



Effect of Sodium Alginate on Gastrointestinal Symptoms after Esophagogastroduodenoscopy with Biopsy: Randomized Controlled Trial

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Background/Aims: After esophagogastroduodenoscopy (EGD) with biopsy, some patients experience gastrointestinal symptoms. This study investigated the effect of sodium alginate on biopsy-related gastrointestinal symptoms.

Methods: In this open-label, randomized, controlled trial, patients undergoing EGD with biopsy were randomly assigned to a treatment or control group. In the treatment group, sodium alginate was orally administered for 3 days after EGD. Patients completed questionnaires about their gastrointestinal symptoms at baseline (past week), the day after returning home, and after another 3 days. Gastrointestinal symptoms, including abdominal pain, epigastric pain/soreness, heartburn, acid reflux, nausea/vomiting, borborygmus, abdominal distension, and belching, were rated using an upper gastrointestinal symptom rating scale (GSRS).

Results: A total of 210 persons (138 men) who underwent EGD with biopsy were enrolled and allocated to the treatment (n=104) or control (n=106) group. At baseline, the demographic factors and GSRS scores were not different between the control and treatment groups. The epigastric pain/soreness score increased in the control group after endoscopic biopsy (+0.056), whereas the score was decreased in the treatment group (-0.067) (p=0.042). In the treatment group, the scores for acid regurgitation and epigastric soreness decreased during follow-up from those at baseline (p<0.05), whereas there were no significant reductions in the control group. The scores for belching and borborygmus decreased during follow-up only in the treatment group. Abdominal bloating decreased in both the control and treatment groups.

Conclusions: Sodium alginate reduced epigastric pain/soreness after EGD with biopsy. Therefore, the prescription of sodium alginate should be considered after endoscopic biopsy. (*Gut Liver* 2022;16:37-43)

Key Words: Alginates; Biopsy; Abdominal pain

INTRODUCTION

Esophagogastroduodenoscopy (EGD) is a very common procedure, and forceps biopsy is often performed during diagnostic endoscopy to clarify the pathology of focal lesions or to identify the presence of *Helicobacter pylori*. Sometimes, patients complain about gastrointestinal symptoms such as upper abdominal pain or soreness after EGD with biopsy. Meanwhile, significant bleeding after diagnostic gastric biopsy is rare.¹ Such gastrointestinal symp-

toms may be related to exposure to acid or food material of the biopsy-related mucosal defect.

The use of a mucosal protector may reduce such gastrointestinal symptoms. Alginic acid is a polysaccharide of the cell wall of brown seaweed. Combined with metals such as sodium and calcium, its salts are known as alginates. Sodium alginate induces a muco-protective effect by covering the surface of the gastrointestinal tract and elicits platelet aggregation.^{2,3} Therefore, it may be useful for the treatment of gastric ulcers and bleeding.⁴ Sodium alginate



may be efficacious in uncomplicated reflux and nonerosive reflux disease^{5,6} and has moreover been shown to reduce indomethacin-induced gastrointestinal mucosal injury in animal models.⁷ Sodium alginate is poorly absorbed and is excreted in the feces⁸ and only few side effects have been reported.

To date, no study has been published regarding the role of sodium alginate in preventing biopsy-related gastrointestinal symptoms. In this randomized controlled trial, we therefore investigated whether administration of sodium alginate could reduce biopsy-related gastrointestinal symptoms.

MATERIALS AND METHODS

1. Study design and baseline enrollment

This study was an open-labeled randomized controlled trial carried out at the Kyungpook National University Hospital, Daegu, Korea. Patients who underwent EGD with biopsy were enrolled. Study individuals were without significant disease and aged between 20 and 80 years. We excluded patients with the following characteristics: (1) previous gastrectomy, (2) severe cardiopulmonary or endocrine disease, (3) renal dysfunction or liver dysfunction, (4) hematologic disease, (5) active peptic ulcer, (6) incomplete resection of gastric cancer, (7) current medication with proton pump inhibitor, H₂ blocker, or muco-protectant, (8) persistent bleeding after biopsy, (9) pregnant women, or (10) a previous history of drug allergy.

2. Randomization and intervention

Subjects undergoing EGD with biopsy were randomly assigned 1:1 to the treatment or the control group. We used a computer-based random number generator to construct the randomization table. In the treatment group, sodium alginate (Lamina-G[®]; Taejoon Pharm Co., Seoul, Korea) was orally administered after EGD for a period of 3 days (1 g of sodium alginate 3 times a day). No gastrointestinal drug was provided in control group.

The Kyungpook National University Hospital Chilgok Institutional Review Board approved the study (IRB number: KNUMC 2016-02-002), and all participants provided written informed consent. This study was registered at ClinicalTrials.gov under registration (NCT04134364).

3. Assessment of gastrointestinal symptom

All patients completed questionnaires for gastrointestinal symptoms at baseline and follow-up. We assessed recent 1-week gastrointestinal symptoms (baseline symptoms) immediately after the endoscope. On the day after return home and 3 days after endoscopy, gastrointestinal

symptoms were surveyed by telephone. Follow-up symptom scores were measured using gastrointestinal symptoms at day 1 and day 3. Gastrointestinal symptom was scaled by upper gastrointestinal symptom rating scale (GSRS) extracting from previous validated GSRS.⁹ They contain eight items and three scales; abdominal pain (abdominal pain, epigastric pain/soreness), reflux symptom (heartburn, acid reflux), indigestion symptom (nausea/vomiting, borborygmus, abdominal distension, belching) (Supplementary Table 1). Individual symptom scores are ranged from 0 to 3 according to severity.

4. Outcome measurement

We measured the individual GSRS and overall GSRS. Changes of GSRS from baseline score were also measured. The calculation equations used to assess these changes were as follows:

$$\begin{aligned} \text{GSRS at follow-up} &= \text{during 3 days symptom after endoscopic biopsy} \\ \text{GSRS change} &= \text{follow-up score} - \text{baseline score.} \end{aligned}$$

5. Statistical analyses

Our calculation of the required sample size is available in Supplementary Material 1. In summary, the sample size was calculated with an alpha error of 0.05 and a statistical power of 0.8, based on the estimated effect of sodium alginate treatment on gastrointestinal symptoms. The sample size was estimated to a total of 210 subjects.

Data are presented as numbers (percent) or means \pm standard deviations. The Pearson chi-square test or the independent t-test was used to investigate the difference in clinical variables between the control group and the treatment group. The independent t-test was used to compare GSRS scores at baseline and follow-up between the control and treatment groups. We also used the independent t-test to compare GSRS changes between control and treatment groups. The paired t-test was used to compare GSRS before and after endoscopy in both the control and the treatment group.

All statistical analyses were performed using STATA software version 15 (StataCorp, College Station, TX, USA). All statistical tests were two-sided, and $p < 0.05$ was considered statistically significant.

RESULTS

1. Baseline clinical characteristics

Among 215 persons, two persons take proton pump inhibitor and three persons refused to participate. A total of 210 patients (138 men) undergoing EGD with biopsy were

enrolled. There were 104 patients in the treatment group and 106 patients in the control group (Fig. 1). Participants were enrolled from March 2017 to August 2019, and they

were followed up over a period of 3 days. There was no difference in mean age or sex distribution between the control and treatment groups (Table 1). Smoking status, drinking

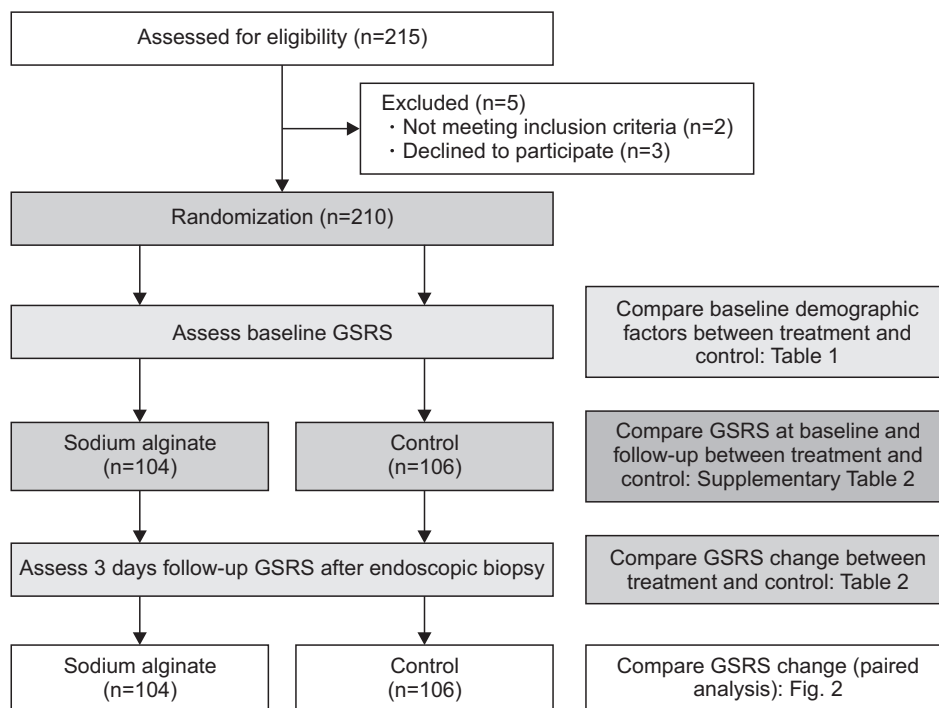


Fig. 1. Flowchart of patients. A total of 210 persons who underwent upper endoscopy and biopsy were randomized to either the treatment group or the control group. GRS, gastrointestinal symptom rating scale.

Table 1. Baseline Clinical Characteristics

Characteristics	Control (n=106)	Treatment (n=104)	p-value*
Male sex	70 (66.0)	68 (65.4)	0.921
Age, yr	61.3±10.4	62.4±60.3	0.470
Smoking status			0.227
Current	24 (22.6)	15 (14.4)	
Never	43 (40.6)	52 (50.0)	
Past	39 (36.8)	37 (35.6)	
Drinking status			0.915
Current	53 (50.0)	49 (47.1)	
Never	34 (32.1)	35 (33.7)	
Past	19 (17.9)	20 (19.2)	
Underlying disease			
Hypertension	41 (38.7)	32 (30.8)	0.229
Diabetes	16 (15.1)	9 (8.7)	0.150
Dyslipidemia	15 (14.2)	17 (16.4)	0.658
CVA/CVD	5 (4.7)	3 (2.9)	0.488
Cured cancer	56 (52.8)	51 (49.0)	0.583
Aspirin/anticoagulant	5 (4.7)	4 (3.9)	0.755
Endoscopic finding			
Erosive gastritis	7 (6.6)	8 (7.7)	0.759
Reflux esophagitis	20 (18.9)	18 (17.3)	0.769
Pieces of tissue acquirement	4.6±1.8	4.7±2.0	0.794
Rapid urease test			0.444
Negative	69 (89.6)	65 (85.5)	
Positive	8 (10.4)	11 (14.5)	

Data are presented as number (%) or mean±SD.

CVA/CVD, cerebrovascular disease/cardiovascular disease.

*p-values were derived from the chi-square test and independent t-tests.

status, types of chronic disease, and use of aspirin did not differ between the two groups. The number of acquired biopsy specimens did not differ either. Finally, endoscopic findings (erosive esophagitis and reflux esophagitis) and the positive rate of *H. pylori*, which may affect gastrointestinal symptoms, did not differ between the two groups.

2. Upper gastrointestinal symptom rate score

Symptomatic participants are infrequent in this study. The most frequent symptom, epigastric pain/soreness, was present in 8.5% (n=9) of the control group and 13.5% (n=14) of the treatment group at baseline. It was present in 10.4% (n=11) of the control group and 5.8% (n=6) of the treatment group. Individual symptom score in each person is ranged from 0 to 2. Data reflecting individual GSRS and overall GSRS did not differ between the control and the treatment group at baseline (Supplementary Table 2). Even though the scores for heartburn, epigastric pain/soreness, and nausea/vomiting were lower in the treatment group than in control group, the difference did not reach statistical significance. The overall GSRS score was lower in the treatment group (0.183) compared with the control group (0.434), but it was also statistically insignificant (p=0.10) (Supplementary Table 2).

3. Outcome of treatment (comparison of GSRS change between two groups)

Epigastric pain/soreness score increased in the control group after endoscopic biopsy (+0.056), whereas epigastric pain/soreness score was markedly reduced in the treatment group (−0.067) during follow-up (p=0.042). A larger reduction in heartburn during follow-up period was observed in the treatment group compared with the control group; however, this difference did not reach statistical significance (−0.048 in the treatment group and +0.028 in the control group, p=0.088). Nausea/vomiting during follow-

up after endoscopic biopsy increased in the control group (+0.090) but decreased in the treatment group (−0.029); this difference also did not reach statistical significance (p=0.096). A reduction in the overall GSRS score after endoscopy was observed in both control and treatment groups, and the change was not statistically different between the control group and the treatment group (Table 2).

4. Individual GSRS changes after endoscopy in each group

The change in abdominal pain score was statistically insignificant in both control and treatment groups (Fig. 2A). The follow-up scores for acid regurgitation and epigastric pain/soreness were significantly reduced compared with baseline scores in the treatment group, whereas those scores had no difference between base and follow-up in the control group (Fig. 2A). The change in nausea/vomiting score was statistically insignificant in both control and treatment groups (Fig. 2B). The scores for belching and borborygmus decreased after endoscopy in the treatment group, whereas those symptoms had no significant difference in the control group (Fig. 2B). The abdominal bloating score decreased after endoscopy in both treatment and control groups (Fig. 2B).

DISCUSSION

In this randomized study, epigastric pain/soreness score increased in control group after endoscopic biopsy, whereas the score was markedly reduced in sodium alginate treatment group. In the treatment group, acid regurgitation and epigastric soreness were markedly decreased during follow-up after endoscopic biopsy compared with baseline, whereas in the control group, those symptoms had no significant reduction. Belching and borborygmus were

Table 2. Changes in GSRS Scores after Endoscopy

Changes	Control (n=106)	Treatment (n=104)	p-value*
GSRS change (follow up–base), mean (SD)			
Individual GSRS			
Abdominal pain	−0.009 (0.16)	−0.010 (0.13)	0.992
Heartburn	0.028 (0.35)	−0.048 (0.29)	0.088
Acid regurgitation	−0.038 (0.41)	−0.086 (0.37)	0.368
Epigastric soreness	0.056 (0.45)	−0.067 (0.42)	0.042
Nausea/vomiting	0.090 (0.24)	−0.029 (0.17)	0.096
Borborygmus	−0.047 (0.29)	−0.086 (0.31)	0.346
Abdominal bloating	−0.066 (0.29)	−0.067 (0.25)	0.978
Belching	−0.047 (0.29)	−0.058 (0.23)	0.772
Total GSRS	−0.104 (1.47)	−0.450 (1.28)	0.069

GSRS, gastrointestinal symptom rating scale.

*p-values were derived from independent t-tests.

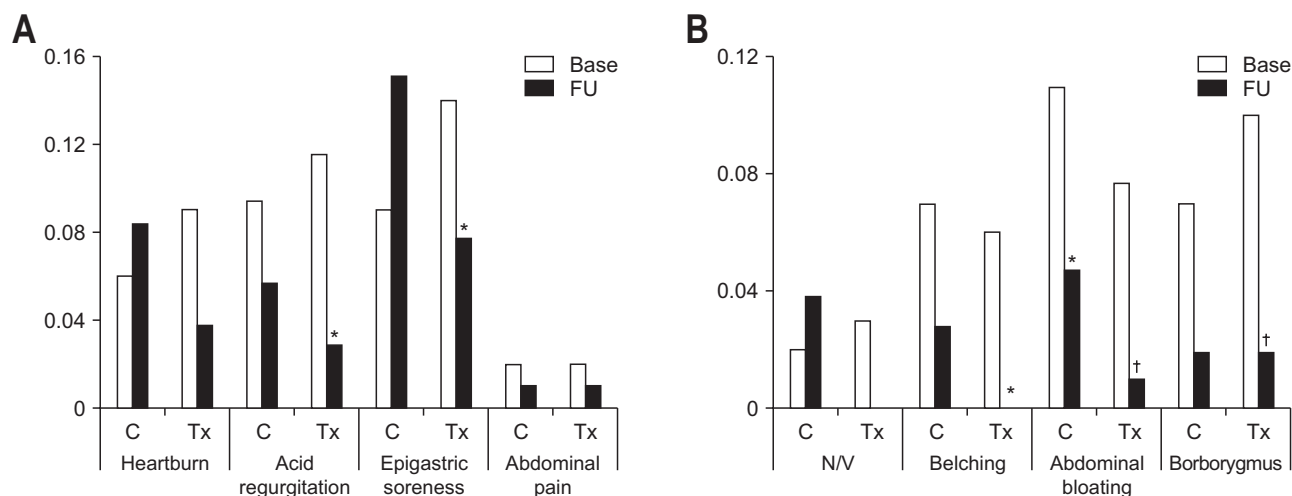


Fig. 2. Changes in scores for individual symptoms on the gastrointestinal symptom rating scale after upper endoscopic biopsy. (A) Changes in scores for heartburn, acid regurgitation, epigastric soreness, and abdominal pain between baseline and follow-up after endoscopic biopsy in the control and treatment groups. (B) Changes in scores for nausea/vomiting, belching, abdominal bloating, and borborygmus between baseline and follow-up after endoscopic biopsy in the control and treatment groups. Paired t-test: follow-up score versus baseline score. C, control group; Tx, treatment group; N/V, nausea/vomiting; FU, follow-up. * $p < 0.05$, † $p < 0.01$.

reduced only in the treatment group. Abdominal bloating was reduced during follow-up period in both groups.

In this study, epigastric pain/soreness score increased in the control group after endoscopic biopsy (+0.056), whereas epigastric pain/soreness score was markedly reduced in the treatment group (-0.067). These results suggest that sodium alginate administration after endoscopic biopsy may be valuable in reducing endoscopic biopsy-related epigastric pain/soreness. Endoscopic biopsy induces mucosal defects such as erosions and small ulcers and exposure to stimuli such as acid and spicy food may induce pain or soreness. There are two different healing mechanisms of gastric mucous epithelia.¹⁰ First, rapid repair of superficial lesions by cell migration (restitution) starts within minutes. Second, continuous regeneration by differentiation and proliferation of progenitor cells (self-renewal) occurs within days to months. In rats, superficial erosion induced by aspirin was completely healed within 24 hours and the median disappearance time of deep erosion was 5 days.¹¹ Superficial mucosal damage after biopsy is healed by rapid restitution and self-renewal. It is similar to epithelialization of gastric ulcer, occurring within 3 to 5 days.¹² Hence mucosal defect-related symptoms usually present within several days. Thus, sodium alginate administration for 3 days after endoscopic biopsy seems to be reasonable in reducing epigastric pain/soreness. In clinical practice, we often have experienced patients' complaints for epigastric pain/soreness or abdominal discomfort after endoscopic biopsy and the symptoms usually subside within 1 week.

In the individual symptom analysis, the scores for acid regurgitation and epigastric soreness significantly de-

creased after endoscopic biopsy compared with baseline score in the treatment group, whereas those scores had no significant reduction in the control group. This favorable outcome might reflect the potential mucosal protective effect of sodium alginate. Reflux symptoms (heartburn/acid regurgitation) had markedly waned in the treatment group, whereas no significant reduction was observed in the control group. The favorable effect of sodium alginate on reflux symptoms is comparable to previous results demonstrating that sodium alginate improves gastroesophageal reflux symptoms and laryngopharyngeal reflux disease.^{5,13} Abdominal pain had no significant change in both control and treatment groups.

In the individual symptom analysis, belching and borborygmus scores had decreased after endoscopy in the treatment group but not in the control group. Abdominal bloating scores decreased after endoscopy in both control and treatment groups. One plausible explanation of the marked reduction in indigestion symptoms after endoscopy may be reflected in the pathophysiology of functional dyspepsia. Psychological distress is often associated with functional dyspepsia.¹⁴ Hence, psychological reassurance in the patients after recognizing that no significant abnormality has been identified on endoscopy may improve dyspeptic symptoms. Second, it may be related to stimulation of upper gastrointestinal tract during endoscopic examination. Third, a follow-up period of 3 days may be too short to allow evaluation of symptoms of indigestion. Last, worrying about endoscopy may partially contribute to the perception of pre-test gastrointestinal symptoms and this stress may be relieved after endoscopy. In any case, the

reduction of indigestion symptoms after EGD was similar across the two groups, and therefore this reduction is supposedly not related to sodium alginate administration.

Sodium alginate has hemostatic and mucosal protection effect. Furthermore, it is poorly absorbed and is excreted in the feces⁸ and side effects have been extremely rarely reported. Therefore, sodium alginate has been widely used for the treatment of gastric ulcers, bleeding,^{2-4,15} and nonerosive reflux disease.⁵ Sodium alginate also inhibits methotrexate-induced gastrointestinal mucositis in animal models.¹⁶ Sodium alginate as hemostatic agents has been used in extragastrintestinal field such as wound healing.^{17,18} Alginate dressings are used for their conformability and ability to provide a moist wound healing environment.¹⁸ Silver alginate dressing has antimicrobial efficacy on burn wound isolates.¹⁷ Recently, sodium alginate has been used to maintain mucosal lifting during endoscopic submucosal dissection.

This study has several strengths. First, this is a randomized controlled trial and therefore, we could investigate the favorable effect of sodium alginate on gastrointestinal symptom after endoscopic biopsy. Second, this study is well randomized for epidemiologic factors and *H. pylori*. In the current study, individual GSRS and overall GSRS had no difference between control and treatment group at baseline. It means that study groups were well randomized without bias of underlying gastrointestinal symptoms. Age, sex, smoking status, drinking status, many kinds of chronic disease, and the use of aspirin also showed no difference between control and treatment groups. Endoscopic findings and positive rate of *H. pylori*, which may be linked to gastrointestinal symptoms, showed no difference between the two groups. These data suggest a good randomization of study group without bias. Nevertheless, this study also has some limitations. For instance, we did not investigate the potentially protective role of sodium alginate in post-endoscopic biopsy bleeding because the event is very rare, and no cases of post-endoscopic biopsy bleeding was observed in this study.

In conclusion, sodium alginate administered after endoscopic biopsy reduced acid regurgitation and epigastric soreness. Therefore, prescription of sodium alginate could be considered in patients who undergo endoscopic biopsy to prevent biopsy-related epigastric soreness. Additionally, the finding that indigestion symptoms had been reduced after EGD in both treatment and control groups could be related to reassurance of endoscopic results.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTIONS

Conceptualization: S.W.J., S.Y.N. Data curation, formal analysis: S.Y.N. Funding acquisition: S.Y.N. Methodology, project administration: S.Y.N., S.W.J. Visualization: S.Y.N. Data acquisition: S.Y.N., S.W.J., Y.H.K., S.W.L. Writing - original draft: S.Y.N., S.W.J. Writing - review & editing: S.Y.N., S.W.J. Approval of final manuscript: all authors.

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SUPPLEMENTARY MATERIALS

Supplementary materials can be accessed at <https://doi.org/10.5009/gnl20298>.

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