Efficacy and Safety of Proton Pump Inhibitors (PPIs) Plus Rebamipide for Endoscopic Submucosal Dissection-induced Ulcers: A Meta-analysis

Jun Wang, Xufeng Guo, Chuncui Ye, Shijie Yu, Jixiang Zhang, Jia Song, Zhuo Cao, Jing Wang, Min Liu and Weiguo Dong

Abstract

Objective To compare the efficacy of proton pump inhibitors (PPIs) with rebamipide versus PPIs alone for the treatment of ulcers after endoscopic submucosal dissection (ESD).

Methods PubMed, Web of Science, Medline, Embase, the Cochrane Central Register of Controlled Trials and China Naitonal Knowledge Infrastructure were searched up to the end of October 2013 in order to identify all randomized controlled trials reporting the effects of PPIs plus rebamipide on healing ulcers after ESD. The outcome measurement was complete ulcer healing.

Results A total of six studies involving 724 patients were included. The pooled data suggested a significantly higher rate of ulcer healing after endoscopic therapy among patients treated with PPIs plus rebamipide than among those treated with PPIs alone [odds ratio (OR)=2.40, 95% confidence interval (CI): 1.68-3.44]. The subgroup analysis showed PPI plus rebamipide therapy to be more effective in healing ESD-induced ulcers than treatment with PPIs alone after both four (OR=2.22, 95%CI: 1.53-3.24) and eight weeks of treatment (OR=3.19, 95%CI: 1.22-8.31). In addition, the combination therapy was found to be significantly more effective than the use of PPIs alone for all ESD ulcers greater than 20 mm in size (OR=4.77, 95%CI: 2.22-10.26). There were no significant differences between the treatment groups with regard to ulcer location (low, middle or upper stomach) or the presence of absence of H. pylori infection. No serious adverse events were observed in either group.

Conclusion The results of this meta-analysis suggest that treatment with PPIs plus rebamipide is superior to PPI monotherapy for healing ESD-induced ulcers over four weeks, particularly large ulcers. However, more well-designed trials are needed to confirm these findings.

Key words: endoscopic submucosal dissection, rebamipide, proton pump inhibitor, meta-analysis

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Introduction

Endoscopic submucosal dissection (ESD) is a minimally invasive treatment for gastric adenoma or early gastric cancer. ESD enables the en bloc resection of gastric lesions, regardless of size or location. The ESD technique can be used to acquire a more accurate histopathological diagnosis relative to that obtained with piecemeal endoscopic resection and may also improve the patient’s subsequent quality of life compared to surgery (1). However, ESD is associated with the occurrence of larger, deeper ulcers after the procedure. Proton-pump inhibitors (PPIs) are the most effective medications for treating ESD-induced ulcers. However, some studies have shown that PPI monotherapy does not result in sufficient healing of ESD-induced ulcers within four weeks (2).

Rebamipide is a mucosal protective drug for the treatment of ulcers developed in Japan that is widely prescribed in Asian nations (3). Many clinical and experimental trials...
have indicated that rebamipide therapy accelerates ulcer healing. In a multicenter randomized controlled trials (RCT), rebamipide (Mucosta, Otsuka Pharmaceutical, Tokyo, Japan) was reported to be efficacious for treating large gastric ulcers following Helicobacter pylori eradication (4). Another recent placebo-controlled trial also found that rebamipide is as effective as omeprazole in treating H. pylori-positive gastric ulcers after eradication (5). In randomized controlled studies, rebamipide has been found to prevent nonsteroidal anti-inflammatory drug (NSAID)-induced peptic ulcers, accelerate gastric ulcer healing and suppress mucosal inflammation in patients with chronic erosive gastritis (6, 7). Recently, several studies (8-14) have examined the efficacy of rebamipide and PPI combination therapy for the treatment of ESD-induced ulcers. However, there is currently no consensus regarding the optimal treatment duration or drug regimen. Therefore, we conducted a meta-analysis of published data in order to evaluate the efficacy of PPI plus rebamipide therapy for successfully treating ESD-induced ulcers.

**Materials and Methods**

**Search strategy**

A literature search was conducted using PubMed, Web of Science, Medline, Embase, the Cochrane Central Register of Controlled Trials and China National Knowledge Infrastructure up to October 2013 without language restrictions. Relevant RCTs were identified using the following terms: “endoscopic submucosal dissection or ESD,” “proton pump inhibitor or PPI” and “rebamipide.” The search was restricted to human subjects. Additional studies were identified using a hand search of references of original or review articles and international conferences on this topic, primarily including Asian Pacific Digestive Week, United European Gastroenterology Week and American Gastroenterological Association Digestive Disease Week.

**Inclusion and exclusion criteria**

Studies were included if they met the following criteria: (1) randomized, controlled human trials with a parallel design, (2) including a comparison of PPI plus rebamipide therapy with PPI monotherapy for healing ESD-induced ulcers, (3) presenting the detailed outcomes of cases and control groups or including such data for calculation in the article text. Meanwhile, the major exclusion criteria were: (1) an unclear study population or trial size, (2) a non-RCT, qualitative study or study without extractable data, (3) the administration of rebamipide in the control arm and (4) case reports, editorials, commentaries, reviews or abstracts only.

**Data extraction and quality assessment**

Two investigators independently extracted the data and reached a consensus for all items. If the investigators generated different results, they checked the data again and had a discussion in order to reach an agreement. If they were unable to reach an agreement, an expert was invited to join the discussion. Data extracted from the selected articles included the first author’s name, year of publication, country of origin, age, gender, patients in the two groups, arms of treatment, medication duration, Helicobacter pylori (Hp) positivity, lesion size, tumor location and endpoints. The ulcer stage was classified using the Sakita-Fukutomi classification system (15): active (A1, A2), healing (H1, H2) and scarring (S1, S2). S-stage was defined as healing of an artificial ulcer. A quality assessment was performed using the scale described by Jadad et al. (16). In this scale, the scores range from 1 to 5, with a higher score indicating higher quality. The scores are based on the method of randomization, level of blinding, concealment of allocation and the use of complete accounting of all randomized patients. We considered RCTs with a score greater than 3 to be high quality.

**Statistical analysis**

A meta-analysis was performed using the Cochrane Collaboration RevMan 5.2 and STATA package version 12.0. The efficacy of PPI plus rebamipide therapy compared with PPI therapy alone for the treatment of ESD-induced ulcers was estimated for each study using the odds ratio (OR) and 95% confidence interval (95%CI). The χ²-test-based Q statistic test was performed to assess the between-study heterogeneity (17). We also quantified the effect heterogeneity according to the I² test. When a significant Q test (p<0.05) or I²>50% indicated heterogeneity across studies, the random effects model was used (18); otherwise, the fixed effects model was used (19). The subgroup analyses were performed considering four- and eight-week durations of treatment. An analysis of sensitivity was performed in order to evaluate the stability of the results. Finally, potential publication bias was investigated using Begg’s funnel plot and Egger’s regression test (20, 21). A p value of <0.05 was regarded as being statistically significant.

**Results**

**Study characteristics**

A total of 310 citations were identified in the search. According to the inclusion criteria, seven studies (8-14) with a full text were included in the meta-analysis. Among these seven publications, we excluded one study (14) because the control arm of patients also received rebamipide. Therefore, six eligible RCTs, including 724 patients, were finally included. The characteristics of the selected studies are summarized in Table. Of the six eligible studies, five were from Japan (8-11, 13, 14), and one was from Korea (12). The quality assessment of the included studies was performed using the Jadad score. No trials met all quality measurements; however, all scores were greater than 3, thus indicating a high quality.
Table. Characteristics of the Included Studies

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Country</th>
<th>Age, mean±SD year (male/female)</th>
<th>Patients</th>
<th>Interventions</th>
<th>Dose</th>
<th>Duration</th>
<th>Endpoints</th>
<th>Quality scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>2012</td>
<td>Japan</td>
<td>69±5(52-85) 30/12 42</td>
<td>PPI</td>
<td>omeprazole 20mg/day, Lansoprazole 30mg/day, or Rabeprazole 10mg/day</td>
<td>28d</td>
<td>(1) ulcer healing</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>2011</td>
<td>Japan</td>
<td>69±7 24/7 31</td>
<td>PPI</td>
<td>omeprazole 20mg/day</td>
<td>56d</td>
<td>(1) ulcer healing</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>2010</td>
<td>Japan</td>
<td>75±7(57-82) 24/7 31</td>
<td>PPI</td>
<td>Rabeprazole 10mg/day</td>
<td>28d</td>
<td>(1) ulcer healing</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>2012</td>
<td>Japan</td>
<td>70±8(9) 68/17 85</td>
<td>PPI</td>
<td>Omeprazole 20mg/day, or Lansoprazole 30mg/day</td>
<td>28-42d</td>
<td>(1) ulcer healing</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>2012</td>
<td>Korea</td>
<td>64.9±10.2 98/44* 129</td>
<td>PPI</td>
<td>Pantoprazole 40mg/day</td>
<td>28d</td>
<td>(1) ulcer healing</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>2013</td>
<td>Japan</td>
<td>70±7.8 36/9 44</td>
<td>PPI</td>
<td>Lansoprazole 30mg/day</td>
<td>28+56d</td>
<td>(1) ulcer healing</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

Quantitative data synthesis

Outcomes

The trials with available data for ESD-induced ulcer healing included 362 patients who received PPI plus rebamipide therapy for the treatment of iatrogenic ulcers after endoscopic therapy and 362 control subjects who received PPI monotherapy. There was no statistical heterogeneity among the included studies (I²=22%, p=0.27); therefore, the fixed-effects model was used. The estimated pooled data showed a significantly higher rate of ulcer healing after endoscopic therapy in the PPI plus rebamipide group than in the PPI alone group (OR=2.40, 95%CI: 1.68-3.44) (Fig. 1). In the subgroup analysis of the duration of treatment, we found that treatment with PPIs plus rebamipide was more effective in healing ESD-induced ulcers than PPI monotherapy over both four- (OR=2.22, 95%CI: 1.53-3.24) and eight-week durations of treatment (OR=3.19, 95%CI: 1.22-8.31) (Fig. 2). The sensitivity analysis performed using sequential excluding of one trial at a time did not alter the results.

Two trials (9, 13) with available data for the location of resection included 165 patients who received treatment with PPIs plus rebamipide and 163 control subjects who received PPI monotherapy. The rate of ulcer healing was not significantly different between the treatment groups.

Two trials (12, 13) with available data for H. pylori infection included 184 patients who received treatment with PPIs plus rebamipide and 186 control subjects who received PPI monotherapy. We also detected no significant differences between the treatment groups.

Two trials (8, 10) with available data for the specimen size included 74 patients who received treatment with PPIs plus rebamipide and 72 control subjects who received PPI monotherapy. The pooled data suggested a significantly higher rate of ulcer healing after endoscopic therapy in the PPI plus rebamipide group than in the PPI alone group for both a specimen size between 20-40 mm (OR=3.58, 95%CI:
1.51-8.52) and >40 mm (OR=12.66, 95%CI: 2.04-78.70) (Fig. 3).

**Adverse events**

Three trials (9, 10, 13) reported adverse events. Only one of these studies reported serious adverse events in the two groups: the study by Fujiwara et al. reported that one patient in the PPI group experienced bleeding from a post-ESD artificial ulcer.

**Publication bias**

Begg’s funnel plot and Egger’s test were performed to assess the potential publication bias in the available literature. The shape of the funnel plots did not reveal any evidence of asymmetry (Fig. 4). Egger’s test also showed that there was no statistical significance for the evaluation of publication bias (p=0.143).

**Discussion**

ESD was developed in Japan to enable the en bloc complete resection of superficial gastrointestinal neoplasms, regardless of the size or location of the lesions. ESD results in the creation of larger artificial ulcers. Although PPIs are the
standard treatment for ESD-induced ulcers and bleeding after ESD, Fujiwara et al. (9) reported that treatment with PPIs and acid-suppressive agents alone has limited effects in patients with a low level acid secretion, such as those with severe atrophic conditions in the gastric mucosa. Terano et al. (4) reported that, in their study, seven weeks of rebamipide treatment without acid-suppressive agents promoted gastric ulcer healing after eradication therapy compared with a placebo. In addition, in patients with little acid secretion (such as those with severe atrophic gastritis), the suppression of acid is not a major factor in ulcer healing. Therefore, it remains insufficient to attempt to successfully treat ulcers using PPIs alone, and the use of combination therapy is therefore needed.

In this study, we conducted a meta-analysis to explore the efficacy of treatment with PPIs plus rebamipide for healing ESD-induced ulcers. The results conclusively showed that PPI plus rebamipide therapy is superior to PPI monotherapy for healing ESD-induced ulcers, particularly large ulcers (size >20 mm). In addition, no episodes of ulcer bleeding or complications related to the drugs used after ESD were observed in any of the study subjects. These results can be explained by the regulatory effects of rebamipide on the inflammatory process. Several studies have been found that rebamipide promotes ulcer healing by increasing the levels of cytoprotective prostaglandins (22), epidermal growth factor (23) and nitric oxide (24) and decreasing the levels of oxygen free radicals (25). These actions increase the gastric mucosal blood flow at the ulcer margin, an important factor for ulcer healing, and accelerate the mucosal or submucosal reconstruction of damaged structures (24, 26). A recent animal study suggested that treatment with rebamipide enhances the quality of ulcer healing by increasing the level of prostaglandin E2 and decreasing the levels of interleukin-8 and malondialdehyde (27). Previous studies have also reported that ulcer healing is associated with both the lesion size and tumor location. In this meta-analysis, two trials evaluated the degree of ulcer healing with respect to the lesion size and tumor location, and we found a significantly higher rate of ulcer healing after endoscopic therapy in the PPI plus rebamipide group than in the PPI alone group for both a lesion size between 20-40 mm and >40 mm (particularly the latter). However, there were no significant differences between the treatment groups with regard to ulcer location (low, middle or upper stomach). Although Hp infection is generally considered to be a causal factor in the pathogenesis of peptic ulcers, a few studies found that the Hp status does not affect the rate of ulcer healing after ESD (28). Similarly, in this study, the pooled data suggested there were no significant differences between the treatment groups. In addition, three trials reported adverse events, and no episodes of ulcer bleeding or complications related to the drugs used after ESD were observed in the two groups. However, because only a few trials were included, these results should therefore be interpreted with caution, and more studies are needed.

It would be difficult to interpret the results if significant heterogeneity was present. However, we did not find any obvious heterogeneity or publish bias across the studies in this meta-analysis. In addition, the sensitivity analysis using sequential excluding of one trial at a time did not alter the results, thus indicating that our results were statistically robust. However, some limitations of this meta-analysis should be addressed. First, the quality of the included RCTs was relatively low, as no trials met all quality measurements, which may have influenced the results. Second, the trials were carried out with less consistency of outcomes, indicating the insufficiency of combinable studies, which limits the subgroup analyses, detection of heterogeneity and evaluation of bias. Third, the use of various types of PPI medications and diverse PPI regimes may have produced a small amount of bias.
In conclusion, this meta-analysis showed that treatment with PPIs plus rebamipide is superior to PPI monotherapy for healing ESD-induced ulcers over a period of four weeks, particularly regarding large ulcers. However, more well-designed trials are needed to confirm these findings.

The authors state that they have no Conflict of Interest (COI).

References

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