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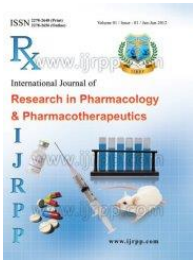

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Synbiotics vs Probiotics in Pediatrics – An interventional study

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ABSTRACT

Background

Probiotics are live bacteria which are intended to colonize the large intestine and confer physiological health benefits to the host. Prebiotics are food or dietary supplement product that confers a health benefit on the host. It may be a fiber but a fiber is not necessarily a prebiotic. Synbiotics are food ingredients or dietary supplements it is a combination of probiotics and prebiotics. They improve the survival of live microbial dietary supplements in GIT.

Methods

The study is conducted in a multi-centered, randomized, open label and controlled clinical trial in children with acute diarrhea. The first group would receive conventional anti-diarrheal drug and ORS therapy / i.v fluids will serve as a control group. The second group and the third group will receive a synbiotic preparation and a probiotic with routine anti-diarrheal and ORS/i.v fluids. The active period of treatment will be 5 days. 75 patients were selected out of which there were 25 in each group. Patients with acute severe diarrhea and patients within 12 years of age are included in the study. Severely ill patients and patients with dysentery are excluded from the study.

Results

In probiotic group as well as synbiotic group there was a quicker improvement in number of stools as well as volume of stool as compared to control group. There were no dropouts. There was no difference in subject characters and no confounding variable in all groups.

Conclusion

Based on our experience and outcomes of this study we conclude that probiotic and synbiotic are useful and equally efficacious and better addition to the treatment of acute watery diarrhea. Both probiotics and synbiotics reduce the frequency of stools and total no of days of hospital stay.

Keywords: Prebiotics, Probiotics, Synbiotics, Pediatric diarrhea, Enteropathogens, Lactobacilli.

INTRODUCTION

"If you don't like bacteria, you're on the wrong planet."

― Stewart Brand

Acute watery diarrhea is one of the common diseases. Acute diarrhea continues to be a leading cause of morbidity, hospitalization and mortality worldwide and also resulting huge economic burden. The main method of therapy for all children with dehydration caused by diarrhea is oral rehydration solution. Water and electrolyte replacement does not substantially shorten the frequency/duration of diarrhea and has not been found to reduce stool volume, prompting a growing interest in adjunctive treatments. Critical illness is characterized by a loss of commensally flora and an overgrowth of potentially pathogenic bacteria, leading to a high susceptibility to nosocomial infections. Causative agents of acute diarrhea can now be identified in nearly 70-80% episodes of acute diarrhea in sophisticated laboratories. In India, rotavirus and enter toxigenic E. coli account for nearly half the total diarrhea episodes among children with severe disease than in mild cases; it is endemic in some parts and may occur in outbreaks. [1] Viral agents are the most common cause of acute infective diarrhea in childhood, followed by bacteria and then protozoa infection. In the young infant who is most at risk from the complication of acute diarrhea a number of protective mechanisms exit to limit the effect of infective pathogens. The acid content of stomach and IgA secreted by the small intestine and in breast milk will limit the growth of bacteria in the upper small intestine and the resulting predominance of bifid bacterial in feces may inhibit colonization by enteric pathogens. These factors all lead to a reduced incidence of acute enteric infection in breast – fed infants. Modifications of the intestinal flora with probiotics may be benefit both in preventing and reducing the severity of acute infective diarrhea. [2] Gastroenteritis is due to infection acquired through the fecal – oral route or by ingestion of contaminated food or water. Enteropathogens that are infectious in a small inoculum (Shigella, enterohemorrhagic E. coli, Campylobacter jejuni, noroviruses, Giadialambia, Entamoeba histolytica) can be transmitted by person-to-person contact, whereas others, such as cholera are generally a consequence of contamination of food or water supply. Pathogenesis and severity of bacterial disease depend on whether organism have performed toxins (S. aureus, Bacillus cereus), produce secretory (cholera, E. coli, Salmonella, Shigella) or cytotoxic (Shigella, S. aureus, Vibrio parahemolyticus, C. difficile, E.coli) toxins or are invasive and on whether they replicate on food. Enteropathogens can lead to either inflammatory or non-inflammatory response in the intestinal mucosa. [3**]**

PROBIOTICS

The term Probiotics is derived from a Greek word meaning "for life" and used to define living non-pathogenic organisms and their derived beneficial effects on hosts. The term "Probiotics" was first introduced by Vergin, when he was studying the detrimental effects of antibiotics and other microbial substances, on the gut microbial population. He observed that "probiotika" was favorable to the gut micro flora. Probiotic were then redefined by Lilly and Stillwell as "A product produced by one microorganism stimulating the growth of another microorganism". Subsequently the term was further defined as "Non-pathogenic microorganisms which when ingested, exert a positive influence on host's health or physiology" by Fuller. The latest definition put forward by FDA and WHO jointly is "Live microorganisms which when administered in adequate amounts confer a health benefit to the host".

Some of the popularly used probiotic microorganisms are Lactobacillus rhamnosus, Lactobacillus reuteri, bifidobacteria and certain strains of Lactobacillus casei, Lactobacillus acidophilus-group, Bacillus coagulans; Escherichia coli strain Nissle 1917, certain enterococci, especially Enterococcus faecium SF68, and the yeast Saccharomyces boulardii. Bacterial spore formers, mostly of the genus Bacillus dominate the scene. These probiotics are added to foods, particularly fermented milk products, either singly or in combinations. New genera and strains of probiotics are continuously emerging with more advanced and focused research efforts.

Probiotic products may contain either a single strain or a mixture of two or more strains. E.g. #VSL3 is a mixture of 8 different probiotic strains. Probiotic effects are very strain specific and cannot be generalized. A single strain may exhibit different benefits when used individually and in combination.

The benefits of a probiotic formulation also differ with the patient group. Limited studies that have been performed have shown greater efficacy with multi-strain probiotics [4]

Research on probiotics, in particular Lactobacilli, has grown exponentially during the last two decades as can be seen from the fact that compared to 180 research articles published during 1980–2000, more than 5700 research articles were published during 2000–2014 on "probiotic Lactobacillus" [5]

FAO and WHO have jointly put forward guidelines in order to set out a systematic approach for an effective evaluation of probiotics in foods to substantiate the health claims and benefits. The FAO/WHO guidelines on Probiotics could be used as global standard for evaluating probiotics in food that could result in the substantiation of health claims.

The guidelines make it necessary to perform the following activities:

- Strain identification.
- Functional characterization of the strain(s) for safety and probiotic attributes.
- Validation of health benefits in human studies.
- Honest, not misleading labeling of efficacy claims and content for the entire shelf life.

Prebiotics

Prebiotics are mostly fibers that are non-digestible food ingredients and beneficially affect the host's health by selectively stimulating the growth and/or activity of some genera of microorganisms in the colon, generally lactobacilli and bifidobacteria [6] An ideal prebiotic should be 1) Resistant to the actions of acids in the stomach, bile salts and other hydrolyzing enzymes in the intestine 2) Should not be absorbed in the upper gastrointestinal tract. 3) Be easily fermentable by the beneficial intestinal micro flora [7].

FAO/WHO defines prebiotics as a non-viable food component that confer health benefit(s) on the host associated with modulation of the micro biota. Prebiotics form a group of diverse carbohydrate ingredients that are poorly understood with reference to their origin, fermentation profiles, and dosages required for health effects. Some of the sources of prebiotics include: breast milk, soybeans, and inulin sources (like Jerusalem artichoke, chicory roots etc.), raw oats, unrefined wheat, unrefined barley, yacon, non-digestible carbohydrates, and in particular non-digestible oligosaccharides. However, among prebiotics only bifidogenic, non-digestible oligosaccharides (particularly inulin, its hydrolysis product oligofructose, and (Trans) galacto-oligosaccharides (GOS), fulfil all the criteria for prebiotic classification [8].

Prebiotics like inulin and pectin exhibit several health benefits like Reducing the prevalence and duration of diarrhea, relief from inflammation and other symptoms associated with intestinal bowel disorder and protective effects to prevent colon cancer [9]. They are also implicated in enhancing the bioavailability and uptake of minerals, lowering of some risk factors of cardiovascular disease, and promoting satiety and weight loss thus preventing obesity [10].

Synbiotics

When Gibson introduced the concept of prebiotics he speculated as to the additional benefits if prebiotics were combined with probiotics to form what he termed as Synbiotics [11]. A synbiotic product beneficially affects the host in improving the survival and implantation of live microbial dietary supplements in the gastrointestinal tract by selectively stimulating the growth and/or activating the metabolism of one or a limited number of health promoting bacteria. Because the word "synbiotics" alludes to synergism, this term should be reserved for products in which the prebiotic compound(s) selectively favor the probiotic organism(s) [12]. Synbiotics were developed to overcome possible survival difficulties for probiotics. It appears that the rationale to use synbiotics is based on observations showing the improvement of survival of the probiotic bacteria during the passage through the upper intestinal tract. A more efficient implantation in the colon as well as a stimulating effect of the growth of probiotics and ubiquitous bacteria contribute to maintain the intestinal homeostasis and a healthy body [13]

Several factors like pH, H2O2, organic acids, oxygen, moisture stress etc. have been claimed to affect the viability of probiotics especially in dairy products like yogurts [14].

The probiotic strains used in synbiotic formulations include Lactobacilli, Bifidobacteriasps, S. boulardii, B. coagulans etc., while the major prebiotics used comprise of oligosaccharides like fructooligosaccharide (FOS), GOS and xylose oligosaccharide (XOS), inulin, prebiotics from

natural sources like chicory and yacon roots, etc. The health benefits claimed by synbiotics consumption by humans include: 1) Increased levels of lactobacilli and bifidobacteria and balanced gut microbiota, 2) Improvement of liver function in cirrhotic patients, 3) Improvement of immunomodulating ability, 4) Prevention of bacterial translocation and reduced incidences of nosocomial infections in surgical patients, etc. [15].

Clinical types of diarrheal diseases [16]

Four clinical types of diarrhea can be recognized, each reflecting the basic underlying pathology and altered physiology

- **Acute watery diarrhea** (including cholera) starts suddenly and lasts several hours or days. The main danger is dehydration; weight loss may occur if feeding is not continued.
- **Acute bloody diarrhea** (dysentery) is similar to acute watery diarrhea, but associated with gross blood in stool. The main dangers are intestinal damage, sepsis and malnutrition; other complications, including dehydration, may occur.
- **Persistent diarrhea** starts as acute watery diarrhea and lasts 14 days or longer. The main danger is malnutrition and serious non-intestinal infection; dehydration may also occur.
- **Diarrhea with severe malnutrition (marasmus or kwashiorkor)** carries risk of severe systemic infection, dehydration, heart failure and vitamin and mineral deficiency.

Causative agents of acute infectious diarrhea [17]

Viruses

- Rotavirus
- Astrovirus
- Adenovirus
- Parvovirus-like (i.e. Norwalk agent)
- Coronavirus

Bacteria

- Camphylobacter sp.
- Salmonella sp.
- Escherichia coli.
- Shigella sp.
- Yersinia enterocolitica
- Vibrio cholerae
- Clostridium difficile

Protozoa

- Giardia lamblia
- Cryptosporidium
- Entamoeba histolytica

Modalities in treatment of acute watery diarrhea

The management of children with acute watery diarrhea hinges upon the treatment of their dehydration status. Mild cases can be treated with ORS any for even moderate cases. ORS remains the treatment of choice although this therapy is underused in developed countries, where i.v. therapy is often used inappropriately. Generally, drug therapy has no role in the management of acute diarrhea. [18]

The treatment is categorized into three plans of treatment based on dehydration where it includes [19]

Plan A: Patients without physical signs of dehydration

The mother should be educated to use increased amount of culturally appropriate home available fluids. In addition, they should be given ORS packets for use at home. ORS is appropriate for prevention and treatment of dehydration. The mother should be asked to take the child to the health worker if the child does not get better in 3 days or develops any of the following danger signs: many watery stools; repeated vomiting, marked thirst, eating or drinking poorly.

Plan B: Patients with mild or moderate signs of dehydration

All cases with obvious signs of dehydration need to be treated with oral fluid therapy

- Correction of existing water and electrolyte deficit (rehydration therapy)
- Replacement of ongoing losses (maintenance therapy)
- Provision of normal daily fluid requirements.

Maintenance fluid therapy

This begins when signs of dehydration disappear, usually within 4hours. ORS should be administered in volume equal to diarrhea losses; approximately 10-20ml per kilogram body weight for each liquid stool. ORS is administered in this manner till diarrhea stops. Offer plain water in between.

Plan C: Patients with severe signs of dehydration

- Start IV fluids immediately.
- Best IV fluid solution is Ringer's lactate solution.
- Give 100ml/kg of chosen solution

All children should be started with on some ORS solution when they can drink without difficulty during the time of getting IV fluids. If one is unable to give IV fluids, immediately start rehydration with ORS using nasogastric tube at 20ml/kg/h (total of 120ml/kg).

ITS Criteria for Treatment of Diarrhea [20]

The Diarrheal diseases control (DDC) Programmer of WHO has since its inception in 1980, advocated several intervention measures to be implemented simultaneously with mutually rein forcing and complementary impacts. These measures center round the widespread practice of "oral rehydration therapy"

Short term

- Appropriate clinical management.

Long term

- Better MCH care practices
- Preventive strategies
- Preventing diarrheal epidemics.

Appropriate clinical management

Oral rehydration therapy

The aim of ORS is to prevent dehydration and reduce mortalities. With introduction of ORS by WHO it is now firmly established the ORS can be safely and successfully used in treating acute diarrheas due to all etiologies, in all groups, and in all countries.

Intravenous rehydration

It is usually required only for the initial rehydration of severely dehydrated patients who are unable to drink.

The solutions recommend by WHO for IV infusion are:

A) Ringer's lactate solution (Hartmann's solution): Commercially available and supplies adequate concentrations of sodium and potassium.

B) Diarrhea Treatment Solution: It is recommending by WHO and contains sodium chloride 4g, sodium acetate 6.5g, potassium chloride 1g and glucose 10g.

Maintenance therapy

After the initial fluid and electrolyte deficit has been corrected oral fluids should be used for maintenance therapy.

GUIDELINES

Amount of diarrhea	Amount of oral fluid
Mild diarrhea (not more than one stool every 2hours or longer)	100ml/kg body weight per day until diarrhea stops
Severe diarrhea (more than one stool every 2hours)	Replace stool losses volume for volume; if not measurable give 10-15ml/kg body weight per hour.

Appropriate Feeding

Medical profession has reeled for centuries under the mistaken assumption that it is important to "rest the gut" during diarrhea. The current view is that during episodes of diarrhea, normal food intake should be prompted as soon as the child whatever its age, is able to eat. This is especially relevant for the exclusively breastfed infants.

Chemotherapy

Unnecessary prescription of antibiotics and other drugs will do more harm than good in the treatment of diarrhea. Antibiotics should be considered where the cause of diarrhea is due to shigella, typhoid or cholera.

Better MCH care practices

Maternal nutrition

Improving prenatal nutrition will reduce the low birth weight problem. Prenatal and postnatal nutrition will improve the quality of breast milk.

Child Nutrition

Promotion of breast feeding

The breast-fed child is at very much less risk of severe diarrhea and death than the bottle-fed child.

Appropriate weaning practices

Poor weaning practices are a major risk factor for diarrhea. The child should be weaned neither too soon, nor too late, in any case not less than six months.

Supplementary Feeding

This is necessary to improve the nutritional status of children aged 6-59 months; here the child enters the high-risk category.

Vitamin A supplementation

It is a critical preventive measure, and studies have shown mortality reductions ranging from 19-54% in children receiving supplements.

Preventive measures

Sanitation

Measures to reduce transmission emphasize the traditional improved water supply, improved excreta disposal and improved domestic and food hygiene. Simple hygiene measures like washing with soap before preparing food, before eating, etc,

Health education

Environmental sanitation measures require educational support, to ensure their proper use and maintenance of such facilities.

Immunization

Immunization against measles is a potential intervention for diarrhea control. When administered at recommend age, the measles vaccine can prevent up to 25% of diarrhea deaths in children under 5 years.

Control and/or prevention of diarrheal epidemics

Primary health care

The concept of primary health care involves the delivery of a package of curative and preventive services at the community level.

Oral rehydration therapy

Oral rehydration therapy today is the core of management of diarrhea. It includes

- Complete oral rehydration salt solution with composition within the WHO recommended range.
- Solutions made from sugar and salt
- Food based solutions
- In presence of continued feeding, a variety or commonly available culturally acceptable fluids irrespective of presence of glucose or without salt when the former are present. [21]

Composition of commercial oral rehydration solutions and commonly used beverages [22]

Solution	Carbohydrate (g/L)	Sodium (mmol/L)	Potassium (mmol/L)	Chloride (mmol/L)	Base (mmol/L)	Osmolarity (m0sm/L)
Oral rehydration solution						
Low osmolality ORS WHO (2005)	13.5	75	20	65	10	245
WHO (2002)	13.5	75	20	65	30	245
WHO (1975)	20	90	20	80	10	311
ESPGHN	16	60	20	65	30	240
Enfalyte	30	50	25	45	34	200
Pedialyte	25	45	20	35	30	250
Rehydralyte	25	75	20	65	30	305
Ceralyte	40	50-90	20	NA	30	220

Commonly used beverages (NOT APPROPRIATE FOR DIARRHEA TREATMENT)						
Apple juice	120	0.4	44	45	NA	730
Coca – cola	112	1.6	NA	NA	13.4	650

When is oral rehydration therapy ineffective? [23]

- High stool purge
- Persistent vomiting
- Abdominal distention
- Glucose malabsorption
- The use of Prebiotics, Probiotics and Synbiotics are known to improve immunity and counter the effects of disease-causing bacteria, probiotics have been proposed as a strategy to prevent and treat AAD.

Health benefits of probiotics, prebiotics and synbiotics

The most important and documented beneficial effects of probiotics include the prevention of diarrhea, constipation, changes in bile salt conjugation, enhancement of antibacterial activity, anti-inflammatory. Furthermore, they also contribute to the synthesis of nutrients and improve their bioavailability; some probiotics are known to exert anti-oxidative activity in the form of intact cells or lysates. Probiotics have also demonstrated their inherent effects in alleviating symptoms of allergy, cancer, AIDS, respiratory and urinary tract infections. There are stray reports on their beneficial effects on aging, fatigue, autism, osteoporosis, obesity and type 2diabetes [24].

As shown below a number of mechanisms are thought to be associated with probiotic beneficial effects:

- Production of inhibitory substances like H2O2, bacteriocins, organic acids, etc.
- Blocking of adhesion sites for pathogenic bacteria.
- Competition with the pathogenic bacteria for nutrients,
- Degradation of toxins as well as the blocking of toxin receptors,
- Modulation of immune responses.

OBJECTIVES

Primary Objective

- To assess and compare the efficacy of a probiotic and synbiotic in reducing
- ✓ The frequency of diarrhoea
- ✓ Volume of diarrhoea
- ✓ Length of hospital stay (LOS)

Secondary Objective

To evaluate the safety of probiotics and synbiotic as a post marketing surveillance.

MATERIALS AND METHODS

The study is conducted in a multi-centered, randomized, open label and controlled clinical trial in children with acute diarrhea. The first group would receive conventional anti-diarrheal drug and ORS therapy / i.v fluids will serve as a control group. The second group and the third group will receive a synbiotic preparation and a probiotic with routine anti-diarrheal and ORS/i.v fluids.

The active period of treatment will be 5 days

Study design: Randomized Controlled Study

This is a prospective, multi centered, randomized, single blinded, placebo controlled, clinical trial in hospitalized children.

If it can be a Placebo controlled study ----have to add sucrose as placebo.

The data collection included weight and height of child, duration of diarrhea, stool consistency, No. of stool per day, signs of dehydration, No. of vomits/day, sensorium and other data.

Study area

- Dhanalakshmi Srinivasan Medical College and Hospital, Perambalur
- District Government Medical Hospital, Perambalur

Study period

- 2 months

Study population

- 75 pediatric patients

Inclusion criteria

- Patients with acute severe diarrhea.
- Patients within 12 years of age.

Exclusion criteria

- Dysentery
- Severely ill patients

PROFORMA

Pre – Hospitalized treatments	Name:					
	Age:					
	Sex:					
		DAY 1	**DAY 2**	**DAY 3**	**DAY 4**	**DAY 5**
	Weight of the child:					
	Stool consistency:					
	No. Of. Stools per day:					
	Signs of dehydration:					
	No. of. Vomits per day:					
	Volume of the stool					
	Side Effects					

Antimicrobial Used **:** Yes/No

If Yes, Name of the drug **:**

RESULTS

75 patients were analyzed in the study. There were no dropouts. There were 25 children in probiotic group, 25 in synbiotic group and 25 in control group. There was no difference in subject characters and no confounding variable in all groups. In probiotic group as well as synbiotic group there was a quicker improvement in number of stools as well as volume of stool.

No. of stools and consistency was every day. From day 2 there was improvement in texture and frequency of stools. It was noted 17 patients in probiotic group and 18 patients in synbiotic group had sticky/solid stools on the 2nd day itself, were as only 12 in control group.

When compared to control group, probiotic group and synbiotic group patients showed a significant remission on no of stools and no of days of hospital stay.

On the 3rd day majority of patients (5/8) in probiotic group, (5/7) in synbiotic group had solid stools, however there were only 7/13 patients had solid stool formed in control group.

This suggest there was a faster improvement in texture of stool in both probiotic and synbiotics group

Subject characteristics	Probiotic group	Synbiotic group	Control group
Number	25	25	25
Age	27.36 months	30.96 months	34.56 months
Sex % male	56	16	68
Stool consistency sticky/solid on 2nd day	17/25	18/25	12/25
No of vomits/day	02	02	03

Duration of diarrhea	2days	2.2days	3days
No of stools/day	08	08	10

The average no days of hospital stay for each group is as following

- Probiotic group – 2 days
- Synbiotic group – 2.2 days
- Control group – 3 days

DISCUSSION

Probiotics are defined as "live Microbe of food supplement or components of bacteria which have been shown to have beneficial effects of human health". Most friendly bacteria used generally fulfilling this criterion are Lactobacilli and Bifiodobateria.

A **Prebiotic** is defined as "non- absorbable food component that beneficially stimulate one or more of the gut beneficial microbe groups and thus have a positive effect on human health".

Synbiotic is the combination of probiotic and prebiotic.

Synbiotic group in this trial contains the best Lactic acid bacteria and Bifiodobateria along with Streptococcus thermophiles. It is worth mentioning that a child specific strain of Bifidobacterium infantis and Streptococcus thermophiles have also been included. This synbiotic also contain the most appreciable and documented prebiotic, Fructooligosaccharide (FOS).

No Side effects were observed during the active treatment period with the use of probiotic and synbiotic; this also highlights the high safety profile.

CONCLUSION

Based on our experience and outcomes of this study we conclude that probiotic and synbiotic are useful and equally efficacious and better addition to the treatment of acute watery diarrhea. Both probiotics and synbiotics reduce the frequency of stools and total no of days of hospital stay.

In our study the average stool remission time in probiotics, synbiotics and control are 2days, 2days, and 3days respectively.

Finally, this study concluded that probiotics and synbiotics are having 83 million numbers of lactobacilli.

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