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Randomized Controlled Trial

Sporulated *Bacillus* as alternative treatment for diarrhea of hospitalized adult patients under enteral nutrition: A pilot randomized controlled study

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SUMMARY

Background & aims: Among hospitalized patients receiving enteral nutrition (EN), malnutrition and antibiotic use are some of the most common causes of diarrhea. Prebiotics and probiotics agents have been used for treatment of diarrhea in such patients. The aim of this study was to assess the efficacy of a sporulated *Bacillus* strain (*Bacillus cereus A 05*), compared to a control group using a prebiotic (soluble fiber), in reducing diarrhea in patients receiving EN and antibiotic therapy.

Methods: Patients with diarrhea receiving EN were randomized to receive either *B. cereus* (study group) or soluble fiber (control group) for five days. The group treated with *B. cereus* received 4 vials with 5 mL $\times$ 10^6 every 6 h. The control group treated with fiber received 10 g of soluble fiber every 8 h. Data assessed were serum albumin, nutrition status through Subjective Global Assessment (SGA), antibiotic use and osmolality (normal or hyperosmolar) of the tube feeding diets.

Results: Twenty-nine patients were treated in each group. There was no significant difference between the groups regarding age, serum albumin, SGA score, dietary osmolality and antibiotic use. There was no significant difference between groups in ceasing diarrhea. However, the group treated with *B. cereus* took fewer days to cease diarrhea (2.5 $\pm$ 1.3 versus 3.7 $\pm$ 1.1 days, $p = 0.011$). Specifically, in the group treated with *B. cereus A 05*, malnourished patients did better than non-malnourished patients regarding diarrhea cessation (100% versus 25%, $p < 0.001$).

Conclusions: *B. cereus A* 05 was more effective than fiber in reducing diarrhea among patients under EN and antibiotic therapy and was more effective among malnourished patients.

1. Introduction

Enteral nutrition (EN) is commonly indicated for hospitalized critically ill patients. However, gastrointestinal complications, such as diarrhea, are frequent in this condition [1]. The etiology of the problem is multifactorial and includes antibiotic effects, C. *difficile* infection, side effects of some medications, high diet osmolality, high infusion rate, low serum albumin, malnutrition status, feeding contamination, among others [1,2].

Prebiotics (soluble fibers) and probiotics (a wide range of microorganism stains) have been used to prevent and treat diarrhea in stable and critically ill patients [3–8]. Although a meta-analysis found that results of prebiotics in diarrhea treatment of critically ill patients are inconclusive [8], its use is common in critical care units. On the other hand, more complicated evaluation is the use of probiotics in diarrhea treatment of critically ill patients. The most confounding factor is the usual use of different mixes of stains.

In Brazil, the use of soluble fibers is a common protocol to treat diarrhea in intensive care units. However, probiotics are not yet commonly used for critically ill patients. In stable outpatients,

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though, probiotics are commonly applied to treat diarrhea. One type commonly used is the sporulated *Bacillus* strain (strain A 05 of *B. cereus*), called biocerin [9]. Biocerin has proved to be effective on gastrointestinal infections and infestations of various etiologies [10,11]. To our knowledge, no previous study has been done with the use of the sporulated strain *Bacillus cereus A* 05 to treat diarrhea of critically ill patients.

The aim of this study was to compare the use of the probiotic *B. cereus* with a commonly used prebiotic (mix of soluble fibers) in the treatment of diarrhea of critically ill patients under EN. The study considered antibiotic use, nutritional status, diet type and osmolality, among other variables.

2. Materials and methods

This was a randomized, prospective, double-blind and interventional study. The research was conducted at Pilar Hospital, Curitiba, Paraná, Brazil.

Data collection occurred from August 2011 to May 2012. Patients admitted to the intensive care unit (ICU) for various conditions were evaluated for their disease profile, its severity according to the Acute Physiology And Chronic Health Evaluation (APACHE) II criteria [12], any antibiotics used, their nutritional status, plasma albumin and the type of diet they had been offered. The nutritional status of patients was measured using the Subjective Global Assessment (SGA) [13], a tool frequently used in critically ill patients [14–16], with the following scores: 1 = normal, 2 = mild/moderate malnutrition, 3 = severe malnutrition. Serum albumin was measured using the bromocresol green method in the hospital laboratory. All of patients received EN during the period and were monitored for the possibility of developing diarrhea. Patients with inflammatory bowel disease (Crohn's disease and ulcerative colitis), short bowel syndrome and specific infectious intestinal conditions were excluded from the study.

In order to identify diarrhea, the King's chart (King's Stool Chart© 2001, King's College, London) was used (Fig. 1). The instrument is validated to characterize when fecal excretion indicates loss (in both weight and volume) compatible with diarrhea [17]. The mean scores indicate the existence of diarrhea when the sum reaches 15 or more points in 24 h.

In case of diarrhea, the research team communicated to a secretary who randomly assigned patients to the intervention. The randomization used 60 tags sealed in an envelope, 30 for each group, *B. cereus* or fiber.

The intervention period was five days. The deadline was based on the methodology of other studies of the treatment of diarrhea using probiotics [18,19]. A pharmacist followed the study patients to avoid the use of medications that could promote diarrhea.

The EN diets were industrialized in closed system, administered through feeding tubes at room temperature and using an infusion pump. The following types of diet were used: 1) polymeric, with 1.0 kcal/mL caloric density and 360 mOsm/L osmolality (IsoSource Standard, Nestle®); and 2) semi-hydrolyzed, with 1.5 kcal/mL caloric density and 490 mOsm/L osmolality (Peptamen, Nestle®). The nutritional composition of the enteral formulas is shown in Table 1. The administration of the diet started with 500 mL/24 h on the first day, according to the institution's protocol, increasing by 250 or 500 mL/day, depending on each patient's gastrointestinal tract tolerance and clinical condition. The diet flow was decreased to 500 mL/day in the event of diarrhea. Therefore, all patients of the study were receiving 500 mL/day of enteral formula before to start the prebiotic or probiotic supplementation.

Patients in the group treated with probiotics received four vials of *B. cereus* (Biovicerin®, Laboratório Geyer) every 6 h through enteral feeding tubes. Each vial contains 5×10^6 of sporulated *B. cereus*, in liquid suspension. A nurse, coauthor of this study, was responsible to administer the probiotic.

Patients in the control group, treated with prebiotics, received 30 g per day (10 g every 8 h) of a mixture of soluble fiber (*Fibermais*®, Nestlé) with 60% guar gum and 40% inulin. The fibers were diluted in distilled water and administered through enteral feeding tubes. A dietitian, coauthor of this study, was responsible to give the fiber supplement.

After the nutritionist assigned to apply SGA and the nurse assigned to apply the evacuation status of the patients, the SGA scores were compared to the diarrhea scores.

Statistical considerations. The outcome of interest in the study was whether diarrhea would stop during the five-day period. The results were reported either as the mean, median, minimum and maximum values and standard deviations (quantitative variables) or as frequencies and percentages (qualitative variables). Student's t test was used to compare the groups defined according to treatment (probiotic or prebiotic) with respect to quantitative variables. A logistic regression model was fitted for the multivariate analysis. Stopping diarrhea was considered the (dependent) variable response. Variables with a value of $p < 0.20$ in the univariate analysis were considered explanatory variables [20]. The Wald test was used to assess the significance of each independent variable for the outcome of stopping diarrhea during the five-day period. Values of $p < 0.05$ indicated statistical significance. The data were analyzed using the computer software Statistical Package for the Social Sciences (SPSS) v.14.0, property of IBM Corp. Copyright IBM Corporation and its licensors, 1989, 2011.

Ethical statement. The Council for Education and Research of the Pontifical Catholic University of Paraná (Conselho de Ensino e Pesquisa da Pontifícia Universidade Católica do Paraná) authorized the project (6163/2011—National System of Research Ethics), Internal Affairs Commission (Sistema Nacional de Ética em Pesquisa, Comissão de Assuntos Internos, SINESP, CAI 1201.0.000.084–11). The informed consent form was read and signed by all of the study patients' legal guardians.

3. Results

Sixty (51.72%) of 116 patients monitored (Fig. 2) had diarrhea and were randomized for the interventional study. Two (one from each group) of the 60 randomized patients were excluded from the study because they had developed sepsis before beginning the intervention. The patient from the control group, treated with fiber, started showing symptoms of sepsis and respiratory insufficiency one day before the intervention. The patient from the group treated with probiotics developed pneumonia and sepsis, with three blood cultures positive for *Staphylococcus* spp, two days before starting the intervention. Twenty-nine patients from each group remained. Most were in the ICU during the study. Table 2 outlines the underlying diseases of patients and indications for EN.

Table 3 shows the demographic age data, serum albumin, SGA, type of diet offered and antibiotic load. No significant difference occurred between the two groups, thus confirming the sample's homogeneity. No significant differences occurred in age ($p = 0.954$), serum albumin levels ($p = 0.643$) and SGA scores ($p = 0.066$) compared to patients without diarrhea, who were not selected for the study ($n = 56$). There was no difference in number of patients using isotonic and hydrolyzed diet, for both, *B. cereus* or fiber treatment (Table 3).

The antibiotics used in the study group are shown in Table 4. There were no changes in antibiotic treatments during the study. There was no significant difference between groups regarding number of antibiotics used ($p = 0.47$) (Table 5).

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