



“EVALUATION ON LACTOBACILLUS GG FOR TREATMENT OF ACUTE CHILDHOOD DIARRHOEA: A HOSPITAL BASED STUDY”

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ABSTRACT

Diarrhoea is a Greek word that's literal meaning is "to flow through like a stream". Diarrhoea is defined as the passage of 3 or more liquid or watery stools in a day with change in consistency and character of the stools. Our study was aimed to evaluate the efficacy and safety of Lactobacillus GG in the treatment of acute diarrhoea in children. Total 100 patients enrolled in the study, 65 (65%) completed the seven days follow up. The baseline characteristics in the two groups were comparable in age, sex and anthropometry. Duration of diarrhoea before enrolment was about two days in both groups (2.18 days in LGG group vs 2.46 days in control group). Duration of vomiting before enrolment, hydration status and rotavirus status were also comparable in both the groups (Table I). Rotavirus status could be assessed in 60 patients. Stool samples of 13 patients (21.6%) were positive for rotavirus. The Lactobacillus GG in dose of 10 billion cfu/ day for five days given to children aged under five resulted in shortening of the duration of diarrhoea and faster improvement in stool consistency.

KEYWORDS : Acute Childhood Diarrhoea and Lactobacillus GG.

Introduction:

Diarrhoea is a Greek word that's literal meaning is "to flow through like a stream". Diarrhoea is defined as the passage of 3 or more liquid or watery stools in a day with change in consistency and character of the stools. Therefore diarrhoea is a symptom but it is also a sign when the loss of water (stool volume) is more than 15gm/kg/day in children < 3 year and > 200gm/day in children > 3year of age.¹ Diarrhoea is an important cause of death in children under 5 years of age in developing countries. It is responsible for about 15 per cent of the 8.79 million annual under-five deaths worldwide and ranks second to pneumonia as the major cause of mortality in children. India contributes significantly to this global burden. Of the 1.83 million child deaths in India in 2010, 13 per cent were caused by diarrhoeal diseases alone.² Though mortality due to diarrhoea has decreased over the years, it is still unacceptably high. Randomized controlled trials in developed countries have reported benefits of Lactobacillus GG (LGG) and *Saccharomyces boulardii* in the treatment of acute watery diarrhoea.^{3,5} This benefit is seen primarily in rotaviral diarrhoea in infants and young children.^{3,4} Similar benefit however, was not seen with other probiotics.⁴ Limited information is available on the potential role of Lactobacillus GG in acute diarrhoea in infants and young children living in the developing world, where diarrhoeal aetiology and gut flora are likely to be different. Basu and colleagues have reported beneficial effects of Lactobacillus GG in acute diarrhoea.^{6,7} Our study was aimed to evaluate the efficacy and safety of Lactobacillus GG in the treatment of acute diarrhoea in children.

Material and Methods:

This present study was conducted in the Department of Pediatrics at K D Medical College and Hospital, Mathura during the period from May 2017 to October 2017. Children were eligible for the study if they were aged between 6 months to 5 years and presented with

acute diarrhoea (less than 7 days duration) to the outpatient department (OPD) or pediatric emergency services. Diarrhoea was defined as passage of three or more loose stools in the last 24 hours.⁸ Children with severe malnutrition (weight for height < 3 SD of WHO charts), dysentery (presence of visible blood in stools), clinical evidence of co-existing acute systemic illnesses (e.g. meningitis, sepsis, pneumonia) and clinical evidence of chronic disease (e.g. chronic gastrointestinal disease, chronic liver disease, chronic renal disease, nephrotic syndrome) were excluded from the study. Subjects in whom probiotics were used in the preceding three weeks or if antibiotics were used for current episode of diarrhoea, were also excluded from the study. The study protocol was approved by the ethical committee of K D Medical College and Hospital, Mathura. Informed written consent was obtained from parents of children enrolled in the study. In a previous study, mean duration of diarrhoea was 58.3 ± 27.6 hours in probiotic group and 71.9 ± 35.8 hours in placebo group.⁹ Using this data set, it was calculated that 100 subjects were needed to be enrolled (50 subjects in each group) to detect a mean difference in duration of diarrhoea of 24 hours in the two group, with 90 per cent power and 2-tailed alpha of 0.05.

Results and Discussion:

Total 100 patients enrolled in the study, 65 (65%) completed the seven days follow up. The baseline characteristics in the two groups were comparable in age, sex and anthropometry. Duration of diarrhoea before enrolment was about two days in both groups (2.18 days in LGG group vs 2.46 days in control group). Duration of vomiting before enrolment, hydration status and rotavirus status were also comparable in both the groups (Table I). Rotavirus status could be assessed in 60 patients. Stool samples of 13 patients (21.6%) were positive for rotavirus.

Table-1: Baseline characteristics in between cases and controls group:

Variables	Cases (N=50) LGG (Mean ± SD)	Controls (n=50) (Mean ± SD)
Age (months)	16.21 ± 10.26	18.5 ± 12.5
Weight (Kg)	8.42 ± 3.5	8.46 ± 4.21
Height (cm)	74.61 ± 9.62	74.62 ± 10.2
Duration of diarrhoea before enrolment (days)	2.18 ± 1.02	2.46 ± 1.05
Vomiting [Number (%)]	12(24)	16 (32)
Stool consistency at the time of enrolment		
Semi-liquid	12	18
Liquid	38	32
Duration of vomiting before enrolment (days)	1.48 ± 0.23	1.56 ± 0.5

Hydration status [Number (%)]		
No dehydration	34 (68)	32 (64)
Some dehydration	14(28)	12 (24)
Severe dehydration	2(4)	6(12)
Rotavirus positive [Number (%)]	14/50 (28)	12/50 (24)
LGG, <i>Lactobacillus</i> GG		

Primary outcome measures: Median duration of diarrhoea was significantly ($P < 0.001$) lesser by about 18 h in children who received LGG in comparison to control group (Table-2). There was faster improvement ($P < 0.001$) in stool consistency by about 6 hours in the LGG group compared to control group (Table-2). The benefits on

duration of diarrhoea and duration of change in stool consistency were seen both in rotavirus positive and rotavirus negative subjects (Table-2). The hazard ratios for both durations did not change when rotavirus status was taken as a covariate in cox proportional hazard analysis (Table-2).

Table-2: Primary outcome variables in between cases and controls group:

Outcome	LGG group (n=50) [Median (IQR)]	Control group (n=50) [Median (IQR)]	Hazard ratio (95% CI)	P value*
Duration of diarrhoea (h)				
All subjects (n=100)	60 (54-72)	78 (72-90)	0.324 (0.241, 0.462)	<0.001
Rotavirus positive (n=13)	60 (54-66)	84 (72-90)	0.328 (0.235, 0.456)**	<0.001
Rotavirus negative (n=87)	60 (54-72)	78 (72-90)		<0.001
Time to improvement in stool consistency (hours)				
All subjects (n=100)	36 (30-36)	42 (36-48)	0.531 (0.386, 0.745)	<0.001
Rotavirus positive (n=13)	36 (30-42)	42 (36-48)	0.532 (0.389, 0.726)**	<0.001
Rotavirus negative (n=87)	36 (30-36)	42 (36-48)		<0.001

Secondary outcome measures: (i) Stool frequency: There was a significant reduction in average number of stool per day in LGG group [mean (95% CI) difference of 1.12. (ii) Effect on vomiting: There was no significant reduction in duration of vomiting in the LGG group [mean (95% CI) difference of 4.34 hours. (iii) Effect on

duration of hospital stay: There was no significant reduction in duration of hospital stay in LGG group [mean (95% CI) difference of 10.7 hours. No adverse effect was noted in any group. Numbers of vomiting episodes were comparable in the LGG and control groups.

Table-3: Secondary outcome variables in between cases and controls group:

Outcome	LGG group (n=32) (Mean ± SD)	Control group (n=33) (Mean ± SD)	P value
Mean number of stools per day during diarrhoeal illness	9.14 ± 1.67	10.26 ± 1.49	<0.001
Duration of vomiting (hours)	14.72 ± 10.5	19.12 ± 9.27	0.076
Duration of hospital stay (hours)	79.5 ± 12.46	90.17 ± 13.56	0.067
Rotavirus Positive (n=13)			
Average number of stools per day	9.6 ± 1.02	10.12 ± 1.05	0.37
Duration of vomiting (hours)	17.52 ± 5.03	21 ± 6.76	0.25
Duration of hospital stay (hours)	80 ± 3.04	83 ± 10.23	0.69
Rotavirus Negative (n=47)			
Average number of stools per day	9.16 ± 1.05	10.41 ± 1.05	<0.001
Duration of vomiting (hours)	13.45 ± 12.52	18.63 ± 10.3	0.10
Duration of hospital stay (hours)	80.0 ± 16.82	99.0 ± 15.04	0.053

This randomized controlled trial conducted in K D Medical College and Hospital, Mathura setting with high background diarrhoeal rates demonstrated that *Lactobacillus* GG in a dose of 10 billion CFU/ day for five days given to children aged under five during an episode of acute diarrhoea results in shortening of the duration of diarrhoea and faster improvement in stool consistency and frequency. The benefits were seen irrespective of their rotavirus status. A meta-analysis of eight randomized control trials including 988 children of 1 to 36 months, reported that LGG was associated with significant reduction in duration of diarrhoea [weighted mean difference (WMD) of -1.1 days]. Contrary to our study, which did not demonstrate any difference in the outcome in relation to rotavirus status, the meta-analysis reported maximum benefit in diarrhoea due to rotavirus (WMD of -2.1 days).¹⁰ The reason could be that most of the studies included in this meta-analysis were from developed countries, where aetiological strains and gut flora could be different.

Lactobacilli to host that downregulates the secretory and motility defences designed to remove perceived noxious substance, and inactivation of viral particles.¹⁵ Donato et al¹⁴ have reported that LGG alleviates the effects of pro-inflammatory cytokines like tumour necrosis factor α (TNF- α) and interferon- γ on epithelial barrier integrity and inflammation, as CXCL-8 (interleukin-8) and CCL-11 (eotaxin) protein levels were decreased in LGG-inoculated, cytokine-challenged cells. It was mediated, at least in part, through inhibition of TNF- α induced nuclear factor (NF)- κ B signalling. Though other species of *Lactobacilli* are commercially available in India, *Lactobacillus* GG is still not available. The results of this trial do not endorse use of other species of *Lactobacilli* or most other probiotics species, as their effects are not similar and these have not been shown to be as effective in acute diarrhoea in children.^{15,16}

Basu et al reported from India that *Lactobacillus* GG given in dose of 60 million cfu twice a day for days 7 had no beneficial effects in children with acute diarrhoea.⁶ The absence of benefit in this study could be because of lesser dose used in their study, as another trial by the same group using LGG in dose of 10 billion cfu twice a day for days 7 reported reduction in duration and frequency of diarrhoea, and in hospital stay. They also reported that further increase in dose to 103 billion cfu twice a day did not exhibit any extra benefits.⁷ Our study also documented the beneficial effects of LGG in dose of 10 billion cfu/day. The benefits of *Lactobacillus* GG in diarrhoea could be related to competitive blockage of receptor sites,¹¹ enhanced immune response by *Lactobacilli*¹², transmission of signal(s) from

Potential limitations of this trial include its open labelled nature and lack of placebo control. Moreover, as majority of subjects were not admitted, we relied on information provided by the parents. However, we contacted our patients frequently by repeated communication at short intervals to ensure compliance and to check for outcome. Although rotavirus status was assessed in the stool samples in 60 patients, other aetiologies for acute diarrhoea were not explored and this also was a limitation. We also could not assess the 24 hour stool output. Although we monitored common clinical symptoms such as fever, vomiting, pain abdomen, development of any other new symptoms and any hypersensitivity reaction like skin rashes as potential adverse effects of intervention, we did not monitor for any asymptomatic bacteremia due to *Lactobacillus* GG.

Conclusion:

These findings suggest that the Lactobacillus GG in dose of 10 billion cfu/ day for five days given to children aged under five resulted in shortening of the duration of diarrhoea and faster improvement in stool consistency. The results are applicable for children presenting to hospital in a setting of a developing country and may not be valid for communities. Large scale community based efficacy and effective trials are needed to confirm these results.

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