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A RANDOMIZED PLACEBO-CONTROLLED TRIAL ON THE USE OF PROBIOTICS IN THE PREVENTION OF NOSOCOMIAL INFECTION IN PEDIATRIC PATIENTS WITH HEMATOLOGIC AND ONCOLOGIC DISEASES

Arlene Grace L. Simon, MD*, Jossie Rogacion, MD*

ABSTRACT

Background: Despite measures to decrease its incidence, nosocomial infection remains to be a major problem in most tertiary hospitals. The use of prophylactic antibiotics leads to an increase in bacterial resistance, rather than decreasing the nosocomial infection rate. Other measures have been proposed to combat antibiotic resistance and the development of nosocomial infection, such as the use of probiotics.

Objective: The efficacy of the use of probiotics in the prevention of nosocomial infection and effect on duration of hospitalization was tested in patients with hematologic and oncologic diseases.

Study design: Randomized placebo-controlled double-blind trial using placebo and probiotics.

Intervention: 50 patients out of 76 predicted sample size, with hematologic and oncologic diseases who had a minimum predicted duration of hospitalization of 3 days were enrolled in a double-blind trial and randomly assigned on admission to take either 1 capsule of probiotics (n=25) containing at least 1.5 billion cells of *Lactobacillus acidophilus, Bifidobacterium bifidus* and *Bifidobacterium longus* or a comparable placebo (n= 25) once daily during their whole hospital stay. The patients were monitored and assessed daily for the development of nosocomial infection and for compliance to administration of the capsules. The patients were also assessed for any possible adverse effects. The counting of the duration of hospital stay started from admission to the emergency room till discharge. Patients were asked to follow up 1 week after discharge.

Results: This paper presents the preliminary results of the study involving 50 patients. Baseline characteristics on admission were found to be similar. The use of probiotics prevented the occurrence of nosocomial infection in patients with hematologic and oncologic diseases as compared to those receiving placebo, 0% vs. 20%, with a relative risk of 0.2 (fisher's exact test= 0.025, $p< 0.05$). However, there was no significant statistical difference between the duration of stay of the 2 groups (placebo = 9.4 days compared to probiotics = 8.6 days). The difference in readmission was analyzed using z-test and was also found to be not statistically significant. No adverse effects were reported in both groups.

Conclusion: The use of probiotics in patients with hematologic and oncologic diseases may play a role in the reduction of the occurrence of nosocomial infection, but may not necessarily cause a reduction in the duration of hospital stay. Further confirmation of the results is recommended upon completion of the study.

INTRODUCTION

Measures have been proposed to prevent the occurrence of nosocomial infection in most tertiary hospitals, such as strict hand-washing, the use of gowns, masks and gloves and the segregation of wards into infectious and non-infectious cases.[1] However, nosocomial infection still remains to be a major problem. It prolongs the stay of the patient in the hospital and is a cause of additional financial burden to the family of the patient. Patients afflicted with chronic illnesses, such as those with hematologic and oncologic diseases are said to be particularly susceptible to nosocomial infection due to the secondary impairment of their immune response. The use of chemotherapy, in particular, contributes to the impairment of the immune response of oncologic patients.[1] Prophylactic antibiotics may be given to prevent the occurrence of opportunistic infections in oncologic patients. However, the use of prophylactic antibiotics may lead to the emergence of resistance to these antibacterial agents and may even lead to the depletion of good microorganisms. It is this growing emergence of resistance to antibacterial agents which gave birth to bacteriotherapy. Bacteriotherapy is the use of harmless bacteria to displace pathogenic organisms and is said to be an alternative and promising way of combating infection.[2]

*Department of Pediatrics, UP-PGH
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Probiotics are live microorganisms which colonize the intestine, modifying the intestinal microflora and their metabolic activities, leading to presumed beneficial effects to the host system.[3] Probiotics are said to be non-pathogenic because they naturally inhabit the human intestine. The use of probiotics in diarrhea have been proven by numerous studies. These studies have shown that probiotics prevent the occurrence of diarrhea, as well as lessen it severity by promoting the growth of these beneficial live microorganisms and preventing the overgrowth of harmful microorganisms by means of their direct effect on the intestinal mucosal system.[4] It is said to promote healing of the intestinal mucosa by reducing gut permeability and by enhancing the local intestinal immune response.[3] A study on the prevention of nosocomial diarrhea on infants was undertaken in Poland by Szajewska et. al. *Lactobacillus GG* was given to hospitalized infants and the results showed that probiotic supplementation caused a decrease in the occurrence of nosocomial diarrhea (6.7% vs. 33.3%), with a resulting decrease in the length of stay of the patients given Lactobacillus GG.[5]

Recently, it has been postulated that probiotics may be beneficial not only in the gastrointestinal tract which they normally inhabit, but also in other mucosal surfaces such as the respiratory tract and urinary tract systems. It has been postulated that probiotics produce a beneficial effect on the over-all host system because of its' effect on both the humoral and cellular immune systems. A study in Finland by Hattaka et. al. explored the use of milk cultured with probiotics in the prevention of respiratory and gastrointestinal infections in healthy children attending day care centers.[6] The study showed a significant decrease in the number of absences due to respiratory and gastrointestinal illnesses in the children supplemented with probiotics compared to the placebo group (16% difference). There have been no studies, however, regarding the use of probiotics in children afflicted with chronic illnesses.

This study was conducted to determine if probiotics can be used in the prevention of the occurrence of nosocomial infection in children with hematologic and oncologic diseases.

OBJECTIVES

General Objectives

To determine if supplementation with probiotics will improve the outcome of hospitalized pediatric patients with hematologic or oncologic diseases.

Specific Objectives

To determine if hospitalized pediatric patients with hematologic or oncologic diseases given probiotic supplements will have a lesser frequency of nosocomial infections compared with hospitalized patients given placebo.

To determine if patients with probiotic supplementation will have a shorter duration of hospitalization as compared with patients given placebo.

Definition of Terms

Probiotics – nutritional supplements containing live bacterial or yeast cultures which commonly inhabit the intestinal system.[3]

Hematologic diseases – disorders that produce either quantitative or qualitative defects involving the cellular elements of the blood and blood tissues and those affecting hemostasis, such as in aplastic anemia and hemophilia.[7]

Oncologic diseases – diseases which cause proliferation of abnormal cells called oncogenes producing cancer and proliferation of tumor suppressor genes, such as in leukemia and retinoblastoma.[7]

Nosocomial infection - infections appearing in hospitalized patients not present nor incubating at time of admission from the hospital. The onset is beyond 72 hours from admission to the hospital, starting from admission to the emergency room.

METHODOLOGY

Setting

This randomized, double blind, placebo-controlled clinical study was conducted at the Philippine General Hospital Pediatrics wards and Emergency Room from July to October, 2002.

Patient Recruitment

Children aged 1 to 16 years of age with hematologic or oncologic diseases, with a predicted length of hospital stay of at least 3 days were recruited in the study consecutively upon admission at the Pediatric Emergency Room. The conduct of the research was explained to the parents by the investigator and written, informed consent was secured prior to enrollment in the study. Children who were placed on nothing per orem, with known allergy to cow's milk, other concomitant disorders, those who were in severe respiratory distress needing oxygen and ventilatory support, as well as those with neurologic deficits such as signs of increased intracranial pressure due to intracranial bleed and patients

with assessment of nosocomial infection on admission were excluded from the study. All the patients whose parents gave written, informed consent were randomized for the trial.

Sample Size Computation

Sample size was calculated based on the assumption that the use of probiotics will result in a 20% reduction in the occurrence of nosocomial infection. This assumption was based on an earlier study by Szajewska et. al.,[5] which reported a 26.6% decrease in the occurrence of nosocomial diarrhea (33.3% in the control group) in normal children. It was estimated that with a power of 90% and at alpha level of 0.10, we needed 38 children per group to show a 20% difference.

Randomization

The patients were recruited as they arrived at the Pediatric Emergency Room. The patients were randomized into the 2 groups by means of a computer generated randomization table.

Random Allocation/Blinding

The GNC Kyo-dophilus® (probiotics) capsules were repackaged by the Industrial Pharmacy laboratory of the University of the Philippines, Manila into yellow size 1 capsules. The same laboratory prepared the placebo capsules and packaged the cornstarch placebo into the same yellow size 1 capsules. This repackaging was necessary to ensure that the physicians and the patients will be blinded during the study. A person not directly involved in care of the subjects was tasked to encode the capsules into 2 groups (1 and 2). The capsules were packaged in air-tight envelopes (7 capsules per pack) labeled 1 or 2 with the corresponding patient number and patient name. Both the physician in charge and the patients were unaware of which capsules contain probiotics or placebo. The code was revealed during the data analysis.

Intervention

On admission to the study, complete history and physical examination were performed. The patients included in the study were given either 1 capsule of probiotics or placebo everyday from day 1 of ER admission until the last hospital day. In the event that the patients get admitted to the wards, intervention and monitoring were continued until discharge. One capsule of the GNC Kyo-dophilus® probiotics contains a minimum of 1.5 billion live cells of Lactobacillus acidophilus, Bifidobacterium bifidum and Bifidobacterium longum. The probiotic capsules were lyophilized, ensuring stability in room temperature.

The mothers were given a set of 7 capsules on admission. The mothers were instructed to give their children 1 capsule once a day after the morning meal. For patients less than 7 years of age or those who had difficulty in swallowing the capsules, the mothers were instructed to mix the powdered contents in 1 tsp of milk to be given after the morning meal. For patients who vomited the capsules or the powdered contents, the mothers were given instructions to give another dose 1 hour after the vomiting. The mothers were instructed to list down difficulties in giving the capsules.

The supplementation was continued until the patient was discharged from the hospital. Patients who developed nosocomial infection were instructed to continue supplementation until discharge. Monitoring for these patients continued until the patients were discharged from the hospital. Parents were instructed not to give their children other products with probiotic organisms.

Infection Surveillance

Baseline laboratories were ordered on the first hospital day, which included a baseline complete blood count, chest x-ray, urinalysis, stool exam and blood culture. The patients were visited daily and were monitored for the occurrence of nosocomial infection and compliance to the administration of the drug. The parents were also instructed to write down problems in administration and noted adverse effects on supplementation. Laboratories were repeated depending on the clinical suspicion of nosocomial infection. The patients were also followed up 7 days after discharge and assessed for the development of nosocomial infection. A diagnosis of nosocomial infection was made if the criteria for nosocomial infection as drafted by the Infectious Disease Section of the Department of Pediatrics of the Philippine General Hospital was fulfilled.

Classification of Nosocomial Infection:

A. Respiratory infection
   1. Clinical signs and symptoms of lower respiratory tract infection (LRTI)
      (cough, fever, increase in purulence of secretions, new auscultatory findings) + new infiltrates on chest x-ray
      1.1 with + culture (ETA/TTA/LT)
      1.2 with (-) blood culture

2. Clinical signs and symptoms of lower respiratory tract infection (LRTI) + new infiltrates on chest x-ray
   2.1 with (+) blood culture
   2.2 with (-) blood culture

B. Urinary tract infection
   1. Colony counts of > 100,000/ml of appropriately collected specimen or visible organism on gram stain in a patient with previously (-) urine culture or normal urinalysis
      1.1 with no clinical signs and symptoms (fever, dysuria, costovertebral angle tenderness, suprapubic tenderness)
   2. Colony counts > 10,000 colonies/ml. Of appropriately collected specimen of a new pathogen with a previously (+) urine culture:
      2.1 with clinical signs/symptoms
      2.2 without clinical signs/symptoms

C. Gastrointestinal tract infection
   1. Diarrhea with a patient with no diarrhea on admission
      1.1 with (+) stool culture
      1.2 with (-) stool culture
   2. Any other signs of GI disturbance (nausea, vomiting, abdominal tenderness) not previously present on admission (peritonitis, NEC, intra-abdominal abscess)
      2.1 with (+) stool culture
      2.2 with (-) stool culture

D. Bacteremia
   1. Presence of a (+) blood culture in a patient with no definite focus of infection
   2. Bacteremia with Infective endocarditis

E. Sepsis
   1. Signs and symptoms of sepsis (poor suck/activity, jaundice, acidosis, hypotension, hyperglycemia, etc.) with definite focus of infection
      1.1 with (+) blood culture
      1.2 with (-) blood culture

Checking of Compliance

The number of remaining capsules and empty shells were checked daily. Patients whose length of stay exceeded 7 days were given a weekly supply of 7 capsules. All remaining capsules were returned on the last hospital day, prior to discharge of the patient.

Outcome Measures

The primary outcome measures were the absence or occurrence of nosocomial infection as defined by the criteria for nosocomial infection by the Section of Infectious Diseases and the number of days the patient was hospitalized starting from the day of admission at the emergency room. A secondary outcome was the number of children with readmissions due to nosocomial infection within 7 days from discharge.

Withdrawals/Deviations From The Study

Withdrawal is defined as those patients who are taken out from the study by their parents, those who are brought home against advice by their parents disrupting therapy and those who are placed on nothing per orem for more than 2 days during the duration of the study. Deviations from the study include those patients who are placed on nothing per orem for less than 48 hours and those who vomited the capsules during the initial administration. The mothers of the patients who were placed on nothing per orem for less than 48 hours were instructed to resume administration once feeding, while the mothers of the patients who vomited during the initial administration were instructed to re-administer the capsules 1 hour after the vomiting.

STATISTICAL ANALYSIS

An intention to treat analysis was performed. Data were analyzed using Statistica software. T-test was done comparing the difference between the means of 2 independent samples. In comparing the distribution of discrete variables between two groups, chi-square test or Fisher's exact test when appropriate were performed. The z test was used to determine the significance of readmissions between the two groups. All tests were performed at a significance level at $p < 0.05$.

RESULTS

A total of 56 patients out of 76 predicted sample size, with hematologic and oncologic diseases were recruited for the study and randomized using a computer generated blocked randomization table. Of the 56 patients recruited, 6 patients were still hospitalized at time of analysis and were not included in the partial analysis of this study. This paper presents the preliminary data analysis of 50 patients included in the study.

Of the 50 patients discharged, there were 2 withdrawals: 1 from each group and were due to the patient being brought home per request of the parents. The patient from the treatment group who was brought home against advice developed intracranial bleed due to hyperleukocytosis on the 3rd ward day and was brought home per request of the parents. This patient did not

develop nosocomial infection during the whole hospital stay. The patient from the control group who dropped out of the study developed nosocomial pneumonia on the 4th hospital day and was brought home per request because the parents did not want to push through with chemotherapy. Since this is an intention to treat type of study, the data up to the day that these patients dropped out of the study were included in the analysis.

DESCRIPTION OF STUDY POPULATION

Data gathered on admission (Table 1) revealed that 74% of the patients were male (n=37) and in the 2-5 years age group (n=21; 42%). Of the 50 patients included in the data analysis, 26 (52%) had oncologic diseases while 24 (48%) had hematologic diseases. Majority of the patients were hospitalized due to fever (n=20; 40%), followed by pallor (n=15; 30%) as the most common presenting symptom.

Table 1. Characteristics of patients included in the study (N = 50)

CHARACTERISTIC	NUMBER	%
AGE Distribution		
2-5 years	21	42%
6-9 years	11	22%
10 – 13 years	11	22%
14 –16 years	7	14%
Presenting complaint		
Fever	20	40%
Pallor	15	30%
Bleeding	12	24%
Diarrhea	3	6%
Disease Type		
Hematologic	24	48%
Aplastic anemia	9	37.5%
Thalassemia	6	25%
Hemophilia	5	20.8%
Others	4	16.7%
Disease Type		
Oncologic	26	52%
ALL	11	42.3%
AML	9	34.6%
Lymphoma	2	7.6%
Others	4	15.4%

Comparison of Baseline Characteristics of Placebo and Probiotic Groups

Table 2 lists the comparison of baseline characteristics of the 2 groups, such as age, disease type and presenting complaints. There was no significant difference in mean age between the placebo group (mean age = 7.92 years) and the probiotics group (mean age = 7.48 years). With regards to the disease type, it was found that there are more hematologic patients (n= 14) in the control group as compared to the treatment group (n = 10). In contrast, the treatment group had more oncologic (n = 15) patients than the control group (n = 11). This difference, however, was found to be not statistically significant, using the Fisher's exact test. Fever was the most common presenting complaint in both groups, with the treatment group having more patients presenting with fever (11 vs. 9). Again, the difference in presenting complaints was not statistically significant (x2= 2.3636, DF =3).

Table 2. Comparison of baseline characteristics of placebo and probiotic groups

Characteristic	Control (N = 25)	Treatment (N= 25)
Age (mean) (1)	7.92 years	7.48 years
Presenting complaint (2)		
Fever	9	11
Disease type (3)		
Hematologic	14	10
Oncologic	11	15

1: t = 0.34, p > 0.05
2: x2 test = 2.3, df = 3, p > 0.05
3: Fisher's exact test = 0.4, df = 2

DATA ANALYSIS

Frequency of Nosocomial Infection

None of the patients in the treatment group developed nosocomial infection compared to 20% in the placebo group (5 out of 25), showing a relative risk reduction of 100% and an absolute risk reduction of 20%, with number needed to treat = 5 patients. The difference was statistically significant using the Fisher's exact test (0.025, p< 0.05).

Of the nosocomial infection detected, 1 patient developed nosocomial candiduria, while 4 patients developed nosocomial pneumonia. It is noteworthy that all the patients who developed nosocomial infection are leukemia patients.

Table 3. Frequency of patients who developed nosocomial infection

	Placebo group	Probiotics group	Total
Nosocomial infection	5	0	5
No nosocomial infection	20	25	45
Total	**25**	**25**	**50**

Duration of Hospitalization

The patients in the placebo group had a mean duration of hospitalization of 9.4 days (sd = 7.0) as compared to the probiotics group with a mean duration of hospitalization of 8.6 days (sd = 6.7; t value = 0.43, p> 0.05).

Secondary Outcome: Readmissions

Of the 25 patients in the probiotics group, 2 patients were readmitted within 1 week due to continuation of chemotherapy, while in the placebo group, 1 patient was readmitted for infection, while 2 patients were readmitted for bleeding and another patient was readmitted for chelation therapy. None of the 50 patients had readmissions for nosocomial infection. The data for re-admissions was analyzed via the z test and was found to be not statistically significant (z value = - 0.879, α = 0.05; significant z value if < -1.65).

There were no mortalities among the patients recruited. Of the 50 patients, only 2 patients were discharged with no improvement. These 2 patients were the 2 drop-outs who were brought home against advice by their parents.

All the patients who developed nosocomial infection received appropriate antibiotic therapy and were discharged improved.

Surveillence for Adverse Effects

No adverse effects were noted during supplementation with either the placebo or probiotic capsules in any of the 50 patients included in the study.

DISCUSSION

This randomized, double blind, placebo-controlled study is the first of its' kind to explore the prophylactic effects of probiotics on nosocomial infection, particularly in the respiratory, gastrointestinal and urinary tract systems, in patients with hematologic and oncologic diseases. The study was undertaken to be able to find a safe alternative to giving prophylactic antibiotics, which in the end leads to an increase in antibiotic resistance. Oncologic and hematologic patients were chosen as the main subjects in the study because they were found to be particularly susceptible to developing nosocomial infection because of their need for frequent admissions and their exposure to immunosuppressive therapy. Hematologic and oncologic patients need frequent admissions due to blood transfusions or chemotherapy.

Baseline characteristics of both groups were similar and statistical analysis showed that group differences were not significant. Results revealed that the treatment group had 0% infection rate as compared to 20% in the control group. Absolute risk reduction was 100% and relative risk was 0.20, with number needed to treat = 5. This means that we need to treat only 5 patients to prevent 1 nosocomial infection. All the patients who developed nosocomial infection were oncologic patients. Oncologic patients were found to be more susceptible to acquiring nosocomial infection due to their impaired neutrophil counts which decreases the body's ability to fight off infection .[1] Furthermore, hematologic patients were found to have a lesser length of stay as compared to oncologic patients, because most of them get admitted for blood transfusions only and not for infection or chemotherapy although the difference did not reach statistical significance.

The lack of statistical significance with regards to duration of hospitalization can be explained by the fact that despite the placebo group having more episodes of nosocomial infection than the probiotics group, which was supposed to result in a longer duration of hospitalization, there were more patients in the placebo group with hematologic disorders than oncologic disorders as compared to the probiotics group. Other factors that may contribute to the lengthening of the duration of stay include the need for chemotherapy, the procurement of funds for chemotherapy, as well as the completion of antibiotic therapy. Despite the lack of difference in the duration of hospitalization, the decrease in occurrence of nosocomial infection in the probiotics group implies a better outcome, since they can proceed to definitive chemotherapy earlier and there is lesser need for funds to acquire antibiotics needed to treat nosocomial infection.

Proposed Mode of action:

Probiotics work by being able to replenish the depleted intestinal microflora which is often caused by the use of antibiotics.[8] It is presumed to promote healing

of the intestinal mucosa by reducing gut permeability and by enhancing the local intestinal immune response, particularly that of IgA. It is also considered safe and has no known adverse effects.[9]

The study in Finland by Hattaka et. al. is the first to examine if probiotics can also be effective in other mucosal systems. They hypothesized that probiotics prevent the occurrence of infection by means of stimulating non-specific immunity or by enhancing humoral and cellular immunity.[5] Probiotics presumably prevent respiratory tract infections, even though it is not in direct contact with it because of its' stimulatory effect on secretory IgAat all mucosal surfaces.[10]

An article published in the Nutrition Hospital Journal in 2001 promotes the use of probiotics in immuno-compromised patients, particularly ICU patients. Listed effects of probiotics in the immune system aside from stimulating IgA response include the inhibition of IgE production, stimulation of the macrophage function, stimulation of the NK activity, stimulation of apoptosis, promotion of growth and regeneration, reduction of endotoxin production and the production of anti-oxidants.[11] Further studies are needed to demonstrate these effects.

CONCLUSION

Probiotics may play a role in the prevention of the occurrence of nosocomial infection in patients with hematologic and oncologic diseases, but it may not necessarily cause a reduction in the duration of hospital stay.

RECOMMENDATIONS/LIMITATIONS

Since this paper presents only the preliminary results of the study, further confirmation of the results is recommended upon completion of the study.

A more objective way of testing compliance should have been done in the form of stool cultures to detect the presence of probiotic organisms. Unfortunately, this was not done due to the unavailability of the test in the country.

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