Original Article

Effect of Rebamipide on Portal Hypertensive Gastropathy: A Prospective Randomized Controlled Trial - A Pilot Study

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ABSTRACT

Background: Portal hypertensive gastropathy (PHG) is a cause of portal hypertensive related bleeding, for which no medications have been shown showed efficacious. In a recent molecular study in PHG rat model, rebamipide was noted to promote healing of damaged gastric mucosa. In the present study, we attempted to demonstrate this effect in PHG patients.

Methods: From October 2009 to December 2009, patients undergoing esophagogastroscopy (EGD) at Maharaj Nakorn Chiang Mai Hospital who were found to have PHG were randomized to receive either rebamipide or placebo. After 12 weeks of treatment, follow up EGD and hemoglobin level were performed to compare endoscopic changes and hemoglobin levels within and between the two groups.

Results: Eight patients were included in the study. Of the 4 patients in the rebamipide group, 1 patient showed an improvement in the PHG score, 2 patients were found to have a worsened PHG score, and 1 patient showed no change. In the placebo group, all 4 patients exhibited no change in the PHG score. No statistically significant changes in the PHG score were noted. Increased in hemoglobin levels after treatment were not statistically significant in the two groups (1.3 ± 0.8 vs 1.4 ± 1.2; $p = 0.773$).

Conclusion: Rebamipide was not shown to exert a beneficial effect on PHG in this small pilot study.

Key words : rebamipide, portal hypertensive gastropathy

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INTRODUCTION

Portal hypertensive gastropathy (PHG) related bleeding is a common problem in patients with decompensated liver cirrhosis and esophagogastric varices, and is a major source of gastrointestinal bleeding approximately one-fourth of all causes of portal hypertensive related upper gastrointestinal hemorrhage. The bleeding is mostly slow and chronic, an acute bleeding episode being found in less than 10% of cases[1]. Furthermore, the incidence of bleeding is much greater in severe PHG than in mild PHG (38-62% vs 3.5-31%)[2].

Currently, non-selective beta blocker is the recommended drug for prevention of PHG related bleed-

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ing. The effect is thought to be mediated by reduction of portal pressure and gastric mucosal blood flow[1,2]. However, controlled studies that supported this recommendation is scarce and showed benefit only in an acute PHG bleeding[3,4]. The efficacy in the more common chronic PHG bleeding is unclear. Interestingly, Bellis L *et al*[5] reported that hepatic venous pressure gradient did not correlate with neither the presence nor the severity of PHG in cirrhotic patients. Other factors may therefore be related to the severity of this condition. Kawanaka *et al*[6] studied PHG in a rat model and found that a defect in extracellular signal-regulated kinases (ERK) caused impairment of proliferation of gut epithelial cells and healing of gastric mucosal injury.

Kinjo N *et al*[7] found that elevated lipid peroxide and nitrotyrosine in portal hypertensive rats caused nitration of ERK of gastric mucosa, resulting in impaired function of ERK. They found that rebamipide, a gastroprotective drug and oxygen free radical scavenger, can normalize the oxidative state and tyrosine nitration of ERK and completely reversing the impaired mucosal healing. This effect of rebamipide in PHG rat model may be of benefits in preventing chronic PHG bleeding. The present prospective study was conducted to investigate whether rebamipide may improve gastric mucosal findings in PHG patients.

Materials and Methods

Study Population

From October 2009 to December 2009, patients undergoing esophagogastroscopy (EGD) at Maharaj Nakorn Chiang Mai Hospital who were found to have PHG were invited to participate in the study.

The inclusion criteria were (1) age between 18 and 70, and (2) no anticipation of esophageal and/or gastric variceal treatment in the subsequent 6 months. Patients were excluded from the study if any of the following conditions was present: (1) history of obvious gastrointestinal hemorrhage in the past 8 weeks; (2) peptic ulceration at the initial EGD; (3) regular alcohol consumption; (4) current usage of a proton pump inhibitor, aspirin, NSAIDs, anticoagulant and iron supplement; (5) renal insufficiency, with creatinine clearance < 30 mL/min. Informed consent was obtained from all patients.

The study was approved by the Ethical Committee of the Faculty of Medicine, Chiang Mai University.

Method

Photographs of endoscopic findings were taken from the gastric fundus, body and antrum. Simultaneous blood test for hemoglobin level is also taken. Patients were randomized to receive either rebamipide (Mucosta®, Tokyo, Japan) 100 mg three times a day or an identical-looking placebo for 12 weeks.

Following completion of treatment, a follow up EGD and hemoglobin level measurement were performed for comparison of changes within and between the two groups. Treatment adherence was assessed by counting the number of tablets consumed (over 80% was considered good adherence).

Evaluation of Endoscopic Findings

EGD photographs taken before and after treatment were assessed by an experienced endoscopist, who was blinded to the study. Severity of PHG was based on Baveno II Consensus Conference[8] (Table 1).

Statistical Analysis

Data in this study were presented as frequency and percentage for nominal data (gender, cause of cirrhosis, type of esophageal varices) and in mean ± SD for continuous data (age, hemoglobin level, blood chemistry parameter). Comparison of baseline characteristics was made using Mann Whitney U test and Fisher's exact test (gender, cause of cirrhosis). Comparison of changes in PHG scores before and after treatment was made by means of Fisher's exact test, which changes of hemoglobin before and after treatment was be Mann Whitney U test. A p-value < 0.05 was considered significant.

Table 1. Severity of PHG based on Baveno II Consensus Conference

Parameter	Score
Mucosal mosaic pattern	
Mild : pink mucosa	1
Severe: diffuse erythema (redness) of mucosa	2
Red markings	
Isolated discrete	1
Confluent	2
GAVE	
Absent	0
Present	2

RESULTS

From October 2009 to December 2009, 97 patients with PHG were noted, but 89 were excluded. Causes of exclusion were necessity for treatment of esophagogastric varices in 45 patients, history of obvious gastrointestinal bleeding in 20 patients, peptic ulcer disease in 14 patients, current alcohol drinking in 2 patients, creatinine clearance less than 30 ml/min in 2 patients, and failure to obtain an informed consent in 6 patients. The remaining 8 patients were randomized into 2 groups, 4 patients in the rebamipide group, and 4 patients in the placebo group. The mean age was 52 ± 11. Most patients were male (7 of 8), with a mean Child Pugh score of 6.4 ± 1.2. Both groups were comparable with regard to baseline characteristics, except the mean serum AST that was higher in the rebamipide group (Table 2).

Comparisons of PHG score and hemoglobin level before and after 12-week treatment were shown in Table 2. Most patients had a stable PHG score, 2 patients had a worsened score and 1 patient had a better score. All patients showed an improvement in hemoglobin level. Most patients had good adherence to treatment. After 12 weeks of treatment, the PHG scores in the rebamipide group were higher than in placebo (3.3 ± 1.0 vs 2.8 ± 1.0), but the difference was not statistically significant. Hemoglobin levels were also comparable between the 2 groups (13.7 ± 2.1 vs 12.5 ±

Table 2. Baseline characteristics of PHG patients

	Rebamipide (n = 4)	**Placebo (n = 4)**	***p*-value**
Age (mean ± SD)	48 ± 12	56 ± 10	0.139
Gender (male:female)	3:1	4:0	1.000
Cause of cirrhosis (%)			
Alcohol	50	50	
Virus (HBV/HCV)	50	50	1.000
Child-Pugh score	6.8 ± 1.0	6.0 ± 1.4	0.294
Esophageal varices (No : small : post EVL)	2:2:0	0:3:1	0.429
Albumin (g/dL)	3.22 ± 0.33	3.22 ± 0.77	0.773
Alkaline phosphatase (U/L)	152 ± 51	122 ± 60	0.386
AST (U/L)	64 ± 29	36 ± 5	0.042
ALT (U/L	37 ± 20	22 ± 3	0.468
Total bilirubin (mg/dL)	2.47 ± 0.59	1.49 ± 0.84	0.110
Prothrombin time (sec)	11.19 ± 7.39	14.50 ± 1.56	0.564
Baseline PHG score (median)	3	2.5	0.647
Baseline Hb (g/dL)	12.4 ± 1.7	11.0 ± 2.6	0.386

Table 3. PHG score and hemoglobin before and after treatment

Patient No.	**Treatment**	**PHG score (before)**	**PHG score (after)**	**Hb (g/dL) (before)**	**Hb (g/dL) (after)**	**Adherence**
1	Rebamipide	2	2	13.4	15.9	G
2	Rebamipide	3	4	14.0	14.6	G
3	Placebo	4	4	11.8	13.7	P
4	Placebo	2	2	9.3	12.2	P
5	Placebo	3	3	8.7	9.2	G
6	Rebamipide	4	3	10.2	11.1	G
7	Placebo	2	2	14.5	14.8	G
8	Rebamipide	3	4	12.0	13.1	G

(Adherence : G, good adherence; P, poor adherence)

Table 4. Comparison of outcome after treatment between the rebamipide group and the placebo group

	Rebamipide (n = 4)	Placebo (n = 4)	*p*-value
PHG score (median)	3.3 ± 1	2.8 ± 1	0.445
Hemoglobin (g/dL)	13.7 ± 2.1	12.5 ± 2.4	0.564
Child-Pugh score	6.5 ± 0.6	6.5 ± 1.3	1.00
Change in PHG score			
Improve 1 point	25%	0%	
Same	25%	100%	
Worsen 1 point	50%	0%	0.143
Increase in Hb level (g/dL)	1.3 ± 0.8	1.4 ± 1.2	0.773

2.4) (Table 4). In 4 patients of the rebamipide group, 1 patient had an improved PHG score, 2 patients had worsened PHG scores which the other showed no change. In the placebo group, all patients had no change in PHG score. Interestingly, the placebo group showed a greater improvement in hemoglobin level than the rebamipide group with no statistical significance.

DISCUSSION

Portal hypertensive gastropathy (PHG) is a cause of chronic blood loss in cirrhotic patients, and currently no medication is effective in the treatment of this condition. From animal model studies, rebamipide appeared to be useful in PHG, but there is no clinical trial to date that explores the benefit of rebamipide in cirrhotic patients with PHG.

The present study was designed to assess the effect of rebamipide on PHG as reflected in improvement of mucosal findings and hemoglobin concentration. Patients in this study were alcoholic or HBV or HCV compensated cirrhosis. The degree of PHG was mild in most patients in this study, while the study had a small number of patients.

We could not demonstrate any beneficial effect of rebamipide on PHG, as after 12 weeks of treatment, the changes in mucosal lesion improvement were varied while the follow up hemoglobin level become even lower.

Limitations in this study were (1) a very small sample size (2) the degree of PHG in study patients was only mild (3) the duration of treatment might be too short to demonstrate any positive effect of rebamipide. A future study with a broader range of patients and a longer duration of treatment may better clarify the benefit of rebamipide in this setting.

CONCLUSION

Rebamipide was not shown any benefit in improvement of PHG in this study. A larger sample size was required for assessing the efficacy of this drug.

REFERENCES

1. Shah VH, Kamath PS. In: Portal hypertension and gastrointestinal bleeding. Sleisenger and Fordtran's gastrointestinal and liver disease. 8th ed, 2006;1927-8.
2. Thuluvath PJ, Yoo HY. Portal hypertensive gastropathy. Am J Gastroenterol 2002;97:2973-8.
3. Atif Z. Portal hypertension-related bleeding: management of difficult cases. Clin Liver Dis 2006;10:353-70.
4. Rosa M. Perez-Ayuso, Josep M. Pique, *et al*. Propranolol in prevention of recurrent bleeding from severe portal hypeetensive gastropathy in cirrosis. Lancet 1991;337:1431-4.
5. Lia B, Sabino N, Alessandra G, *et al*. Hepatic Venous Pressure Gradient Does not correlate with the presence and severity of portal hypertensive gastropathy in patients with Liver cirrhosis. J Gastrointestin Liver Dis 2007;16:273-7.
6. Kawanaka H, Tomikawa M, Jones MK, *et al*. Defective mitogen-activated protein kinase (ERK2) signaling in gastric mucosa of portal hypertensive rats. Potential therapeutic implications. Hepatology 2001;34:990-9.
7. Kinjo N, Kawanaka H, Akahoshi T, *et al*. Significance of ERK nitration in PHG and its therapeutic implications. Am J Physiol Gastrointest Liver Physiol 2008;295:G1016-G1024.
8. Stewart CA, Sanyal AJ. Grading portal gastropathy: validation of a gastropathy scoring system. Am J Gastroenterol 2003;98: 1758-65.