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Prospective Multi-Center Trial for the Efficacy of Ecabet Sodium on the Relief of Dyspepsia in Korean Patients with Chronic Gastritis

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Sumamry **Anti-peptic and anti-inflammatory actions of ecabet sodium might be beneficial in either improving gastritis or relieving dyspeptic symptoms. This study was designed to evaluate the clinical efficacy of ecabet sodium on dyspeptic symptoms and to elucidate the molecular mechanism attributable to symptom relief in patients with chronic gastritis. Two hundred and sixty eight chronic gastritis patients with persistent dyspepsia received ecabet sodium 1 g *b.i.d.* for 2 weeks, after which dyspeptic symptoms were reassessed with a questionnaires as before. The changes of interleukin-8 (IL-8), inducible nitric oxide synthase (iNOS), prostaglandin E_2 (PGE_2), and vascular endothelial growth factor (VEGF) levels in gastric juices were measured by ELISA. The changes of nitrotyrosine in gastric mucosa were measured by immunohistochemical staining. The most common dyspeptic symptom in Korean patients with chronic gastritis was epigastric soreness (76.8%), which was improved significantly after ecabet sodium treatment (81.7%, $p<0.001$). Ecabet sodium was more effective in patients with epigastric pain than vague abdominal discomfort ($p = 0.02$), especially in patients with old age. Complete relief of discomfort was more highly achieved in patients with positive *Helicobacter pylori* than without ($p = 0.01$). In spite of clear tendency that the decreased levels of IL-8, iNOS, and PGE_2 and increased levels of VEGF were measured in gastric juices after ecabet sodium treatment, no statistical significance was noted, which might be due to high inter-individual variations. The nitrotyrosine expressions were significantly decreased after ecabet sodium treatment than before ($p<0.01$). In conclusion, ecabet sodium treatment was very useful for the relief of dyspeptic symptoms in chronic gastritis, to which both attenuated inflammatory and enhanced regenerative mechanisms were contributive.**

Key Words**: chronic gastritis, dyspepsia, ecabet sodium, *Helicobacter pylori***

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Introduction

Dyspepsia is one of the most common clinical problems encountered by either primary physicians or gastroenterology specialists [*1*]. It is estimated that about 20–25% of persons among general population have dyspepsia and the majority of these persons were classified as functional dyspepsia after ruling out organic causes [*2*]. Even though dyspepsia itself is not a life-threatening condition, patients with dyspeptic symptoms often interrupt their daily activities and suffered from poor quality of life. The exact pathogenesis of dyspepsia is not fully documented, but it has been suggested to be multi-factorials; for instances, acid-secretory abnormalities, gastrointestinal motor and sensory dysfunction, altered visceral perception, psychological factors, and *Helicobacter pylori* (*H. pylori*) infection, etc [*3–7*].

Since histological evidence of antral gastritis is often observed in patients with dyspepsia [*3*, *8*, *9*], the possibility that gastric inflammation might contribute to the pathogenesis of dyspepsia has long been considered, but still remains under debates [*10*]. Therefore, there has been no clear agreement which patients with the endoscopic evidence of gastritis should be treated or not. The uncertainty of the exact etio-pathogenic mechanisms of dyspepsia leads to that the variable methods of treatments attempted with controversial results in clinical practice [*11*, *12*]. Patients with dyspepsia usually have been treated with several modalities like acid suppressants, prokinetic drugs, eradication of *H. pylori*, and gastroprotective drugs, but variable treatment outcome has been reported.

In contrast to western countries, where gastric hyperacidity might be an important factor for dyspepsia, Asian patients have somewhat inferior acid secretory capacity compared with Caucasian patients [*13*, *14*], which can explain why real prescription in clinic was so much paid to gastroprotective drugs like prostaglandin derivatives, sucralfate, rebamipide, ecabet sodium, sofalcon, and teprenone in Asian countries including Korea and Japan.

Among these several gastroprotectants, ecabet sodium is derived from pine resin, which has been used for the treatment of gastric disease from ancient China and showed significant efficacy in the treatment of gastritis and peptic ulcer disease [*15*]. Once administered, ecabet sodium granules topically enhance gastric mucosal defense, suppress the urease activity of *H. pylori*, and show anti-inflammatory activities in the stomach [*16*]. Even though several studies documented that gastroprotective drug frequently prescribed for treatment of chronic gastritis could diminish gastric inflammation and enhance the regeneration of damaged mucosa, the report about the real merits of gastroprotectant on symptom relief was scarse until now. This study was designed either to evaluate the clinical efficacy of ecabet sodium on the treatment of dyspeptic symptoms in patients with chronic gastritis or to draw the plausible molecular mechanisms to explain how gastroprotectant like ecabet sodium was effective in relieving dyspeptic symptoms using the measurements of changes of mediators in gastric juice, known to reflect the condition of inflamed gastric mucosa [*17–19*].

Materials and Methods

Patients

Eight university hospitals in Korea nation-widely participated in the current prospective clinical trials. Between February 2002 and January 2003, consecutive patients who had persistent or recurrent dyspeptic symptoms such as epigastric pain, soreness, early satiety, fullness, bloating, nausea, vomiting and belching were recruited to participate. Persistent symptoms defined that symptoms had persisted for at least 3 months during last one year. Careful interview about symptoms like heartburn or substernal pain was performed by the investigator to exclude patients with gastroesophageal reflux disease or irritable bowel syndrome. All patients were underwent upper gastrointestinal endoscopic examination by gastroenterologists of each institution. Patients with gastric or duodenal ulcer, reflex esophagitis classified as higher than LA-A, gastrointestinal malignancy or hiatal hernia on upper gastrointestinal endoscopy were all excluded. Patients who had been treated with antacid, H_2-receptor antagonists, proton pump inhibitors and gastroprotective drugs within 1 week before the study were not eligible to participate and also patients were not allowed to take these medications during the study period. Previous medication history was completely recorded and patients who had history of gastric or duodenal ulcer, previous abdominal surgery and with pregnancy were also excluded. Informed consent was obtained from all patients after detail explanation. The protocols were also reviewed and approved in each participating institution under the review of ethical committee.

Study design

Patient's medical background, smoking, coffee and alcohol drinking habit, allergy history, and combined illness were recorded in detail. Patients with chronic gastritis and erosive gastritis with upper gastrointestinal endoscopic examination were enrolled. *H. pylori* infection was evaluated using rapid urease test, histology or urea breath test. With two biopsy samples obtained each from antrum and body, one biopsy sample each from antrum and body was used for rapid urease test and histology. *H. pylori* infection was considered to be positive if one of the three tests was positive. Blood was obtained for the laboratory study to exclude organic diseases. The following variables were determined; leukocyte, hemoglobin concentration, hematocrit, platelet, total bilirubin, aspartate aminotransferase, alanine aminotrasferase, alkaline

phosphatase, total protein, albumin, and total cholesterol. After the enrollment, patients received ecabet sodium 1 g *b.i.d.* for 2 weeks. Patient compliance was checked by counting returned medications at the end of clinical trials and patients who had taken less than 75% of medications and had not taken for more than 2 consecutive days were excluded from the study.

Dyspepsia symptoms were assessed by the investigator with a questionnaire, consisted of symptoms including epigastric pain, soreness, early satiety, fullness, bloating, nausea, vomiting and belching. The symptoms were scored 4-point Likert scale as follows: 0 (none), no symptoms; 1 (mild), awareness of symptoms but easily tolerated; 2 (moderate), symptoms sufficient to cause interference with normal activities; 3 (severe), incapacitating with an inability to perform normal activities. After the 2 weeks of treatment, the investigators assessed the over-all efficacy of treatment. The degree of improvement was scored 4-point scale as follows: 0, worsened; 1, no change; 2, slight improvement (1-point scale improvement); 3, much improvement (2-point scale improvement). No dyspeptic symptom with ecabet sodium treatment was classified as complete relief. We categorized enrolled subjects into 6 groups by age and symptom improvement was analyzed according to age groups. Adverse events during treatment were evaluated at the end of the study and were recorded in the case record form. An adverse event was defined as any unfavorable or unintended sign, whether or not considered to be related to the study drug.

Sixty patients agreed with the collection of specimens including gastric juices and mucosal biopsies during endoscopic examination. Twenty milliliters of gastric juices was aspirated and collected on blue-cap specimen tube with rapid freezing. These collections of gastric juices were repeated after the complete of clinical trials. Three pieces of gastric mucosa were also biopsied and sent to pathology.

Measurement of iNOS, IL-8, PGE_2, and VEGF levels of gastric juices

Proteins were extracted from collected gastric juices during endoscopic examination and amount of proteins were measured using BCA methods. Inducible nitric oxide (iNOS), interleukin-8 (IL-8), prostaglandin E_2 (PGE_2), and vascular endothelial growth factor (VEGF) were measured using ELISA kits (R&D, Mineapolis, MN) according to manufacturer instruction.

Immunohistochemical staining of nitrotyrosine in biopsied tissues

Using the 5 μm cut section of paraffinized biopsied sample, immunohistochemical staining was done using AEC as chromogen and nitrotyrosine antibody (1:200 dilution, Upstate, NY) with ABC technology. The intensities of nitrotyrosine staining were scored according to the degree of intensities from 0 to 4 (0 = none, 1 = positive staining within one fourth of observed area (100× magnification), 2 = between one forth and two fourth, 3 = between half and three fourth, and 4 = more than three fourth of observed area. Also we considered the intensities of positive staining with similar criteria.

Statistical analysis

The analyses were made by per protocol approach. The percentage of patients with symptom improvement and complete relief according to the individual symptoms were compared by a paired t test. The percentage of patients with symptom improvement and complete relief according to the age groups were compared by a chi-squared test and Fisher's exact test. A p value of <0.05 was considered as significant. Analysis was performed using SAS for Windows version 6.1.

Results

A total of 268 patients were enrolled in this study. Five patients who took less than 85% of medication were excluded, leaving 263 patients eligible for analysis. The demographic characteristics of patients were shown in Table 1. Endoscopic findings showed chronic superficial gastritis more than moderate degree and chronic erosive gastritis in 201 patients and 62 patients, respectively.

The most common symptom was epigastric soreness in 202 (76.8%) patients, followed by epigastric pain (74.1%), fullness (69.2%), bloating (65.0%), early satiety (60.5%), belching (39.2%), nausea (38.4%), and vomiting (10.3%) (Table 2a). Ecabet sodium significantly reduced the score of all dyspeptic symptoms ($p<0.001$). Epigastric soreness was

Table 1. Baseline characteristics of the study population

	Intent to treat (ITT)	Per protocol (PP)
Number of patients	268	263
Sex		
Male	91 (34.0%)	90 (34.0%)
Female	177 (66.0%)	173 (66.0%)
Age (years, mean ± SD*)	48.8 ± 12.7	48.6 ± 12.6
Liver disease	2	2
Renal disease	1	1
Coffee use	114	111
Smoking	39	39
Alcohol use	71	70
H. pylori status		
Positive	58 (52.7%)	56 (53.3%)
Negative	52 (47.3%)	49 (46.7%)

*SD, standard deviation

Table 2. Score of symptoms before and after ecabet sodium treatment

(a) Change of each symptom after treatment with the assessment of treatment outcome

Symptoms (n)	Score (mean ± SD*)			Treatment outcome	
	Treatment			Improvement (%)	Complete relief (%)
	Before	After	*p* value		
Epigastric pain (195)	1.8 ± 0.6	0.5 ± 0.7	<0.001	154/195 (79.0)	116/195 (59.5)
Soreness (202)	1.7 ± 0.7	0.4 ± 0.7	<0.001	165/202 (81.7)	130/202 (64.4)
Fullness (182)	1.6 ± 0.7	0.6 ± 0.7	<0.001	140/182 (76.9)	102/182 (56.0)
Early satiety (159)	1.6 ± 0.7	0.6 ± 0.7	<0.001	118/159 (74.2)	86/159 (54.1)
Bloating (171)	1.6 ± 0.7	0.6 ± 0.7	<0.001	123/171 (71.9)	93/171 (54.4)
Nausea (101)	1.3 ± 0.6	0.4 ± 0.6	<0.001	81/101 (80.2)	70/101 (69.3)
Vomiting (27)	1.4 ± 0.6	0.4 ± 0.8	<0.001	21/ 27 (77.8)	19/ 27 (70.4)
Belching (103)	1.5 ± 0.7	0.6 ± 0.6	<0.001	74/103 (71.9)	51/103 (49.5)

*SD, standard deviation

(b) Statistical significance of treatment outcome according to symptom group

Symptom (n)	Improvement of symptoms (%)		Complete relief of symptoms (%)	
	N (%)	*p* value	N (%)	*p* value
Pain group (62)	52/62 (83.9)		41/62 (66.1)	
Discomfort group (30)	19/30 (63.3)	0.02	17/30 (56.7)	0.27
Combined group (170)				
Pain dominant	130/170 (76.5)		97/170 (57.1)	
Discomfort dominant	111/170 (65.3)	0.02	87/170 (52.1)	0.27

improved most significantly (81.7%) followed by nausea and epigastric pain. Complete relief of symptom was observed in 59.7% of patients. The percentage of patients free from vomiting (70.4%) was the highest among symptoms, followed by nausea and soreness. Belching showed the lowest symptom resolution.

Patients were largely divided into three groups according to feature of complained symptom; epigastric pain and soreness were classified as "pain group" (62 patients) and other symptoms including early satiety, fullness and bloating were grouped as "discomfort group" (30 patients). One hundred and seventy patients had combined symptoms with pain and discomfort ("combined group"). Treatment outcome was compared among these groups as shown in Table 2b. In pain group, 52 out of 62 patients (83.9%) showed symptom improvement and complete relief was observed in 41 of 62 patients (66.1%). In discomfort group, 19 of 30 patients (63.3%) and 17 of 30 patients (56.7%) showed symptom improvement and complete relief, respectively. There was statistically significant difference in symptom improvement between pain group and discomfort group ($p = 0.02$), but not significant in the achievement of complete relief of symptoms ($p = 0.27$). In combined symptom group, there was significant difference in symptom improvement between pain and discomfort ($p = 0.02$) but no difference in complete relief between these two symptoms ($p = 0.27$).

Symptom improvement was compared according to age groups (Table 3a). Higher symptomatic improvements of epigastric pain and soreness were observed in older age group of 60–69 years but no statistical significance. On the other hand, other symptoms except epigastric pain and soreness improved in high frequency in relatively younger age groups than older age group, but it was also not significant. When we did perform the logistic regressional analysis, discomfort in age group less than 50 showed statistically significant improvement with ecabet sodium treatment ($p = 0.02$) (Table 3b).

Since the association between *H. pylori* infection and dyspeptic symptoms had been suggested [*3*, *7–9*], we further analyzed the changes of symptoms after ecabet sodium treatment according to *H. pylori* infection as shown in Table 4. Although the improvement of pain in combined group was highly achieved in *H. pylori* infection group after ecabet sodium treatment, there was no statistical significance ($p = 0.07$). In patients with combined group, complete relief of discomfort was observed in 20 of 29 patients (69.0%) with *H. pylori* infection and in 11 of 30 patients (36.7%) without infection and there was significant difference ($p = 0.01$).

No serious adverse events were reported during the study.

Table 3. Number of patients with improvement of symptoms according to age groups

(a) Statistical significance with the changes of symptom according to age group after treatment

Symptom	Age group (N, %)						*p* value
	20–29	30–39	40–49	50–59	60–69	70–	
Epigastric pain	12/15	21/27	47/60	38/49	33/39	3/5	0.82
	(80.0)	(77.8)	(78.3)	(77.6)	(84.6)	(60.0)	
Soreness	13/16	25/31	49/62	40/48	35/41	3/4	0.94
	(81.3)	(80.7)	(79.3)	(83.3)	(85.4)	(75.0)	
Fullness	14/18	24/28	45/56	28/39	26/35	3/6	0.43
	(77.8)	(85.7)	(80.4)	(71.8)	(74.3)	(50.0)	
Early satiety	14/17	18/25	35/44	25/33	25/35	1/5	0.15
	(82.4)	(72.0)	(79.6)	(75.8)	(71.4)	(20.0)	
Bloating	14/16	19/25	39/51	26/38	23/35	2/6	0.17
	(87.5)	(76.0)	(76.5)	(68.4)	(65.7)	(33.3)	
Nausea	12/14	14/17	22/29	15/18	15/19	3/4	0.98
	(85.7)	(82.4)	(75.9)	(83.3)	(79.0)	(75.0)	
Vomiting	1/2	5/6	6/8	6/6	2/3	1/2	0.44
	(50.0)	(83.3)	(75.0)	(100)	(66.7)	(50.0)	
Belching	11/13	12/15	19/25	15/24	15/22	2/4	0.56
	(84.6)	(80.0)	(76.0)	(62.5)	(68.2)	(50.0)	

(b) Multiple regression analysis of the changes of symptom according to age group after treatment

Symptom	Age group (N, %)					
	20–29	30–39	40–49	50–59	60–69	70–
Pain group	14/18 (77.9)	26/34 (76.5)	54/70 (77.1)	47/59 (79.7)	37/45 (82.2)	4/6 (66.7)
	Multiple regression *p* value 0.93					
Discomfort group	14/18 (77.9)	19/28 (67.9)	45/61 (73.8)	30/46 (65.2)	21/41 (51.2)	1/6 (16.7)
	Multiple regression *p* value 0.02					

Table 4. Improvement and complete relief of symptom in pain and discomfort group according to *H. pylori* infection

Symptom (n)	Improvement (N, %)			Complete relief (N, %)		
	HP (+)	HP(–)	*p* value	HP (+)	HP (–)	*p* value
Pain group (42)	22/26 (84.6)	13/16 (81.2)	1.0	14/26 (53.8)	10/16 (62.5)	0.58
Combined group (59)						
Pain (59)	25/29 (86.2)	20/30 (66.7)	0.07	18/29 (62.1)	13/30 (43.3)	0.07
Discomfort (59)	24/29 (82.8)	21/30 (70.0)	0.24	20/29 (69.0)	11/30 (36.7)	0.01
Discomfort group (4)	1/1 (100)	3/3 (100)	0	1/1 (100)	2/3 (66.7)	0

Five patients stopped medication due to adverse events such as epigastric pain, nausea, swollen face and vertigo. The adverse events were recovered completely and the causal relationship was described as unlikely by the investigators.

In order to search the underlying mechanisms to explain the clinical efficacy of ecabet sodium in the treatment of dyspeptic symptoms of chronic gastritis, we measured the real levels of IL-8, iNOS, PGE_2, and VEGF in gastric juices, based on the previous investigations [*17–19*] adopted the measurements of these mediators to reflect the inflamed and regenerating status of gastric mucosa (Fig. 1a). The mean levels of IL-8, iNOS and VEGF were 27.19 ± 4.15, 5.68 ± 0.43, and 45.08 ± 35.91 ng/ml before ecabet sodium treatment and 24.19 ± 4.22, 4.91 ± 0.60, and 43.39 ± 23.55 ng/ml after ecabet sodium treatment, respectively. Although there was tendency that IL-8 and iNOS was decreased much more after ecabet sodium treatment and VEGF increased after treatment, but none was statistically significant. The PGE_2 level

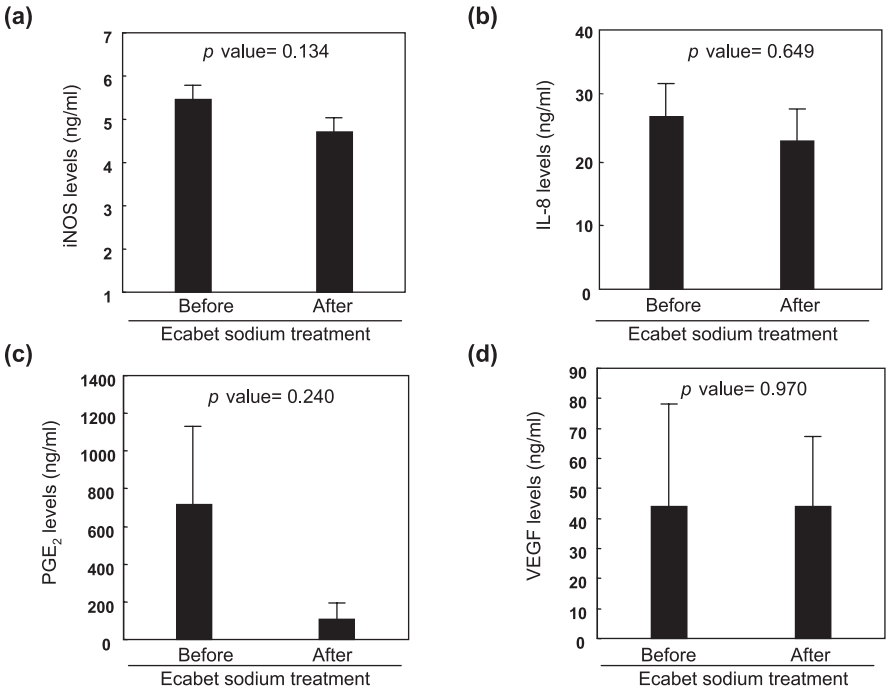

Fig. 1. The changes of iNOS, IL-8, PGE_2, and VEGF amounts in gastric juice after ecabet sodium treatment. ELISA measurements of gastric juices were repeated before and after ecabet sodium according to manufacturer's suggestions.

before ecabet sodium treatment was 704.25 ± 436.69 ng/ml, which was decreased to 149.51 ± 41.1 ng/ml, but also no statistical significance ($p = 0.24$). The reason of this statistical insignificance of these mediators by ELISA measures might be too diverse individual variations of each mediator in spite of tendency of changes. The changes of nitrotyrosine expressions, the index of oxidative stress in gastritis [*20*], were significantly decreased after the treatment of ecabet sodium (Fig. 2a & 2b). The levels of nitrotyrosine expression were markedly decreased after the treatment of ecabet sodium (Fig. 2a). There was statistical significance in the levels of nitrotyrosine between before and after ecabet sodium treatment ($p<0.01$, Fig. 2b).

Discussion

The current study revealed that the gastroprotective drug, ecabet sodium, was very effective in the treatment of dyspepsia symptom originated from chronic gastritis based on the considerable rates of symptom relief, no serious side effects, and high compliance. Moreover, the significant changes in either decreasing cytokines or mediators responsible for perpetuating inflammation or increasing mediators involved in regeneration were observed in gastric juices after ecabet sodium administration, which could explain the mechanisms of clinical improvement in the treatment of dyspepsia of chronic gastritis [*29*].

Although there have been several studies showing that cytoprotective drug revealed several advantages of anti-inflammation, antioxidation, accelerating ulcer healing, and the achievement of quality of healing [*21*, *22*], there were few trials that had addressed the real clinical benefit of symptom resolution in patients with chronic gastritis in addition to attenuated inflammatory activities. The reason for this rarity of reports was due to the absence of the any objective measures available for assessing treatment success of gastric cytoprotective drug [*23*]. In the current study, even though we could document the clear tendency of the changes of inflammatory mediators or cytokines in gastric juices, the statistical significance was not seen due to rather high individual variations of their levels.

Also there was clear difference in life style and perception of dyspeptic symptoms between Western and Orient. For example, Talley N.J. *et al.* [*24*] published one report done with rebamipide that the gastroprotective drug did not show any benefit in the treatment of functional dyspepsia, but which might be due to the inappropriateness of parameter adopted. In addition, a high placebo response has been a matter of concern in previous trials using less stringent endpoints than complete relief of symptoms parameter used in this study [*23*, *25*]. Since the aim of our study was to document the in detail changes of dyspeptic symptoms after ecabet sodium, we did not consider the comparison study including placebo. However, as referenced with placebo response rate like our study, the current study showed symptom improvement in more than 70% of studied subjects

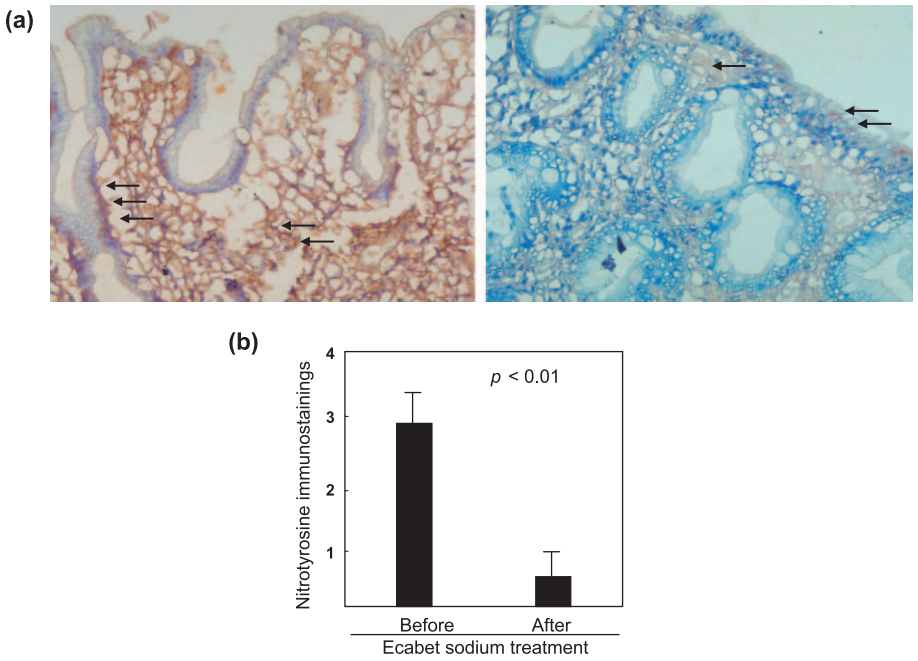

Fig. 2. The change of nitrotyrosine expressions after ecabet sodium treatment. (a) The immunohistochemical expressions of nitrotyrosine (×100 magnification). The expressions of nitrotyrosine were observed in epithelium, submucosal tissues, but its expressions were markedly decreased after ecabet sodium treatment. (b) The changes of mean expression of nitrotyrosine before and after ecabet sodium treatment.

that was higher than placebo response in other studies. Moreover, in the current our trial, we prospectively evaluated the changes of dyspeptic symptoms in detail and classified the symptoms into largely three main groups. All these evaluations were scored objectively by clinical coordinators, who instruct the patient score properly and performed in several institutions with the same protocol guideline. Also we performed the biologic evaluation to support the clinical outcomes.

Although close association between dyspepsia and *H. pylori* infection has been suggested [*3*, *7*–*9*], it still remains not completely documented. In our study, there was no relation between the presence of *H. pylori* and the incidence of dyspepsia in patients with chronic gastritis. Therefore, ecabet sodium was not more effective in patients with *H. pylori*-associated chronic gastritis. Our prospective study was designed to investigate whether cytoprotective therapy with ecabet sodium 1 g *b.i.d.* would provide the real advantage of symptom relief in dyspeptic patients with chronic gastritis. As a result, soreness was the most common symptom and the best responded to ecabet sodium treatment followed by nausea and epigastric pain. Discomfort is a term used to describe a subjective, negative feeling that patient does not interpret as pain, which can include upper abdominal fullness, early satiety, bloating. There was significant difference in symptom improvement between pain group and discomfort group after ecabet sodium treatment and also in combined symptom group with pain and discomfort, the significant difference in symptom improvement was observed. As 2 weeks treatment duration might be short to obtain the best effective therapeutic benefit, longer duration of treatment may have more benefits.

If gastric cytoprotective drugs are efficacious for symptom resolution in patients with chronic gastritis, by what mechanisms do they improve symptoms? The possible explanation may relate to the mucosa being more sensitive in dyspeptic patients with chronic gastritis. The several studies [*8*, *26*, *27*, *29*] showed that gastric inflammatory reaction is basically related to dyspeptic symptoms. Although controversial, it was reported that *H. pylori* infection was associated with significant gastric sensitivity to dyspeptic symptoms [*26*]. As the causal association between *H. pylori* infection and gastritis is well established, gastric mucosal inflammation may play a key role in enhancing gastric sensitivity to dyspeptic symptoms. Although we hypothesized that ecabet sodium might show better efficacy in *H. pylori* infected patients, there was no significant difference in symptom improvement between *H. pylori* positive and negative patients except combined symptom group with pain and discomfort. We inferred that the small number of patients with *H. pylori* infection might make this discrepancy. Therefore, further large scaled studies are necessary to document this suggestion.

In the current study, we compared the real levels of

inflammatory mediators such as IL-8, iNOS, PGE_2 in gastric juices and nitrotyrosine in gastric mucosa which levels were decreased after ecabet sodium treatment whereas VEGF, one of key growth factors essential in mucosal regeneration, were apparently increased after ecabet sodium treatment. Although we could not find statistically significant decrease in IL-8, iNOS, PGE_2 as seen in Fig. 1, this could be explained by the wide variation of the individual levels in spite of clear decreasing tendency. Even though we tried to check the changes of inflammation scores before and after ecabet sodium, non-consistency in scoring among the pathologists of participating institutions and sites of biopsied tissues moved to compare the intensities of nitrotyrosin immunostaining and the levels of some mediators in aspirated gastric juices in the current trial.

Recently it was reported that ecabet sodium might improve symptoms in patients with dysmotility-like dyspepsia by gastric adaptive relaxation in animal model [*28*] and showed similar clinical efficacy with cimetidine on functional dyspepsia [*29*]. Epigastric pain and soreness improved markedly than other symptoms and belching showed the lowest symptom resolution in both improvement and complete relief analysis in this study. This result suggested that symptom improvement with ecabet sodium treatment could be obtained by mainly gastric cytoprotective mechanisms along with by the improvement of decreased reservoir function of stomach. However, further *in vivo* experiments are necessary to confirm this hypothesis.

The current study also suggested that ecabet sodium treatment was well tolerated and safe because no significant adverse effects were noted during the study period. Although five patients stopped the medication, it was finally proved to be not associated with medications.

In conclusion, ecabet sodium was useful in the management of dyspeptic symptoms with chronic gastritis irrespective of *H. pylori* infection in Korea. Epigastric soreness and pain were the best-responded symptoms with ecabet sodium treatment. Even though gastric cytoprotective mechanisms including anti-inflammation, antioxidation, and enhanced regeneration could attribute to the mechanisms to explain the attenuation of dyspeptic symptoms, further investigation about its long-term benefit and more detailed evaluation with larger scales are warranted.

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