Safety and Efficiency of Adding Repamipide to the Triple Eradication Therapy of Helicobacter Pylori.

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Abstract:

Background & aim: Eradication of Helicobacter pylori (H. pylori.) has been reported as an effective strategy in the treatment of peptic ulcer and gastric mucosa-associated lymphoid tissue lymphoma. With the increasing frequency of antibiotic-resistant H. pylori, there is rising concern about the potential decline in the eradication rate. In the current study we aimed to valuated whether rebamipide could improve success rates of anti-H. pylori treatment and treat resistant cases of H. pylori.

Patients & methods: A total of 100 patients with confirmed infection, serologically and/or histopathologically, were enrolled in the study. Patient received 30 mg of lansoprazole, 750 mg of amoxicillin, and 500 mg of clarithromycin twice daily for two weeks and then 100 mg of rebamipide three times daily for 7 weeks

Results: Mean age of enrolled patients was 41.98 ± 12.56 (years). Out of the studied patients; 58 (58%) patients were males. Only 8 (8%) patients developed diarrhea and 4 (4%) patients suffrered from bitter taste. In addition to another 12 (12%) patients were complaining of abdominal distention with gastric upset. All other patients developed no adeverse effects. Based on the current study and follow up testing for H.pylori, we found that majority (84%) of patients achieved complete eradication of the infection while only eight patients were still positive.

Conclusion: This study demonstrated that the addition of rebamipide to H. pylori eradication regimens significantly increases the effectiveness of treatment. But future studies with large number of patients are warranted to confirm such findings

Keywords: rebamipide, H. pylori, eradication

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Introduction

Helicobacter pylori (H. pylori) is one of the most common human pathogens. According to the latest systematic review, approximately 45.4% of the world's population is infected with this microorganism ***(Hooi et al., 2017)***. According to the latest recommendations for the diagnosis and treatment of H. pylori infection, eradication therapy should be administered to all infected people ***(Lee et al., 2013, Xiang et al., 2021)***.

However, in the last decade, there has been a negative trend in the effectiveness of classic eradication therapy regimens, which has largely been determined by the emergence and spread of antibiotic resistance ***(Andreev et al., 2019)***. According to the latest meta-analyses, the effectiveness of one of the eradication schemes most commonly used in clinical practice—triple therapy—is at a relatively low level (approximately 69–77%) ***(Venerito et al., 2013, Feng et al., 2016, Puig et al., 2016)***.

Rebamipide does not have a direct anti-helicobacter action; however, in experimental studies, it was shown that it inhibits the adhesion of H. pylori to epithelial cells of the gastric mucosa and reduces the activation of NF-κB and IL-8 production induced by H. pylori ***(Shin et al., 2011, Andreev et al., 2019)***. Aim of this study was to assess whether rebamipide could improve success rates of anti-H. pylori treatment and treat resistant cases of H. pylori.

Patients and Methods:

Study setting and design:

A prospective cohort study was performed at Gastroenterology Unit of Internal Medicine Department in Assiut University Hospital. The study was conducted in period between January 2021 and December 2021.

Inclusion criteria:

- Twenty years of age or older.
- Single ulcer with size 5 mm or more in longest diameter as seen by upper endoscopy.
- Patients diagnosed to have H. pylori infection by endoscopy and biopsy.

Exclusion criteria:

- Use of medications such as PPIs, H2-receptor antagonists, other gastroprotective drugs, or nonsteroidal anti-inflammatory drugs within a week prior to the start of the trial.
- Previous eradication therapy for H. pylori.
- Acute or duodenal ulcer.
- Gastric ulcer with high risk of massive bleeding.
- Patient's refusal.

Ethical approval:

Approval of the study was obtained from the ethics committee in the Faculty of Medicine, Assiut University. Also, every patient was informed about the nature and steps of the study and a written informed consent was obtained from each patient. The study was registered in *www.clinicaltrials.gov* (NCT04550858).

Sample size calculation

The sample size was calculated by using the following formula: $N = (Z / \Delta)^2 X P (100 – P)$ where:

- Z: a percentile of slandered normal distribution determined by 95% confidence level = 1.96.
- Δ: the width of the confidence interval = 12.
- P: the prevalence of disease = 90%.

So, $N = (1.96/12)^2 X 90 (100 - 90) = 24$ patients, we recruited a total of 100 patients.

Methods and regimen of therapy:

All patients were subjected to thorough history evalaution and clinical assessment. The following baseline data were recorded; age, sex, body mass index and different symptomns and its duration.

The presence of H. pylori infection was determined by histological evaluation (modified Giemsa staining), the rapid urease test (CLOtest ®; Kimberley-Clark, Draper, UT, USA), serum antibody test, or 13C-urea breath test. When one of these tests was positive, we would score the patient as positive for the presence of H. pylori infection ***(Higuchi et al., 2015)***

Prior to the start of the study, and at 8 weeks after study start, all patients were subjected to upper endoscopy. The following data were obtained; site of peptic ulcer, size of ulcer in endoscopy, single or multiple ulcers and multiple biopsies were taken for histopathological evaluation and testing for H. pylori positively.

Statistical analysis:

Recorded data were analyzed using the statistical package for social sciences, version 20.0 (SPSS Inc., Chicago, Illinois, USA). Quantitative data were expressed as mean ± Standard Deviation (SD). Qualitative data were expressed as frequency and percentage and compared.

The Results:

Baseline data of the studied patients (table 1):

Mean age of enrolled patients was 41.98 ± 12.56 (years) while mean body mass index was 26.76 ± 6.09 (kg/m^2). Out of the studied patients; 42 (42%) patients were females and 58 (58%) patients were males. Nearly all patients had epigastric pain. Dyspepsia and nausea/vomiting present in 67 (67%) and 58 (58%) patients, respectively. Only eight patient suffrered from regurgitation.

Table 1: Baseline data of studied patients

	N= 100
Age (years)	29.98 ± 12.56
Body mass index (kg/m^2)	26.76 ± 6.09
Sex	
Male	58 (58%)
Female	42 (42%)
Smoking	25 (25%)
Diabetes mellitus	13 (13%)

Hypertension	8 (8%)
Residnce	
Rural	67 (67%)
Urabn	33 (33%)
Epigastric pain	91 (91%)
Dyspepsia	67 (67%)
Nausea/ vomiting	58 (58%)
Regurgitation	8 (8%)

Data expressed as frequency (percentage), mean (SD). **N**: number

Endoscopic findings among studies patients (table 2):

Based on endoscopic evaluation of those patints; it was found that antral gastritis, prepyloric ulcers and duodenitis were present in 33 (33%), 33 (33%) and 25 (25%) patients, respectively. Only four patient suffrered from gastroduodenitis.

Table 2: Endoscopic findings among the studied patients

	N= 100
Antral gastritis	33 (33%)
Prepyloric ulcers	33 (33%)
Duodenitis	25 (25%)
Gastroduodenitis	8 (8%)

Data expruessed as frequency (percentage). **N**: number

Safety and tolerability of rebamipide among the studied patients (table 3):

Only 8 (8%) patients developed diarrhea and 4 (4%) patients suffrered from bitter taste. In addition to another 12 (12%) patients were complaining of abdominal distention with gastric upset. All other patients developed no adeverse effects. Whatever the adverse effects, all patients continue the course till the end.

Table 3: Safety and tolerability of rebamipide among the studied patients

Adverse events	N= 100
None	83 (83%)
Abdominal distention	12 (12%)
Diarrhea	8 (8%)
Bitter taste	4 (4%)

Data expruessed as frequency (percentage). **N**: number

Discussion

rebamipide was not found to have direct effects (antibacterial effects or urease inhibition) on *H. pylori* in in vitro study.Rebamipide inhibits adherence of H. pylori to gastric cells. This effect may aid antibiotics in curing *H. pylori* infection. In addition, rebamipide scavenges free radicals, inhibits inflammatory cell responses, and reduces interleukin-8 production in response to H. pylori.24-These effects might alter *H. pylori* status ***(Nishizawa et al., 2009)***.

Negative trend in the effectiveness of classic eradication therapy regimens is known, which has largely been determined by the emergence and spread of antibiotic resistance. According to the latest meta-analyses, the effectiveness of one of the eradication schemes most commonly used in clinical practice-triple therapy-is at a relatively low level (approximately 69–77%) ***(Venerito et al., 2013, Feng et al., 2016, Puig et al., 2016)***.

The principal mechanisms of action of rebamipide are the induction of prostaglandin synthesis in the gastric mucosa, neutralization of oxidative stress products, and inhibition of neutrophil activation. Rebamipide does not have a direct anti-helicobacter action; however, in experimental studies, it was shown that it inhibits the adhesion of *H. pylori* to epithelial cells of the gastric mucosa and reduces the activation of NF-κB and IL-8 production induced by *H. pylori* ***(Hayashi et al., 1998, Naito and Yoshikawa, 2010)***.

In the current study we aimed to evaluate whether rebamipide could improve success rates of anti-H. pylori treatment and treat resistant cases of *H. pylori*. A total of 100 patients with confirmed infection, serologically and/or histopathologically, were enrolled in the study.

We found that mean age of enrolled patients was 29.98 ± 12.56 (years) and majority (58%) of patients were males. Fifty-two (25%) patients were smoker while 13 (13%) and 8 (8) patients were known to be diabetic and hypertensive, respectively. Also, majority (67%) of patients came from rural areas.

In line with the current study, ***Haq et al.*** found that a total of 123 individuals with dyspeptic symptoms secondary to *H.pylori* infection were studied in which 54.5% (n=67) were male and 45.5% (n=56) were female patients. Also, they noticed that the highest number of cases were observed in age of 21-30 years with 30.9% (n=38), followed by age 31-40 years (21.1%)***(Haq et al., 2020)***. ***Fujioka et al.*** found that a total of 68.4% in their study were smokers ***(Fujioka et al., 2003)***.

. Different patients infected with H. pylori complaint about various signs and symptoms associated with H. pylori infection ***(Haq et al., 2020)***.

In the current study we found that nearly all patients had epigastric pain. Dyspepsia and nausea/vomiting were presnet in 67 (67%) and 58 (58%) patients, respectively

Comparable with the current study, it was found that aabdominal pain, retrosternal burning, regurgitation, nausea, vomiting, and haematemesis was 86%, 91%, 63%, 57%, 33%, and 5% respectively, were reported in a previous study ***(Haq et al., 2020)***. A study conducted by ***Asaka et al.*** on 2455 patients revealed that gastritis

and intestinal metaplasia are strongly linked with Helicobacter pylori ***(Asaka et al., 2014, Öztekin et al., 2021)***.

Based on endoscopic evaluation of patients in the current study; it was found that antral gastritis, prepyloric ulcers and duodenitis were present in 33 (33%), 33 (33%) and 25 (25%) patients, respectively. Only eight patients had gastroduodenitis. Consistent with this study, ***Agyei-Nkanasah et al.*** stated gastritis was the most frequent endoscopic finidings in such patients ***(Agyei-Nkansah et al., 2019)***.

Here, only eight patients developed diarrhea and four patients suffrered from bitter taste. In addition to another 12 patients were complaining of abdominal distention with gastric upset. All other patients developed no adeverse effects. Whatever the adverse effects, all patients continue the course till the end.

A previous study found that adverse events were observed in 5.9% of patients who received repamipide (6/101) and 12.4% of placebo (12/97) with no significant difference. All of the adverse events developed in the period from the start of the study to 2nd week. Gastrointestinal symptoms including diarrhoea, vomiting, soft stools and stomatitis accounted for 61.1% (11/18) of the whole patients having adverse events. The remaining cases were skin hypersensitivity such as rash or urticaria reported in five patients, dizziness and taste disorder each in one patient ***(Fujioka et al., 2003)***.

Also, a previous meta-analysis of 11 RCTs, data on the incidence of side effects during therapy were available in only five papers. A meta-analysis of the frequency of adverse events did not reveal significant differences between the groups that did or did not receive rebamipide (OR 1.279, 95% 0.915–1.789, $p = 0.150$) ***(Andreev et al., 2019)***.

Based on the current study and follow up testing for H.pylori, we found that majority (83.3%) of patients achieved complete eradication of the infection while only eight patients were still positive. The inclusion of rebamipide in eradication therapy regimens seems to be quite promising. This drug does not have its own direct anti-helicobacter action; however, in experimental studies, it was shown to inhibit the adhesion of *H. pylori* to epithelial cells of the gastric mucosa and to have an anti-inflammatory effect by reducing the production of IL-8 induced by *H. pylori* ***(Lee et al., 2011)***.

A previous meta-analysis showed that the addition of rebamipide to eradication regimens significantly increased the effectiveness of treatment (odds ratio (OR) 1.753, 95% confidence interval (CI) 1.312–2.333, $p < 0.001$). The subgroup analysis demonstrated that rebamipide significantly increased the effectiveness of eradication when added to a dual therapy regimen (OR 1.766, 95% CI: 1.167–2.495, $p = 0.006$); however, no significant improvement in effectiveness was observed when it was added to the triple therapy regimen (OR 1.638, 95% CI 0.833–3.219, $p = 0.152$) ***(Andreev et al., 2019)***.

The main limitations of the current study included relatively small sample size, short durtaion of follow up to assess long term effect of adding rebamipide. Also, we didn't perform comparative study with other regimens without rebamipide. Also, short durtaion of follow up of those patients to assess long term effect of this agent is

recommended. Also, randomized controlled trials about efficacy of rebamipide are warrnted.

Conclusion:

This work demonstrated that the addition of rebamipide to H. pylori eradication regimens significantly increases the effectiveness of treatmen. Also, randomized controlled trials about efficacy of rebamipide are warrnted.

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