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Original Article

USE OF PROBIOTICS AS PROPHYLAXIS FOR POSTOPERATIVE INFECTIONS OF UNDER- 5 CHILDREN FOLLOWING GASTROINTESTINAL SURGERY

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Abstract

Background: Bacterial infection is a frequent complication following operations in the gastrointestinal tract. Despite prophylactic administration of antibiotics the incidence of postoperative infections ranges from 10%–30% in resection surgery.[1] Most infections are caused by bacteria of enteric origin.[2] In spite of restricted use of prophylactic antibiotics, the emergence of antibiotic resistance has increased significantly.[3]

Probiotics when consumed in adequate amounts, confer a health benefit on the host. In vitro, studies suggest that probiotics potentially act favorably on the host through several different mechanisms. They have an antimicrobial effect. Furthermore, administration of probiotics suppresses growth of potentially pathogenic microorganisms, e.g., *E. coli* and Enterobacteriaceae. The effects of these agents may go beyond the gastrointestinal tract to distant areas, such as the urogenital and respiratory mucosa. It has been hypothesized by several authors that these characteristics can be used in a clinical setting of preoperative prophylaxis for reduction of postoperative infections.

Preoperative antibiotic prophylaxis constitutes more than 10% of antibiotic usage in surgery and a reduction could lead to a reduced pressure on development of antibiotic resistance. It may therefore be of interest to study if probiotics may be used in the preoperative preparation of patients undergoing gastrointestinal operations.

Objective: The overall objective of this study is to evaluate the effectiveness of probiotics as prophylaxis for post operative infections in under-5 children undergoing gastrointestinal surgery.

Materials and methods: We are conducting a prospective comparative study with the intention to observe the postoperative periods of 60 purposively selected patients of gastrointestinal surgery in the Department of Pediatric surgery, Dhaka Medical College Hospital (DMCH), Dhaka, over a period of 18 months from October, 2013 to March, 2015. The patients are going to be divided into 2 groups by random sampling- Group A (Control group- without probiotics) and Group B (Study group- with probiotics). Under-5 children are planned to be selected as study subjects. All children are subjected to investigate for white blood cell (WBC) count and C-reactive protein (CRP) preoperatively and on 5th postoperative day (POD) in addition to routine investigations. Structured questionnaire is used to collect information regarding fever, surgical site infection, WBC and CRP count before operation and 5 days after operation (i.e. on 5th POD).

Informed written consent from parents or legal guardian is taken after describing the study objectives. Ethical clearance has been sought from the Ethical Committee of Dhaka Medical College

Results: Total 8 patients are studied till now, 4 in each group. From this limited data we have observed that there has been apparently minimum difference between the cases and controls regarding postoperative infections.

Discussion: Post operative wound infections are quite common and an important reason for administering antibiotics for prolonged periods.[13] Probiotics given preoperatively tends to reduce the incidence of post operative infection, though the accurate mechanism is not known. The use in patients undergoing colorectal surgery does not seem to show any benefit.[18] The result of our study until now has not demonstrated any added benefit of prophylactic use of probiotis in the specified age group. So up to now the available data is compatible with the various data seen in other studies.[18] In our study, it is very early to comment on the results.

Conclusion: This is an on-going study. Definite conclusion could not be drawn at this preliminary stage.

Key words: Probiotics, Postoperative infections, Gastrointestinal surgery, Under -5 children

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Introduction

Bacterial infection is a frequent complication following operations in the gastrointestinal tract. Despite prophylactic administration of antibiotics the incidence of postoperative infections ranges from 10%–30% in resection surgery.[1] Most infections are caused by bacteria of enteric origin.[2] In spite of restricted use of prophylactic antibiotics, the emergence of antibiotic resistance has increased significantly.[3]

The intestinal microflora constitutes a metabolically active microbial environment, dominated by a relatively low diversity of genera, which, in the gut of healthy individuals, exist as part of a stable community. Under normal circumstances, these resident gut bacteria cause neither pathogenesis nor inflammation in the host, but instead contribute to health maintenance, by forming a barrier layer against colonization by pathogens and by aiding in nutrient digestion and assimilation.[4] In addition, the resident intestinal microflora plays other important physiological roles in health maintenance: deconjugating potentially damaging oxidative metabolites and toxins in the gut; degrading potentially allergenic food proteins; regulating cholesterol and

triglyceride uptake; increasing vitamin biosynthesis; and providing immunosurveillance signals to limit intestinal-tract inflammation. Thus, a stable, properly functioning and active intestinal-tract microflora is essential to the continuance of health.[5]

The human fetus has a sterile gastrointestinal tract at birth. After birth, an infant is exposed to numerous species of microorganisms, which begin to colonize the intestinal tract. The colonizing bacteria can originate from the birth canal during delivery, from contact with other humans as the

infant grows older, as well as from the surrounding environment. An infant's intestine is mainly colonized by enterobacteria during first 2 days after birth.

Factors which can influence the development of an infant's normal intestinal microflora includes gestation length, underlying neonatal health, type of birth (vaginal or surgical), immunological status, source of nutrition (bottle or breast fed), gastrointestinal transit time, dietary intake of mother, gastrointestinal pH, probiotic usage of mother and stress.

Premature infants develop a different pattern of colonization and they are generally slower to acquire Lactobacillus species as well as being more susceptible to the colonization of the intestinal tract by pathogens. It is also possible that infants who are born via caesarean section may have a delayed microbial colonization, as they are not exposed to the maternal microflora in the birth canal. They contain less bifidobacteria and higher amount of Clostridium difficile. The source of nutrition can influence the infant's microbial balance: those that are fed milk formula generally have higher concentrations of Enterobacter species initially, whereas infants receiving breast milk have higher concentrations of Bifidobacterium species

The gut microbial flora and mucosa are affected by surgical trauma resulting in the gut barrier dysfunction and intestinal microbial imbalance. This may further aggravate systemic inflammation and depress immune function.[6] These factors contribute to an increased risk of postoperative infections and sepsis. Alternative strategies in preparing patients for gastrointestinal surgery besides mechanical bowel preparation and administration of antibiotics must be considered.

Probiotics mean for life and are defined as live microorganisms, which when consumed in adequate amounts, confer a health benefit on the host. In vitro studies suggest that probiotics potentially act favorably in the host through several different mechanisms. They have an antimicrobial effect through modifying the microflora, secreting antibacterial substances, competing with pathogens to prevent their adhesion to the intestinal epithelium, competing for nutrients necessary for pathogen survival, producing an antitoxin effect and reversing some of the consequences of infection on the intestinal epithelium, such as secretory changes and neutrophil migration.[7,8] Probiotics are also capable of reducing cell proliferation in cancer.[9]

They can stabilize the intestinal barrier by stimulating epithelial growth, mucus secretion and motility as well as enhance innate immunity by inhibition of IL-10 and stimulation of secretory IgA, neutrophils and reduction of inflammatory cytokines.[10] Furthermore, administration of probiotics suppresses growth of potentially pathogenic microorganisms, e.g., *E. coli* and Enterobacteriaceae. The effects of these agents may go beyond the gastrointestinal tract to distant areas, such as the urogenital and respiratory mucosa. It has been hypothesized by several authors that these characteristics can be used in a clinical setting of preoperative prophylaxis for reduction of postoperative infections.

Preoperative antibiotic prophylaxis constitutes more than ten percent of antibiotic usage in surgery and a reduction could lead to a reduced pressure on development of antibiotic resistance. It may therefore

be of interest to study if probiotics may be used in the preoperative preparation of patients undergoing gastrointestinal operations.

In recent years there have been a few randomized trials on the use of prophylactic probiotics in major gastrointestinal surgery mostly for cancer and liver transplantation. Since this is a new concept on the use of probiotics, it is important to critically analyze these studies before a wider application. Very few literatures have demonstrated the effectiveness of probiotics in children, especially under- 5 following gastrointestinal surgery.

The Government of the People's Republic of Bangladesh has set its national health program 2011-2016 to reduce population growth rate and improve nutritional status, especially of women and children.[11]The goal of MDG4 is "reduction of child mortality by 2/3 from 1990 to 2015.

To achieve this, newborn deaths need to be reduced by 50%.

The major causes of deaths in neonates are possible serious infection, birth asphyxia, pneumonia and pre-term births. Neonatal deaths account for 60% of under-five deaths.[12] This study has been designed to demonstrate the use of probiotics as prophylaxis for post operative infections in under- 5 children following gastrointestinal surgery to reduce under-5 mortality and eventually to meet MDG4 goal.

Materials and Methods

We are conducting a prospective comparative study with the intention to include 60 purposively selected patients of suspected gastrointestinal surgery in the Department of Pediatric surgery, Dhaka Medical College Hospital (DMCH), Dhaka, over a period of 18 months from October, 2013 to March, 2015. The patients are going to divided into 2 groups by random sampling- Group A (Control group- without probiotics) and Group B (Study group- with probiotics). Under-5 children are planned to select as study subjects. All children are subjected to white blood cell (WBC) count and C-reactive protein (CRP) before operation and 5 days after operation in addition to routine investigations. Structured questionnaire is used to collect information regarding fever, surgical site infection, WBC and CRP count.

Children older than 5 years and children undergoing emergency operation where preoperative prophylaxis cannot be given are excluded from the study.

Capsule Probio (Square pharmaceutical) is a probiotic preparation. Each capsule contains Lactobacillus acidophilus (2 billion), Lactobacillus bulgaricus (1 billion), Bifidobacterium bifidum(1 billion) and Fructo-oligosaccharides(100mg). Infants are given 2 capsules daily and neonates are given 1 capsule daily. Patient above 1 years of age are given 3 capsules daily. The medication is diluted by expressed breast milk or formula milk.

Prophylaxis is started 3 days prior to surgery and continued for 7 days postoperatively, a total of 10 days.

Structured questionnaire is used to collect information regarding fever after 5th POD, surgical site infection evaluated by ASEPSIS Score on 3rd and 7th POD, WBC and CRP count before operation and on 5th POD.

Results

Total 8 patients are studied till now, 4 in each group. Out of 4 patients 3 were girls and 5 were boys. All the cases were almost of the same age. One of the controls was 5 years old and others were between 1 month to 20 months. One patient was operated for excision of mesenteric cyst and all other patients were operated for Hirschsprung disease. Two patients from each group had fever on 5th POD; others did not have fever recorded on 5th and 7th POD. All the controls and 2 of the cases had positive CRP on 5th POD. All 4 patients had Leukocytosis preoperatively. There was marked reduction in total WBC count in all the patients by 5th POD. ASEPSIS Score for both the groups were almost same. By the 7th POD all patients had ASEPSIS score of 5 or less.

Table-I

The ASEPSIS wound score

Criterion	Points
• Additional treatment	0
• Antibiotics for wound infection	10
• Drainage of pus under local anaesthesia	5
• Debridement of wound under general anaesthesia	10
• Serous discharge[a]	Daily0– 5
• Erythema[a]	Daily 0–5
• Purulent exudate[a]	Daily0–10
• Separation of deep tissues[a]	Daily 0–10
• Isolation of bacteria from wound	10
• Stay as in-patient prolonged over14 days as result of wound infection	5
a. Scored for 5 of the first 7 days only, the remainder being scored if present in the first 2 months.	
• Range- 0 -70	
o 0-10 – Satisfactory healing	
o 11-20 – Disturbance of healing	
o 21-30- Minor wound infection	
o 31-40- Moderate wound infection	
o 40 – Severe wound infection	

Table-II
Preliminary data from the 4 cases

No.	Age	Sex	Diagnosis	Trea-tment	Fever		CRP		WBC		ASEPSIS	
					5th	7th	Preop	5th	Preop	5th	3rd	7th
1	3yr	F	Mesen -teric cyst	Exci-sion	-	-	-	-	TC-15290/cumm DC-N-53.6% L-38.8% M-3.6% E-4%	TC-6500/cumm DC-N-57.6% L-33.5% M-7.3% E-1.6%	5	0
2	3yr	F	Hirsch-sprung Disease	Redopull - Thro-Ugh	-	+	+		TC-18200/cumm DC-N-26.2% L-55% M-7% E-11.8%	TC- 13200/cumm DC-N-69.9% L-18.8% M-4.7% E-6.6%	15	5
3	3yr	M	Hirsch-Sprung Disease	Laparotomy assisted Transanal Pull through	+	-	-	-	TC- 10,900/cumm DC- N-47.6% L- 35% M-5% E-12.2%	TC- 8000/cumm DC- N-52% L-44% M-4% E-2%	5	5
4	3.5yr	M	Hirsch Sprung Disease	Colostomy Closure	+	-	-	+	TC-8300/cumm DC- N-60% L-28% M-8% E-4%	TC-9000/cumm DC- N- 68% L-28% M-3% E-1%	5	0

TC-Total Count ; DC- Differential Count; N-Neutrophils; L-Lymphocytes; M-Monocytes;E-Eosinophils.

Table-III
Preliminary data from the 4 controls

No.	Age	Sex	Diagnosis	Treatment	Fever		CRP		WBC		ASEPSIS	
					5th	7th	Preop	5th	Preop	5th	3rd	7th
1	20m	M	Hirsch sprung Disease	Colostomy Closure	+	-	-	+	TC- 12000/cumm DC- N-43.9% L-39.1% M-5.6% E-11.4%	TC-4200/cumm DC- N-61.9% L-29.8% M-6.6% E-1.7%	10	5
2	14m	F	Ileostomy	Ileostomy closure	-	-	-	+	TC-16400/cumm DC- N-29.5% L-59.5% M-4.3% E-6.7%	TC-6000/cumm DC- N-46% L-45% M-6% E-3%	10	5
3	1 m	M	Hirsch sprung Disease	Transanal Pull Through	-	-	-	+	TC-14,000/ cumm DC- N-60% L-35% M-4% E-1%	TC-9600/cumm DC- N-56% L-40% M-3% E-1%	5	5
4	5yr	M	Hirsch sprung Disease	Colostomy Closure	+	-	-	+	TC-9000/ cummDC- N-50% L-27.3% M-1% E-20.9%	TC- 9500/ cummDC- N-60% L-33% M-1% E-6%	5	5

TC-Total Count ; DC- Differential Count; N-Neutrophils; L-Lymphocytes; M-Monocytes; E-Eosinophils.

Discussion

The overall objective of this study is to evaluate the effectiveness of probiotics as prophylaxis for post operative infections in under-5 children undergoing gastrointestinal surgery. We have planned to conduct a prospective comparative study with the intention to include 60 purposively selected patients of suspected gastrointestinal surgery in the Department of Pediatric surgery, DMCH, over a period of 18 months from October, 2013 to March, 2015. Our hypothesis is prophylactic use of probiotics can reduce the incidence of postoperative infections in under-5 children undergoing gastrointestinal operations. To date from the data we have realized it is very hard to comment on this topic due to very small sample size.

Post operative wound infections are quite common and an important reason for administering antibiotics for prolonged periods.[13] Probiotics given preoperatively tends to reduce the incidence of post operative infection, though the accurate mechanism is not known. There are some indications that the inflammatory response to surgery is reduced.[13, 14] Reduction of potentially pathogenic bacteria (PPM) as a result of bacterial antagonism was observed in some studies.[15, 16, 17] There seems to be striking differences in effects of prophylactic administration of probiotics in different surgical patients. The results relating to reduction in postoperative infections are convincing when used in patients undergoing surgery in the upper gastrointestinal tract and liver transplantation. The use in patients undergoing colorectal surgery does not seem to show any benefit.[18] Most commonly performed elective operations in our department involves the colon and rectum. These sites are very prone to develop surgical site infections and patients in under-5 group rapidly deteriorate in the presence of infection. The result of our study until now has not demonstrated any added benefit of prophylactic use of probiotics in the specified age group. The available data suggests that 50% of the cases were CRP negative in postoperative period whereas all the control patients were CRP positive. CRP is a good indicator of the presence of any infection especially bacterial infection in pediatric group. ASEPSIS Score was used for determining the quality of wound healing. All patients had satisfactory healing by the 7th POD though the ASEPSIS Score was high on 3rd POD in all the controls. All the patients had significant decrease in post operative WBC count. So up to now the available data is compatible with the various data seen in other studies.[18] In our study, it is very early to comment on the results. Administration of probiotics is in general considered safe and many of them are used in different products commercially available to the public. The results of controlled trials performed so far indicate therapy with probiotics seems safe and without any reported serious side-effects. Further studies are warranted to elucidate potential mechanisms of action in order to optimize its use.

Conclusion

This is an on-going study. Definite conclusion could not be drawn at this preliminary stage. Though many literatures have convincingly demonstrated the benefits of prophylactic probiotics in gastrointestinal surgery, others have concluded otherwise. Studies relating to use of probiotics in surgery has not been done before in our country. So the final comment can only be made after proper analysis and interpretation of all the data obtained at the conclusion of the study.

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