Effect of Rebamipide on Fecal *Helicobacter pylori* Antigen Test

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Background and study aim: Fecal antigen testing for *H. pylori* is a non-invasive, cost-effective, and user-friendly diagnostic tool, particularly valuable for screening high-risk populations. Its implementation may enhance early detection and contribute to reductions in the incidence, prevalence, and mortality associated with gastric cancer. Preclinical and animal research has shown that Rebamipide promotes mucosal defense by stimulating the production of gastric mucosal prostaglandins and enhancing mucus secretion. Rebamipide may help relieve upper gastrointestinal symptoms. To the best of our knowledge, no prior research has assessed the impact of Rebamipide on the fecal *H. pylori* antigen (Ag) test, making this study a novel contribution to the field. In the current study, we aim to evaluate the effect of Rebamipide on fecal *H pylori* Ag testing.

Patients and Methods: A total of 73 patients with dyspepsia and positive fecal *H. pylori* Ag test results, were enrolled in a quasi-experimental study "before-and-after study". They were retested for fecal *H pylori* Ag after receiving 100 mg Rebamipide three times daily for 14 days without any other additional therapy.

Results: Seventy-three patients were enrolled in this quasi-experimental study "before-and-after study". Among them, 61 patients (83.6%) showed positive results of fecal *H. pylori* test after prescribing Rebamipide for 2 weeks with the improvement of epigastric pain in (43/73) 58.9% of the study group.

Conclusion: Rebamipide may be prescribed as a bridge while stopping PPIs before *H. pylori* Ag detection in stool test, to overcome epigastric pain and to avoid non-sensitive testing on PPI therapy.

INTRODUCTION

In developing countries, more than 50|% of the population is infected with Helicobacter pylori (H. pylori), largely due to widespread exposure to risk factors such as inadequate access to clean water, poor sanitation, and overcrowded living conditions—circumstances that facilitate fecal-oral transmission [1]. Helicobacter pylori is classified as a gastric cancer Group 1 carcinogen [2], a malignancy that ranks as the fourth most common cancer and the second leading cause of cancer-related deaths globally [3].

Although the precise risk of gastric cancer in developing countries remains uncertain, evidence from Japanese men—a population with relatively low H. pylori prevalence—indicates that infection may result in a lifetime gastric cancer risk of up to 17%, compared to just 1% among uninfected individuals [4].

Fecal antigen testing for H. pylori is a simple, non-invasive, and cost-effective diagnostic method that plays a critical role in screening high-risk populations and may facilitate earlier detection, ultimately contributing to a reduction in gastric cancer incidence, prevalence, and mortality [5].

Rebamipide is widely used as a protective agent against mucosa in East Asia for managing different upper gastrointestinal (UGI) symptoms [6].

Animal research has shown that it improves mucosal defense by stimulating the secretion of gastric prostaglandins and mucus. Additionally, it mitigates gastric mucosal inflammation by suppressing pro-inflammatory cytokines like interleukin-8, and by inhibiting neutrophil activation and their adhesion to the vascular endothelium [7,8,9,10].

Several studies have reported that Rebamipide may improve upper gastrointestinal (UGI) symptoms in Asian patients with chronic gastritis [11] and type 2 diabetes mellitus [12]. Also, continuous co-prescription of Rebamipide significantly reduces the risk of upper gastrointestinal bleeding in new users of non-steroidal anti-inflammatory drugs (NSAIDs) [13].

Rebamipide has been linked to symptom relief in cases of organic dyspepsia, though evidence supporting its effectiveness in functional dyspepsia (FD) remains less conclusive. The therapeutic benefit is likely due to the resolution of chronic gastritis, a condition that is often difficult to detect using standard endoscopic techniques in clinical practice. Given increasing concerns about the long-term safety of proton pump inhibitors [14], Rebamipide may represent a viable alternative for managing FD or for patients susceptible to recurrent NSAID-related peptic ulcers [15].

In addition, Nishizawa et al., 2014 found in a meta-analysis that supplementation with Rebamipide might be effective in increasing H. pylori eradication rates of PPI–amoxicillin dual therapy [16]. In the current study, we aim to estimate the accuracy of fecal H pylori Ag testing while on Rebamipide therapy. To the best of our knowledge, no prior research has assessed the impact of Rebamipide on fecal H. pylori Ag levels, making this study a novel contribution to the field.

PATIENTS AND METHODS

Study Design and Participants:

A quasi-experimental study "before-and-after study" was conducted between 11th March 2025 and 11th April 2025. A total of 73 patients with dyspepsia and positive fecal H. pylori Ag test results were enrolled. Participants were recruited from Elkharga Specialized Hospital, New Valley University, and Aswan University Hospital. All of them received Rebamipide 100 mg three times daily for 14 days without any other additional therapy. At the end of this period, they were retested for fecal H pylori Ag.

Inclusion Criteria :

1. Adults (≥18 years).
2. Presence of dyspeptic symptoms .
3. Positive Fecal H. pylori Ag test at baseline .
4. Willingness to provide informed consent .

Exclusion Criteria :

1. Use of PPIs, H2 blockers, or antibiotics within 4 weeks .
2. Patients who are indicated for immediate therapy with antisecretory drugs [PPI or potassium-competitive acid blocker (PCAB)] or antibiotics for any reason .
3. Red-flag symptoms (e.g., weight loss, hematemesis) require urgent endoscopy .
4. Pregnancy, lactation, or severe comorbidities (e.g., liver/kidney failure.(
5. Patients who had previous experience of any allergic reactions (itching or rash, etc.) to any drugs or food .
6. Patients refusing to participate in the study

Fecal H. Pylori Ag Detection by ELISA

The EDIT™ Fecal H. Pylori Antigen ELISA Kit (Epitope Diagnostics, Cat. No. KT 826) was used for qualitative and quantitative detection of H. pylori antigen in stool samples .

1. **Sample Collection and Preparation**

a) Collection: Fresh stool samples (1–2 g solid or 1–2 mL liquid) were collected in sterile containers and stored at –20°C if not processed within 24 hours .

b) Homogenization :

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- Forty milligrams of stool were suspended in 1 mL of 1X Assay Buffer provided in the kit.

- Vortexed for 1–2 minutes, then centrifuged at 3,000 × g for 5 minutes. A supernatant was used for testing .

2. ELISA Procedure (Quantitative)

a) Coating :

- Added 100 µL of calibrators (Cat. No. 31141–31146), controls (Cat. No. 31147–31148), or patient samples to antibody-coated microplate wells (Cat. No. 30665 .(

- Incubated at room temperature for 1 hour.

b) Washing :

- Washed 5× with 350 µL/well of diluted Wash Buffer (Cat. No. 10010 .(

c) Detection:

- Added 100 µL of HRP-conjugated anti-H. Pylori tracer antibody (Cat. No. 30666 .(

- Incubated at RT for 30 minutes .

d) Substrate Reaction :

- Added 100 µL of TMB substrate (Cat. No. 10020), and incubated for 20 minutes (protected from light .(

e) Stop & Measurement:

- Stopped with 100 µL of sulfuric acid (Cat. No. 10030 .(

- Absorbance was measured at 450/620 nm using a microplate reader.

Interpretation

-Quantitative :

H. pylori concentration (ng/mL) calculated from a standard curve (Calibrators 1–6 .(

-Positive cutoff: ≥3 ng/mL .

-Qualitative :

-Positive: OD ≥ 1.1 × (mean negative control + 0.10 .(

3. Quality Control

-Intra-assay CV < 10% .

-Controls: Positive control OD > 0.8; negative control OD < 0.18.

This protocol aligns with the manufacturer's guidelines (Epitope Diagnostics, KT 826) and clinical standards for H. pylori detection .

Sample size :

The sample size was calculated using OpenEpi, version 3, an open-source calculator considering the outcome frequency as 95%, confidence limits of 5%, and design effect 1. Sample size equation: n = [DEFF*NP (1-p)]/ [(d2/Z21-α/2*(N-1) +p*(1-p)]. The calculated sample was 73 participants with 95% confidence interval [17].

Statistical analysis:

The data was collected and entered the Statistical Package for Social Science (SPSS) version 25; the qualitative data was presented as numbers and percentages, while quantitative data was presented as mean, standard deviations, range, and median with inter-quartile range and according to their distribution the suitable test was used. The confidence interval was 95%, and the accepted error margin was 5%. When the p-value was less than 0.05, it was considered significant.

RESULTS

Seventy-three patients were enrolled in this quasi-experimental study "before-and-after study". Among them, 38 (52.1%) were female and 35 (47.9%) were male. The mean age of the study group was 38.93±14.268 (15-71). After 2 weeks of treatment with three times daily Rebamipide 100mg alone without additional therapy, 43 patients (58.9%) showed no dyspepsia, and 30 patients (41.1%) still had dyspepsia (fig.1). Among the enrolled patients, 12 patients (16.4%) showed negative results of the fecal Helicobacter pylori test after 2 weeks therapy with three times daily Rebamipide 100mg and 61 patients (83.6%) showed positive results (fig.2). There was no significant difference between those with positive and negative results regarding age, gender or improvement of dyspepsia (p = 0.343, 0.274, 0.221 respectively).

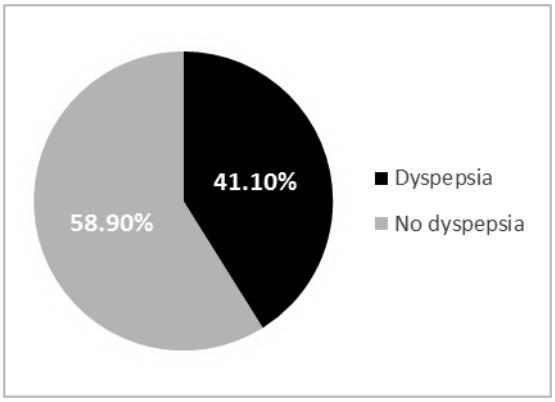

Figure 1: Incidence of dyspepsia improvement after a 2-week monotherapy with Rebamipide 100mg three times daily.

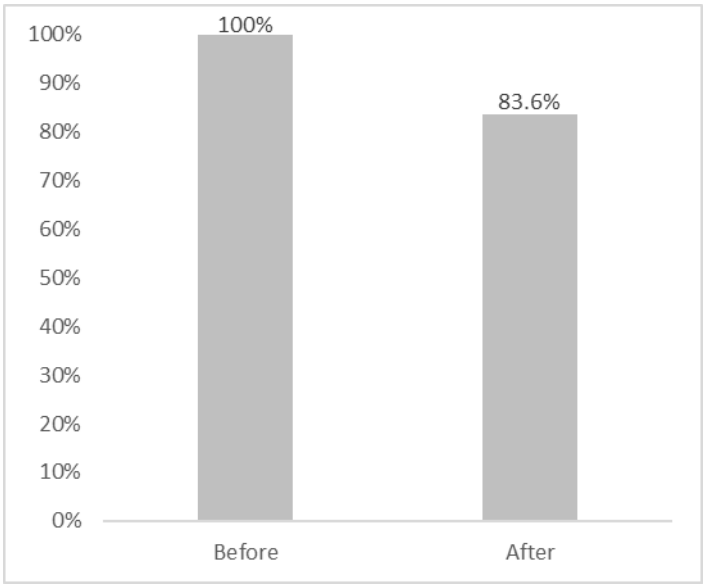

Figure 2: Positive results of stool H. pylori Ag test before and after a 2-week therapy with Rebamipide 100 mg three times daily.

DISCUSSION

According to American College of Gastroenterology (ACG) guidelines, PPI and PCABs should be stopped 2 weeks before fecal H pylori Ag testing [18,19,20,21].

Many studies showed the efficacy and safety of Rebamipide in improving symptoms of dyspepsia and NSAID-induced gastritis which may make it an alternative therapy to PPI [14,15].

According to ACG guidelines, H pylori Ag testing is sensitive and reliable so we did not use any other test as a standard comparative investigation [21,22].

The current study showed that after taking Rebamipide for 2 weeks, the results of fecal H pylori Ag testing were still positive in 61 patients (83.6%). This result is consistent with the already well-established known sensitivity of stool H. pylori Ag testing in different studies (91%, 93.75%, 61.54%, and 94%) [23,24,25].

More than half of the enrolled patients (58.9%) showed improved symptoms of dyspepsia after a 2-week monotherapy with three times daily Rebamipide 100mg without antisecretory drugs. Park et al., 2016 found that Rebamipide therapy for twelve weeks enhanced atypical GI symptoms in patients with Type2 diabetes mellitus [12].

A systematic review and meta-analysis by Jaafar et al. (2018) concluded that Rebamipide is efficacious in the management of organic dyspepsia and may also alleviate symptoms in patients with functional dyspepsia [15]. In contrast, a separate study by Talley et al. (2001) reported no significant improvement in dyspeptic symptoms following a two-week course of Rebamipide [26]. This lack of efficacy may be attributed to the short duration of treatment .

These results may make Rebamipide an accepted therapeutic option to some extent that acts as a bridge after the stoppage of antisecretory drugs before stool H. pylori Ag testing. To the best of our knowledge, this is the first study to investigate the potential association between Rebamipide treatment and fecal H. pylori Ag levels. A thorough literature search revealed no previous reports exploring this relationship, highlighting the novelty of our findings and the need for further research to confirm and expand upon these results.

We think that further studies are needed to overcome the limitations of the present study. Further research should consider larger sample sizes, randomized controlled trials, including tissue biopsy as a gold standard test, and determining the optimum time for fecal H. pylori testing after the stoppage of Rebamipide.

CONCLUSION

The present study demonstrated that most patients continued to exhibit positive fecal H. pylori Ag results following a 2-week course of Rebamipide. These findings suggest that Rebamipide may not have a significant short-term effect on fecal Ag test outcomes. Rebamipide may be empirically prescribed as a bridge while stoppage of PPIs before H. pylori Ag detection in stool test, to overcome epigastric pain and to avoid non-sensitive testing on PPI therapy.

Abbreviations:

H. Pylori: Helicobacter pylori

UGI: upper gastro-intestinal

PPI: proton pump inhibitor

Ag: antigen

NSAIDs: non-steroidal anti-inflammatory drugs

FD: functional dyspepsia

PCAB: potassium-competitive acid blocker

ACG: American Colleague of Gastroenterology

Ethical considerations: The study was conducted by the ethical guidelines of the 1975 Helsinki Declaration and was approved by the local ethics committee of the Faculty of Medicine, New Valley University (20250130001). All participants provided informed consent.

Conflicts of Interest: The authors declare no conflict of interest.

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Author Contributions: All authors contributed substantially to the work, including the conception and design of the study, data acquisition, analysis, and interpretation. They were involved in drafting, revising, and critically reviewing the manuscript, approved the final version for publication, agreed on the target journal, and accepted responsibility for all aspects of the work.

Acknowledgments: not applicable.

Data sharing statement: All generated data are included in the published manuscript. The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

HIGHLIGHTS

- Our findings suggest that Rebamipide may not have a significant short-term effect on the sensitivity of the fecal *H. pylori* Ag test.
- To overcome epigastric pain and to avoid non-sensitive testing on PPI therapy, Rebamipide may be empirically prescribed as a bridge while stopping PPIs before the fecal *H. pylori* Ag test.

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