Optimization of gastroesophageal reflux disease treatment

O. O. Bondarenko[1], M. A. Bychkov[1], O. A. Bidyuk[2]

[1]*Lviv National Medical University n. a. D. Halytsky, Ukraine*

[2]*Municipal clinical hospital No 5, Lviv, Ukraine*

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In the past, the objective of drug therapy of gastroesophageal disease (GERD) was decreasing the intensity and frequency of symptoms. This was achieved through the use of acid-suppressive drugs, such as antacids, alginates, H2-blockers, and proton pump inhibitors (PPI). Disease management was considered "adequate" when GERD symptoms manifested 1-2 times per week in the course of the treatment. Today, the only therapy option recognized as correct is one that achieves complete lack of GERD symptoms. Accordingly, treatment efficacy is assessed based on the percentage of patients with complete alleviation of the disease symptoms [9].

Treating GERD requires combination therapy and must include non-drug methods as well as drug therapy. Gastroenterologists as well as general practitioners are well aware of a range of non-drug treatment methods. First of all, large meals should be avoided, because higher amounts of stomach contents directly correlate with a higher percentage of patients with gastroesophageal reflux (GER) [3]. The rate of food intake also affects GER symptoms. To reduce the frequency of GER symptoms, patients should increase the amount of protein in their daily diet and decrease the intake of fat, because fat slows down the gastric motor activity, decreases the tone of the lower esophageal sphincter (LES), and increases the incidence and duration of the latter’s spontaneous relaxation. The last meal of the day should be takenno later than three hours before bedtime. Exclude fried foods, chocolate and products containing chocolate, black coffee, strong tea, tomatoes, citrus fruits, peppermint, fresh onion and garlic, and carbonated drinks.

It is also mandatory to abstain from smoking, because nicotine decreases pressure in the LES area and reduces saliva production, resulting in lowered

esophageal clearance, which is one of the pathogenetic factors of the more pronounced injury of the esophageal mucosa (development of the erosive form of the reflux disease). Alcohol has a similar effect, therefore, the patient should be encouraged to avoid overindulging in it. White wine has been proven to have a greater negative impact on the esophageal clearance, which is why patients with GERD are advised to choose red wine over white.

All available methods should be used to combat excessive weight and obesity (daily caloric content correction, sufficient exercise, etc.). Avoid tight-fitting clothes and physical exercises that provoke GER.

Correct position during sleep is highly important. During sleep, the patient's head should be elevated by 15-18 cm [2, 6]; seeing as this is rarely observed in practice, sleeping on the left side can be recommended as an alternative (this position results in lower frequency of spontaneous LES relaxation and lower number of GER symptoms) [6].

If possible, exclude or reduce the use of concomitant GERD-inducing drugs that may decrease the LES tone or impair the motor-evacuation function of the stomach (MEFS). These include methylxanthines (caffeine-containing drugs), anticholinergic agents, calcium channel blockers, peripheral vasodilators, antihistamines, oral contraceptives, tricyclic antidepressants, tranquilizers, cardioselective β1-blockers, β-adrenomimetics, α-adrenoblockers, ACE inhibitors, nitrates, prostaglandin analogues, and narcotic analgesics. Drugs that irritate the esophageal mucosa are also contraindicated (tetracycline, doxycycline, potassium chloride, iron salts, and non-steroid anti-inflammatory drugs) [8].

All of the above measures are carried out in combination with an adequate acid-suppressive therapy, because criteria that satisfy evidentiary medicine requirements exist only pertaining to the excess weight factor. Concerning other factors (limited fat intake, elevated head rest, etc.), we can state that although they carry a certain weight, these lifestyle changes alone are unable to influence the GERD symptoms in most patients.

The most effective option for drug treatment during GERD exacerbation is a "step-down" therapy using PPI that provide for the quickest symptom control, healing of the esophageal mucosa (in patients with erosive reflux disease (ERD)), diagnostic certainty, and lower expenses on treatment and additional consultations [4].

In patients with ERD (also known as reflux esophagitis, according to the Montreal Consensus) in a low-acid or acid-free environment, erosion healing is accompanied with a restoration of the stratified squamous epithelium of the mucosa — something that can only be achieved through the use of PPI. Reflux esophagitis in an acidic environment (even minimal) can result in development of Barrett's syndrome, potentially precancerous state. Therefore, treatment of all patients with GERD requires adequate acid suppression [5].

Despite the high efficacy of PPI, treatment fails to reach the desired result in a number of patients. Those are cases of insufficient PPI efficacy or refractory GERD. More frequently, complete alleviation of symptoms is not achieved in patients with non-erosive reflux disease (NERD), severe esophageal mucosa damage (grade C and D according to the Los Angeles classification), extraesophageal syndromes, or GERD complications [2]. Other reasons for insufficient therapy efficacy include low compliance, PPI bioavailability, weakened MEFS (observed in 40% of patients with this pathology), biliary reflux, H. pylori infections (subject to discussion; however, according to the Maastricht Consensus, anti-helicobacter therapy is necessary, primarily for cancer prevention), nocturnal acid breakthroughs, and esophageal mucosa hypersensitivity. Among other reasons that merit attention are the use of low-quality generic medicines, use of PPI after their expiration date or ones that were inappropriately stored, and incorrect diagnosis (the possibility of drug-induced esophagitis, Zollinger-Ellison syndrome, achalasia, gastroparesis, functional hurtburn, etc., should be excluded).

We believe that in order to optimize treatment of patients with GERD, quickly eliminate clinical symptoms of the disease, increase the healing rate of the esophageal mucosa in patients with ERD, and, possibly, prevent recurrence and prolong the remission period, the standardized drug arsenal should be supplemented with

reparative drugs with a defined and pathogenetically substantiated mechanism of action. On the Ukrainian pharmaceutical market, such reparative drugs include Doctovit®, which contains non-specific (universal) constructive metabolism vitamins U and B_5.

Vitamin U (methylmethionine) is a donor of methyl groups required for construction and active division of epithelial cells. It deactivates histamine by methylating it and converting it into the inactive form, therefore contributing to gastric secretion normalization, accelerating the healing of erosions and ulcers, and providing an additional anesthetic effect. Provitamin B_5 (dexpanthenol) facilitates production of energy required for cell division and restoration, and normalizes the secretory function and motility of the gastrointestinal tract (by stimulating peristalsis through acetylcholine synthesis activation). Combination use of the two vitamins creates a synergy that stimulates regeneration processes in the mucosa by supplying the cells with energy and constructive material, accelerates division of the mucosal epithelium stem cells, and improves differentiation and functioning of the newly created cells.

The feasibility of using Doctovit® for treatment of GERD has been demonstrated in a number of trials and remains the subject of active research [1].

The purpose of this study was assessing the efficacy of including Doctovit® in the standard treatment regimen for erosive GERD.

Materials and methods

The study was conducted on the basis of the gastroenterological and outpatient departments of the LvivMunicipal City Clinical Hospital N5. Patient screening took place over the course of 6 months and included thorough physical, clinical, laboratory, and instrumental examination to confirm the GERD diagnosis. The study inclusion criteria were the main GERD symptoms and endoscopic confirmation of the diagnosis. Exclusion criteria included diabetes mellitus, concomitant somatic pathology in the decompensation stage, oncologic conditions, helicobacter infections, and alcohol abuse. Before the start of the study, all patients signed an informed consent form.

A total of 48 patients were randomized, aged 23 to 59, including 32 males and 16 females. Based on the results of the clinical and endoscopic examination, patients were evenly distributed into two groups. The active group (n=24) received the following treatment regimen: 40 mg pantoprazole twice daily, plus the reparative drug Doctovit®, 1 tablet thrice daily. The control group (n=24) received 40 mg pantoprazole twice daily, as monotherapy. The duration of both treatment regimens was 8 weeks.

The dynamics of clinical presentation in both groups before and after treatment was analyzed using the new GERD-Q questionnaire (Table 1). We used the frequency of GERD symptom presentation, assessed on a four-point scale (lack of symptoms; symptoms occurring on 1 day of the week; 2-3 days of the week; or 4-7 days of the week). This criterion conformed to the Montreal definition of GERD [10]. The patients filled the questionnaire personally, over the course of 5 minutes. The questionnaire contained six parameters: heartburn and regurgitation, pointing to the GERD diagnosis (GERD characteristics according to the Montreal definition); nausea and epigastric pain — symptoms that challenge the GERD diagnosis; sleep disruptions; and use of other medications [7].

Table 1

GERD-Q Questionnaire

Question	0 days	1 day	2-3 days	4-7 days
How often have you felt heartburn?	0	1	2	3
How often have you felt regurgitation of food from your stomach into throat or mouth?	0	1	2	3
How often have you felt pain in the top part of the abdomen?	3	2	1	0
How often have you felt nausea?	3	2	1	0
How often has your sleep been disrupted by heartburn or regurgitation?	0	1	2	3
How often do you take medications to manage heartburn or regurgitation?	0	1	2	3

Each of the 6 items of the resulting scale was graded using a four-point scale (0 to 3). For symptoms typical for GERD, grade 0 indicated lack of the symptom, while grade 3, occurrence of the symptom during 4-7 days of the week. For symptoms not typical for GERD, grading was the opposite, with 3 indicating complete lack of the symptom, and 0, its occurrence during 4-7 days of the week. Maximum possible total count on the GERD-Q scale is 18. This questionnaire is also valuable because it allows determining the impact of the symptoms on the patients' quality of life, which can help in selecting the treatment tactic. Patients whoscored 3 and higher (out of a maximum of 6) on questions about GERD-related sleep disruptions and the need for additional medication noted a negative impact of the disease on their general well-being; in general, such patients scored the highest on the questionnaire. Furthermore, analysis of the results showed a direct correlation between the frequency of heartburn symptoms and the total score.

Each patient also kept a diary, where they noted the frequency and occurrence times of their symptoms. That information was processed using the criteria listed in Table 2, and then further analyzed.

Table 2

Patient assessment of heartburn

Parameter	Options	Score
Frequency	Absent	0
	Less than 2 times per week	1
	2-6 times per week	2
	Every day	3
Time of occurrence	Absent	0
	Only during the day	1
	Only at night	1
	During the day and night	2

The data was processed using the methods of variance statistics; the difference reliability of mean values was assessed using Student's t test ($p<0.05$). The results were processedusing a personal computer and SPSS Statistics 17.0 software.

Results and discussion

In all patients included in the study, GERD was recurring in 100% cases. Average length of ERD, based on anamnestic data, was 3.4 ± 0.65 years.

Primary testing of the patients using the GERD-Q questionnaire confirmed the equivalence and comparability of the study groups, because the gastroenterological symptoms in the two study groups before treatment were similar and typical for GERD. Clinical presentation was dominated by reflux syndrome (heartburn, regurgitation), without a reliable difference between the groups ($p>0.05$). Results based on the GERD-Q questionnaire after treatment indicated a considerable improvement in the patients' condition. Both groups displayed a positive dynamic and a reliable decrease ($p<0.05$) or complete alleviation of the reflux syndrome, nearly complete lack of pain, and considerable improvement of the quality of sleep due to the minimization or complete alleviation of night-time GERD symptoms. However, results of the active group indicated higher efficacy.

At the time of enrollment in the study, all patients had complaints of heartburn that considerably impaired their quality of life. Average frequency of this symptom was 4.21±0.67 days/week in the active group and 4.35±0,71 days/week in the control group ($p>0.05$). In both study groups, we observed a daily downward dynamic of the heartburn, as a result of therapy. Effective heartburn control was achieved on day 5±1.3 in 21 (87.5%) patients of the active group, while results in the control group were reliably worse, at 8±1.1 days in 19 (79%) patients ($p<0.05$). Additionally, a comparative analysis of additional heartburn parameters (duration and intensity) showed a reliable advantage of the combination therapy used in the active group over the monotherapy used in the control group (Table 3, Fig. 1-2).

Table 3

Heartburn parameters before and after treatment

Parameter	Active group (Doctovit®)		Control group	
	Before treatment (n=24)	After treatment (n=23)	Before treatment (n=24)	After treatment (n=21)

Frequency, days/week	4.21±0.67	0.08±0.02*	4.35±0.71	0.79±0.29*
Time of occurrence, points	1.94±0.52	0.58±0.15*	1.89±0.46	0.61±0.17

Note: *p<0.05 — reliable difference between groups, after treatment.

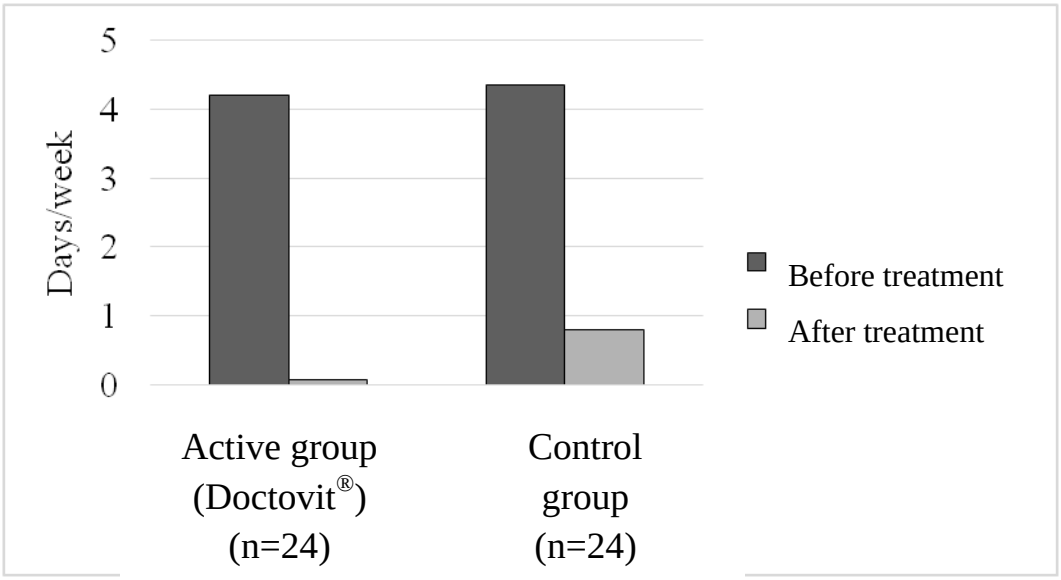

Fig. 1. Comparative analysis of heartburn frequency in the study groups (days/week).

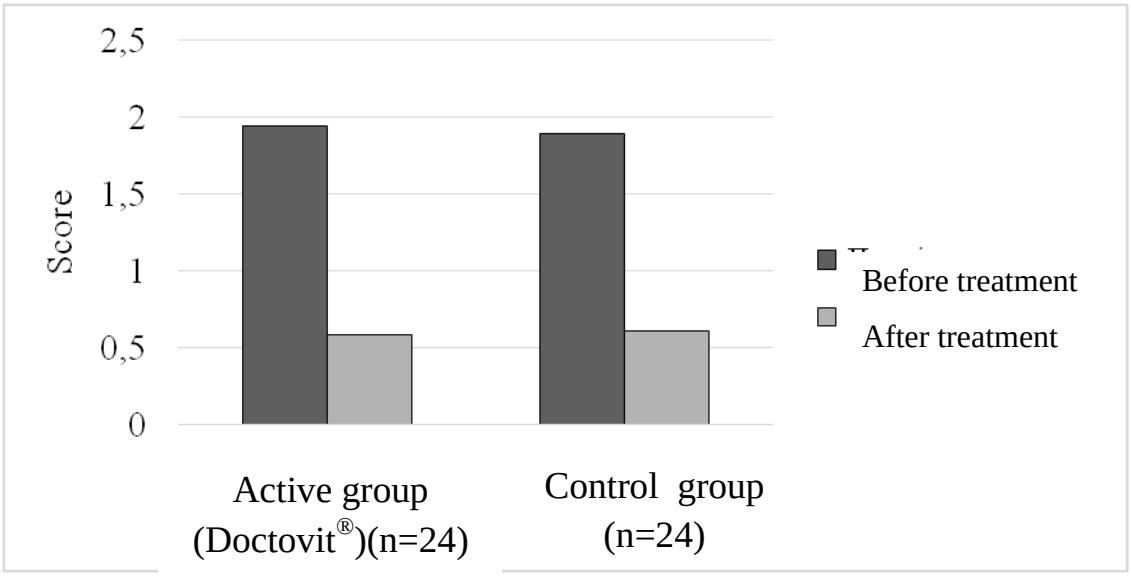

Fig. 2. Comparative analysis of heartburn duration in the study groups (score).

Before the start of treatment, reflux esophagitis was found in all randomized patients. Endoscopic examination results of the patients, using the Los Angeles

severity classification (1996), before treatment and at week 8 of treatment are presented in Table 3 and Figure 3.

Table 4

Endoscopic examination results before and after treatment

Severity	Active group (Doctovit®)		Control group	
	Before treatment (n=24, %)	After treatment (n=23, %)	Before treatment (n=24, %)	After treatment (n=21, %)
Grade A	17 (71%)	0	16 (67%)	1 (5%)
Grade B	4 (17%)	1 (4%)	6 (25%)	2 (9,5%)
Grade C	3 (12%)	1 (4%)	2 (8%)	2 (9,5%)
No pathology	0	21 (92%)	0	16 (76%)

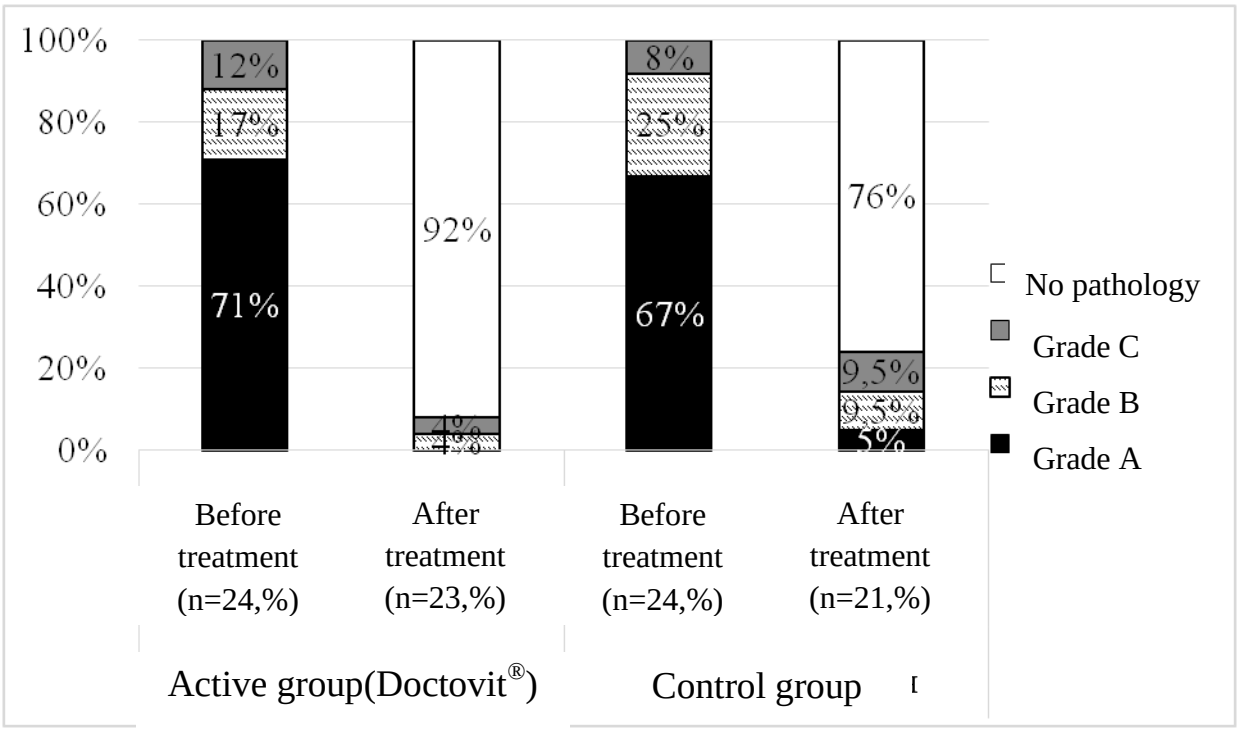

Fig. 3. Comparative analysis of the endoscopy results in the two study group, by severity level (%).

Conclusions

Combination treatment of erosive GERD with pantoprazole and Doctovit® has a higher efficacy compared to PPI monotherapy. Simultaneous administration of

pantoprazole and Doctovit® results in a faster decrease in the intensity of GERD clinical symptoms, particularly, heartburn and associated dyspeptic symptoms. Owing to the reparative properties of Doctovit®, endoscopic ERD symptoms were alleviated in the majority of the active group patients (92%), while only 76% patients in the control group displayed lack of changes in the esophageal mucosa.

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[1]*Lviv National Medical University n. a. D. Halytsky, Ukraine*

[2]*Municipal clinical hospital No 5, Lviv, Ukraine*

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The **aim** was to investigate the effectiveness of the inclusion of Doktovit® preparation into a standard treatment of GERD erosive form.

Materials and methods. The study involved 48 patients GERD aged from 23 to 59, including 32 men and 16 women. The criteria for inclusion in the study were presence of the main symptoms of GERD and endoscopic confirmation of the diagnosis. According to the results of clinical and endoscopic examination, patients were divided into two groups. The main group of 24 patients was treated as follows: pantoprazole 40 mg 2 times a day and reparant Doktovit® 1 tablet 3 times a day. The comparison group of 24 patients received monotherapy with pantoprazole 40 mg twice a day. The duration of both regimens was 8 weeks. The dynamics of clinical manifestations before and after treatment in both groups was analyzed using a new questionnaire GERD-Q. Statistical analysis of the results of research was conducted on the computer with the use of software SPSS Statistics 17.0. Differences were considered probable upon the level of significance $p<0.05$.

Results. The average length of a history of erosive GERD form was 3.4±0.65 years. Reflux syndrome (heartburn, regurgitation) dominated in the clinical picture of disease before treatment in the absence of significant differences between two groups ($p>0.05$). The results of the questionnaire GERD-Q after treatment showed a significant improvement of the patients' condition. Both groups revealed a positive trend and showed a significant decrease ($p<0.05$) or even absence of the intensity of reflux syndrome, as compared with initial indices, almost absent pain syndrome, significantly improved sleep quality by minimizing or absence of nocturnal GERD manifestations. However, better results were obtained in the main group.

Conclusions. It was stated that during treatment of erosive GERD by combination of pantoprazole and Doktovit® faster intensity regression of clinical symptoms of GERD, especially heartburn and related dyspeptic symptoms of disease, was observed, and we also could remove endoscopic features of GERD in the majority of patients of the main group.