in the placebo group.

Outcome of therapy

Following successful rehydration, all patients were managed according to their treatment protocol. One patient in the placebo group vomited the second dose of treatment. No patient in the *Lactobacillus GG* group vomitted. Although recovery was more evident on day 2 of treatment in the group receiving the lactobacillus in terms of decreased stool frequency and volume, the difference was not statistically significant. However, when those presenting with watery, non-bloody diarrhoea ($n=26$) were considered, there was a significant decrease in the duration of diarrhoea in those receiving *Lactobacillus GG*, compared to those receiving placebo (mean duration: 1.9 and 3.3 days, respectively) ($P<0.05$). Stool frequency was also decreased on the second day in the lactobacillus group ($P<0.05$) (see Table 2).

Discussion

The antimicrobial properties of lactobacilli have long been recognized.[12] The colonization of the gut with bifidobacteria and lactobacilli in the breastfed infant is thought to be one of the many advantages of exclusive breastfeeding and contributory to its protective effect against diarrhoeal disease. More recently, it has been shown that lactobacilli may also have an immunostimulatory effect.[9,13] There has been a resurgence of interest in the possible therapeutic benefits of lactobacilli. Aside from the effect on gut pathogens, strains of lactobacilli have also shown some promise in the prevention of colonic cancer.[14]

Lactobacillus casei strain GG is a species of lactobacillus, isolated from the human intestine in 1987,[15] which is stable to acid and bile. Doses of 10^{10} and 10^{11} cfu, as used in this study, will result in successful colonisation of the intestine.[16] *Lactobacillus GG* grows better under anaerobic conditions, although it can grow aerobically in the presence of carbon dioxide. It differs from other *L. casei* subspecies in that it does not ferment lactose, maltose or sucrose, and so its therapeutic value could not be due to any disaccharides activity. This strain has been shown to possess antimicrobial activity against a wide range of bacterial species, both anaerobic and aerobic.[8] It has been successfully used in the treatment of *Clostridium difficile* colitis[17] and has reduced the occurrence of traveller's diarrhoea when used as a preventive measure.[18] Recently, Isolauri *et*

TABLE 1
*Characteristics of patients on admission**

Characteristic	*Lactobacillus* group ($n=20$) Mean	SD	Placebo group ($n=19$) Mean	SD
Age (months)	8.1	6.2	8.6	6.8
Weight (kg)	6.7	2.6	6.2	2.4
Duration of diarrhoea prior to admission (days)	2.2	1.2	3.4	2.9
Stool frequency in previous 24 hours	8.5	6.2	7.5	3.8
Axillary temperature (°C)	37.4	1.1	37.4	1.2
Weight-for-age *Z*-score (Ref: NCHS)				
On admission	−1.15	0.95	−1.8	1.4
At 48 h	−0.96	0.9	−1.63	1.2
Haematocrit (%)	32	5.4	32.1	5.8
Serum electrolytes (mmol/l)				
Sodium	134	6	134	8
Potassium	4.5	0.8	4.2	0.9
Chloride	110	9	112	9
Bicarbonate	17	4	16	4
	Number	(%)	Number	(%)
Character of stool				
Watery, no blood	14		12	
Watery, bloody	6		7	
Degree of dehydration				
Mild	8	(40)	3	(16)
Moderate	10	(50)	12	(63)
Severe	2	(10)	4	(21)
Treatment prior to admission				
Antibiotics	9	(45)	7	(36)
Antidiarrhoeals	3	(15)	5	(26)
ORS	8	(40)	10	(53)

*All characteristics were similar in the two groups ($P>0.05$).

TABLE 2
Outcome of patients with watery diarrhoea on admission

Outcome variables	*Lactobacillus* group ($n=14$) Mean	SD	Placebo group ($n=12$) Mean	SD	*P*-value
Stool frequency					
Day 1	6.3	3.2	6.2	2.3	NS
Day 2	3.5	1.3	5.2	2.8	<0.05
Duration of diarrhoea					
Days	1.9	0.6	3.3	2.3	<0.05

al. studied 71 well nourished Finnish children aged between 4 and 45 months, 82 per cent of whom had rotovirus gastroenteritis.[10] Those receiving *Lactobacillus GG* either as a fermented milk product or as a freeze-dried powder twice daily, had a significantly shorter duration of diarrhoea (mean duration 1.4 days) than those who received a pasteurized yogurt placebo (mean duration 2.4 days). The effect became

apparent on the second day of treatment. A later study from Finland showed a similar outcome.[9]

The aim of this study was to investigate the use of *Lactobacillus GG* in promoting recovery from acute diarrhoea in a developing country, where predisposing factors and the pathogenesis of diarrhoea are likely to differ from the Finnish study population. The children in our study had a lower mean age than the Finnish group, were less well nourished (mean Z score: -1.28), had more severe diarrhoea on presentation and were likely to be infected with a broader range of pathogens. Viruses were identified in just a fifth of cases, which is consistent with the usual pattern specific causes of diarrhoea in this unit. In 1989, rotavirus was found in 20 per cent of cases and a high percentage of bacterial pathogens (62 per cent) were identified, notably *Salmonella* spp., *Shigella*, *Campylobacter*, and diarrhoeogenic strains of *E. coli* (personal communication, Dr S. Harikul).

Overall, *Lactobacillus GG* had no significant effect on reducing either the duration or frequency of diarrhoea of these Thai children when compared to placebo. However, in those presenting with acute watery non-bloody diarrhoea, the use of *Lactobacillus GG* was associated with a significantly shorter duration of diarrhoea and reduction in stool frequency on the second day. These findings resemble those of a simultaneous study undertaken in Pakistan.[19] The precise mechanism by which *Lactobacillus GG* may be effective is not clear. The anti-bacterial activity of *Lactobacillus GG* is well recognized.[8] This is not likely to be the main action, however, as children with viral gastroenteritis have also been shown to respond.[10] A study from Finland has demonstrated that *Lactobacillus GG* enhances the specific antibody secreting cell response in humans with rotavirus gastroenteritis, and this immuno-stimulatory effect may be more important.[9] Finally, colonization with a species with specific affinity for humans may improve nutrient digestibility and absorption. Our experience suggests that once significant mucosal invasion has occurred, as suggested by blood in the stool, it may be less effective.

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