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Effect of Rebamipide on the Premalignant Progression of Chronic Gastritis: A Randomized Controlled Study

Xue Han[1,2] · Kui Jiang[1] · Bangmao Wang[1] · Lu Zhou[1] · Xin Chen[1] · Shu Li[1]

Abstract

Background and Objective Chronic gastritis frequently progresses into precancerous intestinal metaplasia and intraepithelial neoplasia lesions. Rebamipide is a free radical scavenger and we assessed its efficacy on clinical symptoms, gastric mucosal lesions, pathologic grade, and immunohistochemistry in chronic gastritis patients.

Methods 178 eligible patients were randomized into treatment and control groups. Both groups followed an optimized lifestyle for 26 weeks, but the treatment group was additionally medicated with rebamipide 0.1 g three times per day. Upper gastrointestinal endoscopy was performed in all patients to evaluate the severity of gastritis by the Modified Lanza Scoring (MLS) and histological changes were evaluated by the Updated Sydney System Score (USSS). Gastric mucosa immunohistochemistry in the treatment group was performed using the intestinal metaplasia markers caudal type homeobox transcription factor 2 (CDX2) and trefoil factor 3 (TFF3) detection.

Results There were significant outcome differences between the treatment and control groups regarding the clinical symptom scores (2.62 ± 1.86 vs. 1.55 ± 1.61, $P = 0.0001$), gastric mucosal lesion scores (0.57 ± 1.05 vs. 0.16 ± 0.90, $P = 0.002$), and inflammation ($P < 0.05$).

Only in the treated patients were the rates of intestinal metaplasia ($P = 0.017$ vs. $P = 0.123$) and low-grade intraepithelial neoplasia ($P = 0.005$ vs. $P = 0.226$) significantly reduced after 26 weeks. The percentages of CDX2 (31.5 vs. 15.7 %, $P = 0.021$) and TFF3 (44.9 vs. 25.8 %, $P = 0.012$) expressing gastric mucosa cells were significantly lower after rebamipide medication than pre-treatment values.

Conclusions Rebamipide improved the clinical symptoms, gastric mucosal lesions, and pathological grades of chronic gastritis patients and decreased the expression rates of CDX2 and TFF3 in gastric cells.

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Key Points
Chronic gastritis can progress through the precancerous gastric lesions intestinal metaplasia and gastric intraepithelial neoplasia, resulting in gastric cancer.
Besides clinical symptom and gastric mucosal lesion scores, the markers for intestinal metaplasia caudal homeobox transcription factor 2 (CDX2) and trefoil factor 3 (TFF3) can be used to evaluate the progression of chronic gastritis.
Treatment with rebamipide 0.1 g three times per day for 26 weeks significantly reduced clinical symptom and gastric mucosal lesion scores as well as inflammation, intestinal metaplasia, and low-grade intraepithelial neoplasia. The percentages of CDX2 and TFF3 expressing gastric mucosa cells were significantly lower after rebamipide medication than pre-treatment values.

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1 Introduction

Chronic gastritis is prevalent in 80–90 % of patients undergoing upper gastrointestinal endoscopy. A major cause of chronic gastritis and the subsequent development of stomach cancers is *Helicobacter pylori* infections, which have been reported to induce active inflammation as well as the production of oxygen free radicals that produce DNA damage [1, 2]. In an earlier 5-year observation study, it was noted that successful eradication of *H. pylori* infections decreased the grades of gastric corpus and antrum atrophies as well as the levels of metaplasia [3]. Subsequently, it was proposed that the most appropriate intervention prior to the appearance of precancerous lesions is *H. pylori* infection medication [4]. Gastric carcinogenesis originates in the normal mucosa as superficial gastritis and progresses through atrophic gastritis, intestinal metaplasia, and gastric intestinal dysplasia, resulting in gastric cancer. Recently, the term gastric intestinal dysplasia was replaced by intraepithelial neoplasia and defined together with intestinal metaplasia as gastric precancerous lesions [5, 6]. There are several markers for aberrant cell development of the stomach. Ectopic caudal type homeobox transcription factor 2 (CDX2) protein is only expressed in gastric mucosa with intestinal metaplasia [7–9] and, since intestinal metaplasia has been proposed as gastric precancerous lesion, CDX2 overexpression was noted as a potential marker for gastric cancer [10–12]. Another marker for gastric cancer is serum trefoil factor (TFF) 3 [13, 14]. As a mucosa protective agent, rebamipide inhibits the activation of white blood cells [15], scavenges free radicals [16], and increases gastric mucus secretion [17] and prostaglandin levels [18].

In this randomized controlled study, we evaluated the efficiency of rebamipide for medication of chronic gastritis and focused on improvements of symptoms, gastric mucosal lesions, and changes of CDX2 and TFF3 expression.

2 Patients and Methods

2.1 Patients

Participants eligible for the study were patients with diagnosed chronic gastritis by endoscopy within 1 week who had least two of the following symptoms: symptoms of upper abdominal pain; distension; acid reflux; belching; loss of appetite; and nausea and vomiting [19]. Exclusion criteria were as follows: other digestive diseases, such as peptic ulcer or malignant diseases (including high-grade intraepithelial neoplasia); patients with severe cardiac, hepatic, or renal dysfunction and a history of neoplastic diseases; patients treated with drugs such as proton pump inhibitors (PPIs), histamine H_2 receptor antagonists, mucosal protective agents, or antibiotics 2 weeks prior to the initiation of the study; patients administered aminosalicylic acid (aspirin), non-steroidal anti-inflammatory drugs (NSAIDs), or anticoagulants; patients with mental illnesses or alcohol and drug addiction as well as allergies or a medical history of hypersensitivity to the investigational drugs; and, in case of women, pregnancy or lactation.

A total of 180 patients were initially enrolled and 178 patients were included in our randomized controlled study. *H. pylori* infections were diagnosed in 110 participants, and in 108 patients the infections were successfully eradicated. These participants were randomized into treatment group 1 ($n = 54$) and control group 1 ($n = 54$). The other 70 participants without *H. pylori* infections were randomized into treatment group 2 ($n = 35$) and control group 2, but one patient in control group 2 was lost during the study period ($n = 34$) (Fig. 1).

2.2 Detection and Treatment of *Helicobacter pylori* Infection

Helicobacter pylori status was determined using the 13C-urea breath test [20]. Patients with *H. pylori* infections were treated with a combination of esomeprazole 20 mg, colloidal bismuth pectin 200 mg, clarithromycin 500 mg, and amoxicillin 1000 mg twice daily for 14 days. Patients in whom *H. pylori* infections were not eradicated after the first treatment period received an additional 2-week course of medication consisting of levofloxacin 500 mg, furazolidone 100 mg, a standard dose of a PPI, and bismuth.

2.3 Rebamipide Treatment

Patients in the treatment groups received an open-labeled treatment of rebamipide 100 mg (Zhejiang Otsuka Pharmaceutical Co. Ltd., Hangzhou, Zhejiang, China) orally three times per day for 26 weeks. Both the treatment and control groups were advised to avoid alcohol, tobacco, and spicy foods during the treatment period, which was confirmed verbally during the visits.

2.4 Symptom Evaluation

A questionnaire was used to investigate symptoms such as upper abdominal pain, distension, acid reflux, belching, loss of appetite, and nausea and vomiting before and after treatment. All of these symptoms were rated by patients on a visual analog scale from 0 for none to 3 for worst [21].
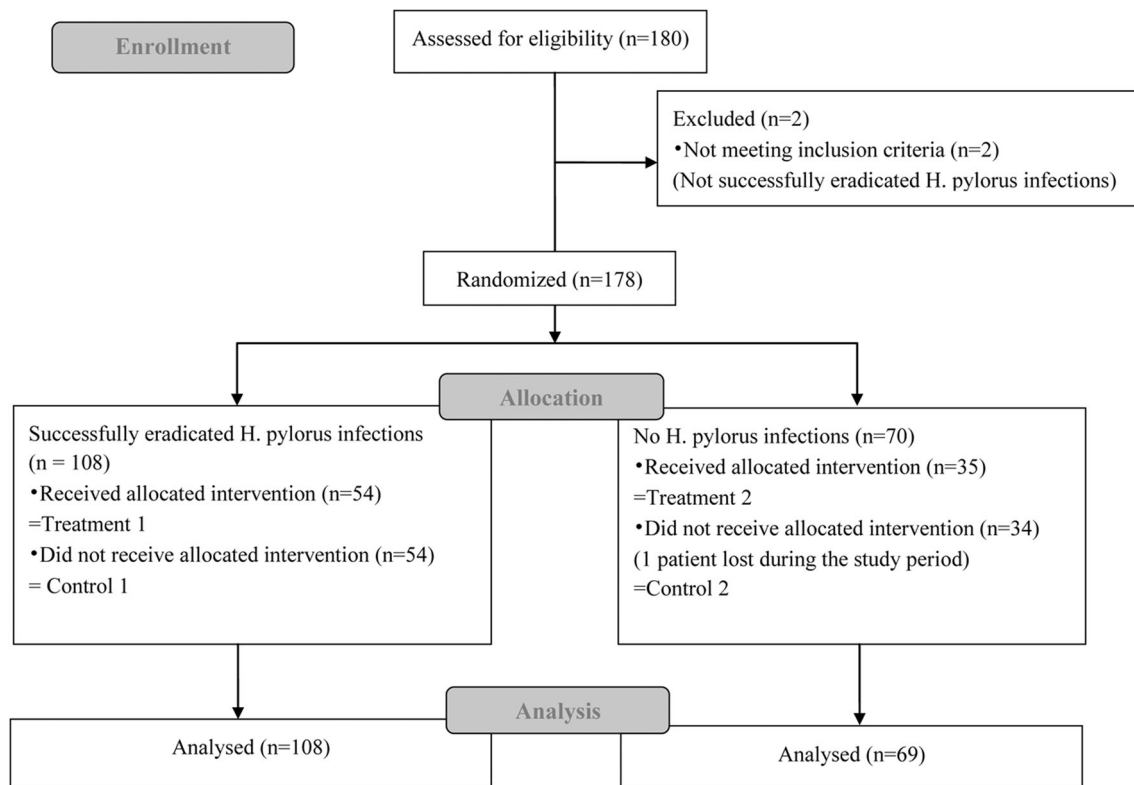
Fig. 1 Flow diagram of patient recruitment and follow-up

2.5 Endoscopic Evaluation

The endoscopic appearance of the mucosa was observed and evaluated according to the modified Lanza Scoring (MLS) [22] from grade 0 to 5: grade 0 = no erosion or hemorrhage; grade 1 = erosion and hemorrhage localized in one area, <2 lesions; grade 2 = erosion and hemorrhage localized in one area, 3–5 lesions; grade 3 = erosion and hemorrhage in two areas, with >6 lesions in one area and <10 lesions in the whole stomach; grade 4 = erosion and hemorrhage appeared in three or more areas; and grade 5 = gastric ulcer.

2.6 Histological Evaluation

Biopsy specimens were taken from the most severe affected site (the same site the biopsy specimen was taken from at enrollment) after 26 weeks of therapy. After the paraffin-embedded tissues were sliced into 4 μm slides, they were dewaxed, dehydrated, and subsequently stained with hematoxylin and eosin (H&E). All specimens were evaluated and graded for gastritis according to the Updated Sydney System Score (USSS) for chronic mononuclear inflammatory cells, neutrophil activity, and intestinal metaplasia: 0 = normal, 1 = mild, 2 = moderate, and

3 = severe [23]. The scores were used to assess the improvement in clinical symptoms. If low-grade intraepithelial neoplasia turned into non-intraepithelial neoplasia, the treatment was considered efficacious. Between-group efficacy differences were used to assess the improvement in low-grade intraepithelial neoplasia.

2.7 Immunohistochemistry Evaluation

Samples harvested from the patients in the treatment groups before and after medication were treated with a standard procedure. Before immunohistochemistry, deparaffinized sections were placed in 0.01 M of citrate buffer (95 °C) for 15–20 min and washed in phosphate buffered saline (PBS) several times after natural cooling. The sections were then placed in the blocking solution (10 % normal goat serum in PBS) for 10 min and then incubated with rabbit polyclonal anti-CDX2 1:400 dilution (Abcam, Shanghai, China) or rabbit polyclonal anti-TFF3 1:200 dilution (Abcam, Shanghai, China) antibodies overnight at 4–8 °C. The streptavidin–peroxidase (S-P) method was used to detect the expression of CDX2 and TFF3. Positive cells were characterized by yellow or dark-brown signals in the nucleus (CDX2) or in the plasma (TFF3). The positive rate was calculated according to the number of

positive cells at magnification (400×): 0 points for ≤5 %; 1 point for 5–25 %; 2 points for 25–50 %; 3 points for 50–75 %; and 4 points for >75 %. The coloring depth of the positive cells was calculated as follows: 0 points for basically non-stained; 1 point for yellow staining; 2 points for brown staining; and 3 points for dark-brown staining. The two points were then multiplied and if the product was 0, it indicated a negative (−) result; if the product was between 1 and 4 points, it indicated a weakly positive result (+); if the product was between 5 and 8 points, it indicated a moderately positive result (++); and if the product was between 9 and 12 points, it indicated a strongly positive result (+++).

2.8 Statistical Analysis

SPSS® (SPSS Inc., Chicago, IL, USA) version 17.0 for Windows software was used for all statistical calculations. Student's t test was used for analysis of normally distributed data. The Wilcoxon test was used for non-normally distributed data. All values were expressed as the mean ± standard deviation. Statistical significance was defined at the $P < 0.05$ level.

3 Results

3.1 Characteristics of the Patients

A comparison of demographic characteristics showed that there were no significant differences between the four groups in terms of age, sex, or clinical and pathologic features (Table 1).

3.2 Effects of Rebamipide on Clinical Symptoms

Pre- and post-treatment differences in clinical symptoms between treatment group 1 and control group 1 in the successful *H. pylori* eradication therapy group were 2.48 ± 1.84 and 1.52 ± 1.81 ($P = 0.004$), respectively. Pre- and post-treatment differences in clinical symptoms between treatment group 2 and control group 2 in the *H. pylori*-negative group were 2.83 ± 1.90 and 1.59 ± 1.81 ($P = 0.001$), respectively. Differences in clinical symptoms between the treatment and control groups were 2.62 ± 1.86 and 1.55 ± 1.61 ($P = 0.0001$), respectively (Tables 2, 3).

3.3 Comparison of Gastric Mucosa Improvements

All patients were graded for endoscopic MLS before and after treatment. Compared with the control groups, a significant improvement in endoscopic scores was observed in the treatment groups after 26 weeks both in the *H. pylori* eradication and the *H. pylori*-negative groups (0.70 ± 1.12 vs. 0.28 ± 0.90, $P = 0.036$ and 0.37 ± 0.91 vs. − 0.03 ± 0.87, $P = 0.015$, respectively) (Table 4). Comparing all treatment patients with all control patients, the gastric mucosal lesion scores improved significantly in the treatment groups ($P = 0.002$) (Table 5).

3.4 Changes in Histology

Patients with chronic gastritis always presented with varying degrees of neutrophil and mononuclear cell infiltration. At the end of the study, significantly higher

Table 1 Comparison of the clinical and pathologic features

Feature	Group with successful *Helicobacter pylori* eradication therapy		*H. pylori*-negative group		P value
	Treatment group 1 ($n = 54$)	Control group 1 ($n = 54$)	Treatment group 2 ($n = 35$)	Control group 2 ($n = 34$)	
Mean age (years)	56.50	57.70	56.10	55.00	0.79
Sex (male/female), n	30/24	25/29	16/19	19/15	0.65
Clinical symptoms	3.87 ± 1.81	4.00 ± 1.39	3.97 ± 1.67	3.62 ± 1.81	0.42
Upper gastrointestinal endoscopy scores (MLS)	1.91 ± 0.85	1.87 ± 0.78	1.83 ± 0.71	1.79 ± 0.64	0.98
Inflammation	1.64 ± 0.95	1.52 ± 0.64	1.60 ± 0.77	1.51 ± 0.87	0.07
Intestinal metaplasia	1.20 ± 0.81	1.28 ± 0.84	1.40 ± 0.93	1.18 ± 0.75	0.83
Low-grade intraepithelial neoplasia (yes/no), n	40/14	34/20	24/11	21/13	0.56

Values are expressed as mean ± standard deviation unless specified otherwise

MLS Modified Lanza Scoring

Table 2 Improvement of post-treatment clinical symptoms

Clinical symptoms	Group with successful *Helicobacter pylori* eradication therapy			*H. pylori*-negative group		
	Treatment group 1 (*n* = 54)	Control group 1 (*n* = 54)	*P* value	Treatment group 2 (*n* = 35)	Control group 2 (*n* = 34)	*P* value
Pre-treatment	3.87 ± 1.81	4.00 ± 1.39	0.467	3.97 ± 1.67	3.62 ± 1.81	0.243
Post-treatment	1.39 ± 1.31	2.48 ± 1.54	<0.001	1.14 ± 1.17	2.03 ± 1.06	0.002
Change	2.48 ± 1.84	1.52 ± 1.49	0.004	2.83 ± 1.90	1.59 ± 1.81	0.001

Values are expressed as mean ± standard deviation

The *P* value of the difference between the treatment group 1 and treatment group 2 was 0.335. The *P* value of the difference between the control group 1 and control group 2 was 0.859

Table 3 Comparison of pre- and post-treatment clinical symptoms

Clinical symptoms	Treatment group (*n* = 89)	Control group (*n* = 88)	*P* value
Pre-treatment	3.91 ± 1.75	3.85 ± 1.56	0.978
Post-treatment	1.29 ± 1.25	2.31 ± 1.38	<0.0001
Change	2.62 ± 1.86	1.55 ± 1.61	0.0001

Values are expressed as mean ± standard deviation

Table 4 Improvement of post-treatment gastric mucosal lesion scores

Gastric mucosal lesions	Group of successful eradication *Helicobacter pylori* therapy			*H. pylori*-negative group		
	Treatment group 1 (*n* = 54)	Control group 1 (*n* = 54)	*P* value	Treatment group 2 (*n* = 35)	Control group 2 (*n* = 34)	*P* value
Pre-treatment	1.91 ± 0.85	1.87 ± 0.78	0.932	1.83 ± 0.71	1.79 ± 0.64	0.879
Post-treatment	1.20 ± 1.09	1.59 ± 0.84	0.031	1.46 ± 1.04	1.82 ± 0.67	0.024
Difference	0.70 ± 1.13	0.28 ± 0.90	0.036	0.37 ± 0.91	−0.03 ± 0.87	0.015

Values are expressed as mean ± standard deviation

The *P* values of the pre-treatment differences were 0.201 for treatment groups 1 and 2 and 0.067 for control groups 1 and 2

Table 5 Comparison of pre- and post-treatment gastric mucosal lesion scores in the treatment and control groups

Gastric mucosal lesions	Treatment groups (*n* = 89)	Control groups (*n* = 88)	*P* value
Pre-treatment	1.87 ± 0.80	1.84 ± 0.73	0.7941
Post-treatment	1.30 ± 1.07	1.68 ± 0.78	0.0075
Difference	0.57 ± 1.05	0.16 ± 0.90	0.002

Values are expressed as mean ± standard deviation

reductions in neutrophil cell infiltration were achieved in treatment groups 1 and 2 (0.44 ± 1.08 vs. 0.04 ± 0.88, $P = 0.037$; 0.40 ± 0.77 vs. −0.04 ± 0.36, $P = 0.006$, respectively) than in control groups 1 and 2. Apparent reductions were observed in control group 1, but the effect did not reach statistical significance, whereas no reduction was observed in control group 2. Besides inflammation

status, intestinal metaplasia before and after treatment were also evaluated, and in the treatment groups apparent reductions were observed but without statistical significance (Table 6).

Next, we investigated the pre- and post-treatment pathologically positive rates of intestinal metaplasia and low-grade intraepithelial neoplasia, which were both

Table 6 Inflammation and intestinal metaplasia before and after rebamipide treatment (Updated Sydney System Score)

Parameter		Group with successful *Helicobacter pylori* eradication therapy			*H. pylori*-negative group		
		Treatment group 1 (*n* = 54)	Control group 1 (*n* = 54)	*P* value	Treatment group 2 (*n* = 35)	Control group 2 (*n* = 34)	*P* value
Neutrophil cell infiltration (inflammation)	Pre-treatment	1.64 ± 0.95	1.52 ± 0.64	0.256	1.60 ± 0.77	1.51 ± 0.87	0.585
	Post-treatment	1.19 ± 0.79	1.48 ± 0.74	0.038	1.20 ± 0.72	1.56 ± 0.91	0.198
	Difference	0.44 ± 1.08	0.04 ± 0.88	0.037	0.40 ± 0.77	–0.04 ± 0.36	0.006
Intestinal metaplasia	Pre-treatment	1.20 ± 0.81	1.28 ± 0.84	0.554	1.40 ± 0.93	1.18 ± 0.75	0.612
	Post-treatment	1.10 ± 0.79	1.35 ± 0.88	0.231	1.13 ± 0.94	1.64 ± 0.92	0.174
	Difference	0.10 ± 1.09	–0.07 ± 0.80	0.508	0.27 ± 1.31	–0.45 ± 0.69	0.07

Values are expressed as mean ± standard deviation

greatly reduced in the rebamipide group compared with the control group ($P = 0.017$ and $P = 0.005$, respectively) (Table 7).

3.5 Changes in Expression of CDX2 and TFF3

To investigate the effect of rebamipide on epithelial cells of the gastric mucosa with intestinal metaplasia further, the expression of CDX2 and TFF3 were determined in samples harvested from 89 patients in the rebamipide group before and after treatment. The immunohistochemistry results showed that the CDX2 and TFF3 positive cell ratio was significantly changed after 26 weeks of therapy (Fisher's exact test: 31.5 vs. 15.7 %, $P = 0.021$ for CDX2 and 44.9 vs. 25.8 %, $P = 0.012$ for TFF3) (Figs. 2, 3, 4, 5; Table 8).

4 Discussion

In our patients, 61 % had *H. pylorus* infections, indicating that these bacteria are a major contributor to chronic gastritis. Gastric carcinoma has been attributed to *H. pylorus* infections [24, 25], but other authors have suggested that *H. pylori* may only produce an environment conducive to carcinogenesis and interact with other lifestyle and environmental exposures [26, 27]. Since eradication of *H. pylori* infections became a common measure to reduce the
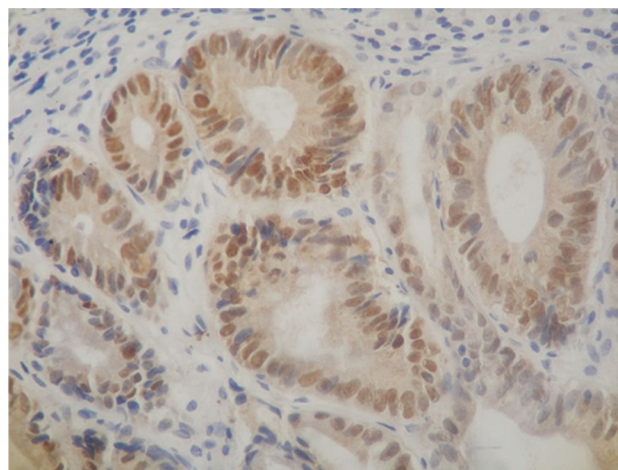

Fig. 2 Expression of caudal type homeobox transcription factor 2 (CDX2) in the gastric mucosa intestinal metaplastic cells (*brown color* indicates expression) (magnification ×400)

incidence of gastric cancer, the question arose whether intestinal metaplasia of the stomach can be reversed [28]. A previous study indicated that eradication alone does not completely prevent gastric cancer, and that this approach may be useful only in patients without atrophic gastritis or intestinal metaplasia [29]. Therefore, drugs that can restore normal gastric cell architecture after chronic gastritis are needed.

Table 7 Comparison of intestinal metaplasia and low-grade intraepithelial neoplasia before and after treatment

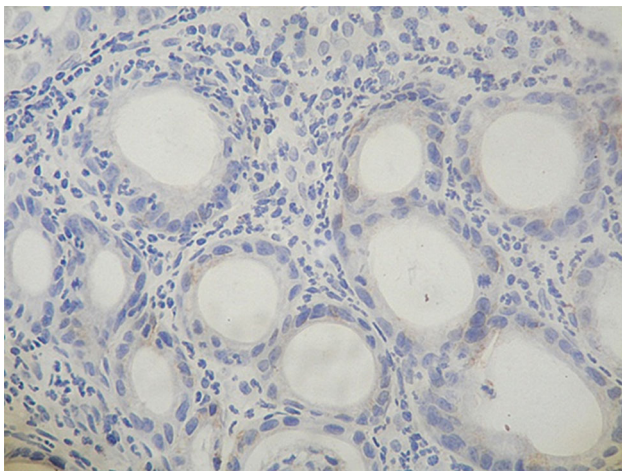| Pathologic features		Treatment group				Control group			
		n	Positive [*n* (%)]	χ^2	*P* value	*n*	Positive [*n* (%)]	χ^2	*P* value
Intestinal metaplasia	Pre-treatment	89	80 (89.9)			88	72 (81.8)		
	Post-treatment	89	67 (75.3)	6.601	0.017	88	80 (90.9)	3.088	0.123
Low-grade intraepithelial neoplasia	Pre-treatment	89	64 (71.9)			88	55 (62.5)		
	Post-treatment	89	45 (50.6)	8.544	0.005	88	46 (52.3)	1.638	0.226

χ^2 Chi-squared

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Fig. 3 Negative control of caudal type homeobox transcription factor 2 (CDX2) expression in the gastric mucosa (*brown color* indicates expression) (magnification ×400)

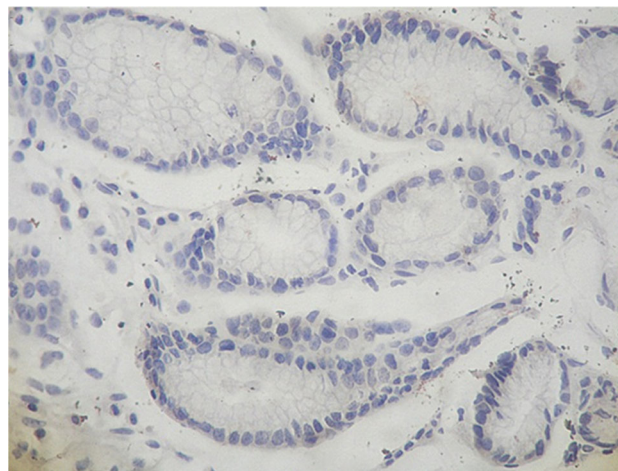**Fig. 5** Negative control of trefoil factor 3 (TFF3) expression in gastric mucosa cells (*brown color* indicates expression) (magnification ×400)
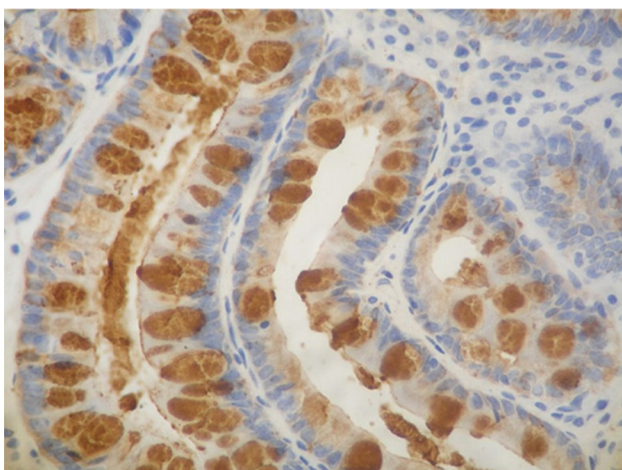

Fig. 4 Expression of trefoil factor 3 (TFF3) in gastric mucosa intestinal metaplastic cells (*brown color* indicates expression) (magnification ×400)

Rebamipide is an amino acid derivative of 2-quinolinone and has been shown to act via several mechanisms. Besides inhibition of reactive oxygen species, it stimulates prostaglandin and the prostaglandin EP_4 receptor, leading to reduced gastric acid and enhanced mucus glycoprotein synthesis. Furthermore, rebamipide has anti-inflammatory properties that act by reducing inflammatory cytokines and chemokines in addition to inhibition of neutrophil cell activation [30]. Notably, rebamipide increased endothelial growth factor (EGF) and EGF receptor (EGF-R) expression in gastric mucosa of rats, thereby facilitating cell proliferation and re-epithelialization [31], and restored sonic hedgehog activity, which has implied an action in reversing gastric atrophy [32]. Other effects of rebamipide were reported to be normalization of the oxidative state and tyrosine nitration of ERK in portal hypertensive gastric mucosa, thereby reversing the impaired mucosal healing [33] and triggering vascularization via induction of proangiogenic genes [34]. In our study, CDX2 and TFF3 were selected as the immunohistochemical indicators to analyze the degree of intestinal metaplasia. Progressive loss of TFF1 and TFF2, together with the induction of TFF3, has been proposed as being involved in the early stages of the multi-step gastric carcinogenesis pathway [35]. CDX2 is a marker for intestinal metaplasia [7–9] and both markers were significantly reduced in the rebamipide treatment groups (Table 8), which indicates a reduction of intestinal metaplasia and low-grade intraepithelial neoplasia cells. Also, inflammation was reduced significantly more in the rebamipide treatment groups, as evidenced by less visible neutrophil cell infiltration (Table 6).

5 Conclusion

Helicobacter pylori eradication therapy and gastric mucosa recovery treatment, with regular follow-ups and periodic upper gastrointestinal endoscopy, are effective procedures

Table 8 Comparison of pre- and post-treatment CDX2 and TFF3 positive rates

	n	CDX2			TFF3		
		Positive [n (%)]	χ^2	P value	Positive [n (%)]	χ^2	P value
Pre-treatment	89	28 (31.5)			40 (44.9)		
Post-treatment	89	14 (15.7)	6.108	0.021	23 (25.8)	7.1	0.012

χ^2 Chi-squared, *CDX2* caudal type homeobox transcription factor 2, *TFF3* trefoil factor 3

in patients with chronic gastritis. Rebamipide is an efficacious medication for mucosa recovery of chronic gastritis patients.

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