**ORIGINAL ARTICLE**

# A randomized, double-blinded, placebo-controlled, multicenter trial, healing effect of rebamipide in patients with low-dose aspirin and/or non-steroidal anti-inflammatory drug induced small bowel injury

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**Short title:** Rebamipide for small bowel injuries

**Key words:** NSAID; Aspirin; Mucosal damage; Small intestinal injury; Capsule endoscopy

**Abstract**

***Background:*** It is not clear what kind of drug is appropriate to heal for NSAIDs-induced enteropathy. Several reports showed the preventive effect of prostaglandin analogue or inducer using healthy subjects who took NSAIDs. However there was no report for healing effect and for patients. The aim of this study was to evaluate the healing effect of rebamipide in patients with NSAIDs-induced enteropathy. In addition, we evaluated for nutritional parameter.

***Methods:*** This study was conducted as a randomized, double-blinded, placebo-controlled, multicenter trial. Study protocol was approved by each hospital's ethical committees. Patients with LDA and/or NSAID more than 3 month were enrolled. Patients with enteropathy were divided into the placebo and the rebamipide groups. Rebamipide 100mg three times daily was administered during 4 weeks. Capsule endoscopies were performed at 0 and 4 week. The number of small intestinal ulcer and erosion were evaluated. Total protein was analyzed as nutritional parameters.

***Results:*** 61 participants were completed this study. Change in number of small intestinal erosion in the rebamipide group was -2.5±3.4, and 2.1±3.9 in the placebo group ($P < .0001$). Change in number of small intestinal ulcer in the rebamipide group was -0.5±1.6, and 0.1±0.7 in the placebo group ($P = .024$). Change in serum total protein levels in the rebamipide group was 0.06±0.36, and -0.27±0.34 in the placebo group ($P = .0005$).

***Conclusions:*** Rebamipide has not only the healing effect for NSAIDs-induced enteropathy compared with placebo, but the improvement of nutritional condition. These results showed a tentative therapeutical strategy for chronic NSAIDs users.

## Introduction

Since capsule endoscopy has developed [1], the prevalence of low-dose aspirin (LDA) and/or non-steroidal anti-inflammatory drug (NSAID)-induced small intestinal injuries has been clinically overt. Graham et al. reported that long-term NSAID use induced small intestinal injuries with high frequency, approximately 70% [2]. Lanas et al. reported an epidemiological data in Spanish population that upper gastrointestinal (GI) complications decreased from 87/100,000 persons in 1996 to 47/100,000 persons in 2005, whereas lower GI complications increased from 20/100,000 to 33/100,000. Lower GI events had a higher mortality rate than upper GI events [3]. However, it is not clear what kind of drug is appropriate to heal and prevent for LDA and/or NSAID-induced lower-GI complication. Then, novel therapeutic strategy for lower GI event should be required.

Several trials were conducted to resolve this problem for LDA and/or NSAID-induced lower-GI complication. Fujimori et al. reported that use of misoprostol, a prostaglandin analogue, prevented in healthy subjects with diclofenac-induced small intestinal injuries [4]. Niwa et al. reported that taking rebamipide, an endothelial prostaglandin inducer, prevented in healthy subjects with diclofenac-induced small intestinal injuries compared with placebo [5]. Furthermore, Watanabe et al. demonstrated that taking misoprostol contributed to heal in patients with LDA-related small intestinal injuries [6]. These agents are cytoprotective agent to indicate gastric ulcer and gastritis, but not suppress acid secretion. These results showed potency of prostaglandin to resolve this problem. On the other hand, small intestine plays an important role such as absorption of nutritional elements. Chronic small intestinal damage by taking LDA and/or NSAID may impair this function. Although, discontinuation of LDA is one of useful means to resolve this problem, it has the serious risk of cardiovascular and cerebrovascular events at the same time. Therefore, novel therapeutic strategy without discontinuation of LDA is desirable for LDA users.

In our present study, we have selected rebamipide as a study drug, because it is less adverse event and endothelial prostaglandin inducer. Several reports showed the preventive effect of rebamipide in healthy subjects with LDA and/or NSAID-induced small intestinal injuries [5, 7, 8], but not investigated in patients. Moreover, there is no report to investigate for the healing effect of drug by comparative, randomized and using placebo study design.

The aim of this study was to evaluate the healing effect of rebamipide in patients with LDA and/or NSAID-induced small intestinal injuries. In addition, we also evaluated nutritional parameter.

## Methods

### Study setting

This study was conducted as randomized, double-blinded, placebo-controlled, multicenter trial, and underwent. Study protocol was approved by each hospital's ethical committees, and written informed consent was obtained from all participants. Ten sites in Hokkaido prefecture participated in this study. This trial is registered with the UMIN Clinical Trials Registry, number UMIN000006625.

### Patients

Inclusion criteria were (1) patients who took LDA and/or NSAID more than 3 months; (2) were observed no legions of GI injuries by examining upper and lower GI endoscopy; and (3) were observed any small intestinal injuries (such as ulcer, erosion, denuded, erythema, and petechiae) by evaluating capsule endoscopy (CE). Exclusion criteria were patients who had (1) been taking gastro-protective drugs; (2) the presence of active GI bleeding; (3) the presence of GI stenosis; (4) a history of GI surgery; (5) a history of drug allergy; (6) severe liver disease; (7) renal dysfunction; and (8) cardiopulmonary dysfunctions.

### Study design

All participants were divided into the placebo group and the rebamipide group (Otsuka Pharmaceutical Co., Ltd. Tokyo Japan). Placebo, corn starch, and 100 mg of rebamipide were contained in white capsule of zero size, 18.7 mm of length. Each group were blinded and allocated by controller manager at Yamanami Pharmacy. Rebamipide 100 mg or placebo (3 times daily) was administered during 4 weeks.

Patients were recruited for the treatment sequences in a random fashion according to a randomization schedule in a 1:1 ratio. A randomization number that was associated with a specific treatment arm was assigned to each patient in this study. Randomized numbers were generated by the SAS program. The controller designed SAS program (SAS Institute, Cary, NC), and defined randomized numbers on this program in both groups.

The EndoCapsule system (Olympus Optical Co., Tokyo, Japan) were performed at 0 (defined as baseline) and 4 week (defined as final evaluation time point). Staring committee to evaluate CE findings was consisted of three members, Sei Kurokawa MD, Mototsugu Kato MD, and Shin-ichi Katsuki MD. CE evaluation committee was held before carrying out double-blind key-open.

**Evaluation**

Primary end point was to evaluate the healing effect of rebamipide in patients with LDA and/or NSAID-induced small intestinal mucosal breaks compared with placebo. Secondary end point was to evaluate the affect of rebamipide for changes in clinical parameters such as total protein and hemoglobin compared with placebo.

Mucosal breaks were defined as lesions of mucosal defect with central pallor and surrounding erythema. Furthermore, mucosal breaks were classified into erosions or ulcers on the basis of the sizes of the small bowel mucosal breaks, because by definition, an ulcer requires some degree of penetration (through the muscularis mucosa), and the angle of the images obtained by the capsule is often such that it is impossible to evaluate the depth of the lesions [2, 4]. Reddened lesions were defined as reddish mucosal changes such as reddened folds, denuded areas, and petechiae, all grouped into a single classification as reddened lesions [10].

Changes in the number of small intestinal injuries (such as mucosal break, ulcer, erosion, and reddened lesion) from baseline to final evaluation time point were calculated in both groups. Number of patients with small intestinal mucosal break at baseline was counted, and then complete remission rate in these patients was evaluated. Complete remission in the small intestinal mucosa was defined as an improvement of small intestinal condition that showed the disappearance of mucosal break by observation of CE at final evaluation time point. In addition, changes in serum total protein and hemoglobin from baseline to final evaluation time point were measured.

**Statistical analysis**

Rebamipide has no report to heal LDA and/or NSAID-induced small intestinal mucosal break. Therefore, we assumed a report of prostaglandin the grounds of the hypothesis. Watanabe *et al*. reported that misoprostol significantly decreased the median number of mucosal breaks from 3 (range, 2.5–7) to 0. We assumed 3 as change in mucosal break, moreover we assumed 4.5 as standard deviation (SD) [6]. Our hypothesis is that small intestinal mucosal break in patients with LDA is not to change in the placebo group, contrarily 3 at least small intestinal mucosal break improves in the rebamipide group. Sample size was calculated based on this hypothesis. A two-sided test, with 0.05 significance level and 90% power ($\alpha = 0.05$, $\beta = 0.10$), would require 26 subjects per group. Assuming that approximately 10% of the patients would not be able to complete the study, we calculated that a minimum of 30 subjects per group would be required for this study.

Primary end point was to evaluate changes in the number of the small intestinal

mucosal breaks. Absolute difference (AD) and 95% confidential interval (95%CI) in the placebo group and the rebamipide group were calculated. AD was defined as the difference from baseline to the final evaluation data. Statistical significance was analyzed by Wilcoxon rank sum test, and chi-square test or Fisher's exact test. Secondary endpoint was to evaluate changes in the total protein and hemoglobin compared with the placebo group. Statistical significance was analyzed by Wilcoxon rank sum test. The continuous data were analyzed by t-test or median test or Wilcoxon rank sum test. Data were expressed as mean ± SD. The category data were analyzed by Fisher's exact test or chi-square test. Statistical significance was defined as $P < 0.05$. All statistical analyses were performed using JMP version 8.0.2 software (SAS Institute, Cary, NC).

**Results**

Sixty-seven of patients obtained informed consent and accepted participation to this study. Five of patients were excluded not to observe small intestinal injuries by evaluating CE. Sixty-two of patients were divided into the placebo group and the rebamipide group. One of patient in the placebo group was not completed this study because of the occurrence of hypertension. Thirty of patients in the placebo group and 31 of patients in the rebamipide group were completion of this study without serious adverse event through this study period. Patients' flow was shown in figure 1. Patients' demographic data and characteristics were shown in table 1. There were no differences in patients' demographic data and characteristics between the placebo group and the rebamipide group. Five of patients with anemia in the rebamipide group were observed and 4 of anemia in the placebo group were observed. Six of patients with abdominal pain in the rebamipide group were observed and 3 of abdominal pain in the placebo group were observed.

**The evaluation of treatment**

Changes in number of median mucosal break from baseline to final evaluation time point were 0 (minimum; -3, maximum; 12) in the placebo group, and -2 (-17, 2) in the rebamipide group ($P < .004$) (2.1 ± 4.0 vs -3.2 ± 4.1: $P < .0001$). And then, patients were stratified according to LDA and/or NSAID taking medicine (Figure 2). Changes in number of mucosal break in patients who received LDA were 0 (-3, 12) in the placebo group, -2 (-8, 2) in the rebamipide group ($P = .040$) (1.9 ± 0.8 vs -1.8 ± 0.8: $P= .002$). Changes in number of mucosal break in patients who received NSAID were 4 (-3, 10) in the placebo group, -4.5 (-17, 0) in the rebamipide group ($P = .003$) (3.4 ± 4.7 vs -7.1 ± 5.8: $P= .007$). Changes in number of mucosal break in patients who received LDA plus NSAID were 2 (-1, 6) in the placebo group, -3 (-5, 0) in the rebamipide group ($P = .119$) (2.3 ± 3.3 vs -2.8 ± 1.9: $P= .02$). Nineteen of patients with small intestinal mucosal break at baseline were observed in the placebo group, and 24 were in the rebamipide group. Complete remission at final evaluation time point was observed 1 patient (5.3%) in the placebo group, and 9 patients (37.5%) in the rebamipide group. Statistical significance was shown ($P = .018$).

Changes in number of small intestinal erosion in the placebo group were 2.1 ± 3.9, and -3.2 ± 4.1 in the rebamipide group ($P < .0001$). Changes in number of small intestinal ulcer in the placebo group was 0.1 ± 0.7, and -0.5 ± 1.6 in the rebamipide group ($P = .024$). Changes in number of reddened lesions were -0.2 ± 3.7 in the placebo group, and -2.3 ± 3.8 in the rebamipide group ($P = .003$) (Table 2).

Changes in serum total protein from baseline to final evaluation time point were -0.3 ± 0.3 in the placebo group, and 0.06 ± 0.4 in the rebamipide group ($P = .0005$). Changes in serum hemoglobin were -0.6 ± 1.6 in the placebo group, and 0.01 ± 0.9 in the rebamipide group ($P = .064$) (Table 3).

**Discussion**

Our present study was the first report to proof the healing effect of a drug in patients with LDA and/or NSAID-related small intestinal injuries by double-blinded, randomized, placebo-controlled trial. Rebamipide was superior to placebo in the improvement of small intestinal mucosal break. Complete remission was achieved for 37.5% of patients in the rebamipide group. It had statistical significant difference in comparison with 5.3% of remission rate in the placebo group. Complete remission by using rebamipide was also shown despite of under continuing administration of LDA. Discontinuation of anti-platelet agents has the high risk on recurrence of cardiovascular or cerebrovascular events [11-13]. Moreover, with the increase in LDA use, the

morbidity rate caused by the lower GI injury increased [3]. It is well-known that administration of LDA also induces upper GI complications, and PPI prevents them [14]. However, no drug to manage lower GI complications exists. Therefore, a tentative drug to prevent and heal on LDA-related small intestinal injury is required. Our findings showed a novel therapeutic strategy and enabled treatment without discontinuation of LDA in patients with cardiovascular or cerebrovascular events.

Furthermore, serum total protein was also improved by taking rebamipide compared with placebo. Long-term use of LDA and/or NSAID leads to hyper-permeation of small intestinal mucosa [10]. Moreover, chronic hyper-permeation in the small intestinal mucosa leads to rhexis of tight junction [15]. On the other hand, reducing prostaglandin leads to decreasing of blood flow [16]. Although these reactions are invisible, this condition occurs all over the small intestinal mucosa. As the result, function of small intestine such as absorption of nutritional elements may be lost. In this study, baseline of serum total protein of patients was lower rather than normal levels. Rebamipide improved serum total protein. Namely, this result might also show avoidance from decrease of serum protein level by reparatory action of rebamipide. Rebamipide has not only the healing effect for LDA and/or NSAID-induced small intestinal injuries compared with placebo, but also the improvement of nutritional condition. This therapeutic strategy is clinically meaningful for chronic LDA and/or NSAID users. This result might be one of appropriate goal as the management of small intestine in patients with LDA.

Rebamipide is a cytoprotective agent, inducing endothelial endothelial prostaglandin [17], protecting rhexis of tight junction [18], and increasing small intestinal blood flow [9]. Misoprostol and rebamipide have healed in patients with LDA-induced small intestinal injuries [6, 8], it might cause by increase of prostaglandin levels. Mizoguchi et al. reported that prostaglandin prevented NSAID-induced small intestinal damages in rats [19]. Moreover, Megraud *et al*. investigated that rebamipide reinforces the distal colonic barrier on mesenteric lymph node cells [20]. These mechanisms of rebamipide might play important roles as the support to the result of our present study.

The limitation of this study was to include several categories of patients, such as patients with LDA mono-therapy group, NSAID mono-therapy group, and LDA and NASID combination group. As the future study, it should be conducted by LDA mono-therapy group.

In conclusion, rebamipide has not only the healing effect for NSAID and/or low-dose aspirin-induced small intestinal injuries compared with placebo, but also the

improvement of nutritional condition. These results showed a tentative therapeutical strategy for chronic LDA and/or NSAID users.

**Contributors**

Kato M. conceived and designed this study. Kato M. was the coordinating principal investigator for the study. Kurokawa S. and Katsuki S. analysed and interpreted the results. Kato M. drafted the report. Kato M. was responsible for the overall planning and conduct of the study. Kurokawa S., Kato M.,and Katsuki S were members of the steering committee. All authors have seen and approved the final version of the manuscript.

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**Figure legends**

Figure 1 Patients' flow and characteristics

Figure 2 Comparison between rebamipide and placebo in the influence that LDA and/or NSAID received for the healing effect of small intestinal mucosal break

Data are expressed as (median, [minimum - maximum]).

A.D.: absolute difference, 95%CI: 95% confidential interval

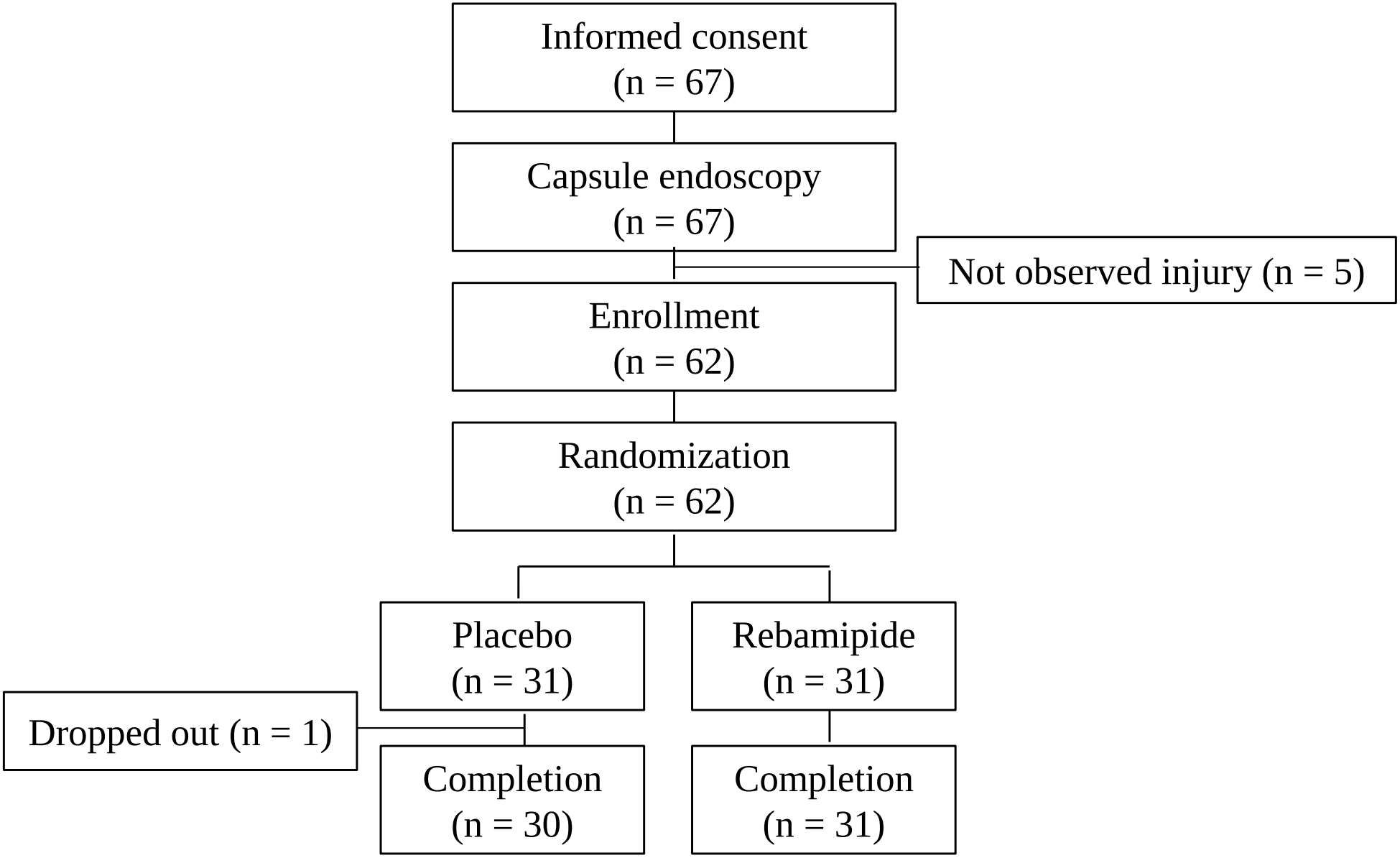
Informed consent
(n = 67)
Capsule endoscopy
(n = 67)
Not observed injury (n = 5)
Enrollment
(n = 62)
Randomization
(n = 62)
Placebo
(n = 31)
Rebamipide
(n = 31)
Dropped out (n = 1)
Completion
(n = 30)
Completion
(n = 31)

Figure 1

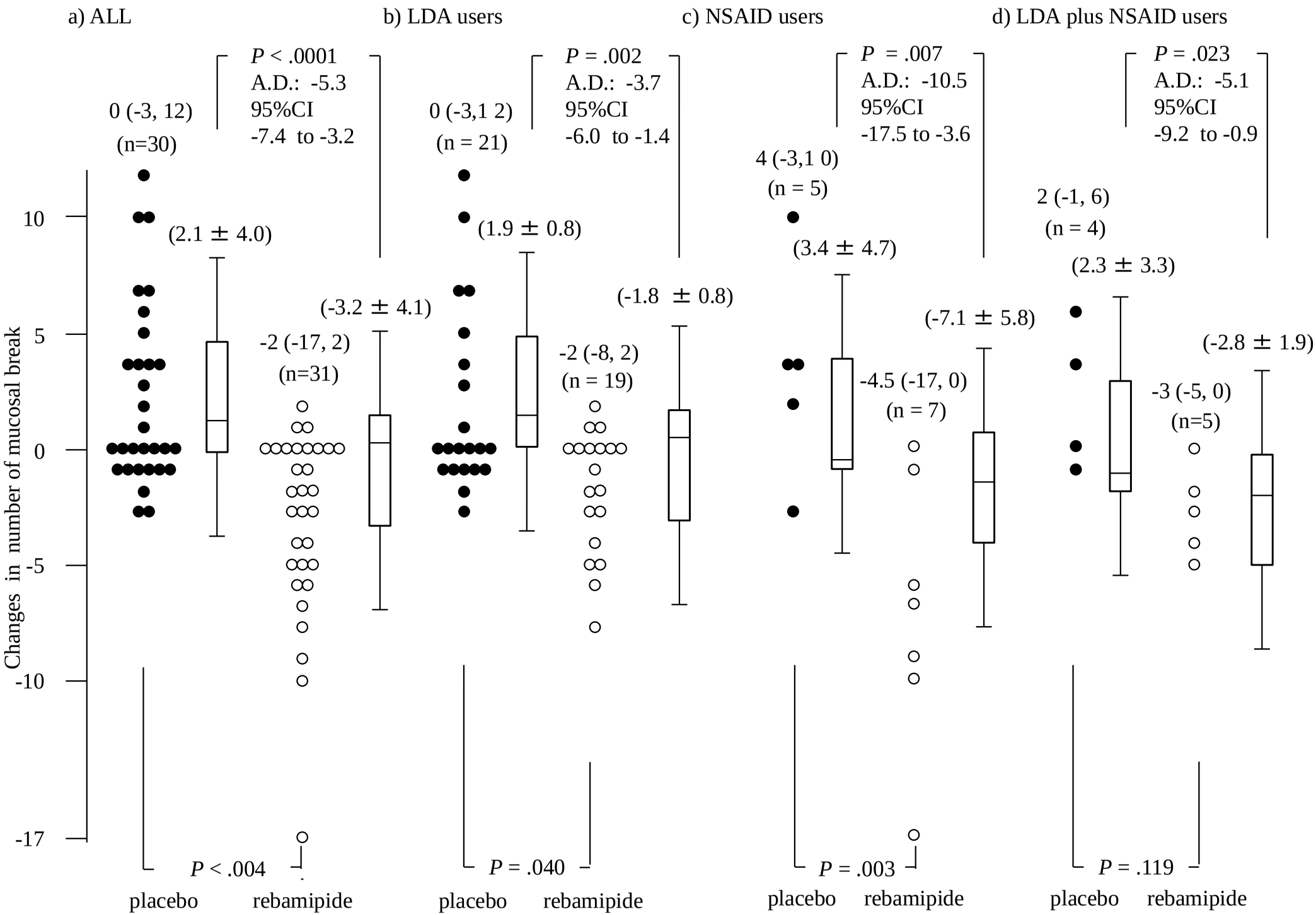
a) ALL
b) LDA users
c) NSAID users
d) LDA plus NSAID users
P < .0001
A.D.: -5.3
95%CI
-7.4 to -3.2
P = .002
A.D.: -3.7
95%CI
-6.0 to -1.4
P = .007
A.D.: -10.5
95%CI
-17.5 to -3.6
P = .023
A.D.: -5.1
95%CI
-9.2 to -0.9
0 (-3, 12)
(n=30)
(2.1 ± 4.0)
-2 (-17, 2)
(n=31)
(-3.2 ± 4.1)
0 (-3,1 2)
(n = 21)
(1.9 ± 0.8)
-2 (-8, 2)
(n = 19)
(-1.8 ± 0.8)
4 (-3,1 0)
(n = 5)
(3.4 ± 4.7)
-4.5 (-17, 0)
(n = 7)
(-7.1 ± 5.8)
2 (-1, 6)
(n = 4)
(2.3 ± 3.3)
-3 (-5, 0)
(n=5)
(-2.8 ± 1.9)
Changes in number of mucosal break
10
5
0
-5
-10
-17
P < .004
P = .040
P = .003
P = .119
placebo
rebamipide
placebo
rebamipide
placebo
rebamipide
placebo
rebamipide

Figure 2

Table 1　demographic data

| Characteristics | Placebo (n = 30) (%) | Rebamipide (n = 31) (%) | Analysis |
|---|---|---|---|
| Age (> 65) | 26 (86.7) | 24 (77.4) | n.s. |
| Gender (male) | 15 (50.0) | 15 (48.4) | n.s. |
| Drugs | 5 (16.7) | 7 (22.6) | n.s. |
| NSAID | 5 (16.7) | 7 (22.6) | n.s |
| LDA | 21 (70.0) | 19 (61.3) | n.s |
| Enteric coated | 18 | 15 | |
| Buffered | 3 | 4 | |
| NSAID+LDA | 4 (13.3) | 5 (16.1) | n.s |
| PPI use | 12 (40.0) | 10 (32.3) | n.s |
| Warfarin | 12 (40.0) | 10 (32.3) | n.s |
| Hemoglobin (g/dL) | 11.0 ± 3.0 | 12.0±2.0 | n.s |
| Total protein (g/dL) | 7.0 ± 0.6 | 7.2±0.7 | n.s |
| Small bowel injuries (mean ± SD) | | | |
| Mucosal break | 2.2 ± 3.1 | 4.6 ± 4.3 | n.s. |
| Ulcer | 0.2 ± 0.5 | 0.8 ± 1.7 | n.s. |
| Erosion | 1.9 ± 2.9 | 3.8 ± 3.8 | n.s. |
| Reddened lesion | 6.1 ± 4.8 | 4.9 ± 4.6 | n.s. |

Table 2 The healing effect of rebamipide in patients with small bowel injuries at 4 week

| | Placebo (n = 30) | Rebamipide (n = 31) | Absolute difference | 95%CI | *P* value |
|---|---|---|---|---|---|
| Erosion | 2.1 ± 3.9 | -3.2 ± 4.1 | - 4.6 | -6.5 to -2.7 | < .0001 |
| Ulcer | 0.1 ± 0.7 | -0.5 ± 1.6 | - 0.6 | -1.4 to -0.1 | .024 |
| Reddened lesion | -0.2 ± 3.7 | -2.3 ± 3.8 | - 2.1 | -4.1 to -0.2 | .003 |

95%CI: 95% confidential interval

Table 3 Changes in hemoglobin and total protein compared with placebo and rebamipide

| | Placebo (n = 30) | Rebamipide (n = 31) | A.D. | 95%CI | *P* value |
|---|---|---|---|---|---|
| Total protein (g/dL) | -0.3 ± 0.3 | 0.06 ± 0.4 | 0.3 | 0.2 to 0.5 | .0005 |
| Hemoglobin (g/dL) | -0.6 ± 1.6 | 0.01 ± 0.9 | 0.6 | -0.04 to 1.3 | .066 |

A.D.: absolute difference, 95%CI: 95% confidential interval