

# Efficacy of acid suppression therapy in gastroesophageal reflux disease-related chronic laryngitis

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## Abstract

**Background:** This research aims to assess the response to acid suppression therapy in gastroesophageal reflux disease (GERD)-related chronic laryngitis (CL).

**Methods:** Data were extracted from Web of Knowledge, Embase, and PubMed for English language article published up to March 2016. Pooled overall response rate (ORR) rates were evaluated to determine acid suppression treatment efficacy. Random effects model was used with standard approaches to sensitivity analysis, quality assessment, heterogeneity, and exploration of publication bias.

**Results:** Pooled data from 21 reports (N=2864, antireflux medicine: 2741; antireflux surgery: 123, study duration 4–108 week) were analyzed. With the random-effect model, the ORR was 66% (95% confidence interval [CI] 54%–78%). The ORRs were 80% for antireflux surgery (95% CI 67%–93%, 3 studies, 123 patients), whereas 64% for antireflux medicine (95% CI 50%–77%, 18 studies, 2741 patients), and the ORR was 70% (95% CI 55%–85%, 15 reports, 2731 patients) for >8 weeks' therapy duration, whereas 57% (95% CI 48%–65%, 6 reports, 133 patients) for ≤8 weeks' duration of therapy.

**Conclusions:** Acid suppression seems to be an effective therapy for GERD-related CL. There was an increase in effect among patients with surgery therapeutic method and longer therapy duration.

**Abbreviations:** CL = Chronic laryngitis, ES = effect size, GERD = gastroesophageal reflux disease, GPR = gastropharyngeal reflux, LPR = laryngopharyngeal reflux, ORR = overall response rate, PPI = proton pump inhibitors.

**Keywords:** antireflux surgery, chronic laryngitis, GERD, laryngopharyngeal reflux, meta-analysis, pharyngitis, proton pump inhibitor

## 1. Introduction

In the last 2 decades, gastroesophageal reflux disease (GERD)-induced reflux laryngitis has become a familiar finding in ear, nose, and throat symptoms. The proportion of chronic laryngitis (CL) in whole patients visiting to otolaryngology clinics in America was about 10%.<sup>[1]</sup> Therefore, acid suppression therapy is usually prescribed to these patients under the presupposition that GERD is related with signs and symptoms of CL.<sup>[2–4]</sup>

It has been revealed that acid suppression improves associated upper esophageal and the gastroesophageal reflux and laryngeal

symptoms, for instance, hoarseness and chronic cough.<sup>[5]</sup> Nevertheless, their efficacy in patients with suspected GERD-related CL has not been definite. GERD-related extraesophageal complications can be controlled efficiently by surgery with a significantly better response than with medicine therapy.<sup>[6]</sup>

We proceeded this meta-analysis to explore an estimate of the overall efficacy of acid suppression treatment (including medicine therapy and surgery therapy) in suspected GERD-related CL.

## 2. Methods

### 2.1. Ethical approval

This is a study of meta-analysis, so that, ethical approval was not necessary.

### 2.2. Study Search

We proceeded a systematic literature search in PubMed, Web of Knowledge, and Embase for English language article published up till March 2016 by relevant keywords and combinations such as “Proton pump inhibitor,” “antireflux therapy,” “any proton pumps/antagonists & inhibitors,” “H(+)-K(+)-Exchanging ATPase/antagonists & inhibitors,” “rabeprazole,” “histamine H2 antagonists,” “pantaprazole,” “esomeprazole,” “omeprazole,” “lansaprazole,” and “laryngitis,” “pharyngitis,” “reflux laryngitis,” “posterior laryngitis,” “reflux laryngopharyngitis,” “reflux pharyngitis,” “laryngopharyngeal reflux (LPR),” “gastropharyngeal reflux (GPR).” We performed this study according

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to the guidelines of PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses).

### 2.3. Data extraction

Suspected GERD-related CL was defined by the occurrence of  $\geq 1$  of the following symptoms: hoarseness, globus sensation, excessive phlegm, frequent throat clearing, chronic cough, and the presence of GERD-attributed signs of laryngitis on laryngoscopy-containing erythema, edema, pachydermia, granuloma, or contact ulcer. Adults aged 18 years of age or older with suspected GERD-related CL were entitled for this study.

The data were collected from every eligible article: first author's surname, publication year, country of origin, methods of diagnosis of GERD, and methods of acid suppression therapy separately. All related reports were assessed independently by 2 authors, and based on consensus. We abstracted the proportion of patients who described  $\geq 50\%$  decrease in laryngeal symptoms compared with baseline.

Exclusion criteria were the following: Case reports, review reports, studies not printed in English language; multiple reports providing outcomes from the same research; cohort reports; and animal researches.

### 2.4. Statistical analysis

The effect size (ES), which is the OOR (%) and 95% confidence interval (95% CI), was assessed for every report. The pooled evaluation of the merged percentage was gotten by the Laid and DerSimonian method in the random effect model. Moreover, we quantified the effect of heterogeneity using  $I^2 = 100\% \times (Q - df) / Q$ . A significant  $I^2$  statistic ( $I^2 > 50\%$ ) or  $Q$  statistic ( $P < 0.10$ ) showed heterogeneity across the reports, then the random effects model was used for the meta-analysis.

### 2.5. Evaluation of publication bias

We calculated the asymmetry of the funnel plot using Begg linear regression and Egger regression test, which evaluated funnel plot asymmetry by means of the natural logarithm scale of the ES. STATA 12.0 (Stata Corporation, College Station, TX) was used in this study.

## 3. Results

### 3.1. The characteristics of the eligible reports

There were 253 potential-related reports recognized with the titles, key words, and abstracts. A summary of the study results is shown in Figure 1. There were 54 potentially related full-text studies retrieved for more in-depth assessment after taking out the unrelated reports by assessment of abstract and title. Lastly, 21 separate reports were involved in this meta-analysis. All patients experienced laryngoscopic assessment to make the diagnosis of suspected GERD-related CL with symptoms, for instance, edema, granuloma, erythema, pachydermia, and/or cobblestone pattern, especially in posterior larynx. Ambulatory pH monitoring was carried out in every report, several patients also experienced esophagogastroduodenoscopy and esophageal manometry before enrollment; the primary sources of recruitment of patients in most studies were Otolaryngology clinics.

As is shown in Table 1, 21 reports were involved in the meta-analysis, and the characteristics of the involved reports are displayed. Totally, 2864 patients who suspected GERD-related

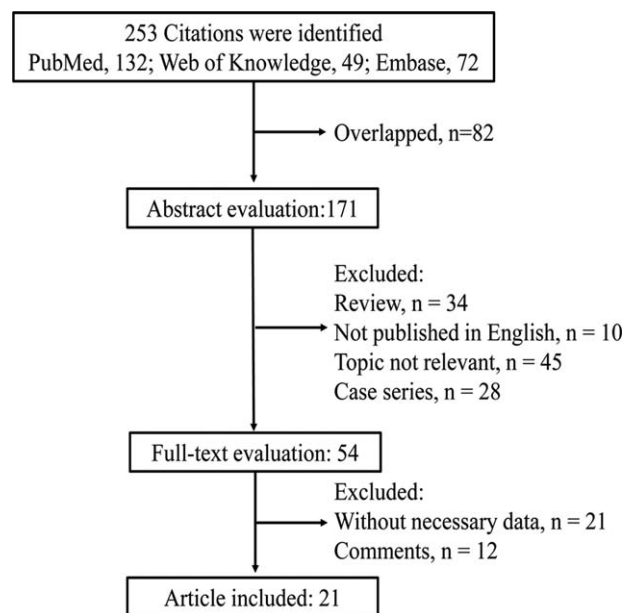


Figure 1. Flow diagram.

CL were considered in this meta-analysis.<sup>[7–27]</sup> The involved reports were published between 1997 and 2013. The sample sizes of the reports were between 8 and 2005. Three studies chose surgical treatment, and the remainder of the studies chose acid suppression medicine treatment.<sup>[9,10,12]</sup> The duration of proton pump inhibitors (PPIs) treatment ranged from 4 to 108 weeks.

### 3.2. Overall effects of acid suppression therapy on GERD-related CL

Twenty-one reports that contained a total of 2864 patients were available to assess the ORR of acid suppression therapy (including medicine therapy and surgery therapy) in suspected GERD-related CL. A random-effect model was used on account of significant heterogeneity ( $I^2 = 97.1\%$ ,  $P < 0.01$ ); ORR was 66% (95% CI 54–78%) (Fig. 3).

### 3.3. Subgroups analyses

In meta regression (Table 2), there was an obvious discordance between the pooled outcomes for reports performed before 2006 (ORR: 62% [95% CI 50%–74%]) and studies performed from 2006 onwards (ORR: 70% [95% CI 51%–89%]). There was an increase in effect among the pooled outcomes for reports of patients with surgery therapeutic method (ORR: 80% [95% CI: 67%–93%]) relative to studies of patients with medicine therapeutic method (ORR: 64% [95% CI: 50%–77%]) (Table 2). When reports were compared with regard to the duration of treatment ( $\leq 8$  week and  $> 8$  week), response to acid suppression therapy was higher in reports with longer duration of therapy (ORR: 70% [95% CI: 55%–85%] vs. ORR: 57% [95% CI: 48%–65%]) (Table 2).

### 3.4. Evaluation of publication bias

No publication bias was obvious in meta-analyses of the association between GERD-related CL and ORR of acid suppression treatment, on the basis of Egger regression test

**Table 1**

**Characteristics of studies included in this review.**

Study	Period of diagnosis	Country	Patient selection source	Inclusion criteria	Therapeutic method	Duration, wk	Outcome measured
Kirch et al (2013) <sup>[7]</sup>	2006/1–2011/1	US	Otolaryngology clinics	LSx and LPR average duration was 1.26 years	Omeprazole 20–40 mg BID	8–12	Significant improvement in self-reported symptoms
Wang et al (2012) <sup>[8]</sup>	2007/7–2009/1	China	Otorhinolaryngology Clinic	Laryngoscopy, and 24-h pH monitoring	Rabeprazole 10 mg BID	12	≥50% reduction after the start of therapy compared with baseline
Ratnasingam et al (2011) <sup>[9]</sup>	2002/1–2008/7	Australia	Otolaryngologist	LSx, GERD at gastroscopy or 24-h pH monitoring	Laparoscopic Antireflux Surgery	12, after surgery	Significant improvement or resolution of symptoms
Salmiinen et al (2010) <sup>[10]</sup>	1998/1–2002/8	Finland	Specialist in otolaryngology and questionnaire	pH-monitoring-proven reflux laryngitis caused by GERD	Laparoscopic Nissen fundoplication	164, after surgery	Excellent, good, or satisfactory at symptom resolution
Karoui et al (2010) <sup>[11]</sup>	2009	Tunisia	Specialist in otolaryngology	LSx; 24-h pH monitoring	pantoprazole 40 mg BID	8	ENT symptoms have decreased significantly
Salmiinen et al (2007) <sup>[12]</sup>	2002	Finland	Otolaryngologist; questionnaire	Reflux laryngitis caused by GERD	Laparoscopic Nissen fundoplication	112, after surgery	Significant improvement in self-reported symptoms
Qua et al (2007) <sup>[13]</sup>	2004/7–2005/1	Malaysia	Otorhinolaryngology Clinic and questionnaire	LSx; Reflux symptoms; 24-h ambulatory pH monitoring	Lansoprazole 30 mg BID	8	Significant improvement in laryngeal symptoms
Dore et al (2007) <sup>[14]</sup>	2005–2006	Italy	Otolaryngologists and questionnaire	diagnosis of GERD; atypical laryngitis symptoms	PPI therapy BID	8–12	complete symptom resolution or had improved symptoms
Monini et al (2006) <sup>[15]</sup>	2004–2005	Italy	Otorhinolaryngology clinical	LSx; LPR symptoms on gastroscopy, pH monitoring	Omeprazole 20 mg BID	12	Significant improvement in laryngeal features
Ahmed et al (2006) <sup>[16]</sup>	To 2004/5	US	ENT physicians questionnaire	reflux-related laryngeal signs and symptoms	Once daily high dose PPI	8–24	Significant improvement in self-reported symptoms
Vaezi et al (2005) <sup>[17]</sup>	2002/2–2003/3	US	Otolaryngologists questionnaire	LSx for 12 wk LPR on laryngoscopy	Esomeprazole 40 mg BID	16	≥50% reduction in the primary symptom
Wo et al (2005) <sup>[18]</sup>	2004	US	Otolaryngology clinics and Newspaper advertisement	LSx for 8 wk; LPR on Laryngoscopy; pH test	Pantoprazole 40 mg once a day	12	≥50% reduction in global symptom score
Steward et al (2004) <sup>[19]</sup>	2004	US	Otolaryngologists questionnaire	LSx for >4 wk LPR on laryngoscopy	Rabeprazole 20 mg BID	8	≥50% reduction in global symptom score
Eherer et al (2003) <sup>[20]</sup>	1998/4–2000/10	Austria	Otolaryngologists questionnaire	Hoarseness for 8 wk LPR on laryngoscopy pH test	Pantoprazole 40 mg BID	12	Significant improvement in self-reported symptoms
Ulualp et al (2001) <sup>[21]</sup>	1996/10–1998/12	US	otolaryngology clinic; questionnaire	PL who received pH monitoring	H <sub>2</sub> receptor-blocking agents or PPI	8–108	Pharyngeal acid reflux, total symptom scores were significantly lower
Hamdan et al (2001) <sup>[22]</sup>	2000–2001	Lebanon	Otolaryngologist and gastroenterologist	LSx; GER by endoscope or by 24-h pH monitoring	pantoprazole 40 mg BID	4	Vocal fatigue and vocal breaks were improved significantly
El-Serag et al (2001) <sup>[23]</sup>	1998/10–1999/12	US	Otolaryngologist questionnaire	LSx for > 3 wk LPR on laryngoscopy	Lansoprazole 30 mg BID	12	Complete symptom resolution
Noordzij et al (2001) <sup>[24]</sup>	2000–2001	US	Otolaryngologists questionnaire	LSx for 12 wk LPR on laryngoscopy pH test	Omeprazole 40 mg BID	8	≥50% reduction in global symptom score
Langvin and Ngo (2001) <sup>[25]</sup>	2000	Canada	Not known	LSx for 12 wk LPR on laryngoscopy pH test	Omeprazole 40 mg once a day	12	≥50% reduction in laryngeal symptoms
Havas et al (1999) <sup>[26]</sup>	1998–1999	Australia	Otolaryngologist	LPR on laryngoscopy	Lansoprazole 30 mg BID	12	≥50% reduction in global symptom score
Wo et al (1997) <sup>[27]</sup>	1996–1997	US	Otolaryngology clinics; questionnaire	LSx for > 1 month; LPR on ambulatory pH monitoring	Omeprazole 40 mg OHS	8	Laryngeal symptom significantly improved

BID = bis in die, ENT = ears, nose, and throat, GER = gastroesophageal reflux, GERD = gastroesophageal reflux disease, LPR = laryngopharyngeal reflux, LSx = laryngeal symptoms, PL = posterior laryngitis, PPI = proton pump inhibitors, QHS = queue hora sonny.

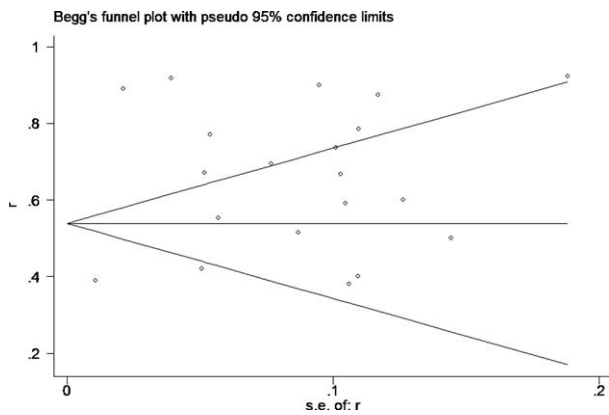


Figure 2. Forest plot for effect of acid suppression success in chronic laryngitis.

and Begg rank correlation test (Egger test,  $P=0.073$ ; Begg test,  $P=0.165$ ) (Fig. 2).

**4. Discussion**

This research is the first study of meta-analysis offering available data on the efficacy of acid suppression therapy in GERD-related CL. Our study confirms formerly published outcomes for ORR in GERD-related CL treated with acid suppression, with ORR of up to 66%.

It is well known that the base for the cure of GERD-related CL in ENT is 8 to 12 weeks' double-dose PPI.<sup>[28]</sup> Nevertheless,

**Table 2**

**Sensitivity analysis of subgroup's effect of acid suppression therapy.**

Variable	Number of trials	Number of patients	Estimated rate (%)	95% CI (%)	$I^2$ (%)	$P$ for heterogeneity
Year of study						
Before 2006	11	257	62	50-74	75.5	<0.01
From 2006	10	2607	70	51-89	98.6	<0.01
Duration of therapy, wk						
≤8	6	133	57	48-65	8	0.365
>8	15	2731	70	55-85	97.9	<0.01
Therapeutic method						
Medicine	18	2741	64	50-77	97.2	<0.01
Surgery	3	123	80	67-93	73	0.025

CI=confidence interval.

placebo-controlled studies showed that PPI therapy is no better than placebo in relieving GERD-related laryngopharyngeal symptoms.<sup>[29]</sup> The assumption for the comparatively poor PPIs response in the researches is a possible selection bias for the reason that GERD diagnosis was not depended on pH-metric standards at all times. Some reports have presented that about 64% to 86% of healthy people could be discovered with laryngeal abnormalities indicative of a laryngeal reflux.<sup>[30,31]</sup> Therefore, esophageal 24-hour pH watching is required to notarize GERD, particularly as the therapeutic test has not been confirmed for the duration of the ENT clinical situation. El-Serag et al<sup>[23]</sup> reported that the only predictors of fine effect to PPI were characterized when pathological acid exposure before treatment. Moreover, it is perhaps owing to the point that some patients

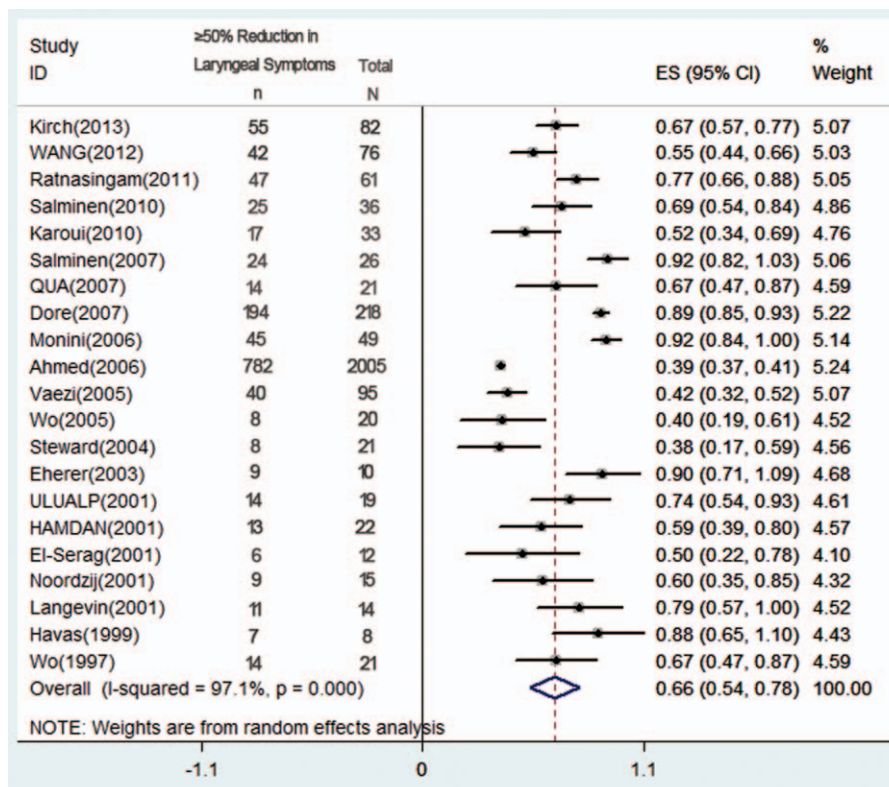


Figure 3. Funnel plot to detect publication bias.



whose laryngeal symptoms were not caused by GERD would weaken the total study populations leading to reduced power to discover a difference between placebo and PPIs.

There is a popular belief that the result of surgical treatment for reflux is best in typical reflux symptom patients. People with typical reflux symptoms and atypical throat symptoms had a good effect undergoing fundoplication; the result of these patients was similar to that of the bigger group experiencing fundoplication for typical reflux indications without throat discomfort. Farrell et al<sup>[32]</sup> assessed the ORR in people with typical against atypical symptoms (hoarseness, cough, asthma, and chest pain) after fundoplication. The authors showed that 99% of primarily reflux symptom patients were improved; in addition, 87% patients were entirely cured postoperatively. So et al<sup>[33]</sup> demonstrated that the treatment of laparoscopic fundoplication had effect on 93% of typical reflux symptoms patients, whereas only 56% atypical symptom patients improved after surgery. The ORR for laryngeal, epigastric/chest pain, and pulmonary was 78%, 48%, and 58%, respectively. Our previous study also indicated that compared to studies of patients with medicine therapeutic method (ORR: 64% [95% CI: 50%–77%]), the effect in the pooled results of patients with surgery therapeutic method was better (ORR: 80% [95% CI: 67%–93%]) (Table 2).

There were some limitations of this study while illustrating the outcomes. First, the heterogeneity in this research is high, which might be rooted in statistical and clinical heterogeneity; the cause might be that the trials are from different districts and the definition of these indicators was not united. Second, a publication bias might lead to the probability of a systematic difference between larger and smaller reports; to be exact, small research possibly overestimated the effects of acid suppression therapy in terms of ORR. Likewise, asymmetry might also root in heterogeneity. Third, comparisons of ORR were hard because of absence of general agreement on the accurate characterization of result and randomization. Last, the reports involved in this study were only printed in English, signifying that a possible language bias occurred.

## 5. Conclusion

This meta-analysis showed that the overall 1 rate of acid suppression therapy (including medicine therapy and surgery therapy) in suspected GERD-related CL is 66% and there was an increase in effect in the pooled outcomes for the reports of patients who underwent surgery therapeutic method (ORR: 80%) relative to studies of patients with medicine therapeutic method (ORR: 64%); moreover, response to acid suppression therapy was superior to the reports with longer period of therapy (ORR: 70% vs. 57%).

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