REVIEW

A systematic review of the role of proton pump inhibitors for symptoms of laryngopharyngeal reflux

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Keypoints

- Proton pump inhibitors are currently used widely for the treatment of laryngopharyngeal reflux.
- This systematic review assessed the efficacy of proton pump inhibitors in the treatment of symptoms of laryngopharyngeal reflux.
- Outcome measures used to assess efficacy of proton pump inhibitors included endoscopic laryngeal signs and pH recordings.
- Only two small randomized-controlled trials included patients with objective evidence of reflux in the 24-h ambulatory oesophageal pH monitoring.
- Pooled analysis of these two randomized-controlled trials failed to show any effect in favour of treatment with proton pump inhibitors.
- Further randomized-controlled trials are required to ascertain the role of proton pump inhibitors in the treatment of laryngopharyngeal reflux.

Laryngopharyngeal reflux is defined as the retrograde flow of gastric contents into the larynx and hypopharynx. It is estimated that 4–10% of patients presenting to an otolaryngology practice and 1% to primary care practice have symptoms and/or signs related to laryngopharyngeal reflux.[1,2] Patients with laryngopharyngeal reflux present with non-specific symptoms such as hoarseness, vocal fatigue, chronic throat clearing, excessive phlegm, chronic cough, dysphagia or globus sensation.[3] They do not usually have the typical symptoms of gastroesophageal reflux such as heartburn and regurgitation.[1]

Laryngoscopic findings are also non-specific and may include oedema and erythema of the posterior larynx, as well as vocal nodules, Reinke's oedema, contact ulcers and granulomas, laryngeal stenosis and paroxysmal laryngeal spasm.[4] However, there is often a lack of correlation between symptoms and signs and as a result laryngeal signs need not be present in order to diagnose laryngopharyngeal reflux. These factors make accurate diagnosis challenging. Many clinicians suggest empirical treatment with anti-reflux therapy as an initial diagnostic strategy for symptomatic patients and negative physical examination. Dual channel 24 h pH monitoring is considered the most sensitive and specific test available to diagnose laryngopharyngeal reflux.[5] However, according to the guidelines of the American Gastroenterological Association, this investigation is reserved for patients who do not respond to initial blind acid suppression therapy.[6]

Standard therapeutic interventions for laryngopharyngeal reflux include lifestyle modifications, medical and surgical treatment.[7] Lifestyle modifications include avoidance of heavy meals, smoking, excessive alcohol and meals before recumbence. Other measures include reducing excessive body weight, avoiding tight clothes and a slightly elevated position in bed. Surgery takes the form of either partial or complete fundoplication, usually performed laparoscopically. However, much more commonly used is medical therapy consisting of prokinetic agents, H_2-receptor antagonists and proton pump inhibitors. Proton pump inhibitors have become the treatment of choice because of their efficacy in treating gastroesophageal reflux disease and their very good safety profile. Several proton pump inhibitors are available now and they are tried at various doses and for variable duration.

This study is a systematic review of all the randomized-controlled trials on the use of proton pump inhibitors for the treatment of laryngopharyngeal reflux. The primary aim of this study is to assess the efficacy of proton pump inhibitors in the treatment of symptoms of laryngopharyngeal reflux. The secondary aim, dependent on the first, is to define an optimal dose and duration of treatment.

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Materials and methods

Literature search

The Cochrane Controlled Trials Register was searched up to October 2004. MEDLINE 1966 to October 2004 and EMBASE 1980 to October 2004 were searched with a strategy sensitive for randomized-controlled trials.[8] Full text articles were obtained when the title, abstract or key words suggested that the study may be eligible for this review.

The medical subject heading (MeSH) used included reflux laryngitis, chronic laryngitis, posterior laryngitis, laryngopharyngeal reflux, gastroesophageal reflux, GER, GOR, GERD, GORD or LPR and proton pump inhibitors, omeprazole, pantoprazole, esomeperazole, rabeprazole, acid suppressive therapy or anti-reflux therapy. These terms were combined in various ways to generate a wide search. In addition, bibliographies of retrieved articles were searched to identify additional pertinent reports. The search was carried out by two of the reviewers independently. No language restriction was applied. However, no attempt was made to contact drug manufacturers or hand search journals.

Inclusion criteria

Participants had to be over 18 years old, identified by that trial as suffering from laryngopharyngeal reflux, with presence of any of the symptoms stated in Table 1. The participants should have had their symptoms for at least 2 months with all other causes excluded by flexible laryngoscopy. All patients should have had objective evidence of reflux in the 24-h ambulatory oesophageal pH monitoring. An oral proton pump inhibitor must have been the intervention tested against placebo. As this review aimed to assess the effectiveness of proton pump inhibitors themselves, studies where another potentially active intervention was also used were excluded.

A symptom score for laryngopharyngeal reflux symptoms must have been collected. This is defined as a summary composite score of throat pain, hoarseness, foreign body sensation in the throat, throat clearing and cough. Five pre-defined methodological criteria were applied to all trials: a sample size of at least 10 patients had to be present, the text had to state explicitly that the intervention/placebo were allocated randomly, its method was 'double blind', loss to follow up was <20% in either arm and a subjective decision could be made that there were no other unanticipated methodological flaws.

Table 1. Symptoms of reflux laryngitis used for the inclusion criteria

Hoarseness	Excessive phlegm
Excessive throat clearing	Sore throat
Globus sensation	Chronic cough

Data extraction and synthesis

A form was generated to document whether individual studies met eligibility criteria and to collect data regarding study design and methodological quality. Two investigators independently reviewed and extracted data from the papers according to the pre-defined criteria. Any differences in opinion about the studies were resolved by discussion between the referees.

Analysis

Revman (4.2) software, available from the Cochrane Collaboration Group, was used for data collection and analysis. All symptom scores were converted to 10-point scales and then the mean and SD of change was calculated for the proton pump inhibitors and placebo groups. The weighted mean difference was then calculated (based on a random effects model) with 95% CI.

Outcome measures of laryngopharyngeal reflux included improvement in endoscopic laryngeal signs and pH recordings by pH metry at the end of the study.

Results

Our literature search identified 21 potentially relevant clinical trials. Four were randomized-controlled trials. A total of 16 open label studies in which both the health providers and the patients were aware of the drug being given were excluded. In most of these studies patients were started on proton pump inhibitors on the basis of a combination of symptom score, laryngoscopy and pH metry. Omeprazole was the most commonly used proton pump inhibitors but the dosage used varied from 20 to 80 mg and the duration of therapy was variable.

Four randomized-controlled trials were identified.[9–12] Twelve patients of 22 patients in El-Serag study[9] and seven of 15 patients in Havas study had negative pH measurements. Table 2 lists the general features of the other two included randomized-controlled trials.

The two studies[11,12] contained data that could be pooled. In both studies patients had symptoms of chronic laryngitis (Table 1) for at least 3 months and other causes for these symptoms excluded after flexible laryngoscopy. Patients had 24-h-dual channel pH probe measurements. The probe was placed with fibreoptic

Table 2. Design and quality characteristics of randomized-controlled trials

Randomized-controlled trials	Noordzij	Eherer
Treatment drug	Omeprazole	Pantoprazole
Duration	60 days	90 days
Sample size	30	21
Estimation of sample size		X
Intention to treat analysis		X
Double-masked	X	X
Randomization by identical drug pack	X	X
Diagnostic measures		
Symptom score	X	X
Laryngoscopy	X	X
pH metry	X	X
Oesophageal manometry		X
Videostrobolaryngoscopy	X	X
Outcome measure		
Improvement in mean symptom score	X	X

guidance and patients were required to have more than four episodes of laryngopharyngeal reflux in Noordzij study. Manometry was used to confirm the position of the probe in the Eherer study, while patients were included if there was evidence of more than one episode of laryngopharyngeal reflux or time of pH < 4 exceeding 4.5% of measurement period. Eherer study was a crossover study, with significant dropout after the first part, so only the first part was pooled in the results. Characteristics of the two studies are shown in Table 3. Eherer reported absence of side effects, while there is no mention of any side effect in Noordzij trial. The pooled results are shown below for composite laryngeal symptom score (0–10): $n = 25$; placebo group $n = 25$; proton pump inhibitor group $n = 25$. In a random effects model: standardized mean difference = −0.440 (95% CI: −3.86 to 2.71) $z = 0.3$, $P = 0.73$; test for heterogeneity $P = 0.0001$. A synthesis of results of the two trials are shown in Fig. 1.

The objective outcomes in the Eherer trial included improvement in laryngopharyngeal reflux as determined by pH metry and laryngoscopic appearance. Eherer noted no statistically significant difference in pH measurements performed 2 weeks following the first half of the crossover trial. There was also no significant difference in laryngoscopic signs in the two groups at the end of the first round of treatment.

Similarly, Noordzij also noted no significant changes in laryngeal signs for either treatment groups over the course of the study. Post-treatment pH metry was not performed in this study.

Discussion

This systematic review showed that there is not enough evidence in the literature on effectiveness of proton pump inhibitors in the management of laryngopharyngeal reflux symptoms. Although there is an abundance of case series there is a paucity of randomized-controlled trials that assess the use of proton pump inhibitors in laryngopharyngeal reflux, despite the fact that their use is common practice. Only two randomized-controlled trials were identified, with contradicting results, and their synthesis failed to show a statistically or clinically significant effect of proton pump inhibitors. However, the outcome of this small analysis must be interpreted with caution, as only two studies, with a

Table 3. Characteristics of studies meeting inclusion criteria

Study	Method + setting	Individuals randomized/loss to follow up	Intervention	Outcome recorded at end of treatment
Noordzij	Parallel Single center Country = USA	30 entered study One in placebo left study prematurely and one in omeprazole was diagnosed with subglottic sarcoidosis	Omeprazole 40 mg bd or Placebo bd for 60 days	Patient assessed Composite VAS (0–1400 points) reflecting severity × frequency Hoarseness, throat pain, lump in throat, cough, throat clearing, excessive phlegm
Eherer	Crossover Single centre Country = Austria	21 entered study Two were lost to follow-up and five refused second treatment phase	Pantoprazole 40 mg bd or Placebo bd for 90 days and crossover after 2 weeks washout period	Patient assessed Composite score (0–72) comprised from four point symptom scale adjusted for frequency Hoarseness, sore throat, globus sensation, dysphonic attacks, cough

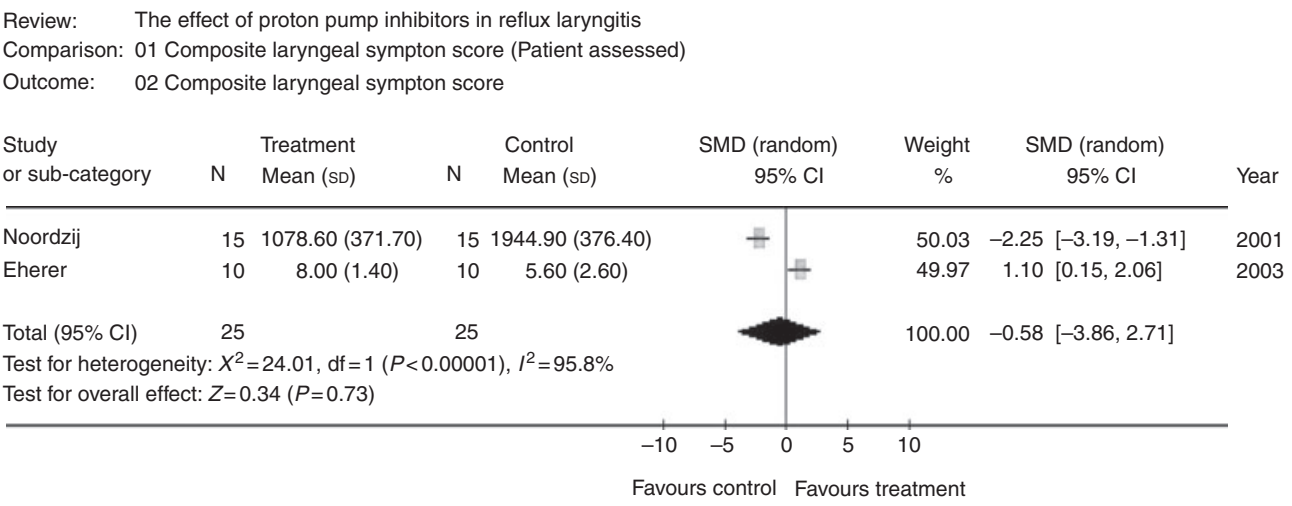

Fig. 1. Forest plot of included studies with composite laryngeal symptom score (different scales).

total of 51 patients were included. On the basis of these findings, we cannot suggest an optimal dose or duration of treatment.

Non-controlled studies strongly suggest a role of proton pump inhibitors in laryngopharyngeal reflux, with a symptom response of 41–100%. However, it is important to keep in mind that laryngopharyngeal reflux is a condition that tends to improve with time, irrespective of treatment: this was demonstrated in all the controlled trials, where patients in the placebo arm of the study invariably improved after a period of 2–3 months; in the Noordzij study improvement in the placebo arm was 20% from baseline symptom score, while it was 57% in Eherer study, with six of 10 patients improving. In the two other randomized-controlled trials that were not included in our analysis, as they included patients without reflux proven by pH measurements, the response rates on placebo were also significant: 30% of patients showed complete or partial resolution of symptoms in the placebo group at 3 months (El-Serag) while an improvement of 33% on baseline symptoms score was apparent in Havas study.

An additional factor that may further dilute the effect of proton pump inhibitors is patient selection: as most patients with laryngopharyngeal reflux present with non-specific symptoms that do not correlate with the clinical examination, the diagnosis is mainly by exclusion of other common disorders. Hence patient selection is an important criterion that determines the results of the studies. We did not include in our analysis studies of patients who were treated empirically with proton pump inhibitors (i.e. without confirmation of reflux) although we are aware that this is current practice. There is no physiological basis to believe that such patients would benefit more than patients with proven reflux – a negative result in our patients is (at least) as valid in patients treated empirically. Secondly, in the absence of positive studies, 'laryngopharyngeal reflux' is a diagnosis of exclusion and is based purely on symptoms and the absence of specific pathology on examination. It is difficult to assess a trial based on such general inclusion criteria and even more difficult to create a synthesis of such trials.

However, even by including only patients with pH monitoring documented reflux, we admit that inclusion criteria were not very specific: The two included trials recruited patients on the basis of (slightly) different definitions of reflux on 24 hr pH monitoring; however, there is no generally accepted, validated cut-off point for the definition of laryngopharyngeal reflux.

Our review would perhaps have been more methodologically robust if it assessed a single symptom (such as hoarseness). However, we feel that this would have been clinically unsound; by using a composite (heterogenous) symptom score, rather than a single symptom, our results are more representative of the multifaceted clinical presentation of patients with laryngopharyngeal reflux which almost always present with multiple variable symptoms.

Emphasis was on the symptom score in both studies. Analysis of the objective outcome measures in the two studies also did not indicate any significant improvement in signs as a result of proton pump inhibitors treatment compared with placebo.

We did not contact manufacturers, experts or search other controlled trials register (apart from Cochrane), so potentially unpublished negative trials (that would help

in reducing publication/reporting bias) were not included. Moreover, because of the small number of randomized-controlled trials, a funnel plot could not be performed to assess publication/reporting bias. However, the two studies included with similar number of patients showed grossly equal results (albeit to the opposite direction) and therefore, publication bias is unlikely.

Conclusion

In conclusion, this review showed that there is not enough evidence to comment on the efficacy of proton pump inhibitors in adult patients with pH measurement proven laryngopharyngeal reflux. Clearly, more well designed, prospective large scale, probably multicentre trials are required. A systematic review of this topic should be part of an on-going system of reviews that is kept up to date and can be used for setting treatment guidelines. Such a system is underway as part of the Cochrane collaboration.[13]

Conflict of interest

None of the authors have any financial interest in this study.

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Commentary

Although the majority of clinicians treat laryngo-pharyngeal reflux empirically the authors report only studies which have reflux proven on pH testing. In addition, despite using pH testing as an inclusion criterion it is not reported as an outcome measure. As the authors recognise that pH testing is not routine, then perhaps the more relevant clinical trial assessment would be that which was based on clinical citeria.

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