Original Article

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Prophylactic Use of Probiotic (Infloran®) to Prevent Antibiotic Associated Diarrhea in Medical Ward Patients at Rajavithi Hospital

Iamharit J
Harnsomburana P

ABSTRACT

Background: Antibiotic associated diarrhea and Clostridium difficile associated diarrhea are complications of treatment with antimicrobial agents and occur in about 5-25% of patients. Several studies conducted in Western countries have supported the benefits of probiotics for the prevention and treatment of antibiotic associated diarrhea.

Aims: To evaluate the efficacy and safety of probiotic (Infloran®) for the prevention of antibiotic associated diarrhea and *C. difficile* associated diarrhea in adult patients.

Methods: A randomized, double-blind, placebo-controlled study was conducted in 50 patients admitted to the Internal Medicine Ward, Rajavithi Hospital, Bangkok. Patients were randomized to receive either 1 capsule of Infloran® or an identical-looking placebo three times daily for 14 days, and were followed up for one month to observe the occurrence of antibiotic associated diarrhea and *C. difficile* associated diarrhea.

Results: Three out of twenty-six patients (11.5%) in the Infloran® group developed antibiotic associated diarrhea, compared with none in the placebo group ($p = 0.246$). One diarrhea patient was shown to harbour *C. difficile* toxin. The most common side effects were bloating and abdominal distension which occurred developed in the Infloran® group more often than in the placebo group, but without a significant difference ($p = 0.369$).

Conclusion: In this study, Infloran® at the dosage of 1 capsule three times daily for 14 days did not prevent antibiotic associated diarrhea and *C. difficile* associated diarrhea. The most common side effects of Infloran® were bloating and abdominal distension.

Key words : probiotic, antibiotic associated diarrhea, Infloran

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INTRODUCTION

Antibiotic associated diarrhea and *Clostridium difficile (C.difficile)* associated diarrhea are complications of treatment with antimicrobial agents, occurring in about 5-25% of patients[1-3] and depending on the given antibiotic. *C. difficile* is responsible for around 15-25% of all cases of antibiotic associated diarrhea, mostly occurring in older patients two to three weeks after cessation of antibiotic treatment[4].

Several studies in Western countries have supported the benefit of probiotics, especially the *Lactobacilli* species and *Bifidobacteria* species, for the pre-

Division of Digestive and Liver Disease, Department of Medicine, Rajavithi Hospital, Bangkok, Thailand.
Address for Correspondence: *Piyatida Harnsomburana, M.D., Division of Digestive and Liver Disease, Department of Medicine, Rajavithi Hospital, Bangkok 10400, Thailand.*

vention and treatment of antibiotic associated diarrhea. Probiotic have been used safely both in children and adults[5-13]. However, data in Thailand relating to the appropriate species, duration and dose effectiveness of probiotics for preventing antibiotic associated diarrhea in adult patients are lacking.

Infloran® comprises lyophilized live *Lactobacillus acidophilus* 1×10^9 colony forming unit plus *Bifidobacterium bifidum* 1×10^9 colony forming unit per capsule. Many studies have confirmed the efficacy and safety of Infloran® for the prevention of antibiotic associated diarrhea in children and neonates[12,16]. We decided to investigate whether Infloran® is as satisfactory in adults as is the case in children.

A randomized double-blind, placebo-controlled study of Infloran® was conducted in patients at the Internal Medicine Ward who had recently received antibiotics. The outcome of this study was to determine an occurrence of antibiotic associated diarrhea and the occurrence of *C. difficile* associated diarrhea.

PATIENTS AND METHOD

Study groups

Patients admitted to the Internal Medicine Ward, Rajavithi Hospital, between April 2009 and December 2009 were recruited. Those meeting the criteria below were enrolled in the study. Inclusion criteria were as follow: the patients who willingness to give a written informed consent, age 20-75, ability to ingest oral medicine, and history of a recent oral or/and intravenous antibiotic treatment. Exclusion criteria were as follow: the patients who diarrhea on admission or within 2 the preceding weeks, intestinal disorder bowel pathology possibly causative of the diarrhea, previous history of antibiotic usage within 4 weeks before admission, severe life threatening conditions including cancer and HIV infection, history of potent immunosuppressive drug use, history of bowel surgery, artificial cardiac valve ulcer placement, rheumatic heart disease, infective endocarditis, and regular probiotic treatments before admission.

Study design

The patients were randomized into 2 groups. The first group received Infloran® (lyophilized live *Lactobacillus acidophilus* 1×10^9 colony forming unit plus *Bifidobacterium bifidum* 1×10^9 colony forming unit per capsule). The second group received an identical-looking placebo capsule. All patients took 1 capsule three times a day for 14 days.

The baseline characteristics, the indications for antibiotics treatment, the types and duration of antibiotic use, baseline laboratory values, and the frequency of bowel movements were recorded. Patients were followed up for 1 month to observe diarrhea events.

For patients who developed diarrhea (defined as loose stools ≥ 3 times/days for at least 2 days, or ≥ 5 times/day for a single day), stool examination and stool culture were performed to exclude other causes of diarrhea. Stool test for *C. difficile* toxin (Remel, X/pect® test kit, immunochromatographic test for *C. difficile* toxin A/B) was also carried out.

Statistical analyses

The baseline characteristics are presented as means or medians for continuous variables and as frequencies for categorical variables. They were compared with student's *t*-test and Mann-Whitney U test for continuous variables and χ^2 tests or Fisher's exact test for categorical variables.

The occurrence of antibiotic associated diarrhea and *C. difficile* associated diarrhea, medication side effects and medication compliance were compared between the Infloran and the placebo group using Fisher's exact test. All tests were two-sided and a significance level of $p = 0.05$ was chosen.

RESULTS

From April 2009 to December 2009, 50 patients fulfilling the criteria were enrolled in the study. Patients were randomized into 2 groups, 26 patients (52%) receiving Infloran® and 24 patients (48%) receiving the placebo, as shown in Figure 1.

The demographic data and the disease-related characteristics are shown in Table 1. There were no significant differences in age, sex, BMI and underlying co-morbidities between the two groups. Most patients were over 40 years old (40 patients, 80%). There were more female subjects (29 patients, 58%). Twenty-three patients (46.9%) had normal BMI, and 29 patients (58%) had comorbidities. The most common comorbidity was hypertension (16 patients, 32%).

Baseline laboratory values and the length of hospital stay are shown in Table 2. The length of stay in the Infloran group was longer than that in the placebo group, but there was no statistically significant differ-

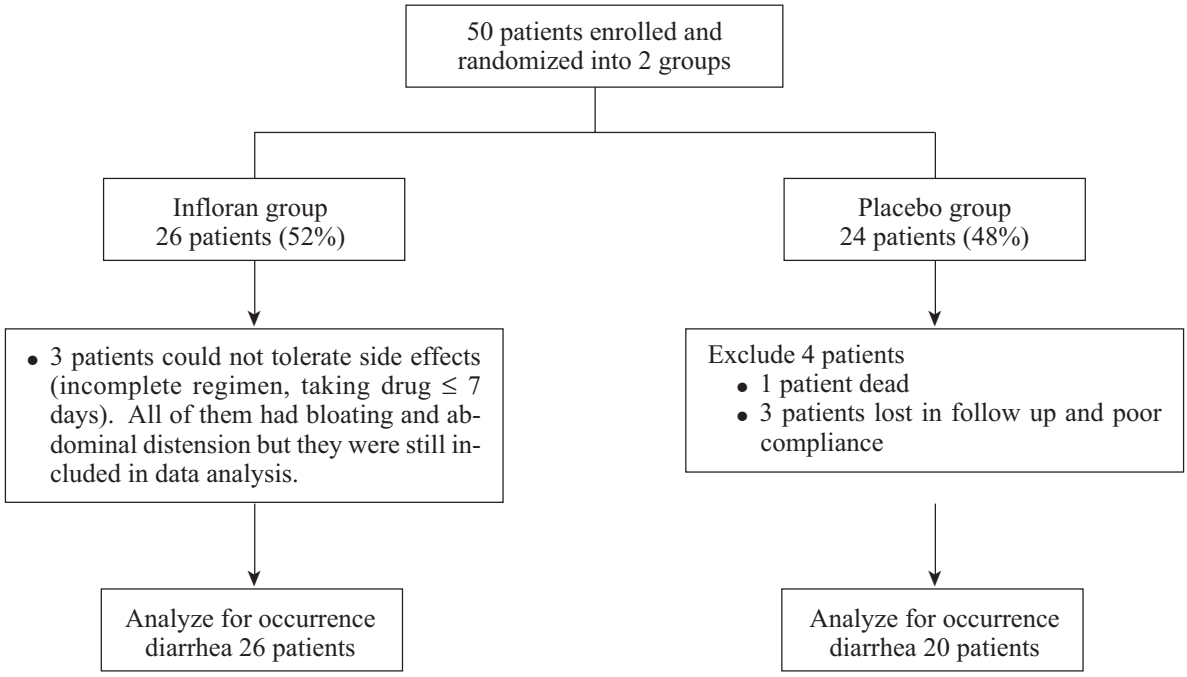

Figure 1.

Table 1. Demographic and disease-related characteristics

	Infloran N (%)	**Placebo N (%)**	**Total N (%)**	***p*-value**
Age (Mean ± SD)	52.3 ± 13.6	52.3 ± 15.16	52.3 ± 14.2	0.987
≤ 40 years	4 (15.4)	6 (25.0)	10 (20.0)	
41-59 years	12 (46.2)	9 (37.5)	21 (42.0)	
≥ 60 years	10 (38.5)	9 (37.5)	19 (38.0)	
Sex				0.536
Male	12 (46.2)	9 (37.5)	21 (42.0)	
Female	14 (53.8)	15 (62.5)	29 (58.0)	
BMI (kg/m^2) (Mean ± SD)	25.4 ± 13.6	22.7 ± 4.2	23.9 ± 6.0	0.242
<18.5	4 (16.0)	3 (12.5)	75 (14.3)	
18.5-24.9	11 (44.0)	12 (50.0)	23 (46.9)	
≥ 25	10 (40.0)	9 (37.5)	19 (38.8)	
Comorbidities				0.963
Yes	15 (57.7)	14 (53.8)	29 (58.0)	
No	11 (42.3)	10 (41.7)	21 (42.0)	
Diabetes	7 (26.9)	5 (28.0)	12 (24.0)	0.614
Hypertension	9 (34.6)	7 (29.2)	16 (32.0)	0.680
Asthma	0	1 (4.2)	1 (2.0)	0.480
COPD	4 (15.4)	2 (8.3)	6 (12.0)	0.669
Cirrhosis	2 (7.7)	2 (8.3)	4 (8.0)	1.000
Ischemic heart disease	4 (15.4)	0	4 (8.0)	0.111
Other	4 (15.4)	5 (20.8)	9 (18.0)	0.446

ence (9.5 vs 5 days, $p = 0.09$).

The indications for antibiotics are shown in Table 3. The most common indications were urinary tract infection (11 patients, 26.2%) and lower respiratory tract infection (9 patients, 21.4%). No significant differences between the two groups were noted.

The types and duration of antibiotic use are shown in Table 4. There were no significant differences between the two groups. The most commonly used antibiotic was ceftriaxone (35 patients, 70%) usually in combination with other antibiotics.

The duration of antibiotic use varied from 3 to 60 days (maximum 60 days in a patient with liver abscess). There was no difference in the median duration between the two groups (11 vs 8.5 days in the Infloran and the placebo group respectively, $p = 0.360$).

The primary and secondary outcome analysis was based on the intention to treat and included all patients with available end point data.

Antibiotic associated diarrhea occurred in 3 patients in the Infloran group, one of whom was positive for stool *C. difficile* toxin assay. There was no difference in statistical significance, as shown in Table 5.

The 3 patients who developed diarrhea received different antibiotics, namely ceftriaxone (1), ciprofloxacin (1) and amoxicillin plus clarithromycin for *H. pylori* eradication (1).

Adverse events and compliance in the two groups

Table 2. Baseline laboratory values and length of stay (LOS)

	Infloran		Placebo		*p*-value
Median LOS (days) (min-max)	9.5	(3-49)	5.0	(1-60)	0.09
Mean hemoglobin (g/dL) (SD)	11.5	(2.3)	10.3	(2.4)	0.98
Mean hematocrit (%) (SD)	34.8	(6.5)	31.3	(7.1)	0.097
WBC (cell/μL) (SD)	10,934.0	(4,176.9)	9,486.4	(3636.6)	0.215
PMN	77.7	(9.0)	76.6	(10.1)	0.649
Lymphocyte	15.3	(6.7)	16.5	(7.6)	0.568
Monocyte	5.1	(2.4)	4.9	(2.8)	0.841
Eosinophil	0.8	(0.0-10.1)	0.4	(0.0-3.3)	0.514
Platelet (cell/μL) (Median) (min-max)	243,500	(109,000-609,000)	280,000	(102,000-428,000)	0.443
BUN (mg/dL) (min-max)	20.0	(5-88)	30	(14-108)	0.139
Creatinine (mg/dL) (min-max)	1.1	(0.5-6.8)	1.4	(0.6-14.9)	0.336
Sodium (mg/dL) (SD)	136.9	(3.3)	136.5	(4.9)	0.754
Potassium (mg/dL) (SD)	3.8	(0.6)	4.2	(0.9)	0.084
Chloride (mg/dL) (SD)	102.7	(5.3)	104.1	(4.0)	0.394
HCO_3 (mg/dL) (SD)	23.1	(4.6)	22.4	(3.7)	0.607

Table 3. Indications for antibiotics

Indications	Infloran (N = 26)	Placebo (N = 24)	Total (N = 50)
Urinary tract infection	7 (26.9%)	5 (20.8%)	12 (24.0%)
Lower respiratory tract infection	6 (23.1%)	6 (25%)	12 (24.0%)
Cellulitis	3 (11.5%)	1 (4.2%)	4 (8.0%)
H. pylori eradication	2 (7.7%)	4 (16.7%)	6 (12.0%)
Other*	6 (23.1%)	7 (29.2%)	13 (26.0%)

$p = 0.869$

* latent syphilis (1), liver abscess (1), SBP (1), sinusitis (1), prophylaxis case upper GI bleeding in cirrhosis (1), post ERCP (1), acute cholangitis (2), acute febrile illness and uncertian indication (5)

Table 4. Types and duration of antibiotic treatment

	Infloran (N = 26)	Placebo (N = 24)	Total (N = 50)	*p*-value
No. of ATB				0.982
single	12 (46.2%)	11 (45.8%)	23 (46.0%)	
multiple	14 (53.8%)	13 (54.2%)	27 (54.0%)	
Median duration (days) (min-max)	11 (3-60)	8.5 (3-21)	-	0.360
Type of ATB				
Ceftriaxone	20 (76.9%)	15 (62.5%)	35 (70.0%)	0.266
Clarithromycin	9 (34.6%)	9 (37.5%)	18 (36.0%)	0.832
Ciprofloxacin	4 (15.4%)	5 (20.8%)	9 (18.0%)	0.721
Amoxicillin	2 (7.7%)	4 (16.7%)	6 (12.0%)	0.409
Cefdinir	2 (7.7%)	2 (8.3%)	4 (8.0%)	1.000

Other type of antibiotic: ceftazidime (3), clindamycin (3), sulperazon (2), doxycycline (1), metronidazole (1), levofloxacin (1), vancomycin (1), penicillin G (1)

Table 5. Cases of antibiotic associated diarrhea (including cases positive for *C. difficile*) and proportion of patients positive or negative for *C. difficile* toxin

	Infloran (N = 26)	Placebo (N = 24)	Total (N = 50)	*p*-value
Diarrhea				0.246
Yes	3 (11.5%)	0 (0%)	3 (6.5%)	
No	23 (88.5%)	20 (100%)	43 (43.5%)	
C. difficile toxin				1.000
Yes	1 (3.8%)	0 (0%)	1 (2.2%)	
No	25 (96.2%)	20 (100%)	45 (97.8%)	

Table 6. Side effects and compliance

	Infloran (N = 26)	Placebo (N = 24)	Total (N = 50)	*p*-value
Side effects				0.369
Yes	4 (15.4%)	1 (5.0%)	5 (10.9%)	
No	22 (84.6%)	19 (95.0%)	41 (89.1%)	
Compliance				1.000
Yes	23 (88.5%)	20 (87.3%)	43 (86.0%)	
No	3 (11.5%)	3 (13.0%)	6 (12.2%)	

are shown in Table 6. Patients in the Infloran group were more prone to side effects than in the placebo group, but there was no statistical difference. The most common side effects noted in 5 patients were bloating and abdominal distension. Three patients in the Infloran group in tolerate side effects, withdrew from the study because while one patient in the placebo group and another in the Infloran group had only mild symptoms and went on to complete the study.

One epileptic patient in the placebo group who was admitted with pneumonia developed seizures at day 3 and died after intubation from ventricular tachycardia and cardiac arrest.

DISCUSSION

The occurrence of antibiotic associated diarrhea in Western studies was about 5-25%[1-3], of which 15-25% being *C. difficile* associated.[4]. Probiotics, including Infloran®, have been used in the prevention

and treatment of antibiotic associated diarrhea and *C. difficile* associated diarrhea. Infloran® has also been shown to be useful in the prevention for antibiotic associated diarrhea in neonates and children aged 1-36 months[12].

A previous study conducted at Rajavithi Hospital noted the occurrence rates of antibiotic associated diarrhea and *C. difficile* associated diarrhea at about 6.5% and 2.17% respectively. In the present study, Infloran® did not appear is not efficacious in preventing diarrhea in adult patients. Three patients in the Infloran® group developed antibiotic associated diarrhea, one of whom with a positive stool *C. difficile* toxin assay, while none in the placebo group had diarrhea. There was no significant difference statistically, however, probably due to the small sample size and a bigger number of patients in the placebo group being lost to follow. A larger randomized controlled trial is required to assess the effectiveness of Infloran® in adults more accurately.

The most common side effects of Infloran® in this study were bloating and abdominal distension, which were not serious and disappeared after medication withdrawal.

CONCLUSION

In this study, Infloran® 1 capsule three times daily for 14 days did not prevent antibiotic associated diarrhea and *C. difficile* associated diarrhea. The most common side effects of Infloran® were bloating and abdominal distension.

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