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# The Effect of Combined Therapy with a Proton Pump Inhibitor and Rebamipide on the Clinical Course and Morphofunctional Changes of the Esophageal Mucosa in Patients with Non-Erosive Reflux Disease

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**Aim:** to evaluate the effect of combined therapy with a proton pump inhibitor and rebamipide on clinical manifestations and morphofunctional changes in the esophageal mucosa in patients with non-erosive reflux disease.
**Materials and methods.** The study included 39 patients with non-erosive reflux disease randomized into the main group (omeprazole 20 mg/day + rebamipide 300 mg/day) and the comparison group (omeprazole 20 mg/day). The duration of treatment was 4 weeks. Histological examination of esophageal mucosa biopsies (hematoxylin-eosin staining), morphometry of intercellular spaces, and immunohistochemical assessment of tight junction protein expression (claudin-1, -4, occludin) were performed. Symptoms were evaluated using the Likert scale.
**Results.** The combined therapy group showed significant reductions in heartburn severity ($p < 0.001$) and belching ($p = 0.004$), with absent/mild symptoms in 63.7 and 72.4 % of patients, respectively. In the proton pump inhibitor monotherapy group, 53 % of patients retained moderate or severe heartburn. Morphologically, the combined group demonstrated reduced eosinophilic infiltration ($p = 0.030$). Occludin expression increased in both groups but reached statistical significance only in the monotherapy group ($p = 0.046$).
**Conclusion.** The combined therapy with proton pump inhibitor and rebamipide improves symptoms and morphological outcomes in non-erosive reflux disease. Increased occludin expression suggests restored integrity of intercellular junctions. Further studies with larger cohorts and extended follow-up are needed to confirm these findings.
**Keywords:** proton pump inhibitors, non-erosive reflux disease, epithelial protective therapy, tight junction proteins
**Conflict of interest:** the authors declare no conflict of interest.

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## Влияние комплексной терапии ингибитором протонной помпы и ребамипидом на клиническое течение и морфофункциональные изменения слизистой оболочки пищевода у пациентов с неэрозивной рефлюксной болезнью

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**Цель исследования:** оценить влияние комплексной терапии (ингибитор протонной помпы + ребамипид) на морфофункциональные изменения слизистой оболочки пищевода и клинические проявления у пациентов с неэрозивной рефлюксной болезнью.
**Материалы и методы.** В исследование были включены 39 пациентов с неэрозивной рефлюксной болезнью, которые были рандомизированы на две группы: основную, получавшую комплексную терапию ингибитором протонной помпы омепразолом (20 мг в сутки) в сочетании с ребамипидом (300 мг в сутки); и группу сравнения, которая получала монотерапию омепразолом (20 мг в сутки). Продолжительность курса терапии составила 4 недели. Все методы обследования проводились до и после лечения. Для оценки морфофункци-

ональных показателей слизистой оболочки пищевода было проведено стандартное гистологическое исследование биоптатов слизистой оболочки пищевода путем окраски гематоксилином и эозином, межклеточные пространства оценивались при помощи морфометрии. Изменения плотных контактов оценивались по экспрессии белков плотных контактов — клаудина-1, -4 и окклюдина методом иммуногистохимии. Наличие и выраженность симптомов оценивались с применением балльной шкалы Лайкерта.

**Результаты.** В группе комплексной терапии после лечения отмечалось снижение выраженности изжоги ($p < 0,001$) и отрыжки ($p = 0,004$). Симптомы изжоги отсутствовали или были слабо выражены у 63,7 % пациентов, отрыжки — у 72,4 %. В группе сравнения было выявлено статистически значимое уменьшение изжоги ($p < 0,001$), однако у 53 % пациентов сохранялась умеренная или значительно выраженная изжога. При анализе морфологических изменений в слизистой оболочке пищевода в группе комбинированной терапии после лечения отмечалось значительное снижение эозинофильной инфильтрации ($p = 0,030$). При оценке экспрессии белков плотных контактов после лечения отмечено повышение экспрессии окклюдина в обеих группах, имеющее достоверное отличие в группе монотерапии ингибитором протонной помпы ($p = 0,046$).

**Заключение.** Применение комбинированной терапии в составе ингибитора протонной помпы и ребамипида является безопасным лечебным подходом, способным приводить к значительному улучшению симптомов у пациентов с неэрозивной рефлюксной болезнью. Комплексная терапия привела к значительному уменьшению эозинофильной инфильтрации слизистой оболочки пищевода. В обеих группах выявлено повышение экспрессии окклюдина, отвечающего за целостность межклеточных контактов. Для окончательного подтверждения клинической эффективности комбинированной терапии необходимы дополнительные клинические исследования с увеличенной выборкой и длительным периодом наблюдения.

**Конфликт интересов:** авторы заявляют об отсутствии конфликта интересов.

**Ключевые слова:** ингибиторы протонной помпы, неэрозивная рефлюксная болезнь, эпителиопротективная терапия, белки плотных контактов

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## Introduction

Gastroesophageal reflux disease (GERD) is a chronic condition characterized by a primary impairment of the motor-evacuation function of the upper gastrointestinal tract, dysfunction of the esophagogastric junction, and the presence of pathological gastroesophageal reflux [1]. Modern data indicate that the global prevalence of GERD reaches 13.98 % [2], with the majority of cases classified as the non-erosive form of the disease. This form is marked by symptoms that significantly reduce quality of life, despite the absence of esophageal erosions upon withdrawal of antisecretory therapy [3]. Beyond its high prevalence, the clinical relevance of GERD is further underscored by the increasing incidence of cases refractory to antisecretory therapy [4, 5].

The mucosal-epithelial barrier serves as the primary protective mechanism of the esophageal mucosa (EM) against the damaging effects of refluxate. A key component of this barrier is the tight junctions located in the apical region of the cytoplasmic membrane. These junctions provide mechanical adhesion between cells, regulate substance transport through intercellular spaces, and maintain the integrity and permeability of the mucosa. Tight junction proteins include claudins, occludin, adhesion molecules, and the *zonula occludens* protein [6, 7]. Studies have demonstrated that pathological refluxate exposure to the esophageal mucosa induces dilation of intercellular spaces and reduced expression of tight junction proteins on epithelial cell membranes. These alterations increase mucosal permeability, enabling gastric contents to penetrate deeper esophageal layers. This process drives chronic inflammation and activates afferent nociceptors, leading to symptom manifestation [8–14]. Thus, heightened epithelial permeability underlies disease progression and symptom development in GERD patients [15].

Rebamipide, an epithelial protective agent, is widely used to treat and prevent gastric mucosal damage caused by nonsteroidal anti-inflammatory drugs and *Helicobacter pylori* infection [16, 17]. The primary mechanisms of rebamipide's anti-inflammatory and cytoprotective effects include stimulation of prostaglandin synthesis via cyclooxygenase-2 expression, induction of mucus secretion, neutralization of free radicals, inhibition of neutrophil activation, and suppression of cytokine production by leukocytes and gastric epithelial

cells [18–21]. Several studies have focused on rebamipide's mucosal protective effects in the esophageal epithelium. In a study by T.G. Gweon et al. [8], the impact of combined therapy with a proton pump inhibitor (PPI) and rebamipide on tight junction protein expression in the esophageal mucosa was investigated in rats with induced GERD. Results demonstrated that claudin-3 and claudin-4 expression levels were significantly higher in the group receiving PPI plus rebamipide compared to both the PPI-only group and the control group. In a study by S.M. Yoon et al. [22], 139 patients with GERD, including 50 individuals with non-erosive reflux disease (NERD), were divided into two groups. One group received combined therapy with a PPI and rebamipide for 8 weeks, while the other received a PPI and placebo. The results showed that NERD patients treated with the combination therapy exhibited a statistically significant reduction in lymphocyte count and a decrease in the size of intercellular spaces within the esophageal epithelium compared to the PPI-plus-placebo group. These findings suggest that enhancing the barrier function of epithelial cells through the regulation of tight junction protein expression and localization represents a potential therapeutic target for achieving long-term remission in NERD patients.

Combined epithelial-protective and acid-suppressive therapy offers a promising approach to improving esophageal mucosal barrier integrity, alleviating symptoms, and promoting sustained remission by targeting key pathophysiological mechanisms of the disease.

## Materials and methods

### *Study Design*

This randomized, prospective, single-center study was conducted at the V.Kh. Vasilenko Clinic of Propaedeutics of Internal Diseases, Gastroenterology, and Hepatology, I.M. Sechenov First Moscow State Medical University (Sechenov University). Participants were recruited from patients aged 18 to 75 years with a confirmed diagnosis of non-erosive reflux disease (NERD). Diagnosis was verified using esophagogastroduodenoscopy (EGD) and 24-hour pH-impedance monitoring.

Exclusion criteria: age < 18 years; pregnancy; complicated GERD (e.g., erosions, strictures, Barrett's esophagus); concurrent esophageal disorders (eosinophilic esophagitis, infectious esophagitis, achalasia, cardiospasm, scleroderma); severe comorbidities (chronic kidney disease of stages 4–5; congestive heart failure > class III according to NYHA (New York Heart Association); chronic obstructive pulmonary disease > stage 3 according to GOLD (Global Initiative for Chronic Obstructive Lung Disease); psychiatric disorders); malignancy. Reasons for post-enrollment withdrawal: voluntary withdrawal of signed informed consent; pregnancy; adverse events classified as definite, probable, or possibly related to the study drug; requirement for additional therapies affecting efficacy parameters; protocol violations deemed significant by the investigator to the study outcomes.

Patients were randomized using a simple randomization method (via a random number generator) into the main group and the control group. The patients in the main group received combination therapy with omeprazole 20 mg (OMEZ®; Dr. Reddy's Laboratories Ltd., India) and rebamipide 300 mg (Rebagit®; PRO.MED.CS Praha, a.s., Czech Republic) daily for 4 weeks. The control group received omeprazole monotherapy 20 mg (OMEZ®; Dr. Reddy's Laboratories Ltd., India) daily for 4 weeks.

To evaluate the impact of therapy, EGD with targeted biopsy sampling from the distal esophageal mucosa (2 cm above the gastroesophageal junction) was performed in both groups before and after treatment. A four-quadrant biopsy (anterior, posterior, right, and left esophageal walls) was conducted. Biopsy specimens were fixed in 10 % neutral buffered formalin and embedded in paraffin. Serial paraffin sections (minimum 22 serial sections per block) with a thickness of 4–5 microns were prepared. Sections were mounted on adhesive-coated glass slides. Microscopic lesions were assessed in the biopsy specimen showing the most pronounced inflammatory changes, based on the standardized histopathological criteria outlined in "The Esohisto Project" – a protocol for evaluating microscopic esophageal mucosal damage in GERD patients, published in 2009 and updated in 2011 by an international independent panel of pathologists [23, 24].

Immunohistochemical (IHC) reactions were performed on deparaffinized sections (4–5 μm thick) mounted on APES-coated glass slides. The following primary monoclonal antibodies were used: Claudin-1, Claudin-4, Occludin (Servicebio Technology, Ltd., Belgium). Antigen-antibody binding was detected using

horseradish peroxidase with hydrogen peroxide as a substrate and 3,3'-diaminobenzidine as the chromogen. Protein expression was evaluated using a standardized 6-point semi-quantitative scoring system based on the percentage of stained nuclei: 2 points — ≤ 20 % stained cells; 4 points — 20–40 % stained cells; 6 points — > 40 % stained cells. Tight junction protein localization was specifically assessed via membrane staining patterns.

Symptom evaluation was conducted using a 5-point Likert scale to standardize the assessment of patient-reported complaints. Participants were asked to rate the frequency and severity of each GERD symptom (heartburn, chest pain, regurgitation, belching) on a scale from 1 to 5: 1 point — symptom absent; 2 points — mild symptom (easily ignored unless attention is directed); 3 points — moderate symptom; 4 points — severe symptom; 5 points — constant symptom, disrupting daily activities.

Written informed consent was obtained from all participants prior to enrollment. The study protocol was approved by the Local Ethics Committee of Sechenov University (Protocol No. 03-23, dated February 16, 2023).

***Statistical analysis***

Statistical analysis was performed using StatTech v. 4.7.2 software (developed by LLC "Stattech", Russia). Quantitative variables were assessed for normality using the Shapiro — Wilk

***Table 1.*** Baseline symptom severity distribution between groups according to Likert scale

***Таблица 1.*** Исходные характеристики клинической картины до лечения согласно опроснику Лайкерта

| **Symptom** ***Показатели*** | **Category** ***Категории*** | **Therapy** ***Терапия*** | | ***p*** |
|---|---|---|---|---|
| | | **Control group** ***Группа сравнения*** | **Main group** ***Основная группа*** | |
| Heartburn *Изжога* | Absent *Отсутствие* | 1 (5.9 %) | 0 (0.0 %) | 0.351 |
| | Mild *Слабовыраженный* | 0 (0.0 %) | 3 (13.6 %) | |
| | Moderate *Умеренно выраженный* | 4 (23.5 %) | 5 (22.7 %) | |
| | Severe *Значительно выраженный* | 8 (47.1 %) | 7 (31.8 %) | |
| | Constant *Постоянный* | 4 (23.5 %) | 7 (31.8 %) | |
| Regurgitation *Регургитация* | Absent *Отсутствие* | 12 (70.6 %) | 17 (77.3 %) | 0.812 |
| | Mild *Слабовыраженный* | 1 (5.9 %) | 1 (4.5 %) | |
| | Moderate *Умеренно выраженный* | 2 (11.8 %) | 1 (4.5 %) | |
| | Severe *Значительно выраженный* | 2 (11.8 %) | 2 (9.1 %) | |
| | Constant *Постоянный* | 0 (0.0 %) | 1 (4.5 %) | |
| Belching *Отрыжка* | Absent *Отсутствие* | 10 (58.8 %) | 6 (27.3 %) | 0.351 |
| | Mild *Слабовыраженный* | 2 (11.8 %) | 4 (18.2 %) | |
| | Moderate *Умеренно выраженный* | 4 (23.5 %) | 8 (36.4 %) | |
| | Severe *Значительно выраженный* | 0 (0.0 %) | 1 (4.5 %) | |
| | Constant *Постоянный* | 1 (5.9 %) | 3 (13.6 %) | |
| Chest pain *Боль за грудиной* | Absent *Отсутствие* | 17 (100.0 %) | 21 (95.5 %) | 1.000 |
| | Mild *Слабовыраженный* | 0 (0.0 %) | 1 (4.5 %) | |

test. Normally distributed data were described using arithmetic means (*M*) and standard deviations (*SD*). Representativeness of means was reported as 95 % confidence intervals (95% CI). Non-normally distributed data were described using median (*Me*) and interquartile ranges (*Q*1–*Q*3). Categorical variables were summarized as absolute values and percentages. Independent groups: for non-normally distributed quantitative variables: Mann — Whitney *U* test; for normally distributed quantitative variables: unpaired Student's *t*-test. Paired groups: for non-normally distributed quantitative variables: Wilcoxon signed-rank test; for normally distributed quantitative variables: paired Student's *t*-test. Binary variables in paired groups: McNemar's test. Statistical significance was defined as $p < 0.05$.

## Results

Among the 39 patients with non-erosive reflux disease (NERD) included in the study, 30.8 % were women ($n = 12$) and 69.2 % were men ($n = 27$). The mean age of the patients was 40.21 ± 12.47 years. All participants were randomized into two groups — main and control — using a simple randomization method. The main group comprised 22 patients who received combined therapy with a proton pump inhibitor (PPI) and rebamipide for 4 weeks, while the control group included 17 patients receiving PPI monotherapy for the same duration. The median duration of symptoms among participants was 48 (12; 99) months. Table 1 presents the baseline clinical characteristics of both groups assessed via the Likert scale questionnaire. The baseline parameters were homogeneous, with no statistically significant differences between the groups. Similarly, comparative analysis of histological and immunohistochemical parameters before treatment revealed no significant intergroup differences ($p > 0.05$). No adverse events were recorded during the study period. Statistical analysis was performed using the per-protocol approach.

### *Assessment of symptom dynamics during treatment*

According to the Likert scale questionnaire, analysis of the "heartburn" symptom revealed a statistically significant improvement in both groups after treatment completion ($p < 0.001$). However, no statistically significant differences were observed between the groups when

***Table 2.*** Heartburn severity grading at baseline and post-treatment according to Likert scale
***Таблица 2.*** Выраженность симптома «изжога» на фоне лечения согласно опроснику Лайкерта

| **Therapy** ***Терапия*** | **Symptom severity grade** ***Градация симптома*** | **Observation time points** ***Этапы наблюдения*** | | ***p*** |
|---|---|---|---|---|
| | | **Before treatment** ***До лечения*** | **After treatment** ***После лечения*** | |
| Control group *Группа сравнения* | Absent *Отсутствие* | 1 (5.9 %) | 3 (17.6 %) | <0.001* |
| | Mild *Слабовыраженный* | 0 (0.0 %) | 5 (29.4 %) | |
| | Moderate *Умеренно выраженный* | 4 (23.5 %) | 7 (41.2 %) | |
| | Severe *Значительно выраженный* | 8 (47.1 %) | 2 (11.8 %) | |
| | Constant *Постоянный* | 4 (23.5 %) | 0 (0.0 %) | |
| Main group *Основная группа* | Absent *Отсутствие* | 0 (0.0 %) | 6 (27.3 %) | <0.001* |
| | Mild *Слабовыраженный* | 3 (13.6 %) | 8 (36.4 %) | |
| | Moderate *Умеренно выраженный* | 5 (22.7 %) | 6 (27.3 %) | |
| | Severe *Значительно выраженный* | 7 (31.8 %) | 2 (9.1 %) | |
| | Constant *Постоянный* | 7 (31.8 %) | 0 (0.0 %) | |
| *p* | | 0.351 | 0.766 | – |

***Note:*** ** — differences are significant ($p < 0.05$).*
***Примечание:*** ** — различия показателей статистически значимы ($p < 0,05$).*

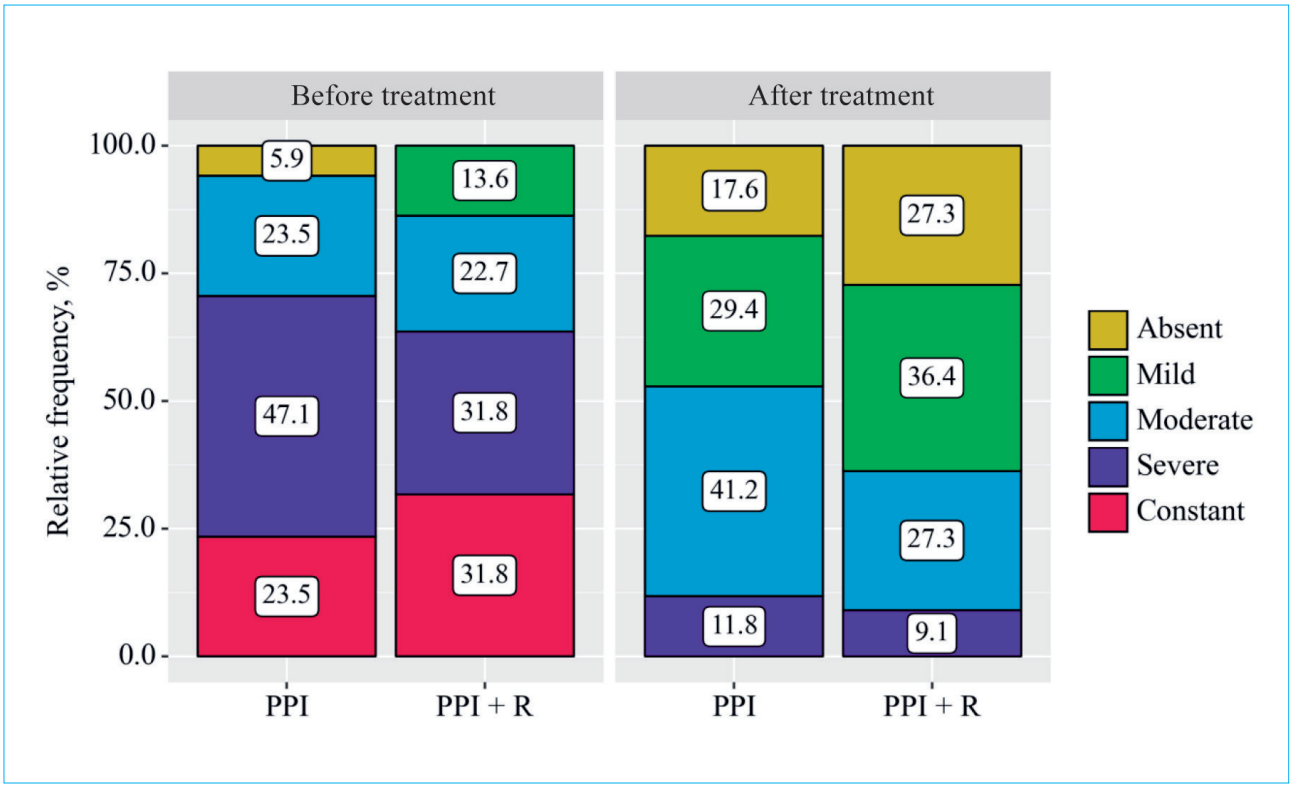


***Figure 1.*** Heartburn severity grading at baseline and post-treatment according to Likert scale

***Рисунок 1.*** Выраженность симптома «изжога» на фоне лечения согласно опроснику Лайкерта

comparing treatment outcomes ($p$ = 0.766) (Table 2). At the end of treatment: in the main group, 63.7 % of patients reported absent or mild heartburn, with complete clinical remission achieved in 27.3 %. In the control group (PPI monotherapy), 53 % of patients continued to experience moderate or severe heartburn, while complete clinical remission was observed in 17.6 % (Fig. 1).

For the "regurgitation" symptom, no statistically significant changes were noted before and after treatment in either group ($p$ = 0.102). In the control group, no participants reported chest pain; thus, statistical analysis for this symptom was not performed. Analysis of the "belching" symptom demonstrated significant improvement in the main group during therapy ($p$ = 0.004) (Table 3), with 72.7 % of patients reporting symptom improvement or complete resolution post-treatment (Fig. 2).

### *Assessment of histological changes during treatment*

The morphological features of esophagitis in patients with NERD were primarily characterized by moderately pronounced dilation of intercellular spaces and spongiosis. Additionally, elongation of vascular-stromal papillae (50–75 %) and moderate hyperemia of lamina propria vessels were observed in the majority of patients (Table 4). No atrophic changes in the esophageal mucosa were detected in any participant. Following treatment, no statistically significant changes were observed in parameters such as intercellular space width, leukocytic infiltration, mononuclear infiltration, basal layer hyperplasia, spongiosis, or elongation of vascular-stromal papillae in either group ($p > 0.05$). However, the main group exhibited a significant reduction in eosinophilic infiltration of the esophageal mucosa after treatment ($p$ = 0.030) (Table 5).

### *Assessment of tight junction protein expression dynamics*

According to IHC analysis, in the main group, 40 % of patients exhibited membrane claudin-1 expression in epithelial cells exceeding 40 % stained cell post-treatment, representing a two-fold increase from baseline (Fig. 3). However, these changes did not reach statistical significance ($p$ = 0.389). The control group (PPI monotherapy) showed similar trends in claudin-1 expression dynamics, but no statistically significant differences were observed before and after therapy ($p$ = 0.465). For claudin-4, 100 %

***Таблица 3.*** Выраженность симптома «отрыжка» на фоне лечения согласно опроснику Лайкерта
***Table 3.*** Belching severity grading at baseline and post-treatment according to Likert scale

| **Therapy** ***Терапия*** | **Symptom severity grade** ***Градация симптома*** | **Observation time points** ***Этапы наблюдения*** | | ***p*** |
|---|---|---|---|---|
| | | **Before treatment** ***До лечения*** | **After treatment** ***После лечения*** | |
| Control group *Группа сравнения* | Absent *Отсутствие* | 10 (58.8 %) | 12 (70.6 %) | 0.129 |
| | Mild *Слабовыраженный* | 2 (11.8 %) | 1 (5.9 %) | |
| | Moderate *Умеренно выраженный* | 4 (23.5 %) | 4 (23.5 %) | |
| | Severe *Значительно выраженный* | 0 (0.0 %) | 0 (0.0 %) | |
| | Constant *Постоянный* | 1 (5.9 %) | 0 (0.0 %) | |
| Main group *Основная группа* | Absent *Отсутствие* | 6 (27.3 %) | 9 (40.9 %) | 0.004* |
| | Mild *Слабовыраженный* | 4 (18.2 %) | 7 (31.8 %) | |
| | Moderate *Умеренно выраженный* | 8 (36.4 %) | 3 (13.6 %) | |
| | Severe *Значительно выраженный* | 1 (4.5 %) | 3 (13.6 %) | |
| | Constant *Постоянный* | 3 (13.6 %) | 0 (0.0 %) | |
| *p* | | 0.351 | 0.056 | – |

***Примечание:*** ** – различия показателей статистически значимы (p < 0,05).*
***Note:*** ** – differences are significant (p < 0.05).*

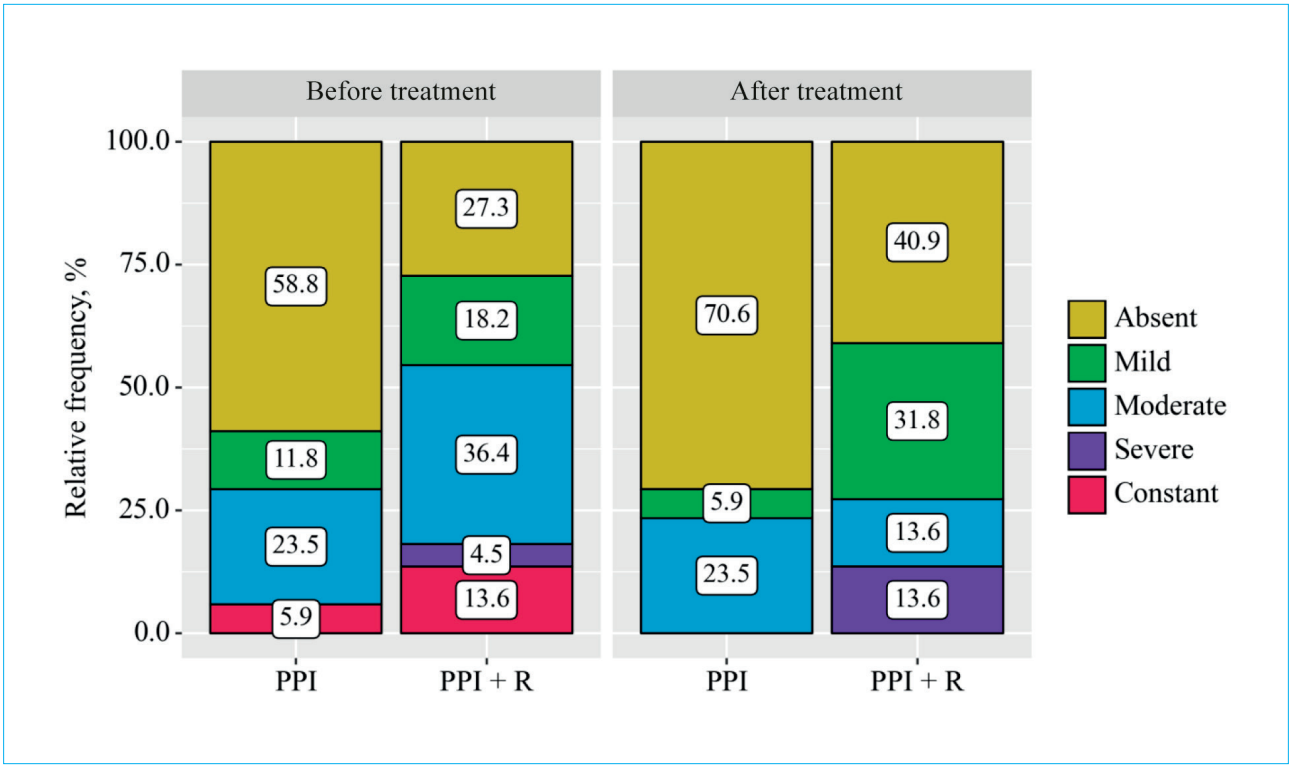


***Figure 2.*** Belching severity grading at baseline and post-treatment according to Likert scale

***Рисунок 2.*** Выраженность симптома «отрыжка» на фоне лечения согласно опроснику Лайкерта

***Table 4.*** Baseline characteristics of morphological parameters of esophageal mucosa according to the results of histological examination

***Таблица 4.*** Исходные характеристики морфологических показателей слизистой оболочки пищевода согласно результатам гистологического исследования

| **Baseline characteristics** ***Показатели до лечения*** | **Categories** ***Категории*** | **Therapy** ***Терапия*** | |
|---|---|---|---|
| | | **Control group** ***Группа сравнения*** | **Main group** ***Основная группа*** |
| Spongiosis *Спонгиоз* | Absent *Отсутствует* | 1 (5.9 %) | 4 (18.2 %) |
| | Mild *Средняя* | 13 (76.5 %) | 16 (72.7 %) |
| | Severe *Выраженная* | 3 (17.6 %) | 2 (9.1 %) |
| Width of intercellular spaces *Ширина межклеточных промежутков* | Absent *Отсутствует* | 1 (5.9 %) | 4 (18.2 %) |
| | Mild (width < 1 lymphocyte diameter) *Невыраженная (диаметр < 1 лимфоцита)* | 13 (76.5 %) | 16 (72.7 %) |
| | Pronounced (width ≥ 1 lymphocyte diameter) *Выраженная (диаметр ≥ 1 лимфоцита)* | 3 (17.6 %) | 2 (9.1 %) |
| Eosinophilic infiltration *Эозинофильная инфильтрация* | Absent *Отсутствует* | 15 (88.2 %) | 15 (68.2 %) |
| | 1–2 cells *1–2 клетки* | 2 (11.8 %) | 3 (13.6 %) |
| | >2 cells *>2 клеток* | 0 (0.0 %) | 4 (18.2 %) |
| Leukocytic infiltration *Лейкоцитарная инфильтрация* | Absent *Отсутствует* | 9 (52.9 %) | 10 (45.5 %) |
| | 1–2 cells *1–2 клетки* | 8 (47.1 %) | 9 (40.9 %) |
| | > 2 cells *> 2 клеток* | 0 (0.0 %) | 3 (13.6 %) |
| Mononuclear infiltration *Мононуклеарная инфильтрация* | 0–9 cells *0–9 клеток* | 16 (94.1 %) | 20 (90.9 %) |
| | 10–30 cells *10–30 клеток* | 1 (5.9 %) | 2 (9.1 %) |
| Basal cell hyperplasia *Базальноклеточная гиперплазия* | < 15 % | 16 (94.1 %) | 22 (100.0 %) |
| | 15–30 % | 1 (5.9 %) | 0 (0.0 %) |
| Elongation of vascular-stromal papillae *Удлинение сосудисто-стромальных сосочков* | < 50 % | 5 (29.4 %) | 6 (27.3 %) |
| | 50–75 % | 11 (64.7 %) | 16 (72.7 %) |
| | > 75 % | 1 (5.9 %) | 0 (0.0 %) |
| Hyperemia of lamina propria vessels *Гиперемия сосудов собственной пластинки* | Absent *Отсутствует* | 4 (23.5 %) | 5 (22.7 %) |
| | Mild *Средняя* | 8 (47.1 %) | 13 (59.1 %) |
| | Severe *Выраженная* | 5 (29.4 %) | 4 (18.2 %) |
| Atrophy of stratified squamous epithelium *Атрофия многослойного плоского эпителия* | Absent *Отсутствует* | 17 (100.0 %) | 22 (100.0 %) |

***Table 5.*** Post-treatment dynamics of eosinophilic infiltration severity
***Таблица 5.*** Динамика выраженности эозинофильной инфильтрации на фоне лечения

| **Therapy** ***Терапия*** | **Categories** ***Категории*** | **Observation time points** ***Этапы наблюдения*** | | ***p*** |
|---|---|---|---|---|
| | | **Eosinophilic infiltration, before treatment** ***Эозинофильная инфильтрация, до лечения*** | **Eosinophilic infiltration, after treatment** ***Эозинофильная инфильтрация, после лечения*** | |
| Control group *Группа сравнения* | Absent *Отсутствует* | 15 (88.2 %) | 16 (94.1 %) | 0.564 |
| | 1–2 cells *1–2 клетки* | 2 (11 %) | 1 (5.9 %) | |
| | > 2 cells *> 2 клеток* | 0 (0.0 %) | 0 (0.0 %) | |
| Main group *Основная группа* | Absent Отсутствует | 15 (68.2 %) | 20 (90.9 %) | 0.030* |
| | 1–2 cells *1–2 клетки* | 3 (13.6 %) | 2 (9.1 %) | |
| | > 2 cells *> 2 клеток* | 4 (18.2 %) | 0 (0.0 %) | |
| *p* | | 0.164 | 1.000 | – |

***Note:*** ** — differences are significant ($p < 0.05$).*
***Примечание:*** ** — различия показателей статистически значимы ($p < 0,05$).*

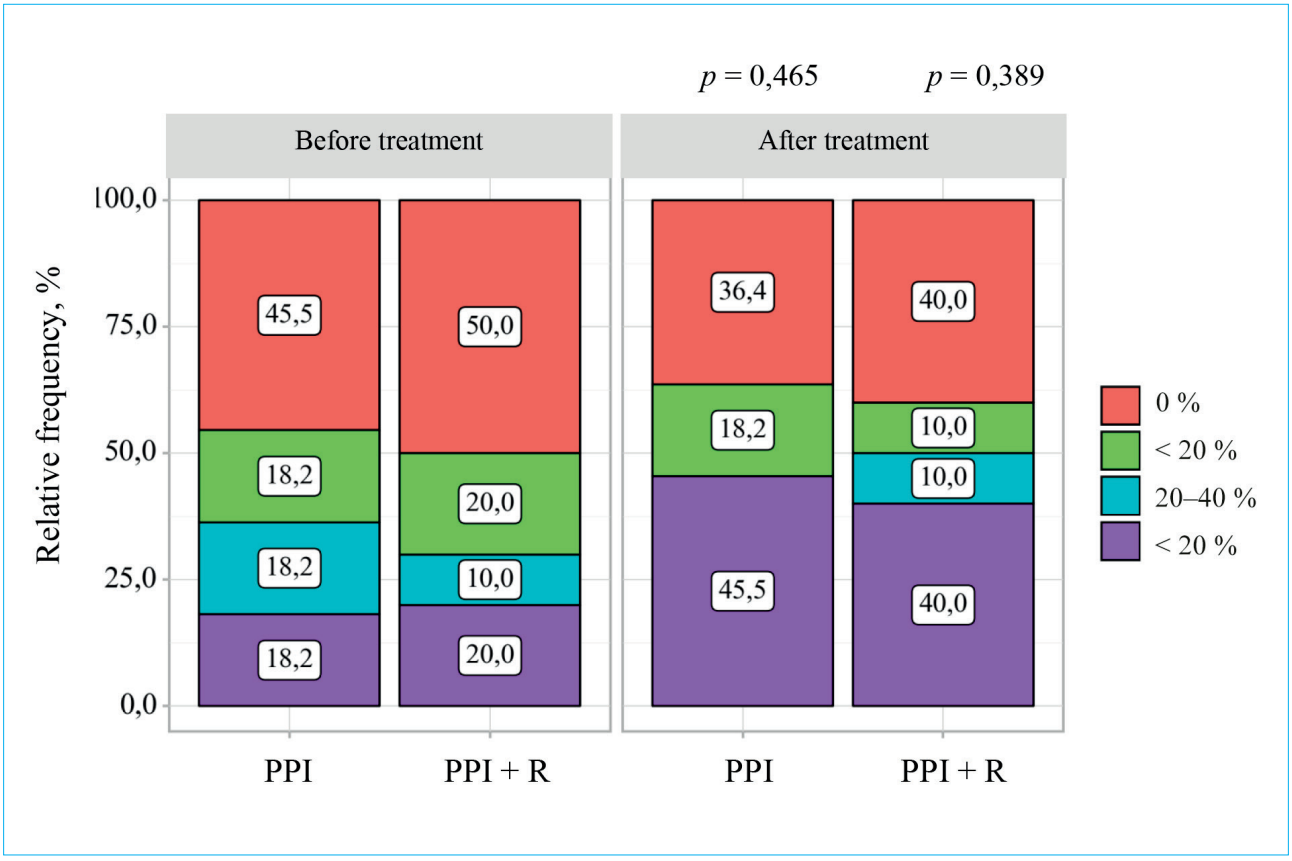


***Figure 3.*** Claudin-1 expression during treatment according to the results of immunohistochemical examination
***Рисунок 3.*** Экспрессия клаудина-1 на фоне лечения согласно результатам иммуногистохимического исследования

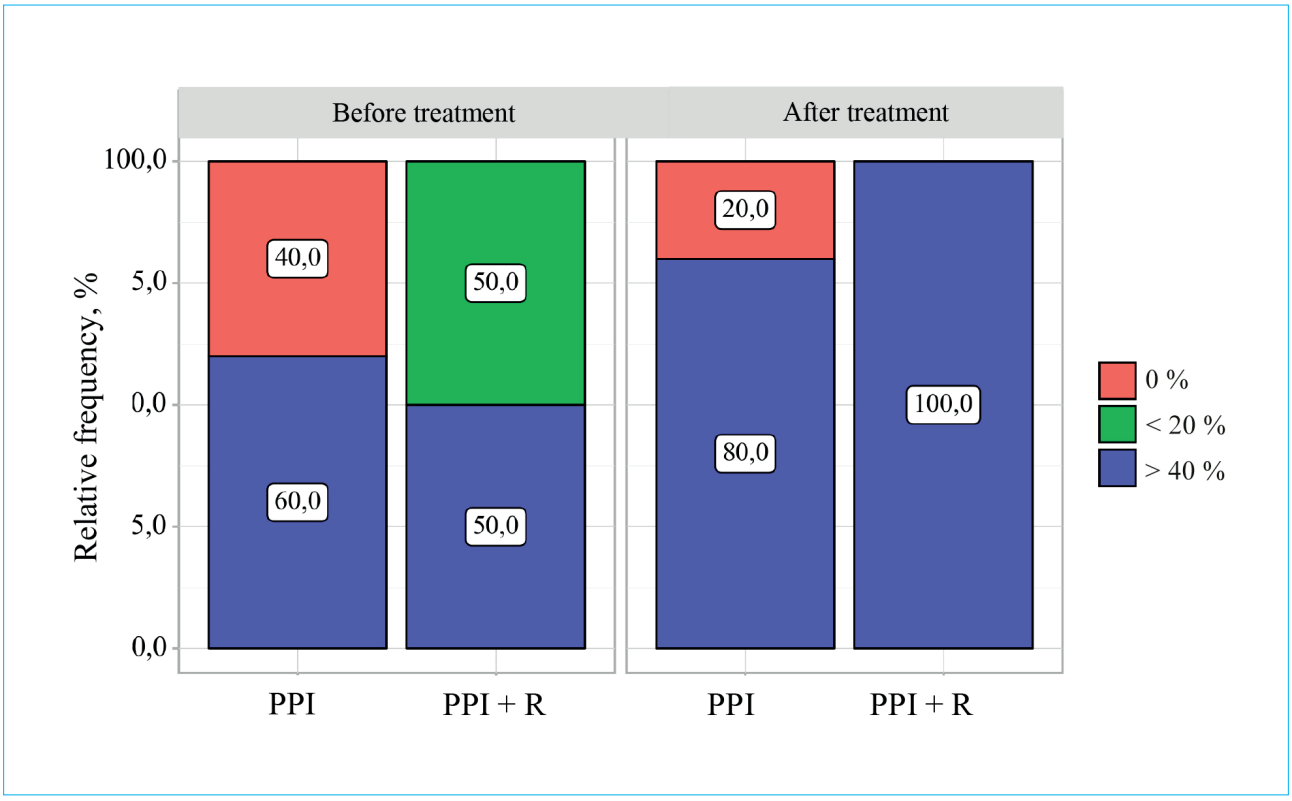


***Figure 4.*** Claudin-4 expression during treatment according to the results of immunohistochemical examination

***Рисунок 4.*** Экспрессия клаудина-4 на фоне лечения согласно результатам иммуногистохимического исследования

of patients in the combination therapy group demonstrated post-treatment expression levels exceeding 40 % (Fig. 4). The lack of statistical significance in these findings is likely attributable to the small sample size. In the PPI monotherapy group, occludin expression showed statistically significant changes post-treatment ($p = 0.046$), with 55.6 % of participants achieving expression levels above 40 % (Table 6). The main group exhibited an upward trend in occludin expression, though the pre- to post-treatment changes were not statistically significant ($p = 0.317$) (Fig. 5).

## Discussion

The findings of this study demonstrate that combination therapy with a PPI and rebamipide significantly reduces clinical manifestations of NERD, including heartburn and belching, even after treatment completion. Although no statistically significant differences were observed between treatment methods, the combination therapy group showed a notable reduction in symptom severity: by the end of treatment, 63.7 % of patients reported absent or mild heartburn, and complete clinical remission was achieved in 27.3 %. For belching, 72.7 % of patients experienced absent or mild symptoms post-treatment, compared to 45.5 % at baseline. These results align with prior studies [25, 26] highlighting the benefits of PPI and rebamipide combination therapy in improving clinical outcomes for GERD patients. For instance, S.J. Hong et al. [25] evaluated symptom intensity (heartburn, epigastric pain, epigastric heaviness, vomiting) in GERD patients before and after combined therapy with esomeprazole and rebamipide versus esomeprazole monotherapy. Their data demonstrated superior efficacy of combination therapy in alleviating GERD symptoms compared to PPI monotherapy. Another study [26] investigated rebamipide's role in managing recurrent GERD. Patients receiving rebamipide and PPI combination therapy exhibited a marked reduction in pro-inflammatory cytokine IL-8 mRNA production. At a 1-year follow-up, symptom recurrence rates were 2.5 times lower in the combination therapy group compared to PPI monotherapy. This underscores rebamipide's ability not only to alleviate symptoms during active treatment but also to promote sustained remission

***Table 6.*** Occludin expression during treatment according to the results of immunohistochemical examination

***Таблица 6.*** Экспрессия окклюдина на фоне лечения согласно результатам иммуногистохимического исследования

| Therapy *Терапия* | Parameters *Показатели* | Observation time points *Этапы наблюдения* | | *p* |
|---|---|---|---|---|
| | | Before treatment *До лечения* | After treatment *После лечения* | |
| Control group *Группа сравнения* | 0 % | 8 (88.9 %) | 4 (44.4 %) | 0.046* |
| | > 40 % | 1 (11.1 %) | 5 (55.6 %) | |
| Main group *Основная группа* | 0 % | 5 (71.4 %) | 4 (57.1 %) | 0.317 |
| | > 40 % | 2 (28.6 %) | 3 (42.9 %) | |
| *p* | | 0.550 | 1.000 | – |

***Note:*** ** – differences are significant ($p < 0.05$).*

***Примечание:*** ** – различия показателей статистически значимы ($p < 0,05$).*

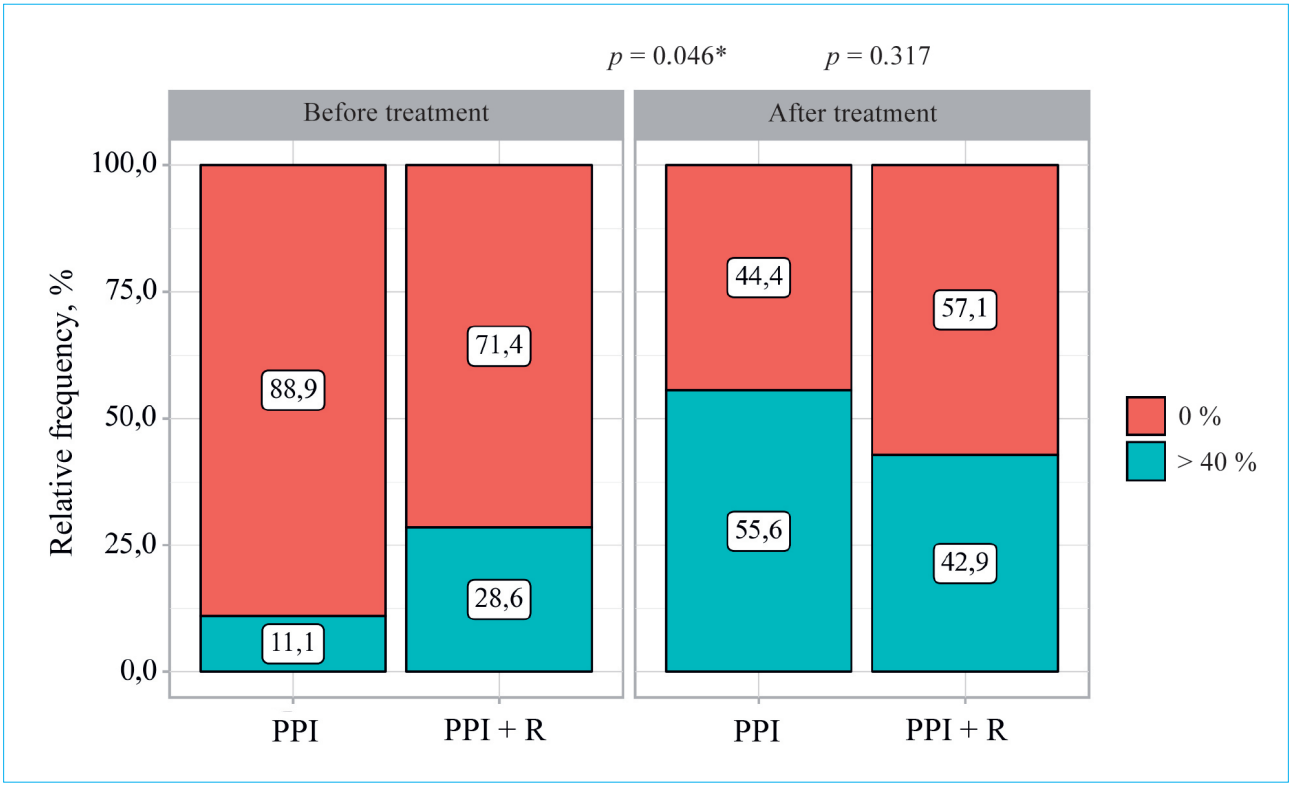


***Figure 5.*** Occludin expression during treatment according to the results of immunohistochemical examination; * – differences are significant ($p < 0.05$)

***Рисунок 5.*** Экспрессия окклюдина на фоне лечения согласно результатам иммуногистохимического исследования; * – различия показателей статистически значимы ($p < 0,05$)

in the long term. A key morphological outcome of this study was the reduction in eosinophilic infiltration observed in the combination therapy group post-treatment, underscoring rebamipide's anti-inflammatory potential. Immunohistochemical analysis revealed increased occludin expression in both groups. Notably, experimental rat models [8] demonstrated that PPI and rebamipide combination therapy significantly upregulated claudin-3 and claudin-4 expression compared to controls. These findings align with evidence that reduced claudin-3 and -4 levels are characteristic of GERD patients [27–29], and their restoration may mitigate mucosal permeability.

The primary limitation of this study was it small sample size, which may have underpowered

the detection of statistically significant changes in tight junction protein expression. Additionally, the 4-week observation period might have been insufficient to evaluate long-term therapeutic effects. These constraints highlight the need for larger-scale studies with extended follow-up to further elucidate rebamipide's role in NERD management.

## Conclusion

Rebamipide represents a promising therapeutic component for reflux disease, particularly in patients with pronounced inflammation. Further investigation of its effects in large-scale studies with extended follow-up periods is warranted.

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