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Efficacy of Albis for the Prevention of Gastric Mucosal Injury Concomitant with the Use of Low-Dose Aspirin: A Prospective, Randomized, Placebo-Controlled Study

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Background/Aims: Long-term use of aspirin can be a risk factor of peptic ulcer diseases. The aim of this study was to evaluate the efficacy of Albis (Daewoong Pharmaceutical Co., Ltd.) for the prevention of gastric mucosal injury caused by aspirin.
Methods: Aspirin users were enrolled and randomized into the Albis or placebo group. Screening and follow-up endoscopy were performed for modified Lanza scores (MLSs). Primary outcome was measured by the incidence rate of peptic ulcer, and secondary outcomes were measured by the incidence rate of gastritis, improvement in MLS and subjective symptoms.
Results: In total, 81 aspirin users were randomized, 43 in the Albis group and 38 in the placebo group. There was no incidence of peptic ulcer in both groups. The incidence of gastritis was significantly higher in the placebo group (44.4% vs. 10.0%, p=0.003); however, the scores of mucosal edema, hyperemia and hemorrhage were not statistically different between the two groups (p>0.05). The frequency of subjective symptoms were more improved in the Albis group than in the placebo group (p=0.023).
Conclusions: The incidence of gastritis was lower in the group that received low-dose aspirin and Albis. The development of peptic ulcer due to long-term use of aspirin might be prevented with concomitant use of Albis. **Clin Endosc 2017;50:179-184**

Key Words: Peptic ulcer; Aspirin; Albis; Modified Lanza score

INTRODUCTION

Low-dose acetylsalicylic acid (ASA; aspirin) has been widely used for the prevention of cardio- and cerebrovascular diseases in patients at high risk.[1,2] It is well-known that the risk of upper gastrointestinal (GI) tract complications such as ulcer, bleeding, perforation, or stricture can increase even in patients on low-dose ASA rather than the conventional dose.[3] Proton pump inhibitors (PPIs) are usually recommended for the prevention of GI complications caused by low-dose ASA. However, long-term maintenance with PPIs may also give rise other problems such as treatment cost, compliance, and adverse events such as infection, osteoporosis or interaction with clopidogrel.[4-6]

Albis (Daewoong Pharmaceutical Co. Ltd., Seoul, Korea) contains 150 mg ranitidine, 300 mg sucralfate, and 100 mg bismuth subcitrate. Albis has a gastroprotective effect by inhibition of gastric acid secretion of histamine-2 receptor antagonist (H2RA), mucosa-coating and production of prostaglandin, respectively. It has been demonstrated that H2RAs prevent peptic ulcer in patients taking low-dose ASA, and concomitant administration of sucralfate and bismuth is well-tolerated and beneficial for the improvement of symptoms.[7-9] The effect of peptic ulcer prevention in ASA-users by PPIs, H2RAs, and other mucoprotective agents has been eval-

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uated in many studies. However, it has not yet been demonstrated whether the compounds of H2RA, sucralfate and bismuth could be effective for ulcer prevention during long-term use of ASA.[7,10,11] The aim of this study was to evaluate the effect of peptic ulcer prevention by Albis in patients on long-term low-dose ASA.

MATERIALS AND METHODS

Patients

Patients aged between 20 to 80 years were eligible for enrollment if they were expected to start taking low-dose ASA (100 mg a day), had a modified Lanza score (MLS) of 0 or 1 in screening endoscopy, and had no GI symptoms (Table 1).[12] The exclusion criteria were as follows: (1) presence of peptic ulcer or reflux esophagitis; (2) history of gastrectomy or vagotomy; (3) current ASA user; (4) use of PPI, H2RA, anti-platelets, anti-coagulants, or nonsteroidal anti-inflammatory drugs within 2 weeks of enrollment; (5) comorbidity with serious liver disease, renal disease, or cardiac disease; (6) pregnancy or lactating during the study period. The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of Seoul National University Hospital (IRB No. 1105-100-363). All subjects were provided with written informed consent before enrollment.

Table 1. Modified Lanza Score and Subjective Symptoms

Grade of modified of lanza score	
0	No visible lesion
1	Mucosal hemorrhage only
2	One or two erosions
3	Numerous (3–10) areas of erosions
4	Large numerous (>10) of erosions
5	Ulcer
Edema	
1	None
2	Prominent
Hyperemia	
1	None
2	Mild
3	Moderate
4	Severe
Hemorrhage	
1	None
2	Single lesion
3	2–5 Lesions
4	6–10 Lesions
5	>10 Lesions

Study design

Enrolled patients were randomly allocated to Albis (2 tabs twice a day) or placebo group, and provided with the study medication and 100 mg of ASA a day for 12 weeks. Medications that could affect mucosal healing, such as PPIs, acid pump antagonists, H2RAs, and mucoprotective agents were prohibited during the study period. If a patient had GI symptoms during the study period, a rescue medication (antacid) was allowed up to three times a day at a standard dose.

Primary and secondary outcomes

The primary outcome was measured by the incidence rate of peptic ulcer at 12 weeks of study. Peptic ulcer was defined as a defect more than submucosal layer in the stomach or duodenum with at least 3 mm in diameter measured by follow-up endoscopy.

The secondary outcomes were measured by the incidence rate of gastritis, improvement of MLS, subjective symptoms, and use of rescue medications. The presence of gastritis was defined as a score of 2 to 4 in MLS. The presence of mucosal edema, hyperemia, and hemorrhage was compared between the two groups. The improvement of MLS was compared in terms of the mean between the groups. The presence of subjective symptoms was also compared in terms of frequency and severity of the symptoms between the groups. The use of rescue medication was compared between the groups.

Adverse events were also assessed during study period.

Statistical analysis

Efficacy was analyzed for the full analysis set (FAS), which included all randomized patients who received at least a study medication, with the exception of patients who did not meet the inclusion criteria.

The Kaplan-Meyer method was used for determining the primary outcome, and the log-rank test for the statistical differences. Fisher exact test, Student *t*-test, chi-square test, and Wilcoxon rank-sum test were used to assess the differences after treatment.

The sample size was calculated based on the results of a previous study, and this resulted in a total of 80 subjects (40 in each group) with an alpha error of 0.05, 80% power, and a dropout rate of 20%.[13] All statistical tests were performed 2-sided, and *p*-values less than 0.05 were considered to be significantly different. The data were analyzed using SPSS version 21.0 (IBM Co., Armonk, NY, USA).

RESULTS

Patients characteristics

A total of 81 patients were randomized to either Albis (43 patients) or placebo group (38 patients). One patient in the placebo group refused to receive the medication and was excluded from the study. Overall, 13 patients in the Albis group and 10 patients in the placebo group were excluded because of violation of exclusion criteria or they dropped out of the study. The FAS population comprised 30 patients in the Albis group and 27 patients in the placebo group (Fig. 1).

The mean age was 60.3 in the Albis and 56.7 years in the placebo group. The proportion of males was about 50% in both groups. The score of MLS was 0 for over 92% of patients in both groups, and the score of mucosal edema, hyperemia, and hemorrhage were 1 in over 83% of patients in both groups. The baseline characteristics were not significantly different between the two groups in terms of sex, age, MLS, hyperemia, edema, and hemorrhage of mucosa (Table 2).

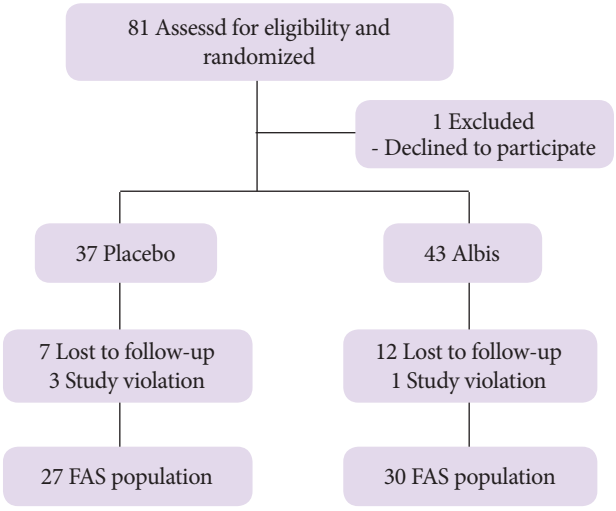

Fig. 1. Flow of the study population. A total of 81 patients were enrolled and randomized to Albis (Daewoong Pharmaceutical Co., Ltd.) or placebo group. Thirty patients in Albis group and 27 patients in placebo group were analyzed in full analysis set (FAS).

Changes in gastric mucosal lesions

During the 12-week study period, no peptic ulcer developed in any patient. The incidence of gastritis, determined by MLS greater than 1, was significantly higher in the placebo group (44.4% vs. 10.0%, p=0.003) (Fig. 2). The mean change of MLS was also significantly higher in the placebo group (p=0.001). However, the mean changes of scores of edema, hyperemia, and hemorrhage of mucosa were not significantly different between the two groups (p>0.05) (Table 3).

Changes in subjective symptoms and adverse events

The mean changes in the frequency and severity of subjective symptoms were 0.07 in the Albis group and 0.67 in the placebo group, and the values were not significantly different between the two groups (p>0.05) (Table 4). The mean use of antacids as a rescue medication was 18.2 in the Albis group and 17.6 in the placebo group, and the values were not significantly different between the two groups (p=0.92). The incidence of drug-related adverse events was 37.2% in the Albis group and 18.9% in the placebo group, and the value was not also significantly different between the two groups (p=0.09). The most common adverse events were GI discomforts such

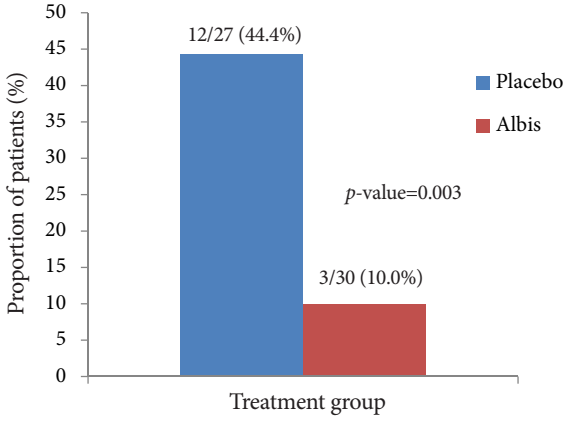

Fig. 2. The incidence of gastric mucosal injury in terms of modified Lanza scores. The incidence of gastric mucosal injury was higher in the placebo group.

Table 2. Baseline Characteristics of Patients

Characteristic	Albis (n=30)	Placebo (n=27)	p-value
Median age, yr	60.3	56.7	0.19
Male sex, %	15 (50.0)	13 (48.2)	0.89
MLS 0, %	29 (96.7)	25 (92.6)	0.60
Edema 1, %	29 (96.7)	25 (92.6)	0.60
Hyperemia 1, %	25 (83.3)	25 (92.6)	0.67
Hemorrhage 1, %	29 (96.7)	26 (96.3)	0.73

Values are presented as number (%).
MLS, modified Lanza score.

Table 3. Changes of MLS and Secondary Outcomes between the Two Groups

Variable	Albis (*n*=30)	Placebo (*n*=27)	*p*-value
Change of MLS	0.17±0.65	1.19±1.39	0.001
Changes of edema score	0.00±0.26	0.00±0.28	1.000
Changes of hyperemia score	–0.03±0.41	0.04±0.19	0.426
Changes of hemorrhage score	0.03±0.56	0.11±0.42	0.625

Values are presented as mean±SD.
MLS, modified Lanza score.

Table 4. The Mean Changes of Frequency and Severity of Subjective Symptoms

Variable	Albis (*n*=30)	Placebo (*n*=27)	*p*-value
Change of subjective symptoms score	0.07±2.83	0.67±1.66	0.321

Values are presented as mean±SD.

Table 5. Adverse Events between the Two Groups

Variable	Albis (*n*=43)	Placebo (*n*=37)	*p*-value
Patients with all adverse event	16 (37.2)	7 (18.9)	0.09
Gastrointestinal symptoms	10 (23.2)	4 (10.8)	
Headache, dizziness	2 (4.7)	2 (5.4)	
Nasopharyngitis	1 (2.3)	3 (8.1)	
Edema	1 (2.3)	0 (0.0)	
Chest discomfort	2 (4.7)	0 (0.0)	
Conjunctival hemorrhage	1 (2.3)	0 (0.0)	
Breast calcification	0 (0.0)	1 (2.7)	
Phlebitis	1 (2.3)	0 (0.0)	
Serious adverse event	0 (0.0)	0 (0.0)	1.00
Use of rescue medicine, mean	18.2	17.6	0.92

Values are presented as number (%).

as abdominal pain, constipation, and flatulence (Table 5). No serious adverse event was reported in both groups during the study period.

DISCUSSION

In this study, Albis (containing ranitidine, sucralfate, and bismuth) prevented the gastric mucosal injury provoked by long-term use of ASA. There was no development of peptic ulcer in either of the groups during the study period. This might be due to the study period being too short to allow peptic ulcer to develop by the use of low-dose ASA. However, gastric mucosal injury measured by the MLS developed, but was reduced by concomitant use of Albis. Although several studies have reported the efficacy of PPIs or H2RAs in the prevention of peptic ulcer and gastric mucosal injury caused by ASA, there is no report of the efficacy of fixed-dose combination of H2RA, sucralfate, and bismuth.[3,7,11,14-17] This is the first prospective trial to evaluate the efficacy of combination of H2RA, sucralfate, and bismuth for the prevention of peptic ulcer or gastric mucosal injury due to long-term use of low-dose ASA.

Peptic ulcer did not develop even in placebo group during study period. As only ASA was administered in the group with low risk of peptic ulcer, the risk of peptic ulcer development was expected to be low. Moreover, the duration of the study was too short for peptic ulcer to develop due to ASA use even in the placebo group. In a previous study similar to ours but conducted over 26 weeks, patients developed peptic ulcer.[10] Therefore, the effect of Albis in preventing peptic ulcer caused by ASA may be better demonstrated if the study period is extended over 26 weeks.[10]

Protection against mucosal injury caused by ASA use was higher in the Albis group than in the placebo group, and the changes in MLS scores were lower in the Albis group than in the placebo group. However, mucosal injury due to ASA did not aggravate any subjective symptoms, which were minimal

in both groups owing to a low dose of only ASA being administered and due to the duration of study being relatively short.

ASA inhibits the cyclooxygenase pathway in the arachidonic acid metabolism. This results in inhibition of the production of prostaglandin and thromboxane which are indispensable for gastric mucoprotection and platelet aggregation. H2RAs inhibit the secretion of gastric acid and thereby protect the gastric mucosa from injury provoked by a decreased production of prostaglandin and thromboxane caused by ASA. Sucralfate exerts gastroprotective effects by coating and binding to mucosal injury caused by ASA. Bismuth also protects against mucosal injury caused by ASA by increasing the secretion of prostaglandin. Therefore, Albis can protect against gastric mucosal injury caused by ASA, via various mechanisms of H2RA, sucralfate, and bismuth.

Helicobacter pylori infection induces chronic inflammation of the gastric mucosa, which can be aggravated by long-term use of ASA. ASA can be a risk factor for peptic ulcer in *H. pylori*-positive patients.[18] However, *H. pylori* eradication alone increases the risk of peptic ulcer more than *H. pylori* eradication combined with PPI maintenance in long-term ASA users. Therefore, *H. pylori* eradication is not currently recommended for long-term ASA users without a previous history of peptic ulcer.[19,20]

As the status of *H. pylori* infection was not evaluated in this study, the effect of Albis in the prevention of gastric mucosal injury caused by ASA could not be analyzed according to *H. pylori* infection. Although the influence of *H. pylori* infection on our results could not be evaluated, no ulcers were developed during the study period in both the treatment and placebo groups. Furthermore, the mucosal injury might not differ per the status of *H. pylori* infection. In previous studies, the preventive effect of PPIs on peptic ulcers in long-term ASA users was not different according to the status of *H. pylori* infection at 12 weeks, but evident in *H. pylori*-negative patients at 26 weeks.[10,14]

The subjective symptoms were not significantly different between the treatment and placebo groups. Although mucosal injuries were more evident in the placebo group, they were not sufficient to provoke patient discomfort. The incidence of adverse events was also not significantly different between the groups.

This study had some limitations. Firstly, the drop-out rate was too high and the FAS population was too small to compare the results between the treatment and placebo groups. Secondly, the study period was too short to provoke the development of ulcer by ASA. Thirdly, the effect of *H. pylori* infection was not evaluated, which could influence the development of ulcers in long-term ASA users. Nevertheless, this is the first report on the gastroprotective effect of a combination of ranitidine, sucralfate, and bismuth in long-term ASA users.

In conclusion, Albis prevented gastric mucosal injury in ASA users. However, further studies are warranted to demonstrate the preventive effect of Albis against peptic ulcer in long-term ASA users for over 24 weeks.

Conflicts of Interest

This study was supported by a grant from Daewoong Pharmaceuticals Co. Ltd., Seoul, Korea

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