Cellular and Molecular Biology
E-ISSN : 1165-158X / P-ISSN : 0145-5680
www.cellmolbiol.org

Original Research

The combination therapy with esomeprazole and flupenthixol/melitracen in symptom improvement of erosive gastritis complicated with negative feelings compared with Esomeprazole alone

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Received December 28, 2019; **Accepted** May 22, 2020; **Published** July 31, 2020

Doi: http://dx.doi.org/10.14715/cmb/2020.66.5.3

Abstract: The purpose of this study was to evaluate the co-prescription efficacy of esomeprazole and flupenthixol/melitracen relative to that of solitary esomeprazole on erosive gastritis complicated with negative feelings. 140 erosive gastritis patients complicated with negative feelings enrolled in the present study. Seventy cases in the control group took esomeprazole, and 70 cases in the observation group received esomeprazole plus flupenthixol/Melitracen, both for 4 weeks. We gastroscopically checked the clinical symptoms, mucosal erosion, PGE2 and MDA levels in gastric mucosa, anxiety, depression, and recurrence before and after treatment in the groups. After treatment, the observation group had lower scores of clinical symptoms, mucosal erosions, Hamilton Depression Rating Scale (HAMD), and Hamilton Depression Rating Scale (HAMA) than the control group ($p<0.05$); as well, the observation group showed higher PGE2 and lower MDA levels than the control group ($p<0.05$); during six months of follow-up (100% follow-up rate), 16 and 34 recurrent cases occurred, respectively, in the observation and control groups ($p<0.05$). Co-prescription of esomeprazole and flupenthixol/melitracen improved the clinical symptoms and mucosal erosions, relieved negative feelings and reduced the recurrence rate. The efficacy of the co-prescription is higher than that of the solitary prescription.

Key words: Gastric mucosa; Mucosal erosion; PGE2; MDA; Negative feelings.

Introduction

As a common gastrointestinal disease, chronic erosive gastritis is indicated by a variety of signs extending from nausea and obscure gastric inconvenience to anorexia, vomiting, and weight loss (1, 2). Moreover, *Helicobacter pylori*-induced atrophic gastritis is epidemiologically related to gastric carcinoma (3, 4). The patients who have premalignant gastric lesions are exposed to a significant risk of gastric carcinoma for ten years of follow-up, and the annual incidence of gastric carcinoma is 0.1% for the patients who have atrophic gastritis for five years after diagnosis (5).

Under the effect of inflammatory factors, the gastric mucosal tissues might lead to atrophic gastritis. The decrease in blood supply, as well as damage and stimulation caused by various inflammatory factors, alterations, and atypical hyperplasia, might lead to gastric carcinoma a silent killer with the hidden onset and slow progression but tremendous damages (6). Proton pump inhibition is a common method to clinically treat erosive gastritis, despite its limited efficacy on erosive gastritis with negative feelings, like anxiety and depression, which might be relieved by a therapeutic strategy (7). Therefore, in the present paper we compared the co-prescription efficacy of esomeprazole and flupenthixol/melitracen (as an antipsychotic/anxiolytic) with the prescription of solitary esomeprazole on erosive gastritis with negative feelings.

Materials and Methods

General materials

A total of 140 erosive gastritis patients with negative feelings referred to Chongqing hospital since January 2015 to December 2016 were enrolled in this study in accordance with the following inclusions: a) patients who have abdominal pain or distension, sour regurgitation, or belching; b) patients who have gastroscopically erosive alterations in the gastric mucosa; c) patients who have chronic negative feelings (HAMA score > 18 points; HAMD score > 18 points); d) voluntary patients. The patients were randomly divided into an observation group and a control group. Table 1 shows the number of cases, gender, and age. Comparing the descriptive data showed no significant difference between the groups ($p>0.05$).

Table 1. Descriptive data of the erosive gastritis patients.

Group	n	Gender	Age (year)
Observation	70	38♂:32♀	46-65 (56.7±7.3)
Control	70	41♂:29♀	47-66 (56.9±6.9)

Treatment methods

The control group took orally the tablets of Esomeprazole Magnesium (20 mg, twice a day for four weeks; AstraZeneca Pharmaceutical Co., Ltd.); whereas the observation group received the previous prescription plus the flupenthixol/melitracen [one tablet, twice a day for four weeks; Lundbeck (Denmark) Pharmaceutical Consulting Co, Ltd.].

Observation indexes

Clinical symptoms and mucosal erosion

We examined and scored the clinical symptoms and mucosal erosion of the groups before the treatment and four weeks after the treatment based upon the following criteria: a) assessment of clinical symptoms: grade 0 for no clinical symptom, grade 1 for mild symptoms which slightly affected the health, grade 2 for obvious symptoms which remarkably affected the health, and grade 3 for severe symptoms which would be alleviated medically; b) assessment of mucosal erosion: grade 0 for no erosion, grade 1 for the number of erosions ≤ 2 in one region, grade 2 for three-five erosions in one region, grade 3 for two erosive regions, and grade 4 for three erosive regions.

PGE2 and MDA in gastric mucosa

Before the treatment and four weeks after the treatment, we gastroscopically sampled the gastric mucosa; RIPA buffer homogenized the samples. After centrifugation, we isolated the supernatant for protein detection based upon the BCA method, and we measured PGE2 and MDA levels in 1 mg gastric mucosal tissues through the ELISA test.

Negative feelings

Before the treatment and four weeks after the treatment, we evaluated the depression using the Hamilton Depression Rating Scale (HAMD) and the anxiety using the Hamilton Anxiety Rating Scale (HAMA).

Recurrence in 6 months of follow up

After six months of follow-up, we gastroscopically examined all the patients to indicate the recurrence of the symptoms.

Statistical processing

We used SPSS software (version 18 for Windows; SPSS Inc. Chicago, Illinois, USA) to statistically analyze the data. Measurement data were presented as ($\bar{x}\pm s$ $\bar{x} \pm s$). We used independent samples *t*-test for intergroup comparison and paired-samples *t*-test to compare the pretreatment and post-treatment data. Data were considered statistically different at p-value < 0.05.

Results

Clinical symptoms and mucosal erosion

In the pretreatment condition, no significant difference existed between the groups ($p>0.05$) when comparing clinical symptoms and mucosal erosion. In the post-treatment condition, both the groups had significantly lower scores relative to the pretreatment condition, and the observation group had remarkably lower scores than the control (Table 2).

PGE2 and MDA analysis results

In the pretreatment condition, no significant difference existed between the groups regarding comparing PGE2 and MDA levels in the gastric mucosa ($p>0.05$). In the post-treatment condition, the groups had higher PGE2 and lower MDA levels compared to the pretreatment one; similarly, the observation group had higher PGE2 and lower MDA levels than the control (Table 3).

Negative feelings

In the pretreatment condition, no significant difference existed between the observation group and the control group regarding comparing the negative feelings ($p>0.05$). In the post-treatment condition, the negative feeling in the observation group was significantly lower than that in pretreatment one, but no significant alteration existed in the pretreatment and post-treatment scores of the negative feeling in the control group ($p>0.05$). Moreover, the observation group had lower HAMA and HAMD scores than the control (Table 4).

Recurrence rate

In the pretreatment condition, all the patients of both the groups attended the follow-up for six months (follow-up rate = 100%). The patients of both the groups

Table 2. The scores of clinical symptoms and mucosal erosion of the groups ($\bar{x} \pm s$).

Group		Case (n)	Clinical symptoms				
			Abdominal pain	Abdominal extension	Belching	Sour regurgitation	Mucosal erosion
Observation	Pre-treatment	70	2.4±0.6	2.2±0.5	1.6±0.4	1.8±0.5	2.9±0.8
	Post-treatment	70	0.6±0.2$^{*\#}$	0.5±0.1$^{*\#}$	0.4±0.1$^{*\#}$	0.4±0.2$^{*\#}$	0.7±0.2$^{*\#}$
Control	Pre-treatment	70	2.3±0.5	2.0±0.5	1.7±0.5	1.9±0.6	3.0±0.7
	Post-treatment	70	1.3±0.4*	1.2±0.3*	0.9±0.2*	1.0±0.3*	1.5±0.4*

Note: $^{*}p<0.05$ vs. the same group before treatment; $^{\#}p<0.05$ vs. the control group after treatment.

Table 3. PGE2 and MDA levels in gastric mucosa $\bar{x} \pm s$).

Group		Case (n)	PGE2 (ng/mg)	MDA (ng/mg)
Observation	Pre-treatment	70	1.6±0.3	3.3±0.9
	Post-treatment	70	5.5±1.0*#	0.9±0.2*#
Control	Pre-treatment	70	1.5±0.3	3.5±0.8
	Post-treatment	70	3.3±0.6*	2.2±0.9*

Note: *p<0.05 vs. the same group pretreatment; #p<0.05 vs. the control group post-treatment.

Table 4. Pretreatment and post-treatment negative feelings in the groups$\bar{x} \pm s$).

Group		Case (n)	HAMA	HAMD
Observation	Pre-treatment	70	21.9±4.3	23.3±3.9
	Post-treatment	70	12.5±2.2*#	14.9±2.4*#
Control	Pre-treatment	70	22.2±3.8	23.5±3.8
	Post-treatment	70	19.3±3.2*	22.8±3.5*

Note: *p<0.05 vs. the same group before treatment; #p<0.05 vs. the control group after treatment.

Table 5. the recurrence rates between the groups.

Group	Case (n)	Recurrence	No recurrence	Recurrence rate (%)
Observation	70	16	54	22.9
Control	70	34	36	48.6

were examined gastroscopically; 16 cases in the observation group and 34 cases in the control group showed the recurrence. The groups showed significant differences in the recurrence rate (p<0.05; Table 5).

Adverse reaction

During four weeks of the treatment, just one patient showed debilitation, and after medication, the symptom alleviated. The control group showed no adverse reaction. After the treatment, no hepatic and renal damages and no adverse reaction in the hemopoietic system were recorded.

Discussion

Chronic erosive gastritis is a common disease mainly characterized by mild discomforts in the gastrointestinal tract. Long-term exposure to stimulating food, crapulence, irregular diet, non-steroidal anti-inflammatory drugs, mental strain, stress and major trauma (8) are the main causes. Pathogenically, the retarded recovery of the protective mucosal layer, caused by the insufficient blood supply and injuries faster than its recovery, can damage the gastric mucosa under the stimulation of gastric acid (9). Superficial damages are difficult to be identified, and constant stimulation if not been alleviated or remedied will exacerbate the signs recurrently (10). The long-term recurrent stimulus and inflammatory factors will further induce pathogenic progression and aggravate the patients' clinical symptoms (8). The patients with acute injury are prone to complications like ulcer and gastrointestinal bleeding, whereas those with chronic injury suffer from the long-term muscular hypertrophy in the mucosa leading to atrophic gastritis, extensive infiltration of inflammatory cells, attenuation of gastric mucosa, and reduction in glands (10). Thereupon, this process will further affect the recovery, cell apoptosis, and cytophagy; abnormal hyperplasia, intestinal metaplasia, or even oncogenesis might occur in the gastric mucosa (11).

Cytologically, the parietal cell is responsible for releasing the gastric acid (12), and three stimulants directly induce it (13-15): 1) Acetylcholine (Ach), which would be secreted by vagal parasympathetic fibers synapsing directly onto the cell; 2) Histamine (H), which would be secreted by enterochromaffin-like cells (ECLs) adjoining the cell in the oxyntic gland; and 3) Gastrin, which would be secreted by G Cells located in the pyloric glands. Physiologically, the acid secretion occurs through three phases (16,17): 1) cephalic phase, mainly induced by the brain activation of the vagus nerve through the stimuli including seeing and eating a meal; 2) gastric phase, commenced following entering food into the stomach. The gastric dilation induces the vagal reflex increasing further vagus nerve stimulation. Moreover, food metabolites, especially amino acids and proteins, directly induce gastrin secretion from G Cells; 3) intestinal phase, triggered following entering food into the duodenum probably owing to gastrin secretion by the duodenal mucosa.

Molecularly, esomeprazole, like other proton-pump inhibitor drugs, reduces the acid secretion through inhibiting the H+/K+-ATPase enzyme —the proton pump (18,19). In the parietal cells, the drug protonates and converts to its active form, i.e., the achiral sulfenamide, reacting with special cysteines to inhibit the pump (20). Flupenthixol, as a neuroleptic drug, plays a powerful antipsychotic role through blockade of the postsynaptic dopamine receptors, D1 and D2, in the brain (21), and melitracen as a tricyclic antidepressant inhibits the reuptake of norepinephrine and serotonin in the brain to treat depression and anxiety (22,23).

The vagus nerve is the major part of the parasympathetic system relating to the brain and peripheral organs (24). The vagal nucleus consists of four nuclei located in the medulla oblongata: 1) dorsal motor nucleus;

2) nucleus ambiguous; 3) solitary nucleus; and 4) spinal trigeminal nucleus (25). One of the functions of the dorsal motor nucleus includes innervating the gastrointestinal system (25). Studying the effect of antipsychotic drugs, for example olanzapine, showed a decrease in the excitability of the dorsal motor nucleus (26). Most tricyclic antidepressants show anticholinergic effects (27,28). Johnsson et al. (29) showed that vagal stimulation is significantly inhibited after injecting imipramine, clomipramine and zimelidine; but Ghia (30) noted that tricyclic antidepressants activate the vagus nerve. However, melitracen might relieve gastritis through its anxiolytic effect (31); In most treatments, the physicians prescribe H antagonists (e.g ranitidine, cimetidine, etc) or proton-pump inhibitors (e.g. esomeprazole, omeprazole, pantoprazole, etc.) plus antibiotics (e.g. Metronidazole, Amoxicilne, etc) to eradicate Helicobacter pylori infection (32). However, Fujiwara et al. suggested that no consistency exists in the clinical efficacy of the co-prescription of omeprazole and amoxicillin (33). Peura et al. (34) found that for the patients who failed to improve, over 60.0% of them had negative feelings, suggesting that psychiatric factors are closely related to the onset of erosive gastritis and its treatment.

According to the modern medical theory, some somatic symptoms clinically, like tiredness, insomnia, slowness of thought, loss of appetite, and abdominal distension and pain accompany the negative feelings, including anxiety and depression (35). It is reported that gastritis, gastroesophageal reflux, and gastric ulcer in patients who have anxiety or depression are two to three times more than the healthy population (36). On one hand, persistent negative feelings can stimulate the cerebral cortex, affect the regulatory function of the subthalamic nerve center inducing disorders in the function of autonomic nerve, and decrease in PG synthesis in local parts, vasospasm under gastric mucosa, and ischemia in the gastric mucosa (37); On the other hand, they might give rise to the endocrine disorder, acid secretion abnormality, and gastric mucosal damage (38). Accordingly, medication of erosive gastritis complicated with the negative feelings needs managing the negative feelings as well as inhibiting the proton pump secretion (39,40). So we motivated to examine improvement in the efficacy of erosive gastritis by relieving the negative feelings through ameliorating the autonomic nerves and endocrine system. So in our study, Flupenthixol, as a nerve blocker, alleviates the anxiety and depression in a small dose, and melitracen, as an antidepressant, excites the nerves instantly.

In the present study, the observation group showed a promising overall efficacy regarding the scores of clinical symptoms and mucosal erosion. Moreover, negative feelings were obviously improved in the observation group.

PGE2, as a protective factor of the gastric mucosa (41), can improve the function of the gastric mucosa through dilating the vessels under gastric mucosa (42); and MDA is one of the metabolites of oxygen radical which would be the main cause of ischemic injury in the gastric mucosa (43). The immune system eliminates the oxygen radical, but once oxygen radical overload exceeds the scavenging activity of the immune system, the extracellular oxygen radical accumulation damages the adjacent tissues as well as the gastric mucosa (44). The levels of PGE2 and MDA in the gastric mucosa can reflect the function and pathology of the mucosa and it will controllable by genome editing (45, 46). In our results, the pre- and posttreatment levels of PGE2 and MDA determined the effect of the co-prescription of esomeprazole and flupenthixol/melitracen on the gastric mucosa indicating that the levels of the protective factors and pathogenic factors in the gastric mucosa are, respectively, higher and lower in the observation group; it illustrates that following the co-prescription, the protective effect of the gastric mucosa is much stronger with weaker pathogenesis and better efficacy in the observation group. Hence, the co-prescription can produce promising efficacy by increasing the level of PGE2 and decreasing the level of MDA.

Conclusively, the co-prescription can improve the clinical symptoms and mucosal erosions, relieve negative feelings, and reduce in recurrence rate. The overall efficacy of this medical co-prescription is higher than that of the solitary prescription of esomeprazole.

Acknowledgment

National Natural fund for young people: the role of prefrontal orbital area return inhibition in antidepressant therapy (NSF31200774).

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