Acid reflux treatment for hoarseness (Review)

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ABSTRACT

Background
Acid reflux is a common problem, and is thought to occur in 4% to 10% of patients presenting to ENT clinics. A recent study of reflux and voice disorders suggests that up to 55% of patients with hoarseness (dysphonia) have laryngopharyngeal reflux. Anti-reflux therapy is often used empirically in treating patients with hoarseness, where no other cause has been identified by examination.

Objectives
The aim of the review was to assess the effectiveness of anti-reflux therapy for patients with hoarseness, in the absence of other identifiable causes, whether or not a definitive diagnosis of laryngopharyngeal and gastro-oesophageal reflux has been made. This was assessed by evaluation of prospective randomised controlled studies that were identified by a systematic review of the literature. Both medical and surgical treatments were evaluated.

Search strategy
The Cochrane ENT Group Specialised Register, the Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane Library Issue 3, 2005), MEDLINE (1966 to 2005), EMBASE (1974 to 2005) and conference proceedings were searched with prespecified terms. The date of the last search was September 2005.

Selection criteria
Randomised controlled trials recruiting patients with hoarseness in the absence of other identifiable causes, such as malignancy, cord palsy or nodules, whether or not a definitive diagnosis of laryngopharyngeal and gastro-oesophageal reflux has been made.

Data collection and analysis
Three reviewers examined the search results and identified studies before deciding which would be included in the review.

Main results
302 potential studies were identified by the search strategy. No trials were identified which met our inclusion criteria. Six randomised controlled trials were identified in which some, but not all patients presented with hoarseness, and were treated with proton pump inhibition. As we could not determine with certainty whether all these patients had hoarseness among the other laryngeal symptoms, these were excluded. However, these studies suggest a significant placebo response, which is comparable to the benefit derived from anti-reflux therapy in some studies. As no trials met our criteria, we are unable to reach any firm conclusions regarding the effectiveness of anti-reflux treatment for hoarseness.

Authors' conclusions
There is a need for high quality randomised controlled trials to evaluate the effectiveness of anti-reflux therapy for patients with hoarseness which may be due to laryngopharyngeal and gastro-oesophageal reflux.

PLAIN LANGUAGE SUMMARY

There is not enough evidence that anti-reflux therapies are effective in treating hoarseness

Hoarseness is a common disorder. A recent study suggested that up to 55% of patients with hoarseness have acid reflux (where stomach acid flows back up into the oesophagus), which affects their throat and voice box. Anti-reflux therapy includes drugs, lifestyle changes and sometimes surgery. These treatments are often used for patients with hoarseness, where no other cause has been found by examination. This review found no randomised controlled trials of patients with hoarseness treated by anti-reflux therapy. Some studies were found, however, where patients had hoarseness among other symptoms of acid reflux. These studies suggested a significant response of such symptoms to placebo therapy. More good quality studies are needed to test the effectiveness of anti-reflux therapies in patients with hoarseness.

BACKGROUND

Definition

Gastro-oesophageal reflux disease (often abbreviated to GERD or GORD) is defined as the retrograde flow of gastric contents into the oesophagus or above. Gastro-oesophageal reflux disease is characterised by symptoms and/or signs of mucosal injury of the oesophagus or upper aerodigestive tract secondary to this reflux. Laryngopharyngeal reflux (LPR) is
reflux that affects the pharynx and larynx. Not all episodes of gastro-oesophageal reflux are associated with laryngopharyngeal reflux, but also not all patients with laryngopharyngeal reflux have typical features of gastro-oesophageal reflux disease.

Symptoms, prevalence and aetiology

Typical symptoms of gastro-oesophageal reflux disease include heartburn and regurgitation. The reflux episodes often occur at night in the supine (lying face up) position or if the patient bends forward (Marks 1991). In clinical practice heartburn is a daily complaint in up to 7% of the population in the US (Talley 1992). Most patients with symptoms of gastro-oesophageal reflux disease will exhibit little or no objective evidence on examination (Gaynor 1991). The complications of gastro-oesophageal reflux disease include peptic stricture, dysphagia, odynophagia, oesophagitis and Barrett's oesophagus (Johanson 2000). The aetiology of gastro-oesophageal reflux disease is not certain, but there are several factors which may contribute. These factors are delayed gastric emptying, impaired function of the lower oesophageal sphincter (Bain 1983) and incomplete oesophageal clearance (Johanson 2000). Other factors such as infection (e.g. Helicobacter pylori), obesity, allergy, smoking, food intolerance and swallowing dysfunction have also been suggested (Gaynor 1991).

It is estimated that 4% to 10% of patients presenting to otorhinolaryngology clinics have laryngopharyngeal reflux related disease (Koufman 1991). This may manifest as hoarseness, dysphagia, chronic cough, post nasal drip, throat clearing or globus sensation (Koufman 2000). Signs on laryngological examination include arytenoid erythema (which can be graded), interarytenoid mucosal oedema, contact ulcers and granulomas (Gaynor 1991). Extralaryngeal symptoms include excess salivation, otalgia, hiccups, erosion of dental enamel, asthma, bronchitis and recurrent pneumonia (Gaynor 1991). Amongst these symptoms of laryngopharyngeal reflux disease, hoarseness (dysphonia) is the most common (McNally 1989).

Hoarseness is a common cause of referral to otorhinolaryngology. It is associated with anxiety as to the underlying cause, and can affect quality of life by reducing the ability to verbally communicate effectively. Underlying causes include malignancy, vocal cord palsy, cysts, polyps and nodules of the vocal cords, laryngitis and functional disorders such as muscle tension dysphonia (Carding 1997). Acute laryngitis is usually infective, whereas chronic laryngitis is often attributed to 'vocal abuse'. This encompasses a spectrum of insults including cigarette smoke, dehydration, muscular imbalance and acid reflux.

A recent study of reflux and voice disorders suggest that up to 55% of patients with hoarseness have laryngopharyngeal reflux (Koufman 2000). Patients with laryngopharyngeal reflux often differ from patients with classical gastro-oesophageal reflux disease in that heartburn and dyspepsia are absent in more than 50% (Koufman 1996; Ulualp 1999). Patients with
laryngopharyngeal reflux are more likely to experience reflux episodes in the daytime in an upright position than those with gastro-oesophageal reflux disease (Koufman 1991). Mucosal injury is thought to occur by direct contact of the laryngeal mucosa with acid, pepsin and bile. Minute amounts of acid applied experimentally in animal models causes dramatic laryngeal injury (Ludemann 1998). Direct evidence for laryngopharyngeal reflux in vivo comes from dual chamber acid monitoring, demonstrating reflux into the hypopharynx in patients with hoarseness (Katz 1990). The association between laryngopharyngeal reflux and gastro-oesophageal reflux has not been firmly established. Laryngopharyngeal reflux has been found in healthy individuals, albeit less frequently than in patients with chronic laryngitis (Shaker 1995). Not all patients with gastro-oesophageal reflux disease will develop laryngeal symptoms, although a subset is thought to have significantly greater proximal acid exposure (Jacob 1991). It has been found that 23% of patients with confirmed laryngopharyngeal reflux on pH monitoring have normal levels of acid exposure in the distal oesophagus (Ormseth 1999). Hoarseness is present in 92% of patients with reflux laryngitis (Toohill 1997).

Diagnosis

The diagnostic tests used for gastro-oesophageal reflux disease are divided into following subgroups:

1) Evaluation of the presence of gastro-oesophageal reflux disease:
a) Ambulatory 24-hour dual probe pH-metry measures of acidic reflux. Pathological reflux is defined as pH < 4, 5cm or more above the lower oesophageal sphincter for > 4% of the 24-hour time period, during which the patients keep a diary of the activities during the day, e.g. eating, exercise, sleeping etc.;
b) Oesophageal manometry measurements of the lower oesophageal sphincter (LOS) pressure, both when the oesophagus is relaxed and when it contracts, i.e. during swallowing;
c) Oesophageal impedance measurements are useful in evaluating the volume and height of the refluxate. An advantage is that this measures non-acidic as well as acidic reflux;
d) Spectrophotometric measurement of bile reflux;
e) Barium swallow study gives a static image of the oesophageal function, while video fluoroscopy provides dynamic images of reflux.

2) Evaluation of the mucosal injury:
a) Flexible fibre-optic oesophagoscopy to grade the oesophagitis, if present. Different grading systems are available and quantify features including the circumferential extent of oesophagitis and the presence of exudate (Lundell 1999). There is inconsistency between the different classifications;
b) Mucosal biopsy is relevant if Barrett's oesophagus (metaplasia of the epithelium) or malignancy is suspected.

The diagnostic tests used for laryngopharyngeal reflux are divided into the following subgroups:

1) Evaluation of the presence of laryngopharyngeal reflux:
a) Ambulatory 24-hour dual or triple probe pH-metry. Probes are positioned at the level of the lower oesophageal sphincter and above and/or below the upper oesophageal sphincter. The results of this measurement are not easy to interpret because there is no consensus about pathological reflux at the level of the laryngopharynx (Nostrant 2000).The level of acidity considered to be abnormal should be less than at the lower oesophageal sphincter (i.e. pH > 4) as there may be neutralisation of acidity by saliva (Nostrant 2000), and there is a lesser ability to clear acid from the laryngopharynx compared with the lower oesophagus. In addition, there is speculation that the presence of a pharyngeal probe may precipitate reflux secondary to irritation (Mittal 1992), and loss of contact between the probe and mucosa may result in false-positive results.
b) Barium swallow study. This study gives an image of oesophageal function at a single point in time. Since a reflux episode might occur before or after the image the method is not reliable.

2) Evaluation of the mucosal injury:
Laryngoscopy (i.e. flexible, rigid or mirror, with or without stroboscopy) to demonstrate the presence of erythema, oedema, granuloma or ulcer on the vocal folds. There is confusion in the definitions used for benign laryngeal lesions, leading to considerable inter-observer variability describing laryngoscopy findings (Chau 2004). The severity of mucosal injury may be graded according to the reflux finding score (Belafsky 2001). The reflux finding score (RFS) is an 8-item clinical severity scale based on findings during fiberoptic laryngoscopy. The items included in the scale include subglottic oedema (pseudosulcus vocalis), ventricular obliteration, erythema/hyperemia, vocal fold oedema, diffuse laryngeal oedema, posterior commissure hypertrophy, granuloma/granulation tissue, and excessive endolaryngeal mucus (Lundell 1999). The reflux finding score has been shown to have high intra-observer variability. However, the clinical appearances described above are not specific for reflux laryngitis, but may also be demonstrated in patients with typical symptoms of gastro-oesophageal reflux disease and in asymptomatic, healthy volunteers (Powitzky 2003). Furthermore, there is considerable confusion in the definitions.

3) Objective evaluation of voice disability (including acoustic measurements of fundamental frequency, jitter, intensity with shimmer, signal to noise ratio and spectral analysis).

Management options

The options for management of gastro-oesophageal reflux disease are non-surgical and surgical interventions.

Lifestyle modification and patient education is the first line of treatment and includes, for example, elevation of the bed head, individual-based dietary modifications, changing smoking habits and avoiding potentially harmful medications (Katz 2000).

Pharmacological treatment most commonly includes the use of proton pump inhibitors (PPIs) (omeprazole, esomeprazole, lanzoprazole, pantoprazole, rabeprazole). Other drugs used are H2-receptor antagonists (cimetidine, ranitidine, nizatidine, famotidine), which inhibit gastric acid secretion. Prokinetic agents (cisapride, metoclopramide), which accelerate oesophageal clearance and increase the lower oesophageal sphincter pressure, are rarely used due to potential side-effects, e.g. diarrhoea and ventricular arrhythmias. Antacids (including aluminium- and magnesium-containing antacids, and sodium bicarbonate) can often relieve symptoms related to gastro-oesophageal reflux disease in the lower oesophagus but may not prevent mucosal injury in the larynx. Erythromycin, a macrolide antibiotic, effective in the emptying of the stomach, is only used as an alternative when other drugs are ineffective. The medical treatment is often combined with lifestyle modification and patient education, e.g. elevation of bed head, individual-based dietary modifications, changing smoking habits and avoiding potentially harmful medications (Katz 2000).

If non-surgical treatments do not improve the patient's quality of life then surgery is considered; this group primarily consists of patients in whom the volume of liquid that refluxes is high. Surgical treatment includes both fundoplication (where the stomach is wrapped around the distal oesophagus) and non-fundoplication procedures (where other surgical techniques are employed). Fundoplication is the most commonly used surgical procedure. It may be complete (Nissen and Rossetti) or partial (Toupet, i.e. oesophagus behind the stomach, and Bore, i.e. oesophagus in front

of the stomach). The surgical procedures are preferentially performed laparoscopically. Open surgery is usually undertaken only in cases where complications occur during laparoscopic procedures, or where laparoscopic surgery is contraindicated.

Pilot studies have indicated that management of reflux results in resolution of hoarseness, but the effectiveness of such treatments is not firmly established. The aim of this systematic review is to evaluate the literature with regards to this problem.

OBJECTIVES

To assess the effectiveness of anti-reflux therapy for adult patients with hoarseness in the absence of other identifiable causes, whether or not a definitive diagnosis of laryngopharyngeal and gastro-oesophageal reflux has been made.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

All randomised and quasi-randomised, controlled, double-blinded trials. Controlled clinical trials (trials using a control group but no adequate randomisation procedure) and quasi-randomised trials were also identified.

Types of participants

All adult (aged 18 or over) patients with hoarseness (dysphonia). The participants should have had the symptom for at least six weeks (to differentiate between acute and chronic hoarseness). The participants will be included whether or not there is a definitive diagnosis of gastro-oesophageal reflux disease. All patients should have undergone laryngoscopy to exclude other identifiable causes of hoarseness including malignancy, vocal cord paralysis and vocal cord nodules.

Types of intervention

The interventions will be divided into non-surgical and surgical.

Non-surgical treatments include:

1) Lifestyle modification and patient education

2) Pharmacological treatment:

Proton pump inhibitors (PPIs)
Antacids
H2-receptor antagonists
Prokinetic agents
Erythromycin

Surgical treatments include:

1) Fundoplication repair:

Nissen fundoplication
Rossetti fundoplication
Toupet fundoplication (partial fundoplication)
Bore fundoplication (partial fundoplication)
Collis gastroplasty followed by fundoplication

2) Non-fundoplication repairs:

Hill repair (gastropexy)
Bilsey MK-4

Anti-reflux therapy will be compared with placebo or no medication where possible since the spontaneous improvement without any medication and the placebo response have been reported as being substantial.

Types of outcome measures

The following outcomes will be assessed:

1. Primary measures

The primary aim of treatment for hoarseness or dysphonia is the improvement of the patient's voice quality and, in turn, their quality of life. It is therefore essential to include quality of life measures in primary outcome assessment. These are specifically designed and validated tools which measure global and disease-specific quality of life. Such outcome measurement usually involves a measurement of health-related quality of life, disease status, and disease-related functional status. For example, a patients' ability to perform normal daily activities may be reduced by their dysphonia. Questionnaires, known as instruments, are used to measure these domains. There are now many such questionnaires available that may measure general health and well being, such as the Medical Outcome Study Short Form 36 (SF 36), or measure disease-specific quality of life (VHI, VRQL).

a) Hoarseness. The proportion of patients with complete and partial resolution of symptoms was assessed
b) Quality of life measures (QOL)
i) Global instruments e.g. SF-36
ii) Disease-specific instruments (e.g. Voice handicap index (VHI) (Rosen 2000), Voice related quality of life (VRQL) (Hogikyan 1999)). These instruments have been validated and shown to be responsive to change following treatment for dysphonia. They measure the patient's perception of the impact of their dysphonia on quality of life, separated into emotional, physical and functional domains. However, there appears to be poor correlation between such subjective measures and voice laboratory measurements in dysphonia (Hsuing 2002).

2. Secondary measures

Our secondary measures include 'objective' findings such as laryngeal appearances and acoustic measurements due to the controversy surrounding their validity in diagnosis of symptoms.

a) Laryngeal measures
i) Visual appearance of the laryngeal mucosa, including the vocal folds

ii) Number of reflux episodes measured by pharyngeal pH-metry

b) Voice-related measures
i) Acoustic measures of continuous speech or sustained vowels
ii) Fundamental frequency with jitter
iii) Intensity with shimmer
iv) Aerodynamic measures, e.g. mean flow rate and peak flow
v) Signal to noise ratio
vi) Signal to harmonics ratio
vii) Spectral analysis (fast Fourier transform (FFT), spectrography, long-term average spectrum (LTAS), power spectrum)

Desirable time points of outcome assessment are: short-term: 1 month; medium-term: 6 months; long-term: 1 to 5 years.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: Cochrane Ear, Nose and Throat Disorders Group methods used in reviews.

We searched the Cochrane ENT Group Specialised Register and the Cochrane Central Register of Controlled Trials (The Cochrane Library, Issue 3, 2005). Additional studies were searched for using MEDLINE (1951 to 2005) and EMBASE (1974 to 2005), CINAHL (1982 to 2005), Biological Abstracts and review articles. Handsearching of the authors' own files was carried out as well as searches of databases of theses. The date of the last search was September 2005. The following search terms were used:

1) Gastro-oesophageal reflux OR gastroesophageal reflux OR gastro-esophageal reflux OR reflux OR GORD OR GERD OR GOR OR GER OR laryngeal reflux OR pharyngeal reflux OR laryngopharyngeal reflux OR laryngo-pharyngeal reflux OR LPR OR posterior laryngitis
2) AND hoarseness OR dysphonia OR impaired voice function OR posterior laryngitis OR chronic laryngitis OR reflux laryngitis
3) AND anti-reflux treatment OR anti-reflux therapy OR anti-reflux medication OR omeprazole OR esomeprazole OR lanzoprazole OR pantoprazole OR rabeprazole OR H2-antagonist OR cimetidine OR ranitidine OR nizatidine OR famotidine OR prokinetic OR cisapride OR metoclopramide OR antacids OR sodium bicarbonate OR erythromycin OR fundoplication OR Nissen OR Rossetti OR Toupet OR Bose OR gastropexy OR gastroplasty OR lifestyle modification OR gaviscon OR mucosal protective drugs

For the identification of randomised controlled trials on MEDLINE and EMBASE, including congress reports and review articles, these terms were combined with the highly sensitive search strategy developed by the Cochrane Collaboration for identification of randomised controlled trials (RCTs). The search was carried out by the authors. Reference lists of identified publications were scanned for additional trials and authors contacted where necessary. In addition, the reference lists of previous reviews of the subject and the reviewer's own files were scanned for relevant studies, including hand searching.

METHODS OF THE REVIEW

Study selection
The full text articles of the retrieved trials were reviewed by the authors and the inclusion criteria applied independently. Any differences in opinion about the inclusion of studies in the review were resolved by discussion between the authors.

We did not identify any randomised controlled trials suitable for inclusion in the review. Should such studies be identified for future updates of the review the following methods will be employed:

Data extraction
Data from the studies will be extracted by the reviewers using standardised data forms. Data will be extracted so as to allow an intention to treat (ITT) analysis. After all the data forms are filled in, all first authors of the trials to be included and possibly included will receive a copy for comments. Where data are missing, the reviewers will write to the authors of the study requesting the missing data.

Quality assessment
The quality of all trials will be assessed by the authors. Differences in opinion will be resolved by discussion. The selected studies will be assessed for the following characteristics:

1) The adequacy of the randomisation process and of allocation, i.e. A: adequate, B: uncertain, C: not adequate.
2) The potential selection bias after allocation to study group, i.e. losses to follow up and whether analysis was by intention to treat.
3) Whether there was blinding of outcome assessors to the participants' study group.
4) Quality of outcome assessment, i.e. A: adequate, B: uncertain, C: not adequate.

Data analysis
Data will be analysed by intention to treat (ITT). If data are of sufficient quality, i.e. categories A and B, they will be combined to give a summary of effect, otherwise data will not be combined. Study quality will be used in a sensitivity analysis. If the data permit, analysis will be carried out separately for different types of treatment, as well as considering non-surgical versus surgical treatment as a whole. Study outcomes are likely to be measured in a variety of ways using several categorical variables. Data may be stratified if appropriate, including whether a definitive diagnosis of reflux has been obtained or not. Statistical advice will be sought to determine the best way of presenting and summarising the data.

DESCRIPTION OF STUDIES

A total of 302 studies of hoarseness were identified through electronic searching. Among these only six randomised controlled trials (RCT) were identified, comparing gastric acid suppression with proton pump inhibitors versus placebo. There were no randomised trials of other methods of anti-reflux treatment.

El-Serag 2001

The first randomised controlled trial (El-Serag 2001) evaluated the efficacy of lansoprazole versus placebo among patients with chronic idiopathic laryngitis. The study included 22 patients with symptoms and signs of chronic laryngitis. Twenty patients completed the study. The patients were randomised to receive either lansoprazole 30 mg by mouth, twice a day or placebo for 12 weeks. Entry criteria were the presence of hoarseness, throat clearing, dry cough, globus or persistent sore throat. However, we were unable to determine the proportion of included patients with hoarseness, and the outcome in this particular group. Quality assessment: the randomisation process and allocation was adequate. There was no potential selection bias. There was blinding of outcome assessors to the participants' study group. Quality of outcome assessment was not adequate.

Havas 1999

The second randomised controlled trial (Havas 1999a) included 15 patients with posterior pharyngolaryngitis, treated with lansoprazole 30 mg twice a day, or placebo for 12 weeks. Inclusion criteria were persistent symptoms of cough, sore throat, throat clearing or hoarseness, in association with findings of posterior laryngitis. We were again unable to determine if all patients in the study had hoarseness at presentation. Quality assessment: the randomisation process and allocation was adequate. There was no potential selection bias. There was blinding of outcome assessors to the participants' study group. Quality of outcome assessment was not adequate.

Noordzij 2001

The third randomised controlled trial (Noordzij 2001) included 30 patients with laryngopharyngeal reflux proven by pH-monitoring. Fifteen patients received 40 mg omeprazole twice a day, the remainder received placebo for a period of two months. Symptoms scores and videostroboscopy were recorded initially, at one month, and at two months. The proportion of patients with hoarseness could not be determined. Quality assessment: the randomisation process and allocation was adequate. There was no potential selection bias. There was blinding of outcome assessors to the participants' study group. Quality of outcome assessment was not adequate.

Vaezi 2004

The fourth randomised controlled trial (Vaezi 2004) included 145 patients with suspected laryngopharyngeal reflux, 95 patients received 40 mg esomeprazole twice daily for 16 weeks and 50 patients received matching placebo. Symptoms and laryngeal sign index were used to evaluate the presence of laryngopharyngeal reflux. Again, we could not establish the proportion of patients with hoarseness. Quality assessment: the randomisation process and allocation was adequate. There was no potential selection bias. There was blinding of outcome assessors to the participants' study group. Quality of outcome assessment was not adequate.

Eherer 2003

One study randomised patients with pH-metry proven laryngopharyngeal reflux to pantoprazole 40 mg twice a day or placebo for three months, followed by a similar cross-over period (Eherer 2003). We were again unable to determine with certainty whether all included patients had hoarseness. Quality assessment: the randomisation process and allocation was adequate. There was no potential selection bias. There was blinding of outcome assessors to the participants' study group. Quality of outcome assessment was not adequate.

Steward 2004

The final, and most recent study randomized 42 patients to rabeprazole 20 mg twice a day, or placebo for two months (Steward 2004). Again, entry to all of these studies was determined by the presence of one or more symptoms of reflux laryngitis; the proportion with hoarseness in each study was not recorded. Quality assessment: the randomisation process and allocation was adequate. There was no potential selection bias. There was blinding of outcome assessors to the participants' study group. Quality of outcome assessment was not adequate.

As our objectives were to assess the effectiveness of anti-reflux therapy for adult patients with hoarseness, and we were unable to determine reliably whether all patients in the above studies had hoarseness on entry into these studies, we felt unable to include them in our review.

Thirty-three further evaluated studies were of acid reflux treatment for clinically diagnosed hoarseness, and had appropriate outcome methods and follow up, but most were without control groups, and four were retrospective. These studies were therefore excluded. There was no disagreement between the reviewers on the final exclusion of studies.

METHODOLOGICAL QUALITY

Not applicable.

RESULTS

No randomised controlled trials met the inclusion criteria of the review.

DISCUSSION

A comprehensive search strategy was used for the review. Every effort was made to identify relevant studies including attendance and presentations at conferences in 2004. Our search strategy was designed to identify non-English studies and no studies were excluded due to language. While several attempts were made to identify unpublished studies, it is still possible that some studies will have been missed. No studies were identified that met our inclusion criteria, and we are therefore unable to make robust conclusions regarding the effectiveness of anti-reflux treatment for hoarseness. In the absence of acceptable randomised controlled trials, the excluded trials will be discussed briefly.

The studies which were excluded could be divided into three groups:

1. Randomised controlled trials of proton-pump inhibition in patients with symptoms of laryngopharyngeal reflux, including hoarseness
2. Prospective studies without control group
3. Retrospective studies

The randomised trials of proton-pump inhibitors, as noted previously, were excluded as patients were recruited if presenting with any symptoms consistent with laryngopharyngeal reflux. Although many of these patients may have had hoarseness, we could not determine if this symptom was present in all patients, and therefore all six studies were excluded on this basis.

Noordzij (Noordzij 2001) et al randomised 30 patients with LPR proven pH probe testing to either omeprazole 40 mg twice a day or placebo for two months. Outcome was measured at one and two months, using unvalidated symptom scores and endoscopic assessment of laryngeal signs. Overall, symptoms and endoscopic appearances improved equally in both arms. However, hoarseness demonstrated a statistically significant improvement when patients were given omeprazole rather than placebo (p=0.021), although there were significant baseline differences between the omeprazole and the placebo arm.

Havas (Havas 1999a) et al randomised 15 patients with laryngoscopic appearances of posterior laryngitis to lansoprazole twice a day or placebo for 12 weeks. Patients underwent dual probe pH-metry, however only four were found to have proximal acidification. Outcome was measured at 6 and 12 weeks, using a different unvalidated symptom score, and laryngoscopic appearances. Patients in both groups showed improvement in both symptom scores and laryngoscopic appearances, with no significant differences between the two treatment groups.

Steward (Steward 2004) randomised 42 patients with symptoms and signs of laryngopharyngeal reflux to lifestyle modification and either rabeprazole 20 mg twice a day or placebo for two months. Only 12 patients underwent pH-metry, of whom less than half had abnormal results. Outcome was measured at 0 and two months using a modification of a previously validated disease specific questionnaire, part of the SF-36, and grading of videostroboscopy images. Compared to baseline, both groups had a significant improvement in reflux symptoms, but there was no significant difference between the two groups. There was no significant improvement in signs of reflux disease in either treatment group.

Eherer (Eherer 2003) randomised 21 patients with pH-metry proven reflux to a crossover study of treatment with pantoprazole 40 mg twice a day and placebo, each for three months, with a washout period of two weeks between treatments. Only 14 patients completed the study. Outcome was measured on completing each treatment period, using an unvalidated symptom questionnaire and grading of laryngeal signs. Both symptom scores and laryngeal grading improved significantly in the first treatment period in both the pantoprazole and control arms, with no significant difference between groups.

In the study by El-Serag (El-Serag 2001), 22 patients with symptoms of chronic idiopathic laryngitis were randomly assigned to receive either lansoprazole 30 mg twice a day or a matching placebo twice a day for three months. All patients underwent dual probe pH-metry, however only five patients were shown to have proximal reflux. Outcome was measured as the proportion of patients in each treatment group who reported complete resolution of all presenting symptoms. There was a significant difference between the lansoprazole (50%) and placebo group (10%, p=0.04).

The largest, but unpublished study (Vaezi 2004) randomised 145 patients to either esomeprazole or placebo. Only 20% of patients reported hoarseness, and at baseline, less than 30% of patients had abnormal pH results (hypopharyngeal 15%, proximal 9%, distal 29%). The presence of laryngeal signs or symptoms did not correlate with abnormal baseline pH. There ws no significant difference in the improvement in symptoms between treatment and placebo arms. A further trial is currently recruiting patients (identifier: NCT00170001).

These studies highlight a number of problems with the evidence relating to this topic. Firstly, several trials recruited patients with symptoms and signs typical of laryngopharyngeal reflux, but pH-metry demonstrates that only a small proportion of these patients have proven reflux events. Some studies excluded patients who had allergies and food intolerance, although these are possible aetiological factors in hoarseness due to reflux. Several different, mostly unvalidated, symptom questionnaires are used for outcome assessment. The assessment period may not be long enough to allow the resolution of laryngeal signs, which seems to occur after resolution of symptoms, and grading of laryngeal signs has been shown to have a low interrater and intrarater reliability. Most studies lacked an adequate, objective evaluation of hoarseness. Trials involve small numbers, and may therefore be underpowered. However, it is important to note that these studies demonstrate a significant placebo effect, which must be considered when evaluating non-randomised studies.

AUTHORS' CONCLUSIONS

Implications for practice

Sufficient evidence based on randomised controlled trials is lacking and therefore we can draw no reliable conclusions about the comparative effectiveness of medical and surgical interventions of hoarseness due to reflux. However, the studies identified, but excluded from this review, suggest there may be a considerable response to placebo treatment in this condition.

Implications for research

There is a significant need for high quality randomised controlled trials to evaluate the effectiveness of surgical and non-surgical treatment of hoarseness associated with laryngopharyngeal reflux. Future research must define the best direct method of documenting the presence of reflux among patients with hoarseness. There is no consensus about when to define reflux as pathological when using dual or triple probe pH-monitoring. Studies should use a validated measure of symptoms, and should include a disease-specific instrument for measuring voice related quality of life. There are no validated scoring systems for the grading of laryngeal signs, and both inter- and intrarater reliability of the present scoring systems is low.

The best objective measure of evaluating hoarseness is yet to be defined. Research is further complicated by the fact that the aetiology of hoarseness is multifactorial and not fully understood. There is still misunderstanding about the relationship between gastro-oesophageal reflux disease and laryngopharyngeal reflux.

There is a need for a carefully designed prospective study to determine whether anti-reflux treatment is effective in hoarseness, and if so, the optimal mode of treatment.

POTENTIAL CONFLICT OF INTEREST

None known.

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* *Indicates the major publication for the study*

TABLES

Characteristics of excluded studies

Study	Reason for exclusion
Ahmad 2004	ALLOCATION: Not randomised (prospective) OUTCOME: Recurrence rate not given
Beck 1997	ALLOCATION: Not randomised (prospective) OUTCOME: Recurrence rate not given
Belafsky 2001a	ALLOCATION: Not randomised (prospective without control group) OUTCOME: Recurrence rate not given
Bilgen 2003	ALLOCATION: Not randomised (prospective without control group) OUTCOME: Recurrence rate not given
Charbel 2005	ALLOCATION: Not randomised (retrospective) OUTCOME: Recurrence rate not given
DelGaudio 2003	ALLOCATION: Not randomised (prospective without control group)

	PARTICIPANTS: Demographic data missing
Eherer 2003	ALLOCATION: Randomised controlled trial (cross-over study) PARTICIPANTS: Demographic data missing
El-Serag 2001	ALLOCATION:Randomised controlled trial PARTICIPANTS: Unable to determine with certainty if all included patients had hoarseness
Eubanks 2001	ALLOCATION: Not randomised (prospective without control group) PARTICIPANTS: Demographic data missing OUTCOME: Recurrence rate not given
Giacchi 2000	ALLOCATION: Not randomised (prospective without control group) OUTCOME: Recurrence rate not given
Habermann 1999	ALLOCATION: Not randomised (prospective without control group) OUTCOME: Recurrence rate not given
Habermann 2002	ALLOCATION: Not randomised (prospective without control group) OUTCOME: Recurrence rate not given
Hamdan 2001	ALLOCATION: Not randomised (prospective without control group) PARTICIPANTS: Demographic data missing OUTCOME: Recurrence rate not given
Hanson 1995	ALLOCATION: Not randomised (prospective without control group) PARTICIPANTS: Demographic data missing OUTCOME: Recurrence rate not given
Hanson 1997	ALLOCATION: Not randomised (prospective without control group) PARTICIPANTS: Demographic data missing OUTCOME: Recurrence rate not given
Harding 1996	ALLOCATION: Not randomised (prospective without control group) OUTCOME: Recurrence rate not given
Harrell 2005	ALLOCATION: Not randomised (prospective) OUTCOME: No follow up
Havas 1999a	ALLOCATION: Randomised controlled trial PARTICIPANTS: Unable to determine with certainty if all included patients had hoarseness
Havas 1999b	ALLOCATION: Not randomised (retrospective study)
Jaspersen 1996	ALLOCATION: Not randomised (prospective without control group) PARTICIPANTS: Demographic data missing OUTCOME: Recurrence rate not given
Kamel 1994	ALLOCATION: Not randomised (prospective without control group) OUTCOME: Recurrence rate not given
Lindstrom 2002	ALLOCATION: Not randomised (retrospective study) PARTICIPANTS: Demographic data missing OUTCOME: Recurrence rate not given
Marambaia 2002	ALLOCATION: Not randomised (prospective without control group) PARTICIPANTS: Demographic data missing OUTCOME: Recurrence rate not given
Metz 1997	ALLOCATION: Not randomised (prospective without control group) OUTCOME: Recurrence rate not given
Noordzij 2001	ALLOCATION: Randomised controlled trial PARTICIPANTS: Unable to determine with certainty if all included patients had hoarseness
Oelschlager 2005	ALLOCATION: Not randomised (consecutive study without control group) PARTICIPANTS: Demographic data missing

	OUTCOME: Recurrence rate not given
Park 2005	ALLOCATION: Not randomised (prospective) PARTICIPANTS: Only comparison of different forms of doses and medication
Pribuisiene 2005a	ALLOCATION: Not randomised (prospective case control study) OUTCOME: recurrence rate not given
Pribuisiene 2005b	ALLOCATION: Not randomised (prospective case control study) OUTCOME: recurrence rate not given
Rouev 2005	ALLOCATION: Not randomised (prospective without control group) OUTCOME: Mean follow up 6 months
Shaw 1996	ALLOCATION: Not randomised (prospective without control group) OUTCOME: Recurrence rate not given
Shaw 1997	ALLOCATION: Not randomised (prospective without control group) OUTCOME: Recurrence rate not given
Siupsinskiene 2003	ALLOCATION: Not randomised (prospective without control group) PARTICIPANTS: demographic data missing OUTCOME: Recurrence rate not given
Steward 2004	ALLOCATION: Randomised controlled trial PARTICIPANTS: Unable to determine with certainty if all included patients had hoarseness
Ulualp 2001	ALLOCATION: Not randomised (retrospective study) OUTCOME: Recurrence rate not given
Vaezi 2004	ALLOCATION: Randomised controlled trial PARTICIPANTS: Unable to determine with certainty if all included patients had hoarseness
Waring 1995	ALLOCATION: Not randomised (prospective without control group) PARTICIPANTS: Demographic data missing OUTCOME: Recurrence rate not given
Wo 1997	ALLOCATION: Not randomised (prospective without control group) OUTCOME: Recurrence rate not given
Wright 2003	ALLOCATION: Not randomised (prospective without control group)

GRAPHS AND OTHER TABLES

This review has no analyses.

INDEX TERMS

Medical Subject Headings (MeSH)

Gastroesophageal Reflux [complications; *drug therapy]; Gastrointestinal Agents [therapeutic use]; Histamine H2 Antagonists [therapeutic use]; Hoarseness [*drug therapy; etiology]; Proton Pumps [therapeutic use]

MeSH check words

Humans

COVER SHEET

Title	Acid reflux treatment for hoarseness
Authors	Hopkins C, Yousaf U, Pedersen M

Contribution of author(s)	C Hopkins registered the title, designed the protocol, performed the searches and drafted the review. U Yousaf designed the protocol, performed the searches and drafted the review. M Pedersen designed the protocol, performed the searches, advised on and edited the review.
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Date new studies sought but none found	Information not supplied by author
Date new studies found but not yet included/excluded	Information not supplied by author
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