ORIGINAL ARTICLE

SACCHAROMYCES BOULARDII IN THE PREVENTION OF ANTIBIOTIC-ASSOCIATED DIARRHEA IN CHILDREN: A RANDOMIZED CONTROLLED TRIAL

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ABSTRACT

Background: Diarrhea is one of the most common adverse effects of antibiotic treatment. In Saint Louis University-Hospital of the Sacred Heart (SLU-HSH), about three out of ten patients at the outpatient department and one third of admitted pediatric patients are given antibiotics. Although international studies document the efficacy of probiotics in preventing antibiotic associated diarrhea (AAD), there is limited research in our country about this.

Objectives: The main objective of this study was to evaluate the efficacy of a yeast probiotic, *Saccharomyces boulardii*, in preventing AAD.

Methods: This was a randomized clinical trial conducted between June and October 2012 at Saint Louis University-Hospital of the Sacred Heart. A total of 140 patients aged 6months to 18years with PCAP were enrolled. The patients either received the standard antibiotic treatment alone (control group n=71) or the oral antibiotic treatment plus 250mg of Saccharomyces boulardii (treatment group n=69) twice a day for the entire duration of treatment. Analyses were based on treatment and included data from 136 patients.

Results: Patients who received *S. boulardii* had shorter duration of diarrhea than those who did not receive it [3.06 days (0.68) vs. 2.45 days (0.69), P value of 0.032]. However, the incidence of diarrhea between the two groups was not statistically significant [16 of 68 (23.5%) vs. 11 of 66 (16.7%), P value of 0.391].

Conclusion: This is the first randomized-controlled trial in our locality which showed evidence that *S. boulardii* shortens the duration of antibiotic-associated diarrhea.

INTRODUCTION

Antibiotic-associated diarrhea (AAD) is defined as an unexplained diarrhea that occurs in association with the administration of antibiotics. Almost all antibiotics are implicated in AAD, since most antibiotics cause the disruption of colonization of normal gastrointestinal flora leading to acute inflammation of the intestinal mucosa. However, there is a higher risk for AAD with broad-spectrum antibiotics and those that are considered active against anaerobes, such as aminopenicillins, a combination of aminopenicillins and clavulanate, cephalosporins and clindamycin.[1] This illness occurs in approximately 5% to 30%, and up to 40%, of patients receiving broad-spectrum antibiotics from the initiation of therapy and up to two months after cessation of treatment.[2,3,4]

Probiotics are live microbial supplements or food products that alter the microflora of the host and have the potential for beneficial health effects; it may be administered to prevent AAD.[5,6] The most commonly used probiotics are lactic acid bacteria, such as lactobacilli or bifidobacteria, but non-bacterial organisms, such as a non-pathogenic yeast Saccharomyces boulardii, have also been used. *S. boulardii* has been used widely for a variety of causes and is generally well tolerated with few adverse effects, including abdominal pain and vomiting. There are approximately 30 case reports documenting *S. boulardii* fungemia. However, since it is generally not absorbed systemically, adverse effects is rare.[7]

In AAD, there is interruption in the normal intestinal flora. According to literature, this event is minimized by probiotics by normalizing unbalanced indigenous microflora, thus preventing diarrhea.[8,9] The mechanism of action of *S. boulardii* in preventing AAD has not been fully established. In studies conducted on animals, it has been shown to secrete a protease which binds to toxin A receptors, thus decreasing enterotoxic effects. Another hypothesis is that it stimulates the host to release secretory immunoglobulin A, which in turn stimulates chloride absorption and activates reticuloendothelial and complement systems. This process also has an immunoprotective effect that alleviates AAD symptoms in humans.[9] In vitro, *Saccharomyces boulardii* has also been shown to block *C. difficile* adherence to cells. A combination of these effects may also account for the reduction in the development of AAD.

The aim of this study was to determine whether *S. boulardii* prevents antibiotic-associated diarrhea in children who were treated for Pediatric Community Acquired Pneumonia.

Specifically, this study aimed to determine the effect of *S. boulardii* co-treatment on the incidence, frequency per day, and duration of diarrhea within two weeks of antibiotic treatment, determine its safety, and the patients' tolerability to it.

METHODOLOGY

The study was conducted between June and October 2012 at Saint Louis University-Hospital of the Sacred Heart. Eligible subjects were those who were between the ages of six months and 18 years, out-patient or admitted patients, diagnosed with Pediatric Community Acquired Pneumonia (PCAP) based on the Philippine Pediatric Society (PPS) Clinical Practice Guidelines (CPG) (Appendix B), and were on IV or oral antibiotics within 24 hours of enrolment. The choice of antibiotics was in line with the PPS CPG for PCAP. The exclusion criteria were the following: presence of a severe or generalized bacterial infection or those with PCAP-D; antibiotic treatment within the previous two months; inability to tolerate oral medications; prophylactic antibiotic treatment; use of a probiotic product for medicinal purposes within

the previous seven days; immunodeficiency; chronic gastrointestinal disease; and acute or chronic diarrhea.

Materials and Methods

The eligible patients were randomly assigned to two groups, control and treatment. The control group received the antibiotic treatment alone, while the treatment group received the antibiotic with *S. boulardii* as co-treatment. *S. boulardii* 250mg was orally taken twice daily for the duration of the antibiotic treatment. Admitted patients who were discharged from antibiotics were also given the probiotic. The probiotic was either swallowed or dissolved in 10ml-15ml of water, depending on the patient's preference.

Each patient or the primary caregiver received a chart to record the frequency of bowel movements as well as any untoward symptoms, such as fever, abdominal pain, or vomiting. Number of stools, consistency (according to Modified Bristol Stool Form Scale (MBSFS) chart, and duration of diarrhea were recorded daily. Routine fecalysis was done to rule out other causes of loose or watery stools. The patients or primary caregiver were interviewed directly and their charts were reviewed to assess their compliance to treatment.

Measurement of Outcome

The incidence of diarrhea between the two groups was measured as the primary outcome. In this study, diarrhea is defined as three or more loose or watery stools (MBSFS 4 or 5) per day, which lasts for a minimum of 48 hours during the course of the antibiotic treatment or up to two weeks after the therapy. Secondary outcomes, such as the frequency of diarrhea per day, duration of diarrhea in days, need for discontinuation of the antibiotic treatment, hospitalization to manage the diarrhea (for out-patients), delay in discharge (for in-patients), intravenous rehydration in any of the study groups and other adverse events, were also measured.

Sample Size and Randomization

A previous RCT revealed that the addition of *S. boulardii* vs. placebo to antibiotic therapy reduced the risk of diarrhea [nine of 119 (7%) vs. 30 of 127 (23%), RR 0.3, 95% CI: 0.2–0.7; NNT 7, 95% CI: 5–16].[10] Using the same expected proportion and assuming a confidence level of 95% and power of 80%, the sample size required was 64 children per treatment arm.

Patients were randomized using a computer-generated random sequence tool from http://www.randomizer.org. The Interns assigned the patients to their respective groups. No blinding was done due to lack of placebo.

Statistical Analysis

The T-test was used to compare mean values of continuous variables approximating a normal distribution. For non-normally distributed variables, the Mann-Whitney U test was used. The Chi-Square test or Fisher exact test was used to compare differences between groups. Statistical analysis was processed using the computer software Statistical Package for Social Sciences (SPSS) version 20. All statistical tests were two-tailed and were performed at the 5% level of significance. A P value of <0.05 was considered significant.

Ethical Considerations

Parents were fully informed about the aims of the study. A consent form approved by the hospital's ethical review committee was signed by at least one parent. The study protocol was reviewed and approved by the hospital's ethical review committee. The identities of the subjects were not disclosed.

RESULTS

The progression of the subjects throughout the study is shown in the following diagram (Fig 1). Out of the 140 children enrolled

in the study, there were 71 patients under the control group and 69 patients under the treatment group. Three patients from the control group did not follow-up. Meanwhile, three subjects dropped out from the treatment group because one did not follow up and the other two did not comply with the intervention. Therefore, only 136 subjects were available for analyses.
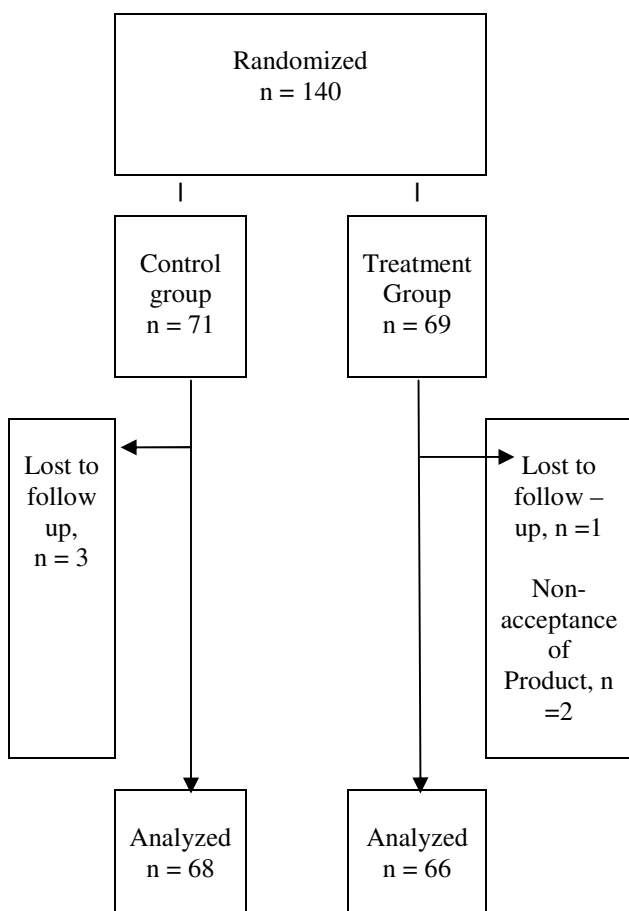

Fig 1. Flow diagram of patients' progression

Table 1 summarizes the baseline demographic and clinical characteristics of the children enrolled in this study. In summary, the difference in gender between groups was not statistically significant (*P* value = 0.852) as well as the differences in ages between age groups (*P* value = 0.254). Since there were 13 different

antibiotics and combination of antibiotics, the difference between single antibiotic and dual antibiotics were assessed. It was found that the difference of single vs. dual antibiotics was significant within their respective groups but was not statistically significant between them. Finally, the difference in duration of antibiotics was also not statistically significant.

Table 1. Baseline Characteristics of the Study Groups

	Control Group n = 68	Treatment Group n = 66	T-test/ Chi Square *P*-value
Gender			0.035(0.852)
Male	36 (52.9%)	36 (54.5%)	
Female	32(47.1%)	30 (45.5%)	
Age (±SD)	3.54 ±3.42	4.19 ±3.09	-1.144 p=0.254
Antibiotic Used			4.41 p=0.332
Single	50	58	
Multiple	18	8	
Duration of Antibiotics (mean ± SD)	7.59 ±1.17	7.29 ± 0.92	1.642 P=0.103

The primary outcome measured was the frequency of diarrhea. Generally, a total of 27 patients presented with diarrhea, 16 patients from the control group and 11 patients from the treatment group (Table 3). All of these patients submitted specimens for routine stool examination at SLU-HSH Laboratory. All stool samples had negative results, which were suggestive, but not confirmatory, of AAD. Upon analysis of the results using the per-protocol method, it was shown that the presence of diarrhea in PCAP patients who were given *S. boulardii* was not statistically significant [16 of 68 (23.5%) vs. 11 of 66 (16.7%), *P* value of 0.391].

Table 3. Incidence, Frequency and Duration of Diarrhea on the Control and Treatment Groups.

Diarrhea	Control N=68	Treatment N=66	t Test/Chi Square (*P* value)
Incidence	16 (23.5%)	11 (16.7%)	0.98 p = 0.322
Frequency per day (mean + SD)	3.25 + 0.77	3.27 + 0.64	-0.08 p = 0.937
Duration in days (mean/SD)	3.06 + 0.68)	2.45 + 0.69	2.27 p = 0.032

The mean frequency of diarrhea per day in the control group was 3.25 episodes/day (SD = 0.77) while in the treatment group, it was 3.27episodes/day (SD = 0.64). This showed that the frequency of diarrhea per day between the two groups was not statistically significant (P value of 0.937). However, there was a significant reduction in the duration of diarrhea among patients given *S. boulardii* as co treatment [3.06 days (0.68) vs. 2.45 days (0.69), *P* value of 0.032].

In both study groups, no patient needed to discontinue antibiotic treatment, hospitalized to manage the diarrhea (for out-patients), delayed in being discharged (for in-patients), or was given intravenous rehydration. The *S. boulardii* was generally well tolerated and there was no documented or reported adverse event.

DISCUSSION

This is the first RCT in our locality to assess the effectiveness of *S. boulardii* in preventing AAD in children with PCAP-C. The findings in this study did not coincide with the findings in various researches done abroad. It also indicated that the use of *S. boulardii* as co-treatment to prevent AAD was not statistically significant during the per-protocol analysis. However, it is important to note that patients given *S. boulardii* had a significantly shorter duration of diarrhea.

The baseline demographic and clinical characteristics in the two groups were generally not significant. However, in the use of antibiotics, whether it was single or dual antibiotics, the difference within groups were significant. Both groups had more patients who were given single antibiotics than dual antibiotics. This is consistent with the Pediatric Community Acquired Pneumonia Clinical Practice Guidelines by the Philippine Pediatric Society. The guidelines suggest treatment with a single antibiotic unless additional antibiotics are warranted for synergistic effect or additional coverage for atypical etiologic agents. Some patients were also given two antibiotics because the initial IV antibiotic stated did not have an oral preparation, hence a different step-down antibiotic was given.

There have been various randomized control trials regarding the use of *Saccharomyces. boulardii* in preventing AAD and numerous studies involving the adult population established its effectiveness. This probiotic was associated with a statistically significant decrease in the incidence of AAD (odds ratio0.39; 95% CI: 0.25–0.62) in a recently published meta-analysis of four randomized-controlled trials (RCTs) involving 688 adults.[11,12,13] Meanwhile, an RCT was done on children between the ages of six months and 14years, where it was concluded that giving *S. boulardii* was effective in preventing AAD. Children involved in this study were diagnosed to have otitis media and respiratory tract infections and were given either a placebo or *S. boulardii* as treatment with antibiotics.[14] The researchers found that the yeast *S. boulardii* had some effect in reducing the risk of *Clostridium difficile* infection (CDI) and AAD.[15] However, in 2006 a meta-analysis of randomized control trials was done involving six studies on the probiotics *Lactobacillus GG, L. sporogens* and *Saccharomyces* boulardii. The combined results, analyzed with a per-protocol method that reported on the incidence of diarrhea during antibiotic treatment, showed significant benefit for the use of probiotics over placebo (relative risk [RR] 0.43, 95% confidence interval [CI] 0.25–

0.75, I2 = 70.1%). In contrast, results from intention-to-treat analysis were not significant overall (RR 1.01, 95% CI 0.64–1.61). The meta-analysis concluded that the potential protective effects of probiotics to prevent AAD in children do not withstand intention-to-treat analysis. Said study also concluded that before routine use is recommended, further studies should be done.[16]

The study done by Kotowska, M. et al, found the antibiotics IV Cefuroxime and Amoxicillin + Clavulanic Acid can cause AAD. However, the antibiotics that were frequently used by the patients in our study and in our practice such as Penicillin, Amoxicillin, and Clarithromycin did not show a statistically significant increase in the incidence of AAD. Furthermore, the patients involved in said study were treated for various illnesses including Otitis Media, for which the empiric dose of an antibiotic is higher and the duration of intake is longer than that for Pneumonia. Perhaps, the difference in preference, dose, and duration of antibiotics could account for the inconsistency of results.

Some literatures also suggested that *S. boulardii* was statistically more useful in preventing *Clostridium difficile* infection. Since our study employed the use of a routine fecalysis and no stool culture or assays were done, the infection may have been missed.

It is therefore recommended that further research be done to include patients diagnosed with Otitis Media and the dose and duration of the antibiotics be compared. Also, it is recommended that additional diagnostics such as stool culture and Rotavirus assay be included to totally rule out infectious causes that may have been missed by routine fecalysis.

CONCLUSIONS

Although the duration of diarrhea was significantly reduced in patients who were given

S. boulardii, there is a need to do further investigations regarding the efficacy of *S. boulardii* in preventing AAD in children in our locality.

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