Efficacy Of A Mixture Of Probiotic Containing Saccharomyces Boulardii and Lactobacillus in Preventing Antibiotic Associated Diarrhea In Patients Taking Triple Therapy For H Pylori Eradication

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ABSTRACT

INTRODUCTION: Antibiotic Associated Diarrhea (AAD) is a common complication in patients taking antibiotics. The incidence of Antibiotic Associated Diarrhea varies according to antibiotic treatment and its course. The incidence of Antibiotic Associated Diarrhea for Amoxycillin is reported to be up to 25% and that the incidence increases further if multiple antibiotics are used. Meta-analyses reveal that especially Saccharomyces boulardii and also Lactobacillus species of the probiotics have a definite role in preventing Antibiotic Associated Diarrhea. Administering different drug regimes for eradication of Helicobacter infection is a commonplace in today’s era. These patients are administered antibiotics as part of the treatment. Therefore, we undertook this study in patients taking 14 days’ course of triple therapy including Clarithromycin, Amoxycillin and Pantoprazole to see the efficacy of a mixture of probiotics containing S. boulardii and Lactobacillus in preventing Antibiotic Associated Diarrhea.

METHOD: A total of 40 patients were enrolled in this single centered prospective, interventional, intention to treat clinical trial. Both peptic ulcer and non-ulcer dyspepsia patients were included in the study. Patients were randomly assigned into two groups. The treatment group comprised of 20 patients taking H. Pylori (Helicobacter Pylori) eradication triple therapy along with probiotics for 14 days; who were given the treatment on the basis of evidence of H pylori infection, either endoscopy and tissue biopsy or clinical features and positive serology for H Pylori.

The control group comprised of 20 patients receiving the same triple therapy drugs for H Pylori eradication for the same duration; but not receiving the Probiotics. In this group too, indication for H pylori eradication therapy was same like in the control group.

RESULT: The ages of the patients in the two groups and male female ratios were comparable. The median age of patients in the treatment group was 41.95 years with SD 14.7 and it was 43.7 with SD 14.7 years in the control group. In the treatment group, only one out of twenty (5%) patient developed diarrhea on the 6th day of commencing the treatment. In the control group, a total of 5 out of 20 (25%) patients developed diarrhea on various days of having started the treatment, but all developing it within a week. The median duration of development of diarrhea was 3.4 ± 1.1 days. There was lower incidence of occurrence of diarrhea in the treatment group.

CONCLUSION: A probiotic mixture containing Saccharomyces boulardii (S. boulardii) & lactobacillus is effective in preventing Antibiotic Associated Diarrhea in patients receiving triple therapy for Helicobacter Pylori eradication.

KEY WORDS: Probiotics, Antibiotic Associated Diarrhea, Triple therapy, H Pylori

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INTRODUCTION

Diarrhea is a common side effect of antibiotic use and can result from a variety of mechanisms. The most common type of diarrhea, often called simple antibiotic-associated diarrhea (AAD), is believed to result from a disturbance of the normal colonic microflora, leading to alterations in bacterial degradation of nonabsorbed carbohydrates and bile salts. Colonic bacteria normally ferment the complex carbohydrates in dietary fiber and other carbohydrates that are not absorbed in the small intestine, and the fermentation products are then metabolized and absorbed in the colon. Disruption of this process by antibiotic therapy is believed to cause osmotic diarrhea. Some, but not all, bacteria can deconjugate bile salts, and unconjugated bile salts are known to stimulate fluid secretion by the colonic mucosa; another mechanism for AAD may be reduced bacterial degradation of bile salts within the colonic lumen. Other mechanisms that can account for AAD include stimulation of intestinal motility through the motilin-like effect of erythromycin, an allergic reaction, or infection with microorganisms other than Clostridium difficile, including Clostridium perfringens type A, Staphylococcus aureus, and Salmonella enterica.

AAD complicates 2% to 5% of antibiotic treatment courses, but the incidence varies depending on the antibiotic used; it is more common, for example, during therapy with ampicillin (5%-10%), amoxicillin-clavulanate (10%-25%), or cefixime (15%-20%).

Because AAD is believed to result from an alteration of the normal colonic microflora, a variety of probiotic agents has been evaluated for its treatment and prevention. In a double-blind controlled clinical trial, oral capsules containing viable Saccharomyces boulardii, a nonpathogenic yeast, were co-administered with antibiotics; this combination treatment reduced the incidence of AAD in hospitalized patients from 22% in the placebo group to 9.5% in the S. boulardii group (P = 0.04).

Lactobacillus species, in particular Lactobacillus rhamnosus GG, also have been studied in clinical trials of AAD. In one study, Lactobacillus GG was effective in reducing the incidence of AAD to 5% in children being treated for respiratory tract infections compared with a 16% incidence in the placebo group.

A meta-analysis examined the results of randomized, double-blind, placebo-controlled trials of probiotic therapy for AAD published between 1966 and 2000. Nine studies were analyzed, including four using S. boulardii and four using Lactobacillus GG. The combined odds ratio for AAD in the probiotic-treated groups was 0.37 compared with placebo (95% confidence interval [CI]: 0.26-0.53; P < 0.001). For S. boulardii, the odds ratio in favor of active treatment over placebo was 0.39 (95% CI: 0.25-0.62, P < 0.001) and for lactobacilli the odds ratio was 0.34 (95% CI: 0.19-0.61, P < 0.01). A second meta-analysis yielded similar results.

AAD occurs anytime after the onset antibiotic treatment and within 2 months after the cessation of therapy. In patients who develop diarrhea with C. difficile, symptoms usually begin soon after colonization. The incubation period is usually less than a week, with a median time of onset of approximately two days.

Helicobacter pylori, a common pathogen infecting many people worldwide causes chronic gastritis and is strongly associated with increased risk for peptic ulcer and gastric cancer.

It is commonplace to screen gastritis patients, even the ones with mild symptoms for H Pylori infection and to treat them actively. Owing to higher eradication rates of 70%-85%, the eradication first line regime usually consists of PPI, clarithromycin 500 mg and amoxicillin 1000 mg each administered twice daily for 10-14 days.

In a study by Duman DG et al, coadministration of S. boulardi reduced the AAD from 15.6% in the control group to 6.9% in the probiotic group.(p=0.09)

In another study by Cidoruk M et al, administration of S. boulardi resulted in reduction of AAD from 30.6% in the placebo group to 14.5% in the treatment with S. boulardi group.

That’s why we decided to undertake a study to see the differences in AAD in patients undergoing a 14 days H Pylori eradication treatment with and without a probiotic containing S. boulardi& Lactobacillus.

METHOD

This study was conducted amongst the patients attending the OPD of Gastroenterology department,
Bir Hospital from June 2012 to September 2013.

This was a hospital OPD based prospective, comparative, efficacy study with the primary purpose of treatment.

A total of 40 patients taking 14 days’ triple therapy comprising of Amoxycillin 1000 mg, Clarithromycin 500 mg, and Pantoprazole 40 mg, all administered twice daily for 14 days were randomly assigned into the treatment and the control group.

All patients receiving the H Pylori eradication therapy were given the treatment on the basis of evidence of H pylori infection, either endoscopy and tissue biopsy or clinical features and positive serology for H Pylori. Patients above the age of 16 years without Human Immunodeficiency Virus infection were included in the study. Patients less than 16 yrs of age and with Human Immunodeficiency Virus infection were excluded from the study.

In the treatment group, patients in addition to the 14 days’ triple therapy as mentioned, also received 2 Probiotic capsule twice daily for 14 days. Each probiotic capsule contained not less than 2.5 billion cells of Saccharomyces boulardii, Lactobacillus and Bifidobacterium longum.

In the control group, patients took the 14 days’ triple therapy only.

There were 20 patients in each group. Patients in both groups were observed for the occurrence of diarrhea within 14 days of treatment.

Diarrhea was defined by the occurrence of three or more than three loose stools per day. Stool volume wasn’t included as a measure to define diarrhea.

Test applied to analyze the observations were independent t test and Fisher’s exact test.

RESULT

| Table 1. Age and Sex distribution of patients in percentage: |
|---------------------------------|-----------|-----------|-----------|
| Age                             | Treatment | Control   | Total     |
| 20-29                           | 30        | 20        | 25        |
| 30-39                           | 15        | 25        | 20        |
| 40-49                           | 30        | 20        | 25        |
| 50-59                           | 5         | 15        | 10        |

>=60 20 20 20
Gender
Male 65 55 60
Female 35 45 40
Total 20 20 40

Mean age in treatment group was 41.9 with SD of 14.7 whereas the mean age in control group was 43.7 with SD of 14.7 (p=.709).

Day of onset of diarrhea was day 6 in treatment group whereas 2 cases in control group developed diarrhea on 3rd day and one each on 2nd, 4th and 5th day. Mean days of developing diarrhea was 3.4 ±1.1 days.

DISCUSSION

The results of this study reveal that one out of 20 patients (5%) in the treatment group receiving the probiotic mixture containing S. boulardii & Lactobacillus developed diarrhea. In the control group, 5 out of 20 patients (25%) not receiving the probiotic mixture developed diarrhea. There was substantially lower incidence of occurrence of diarrhea in the treatment group.

In the treatment group, the only patient developing diarrhea developed diarrhea on the 6th day. In the control group, all 5 patients developed diarrhea within 7 days, the mean period of developing diarrhea was 3.4±1.1 days.

Our result of lower incidence of diarrhea in the treatment group is in line with many observations by researchers elsewhere. The weight of published evidence suggests that probiotic agents such as S.
boulardii and Lactobacillus, when used in combination with antibiotics, reduce the risk for antibiotic associated diarrhea.\textsuperscript{20}

In the “Meta-analysis: probiotics in antibiotic-associated diarrhea” by EJ Videocket al,\textsuperscript{21} a total of 34 studies were included with 4138 patients. The pooled RR for antibiotic associated diarrhea during treatment for Helicobacter pylori (H. pylori) was 0.37 (95% CI 0.20–0.69), corresponding to a NNT of 5 (95% CI 4–10). They conclude in the meta-analysis, the preventive effect of probiotic supplementation on the incidence of AAD to be relatively consistent across different probiotic species used, various antibiotic regimens and indications, including H. pylori eradication, and in adult and pediatric populations.

Cremonini et al\textsuperscript{22} did a parallel group, triple blind, placebo-controlled study each group containing 42 patients and they tried to see the individual efficacies of Lactobacillus, S. boulardii and a combination probiotic containing bifidobacteria in preventing AAD in patients undergoing H pylori eradication therapy. When each group in the study was analyzed separately, it was found that in each group, the probiotic used had a protective effect in preventing AAD.

Cindoruk M, Erkan G et al\textsuperscript{19} in their study included 124 patients with H. Pylori infection and taking 14 days’ triple therapy (Amoxycillin, Clarithromycin and Lansoprazole) for its eradication (male:female=44:80, mean age 48±14.25 yrs). The patients were randomly assigned into two groups, with 62 patients in each group. The treatment group received S. boulardii and the placebo group received placebo. 9 out of 62 (14.5%) in the treatment group developed diarrhea, whereas 19 out of 62 (30.6%) in the placebo group developed diarrhea. (p<0.05) They concluded in the study that S. boulardii improved antibiotherapy associated diarrhea. The median age of patients in this study and the result is comparable with the study that we have conducted.

Duman DG, Bor S et al\textsuperscript{18} included 376 patients who completed the study in another similar study as conducted by us. They randomly assigned these patients taking 14 days’ triple therapy (amoxicillin, Clarithromycin& Omeprazole) to either receive S. boulardii (Treatment group) or no treatment (control group). Their primary outcome measure was the development of diarrhea during treatment period or within 4 weeks of treatment (follow up period). Occurrence of diarrhea was observed in 5.9% of patients in the treatment group and 11.5% of patients in the control group. (p=0.049) This result of lower incidence of diarrhea in the probiotic group is similar to what is observed in our study.

deVrese M\textsuperscript{23} reports that administration of fermented milk also containing Lactobacillus for 4 weeks before and during a H Pylori eradication therapy led to significantly fewer episodes of diarrhea compared with placebo group (7% vs 22%).

Most of the studies cited have revealed lower incidence of diarrhea in the probiotic group with statistically significant values. Our study too reveals lower incidence of diarrhea in the probiotic group, but with insignificant p value. The insignificant p value in our study maybe because of the smaller patient numbers in our study.

AAD is defined as a diarrhea which occurs at anytime between the initiation of the therapy and up to 2 months after the cessation of treatment.\textsuperscript{5, 11,12} However in this study we observed the patients only for the 14 days period that they were on antibiotic therapy for the development of diarrhea. If we had observed the patients for 2 months more, perhaps the incidences of diarrhea would have slightly increased in both the treatment and the control groups.

All our study patients were screened for HIV status, and administered the probiotic mixture, also containing S. boulardii after ensuring that they were HIV negative because S. boulardii should not be administered to immunocompromised patients because of the risk of fungemia.\textsuperscript{20}

CONCLUSION

A probiotic mixture containing S. boulardii& lactobacillus is effective in preventing Antibiotic Associated Diarrhea in patients receiving triple therapy for Helicobacter Pylori eradication.

REFERENCES


