Purpose: Evaluation of the efficacy of use of probiotics as prophylaxis for postoperative wound infection in under-five children following gastrointestinal surgery.

Materials and Methods: This randomized control trial was conducted over a period of 2 years in the pediatric surgery units of a tertiary level hospital in Dhaka, Bangladesh. A total of 60 patients undergoing gastrointestinal surgery under the age of 5 years were included in the study and randomly assigned to two groups – probiotics group (n = 30) and nonprobiotics group (n = 30). Patients in the probiotics group received probiotics in the preoperative (3 days) and postoperative period (7 days) along with traditional gut preparation (antibiotics and mechanical bowel wash). Patients in the nonprobiotics group got only antibiotics and traditional gut preparation. Outcome variables were surgical site infection, fever, c-reactive protein (CRP), total white blood cell (WBC) count, and neutrophil count.

Results: Postoperative wound infection was less in the probiotic group (n = 2) compared to the nonprobiotics group (n = 3), but the difference was not statistically significant (P = 0.640). Postoperative CRP level was significantly lower in the probiotics group (P = 0.020). There was more decline in total count of WBCs in postoperative period in the probiotic group. No statistical difference was seen between the groups in postoperative pyrexia, the total count of WBC, and neutrophil count.

Conclusion: Use of probiotics along with traditional gut preparation as prophylaxis for postoperative infection in children showed no added benefit in comparison to the use of traditional gut preparation only.

Keywords: Gastrointestinal surgery, postoperative infections, probiotics, under-five children

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% to 30% in resection surgery.[1] Most infections are caused by bacteria of enteric origin.[2] Despite restricted use of prophylactic antibiotics, the emergence of antibiotic resistance has increased significantly.[1]

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 contribute to health maintenance by forming a barrier layer against colonization by pathogens and by aiding in nutrient digestion and assimilation.[4] A stable, properly functioning, and active intestinal-tract microflora is essential to the continuance of health.[5] The bacteria that colonize the gastrointestinal tract after birth can originate from

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the mother, other human contacts, and evens from the surrounding environment.

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. Probiotics mean for life and are defined as live microorganisms, which when consumed in adequate amounts, confer a health benefit on the host. Probiotics have an antimicrobial effect through modifying the microflora, secreting antibacterial substances, and competing with pathogens to prevent their adhesion to the intestinal epithelium and by many other mechanisms. Probiotics are also capable of reducing cell proliferation in cancer.

They can stabilize the intestinal barrier by stimulating epithelial growth, mucus secretion, and motility as well as enhance innate immunity. Probiotics suppress the growth of potentially pathogenic microorganisms, for example, Escherichia coli and Enterobacteriaceae. Antibiotic resistance can be reduced by judicial reduction in the use of prophylactic antibiotics and by utilizing the beneficial effects of probiotics.

It may therefore be of interest to use probiotics in the preoperative preparation of patients undergoing gastrointestinal operations.

In recent years, few trials have evaluated the use of prophylactic probiotics in major gastrointestinal surgery mostly for cancer and liver transplantation. Very few literature have demonstrated the effectiveness of probiotics in children, especially under-five following gastrointestinal surgery.

MATERIALS AND METHODS
This is a randomized control trial Participants were randomly allocated into two groups: probiotic group (intervention group) and nonprobiotic group (control group). Randomization is done using sealed envelopes. Each envelope contained the name of a single group.

The study was conducted in the Department of Pediatric Surgery at a Tertiary Level Hospital in Dhaka, Bangladesh over a period of 2 years. Ethical clearance was taken accordingly (Ethical Clearance Certificate reference number – Memo No. DMC/ECC/2015/19). Patients under the age of 5 years admitted for different types of elective gastrointestinal surgery were considered as the study population. Elective gastrointestinal surgery done by senior surgeons was included and patients having previous surgery for malignancy (e.g., gastrointestinal stromal tumor, familial adenomatous polyposis coli); and hepatobiliary surgery (e.g., choledochal cyst, biliary atresia); laparoscopic gastrointestinal surgery (e.g., appendectomy) were excluded from the study. Data were collected using predesigned, semi-structured questionnaire, a review of clinical notes, and investigation reports. The Statistical Package for the Social Sciences (SPSS) software, version 21, manufactured by IBM, Chicago, USA was used for data analysis. Chi-square test was done to test for differences of proportion for categorical variables and unpaired Student’s t-test for the differences in mean for continuous variables. The repeated measure was done to see the estimated marginal means of white blood cell (WBC) count. A two-tailed P < 0.05 was the level of significance selected for all the analyses.

All the patients in both the groups were given the same preoperative preparation with antibiotics (a 3rd generation cephalosporin and metronidazole), mechanical bowel wash with polyethylene glycol according to weight, starting on the morning of the day before surgery at a dose of 0.8 g/kg/dose, 2–3 times per day till clear effluent is seen and postoperative antibiotics. The probiotic group was given additional oral probiotics in specific doses for 3 days preoperatively and from the time of restarting oral feeding onward for 7 days postoperatively. Each probiotics capsule contained Lactobacillus acidophilus (2 billion), Lactobacillus bulgaricus (1 billion), Bifidobacterium bifidum (1 billion), and fructo-oligosaccharides (100 mg). Patients below 1 year were given two capsules daily and patients above 1 year of age were given three capsules daily.

Forty-six patients underwent enterostomy closures – 24 in the probiotic group and 22 in the nonprobiotic group. Thirteen patients underwent abdominoperineal pull through for Hirschsprung disease or anorectal malformations-5 in the probiotic group and 8 in the nonprobiotic group. One patient in the probiotic group had excision of mesenteric cyst. Per-operative dissection was done meticulously with minimum tissue injury by senior surgeons of the unit. In case of spillage, thorough peritoneal wash was given by normal saline. The abdomen was closed in layers. Skin in every case was closed by subcuticular continuous stitches using absorbable sutures (polyglactin violet 910). Wound dressing was given with dry gauze with no local antiseptic/antibiotic ointment.

Postoperative evaluation of the outcome variables

Surgical Site Infection (SSI) – evaluated by ASEPSIS Score on the 3rd and 7th POD.

• Fever – on 5th POD and 7th POD
• C-reactive protein (CRP) – 5th POD
• Total WBC count – on 5th POD
• Neutrophil count – on the 5th POD.

Postoperative pyrexia before the 5th POD is usually due to conditions such as atelectasis and stress.

Hence, fever appearing after the 5th POD was considered statistically significant. Serum CRP, total WBC count, differential count of neutrophils, and fever were recorded to evaluate the postoperative inflammatory response.

RESULTS

The mean age in the probiotics and nonprobiotics group was 32.47 ± 14.77 months and 40.37 ± 17.30 months, respectively. More than 50% were male and 23 were female. Out of the 60 patients, 80% of the patients in the probiotic group and 73.33% in the nonprobiotic group underwent closure of enterostomies (colostomy, ileostomy, and ileocolostomy).

In probiotic group out of 30 patients, two developed wound infection (6.7%) and in nonprobiotic group out of 30 patients, three developed wound infection (10%) [Tables 1 and 2]. Although nonprobio group had more infection rate, the Chi-square test revealed a $P = 0.640$, which was >0.05. Hence, the difference was not statistically significant.

Fever was present in 23.3% patients of probiotic group and 43.3% patients of the nonprobiotic group on the 5th POD. Moreover, on the 7th POD, 10% patients of the probiotic group and 20% patients of the nonprobiotic group had fever. $P$ value on 5th and 7th POD was insignificant; hence, there was no difference in the incidence of postoperative pyrexia among the groups.

Preoperative difference in CRP among the groups was not statistically significant ($P = 0.688$). Postoperative serum CRP was positive in 40% cases in the probiotic group and in 70% cases in the nonprobiotic group. The difference was significant ($P = 0.020$). This indicates that the administration of prophylactic probiotics had significantly reduced the systemic inflammatory response in postoperative patients.

There was no difference between the study groups regarding the postoperative total WBC count [Figure 1]. The probiotic group had a lower mean neutrophil count (49.07) than the nonprobiotic group (52.40) though the difference was not significant ($P = 0.374$). The postoperative neutrophil count was measured in all patients on the 5th POD. There was no significant difference between the groups.

The repeated measure was done to compare the estimated marginal means of preoperative and postoperative WBC count between the study groups, which showed that total WBC count decreased more in the probiotic group after the operation than in the nonprobiotic group [Figure 1].

Table 1: The ASEPSIS wound score

| Criteria | Points |
|----------|--------|
| Additional treatment | 0 |
| Antibiotics for wound infection | 10 |
| Drainage of pus under local anesthesia | 5 |
| Debridement of wound under general anesthesia | 10 |

Serous discharge<sup>a</sup> Daily: 0-5
Erythema<sup>a</sup> Daily: 0-5
Purulent exudates<sup>a</sup> Daily: 0-10
Separation of deep tissues<sup>a</sup> Daily: 0-10
Isolation of bacteria from wound | 10 |
Stay as inpatient prolonged over 14 days as a result of wound infection | 5 |

<sup>a</sup>Scored for 5 of the first 7 days only, the remainder being scored if present in the first 2 months. Range: 0-70 (0-10 - Satisfactory healing, 11-20 - Disturbance of healing, 21-30 - Minor wound infection, 31-40 - Moderate wound infection, 40 - Severe wound infection).

Table 2: Surgical Site Infection

| Wound characteristics | Proportion of wound affected (%) |
|-----------------------|----------------------------------|
|                       | 0 | <20 | 20-39 | 40-59 | 60-79 | >80 |
| Serous exudates       | 0 | 1   | 2     | 3     | 4     | 5    |
| Erythema              | 0 | 1   | 2     | 3     | 4     | 5    |
| Purulent exudates     | 0 | 2   | 4     | 6     | 8     | 10   |
| Separation of deep tissues | 0 | 2   | 4     | 6     | 8     | 10   |

Table 3: Comparison of postoperative CRP between the probiotic and nonprobiotic group

| C-reactive protein | Probio group (n=30), n (%) | Nonprobio group (n=30), n (%) | $P$ |
|--------------------|----------------------------|-------------------------------|-----|
| Positive           | 12 (40)                    | 21 (70)                      | 0.020 (S) |
| Negative           | 18 (60)                    | 9 (30)                       |     |

S: Significant
DISCUSSION
Postoperative wound infection is a considerable problem in abdominal surgery in both pediatric and adult surgical patients. A large prospective multicenter study conducted over 846 pediatric patients mentioned the overall SSI rate of 4.4%.[12] Despite advances in surgical procedures, antibiotic prophylaxis, and optimum sterilization techniques, postoperative wound infection is still a big problem. Major source of the pathogen in SSI following abdominal/gastrointestinal surgery is enteric origin caused by bacterial translocation into mesenteric lymph nodes or blood.[13]

Probiotics have been used in various clinical trials mostly in adult patients to prevent bacterial translocation by replenishing the gut barrier and reducing the postoperative inflammatory response. The results showed variable responses.

This experimental study has been done to find out the role of probiotics in the perioperative period in prevention of wound infection in under-five children following gastrointestinal surgery.

In this study, both the groups had almost similar age distribution, the total range from 6 months to 60 months. There was a significant difference regarding the sex of the participants, 76% of the nonprobiotic group was the male in comparison to 46% in the probiotic group though in prepubertal age, sex is not considered a risk factor for wound infection. Both the groups underwent almost similar types of operation. In this study, no significant benefit was seen in the patients getting probiotics compared to nonprobiotic group regarding postoperative wound infection. Sadahiro et al. had similar results in a prospective randomized trial done to compare between oral antibiotics and probiotics as bowel preparation for elective colon cancer surgery to prevent infection.[14] Horvat et al. showed no statistical differences in postoperative complications between the study groups comparing synbiotics, prebiotics with heat-deactivated probiotics and mechanical bowel preparation for elective colorectal surgery.[15] However, several other studies differ from this conclusion. Rayes et al. had a significantly lower incidence of postoperative bacterial infection with lactobacillus and fibers (12.5%) than with fibers only (40%) after pylorus-preserving pancreaticoduodenectomy.[13]

A double-blind study on the effects of probiotic treatment on postoperative infectious complications in colorectal cancer surgery showed significantly less rate of incision infection in patients getting pre and postoperative probiotics.[16] Wound infection was found to be much less in liver transplant patients getting probiotics compared to patients getting only fiber in postoperative period, though probiotics were given in very high doses of 27 billion units every twelve hourly.[17] Sugawara et al. found a lower wound infection rate (4.8%) in patients getting preoperative plus postoperative synbiotics in biliary cancer surgery.[18]

Most of the studies having good results with probiotics were conducted in adult patients and mostly in surgery of the upper GI tract and hepatobiliary system. A review article analyzed 14 randomized trials and it seemed that in patients undergoing liver transplant or elective surgery in the upper gastrointestinal tract, prophylactic administration of different probiotic strains in combination with different fibers results in a three-fold reduction in postoperative infections along with a reduction in postoperative inflammation, but the similar concept in colorectal surgery has not been successful.[19]

Measurement of postoperative serum CRP, the total count of WBC, neutrophil count, and postoperative pyrexia was done in this study to see postoperative inflammatory response was compared between both probiotic and nonprobiotic groups. Here, we found that serum c-reactive protein (CRP) was positive in 70% of patients nonprobiotic group compared to 40% positive in the probiotic group. This difference was found statistically significant ($P = 0.020$) [Table 3]. Sugawara et al. compared between a group receiving postoperative enteral feeding and synbiotics with another group getting preoperative plus postoperative synbiotics in biliary cancer surgery and found that postoperative serum WBC, CRP, and Interleukin (IL)-6 were significantly lower in the latter group.[18] Reddy et al. found no significant difference between the study groups in mean CRP and IL-6 levels measured before surgery and on days 1 and 7 after the operation.[20]

Rayes et al. studied leukocyte count, CRP, and other parameters preoperatively and on postoperative days 1, 5, and 10 in 90 patients to compare the early enteral supply of fiber and Lactobacilli versus conventional nutrition following major abdominal surgery and found no difference between the study groups.[21] Similar result was seen by Zhang et al.[17]

In this study, the total WBC count was significantly raised in the probiotic group before the operation, which explains the raised level of postoperative total WBC count. Rayes et al. showed that leukocyte count on the 5th POD is higher in patients receiving live and heat-killed lactobacillus compared to nonprobiotic group, though it was not statistically significant.[22] In a randomized controlled trial, patients getting pre and postoperative synbiotics had lower WBC counts...
compared to patients getting only postoperative synbiotics in patients in biliary cancer surgery.\[18\] Other studies also concluded that there is no difference of postoperative WBC count among probiotic and nonprobiotic groups.\[15,21\]

In this study, there was almost similar number of patients with raised neutrophil count (≥70%) in the postoperative period in both groups, which may be due to factors such as tissue trauma and reaction to operative stress. Probiotics were not able to reduce the postoperative neutrophilia.

The results in this study show less occurrence of fever in patients getting probiotics though it was not statistically significant. A randomized clinical trial on colorectal cancer surgery patients showed that the length of postoperative pyrexia was significantly less in patients getting preoperative plus postoperative probiotics compared to the control group.\[16\]

Mesenteric lymph node culture and serum IL-6 were seen to assess bacterial translocation and inflammatory response in almost all the articles reviewed here, but it was not possible in our setup.

There has been a marked disparity among the study results in the reviewed literature. This may be due to differences in operation or the type, dose, and duration of medication.

The present study included varieties of gastrointestinal operations, which may be one of the reasons of equivocal results regarding postoperative wound infection. The dose of probiotics was variable, with doses as high as 450 billion units twice daily and as low as 1 billion units twice daily.\[22\]

Very few have studied the effect of probiotics in pediatric surgical patients though there are many studies in pediatric medicine. No specific dosing could be found in the pediatric age group. Hence, based on conventionally used dose of probiotics in the respective department, the dose for this study was determined.

In majority of the studies showing beneficial effects of probiotics, medication was given in the preoperative plus postoperative period.\[16,18,20,23\]

**Limitations**

It is a single institution study. The study includes patients requiring varieties of gastrointestinal surgery. All the operations were not done by the same surgeon.

In this study, the use of probiotics as prophylaxis for postoperative wound infection did not show any added benefit in comparison to the nonprobiotic group though probiotics administration reduced the postoperative inflammatory response as indicated by the higher percentage of negative postoperative CRP level and more decrease in the total WBC count in the probiotic group.

**CONCLUSION**

This study showed no added benefit in using probiotics as prophylaxis for postoperative infection in children. The postoperative inflammatory response was almost similar in both groups though postoperative C-reactive protein level was significantly less in the probiotic group.

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**Conflicts of interest**

There are no conflicts of interest.

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