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Systematic review

Treatment of PPI-resistant gastro-oesophageal reflux: A systematic review

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ABSTRACT

Background and study aims: Several studies have demonstrated the superiority of proton-pump inhibitors (PPIs) in resolving erosive gastro-oesophageal reflux disease (GORD). However, this first line of treatment can fail to control symptoms in around 30% of cases, especially in the presence of non-erosive GORD. In situations where the first line of treatment fails, there is a lack of concordance regarding the best strategy to apply. This study presents a systematic review of the trials which have tested second-line treatments after PPI failure.

Methods: The study was conducted according to the PRISMA statement. The systematic review included medical trials written in English which were published between 2000 and 2016 and were retrieved from PubMed and Scopus using the keywords 'PPI-resistant gastro-oesophageal reflux', 'alginate AND gastro-oesophageal reflux', 'hyaluronic acid AND gastro-oesophageal reflux', 'prokinetics AND gastro-oesophageal reflux', 'sucralfate AND gastro-oesophageal reflux' and 'baclofen AND gastro-oesophageal reflux'.

Results: Ten randomised and non-randomised studies were included, which included 1515 patients of both sexes (mean age = 49.19 years, age range = 18–85, males = 700; 46.2%).

Conclusions: A personalised choice of the best treatment for PPI-resistant GORD should be based on the results of an upper endoscopy and pH/MII monitoring. For patients in situations where the first line of treatment fails, we encourage the execution of trials for testing double doses of PPIs against alternative medicaments.

Introduction

Every year, between 9% and 57.6% of the adult population experience symptoms of gastro-oesophageal reflux, such as heartburn, regurgitation, bolus sensation and/or atypical reflux-associated symptoms including chest pain, cough, dyspnoea and pharyngitis/laryngitis [1]. The clinical heterogeneity of this disease is well known. In fact, when the above-mentioned symptoms are present, an upper endoscopy can show conditions ranging from the absence of mucosal lesions to severe ulcerative disease, Barrett's oesophagus or fibrous peptic stenosis. There can also be low correspondence between symptoms and the severity of mucosal lesions [2]. These observations lead to the consideration that control of symptoms represents a distinctive end-point of the treatment from that of mucosal healing. Although several studies have demonstrated the superiority of proton-pump inhibitors (PPIs) in resolving erosive GORD, as the first line of treatment, they can fail to control symptoms in around 30% of cases, especially in the presence of non-erosive gastro-oesophageal reflux disease (NERD) [3]. In patients who do not completely respond symptomatically to a standard dose of PPIs, there is a lack of concordance regarding the best strategy to apply. The aim of this study is to present a systematic review of the trials which have tested second-line treatments after PPI failure.

Materials and methods

The study was conducted according to the PRISMA statement [4]. The systematic review included articles written in English which were published between 2000 and 2016 and were retrieved from PubMed and Scopus using the keywords 'PPI-resistant gastro-oesophageal reflux'. More specifically, we filtered the research for 'clinical medical trials' on 'human adults'. Of the 26 initially retrieved articles, which is a relatively small number, we excluded

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22 articles because they did not meet our inclusion criteria: They lacked a clear diagnosis of GORD supported by standardised questionnaires and/or interventional diagnostic tools, they were not clinical medical trials conducted on human adults, they comprised surgical treatments and/or they were published before 2000. Therefore, only four prospective interventional medical trials remained, which were published as original articles. Three of these studies were not randomised [5–7] and one was randomised and placebo controlled [8]. A more in-depth analysis of their contents showed that a wide range of possible second-line therapeutic options commonly used for GORD/NERD after failure of PPIs had been accidentally left out. Therefore, we made the following adjunctive systematic searches: 'alginate AND gastro-oesophageal reflux', 'hyaluronic acid AND gastro-oesophageal reflux', 'prokinetics AND gastro-oesophageal reflux', 'sucralfate AND gastro-oesophageal reflux', and 'baclofen AND gastro-oesophageal reflux'. We considered all clinical medical trials on human adults with proved gastro-oesophageal reflux previously treated with a PPI and a lack of clinical response to the first-line treatment (Fig. 1). The last search on PubMed and Scopus was made on June 19, 2016, and all articles published between January 2000 and June 19, 2016 were considered. According to the above-mentioned inclusion and exclusion criteria, we retrieved six more original articles: Four prospective non-randomised clinical trials [5–7,14] and two prospective double-blinded randomised and placebo-controlled trials [9–10]. Eligibility assessment was performed in a standardised manner by one review author who extracted the following information: Type of study, number and age of participants, diagnostic tools, presence of previous failure to PPIs and primary and secondary end-points. A senior investigator checked the reliability of the selected articles proposed by the first reviewer and made corrections where needed.

Results

Characteristics of the studies and patients

The selected papers are studies conducted in both occidental and oriental countries: two in Germany [5–6], two in Belgium [7–8], one in Italy [9], one in the U.S. [10], three in Japan [11–13] and one in China [14] (Table 1). The studies are randomised (3 studies) [8–10] and non-randomised (7 studies) [5–7,11–14] interventional pharmacological trials involving patients affected by persistent GORD despite a regular first-line treatment with PPIs. This review, which included 1515 patients of both sexes (mean age = 49.19 years, age range = 18–85, males = 700; 46.2%), evaluated the presence of gastro-oesophageal reflux and the different diagnostic tools used in the clinical trials; sometimes, one tool was used in association with another. Specifically, four studies used pH/MII [5–6,8,14], one study used pH/Bilitec monitoring [7] and seven studies performed an endoscopy [7–13]. Additionally, in six studies, the symptoms were recorded using a validated questionnaire [6,9–13]. The patients in the selected studies were affected by GORD/erosive reflux esophagitis (270 patients), NERD (922 patients), NERD associated with delayed gastric emptying (24 patients), GORD associated with chronic cough (103 patients), duodeno-gastric reflux (mixed or predominantly biliary reflux) (16 patients) or symptoms of GORD despite a negative pH/MII (180 patients).

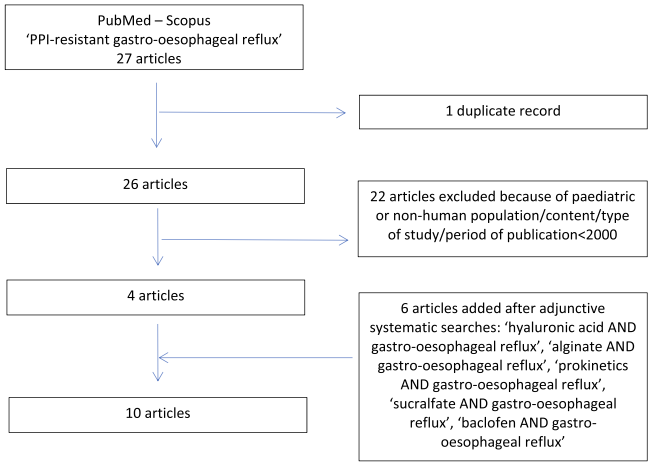

Fig. 1. Flow chart of systematic review.

Treatments

Regarding the treatments, the studies did not identify the use of alginates and/or antacids in the setting of GORD resistant to PPIs. On the contrary, four of the studies assessed the efficacy of a progressive increase in the PPI dose guided by the symptoms [5–6,13–14], five tested the efficacy of adding arbaclofen placarbil/racemic baclofen to standard PPI treatment [6–8,10,14], three evaluated the efficacy of adding prokinetics (mosapride citrate or domperidone) to standard PPI treatment [11–12,14] and one study described the results of a combination of hyaluronic acid and chondroitin sulphate as an addition to ongoing first-line treatment with PPIs and other drugs [9].

With respect to the use of increased PPI doses, (i) a double dose of PPIs (esomeprazole 40 mg bid, rabeprazole 20 mg bid) was found to be associated with a high rate of normalisation of pH/MII reports (71%), and it resolved (53.2%) or significantly ameliorated symptoms (84.4–91.7%) [5–6,13]; (ii) the highest probabilities of achieving good results with this regimen are associated with the presence of abnormal acidic refluxes, female sex, non-smoking and high scores for 'stomach heaviness after meal' [13–14]; and (iii) failure to respond to therapy with high doses of PPIs is significantly associated with normal pH/MII (partial control of symptoms only in 43.3%) [5], frequent recurrence of heartburn, high scores for 'discomfort of the throat' [13] and abnormal non-acidic refluxes [14].

The studies conducted on baclofen (in its two available molecular forms) present concordant evidence that therapy with this molecule in combination with PPIs is associated with (i) a significant reduction (35.6%–56%) in the number of total reflux episodes in the oesophagus and in the presence of duodeno-gastric reflux [7–8]; (ii) a significant but slight global amelioration of symptoms (especially heartburn), with a suboptimal efficacy on regurgitation and none for burping [7,10,14]; and (iii) a significant reduction in the proximal extent of refluxes (32.2%–57.1%), independently from the presence of a hiatal hernia [8].

Concerning the addition of prokinetics to PPI therapy, (i) prokinetics (domperidone 10 mg tid, mosapride citrate 5 mg tid) are used as an add-on to PPIs (at low or high dose) in coughs due to GORD, in NERD associated with dysmotility-like symptoms and in NERD associated with delayed gastric emptying [11–12,14], with good rates of symptom control (78.7%); (ii) mosapride citrate (5 mg tid) is associated with a significant reduction of reflux symptoms in patients with delayed gastric emptying and with a significant amelioration of dysmotility-like symptoms [11–12]; and (iii) mosapride citrate (5 mg tid) significantly reduces the time for gastric emptying in 83% of patients with delayed gastric emptying [12].

Finally, only one study conducted in Italy [9], which evaluated the use of an oral fixed combination of hyaluronic acid and chondroitin sulphate (HA + CS) for the treatment of PPI-resistant

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