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CELIAC DISEASE;
EFFICACY OF PROBIOTICS IN CHILDREN

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ABSTRACT… Objectives: Probiotics are alive organisms which confer health benefit when taken at an appropriate dosage. This study was done to determine the efficacy of probiotics in decreasing the frequency of diarrhea in children with celiac disease. **Study Design:** Randomized controlled trial. **Setting:** Department of Pediatrics/DHQ Allied Hospital, Faisalabad. **Period:** November 2011 to October 2012. **Methods:** Newly diagnosed patients with CD having diarrhea were included by consecutive non-probability sampling. Patients were randomized in two groups using computer generated numbers. One group was given probiotic along with gluten free diet while other was only prescribed gluten free diet. Reduction in frequency of diarrhea in two groups was compared after a period of 28 days. **Results:** A total of 116 cases (58 in each group) were enrolled. Mean age was 9.11 years. The groups were similar in age and gender of patients. Comparison of efficacy of probiotics in children with CD was done with control group which revealed reduction in stools frequency to less than half in 86.21% (n=50) in probiotic group but only 62.07% (n=36) in control group. P-value was 0.00015 which shows a highly significant difference in both groups. **Conclusion:** Probiotics in addition to gluten free diet are highly effective in reducing the frequency of diarrhea in newly diagnosed patients with CD, in comparison with gluten free diet alone.

Key words: Celiac Disease, Children, Management, Probiotic, Efficacy

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INTRODUCTION

Celiac disease (CD) is a common inflammatory disease of small intestine that is mainly triggered and maintained by a storage protein of gluten, rye and barley in genetically predisposed individuals. It affects up to 1% of population.[1,2] The presentation of CD is quite variable including loose motions, abdominal distension, failure to thrive, pallor, rash, poor appetite, irritability, fatigue, arthritis, infertility,[3] liver failure, neuropathy, schizophrenia, or autism.[4] It has association with other autoimmune disease like diabetes mellitus, arthritis, hepatitis and thyroiditis.[5]

CD is a prototype of multifactorial pathophysiology with genetic factors in the form of HLA DQ2 and DQ8 and environmental factors in form of gluten exposure play a key role in the disease causation. Other disease modifiers include early feeding practices and microbial exposure. Bacteriological pattern of the intestinal content has been found to significantly alter the inflammation in gut. Gram negative organisms such as Bacteroides fragilis, Escherichia coli, and Shigella increase the secretion of pro-inflammatory cytokines like interleukin 12 and interferon gamma. Contrary; Bifidobacterium species decrease the pro-inflammatory cytokines.[6]

The only treatment of CD is lifelong withdrawal of gluten from diet[7] that is partially impossible therefore several agents have been tried to help in reduction in symptoms of CD. One of those is use of probiotics which are naturally occurring beneficial organisms that aid in digestion and inhibit disease causing bacteria in intestine.[8] They reduce inflammation of intestine.[9] They have been tried in CD, inflammation, bowel disease, diarrhea, lactose intolerance, helicobacter pylori infection.[10]

Probiotics are diverse group of organisms and

they include bifidobacterium lactis, sacchromyees boulardie, bifidobacteriam infantis, lactobacillus rhammosus and lactobacillus plantarum etc.[11]

The rationale of the study was to explore the role of probiotics in reduction of diarrhea in patients of CD on the basis of its mechanism of action as compared to gluten free diet alone.

OBJECTIVES

To determine efficacy of probiotic along with gluten free diet in reducing diarrhea frequency in newly diagnosed patients with Celiac Disease and compare it with gluten free diet alone.

HYPOTHESIS

Probiotic along with gluten free diet is effective in reducing diarrhea in patients of celiac disease as compared gluten free diet alone.

MATERIAL AND METHODS

It was a randomized controlled trial conducted at the Department of Pediatrics, DHQ Allied Hospital, Faisalabad over a period of one year; from 1st November 2011 till 31st October 2012.

Sample size was calculated using WHO sample size calculator keeping level of significance 5%, power of test 80%, anticipated population (P1) 85.7% and anticipated population (P2) 66%. Sample size was 58 patients in each group (total 116 patients). Sample collection was done by consecutive non-probability sampling.

Inclusion Criteria

- Age 1-15 years.
- Newly diagnosed biopsy proven patients of celiac disease (Biopsy findings are villous atrophy, crypt elongation, increased no. of intraepithelial)

Exclusion Criteria

- Children with other causes of diarrhea like cystic fibrous, immunodeficiency, chronic amoebiasis and chronic giadiasis.
- Children with severe malnutrition (weight less than 5th percentile for age)
- Atypical manifestation of celiac disease like isolated short stature and unexplained pallor alone etc.

After taking approval from the hospital ethical committee, and taking informed consent from parents/guardian of all patients meeting inclusion criteria; patients were randomized by computer generated table of random numbers to receive one of the following two groups:
Group-A
Group-B

Thorough history and physical examination of patients was done. Number of stools per day was recorded at the time of entry into the study. Group-A was given Gutcare sachet 500mg (Clostridium butyricum and bifidobacterium) diluted in 75-100ml of boiled water twice a day for 28 days along with gluten free diet and group B was given only gluten free diet. After 28 days of treatment, all patients were followed and the stool frequency at the end of treatment was also recorded. Efficacy was defined as reduction in stool frequency to more than half after a treatment of 28 days. Data was collected by researcher on especially designed proforma. Follow up of the patients was ensured by taking their contact number and their address.

Data was analyzed by using SPSS version 10. Quantitative variables like age, number of stools per day were presented as mean and standard deviation. Qualitative variables like sex and efficacy was presented as frequency and percentage. Chi square test was applied to compare efficacy in two groups. P value <0.05 was considered as statistically significant.

RESULTS

A total of 116 cases (58 in each group) were enrolled. To determine the efficacy of probiotics in children with CD by comparing with controls. Mean age was 9.11 years and there were equal number of male and female patients in the study population. There was no significant difference among the groups regarding age and gender (Table-I).

	Group-A (n=58)		Group-B (n=58)	
Age(Years)	8.45±3.21		9.76±4.56	
Gender	**No. of patients**	**%**	**No. of patients**	**%**
Male	32	55.17	28	48.28
Female	26	44.83	30	51.72

Table-I. Age & Gender Distribution of the Patients

	Group-A (n=58)		Group-B (n=58)	
	Mean	SD	Mean	SD
Before Treatment	3.56	0.54	4.87	1.12
After Treatment	1.34	1.05	3.141	1.82

Table-II. Mean Number of Stools per day

Comparison of efficacy of probiotics in children with CD in both groups was done which revealed reduction in stools frequency to less than half in 86.21% (n=50) in Group-A but only 62.07%(n=36) in Group-B (Table-III). P-value was calculated using chi-square test and it was 0.00015 which shows a highly significant difference in both groups.

	Group-A (n=58)		Group-B (n=58)	
	Freq	**%**	**Freq**	**%**
Effective	50	86.21	36	62.07
Not Effective	8	13.79	22	37.93

Table-III. Efficacy of the two groups

DISCUSSION

Large variety of probiotics are available and are being used widely by Pediatricians. Although probiotics can be helpful for specific disorders, they have been broadly prescribed for disorders without clear evidence to support their use. It is important to understand that probiotics are highly heterogeneous with respect to composition, effective dosage and biological activity among the different probiotic preparations. The current study was planned to explore the role of probiotics in reduction of diarrhea in patients of CD on the basis of its mechanism of action as compared to gluten free diet alone.

Total number of 116 patients, newly diagnosed with CD were entered into study. Mean age at diagnosis was 9.11 years in present study; while male to female ratio was equal. Patients were randomized into two groups and there was no significant difference of age or gender among the two groups. Mean age at diagnosis was 6 years in the study done by Cheema HA[3] which is much less than the results of present study. On the other hand, mean age in another study done by Ikram MA was 8.9 years which in very close agreement with current study. Male to female ratio was 1.5:1 in the study by Ikram MA which is somewhat higher than the results in present study.[12]

Present study excluded the non-diarrheal, atypical presentation of CD. The reason for the exclusion was the lack of quantifiable variable to measure outcome in such patients. Atypical presentation is a major proportion of patients with CD. It ranges between 20.7%[13] to 48.1%[3] in different studies from Pakistan. This is a major drawback of the current study which limits the application of results to a proportion of CD patients with diarrhea.

Present randomized controlled trial compared the efficacy of probiotic in reducing the frequency of diarrhea in newly diagnosed patients with CD. Combined probiotic containing Clostridium butyricum and Bifidobacteriumin was used in this study. This combination probiotic was highly effective in reducing the frequency of diarrhea in patients with CD.

Probiotics constitute an emerging group of biological agents that have shown promising results in multiple indications; mainly related to the Gastro-intestinal tract. One of the pioneer studies evaluating the role of probiotics in CD was done in Spain by Olivares M and colleagues. The study compared multiple facets of gut immunity among Bifidobacterium longum and placebo group. After a 03 months treatment, Bifidobaterium longum was able to significantly reduce the number of Bacteroides fragilis and secretory IgA in stool; however, there was no difference the blood T lymphocytes and serum cytokines among the two groups.[14] Results of the study are supportive

towards the result of present study.

Immune modulator effect of probiotics is considered the main mechanism of beneficial effects in immune mediated diseases such as CD and Inflammatory Bowel Disease. In another double blind, placebo controlled study by Klemenak M; 03 months treatment with Bifidobacterium breve was found to decrease the level of cytokine tumor necrosis factor in patients with CD. Thus shifting the gut biome away from the pro-inflammatory state.[15]

In a study done by De Palma G, gluten free diet was found to decrease the colonization of healthy bacteria including Lactobacilli and Bifidobacterium species, while harmful gram negative bacteria such as E. coli and Enterobacteriaceae and increased significantly.[16] This makes gluten free diet a necessary evil, as it is the corner stone of CD treatment but promotes harmful bacteria colonization at the same time. This adds to the rationale of using probiotics in addition to gluten free diet in patients with CD. The alteration of bowel organisms with introduction of gluten free diet, seems to be directly related to the polysaccharides in wheat cereal which are essential for the colonization of healthy bacteria. This effect is not limited to patients with CD. Studies have shown similar alteration in intestinal colonization of bacteria in healthy adults as well; as early as one months of gluten free diet.[17] This adds to the evidence and rationale for probiotics in combination with gluten free diet.

Apart from the healthful effects of probiotics on intestinal environment already discussed; probiotic strain Lactobacillus paracasei was found to inhibit the entry of partially digested gluten peptides in Caco-2 cells in vitro. This represents yet another mechanism by which probiotics exert their beneficial effect; specifically in the intestine of CD patients. It can theoretically improve tolerability to small amounts of gluten, however, clinical evidence is lacking at the moment.[18]

Most important part of therapeutic interventions for CD remains Gluten exclusion from diet. The goal of complete gluten withdrawal is very difficult to achieve because even small amounts are harmful. role of dietician and counselor becomes vital to achieve good compliance. A number of approaches are being tried to supplement dietary restriction of gluten; and possibly, to replace it. Important arenas for exploration are proteolytic enzyme to degrade gluten, pre-ingestion bacterial treatment to breakdown gluten, HLA DQ2 blockers, tissue transglutaminase blockers, zonulin antagonists which decrease the permeability of intestinal mucosa to immunogenic peptides, anti-inflammatory drugs, anti-TNF and anti-interleukin-15 antibodies. Zonulin antagonists and gluten degrading enzymes have shown the most promise so far.[19]

Probiotics most extensively studied in CD are Lactobacilli and bifidobacteria species. These and other probiotics also, have shown excellent safety profile and have been used in all age groups from premature neonates till geriatric age group and even in patients with HIV infection. Results of current study also support the safety of probiotics. However, it is very important for the treating physician to be vigilant about any undesirable side effects.[20]

Probiotics are an emerging form of therapy, finding use in multiple indications, primarily in the Gastro-intestinal tract diseases. Much more research is still needed to elucidate their role and safety in different conditions; including CD.

CONCLUSION

Probiotics in addition to gluten free diet are highly effective in reducing the frequency of diarrhea in newly diagnosed patients with CD, in comparison with gluten free diet alone.

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