Acid reflux treatment for hoarseness (Cochrane review by Hopkins, Yousaf and pedersen 2006) Survey by Mette Pedersen

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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.

Abstract

- 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.

- 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.

Abstract

- Main results
- 302 potential studies were identified by the search strategy. No trials were identified which met our inclusion criteria. Six randomized controlled trials were identified in which some, but not all patients presented with hoarseness, and were treated with proton pump inhibitors. 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 randomized controlled trials to evaluate the effectiveness of anti-reflux therapy for patients with hoarseness which may be due to laryngopharyngeal and gastro-oesophageal reflux.

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.

Background

- 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. 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.

Background

- 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

- 1) Evaluation of the gastro-oesophageal reflux disease
- 2) Evaluation of the mucosal injury.
- 3) Flexible fiber-optic oesophagoscopy to grade the oesophagitis and hernia if present.

- 1) Evaluation of the presence of laryngopharyngeal reflux
- 2) Evaluation of the mucosal injury: Laryngoscopy (i.e. flexible, rigid or mirror, with or without stroboscopy) .
- 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 are seldom used.

Management options

- 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 was 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 randomized and quasi-randomized, controlled, double-blinded trials. Controlled clinical trials (trials using a control group but no adequate randomization procedure) and quasi-randomized 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.

- The following outcomes will be assessessed

- 1.Primary measures
- a) Hoarseness. The proportion of patients with complete and partial resolution of symptoms was assessed
- b) Quality of life measures (QOL)
- c) Specific instruments (e.g. Voice handicap index (VHI) (Rosen 2000), Voice related quality of life (VRQL) (Hogikyan 1999)).

- 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

SEARCH STRATEGY FOR IDENTIFICATION OF STUDIES

- 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

METHOD OF THE REVIEW

- 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 randomization 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.

Description of studies

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

Description of studies

- El-Serag 2001 :
- The first randomized 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 randomized 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 randomization 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.

Description of studies

- Havas 1999:
- The second randomized 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 randomization 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.

Description of studies

- Noordzij 2001:
- The third randomized 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 randomization 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.

Description of studies

- Vaezi 2004:
- The fourth randomized 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 randomization 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.

Description of studies

- Eherer 2003:
- The study randomized 21 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 randomization 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.

Description of studies

- Steward 2004:
- The final 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 randomization 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.

Results and discussion

- 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-randomized studies.

Results and discussion

- No randomized controlled trials met the inclusion criteria of the review.

Results and discussion

- 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.

Authors' conclusion

- Implications for practice:
- Sufficient evidence based on randomized 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.
- The studies identified, but excluded from this review, suggest there may be a considerable response to placebo treatment in this condition.

Authors' conclusion

- Implications for research:
- There is a significant need for high quality randomized 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.

Authors' conclusion

- 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.

Authors' conclusion

- 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.

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