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<th>Head-to-head comparison of H2-receptor antagonists and proton pump inhibitors in the treatment of erosive esophagitis: A meta-analysis</th>
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<tr>
<td>Author(s)</td>
<td>Wang, WH; Huang, JQ; Zheng, GF; Xia, HHX; Wong, WM; Lam, SK; Wong, BCY</td>
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<td>Citation</td>
<td>World Journal Of Gastroenterology, 2005, v. 11 n. 26, p. 4067-4077</td>
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<td>This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License.</td>
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Head-to-head comparison of H₂-receptor antagonists and proton pump inhibitors in the treatment of erosive esophagitis: A meta-analysis

Wei-Hong Wang, Jia-Qing Huang, Ge-Fan Zheng, Harry Hua-Xiang Xia, Wai-Man Wong, Shiu-Kum Lam, Benjamin Chun-Yu Wong

Abstract

AIM: To systematically evaluate the efficacy of H₂-receptor antagonists (H₂-RAs) and proton pump inhibitors in healing erosive esophagitis (EE).

METHODS: A meta-analysis was performed. A literature search was conducted in PubMed, Medline, Embase, and Cochrane databases to include randomized controlled head-to-head comparative trials evaluating the efficacy of H₂-RAs or proton pump inhibitors in healing EE. Relative risk (RR) and 95% confidence interval (CI) were calculated under a random-effects model.

RESULTS: RRs of cumulative healing rates for each comparison at 8 wk were: high dose vs standard dose H₂-RAs, 1.17 (95%CI, 1.02-1.33); standard dose proton pump inhibitors vs standard dose H₂-RAs, 1.59 (95%CI, 1.44-1.75); standard dose other proton pump inhibitors vs standard dose omeprazole, 1.06 (95%CI, 0.98-1.06). Proton pump inhibitors produced consistently greater healing rates than H₂-RAs of all doses across all grades of esophagitis, including patients refractory to H₂-RAs. Healing rates achieved with standard dose omeprazole were similar to those with other proton pump inhibitors in all grades of esophagitis.

CONCLUSION: H₂-RAs are less effective for treating patients with erosive esophagitis, especially in those with severe forms of esophagitis. Standard dose proton pump inhibitors are significantly more effective than H₂-RAs in healing esophagitis of all grades. Proton pump inhibitors given at the recommended dose are equally effective for healing esophagitis.

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Key words: Erosive esophagitis; H₂-receptor antagonists; Proton pump inhibitors; Meta-analysis

INTRODUCTION

Gastro-esophageal reflux disease (GERD) is one of the most common chronic conditions affecting 20-40% of adult populations and has a major adverse impact on the quality of life[1-3]. About 40-60% of patients with symptoms of GERD may have substantial injury of esophageal mucosa ranging from mild inflammation and erythema to various grades of erosions. The major complications of GERD are esophageal ulcer and bleeding, esophageal stricture, and Barrett’s esophagus[1-4].

Reflux esophagitis is generally considered to be the result of prolonged and repeated exposure of the distal esophageal mucosa to acidic gastric contents[5-9]. It is increasingly clear that the key to reducing symptoms and to healing erosive esophagitis is to decrease the duration of exposure to the acidic refluxate. Acid-suppressing drugs that have been used to treat GERD include H₂-receptor antagonist (H₂-RAs) and proton pump inhibitors. The efficacy of medical treatment depends on the ability to increase and maintain the intra-esophageal pH above 4.0 over the 24-h period[7,8]. H₂-RAs are limited in their ability to inhibit postprandial gastric acid secretion and are ineffective in controlling reflux symptoms and healing esophagitis[8,9]. In contrast to H₂-RAs, proton pump inhibitors block the final step of acid secretion, resulting in a profound and long-lasting acid suppression regardless of the stimulus[10,11]. Results from 33 randomized clinical trials with over 3 000 patients showed that symptomatic relief could be anticipated in 83% of proton pump inhibitor-treated patients compared with 60% of patients receiving H₂-RAs. Similarly, esophagitis was healed in 78% and 50%
of patients treated with proton pump inhibitors and H₂RAs, respectively[3]. Previously there have been several systematic reviews and meta-analyses of clinical trials assessing the effects of medical treatments for erosive esophagitis[14-17]. Chiba and colleagues[14], and Caro and colleagues[18] compared the effectiveness of proton pump inhibitors and H₂RAs in the healing of esophagitis, whereas the comparative efficacy among proton pump inhibitors was analyzed by Sharma et al[16] and Edwards et al[17]. However, comparison of the effects between treatments with proton pump inhibitors and H₂RAs in patients with esophagitis has been difficult because of the difference in the study design. For example, studies included in the previous meta-analyses were not all head-to-head comparative trials[14,18]. The overall estimates of healing rate calculated by one-step pooling from different pairs of comparatives, may produce bias due to the ignorance of study differences such as sample size and differential difference in effect sizes. In addition, healing of esophagitis is significantly influenced by the initial grade of esophagitis, with healing rate being lower for the severe form of esophagitis than for the mild form of esophagitis[18-20]. However, no meta-analysis has been published to systematically evaluate the impact of the initial grading of esophagitis on esophagitis healing rates in head-to-head comparative trials. Therefore, the objectives of the current study were firstly to evaluate any difference in healing erosive esophagitis between proton pump inhibitors and H₂RAs in head-to-head comparative trials, and secondly to estimate the impact of baseline grade of esophagitis on esophagitis healing rates.

MATERIALS AND METHODS

Literature search
A computerized literature search was performed in the PubMed, Medline, Embase and Cochrane databases for clinical trials published in English up to May 2004 with the following MeSH terms and/or text words in various combinations: gastroesophageal reflux, GERD, GORD, esophagitis, and healing, as well as the name of each respective drug (H₂-receptor antagonists: cimetidine, ranitidine, famotidine, nizatidine, roxatidine; proton pump inhibitors: omeprazole, lansoprazole, pantoprazole, rabeprazole, esomeprazole). The title and abstract of all potentially relevant studies were screened for their relevance before retrieval of full articles. Full articles were also scrutinized for relevance if the title and abstract were ambiguous. Fully recursive searches were performed from the reference list of all retrieved articles to ensure a complete and comprehensive search of the published literature. All searches were conducted independently by at least two reviewers.

Study selection
The inclusion criteria were as follows: (1) Randomized, controlled clinical trials in adults with an endoscopically confirmed diagnosis of GERD. (2) Two or more treatment arms: high dose vs standard dose H₂RAs; proton pump inhibitors vs H₂RAs, or one proton pump inhibitor vs another proton pump inhibitor. We defined standard dose of each drug as: ranitidine 300 mg/d, famotidine 40 mg/d, nizatidine 300 mg/d, cimetidine 800 mg/d, omeprazole 20 mg/d, lansoprazole 30 mg/d, pantoprazole 40 mg/d, rabeprazole 20 mg/d, esomeprazole 40 mg/d. The newer proton pump inhibitors include lansoprazole, pantoprazole, rabeprazole and esomeprazole.

The outcomes considered were healing rates of esophagitis for each group at different time points (2, 4, 6, 8, and 12 wk), based on initial grade of esophagitis, if applicable. Healing rate was calculated by pooling raw data from qualified studies within each group. These data were then expressed as a healing-time curve that plotted the cumulative percentage of patients healed vs the end point in weeks.

Relative risk (RR) and 95% confidence interval (CI), under a random-effects model[21], were calculated using raw data of the selected studies at specified time points (2, 4, 6, 8, and 12 wk). The potential effect of publication bias was assessed using a funnel plot suggested by Egger et al[22].

dosage and schedule, and healing rate of esophagitis.

We excluded studies that only assessed symptom relief without endoscopic documentation of esophagitis healing. Also excluded were studies dealing only with relapsed or recurrent esophagitis, studies of pediatric patients, duplicate publications or studies published only in abstract form, or those focusing on pharmacokinetics and pharmacodynamics. Combination treatments such as an anti-secretory agent and a prokinetic drug were also excluded.

Data extraction
Data was extracted from each study independently and entered into a computerized database. Differences were resolved by discussion to reach consensus between the reviewers. The information retrieved covered country of study, study design, characteristics of population, grading of esophagitis, treatment regimen, number of patients treated, evaluated and healed, and confounding variables such as alcohol use, cigarette smoking, and caffeine use, where applicable. Healing data, up to 12 wk were extracted for both intention-to-treat (ITT) and per-protocol (PP) analyses. Data on healing based on the initial grade of esophagitis were also extracted, if applicable. In studies where only per-protocol healing rates were reported, we calculated the ITT healing rates based on the initial randomized number of patients. Articles that did not specify the type of analysis were assumed to report per-protocol data.

Quality assessment
Study quality was assessed by a series of validity criteria, including study design, level of blinding, method of randomization, patient selection, baseline characteristics, severity of esophagitis, definition of healing, compliance, and analysis by intention to treat criteria. Discrepancies in quality assessment were resolved by consensus among the authors. No quality score was assigned to any study to avoid possible introduction of subjectivity by the authors.

Statistical analysis
The data were grouped as follows: high dose vs standard dose H₂RAs; proton pump inhibitors vs H₂RAs, or one proton pump inhibitor vs another proton pump inhibitor. We defined standard dose of each drug as: ranitidine 300 mg/d, famotidine 40 mg/d, nizatidine 300 mg/d, cimetidine 800 mg/d, omeprazole 20 mg/d, lansoprazole 30 mg/d, pantoprazole 40 mg/d, rabeprazole 20 mg/d, esomeprazole 40 mg/d. The newer proton pump inhibitors include lansoprazole, pantoprazole, rabeprazole and esomeprazole.

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Statistical heterogeneity between studies was assessed using the \( Q \) value calculated from the Mantel-Haenszel method. In the presence of statistical heterogeneity, we searched for the sources of any possible clinically important heterogeneity, i.e., methodological or biological heterogeneity. We did not simply exclude outliers on the basis of statistical test of heterogeneity. Furthermore, to test the robustness of the analysis, we performed sensitivity analyses to evaluate whether exclusion of a single study substantially altered the result of the summary estimate.

All analyses were carried out using EasyMa software for meta-analysis written by M Cucherat, Lyon, France (EasyMa, 2001).

**RESULTS**

**Study characteristics**

We identified a total of 485 citations with the computerized search. Screening of the title and abstract of the citations identified 72 potentially relevant studies for full article retrieval. Of these, 52 studies met the inclusion criteria\(^{[19,20,24-30]}\), and 20 studies were subsequently excluded for the following reasons: 17 were not head-to-head comparative studies\(^{[33-36]}\), 1 duplicate publication\(^{[37]}\), 1 without raw data\(^{[38]}\), and 1 with a confusing treatment allocation\(^{[39]}\). The manual search of the reference list of the retrieved articles did not yield any additional studies. Of the 52 studies, the majority were double blind studies (51/52, 98.1%). Ten (19.2%) compared high dose H\(_2\)RA with standard dose H\(_2\)RA\(^{[33-35]}\), 26 (50.0%) compared a proton pump inhibitor with an H\(_2\)RA\(^{[33-37,71]}\), and 16 (30.8%) compared a proton pump inhibitor with another proton pump inhibitor\(^{[19,20,58-70,72]}\). Only 25 (48.1%) reported raw healing data by the initial grade of esophagitis\(^{[19,20,32,34,35,38,43-47,49,52,53,55,58,60,61,69-71]}\). The proportion of patients with a smoking history was reported in 61.5% of studies, alcohol consumption was reported in 48.1% of studies. The initial grade of esophagitis was reported in 58% studies. However, only 48.1% studies provided raw data on healing by the initial grade of esophagitis.

**Healing of esophagitis**

**High dose H\(_2\)RAs vs standard dose H\(_2\)RAs**

Ten studies involving 27 treatment arms compared high dose (\( n = 2041 \) patients) with standard dose H\(_2\)RAs (\( n = 1967 \) patients)\(^{[23-33]}\). Table 1 summarizes the pooled healing rates of esophagitis in patients treated with high dose H\(_2\)RAs vs standard dose H\(_2\)RAs. Statistical significance was achieved at 4, 8 and 12 wk, indicating that high dose H\(_2\)RAs healed significantly more esophagitis than did standard dose H\(_2\)RAs (Table 1).

No comparative study reported data on the healing of esophagitis at 2 wk. Only one study\(^{[30]}\) reported healing rates at 3 wk, of 17.2% (29/169) for high dose H\(_2\)RAs and 19.6% (33/168) for standard dose H\(_2\)RAs (RR 0.87, 95%CI 0.56-1.37) (Table 1).

**Proton pump inhibitors vs H\(_2\)RAs**

There were 14 studies with 28 treatment arms comparing standard dose proton pump inhibitors (\( n = 861 \) patients) with standard dose H\(_2\)RAs (\( n = 752 \) patients)\(^{[33-45,71]}\). The pooled healing rates achieved with the standard dose proton pump inhibitors were superior to that of H\(_2\)RAs at all given time points (Table 2). Similar findings were observed when the comparison was made between high dose H\(_2\)RAs (\( n = 234 \) patients) and the standard dose proton pump inhibitors (\( n = 237 \) patients)\(^{[33-35]}\) (Table 2).

Three studies compared low dose proton pump inhibitors (\( n = 279 \) patients) with standard dose H\(_2\)RAs (\( n = 276 \) patients) for healing esophagitis\(^{[33,35,71]}\). The pooled healing rates of the low dose proton pump inhibitors were higher than that of the standard dose H\(_2\)RAs at both 4 and 8 wk (Table 2).

**Omeprazole 20 mg daily vs other proton pump inhibitors**

Eleven studies with 23 treatment arms reported comparative results on the healing of esophagitis between omeprazole 20 mg daily (\( n = 3137 \) patients) and other proton pump inhibitors at standard doses (\( n = 3397 \) patients)\(^{[20,59-68]}\). No significant difference in the healing rate was observed between omeprazole 20 mg daily and other proton pump inhibitors at 2-8 wk (Table 3).

The esophagitis healing time curves are depicted in Figures 1-3. As shown in Figure 1, high dose H\(_2\)RA achieved higher healing rates than standard dose H\(_2\)RA. However, the healing rate achieved with standard dose proton pump inhibitors at 2 wk was even higher than that of H\(_2\)RAs at wk 8 (63.4% vs 52.0%), suggesting that proton pump inhibitors healed esophagitis significantly faster than did H\(_2\)RAs (Figure 2). Similar healing rates were also observed when the newer proton pump inhibitors were compared with omeprazole 20 mg daily (Figure 3).

**Refractory esophagitis**

Refractory esophagitis was defined as treatment failure with a standard dose of H\(_2\)RAs given for at least 12 wk\(^{[35-37]}\). Three studies compared the effectiveness of proton pump inhibitors with ranitidine for the treatment of refractory esophagitis\(^{[35-37]}\) (Table 4). Two of them reported that lansoprazole 30 mg daily achieved significantly higher healing

| Table 1 | Healing rate of esophagitis by ITT with standard dose vs high dose of H\(_2\)RA at 3, 4, 6, 8, 12 wk |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                | 3-wk            | 4-wk            | 6-wk            | 8-wk            | 12-wk           |
| Number of comparisons | 1               | 5               | 9               | 5               | 12              |
| High dose       | Pooled data     | 29/169          | 297/669         | 607/1 294       | 413/669         | 1 142/1 729     |
| Pooled healing rate (%) | 17.2            | 44.4            | 46.9            | 61.7            | 66.0            |
| Standard dose   | Pooled data     | 33/168          | 198/573         | 584/1 361       | 309/573         | 920/1 520       |
| Pooled healing rate (%) | 19.6            | 34.6            | 42.9            | 53.9            | 60.5            |
| Summary RR      | 0.874           | 1.281           | 1.096           | 1.165           | 1.084           |
| 95% CI          | 0.557-1.371     | 1.036-1.583     | 0.930-1.293     | 1.020-1.329     | 1.019-1.152     |

ITT, intention-to-treat analysis; No, number; RR, relative risk; 95% CI.
rates than ranitidine 300 mg, daily at 4 wk (RR 1.38; 95%CI 1.31-1.83) and 8 wk (RR 2.54; 95%CI 1.86-3.46) [55,56]. The other study indicated that treatment with high dose omeprazole (40 mg/d) in patients refractory to H2RAs therapy significantly improved esophagitis healing when compared to high dose ranitidine (600 mg/d) (RR 3.69, 95%CI 2.30-5.90 at 4 wk; and RR2.03, 95%CI 1.54-2.67 at 8 wk) [57].

Healing by initial grade of esophagitis
Twenty-five studies [19,20,23,24,30,32,35,38,43-47,49,52,53,55-58,60,61,69-71] with 54 treatment arms provided raw data on healing by the initial grade of esophagitis (Tables 5-7). Because data by intention-to-treat analysis were not available from the majority of trials, the healing rate by per-protocol analysis was therefore used.

When the healing rate was adjusted according to the initial severity of esophagitis, no significant differences in the healing rates was observed when patients with the severe

Table 2 Healing rate of esophagitis by ITT at 2, 3, 4, 8, 12 wk comparing proton pump inhibitors (PPIs) with H2RA

<table>
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<th>2-wk</th>
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<th>8-wk</th>
<th>12-wk</th>
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<tr>
<td>Pooled data</td>
<td>116/183</td>
<td>577/824</td>
<td>640/783</td>
<td></td>
<td>2-wk</td>
<td>13/183</td>
<td>577/824</td>
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<td>95%CI</td>
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<td>1.622-2.070</td>
<td>1.438-1.749</td>
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<tr>
<td>95% CI</td>
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<td>1.622-2.070</td>
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<td></td>
<td>2-wk</td>
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<td>Pooled healing rate (%)</td>
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<td>Pooled healing rate (%)</td>
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<td>78.5</td>
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<td>1.156-2.229</td>
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hd: high dose; sd: standard dose; ld: low dose; ITT, intention-to-treat analysis; No., number; RR, relative risk; 95% CI, 95% CIs.
form of esophagitis (≥ grade III) were treated with either high dose or standard dose H₂RAs. However, a significant difference was observed for patients with grade II esophagitis at 4 wk (Table 5). No patients with grade IV esophagitis were included in any of the studies comparing high dose with standard dose H₂RAs.

Proton pump inhibitors achieved consistently and significantly higher healing rates than H₂RAs across all grades of esophagitis, irrespective of the dose and duration of treatment (Table 6). With a wide range of CI, the superiority of proton pump inhibitors over H₂RAs was even greater when the initial grade of esophagitis was considered in studies of patients with refractory esophagitis (Table 6) despite that one study reported the same effects on grade I esophagitis at 12 wk, when omeprazole 40 mg daily was compared with ranitidine 300 mg daily.[47] The healing rates

### Table 3 Healing rate (ITT) of esophagitis at 2, 4, 8 wk comparing PPIs with omeprazole

<table>
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<td>sd PPIs vs sd Omeprazole</td>
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<td>95%CI</td>
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ld PPIs vs sd Omeprazole

|                        |            |            |            | 2          | 2          | 2          |
| Number of arms         | 2          | 2          | 2          | 2          | 2          | 2          |
| Pooled data            | 590/822    | 724/822    | 551/811    | 707/811    |
| Pooled healing rate (%)| 71.8       | 88.1       | 67.9       | 87.2       |
| Summary RR             | 1.026      | 0.981      |            |            |
| 95%CI                  | 0.904–1.164| 0.870–1.105|            |            |

sd PPIs vs hd Omeprazole

|                        |            |            |            | 2          | 1          | 2          |
| Number of arms         | 2          | 1          | 2          | 1          |
| Pooled data            | 310/440    | 284/337    | 302/434    | 282/332    |
| Pooled healing rate (%)| 70.5       | 84.3       | 69.6       | 84.9       |
| Summary RR             | 1.031      | 0.985      |            |            |
| 95%CI                  | 0.937–1.015| 0.883–1.099|            |            |

Table 4 Healing rate of refractory esophagitis at 2, 4, 6, 8, 12 wk comparing PPIs with H₂RA

<table>
<thead>
<tr>
<th>Author</th>
<th>Drug</th>
<th>Dose</th>
<th>Patient</th>
<th>Healing rate (ITT)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4 wk</td>
</tr>
<tr>
<td>sd PPIs vs sd H₂RA</td>
<td>Lan</td>
<td>30 o.d.</td>
<td>61</td>
<td>54/61</td>
</tr>
<tr>
<td>Feldman (55)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sontag (56)</td>
<td>Lan</td>
<td>30 o.d.</td>
<td>105</td>
<td>75/105</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pooled data</td>
<td>166</td>
<td>75/105</td>
<td>138/166</td>
<td>86</td>
</tr>
<tr>
<td>Pooled healing rate (%)</td>
<td>71.4</td>
<td>83.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Summary RR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>95%CI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

hd PPIs vs hd H₂RA

<table>
<thead>
<tr>
<th>Author</th>
<th>Drug</th>
<th>Dose</th>
<th>Patient</th>
<th>Healing rate (ITT)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4 wk</td>
</tr>
<tr>
<td>Lundell (57)</td>
<td>Ome</td>
<td>40 o.d.</td>
<td>51</td>
<td>32/51</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ran</td>
<td>b.d.</td>
<td></td>
<td>8/47</td>
</tr>
</tbody>
</table>

Ome: omeprazole; Lan: lansoprazole; Ran: ranitidine; o.d.: once daily in the morning; b.d.: twice daily; h.d.: high dose; sd: standard dose. †This study did not report cumulative healing rate at 8 wk. All patients' endpoint was at 8 wk. The decreased healing rate at 8 wk for ranitidine group may be due to subsequent relapse of esophagitis.

<table>
<thead>
<tr>
<th>Author</th>
<th>Drug</th>
<th>Dose</th>
<th>Patient</th>
<th>Healing rate (ITT)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4 wk</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 5 Healing by grade with standard dose vs high dose of H₂RA at 4, 6, 8, 12 wk (PP rate)

<table>
<thead>
<tr>
<th>Grade</th>
<th>4-wk</th>
<th>6-wk</th>
<th>8-wk</th>
<th>12-wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>III</td>
<td>I</td>
<td>II</td>
<td>III</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Pooled rate (%)</td>
<td>44.2</td>
<td>21.0</td>
<td>62.8</td>
</tr>
<tr>
<td>High dose</td>
<td>Pooled data</td>
<td>177/325</td>
<td>60/198</td>
<td>112/157</td>
</tr>
<tr>
<td></td>
<td>Pooled rate (%)</td>
<td>54.4</td>
<td>30.3</td>
<td>71.3</td>
</tr>
<tr>
<td>Summary RR</td>
<td>95% CI</td>
<td>1.231</td>
<td>1.430</td>
<td>1.136</td>
</tr>
</tbody>
</table>

PP, per-protocol analysis; No., number; RR, relative risk; 95% CI, 95% CIs.
were similar between omeprazole and the newer proton pump inhibitors across all grades of esophagitis (Table 7).

Testing for between-study heterogeneity and sensitivity analyses

In the comparison of the healing rates achieved within omeprazole and the newer proton pump inhibitors, a significant heterogeneity was found at 4 and 8 wk ($P<0.001$). However, no further heterogeneity ($P = 0.43$ at 4 wk, and $P = 0.92$ at 8 wk) was found after exclusion of the studies from Kahrilas et al\cite{67}, and Richter et al\cite{68}, suggesting that the heterogeneity was caused by these two studies. Further scrutiny of these two studies revealed that *Helicobacter pylori* ($H. pylori$) positive patients were excluded in both studies, whereas other studies did not use *H. pylori* status as an exclusion criterion. No additional confounding factors such as the study design, level of blinding and compliance of patients were identified. Sensitivity analysis showed no difference in the healing rates of erosive esophagitis between omeprazole and the newer proton pump inhibitors (RR 1.00, 95% CI 0.96-1.04 at 4 wk; and RR 0.99, 95% CI 0.97-1.02) when the data from the two studies were excluded. There was no evidence of heterogeneity in any other comparisons.

**Table 6** Healing by grade at 4, 8, 12 wk comparing PPIs with $H_2$RAs (PP rate)

<table>
<thead>
<tr>
<th></th>
<th>4 wk</th>
<th>8 wk</th>
<th>12 wk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I</td>
<td>II</td>
<td>III</td>
</tr>
<tr>
<td>Number of arms</td>
<td>2</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>sd PPIs Pooled data</td>
<td>53/60</td>
<td>128/162</td>
<td>20/54</td>
</tr>
<tr>
<td>Pooled rate (%)</td>
<td>88.3</td>
<td>79.0</td>
<td>37.0</td>
</tr>
<tr>
<td>sd $H_2$RAs Pooled data</td>
<td>27/54</td>
<td>65/172</td>
<td>2/41</td>
</tr>
<tr>
<td>Pooled rate (%)</td>
<td>50.0</td>
<td>37.8</td>
<td>4.9</td>
</tr>
<tr>
<td>Summary RR</td>
<td>1.760</td>
<td>2.037</td>
<td>5.508</td>
</tr>
<tr>
<td>95%CI</td>
<td>1.158-2.228</td>
<td>0.835-25.337</td>
<td>1.575-2.845</td>
</tr>
</tbody>
</table>

**Table 7** Healing by grade at 4, 8 wk comparing standard dose of other PPIs vs omeprazole

<table>
<thead>
<tr>
<th></th>
<th>4-wk</th>
<th>8-wk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I</td>
<td>II</td>
</tr>
<tr>
<td>Number of arms</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>sd PPIs Pooled data</td>
<td>195/239</td>
<td>302/362</td>
</tr>
<tr>
<td>Pooled rate (%)</td>
<td>81.6</td>
<td>83.4</td>
</tr>
<tr>
<td>sd omeprazole Pooled data</td>
<td>190/238</td>
<td>315/393</td>
</tr>
<tr>
<td>Pooled rate (%)</td>
<td>79.8</td>
<td>80.2</td>
</tr>
<tr>
<td>Summary RR</td>
<td>1.022</td>
<td>1.041</td>
</tr>
<tr>
<td>95%CI</td>
<td>0.936-1.116</td>
<td>0.973-1.113</td>
</tr>
</tbody>
</table>

sd: standard dose; ld: low dose.

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**Table 6** Healing by grade at 4, 8, 12 wk comparing PPIs with $H_2$RAs (PP rate)

<table>
<thead>
<tr>
<th></th>
<th>4 wk</th>
<th>8 wk</th>
<th>12 wk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I</td>
<td>II</td>
<td>III</td>
</tr>
<tr>
<td>Number of arms</td>
<td>2</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>sd PPIs Pooled data</td>
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</table>

**Table 7** Healing by grade at 4, 8 wk comparing standard dose of other PPIs vs omeprazole

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<tr>
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<th>4-wk</th>
<th>8-wk</th>
</tr>
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<tbody>
<tr>
<td></td>
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<td>II</td>
</tr>
<tr>
<td>Number of arms</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>sd PPIs Pooled data</td>
<td>195/239</td>
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</tr>
<tr>
<td>Pooled rate (%)</td>
<td>81.6</td>
<td>83.4</td>
</tr>
<tr>
<td>sd omeprazole Pooled data</td>
<td>190/238</td>
<td>315/393</td>
</tr>
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<td>Pooled rate (%)</td>
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<td>Summary RR</td>
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<tr>
<td>95%CI</td>
<td>0.936-1.116</td>
<td>0.973-1.113</td>
</tr>
</tbody>
</table>
funnel plots did not demonstrate strong patterns. Therefore, figures are not shown.

**DISCUSSION**

There have been a few systematic reviews and meta-analyses summarizing the effect of medical treatments for reflux esophagitis[14-17]. However, most of them suffered from methodological flaws. The current study was the first attempt to systematically evaluate the effects of antisecretory agents in healing esophagitis based on head-to-head comparative trials. We believe that analysis of comparative trials provides more robust results than that obtained from simple pooling of results from non-comparative trials because no stratification was used in the latter form of analysis. We found that high dose H2RAs was superior to standard dose H2RAs in healing erosive esophagitis at wk 4, 8, and 12, and proton pump inhibitors achieved significantly higher healing rates of esophagitis than did H2RAs, irrespective of dose and treatment duration. However, no statistically significant difference in healing rates was observed between standard dose omeprazole and the newer proton pump inhibitors after 4 and 8 wk of treatment.

The difference in the rate of healing esophagitis between proton pump inhibitors and H2RAs can also be expressed as a healing-time curve for the ease of comparison[14]. Using this method, we have shown that proton pump inhibitors healed esophagitis at a rate approximately twice that of H2RAs at all time points and the healing rate achieved at 2 wk with proton pump inhibitors was greater than that obtained with H2RAs at 8 wk. This is consistent with the findings from previous meta-analyses using a different study design[14-17].

H2RAs are less effective for healing esophagitis because they cannot effectively inhibit meal-stimulated acid secretion[9,10]. Moreover, tolerance may occur to H2RAs, resulting in a significant decrease in their anti-secretory effect[9,10]. Therefore, patients with reflux esophagitis often require high dose H2RAs to maintain an intragastric pH above the critical threshold of 4.0 to achieve satisfactory symptom relief and remission of esophagitis[7,9]. Proton pump inhibitors have been proved to be effective in suppressing gastric acid secretion throughout the 24-h period, including meal-stimulated acid production[9,10]. So far, tolerance to proton pump inhibitors has not been reported in the literature even after long-term treatment.

The severity of esophagitis is a good predictor of a successful treatment[97]. In this analysis, we have shown that high dose H2RAs achieved a significantly better healing rate of esophagitis than standard dose H2RAs. However, this difference disappeared when the results were adjusted by the initial grade of esophagitis except for the comparison at 4 wk when high dose H2RAs healed 10% more esophagitis (Table 5). A possible explanation for the rapid loss of superiority of anti-secretory effect of high dose H2RAs over standard dose H2RAs after 4 wk could be due to the subsequent development of tolerance to the continuous use of H2RAs[93,94].

Our study has confirmed that proton pump inhibitors were significantly more effective than H2RAs in healing erosive esophagitis across all grades. In patients with mild forms of esophagitis (grades I and II), the healing rate achieved with proton pump inhibitors was significantly higher than that with H2RAs (100.0% vs 64.0% for grade I, and 93.3% vs 55.5% for grade II) at 8 wk (Table 6). This suggested that, even in patients with the mild form of esophagitis, H2RAs is a less effective treatment compared to proton pump inhibitors. The difference was even greater in patients with grade III/IV esophagitis. The healing rate achieved with proton pump inhibitors at 8 wk was 59.6%, but only 17.6% with H2RAs (Table 6). In patients refractory to H2RAs, proton pump inhibitors healed 50.0% and 62.1% of grade IV esophagitis after 4 and 8 wk of treatment, respectively (Table 4). Thus, proton pump inhibitors are significantly more effective than H2RAs for treating all grades of esophagitis, including patients refractory to H2RAs.

It is known that individual proton pump inhibitors differ with respect to the onset of action and duration of effect because of the variability in their bioavailability. Although omeprazole has a relative lower bioavailability than other proton pump inhibitors[98-100], which may contribute to the late onset of symptom relief, this has not been translated into a disadvantage in healing rate of esophagitis of all grades when compared with the newer proton pump inhibitors according to the results of this analysis.

A statistically significant heterogeneity was found in the overall analysis comparing the efficacy of healing esophagitis among different proton pump inhibitors. Two studies identified to have contributed to the heterogeneity, compared esomeprazole to omeprazole and excluded patients with H pylori infection in their analyses[97,98]. Although a higher healing rate of reflux esophagitis has been observed in patients with H pylori infection compared to uninfected patients when treated with proton pump inhibitors[98,100], there is no evidence that esomeprazole would work better on H pylori negative patients. Therefore, there might in fact be real difference in efficacy between esomeprazole and omeprazole, because esomeprazole is the enantiomer of omeprazole and the active compound is the achiral cyclic sulfenamide. Comparing 40 mg of esomeprazole with 20 mg of omeprazole would be more or less the same, as comparing double dose of omeprazole[103]. More data are needed to further confirm the presumption.

There are several limitations in this meta-analysis. Firstly, the quality of a meta-analysis, in general, is dependent on the quality of original studies, particularly the study design and reporting. To correct reporting bias from original studies is difficult and requires collaboration of investigators involved. Because of the practical difficulties, such as lapse in time between the time of publication and the time of this analysis, we did not contact investigators for raw data or clarification of unclear presentation. Secondly, three different esophagitis grading systems were used in the individual studies, which might have confounded the results of analyses. Huang et al., previously reported that there is a systematic difference in healing rates between studies using Hetzel-Dent scoring system and those using Savary-Miller system[104]. Therefore, we considered that the impact of different esophagitis scoring systems on the analysis of esophagitis healing rates deserves a systematic evaluation in its own right. This warrants an immediate consensus of using a
standard esophagitis scoring system among investigators so that a truly meaningful comparison of the efficacy of different drugs can be made. Thirdly, the stratified analysis by the initial grade of esophagitis may also be biased because per-protocol data were used in the analysis. Fourthly, we excluded meeting abstracts and non-English publications for technical reasons such as inadequate reporting of outcomes in meeting abstracts and no resources for translation of non-English articles. This might have introduced selection bias. To estimate the magnitude of possible impact, we searched the literature and identified six articles published in non-English literature, but with an English abstract. Four studies compared a standard dose proton pump inhibitor with an H$_2$RA, one between two H$_2$RAs and one between two different doses of cimetidine. The conclusions of these trials are consistent with those of this meta-analysis. Therefore, we believe that the inclusion of non-English studies would not change the conclusions of this analysis. Fifthly, relief of reflux symptoms is another important aspect in the management of patients with GERD. However, the large variability in measuring and reporting symptom data in the literature prohibited us from conducting a reliable meta-analysis of the effects of antisecretory agents on relieving reflux symptoms. This requires an urgent attention to establishing a standard instrument for the assessment of symptom response in patients with GERD.

In conclusion, this meta-analysis of comparative trials clearly identifies that H$_2$RAs are not effective treatment for patients with esophagitis of all grades irrespective of dose. Proton pump inhibitors are significantly more effective than H$_2$RAs for healing esophagitis of all grades including those refractory to H$_2$RAs. No significant differences in healing esophagitis exist among standard dose of different proton pump inhibitors. Therefore, proton pump inhibitors should be used for patients with esophagitis of all grades.

ACKNOWLEDGMENT

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