Effect of Probiotic Lactobacillus (Lacidofil® Cap) for the Prevention of Antibiotic-associated Diarrhea: A Prospective, Randomized, Double-blind, Multicenter Study

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INTRODUCTION

Antibiotic-associated diarrhea (AAD) is a common complication of antibiotic use. There is growing interest in probiotics for the treatment of AAD and Clostridium difficile infection because of the wide availability of probiotics. The aim of this multicenter, randomized, placebo-controlled, double-blind trial was to assess the efficacy of probiotic Lactobacillus (Lacidofil® cap) for the prevention of AAD in adults. From September 2008 to November 2009, a total of 214 patients with respiratory tract infection who had begun receiving antibiotics were randomized to receive Lactobacillus (Lacidofil® cap) or placebo for 14 days. Patients recorded bowel frequency and stool consistency daily for 14 days. The primary outcome was the proportion of patients who developed AAD within 14 days of enrollment. AAD developed in 4 (3.9%) of 103 patients in the Lactobacillus group and in 8 (7.2%) of 111 patients in the placebo group (P=0.44). However, the Lactobacillus group showed lower change in bowel frequency and consistency (50/103, 48.5%) than the placebo group (35/111, 31.5%) (P=0.01). Although the Lacidofil® cap does not reduce the rate of occurrence of AAD in adult patients with respiratory tract infection who have taken antibiotics, the Lactobacillus group maintains their bowel habits to a greater extent than the placebo group.

Key Words: Probiotics; Lactobacillus; Antibiotic-associated Diarrhea
gut microflora is to protect against colonization by intestinal pathogens (4). Once this protective barrier is broken, patients are more susceptible to infection with opportunistic pathogens. Probiotics have been proposed to treat AAD and *Clostridium difficile* disease. Probiotics mainly assist in re-establishing the disrupted intestinal microflora, enhancing immune responses and clearing pathogens and their toxins from the host (5-7).

There is growing interest in probiotics for the treatment of AAD and *C. difficile* disease because of the wide availability of probiotics as dietary supplements and concern over recent outbreaks of severe *C. difficile* disease in Canada and the United Kingdom (8, 9). Research on probiotics has been reported for the past 28 yr (1977-2005), but the studies have been variable in trial design, type of probiotic and dosage and duration of treatment, and thus have often yielded contradictory results (10).

Twenty-five randomized, controlled trials (RCTs) provided adequate data regarding the efficacy of probiotics for the prevention of AAD (10). Of the 25 RCTs, only 6 utilized *Lactobacillus rhamnosus* (11-16).

There were a few RCTs that proved the efficacy of *Lactobacillus* in preventing AAD, and debate arose regarding the study populations. A study on the use of *L. rhamnosus* (2×10^10^ colony-forming units per day) for preventing AAD in 302 adults receiving antibiotics at the Mayo Clinic showed no efficacy of *L. rhamnosus* in decreasing the overall incidence of AAD because quite a few patients had stool cultures, additional tests for diarrhea, or a positive diagnosis of *C. difficile* (15). However, 89 patients in a recent RCT on the daily administration of a *Lactobacillus*-fermented milk product showed that it was safe and effective in the prevention of AAD (17). A recent RCT involving 135 patients demonstrated that a probiotic *Lactobacillus* preparation prevented AAD and *C. difficile*-associated diarrhea (18).

Therefore, we conducted a multicenter, randomized, placebo-controlled, double-blind trial to assess the efficacy of probiotic *Lactobacillus* (Lacidofil® cap) for the prevention of AAD in Korean adults.

**MATERIALS AND METHODS**

**Participants**

Adult patients receiving antibiotic therapy for respiratory tract infection were screened at 10 tertiary hospitals. The inclusion criteria were adult inpatients aged >18 yr who received oral or injected antibiotics for respiratory tract infections within 48 hr of enrollment. The following patients were excluded from the study: 1) those who were diagnosed with *C. difficile* colitis within the previous 3 months, 2) those who were given tube feeding or who underwent an ileostomy or colostomy, 3) those with basal diarrheal disease (acute enteritis, inflammatory bowel disease, radiation enteritis, ischemic colitis and diarrhea caused by carcinoid), 4) those receiving other probiotics during the previous 15 days, 5) those treated with immunosuppressant drugs and those with immune deficiency, 6) those who underwent radiotherapy or chemotherapy treatment for cancer, 7) those treated with anti-diarrheal, antispasmodic or motility agents for other diseases, 8) pregnant or lactating women, 9) those who underwent gastrointestinal surgery 3 months prior to the study, 10) those with a history of hypersensitivity to cephalosporins, penicillin or clavulanic acid, 11) those with verified diabetic autonomic neuropathy, 12) those who underwent organ transplantations, and 13) those with underlying conditions or diseases who, in the opinion of the investigator, were unsuitable for inclusion.

**Study design**

Between September 2008 and November 2009, a total of 214 patients with respiratory tract infection who had begun to receive antibiotics were randomly allocated to receive *Lactobacillus* (Lacidofil® cap) or a placebo for 14 days. This study was conducted at 10 investigational centers. Participants recorded their bowel frequency and stool consistency every day for 14 days. The primary outcome (AAD-1) was defined as loose or watery stools more than 3 times per day for at least 2 days within 14 days of enrollment. The secondary outcome (AAD-2) was defined as loose or watery stools more than 2 times per day for at least 2 days within 14 days of enrollment.

The admitting medical team identified eligible patients who had an antibiotic prescription for the treatment of respiratory tract infection. After the investigators obtained informed consent, they collected baseline data and prescribed the study drug on a randomized basis. The hospital pharmacy dispensed the drug. The treatment group received a probiotic preparation (Lacidofil® cap) containing *L. rhamnosus* R0011-1 *L. acidophilus* R0052 bacterial culture (2×10^10^ colony-forming units), maltodextrin, Mg stearate, and ascorbic acid. The control group received a placebo drug composed of maltodextrin, Mg stearate and ascorbic acid. Participants began using the Lacidofil® cap or placebo drug within 48 hr of initiation of antibiotic therapy. The Lacidofil® cap and placebo were administrated at a dose of 1 capsule twice a day for 14 days. The administration of other drugs for accompanying diseases permitted subject to the investigator’s judgment. The use of antidiarrheal (e.g., loperamide, polypcarbophil), antispasmodic (e.g., tiopramide, pinaeverum, buscopan) or motility agents (e.g., domperidone, mosapride, itopride, levosulpiride) that could affect the symptoms was prohibited. These drugs were withhold until the patient developed AAD, after which their use was allowed.

Investigators followed up participants for 14 days to check stool frequency, stool consistency and compliance. If participants had AAD, investigators collected further data on clinical symptoms and blood test results. As the safety of Lacidofil® cap has already been proven, its safety was not evaluated in this study.
Sample size
We estimated that the minimum sample size was 220 for each group. The sample size was calculated on the basis of an 18% difference in the proportion of AAD compared with the control group with an expected compliance rate of 80%, a statistical power (two sided) of 90%, a significance level of 5% and a dropout rate of 10%.

Randomization and double blinding
Among patients with respiratory tract infection, those who met the inclusion criteria were selected and allocated trial numbers. The subjects were allocated to the treatment (Lacidofil® cap treatment) or control groups (placebo) according to their trial numbers. To maintain double-blinding, the envelope containing the random trial number allocation code was sealed by the investigators, and the treatment allocations were not disclosed until the clinical trial was completed, except for cases for which access to the code was necessary. All investigators, participants, outcome assessors and data analysts were blinded throughout the study.

Statistical analysis
SPSS for Windows software (V. 13.0, SPSS, Chicago, IL, USA) was used for statistical analysis. The chi-square test was used to determine the difference in the incidence of AAD between the 2 groups, and the Student's t-test was used for analysis of continuous variables. Multiple logistic regression analysis was used to identify the risk factors for AAD, and effect estimates are presented as the odds ratio (OR) and 95% confidence interval (CI).

RESULTS

Participant flow and baseline characteristics of participants
Patient flow is summarized in Fig. 1. Over the 14-month study period, 286 patients were screened as potential candidates for this study by nurses. Of the 286 patients screened, 18 met 1 or more of the exclusion criteria, 28 did not meet all of the inclusion criteria, and 26 refused to participate in the study. Of the 214 patients who met the inclusion criteria and agreed to participate in the study, 42 failed to complete the study. Finally, 172 patients completed the study. Of the 42 patients who failed to complete the study, 5 had adverse events, 12 received contraindicated drugs, 21 did not continue the treatment protocol, and 4 were lost to follow-up. We performed intention-to-treat (ITT) analysis of data from 214 patients and per-protocol (PP) analysis of data from 172 patients.

Baseline characteristics are summarized in Table 1. The placebo (n=111) and the Lactobacillus groups (n=103) were similar in terms of their demographics and medical profiles at enrollment. There were no significant differences in total dose of antibiotics, baseline bowel movement, drug compliance, or pulmonary infections between the 2 groups. Respiratory tract infections, in descending order of frequency, were pneumonia, pulmonary tuberculosis, bronchitis, bronchiectasis, pleural effusion and upper respiratory tract infection.

| Parameters                        | Placebo (n=111) | Lactobacillus (n=103) | P value* |
|-----------------------------------|----------------|-----------------------|----------|
| Sex (male:female)                 | 69:42          | 63:40                 | 0.99     |
| Age (yr)                          | 60±16          | 61±15                 | 0.88     |
| BMI (kg/m²)                       | 22.0±3.3       | 22.4±3.4              | 0.32     |
| No medical illness                | 48 (43.2%)     | 43 (41.8%)            | 0.93     |
| Total antibiotic use (days)       | 12.3±3.4       | 11.7±3.8              | 0.24     |
| Baseline bowel movement (per day) | 1.0±0.5        | 1.1±0.4               | 0.52     |
| Drug compliance                   | 88 (80.0%)     | 83 (86.0%)            | 1.00     |
| Respiratory tract infection       |                |                       |          |
| Pneumonia                         | 79 (71.2%)     | 80 (77.7%)            | 0.35     |
| Pulmonary tuberculosis            | 17 (15.3%)     | 11 (10.7%)            | 0.42     |
| Bronchitis                        | 6 (3.4%)       | 12 (11.7%)            | 0.16     |
| Bronchiectasis                    | 9 (8.1%)       | 4 (3.9%)              | 0.31     |
| Pleural effusion                  | 1 (0.9%)       | 3 (2.9%)              | 0.35     |
| Upper respiratory tract infection | 0 (0.0%)       | 1 (1.0%)              | 0.48     |

*Chi-square or Fisher exact test.
BMI, body mass index.
Antibiotics use for both groups is summarized in Table 2. The antibiotics used were, in descending order, cephalosporin, macrolides, fluoroquinolones, antituberculosis drugs, clindamycin and penicillin. β-lactam antibiotics, including cephalosporins and penicillin, were commonly used in both the placebo and the Lactobacillus groups (75.7% vs 76.8%) (P=0.72). There were no significant differences in antibiotic use between the 2 groups.

### Analysis of outcome measures

In ITT analysis (n=214), AAD-1 developed in 4 (3.9%) of 103 patients in the Lactobacillus group and in 8 (7.2%) of 111 patients in the placebo group (P=0.44). AAD-2 developed in 9 (8.7%) of 103 patients in the Lactobacillus group and in 16 (14.4%) of 111 patients in the placebo group (P=0.28). There was no significant difference in AAD occurrence between the 2 groups. However, no changes in bowel frequency or consistency were reported by 50 (48.5%) of 103 patients in the Lactobacillus group and by 35 (31.5%) of 111 patients in the placebo group (P=0.01). Increased bowel frequency over a period of more than 3 days during the 14-day period was observed in 47 (42.3%) of 111 patients in the placebo group (P=0.07). Lactobacillus group was less likely to experience changes in bowel frequency and consistency compared with the placebo group (OR 0.53, 95% CI 0.27-1.05, P=0.07).

### Risk factors for AAD

The results of ITT analysis (n=214) of risk factors for AAD-1 (n=12) and non-AAD-1 (n=202) are shown in Table 7. AAD-1 was not related to the duration of total antibiotic use.

### Table 2. Antibiotics use in the placebo and the Lactobacillus groups

| Antibiotics in use | Placebo (n=111) | Lactobacillus (n=103) | P value |
|--------------------|-----------------|-----------------------|---------|
| Cephalosporins     | 83 (74.8%)      | 80 (77.7%)            | 0.73    |
| Macrolides         | 47 (42.3%)      | 47 (45.6%)            | 0.72    |
| Fluoroquinolones   | 38 (34.2%)      | 40 (38.8%)            | 0.57    |
| Antituberculosis drugs | 18 (16.2%)     | 11 (10.7%)            | 0.32    |
| Clindamycin        | 10 (9.0%)       | 8 (7.8%)              | 0.93    |
| Penicillin         | 6 (5.4%)        | 5 (4.9%)              | 1.00    |
| Aminoglycosides    | 6 (5.4%)        | 4 (3.7%)              | 0.74    |
| Metronidazole      | 4 (3.6%)        | 3 (2.9%)              | 1.00    |
| Sulfamethoxazole/trimethoprim | 1 (0.9%) | 3 (2.9%)              | 0.35    |
| Glycopeptides      | 1 (0.9%)        | 0 (0.0%)              | 1.00    |
| β-lactam antibiotics* | 84 (75.7%)  | 81 (78.6%)            | 0.72    |

*Cephalosporins plus penicillin.

### Table 3. Comparison of AAD between the placebo and the Lactobacillus groups (ITT analysis, n=214)

| Outcomes                             | Placebo (n=111) | Lactobacillus (n=103) | P value |
|--------------------------------------|-----------------|-----------------------|---------|
| AAD-1 (primary outcome), n=12        | 8 (7.2%)        | 4 (3.9%)              | 0.44    |
| AAD-2 (secondary outcome), n=25      | 16 (14.4%)      | 9 (8.7%)              | 0.28    |
| No change in bowel frequency         | 35 (31.5%)      | 50 (48.5%)            | 0.01    |
| and consistency                      |                 |                       |         |
| Increased bowel frequency more than 3 days during the 14-day period | 47 (42.3%) | 31 (30.1%) | 0.08 |

### Table 4. Odds ratio of Lactobacillus (ITT analysis, n=214)

| Outcomes                             | Odds ratio* (CI) | P value |
|--------------------------------------|------------------|---------|
| AAD-1 (primary outcome), n=12        | 0.64 (0.14-2.92) | 0.56    |
| AAD-2 (secondary outcome), n=25      | 1.02 (0.35-2.96) | 0.96    |
| No change in bowel frequency         |                  |         |
| and consistency                      |                  |         |
| Increased bowel frequency more than 3 days during the 14-day period | 0.75 (0.39-1.45) | 0.39    |

*Logistic analysis: adjusted for age, baseline bowel movement, medical illness, duration of total antibiotic use, and reintroducing drugs.

### Table 5. Comparison of AAD between the placebo and the Lactobacillus groups (PP analysis, n=172)

| Outcomes                             | Placebo (n=89) | Lactobacillus (n=83) | P value |
|--------------------------------------|-----------------|-----------------------|---------|
| AAD-1 (primary outcome), n=8         | 5 (5.6%)        | 3 (3.6%)              | 0.72    |
| AAD-2 (secondary outcome), n=17      | 9 (10.1%)       | 8 (9.6%)              | 1.00    |
| No change in bowel frequency         |                  |                       |         |
| and consistency                      |                  |                       |         |
| Increased bowel frequency more than 3 days during the 14-day period | 38 (42.7%) | 28 (33.7%) | 0.29 |

*Logistic analysis: adjusted for age, baseline bowel movement, medical illness, duration of total antibiotic use, and reintroducing drugs.

### Table 6. Odds ratio of Lactobacillus (PP analysis, n=172)

| Outcomes                             | Odds ratio* (CI) | P value |
|--------------------------------------|------------------|---------|
| AAD-1 (primary outcome), n=12        | 0.64 (0.14-2.92) | 0.56    |
| AAD-2 (secondary outcome), n=25      | 1.02 (0.35-2.96) | 0.96    |
| No change in bowel frequency         |                  |         |
| and consistency                      |                  |         |
| Increased bowel frequency more than 3 days during the 14-day period | 0.75 (0.39-1.45) | 0.39    |

*Logistic analysis: adjusted for age, baseline bowel movement, medical illness, duration of total antibiotic use.

CI, confidence interval.
more prevalent in patients with no medical illness (75.0% vs 40.6%) \((P=0.04)\) and those with a longer duration of antibiotic use \((13.8±2.0\text{ vs } 11.9±3.6\text{ days})\ \(P=0.01)\). There was also a tendency for AAD-1 patients to have greater baseline bowel movement \((1.3±0.6\text{ vs } 1.0±0.4\text{ per day})\ \(P=0.06)\), remnant drugs \((9.2±8.8\text{ vs } 3.7±7.7\text{ capsules})\ \(P=0.07)\), or to use β-lactam antibiotics \((92.0\%\text{ vs } 75.1\%)\ \(P=0.02)\). In addition, patients with AAD-2 had a tendency to have an increased baseline bowel movement \((1.3±0.5\text{ vs } 1.0±0.4\text{ per day})\ \(P=0.06)\).

**Adverse events**

Mild abdominal discomfort was reported by 1 patient \((0.9\%)\) in the placebo group and by 3 patients \((2.9\%)\) in the *Lactobacillus* group \((P=0.35)\). Skin eruption was reported by 1 patient \((0.97\%)\) in the *Lactobacillus* group. However, there were no significant adverse events associated with the use of Lacidofil® cap.

**DISCUSSION**

This study evaluated the efficacy of a *Lactobacillus* probiotic single-agent regimen for AAD. In our study, the number of AAD cases was not statistically different between the 2 groups and the prevalence of AAD was low \((3.9\%\text{- }7.2\%)\) compared with a previous report \((2-25\%)\) as assessed by ITT analysis \((2)\). This result may be attributed to the short-term follow-up period because AAD may occur up to 2 months after stopping antibiotic treatment \((1)\). Recent meta-analysis of 10 randomized, blinded, placebo-controlled trials showed that the combined risk ratio (RR)
of developing AAD was significantly lower in the Lactobacillus groups than in the placebo group (RR 0.35, 95% CI 0.19-0.67) (19). Large differences exist among trials, including our study. The indications for antibiotic therapy differed among the studies and included respiratory tract infection, otitis media, urinary tract infection and Helicobacter pylori infection (19).

According to a previous report, doses used in Lactobacillus regimens range from $2 \times 10^8$ to $4 \times 10^{10}$ colony-forming units per day (19). There was considerable variation in the probiotic regimens used. It has been suggested that doses of probiotics should exceed $10^{10}$ colony-forming units per day (10). In our study, the dose of the Lactobacillus regimen was $4 \times 10^9$ colony-forming units. This may be the reason why the Lactobacillus group preparation did not exhibit a protective effect for AAD. Thus, it is expected that if the doses had been greater ($>10^{10}$ colony-forming units per day), it may have had a preventive effect on AAD. The effects of increasing dosages of probiotics should be monitored, irrespective of whether adverse events are expected. Further evaluations using standardized Lactobacillus dosage forms and regimens are warranted.

AAD was defined as loose or watery stools more than 3 times per day for at least 2 days. This stringent definition enabled us to differentiate between clinically relevant and clinically unimportant changes in the consistency of stools. The secondary outcome, AAD-2, was defined as loose or watery stools more than 2 times per day for at least 2 days. However, definitions of AAD vary between published studies. For example, Vanderhoof et al. defined diarrhea as ≥2 liquid stools per 24 hr on ≥2 days (13). Bowl frequency and consistency reflects bowel habits. Tables 3 and 4 showed that there were significant differences in bowel frequency and consistency. These results suggest that maintenance of usual bowel habit was promoted by the probiotic. This result is consistent with that of a previous trial (20) performed on children. Although the overall incidence of diarrhea was surprisingly low and the administration of a combination of Bifidobacterium longum PL03, L. rhamnosus KL53A, and L. plantarum PL02 did not significantly alter the incidence of diarrhea, it reduced the daily frequency of stools (20).

In our study, ITT (n=214) analysis gave better results than PP (n=172) analysis. Forty-two patients did not complete the study. Thus, the number of patients enrolled was less than that required to achieve the target statistical power for the PP analysis. Studies involving larger numbers of patients are necessary. Regarding risk factors, patients who had elevated baseline bowel movements, more remnant drugs, and greater use of β-lactam antibiotics had higher incidences of AAD-1 and AAD-2. These results show that patients with elevated bowel movement and low drug compliance had a higher incidence of AAD. However, increased bowel movements may have affected the underlying risk for development of AAD or their response to the probiotic. Thus, for analysis of the OR of Lactobacillus (Tables 4, 6), we adjusted the data for baseline bowel movement and other confounding factors (age, medical illness, duration of total antibiotic use, and remnant drugs). β-lactam antibiotics, including penicillin and cephalosporins, are proven risk factors for AAD (1). In addition, AAD was more prevalent in subjects who were young, had no medical illness and had used antibiotics for a long period. Our result is not in accord with that of a previous report (1). The reason for this may be selection bias in our study.

L. rhamnosus has inhibitory activity against a wide range of bacteria, including C. difficile (21). In addition, L. rhamnosus is expected to be useful for the prevention of AAD because it survives the digestive process and is not killed by the acidic pH of the stomach or by bile (22). When administered exogenously, L. rhamnosus persists in the colon for at least a week and modifies the colonic environment with potential positive health effects (23, 24). There are 3 reports showing L. rhamnosus prevents AAD in children (12-14). For adults, 2 reports have been published concerning the synergistic effect of L. rhamnosus with anti-H. pylori eradication therapy (11, 16). The rationale for the use of probiotics is that the use of antibiotics may result in a disturbance of the normal intestinal microflora, which is one of the key factors in the pathogenesis of AAD and C. difficile infection (25).

There are several possible mechanisms by which probiotics, including Lactobacillus, exert preventative effects on AAD. These include the synthesis of antimicrobial substances (17, 22, 26), competition for nutrients required for the growth of pathogens, competitive inhibition of adhesion of pathogens, and modification of toxins or toxin receptors (27).

Concerns about the safety of probiotics have been raised because probiotics are living organisms that, when given to ill patients, could elicit adverse reactions. As some intestinal bacteria have been shown to migrate from the intestine to other organs, antibiotic-resistant gene acquisition is also a potential concern (10). Although bacteremia and fungemia have been reported in the literatures (28, 29), our study showed only mild abdominal discomfort in 1 patient and skin eruption in 3 patients without any significant adverse events. Caution should be exercised for patients who are severely ill and are receiving nutrition or antibiotics through a potentially open portal catheter or a nasogastric tube.

Our study had some limitations. First, the incidence of AAD was much lower in our study than in previous studies. Our patients were followed up for only 2 weeks after antibiotic therapy. As AAD can occur up to 2 months after stopping antibiotic treatment (1), some cases might have been missed. Second, the patients were not normally distributed. Some centers recruited more patients than allocated, and others had fewer cases. This imbalance was caused by differences in the hospital size and location, and the incidence of antibiotic-naïve respiratory infections at the hospitals. Third, the difference between hospitals in the main antibiotic prescribed is a potential weakness because
the incidence of AAD differs between groups of antibiotics. However, there was no significant difference in antibiotic use between the 2 groups. Finally, although the required sample size was 220, we performed the study using 214 patients. The most frequent limitation of previous studies may also have been insufficient power to detect significant differences (19). Few investigators have calculated required sample sizes, and 3 investigators reported that slow recruitment of study patients resulted in premature termination of the trial (10, 30). However, our study has value as the first prospective, randomized, double-blind, multicenter study on the effect of probiotic *Lactobacillus* for the prevention of AAD in Korea.

In conclusion, although Lacidofil® cap does not reduce the occurrence of AAD in adult patients with respiratory tract infection who have taken antibiotics, the *Lactobacillus* group maintains their bowel habits to a greater extent than the placebo group without any significant adverse events.

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