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Original Article

Comparative effectiveness of different recommended doses of omeprazole and lansoprazole for gastroesophageal reflux disease: a meta-analysis of published data

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Abstract: This meta-analysis aims to evaluate the effectiveness of different recommended doses of omeprazole and lansoprazole on gastroesophageal reflux diseases (GERD) in adults. The electronic databases of PubMed, EMBASE, Cochrane Library, and ClinicalTrials.gov were searched before September 13 2016. Fifteen eligible studies were identified involving 8752 patients in our meta-analysis. For the healing outcome of esophagitis, compared with 15 mg per day of lansoprazole, there were significant difference of both 30 mg per day of lansoprazole (RR=1.29, 95% CI [1.01, 1.66], I^2=79.3%, P=0.028) and 60 mg per day of lansoprazole (RR=1.59, 95% CI [1.28, 1.99], I^2=Not applicable (NA), P=NA), and the other result were not significantly different between 60 mg per day and 30 mg per day. For relief of symptoms, our result indicated a significant difference between 20 mg per day and 10 mg per day of omeprazole (RR=1.21, 95% CI [1.06, 1.39], I^2=53.9%, P=0.089); the overall result indicated a significant difference between lansoprazole and omeprazole (RR=0.93, 95% CI [0.86, 0.999], I^2=60.7%, P=0.038). This suggests that lansoprazole had superior quality effectiveness and that dose was a critical factor for effectiveness. No publication bias was observed. On the basis of these results, we recommend the use of lansoprazole with higher doses for the treatment of GERD in adults.

Keywords: GERD, lansoprazole, omeprazole, effectiveness, meta-analysis

Introduction

Gastroesophageal reflux disease [1] (GERD) is one of the most common chronic diseases for general adults. GERD impairs normal esophageal clearance and damages the ability of the mucous membrane to protect the esophagus. This disease affects approximately 20%-30% of the population worldwide, particularly in Western countries [2].

Currently, the main treatments of GERD including medication, surgery, and lifestyle intervention [3]. The most important and widely used therapeutic regimen is medication, such as proton pump inhibitors (PPIs), due to effectiveness and safety [4]. Omeprazole and lansoprazole are two of the most common medications of PPIs, but their efficacies may differs. Only a few head-to-head meta-analyses and systematic reviews have evaluated the efficacy of these drugs with different recommended doses for GERD in adults, leading to the lack of reliable evidence [5].

In this study, we elucidated the properties of both omeprazole and lansoprazole for the treatment of GERD in adults by focusing on the clinical effects of these drugs using meta-analysis methods to combine all evidence-based medical studies [6].

Materials and methods

Search strategy

We performed a series of electronic search on PubMed, EMBASE, the Cochrane Library and ClinicalTrials.gov up to September 13 2016 for eligible randomized clinical trials investigating

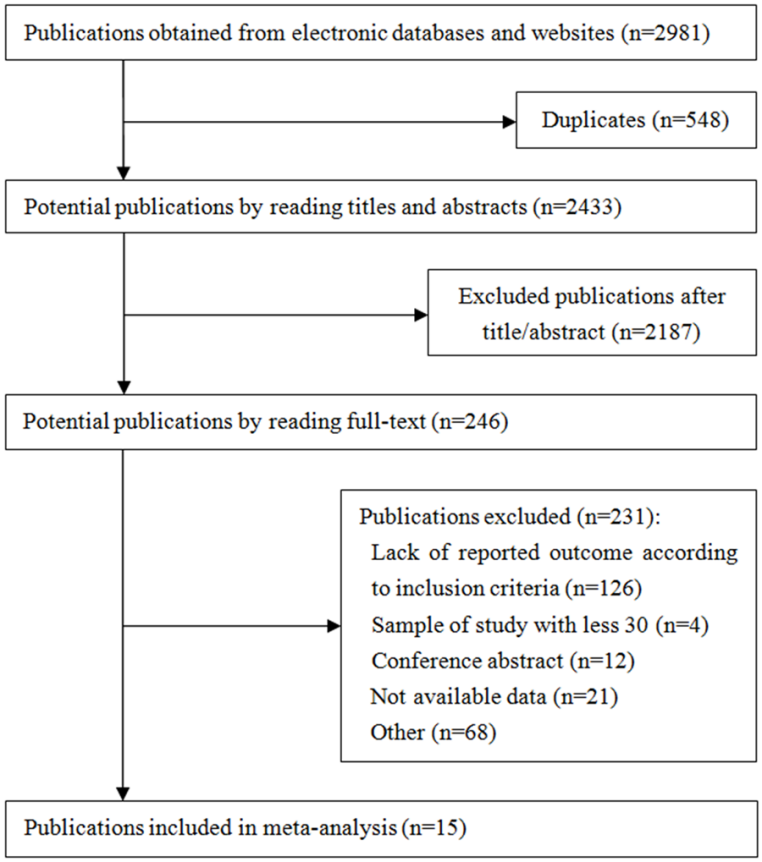

Figure 1. Summary of trial identification and selection.

esomeprazole and omeprazole for the treatment of GERD using Medical Subject Headings (MeSH) and text words: "gastroesophageal reflux", "GERD", "esophagitis", "reflux", "proton pump inhibitors", "omeprazole", "lansoprazole".

Literature selection and exclusion

All studies were selected in accordance with following inclusion criteria: (1) Studies in our meta analysis must be randomized or parallel-group design clinical trials; (2) Interested population should be GERD patients older than 18 years; (3) Studies compared the effectiveness of lansoprazole and omeprazole, or compared the effectiveness between them, whether what its doses and usages were; (4) Eligible studies should include at least one of the following outcomes: ① The healing rate, as the main outcome, was defined that the esophageal mucosal erosions had repaired complete using endoscopic examination by of physicians; ② The relieving symptoms, as the second outcome, was defined as the GERD symptoms of heartburn, regurgitation, or other related symptoms were well controlled or relieved.

Studies were excluded if: (1) GERD symptoms were caused by chronic cough, asthma and simple laryngitis; (2) Explicitly contained the laryngopharyngeal reflux disease; (3) Duplicate publications; (4) Data were insufficient or cannot be obtained by contacting the correspondent author; (5) Arm sample size less than 30.

Data extraction and quality assessment

Relevant information included study design, patients' characteristics, interventions, comparisons, outcomes (healing rate and relieving symptoms) were independently extracted and entered it into a database by two investigators. When relevant research information is missing, particularly design or outcomes, we contacted the original authors for clarifications. Then, Intention-to-treat (ITT) datasets were used for all outcomes whenever available.

Two investigators independently evaluated the methodological quality of eligible trials by using the Cochrane Collaboration's tool [6] for assessing risk of bias (random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias).

Disagreements between the two authors on data extraction and quality assessment were resolved by discussion. If the dispute persisted, other senior investigators were consulted to attain consensus.

Statistical analysis

For all outcomes based on dichotomous data [6, 7], we used relative risk (RR), 95% confidence interval (CI) using STATA software. We performed a statistical test for heterogeneity

Table 1. Characteristics information of the included studies

Study	Year	County	Age Mean ± SD (range) (I/C)	Total (female) (I/C)	Drugs, dose, usage (I/C)	Level of disease from endoscopy or symptoms	Mean courses of disease	Follow-up from start of treatment (weeks)	ITT/PP	Outcomes
Zheng [11]	2009	China	57.9±14.1; 58.1±13.0	68 (35); 69 (34)	Omeprazole 20 mg QD; Lansoprazole 30 mg QD	LA: A-D	NA	8	PP	Healing
Peura [12]	2009	USA	48.2±14.5; 48.8±14.1	291 (173); 284 (183)	Lansoprazole 15 mg QD; Lansoprazole 30 mg QD	Heartburn: Mild; Moderate; Severe	NA	2	ITT	Relief of symptoms
Uemura [13]	2008	Japan	44.4±16.2; 43.8±16.4	96 (49); 93 (40)	Omeprazole 10 mg QD; Omeprazole 20 mg QD	Heartburn: Mild; Moderate; Severe	NA	4	ITT	Relief of symptoms
Pilotto [14]	2007	Italy	77.9±6.4; 77.8±9.2	80 (36); 80 (44)	Omeprazole 20 mg QD; Lansoprazole 30 mg QD	SM: 1-4	NA	8	ITT	Healing, Relief of symptoms
Mulder [15]	2002	Netherland	51.6±15.0; 50.8±14.5	151 (63); 156 (66)	Omeprazole 20 mg QD; Lansoprazole 30 mg QD	Modified SM: 1-4	NA	8	ITT	Relief of symptoms
Richter [16]	2001	USA	46.9±13.6; 47.8±13.8	1756 (772); 1754 (747)	Omeprazole 20 mg QD; Lansoprazole 30 mg QD	SM: 1-4	NA	8	ITT	Relief of symptoms
Richter [17]	2000	USA	50.0; 49.5	118 (53); 118 (57)	Omeprazole 10 mg QD; Omeprazole 20 mg QD	NA	≥ 12 months	4	ITT	Relief of symptoms
Fass [18]	2000	USA	57.8±14.7; 57.8±12.1	46 (2); 44 (4)	Omeprazole 40 mg QD; Lansoprazole 30 mg BID	NA	≥ 3 months	6	ITT	Relief of symptoms
Jones [19]	1999	UK	46; 47	279 (143); 283 (143)	Omeprazole 10 mg QD; Lansoprazole 15 mg QD	NA	NA	4	ITT	Relief of symptoms
Earnest [20]	1998	USA	NA	NA	Lansoprazole 15 mg QD; Lansoprazole 30 mg QD; Lansoprazole 60 mg QD	NA	NA	8	ITT	Healing
Venables [21]	1997	UK	51±15; 51±14	338 (51); 320 (48)	Omeprazole 10 mg QD; Omeprazole 20 mg QD	Modified SM: 0-1	NA	4	ITT	Relief of symptoms
Galmiche [22]	1997	Europe	51±15; 50±16	144 (89); 141 (78)	Omeprazole 10 mg QD; Omeprazole 20 mg QD	Heartburn: Mild; Moderate; Severe	≥ 3 months	8	ITT	Relief of symptoms
Mee [6]	1996	UK, Ireland	18-80	NA	Lansoprazole 30 mg QD; Omeprazole 20 mg QD	SM: 1-4	NA	8	ITT	Healing
Castell [23]	1996	UK	47.5 (19-78); 45.8 (20-82); 48.6 (18-84)	431 (171); 218 (73); 421 (133)	Omeprazole 20 mg QD; Lansoprazole 15 mg QD; Lansoprazole 30 mg QD	HD: 2-4	NA	8	ITT	Healing
Bardhan [24]	1995	UK	48 (19-78); 47.9 (18-74)	77 (27); 75 (25)	Lansoprazole 30 mg QD; Lansoprazole 60 mg QD	Reflux grades: 1-3	NA	8	ITT	Healing, Relief of symptoms

I: Intervening group, C: Control group, QD: Quaque die, BID: Bis in die, LA: The Los Angeles grade, SM: The Savary-Miller criteria, HD: The Hetzel-Dent scale, ITT: Intention-to-treat data, PP: Per-protocol data, NA: Not obtainable.

Table 2. Risk of bias in included studies

Study	Year	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Zheng [11]	2009	Low	Low	Low	Unclear	Low	Low	Low
Peura [12]	2009	Low	Unclear	Low	Unclear	Low	Low	Unclear
Uemura [13]	2008	Low	Unclear	Low	Unclear	Low	Low	High
Pilotto [14]	2007	Unclear	Unclear	High	High	Low	Low	High
Mulder [15]	2002	Low	Unclear	Low	Unclear	Low	Low	High
Richter [16]	2001	Low	Low	Low	Low	Low	Low	Low
Richter [17]	2000	Unclear	Unclear	Low	Unclear	Low	Low	High
Fass [18]	2000	Unclear	Unclear	High	High	Low	Low	High
Jones [19]	1999	Low	Low	Low	Unclear	Low	Low	High
Earnest [20]	1998	Unclear	Unclear	Low	Unclear	Low	Low	Unclear
Venables [21]	1997	Unclear	Unclear	Low	Unclear	Low	Low	Unclear
Galmiche [22]	1997	Unclear	Unclear	Low	Unclear	Low	Low	High
Mee [6]	1996	Unclear	Unclear	Low	Unclear	Low	Low	Unclear
Castell [23]	1996	Unclear	Unclear	Low	Unclear	Low	Low	Low
Bardhan [24]	1995	Unclear	Unclear	Low	Unclear	Low	Low	Unclear

and adopted I^2 of greater than 50 and $P \leq 0.1$ as evidence for heterogeneity according to the Cochrane handbook [6, 8]. We would see the doses [4] as the fundamental sources of the heterogeneity, and deal with heterogeneity by subgroups according to the different doses. If the data were still heterogeneous, we performed a random effects model [6]. Observing asymmetry of funnel plot was determined whether there have publication bias as qualitative method [9]. In a funnel plot, larger studies that provide a more precise estimate of an intervention's effect form the spout of the funnel, whereas smaller studies with less precision form the cone end of the funnel. Asymmetry in the funnel plot indicates potential publication bias. Additionally, Egger's test was employed for quantitative detection bias [10].

Results

Study selection and data collection

We first obtained 887 records in the electronic databases (**Figure 1**). Using selection criteria, we identified quantitative data for our meta-analysis after reading all titles, abstracts, and full texts. Fifteen eligible studies [6, 11-24] were enrolled in our analysis.

Study characteristics

The included 15 studies involved 8752 patients. The rate of healing of esophagitis assessed via endoscopy was determined for 1991 of 2411 patients from 6 studies. The relief of symptoms via subjective evaluation was evaluated in 4892 of 6734 patients from 11 studies. **Tables 1** and **2** described the clinical and methodological characteristics of these studies.

Rate of healing of esophagitis via endoscopic examination

The comparison of the rate of healing of esophagitis for lansoprazole at different doses via endoscopic examination shown in **Figure 2** indicated a significant difference between 30 mg per day and 15 mg per day of lansoprazole (RR=1.29, 95% CI [1.01, 1.66], I^2=79.3%, P=0.028) and between 60 mg per day and 15 mg per day (RR=1.59, 95% CI [1.28, 1.99], I^2= Not applicable (NA), P=NA) by subgroups, according to the different doses, under the random effects model, whereas the other result indicated no significant difference between 60 mg per day and 30 mg per day (RR=1.08, 95% CI [0.95, 1.22], I^2=50.1%, P=0.157) of lansoprazole. However, these results tended to indicate the effectiveness of higher doses.

The comparison of the rate of healing of esophagitis for lansoprazole and omeprazole at different doses via endoscopic examination shown in **Figure 3** indicated the absence of a significant difference between omeprazole at

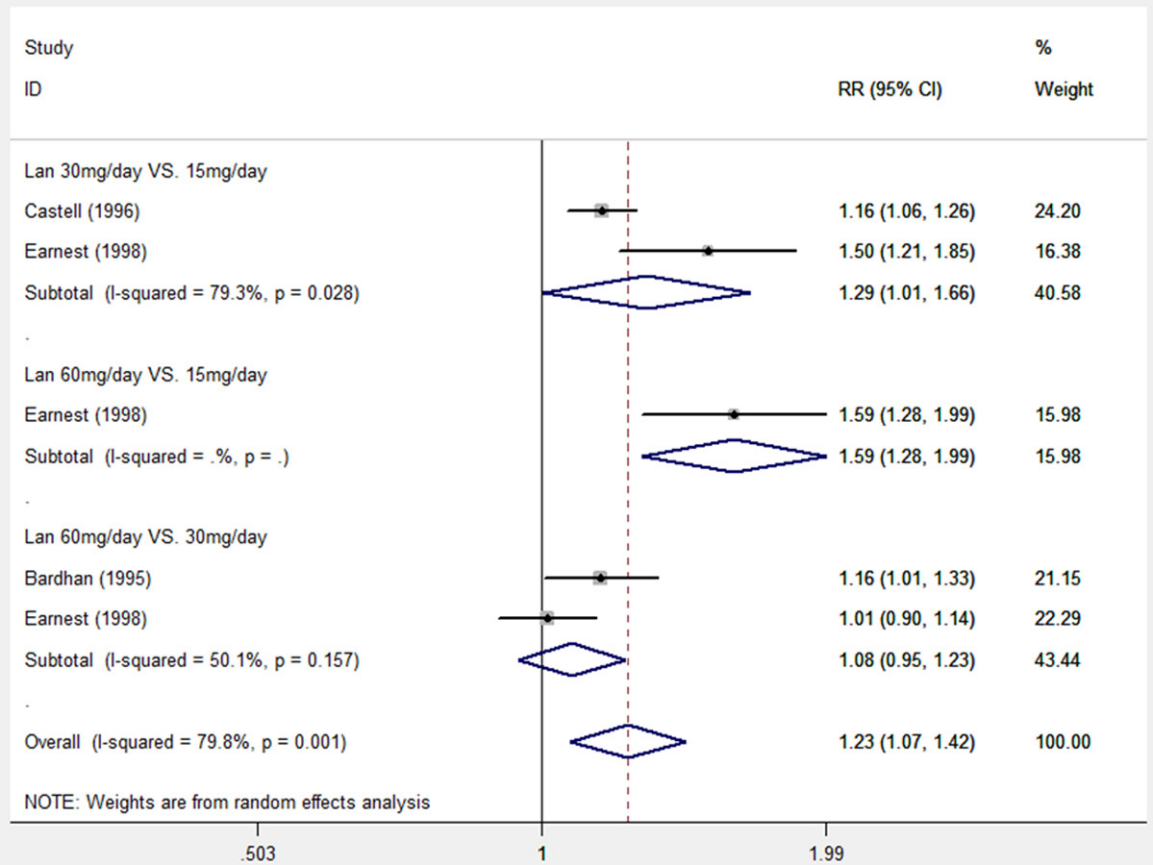

Figure 2. Forest plot of healing rate using endoscopic examination from lansoprazole with different doses.

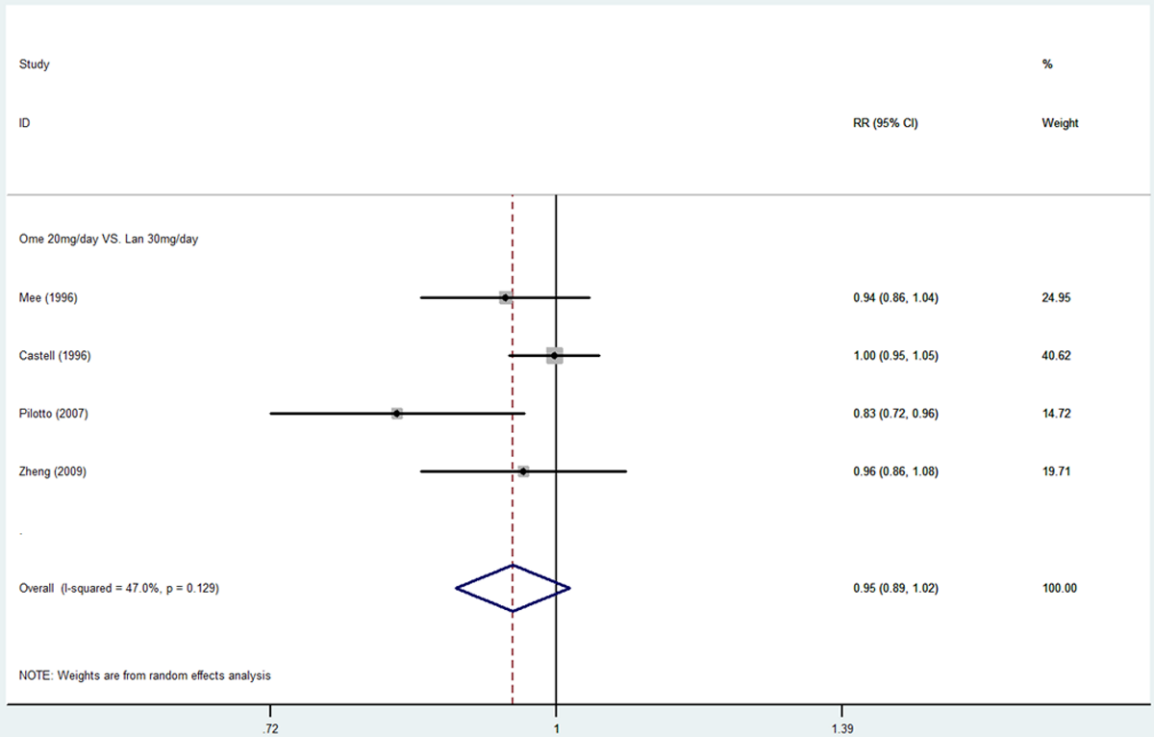

Figure 3. Forest plot of healing rate using endoscopic examination from lansoprazole and omeprazole with different doses.

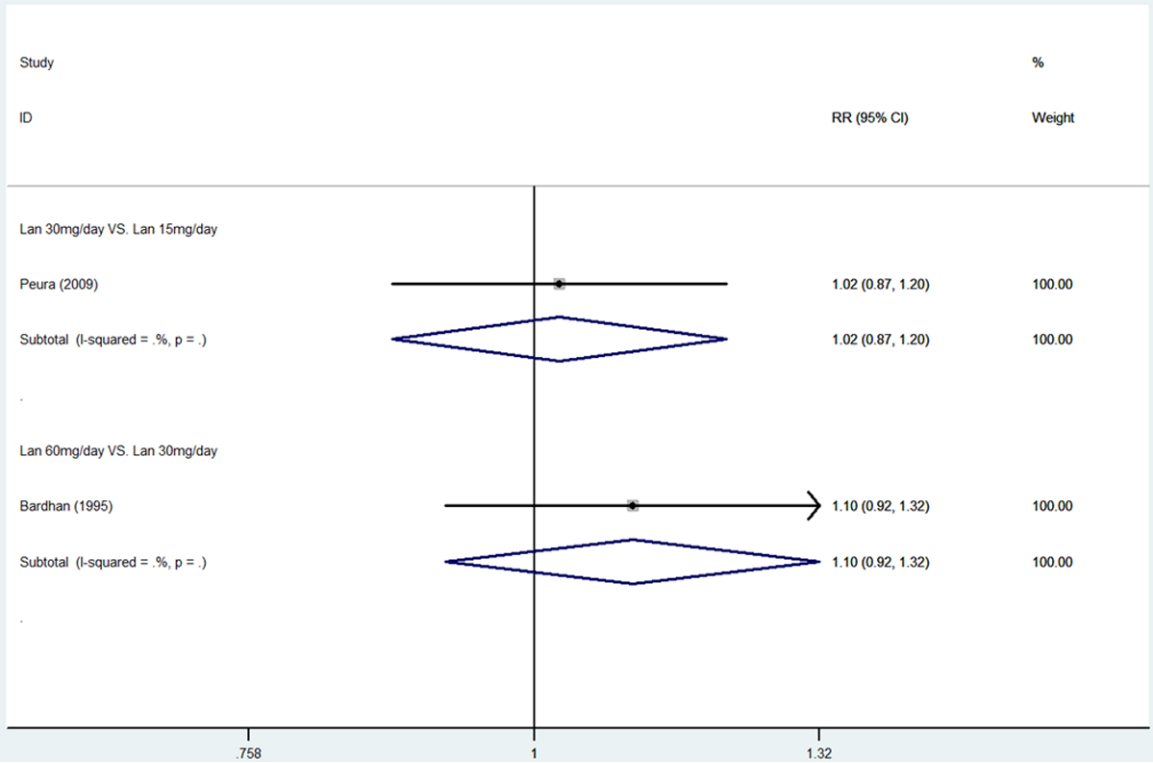

Figure 4. Forest plot of relieving symptoms using patient's subjective evaluation from lansoprazole with different doses.

20 mg per day and lansoprazole at 30 mg per day (RR=0.95, 95% CI [0.89, 1.02], I^2=47.0%, P=0.129) under the random effects model. This result tended to indicate the effectiveness of lansoprazole.

Relieving symptoms from patient's subjective evaluation

The comparison of the patient's subjective evaluation of the relief of symptoms for lansoprazole shown in **Figure 4** indicated the absence of a significant difference between 30 mg per day and 15 mg per day (RR=1.02, 95% CI [0.87, 1.20], I^2=NA, P=NA) and between 60 mg per day and 30 mg per day (RR=1.10, 95% CI [0.92, 1.32], I^2=NA, P=NA) of lansoprazole considering the results from all subgroups according to the different doses under the fixed effects model. These results tended to indicate the effectiveness of higher doses.

By contrast, the comparison of the patient's subjective evaluation of the relief of symptoms for omeprazole at different doses shown in **Figure 5** indicated a significant difference between 20 mg per day and 10 mg per day of omeprazole (RR=1.21, 95% CI [1.06, 1.39], I^2=54%, P=0.005) under the random effects model.

The comparison of the patient's subjective evaluation of the relief of symptoms for lansoprazole and omeprazole at different doses shown in **Figure 6** indicated a significant difference between lansoprazole and omeprazole (RR=0.93, 95% CI [0.86, 1.00], I^2=60.7%, P=0.038) under the random effects model. The analysis by subgroups according to the different doses under the random effects model indicated the absence of a significant difference between omeprazole at 10 mg per day and lansoprazole at 15 mg per day (RR=0.86, 95% CI [0.74, 1.00], I^2=NA, P=NA), between omeprazole at 20 mg per day and lansoprazole at 30 mg per day (RR=0.94, 95% CI [0.87, 1.02], I^2=73.1%, P=0.024), and between omeprazole

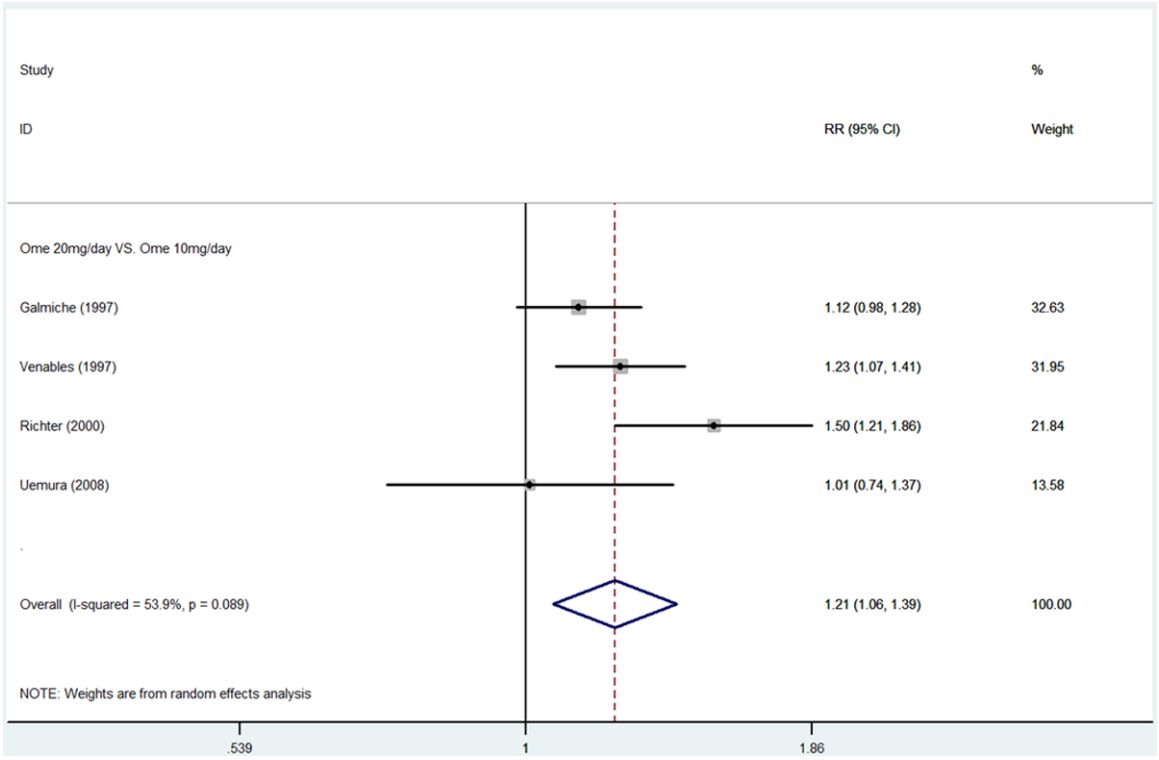

Figure 5. Forest plot of relieving symptoms using patient's subjective evaluation from omeprazole with different doses.

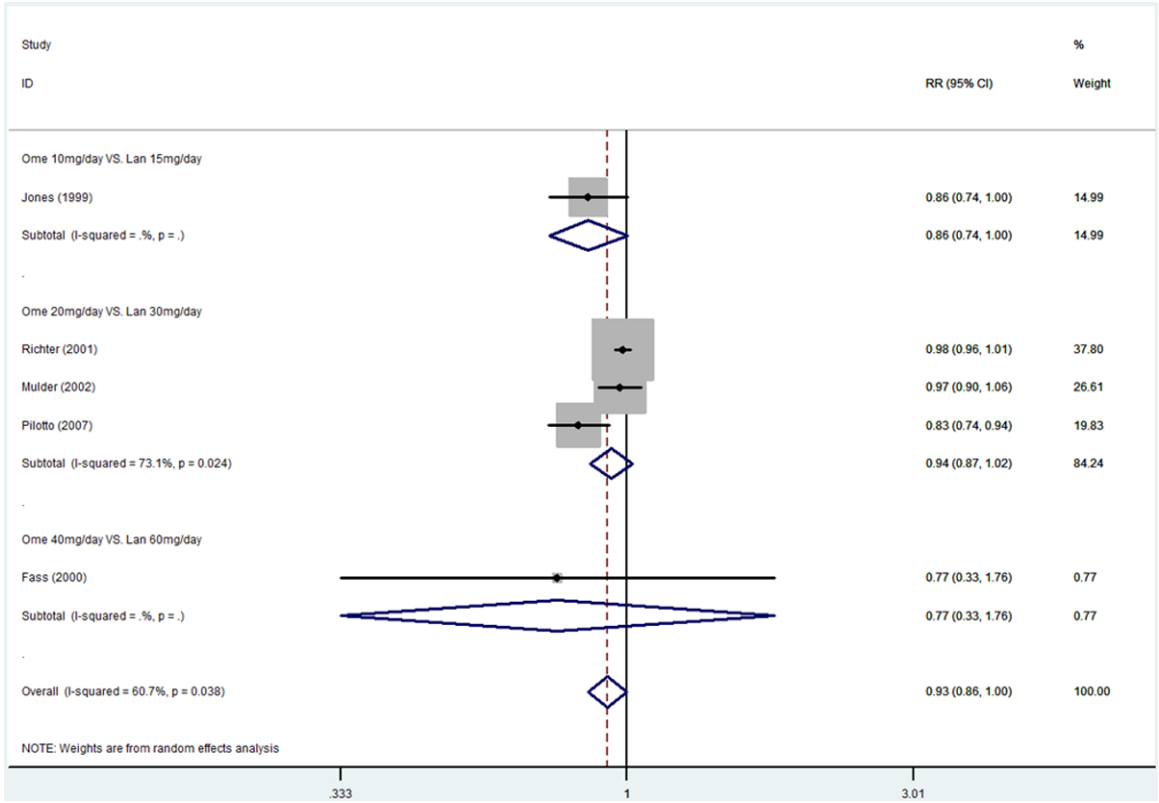

Figure 6. Forest plot of relieving symptoms using patient's subjective evaluation from lansoprazole and omeprazole with different doses.

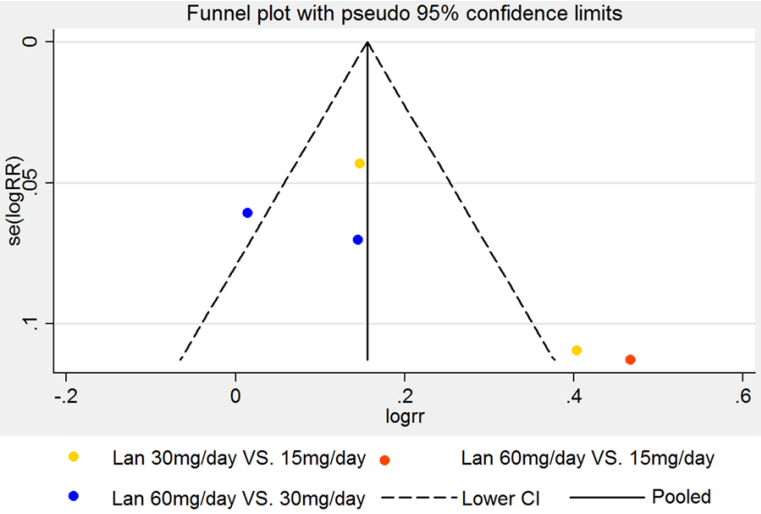

Figure 7. Funnel plot of healing rate using endoscopic examination from lansoprazole with different doses.

at 40 mg per day and lansoprazole at 60 mg per day (RR=0.77, 95% CI [0.33, 1.76], I^2=NA, P=NA). These results tended to indicate the effectiveness of lansoprazole.

Publication bias

No publication bias was observed on the basis of the symmetry of funnel plots for all outcomes, as observed in **Figure 7** for the rate of healing of esophagitis for lansoprazole at different doses via endoscopic examination, but there was a paucity of large sample trials in the top of the funnel plot. The result of Egger's test showed there was not a significant difference between omeprazole at 20 mg per day and lansoprazole at 30 mg per day for healing rate outcome (Bias=-2.60 [-7.03, 1.74], P=0.122), and between omeprazole at 20 mg per day and omeprazole at 10 mg per day for healing rate outcome (Bias=3.02 [-12.67, 13.34], P=0.922).

Discussion

This meta-analysis evaluated 15 eligible studies that included GERD patients older than 18 years, and all of these studies were randomized controlled clinical trials. These two interventions, which involved the use of either lansoprazole or omeprazole with different doses, focused on the effectiveness outcomes, and these methodological characteristics included were relevant.

For the healing of esophagitis, we found that a higher dose was more efficient than a lower dose, and lansoprazole was more efficient than omeprazole. The results showed that the 60 mg or 30 mg per day of lansoprazole was more effective than 15 mg per day. However, there was no significant difference between 60 mg per day and 30 mg per day of lansoprazole, this result may be due to the inaccuracy derived from a single study on lansoprazole [20]. We also found that the level of disease from Earnest was failure to be extracted. The result on the difference between 60 mg per day and 30 mg per day of lansoprazole needs to be treated with caution. We found that the lansoprazole was more effective than omeprazole. In addition, factors derived from lansoprazole itself may explain the increased effectiveness of lansoprazole at 30 mg per day compared with omeprazole at 20 mg per day. This result was only observed in the comparison between omeprazole at 20 mg per day and lansoprazole at 30 mg per day.

With regard to the patient's subjective evaluation of the relief of symptoms, we found a higher dose was more efficient than a lower dose. The effectiveness of different doses was not significantly different for lansoprazole but was significantly different for omeprazole. This may be due to the small sample size. There is no doubt that the efficacy of lansoprazole is proportional to the dosage. For lansoprazole and omeprazole, the overall results, but not the subgroup results, were significantly different. Because the standard recommended doses were similar, lansoprazole was most effective than omeprazole.

As the PPIs, the curative effects of lansoprazole and omeprazole have been controversial. Previous studies [25, 26] have indicated that these two drugs have similar effectivenessfor the relief of heartburn and healing of esophagitis in patients with GERD but the former is less costly [27]. For patients with esophageal mucosal burn, although the standard recommended dosage of lansoprazole and omeprazole is similar, esophageal acid exposure in patients is normalized more easily with lansoprazole [28].

Combined with our body of evidence, the curative effect of lansoprazole was not obvious, but our results tended to indicate this effect. In addition, our results suggested the improved curative effect of lansoprazole; however, further studies with larger sample sizes are necessary to confirm this evidence.

The advantage of our study was that all the included studies were randomized controlled clinical trials with high-quality data [6]. When performing the meta-analysis, we considered the different doses that could impair the reliability of the results and could lead to greater heterogeneity [4]. Our study has several limitations. First, only a few clinical trials met the inclusion and exclusion criteria, and therefore, more clinical studies are required to confirm our results [6]. Second, some clinical trials missed data on basic characteristics [29], leading, to some extent, to the generation of heterogeneity because of the failure to perform a meta-regression for confounding factors. Third, the dose-response relationship [30] of lansoprazole and omeprazole was not determined because of that the levels of different doses were too less and that these sample sizes were insufficient [6]. Fourth, although all the included studies were RCTs, their overall quality needs improvement [31].

In summary, this study compared the effectiveness of lansoprazole and omeprazole with different recommended doses, and this result indicated that lansoprazole has higher effective and that dose is a key factor in effectiveness. On the basis of this evidence, we recommend the use of lansoprazole with high doses for the treatment of GERD in adults.

Disclosure of conflict of interest

None.

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