A comparison of different symptomatic reflux esophagitis treatments: A real-world study

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Abstract

Background. Proton pump inhibitors (PPIs) are currently the reference drugs for gastroesophageal reflux disease (GERD), but symptoms often recur after their withdrawal. Moreover, whether prokinetics or barrier drugs used alongside PPIs are more effective remains under debate.

Objectives. The aim of the study was to assess the efficacy of different therapeutic approaches to GERD treatment.

Materials and methods. We enrolled 211 grade A reflux esophagitis patients who consented to participate in this non-randomized, open-label trial. The study consisted of 6 sequentially administered medical treatments for GERD, lasting 2 months, with a 3-week washout period between each drug schedule:
Group A: PPI (esomeprazole 40 mg/day before breakfast);
Group B: mucosal protective drugs (a combination of hyaluronic acid, chondroitin sulfate and poloxamer 407, or a combination of hyaluronic acid, chondroitin sulfate and aluminum, 3 times daily after a meal);
Group C: prokinetics (levosulpiride 25 mg or domperidone 10 mg, 3 times daily before a meal);
Group D: barrier drug (alginate 3 times daily after a meal);
Group E: PPI (esomeprazole 40 mg/day before breakfast) and mucosal protective drugs (a combination of hyaluronic acid, chondroitin sulfate and poloxamer 407, or a combination of hyaluronic acid, chondroitin sulfate and aluminum, before sleep);
Group F: PPI (esomeprazole 40 mg/day before breakfast) and prokinetics (levosulpiride 25 mg or domperidone 10 mg before lunch and dinner).
Symptoms were evaluated using the visual analogue scale (VAS) and global symptomatic score (GSS), as follows: heartburn: 0–3; retrosternal chest pain: 0–3; regurgitation: 0–3.

Results. All but 2 treatments (groups C and D) significantly improved VAS and GSS, with group E showing the most significant GSS improvement. Group C had the highest number of dropouts due to treatment failure and reported more side effects.

Conclusions. Using PPIs and mucosal protective drugs resulted in significant symptom alleviation. However, the administration of prokinetics caused higher dropouts due to treatment failure.

Key words: GERD, PPIs, prokinetics, barrier drugs, protective mucosal devices

Background

Gastroesophageal reflux disease (GERD) is one of the most frequently diagnosed digestive disorders in primary care.[1–4] The prevalence of reflux disease varies depending on the geographical area.[5] The first line of medical treatment for GERD consists of proton pump inhibitors (PPIs).[6–9] However, other drugs are used in GERD therapy, including antiacids pro-kinetics and alginates.[10–15]

Recently, new solutions have been proposed for GERD therapy, such as hyaluronic acid, which promotes re-epithelization of the upper gastrointestinal (GI) mucosa, epithelial cell turnover and ulcer healing.[16–20] Also, chondroitin sulfate, a glycosaminoglycan secreted in the upper stomach, inhibits pepsin-induced gastric and duodenal mucosa damage.[21–24] Using these 2 compounds in addition to PPIs alleviates symptoms in non-erosive reflux disease (NERD) patients.[25] A melt-in-the-mouth tablet containing hyaluronic acid, chondroitin sulfate and aluminum (HYCHSA: 1100 mg) has been administered to subjects with poor or no response to alginates and/or PPIs and induced satisfactory symptom relief.[26] A possible hypothesis was suggested by an experimental model of esophageal mucosa.[27] A multi-center study on NERD patients using a hyaluronic acid–chondroitin sulfate-based bioadhesive formulation, including poloxamer 407, a hydrophilic non-ionic surfactant, showed symptom alleviation.[28]

One major criticism is the variability between the samples, the targets (esophagitis or NERD) and the drugs used. However, studies comparing different drugs in the same sample are lacking.

Objectives

The aim of the study was to assess the efficacy of 6 different therapeutic approaches to GERD using PPIs, pro-kinetics, alginate, and hyaluronic acid combined with chondroitin sulfate, in a unique homogeneous GERD sample (all patients diagnosed with esophagitis A according to the Los Angeles (LA) classification[29]), in which every patient acts as their own control.

Materials and methods

Study design

We enrolled a sample of consecutive patients suffering from typical GERD symptoms (heartburn, retrosternal chest pain and regurgitation) who were under the care of 37 general practitioners in a primary care setting in Northeast Italy. All patients consented to participate in this non-randomized, open-label study of 6 different medical treatments for GERD, lasting for 2 months. Patients were sequentially administered drugs, with a 3-week washout period between every schedule. The drug schedules were designed as follows:

Group A: PPI (esomeprazole 40 mg/day before breakfast);

Group B: mucosal protective drugs (a combination of hyaluronic acid, chondroitin sulfate and poloxamer 407, or a combination of hyaluronic acid, chondroitin sulfate and aluminum, 3 times daily after a meal);

Group C: prokinetics (levosulpiride 25 mg or domperidone 10 mg, 3 times daily before a meal);

Group D: barrier drug (alginate, 3 times daily after a meal);

Group E: PPI (esomeprazole 40 mg/day before breakfast) and mucosal protective drugs (a combination of hyaluronic acid, chondroitin sulfate and poloxamer 407, or a combination of hyaluronic acid, chondroitin sulfate and aluminum, before sleep);

Group F: PPI (esomeprazole 40 mg/day before breakfast) and prokinetics (levosulpiride 25 mg or domperidone 10 mg before lunch and dinner).

Symptoms were evaluated before and after each treatment using the visual analogue scale (VAS) and global symptomatic score (GSS), as follows: heartburn: 0–3; retrosternal chest pain: 0–3; regurgitation: 0–3.

The number of patient dropouts for each group was considered a secondary aim. Figure 1 presents the flowchart of the study. Figure 2 summarizes the details of VAS and GSS.

Statistical analyses

Changes from baseline for VAS and GSS were evaluated with the Wilcoxon test for paired data using median and 1st quartile–3rd quartile (Q1–Q3) intervals. The Mann–Whitney test was employed to compare the differences between drug schedules. A value of $p < 0.05$ was considered statistically significant. All statistical analyses were performed IBM SPSS v. 28.0 software (IBM Corp., Armonk, USA).

Results

A total of 211 patients (98 females and 113 males with a mean age of 51 years, ranging from 27 to 73 years) were enrolled in the study. They underwent upper GI endoscopy and were diagnosed with grade A esophagitis according to the LA classification. The distribution of patients between the 37 general practitioners was homogeneous, with around 6 individuals per physician, ranging from 3 to 9. Figure 2 summarizes the results obtained from assessing symptom scores using VAS and GSS after the 6 drug schedules.

All treatments resulted in significant alleviation in VAS and GSS (Fig. 2). Group E showed the most improvement in VAS ($p = 0.001$) and GSS ($p = 0.028$), though there were no statistically significant differences between schedules for either VAS or GSS ($p = 0.082$ for both). The dropouts and improvements (%) in the different groups are shown in Table 1.

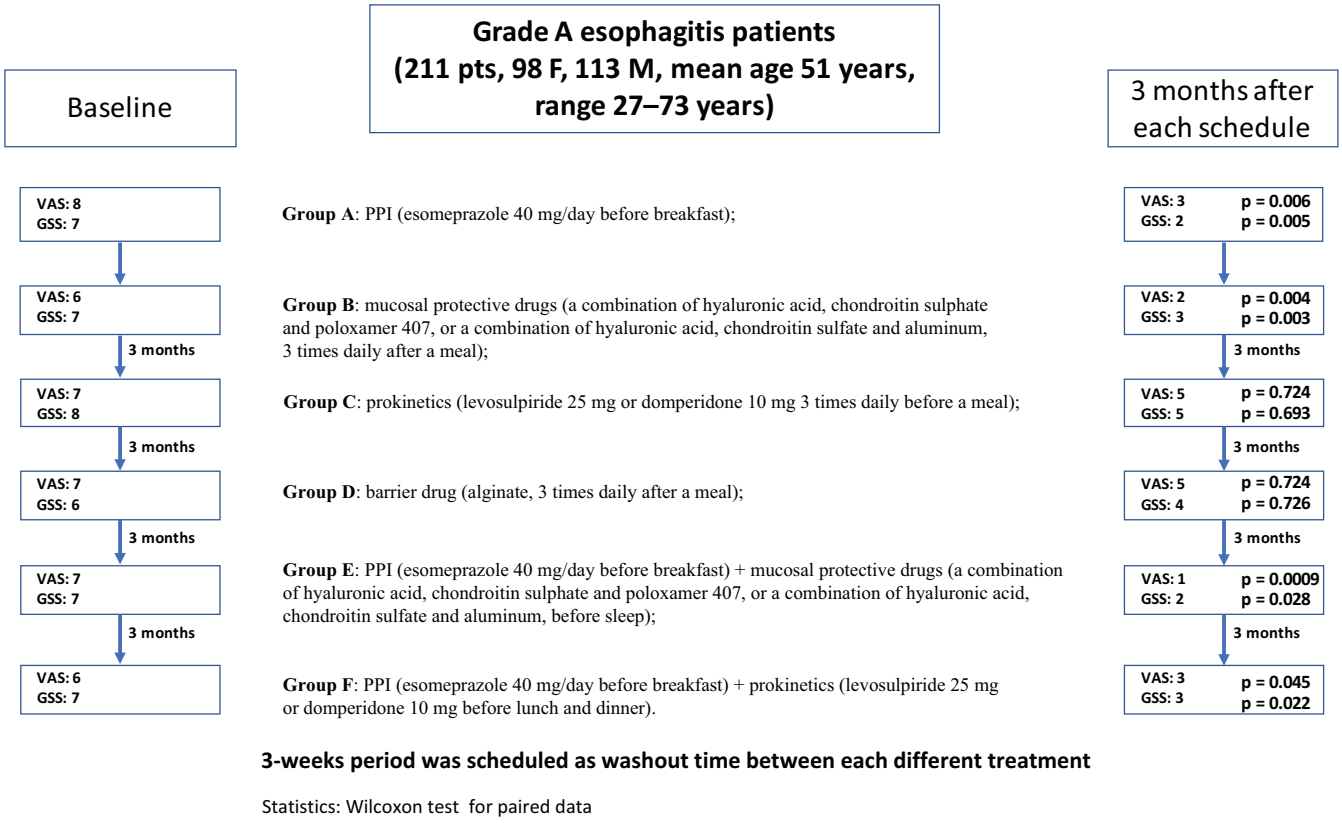

Fig. 1. Study flowchart

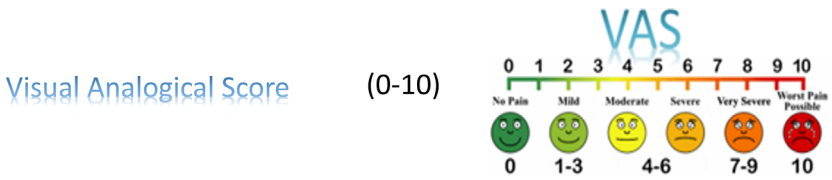

Fig. 2. Assessment of symptoms using the Visual Analogue Scale (VAS) and the Global Symptomatic Score (GSS)

PPI – proton pump inhibitor.

Global Symptomatic Score (0= absent, 1= mild, 2= moderate, 3=severe)

1. Heartburn
2. Regurgitation
3. Retrosternal chest pain

Table 1. Patient population, dropouts and improvements of symptoms according the systemic grouping

Group	Patients, n (F, M)	Dropouts, n	Improvements, n
A	211 (98, 113)	19	86
B	192 (91, 101)	13	81
C	179 (85, 94)	28	54
D	151 (79, 72)	8	69
E	143 (76, 67)	8	94
F	135 (74, 61)	7	90

Group C had the highest number of dropouts due to treatment failure or side effects, while group E had the lowest number of dropouts.

Discussion

Patient compliance with a long-term PPI use in the absence of symptoms is low, and asymptomatic subjects spontaneously withdraw from treatment.[30,31] The prolonged PPI use is thought to impact the intestinal microbiota.[32,33] However, almost 30% of GERD patients show an early relapse of symptoms after withdrawal of PPIs.[9]

Besides PPIs, other drugs and/or agents have been proposed, alone or in combination, to improve GERD symptoms, maintain healing and reduce relapses.[34] Novel products include levosulpiride,[10,11] domperidone,[13] alginate,[12,14,15] and mucosal protective devices (MPDs) (hyaluronic acid, chondroitin sulfate).[25–28] One of the most

cited studies on the association between PPIs and prokinetics demonstrated the superiority of using a second drug with a different mechanism of action.[35] Therefore, to test the real-world efficacy of these different compounds for GERD treatment, we designed a study based on:

a) A non-randomized population of GERD patients who were referred to a primary care clinical center and were under the care of general practitioners for GERD treatment within a well-defined geographical area. As such, 37 general practitioners enrolled between 3 and 9 patients with a confirmed GERD diagnosis;

b) A homogeneous sample of GERD patients, i.e., only subjects with typical symptoms (heartburn, regurgitation and pain), with grade A esophagitis (according to the LA Classification) at endoscopy. This point is important because GERD patients could be classified as NERD or ERD and show a variety of symptoms (such as typical, atypical and extraesophageal), with possible biases when comparing results to clinical trials. Grade A reflux esophagitis is not a conclusive diagnosis of GERD based on the recent Lyon consensus.[36] In the present study, the subjects suffering from typical GERD symptoms (heartburn and regurgitation) and erosions in the esophagus were considered true GERD patients;

c) Every patient acting as their own control. Several factors could influence the response of GERD patients in clinical trials, including individual variability, different risk factors, compliance, and type of reflux (acid, weakly acidic or non-acid). For these reasons, we asked patients to undergo 6 different medical treatments for GERD step-by-step, using the drug schedules described above;

d) Comparisons between single drugs or devices: PPIs compared to alginate compared to prokinetics compared to MPDs, and the association between PPIs (as reference drugs) and prokinetics or MPDs. Recently, important American (American Gastroenterological Association (AGA) and American College of Gastroenterology (ACG)) guidelines suggested modifications in the use of alginates, prokinetics and histamine receptor (H2) antagonists.[37–39] However, we decided to perform the study in a real-world setting that represents the daily life of those receiving GERD therapy;

e) An acceptable duration of therapy for each drug or agent (3 months), separated by a standardized washout period (3 weeks) between different schedules;

f) A validated instrument for assessing symptom modifications, i.e., VAS and GSS, administered before and after each treatment schedule by the same medical team.

The results of the study showed a statistically significant alleviation of symptoms for group A (PPI), group B (MPD) and group E (the association between PPI and MPD). We also considered compliance with different schedules by assessing dropouts motivated by both failures in efficacy and side effects. The highest number of dropouts was observed in group C (prokinetics) due to reduced efficacy and side effects such as hyperprolactinemia and extrapyramidal symptoms.[40–42]

Study strengths and weaknesses

Weaknesses

Open study design

One significant weakness of the study was its open-label design, which lacks blinding and can introduce bias. Since participants and researchers were aware of the administered treatments, there is a potential for placebo effects, experimenter bias and participant expectations to influence the outcomes, making it difficult to establish a clear cause-and-effect relationship.

Lack of randomization

Another weakness was the absence of randomization in participant assignment to the treatment groups. Without random allocation, the study's internal validity is at risk, as confounding variables may unevenly distribute among groups, leading to inaccurate attributions of observed effects to the treatments. This limitation diminishes the study's ability to confidently assert that any observed differences are solely due to the treatments and not to other factors.

Strengths

Overall, the strengths of the study are as follows: 1) each patient being their own control; 2) the homogeneous patient sample, i.e., grade A esophagitis; 3) the adequate treatment period (3 months for every schedule); 4) validated instruments for symptom assessment (VAS and GSS); and 5) the primary care setting.

Longitudinal design

An important strength of the study was its longitudinal design, which allowed for the examination of changes and trends over an extended period of 3 months, separated by a standardized washout period of 3 weeks between different schedules. By collecting data in this manner, the study could better capture the dynamics of the phenomenon under investigation, enhancing the understanding of potential causal relationships.

Large and diverse sample

The study's robustness was bolstered by its large and diverse sample, encompassing a wide range of demographics and backgrounds. Such inclusivity enhanced the generalizability of the findings, enabling us to draw more comprehensive conclusions that apply to a broader population.

Conclusions

In the present study, we demonstrated the possibility of using other drugs and agents besides PPIs to obtain comparable results in the treatment of GERD patients.

In particular, MPDs (hyaluronic acid, chondroitin sulfate, and aluminum or poloxamer 407) seemed to provide better results alone or in combination with PPIs.

The study, performed in a primary care setting with a sample of non-randomized patients, offers a potentially promising approach to the medical treatment of GERD in daily life.

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