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Treatment of Functional Dyspepsia in Outpatients after COVID-19 Infection

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Aim: to compare the efficacy of different therapeutic regimens for managing functional dyspepsia in outpatients after COVID-19 infection.
Materials and methods. 42 post-COVID-19 outpatients (age: 26–47 years) diagnosed with functional dyspepsia (FD) according to the Rome IV Criteria were enrolled in two parallel groups. All patients were divided in 2 groups by randomization: Group 1 received omeprazole at a dose of 80 mg/day, Group 2 received a combination of omeprazole and Kolofort® (a combined action drug product containing technologically processed antibodies to S100, TNF-alpha, and histamine) at a dose of 80 mg/day. At baseline and after treatment, a 10-point VAS was used to measure symptoms and an SF-36 questionnaire to evaluate the quality of life.
Results. By Day 28 of the treatment, the intensity of epigastric pain (VAS score) in the group receiving proton-pump inhibitor (PPI) + Kolofort® was significantly lower. In both groups, fully resolved dyspeptic syndrome was observed in up to 90 % of patients, without significant differences ($p < 0.06$). According to the SF-36 data, a combination treatment resulted in higher scores (pain and general health subscales) as compared to the PPI alone.
Conclusion. Kolofort® relieves symptoms and improves the quality of life when added to the treatment regimen against functional dyspepsia in post-COVID-19 patients.
Key words: functional dyspepsia, COVID-19, outpatient visit
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Лечение функциональной диспепсии у амбулаторных пациентов, перенесших новую коронавирусную инфекцию

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Цель исследования: сравнить эффективность различных схем терапии функциональной диспепсии у амбулаторных пациентов, перенесших новую коронавирусную инфекцию.
Материалы и методы. В параллельные группы были включены 42 амбулаторных пациента, которые перенесли COVID-19, в возрасте от 26 до 47 лет, с диагнозом «функциональная диспепсия» (ФД) согласно Римским критериям IV. Все пациенты методом рандомизации были разделены на 2 группы: первая группа получала омепразол в дозе 80 мг/сут, вторая получала омепразол в дозе 80 мг/сут в сочетании с комплексным препаратом, содержащим технологически обработанные антитела к белку S-100, фактору некроза опухоли альфа и гистамину (Колофорт®). До начала терапии и по окончании лечения для оценки симптомов использовали 10-балльную шкалу ВАШ, для оценки качества жизни — опросник SF-36.
Результаты. К 28-му дню терапии интенсивность эпигастральной боли по ВАШ в группе, получающей сочетанную терапию ИПП и препаратом Колофорт®, была достоверно ниже. Полное купирование диспепсического синдрома в обеих группах составляло до 90 % пациентов без значимых отличий ($p < 0,06$). По данным SF-36 на фоне сочетанной терапии после лечения отмечен более высокий балл по шкалам боли и общего состояния здоровья по сравнению с монотерапией ИПП.
Заключение. Включение препарата Колофорт® в схему терапии функциональной диспепсии у пациентов, перенесших новую коронавирусную инфекцию, позволяет купировать симптомы и улучшить показатели качества жизни.
Ключевые слова: функциональная диспепсия, COVID-19, амбулаторный прием
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Introduction

The prevalence of functional gastrointestinal (GI) disorders has been increasing over the past years. This may be associated with the changing lifestyle of the population (eating disorders, regular exposure to informational stress, uncontrolled use of medications, etc.). Functional disorders are often regarded by various healthcare professionals as of little notice, whereas these are the conditions that lead to a significant decrease in patients' quality of life [1–3]. Functional GI disorders are caused not only by impaired motility or gut-brain interaction. This shows that combination treatment is required for such patients [1, 4].

The prevalence of functional dyspepsia (FD) and irritable bowel syndrome (IBS) has increased since the onset of the COVID-19 pandemic. Manifestations of COVID-19 infection are mostly respiratory symptoms, which is related to the tropism of the virus to cells that have angiotensin-converting enzyme type 2 (ACE2) receptors present in the respiratory tract. Also, the disease is often manifested in gastrointestinal symptoms such as diarrhea, loss of appetite, nausea, vomiting, and abdominal pain syndrome. This may be associated with the fact that the epithelial cells in the gastrointestinal tract (GIT) are also characterized by high expression of ACE2 receptors. SARS-CoV-2 virus RNA has been found in stool samples from patients with diarrhea associated with coronavirus infection [5–7].

It turned out that, along with gastrointestinal disorders during active COVID-19 infection, dyspeptic symptoms often persist in the post-covid period. The risk factors for the development of post-covid functional GI disorders were anosmia (impaired odor perception) and ageusia (loss of taste) during the infection period, the presence of dyspeptic and intestinal symptoms or their overlap 1 and 3 months after infection, concomitant anxiety and depressive disorders [6, 8, 9].

Specific indicators of the incidence rate of functional GI disorders after COVID-19 infection vary widely in different works [5, 6, 8, 10–12]. Post-covid gastroenterological symptoms had almost the same incidence rate regardless of the gastrointestinal symptoms during COVID-19. There is evidence of a correlation between the severity of FD and IBS symptoms and the presence of psychological distress caused by COVID-19 infection [6, 8, 12].

Study aim: to compare the efficacy of different therapeutic regimens for managing functional dyspepsia in outpatients after covid-19 infection.

Materials and methods

The study enrolled 42 outpatients who visited a gastroenterologist with dyspepsia symptoms that occurred within 6 months after a coronavirus infection. These symptoms met the Rome IV Criteria for FD (pain, epigastric burning, feeling of fullness in the epigastric region after eating, feeling of early satiety observed in patient during the last 3 months (with a total duration of complaints of at least 6 months) and that cannot be explained by organic diseases). Patients underwent esophagogastroduodenoscopy and abdominal ultrasound to exclude any organic disease. In addition, the study did not include patients with a positive test for *Helicobacter pylori* as diagnosed using the ^{13}C-urea breath test.

The study did not enroll patients with IBS symptoms or severe concomitant somatic conditions that could affect the severity of dyspeptic symptoms.

All patients included in the study signed an informed consent form and were divided into two groups by simple randomization. Group 1 received omeprazole at a dose of 80 mg/day, group 2 received omeprazole (80 mg/day) combined with Kolofort® (2 tablets twice a day for 4 weeks).

At baseline and after therapy, a 10-point VAS scale was used to measure clinical manifestations, and the SF-36 questionnaire was used to assess the quality of life.

The primary endpoint of the study was change in the severity of dyspepsia symptoms.

Results are presented as mean ± standard deviation. Statistical analysis was performed using Student's tests. A p-value less than 0.05 ($p < 0.05$) was statistically significant.

Results

The study enrolled 42 patients. There was no significant difference among all patients in terms of age, gender, and baseline severity of dyspepsia symptoms (Table 1).

Epigastric pain was the most common FD symptom in patients after coronavirus infection. Changes in pain severity were assessed at the first visit and at subsequent visits on Days 5, 14, and 28 of treatment (Fig. 1). At the same time, there

Table 1. Characteristics of subjects enrolled

Parameter	Group 1 (omeprazole 80 mg/day) (n = 21)	Group 2 (omeprazole 80 mg/day + Kolofort®) (n = 21)	p
Age	35 ± 9	39 ± 8	0.012
Males/females	8/13	6/15	0.010
VAS severity score for epigastric pain	6.1 ± 1.8	5.6 ± 1.5	0.001
VAS severity score for other dyspeptic symptoms	7.8 ± 1.0	7.6 ± 1.2	0.001

were no significant differences between the groups on Day 5 of therapy, whereas by Day 28 the intensity of epigastric pain in the group receiving a PPI+Kolofort® combination was significantly lower ($p < 0.01$).

The VAS was also used to assess changes in other dyspeptic complaints (feeling of heaviness in the epigastric area, feeling of early satiety, nausea). In Group 2 receiving Kolofort® in combination with the PPI, there was a significant improvement on Day 5 compared to Group 1 receiving the PPI alone ($p < 0.02$). By Day 28 of treatment, dyspeptic syndrome was fully resolved in up to 90 % of patients in Groups 1 and 2, with a statistically significant difference no longer observed between the groups ($p < 0.06$) (Fig. 2).

The quality of life of patients was measured using SF-36 questionnaire before the treatment and on Day 28. Patients treated with PPI + Kolofort® experienced a more significant reduction in pain. Moreover, patients who received combination treatment demonstrated better outcomes at the end of the treatment as measured by the SF-36 (Role-Emotional and Mental Health scales). This may be associated with the ability of the product to affect the S100 brain-specific protein. Combination treatment also resulted in a higher General Health score as compared to the PPI monotherapy (see Table 2).

Discussion

Current therapeutic methods for functional dyspepsia demonstrate moderate efficacy compared to placebo, and not all therapies are effective for different types of the disorder. Proton pump

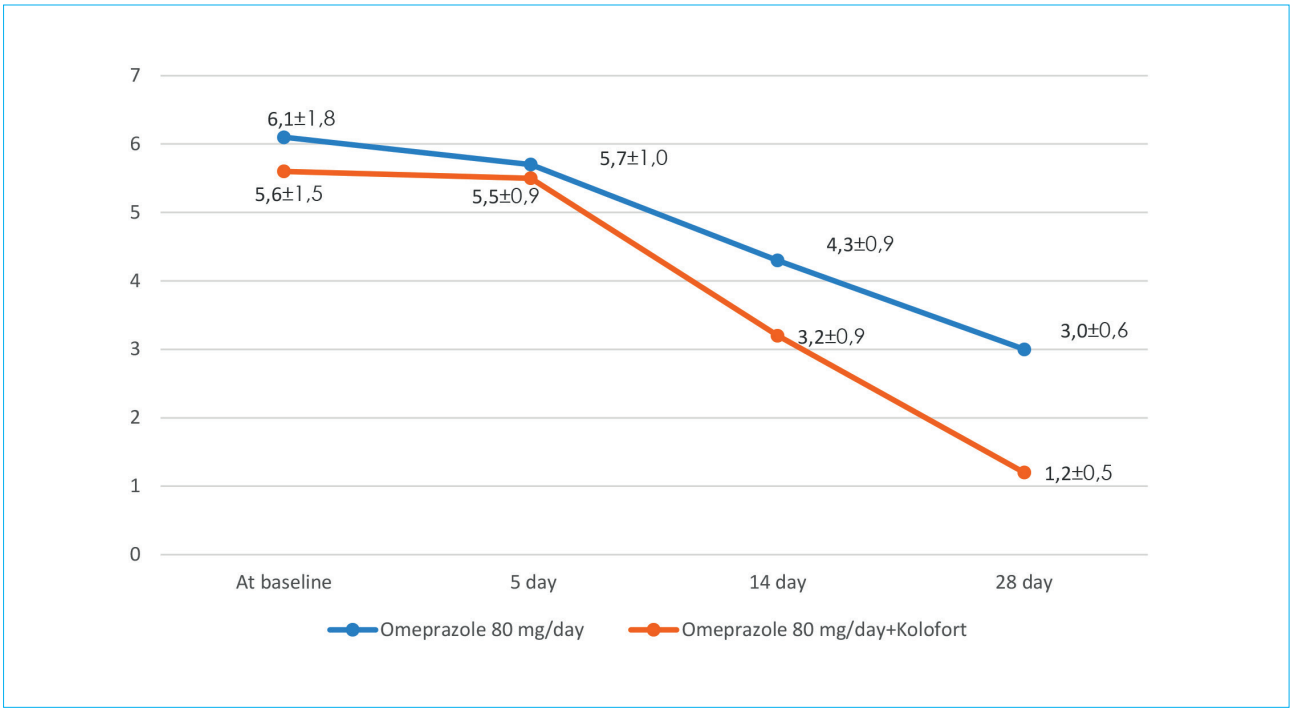

Fig. 1. Changes in the VAS score for epigastric pain in patients with FD after coronavirus infection

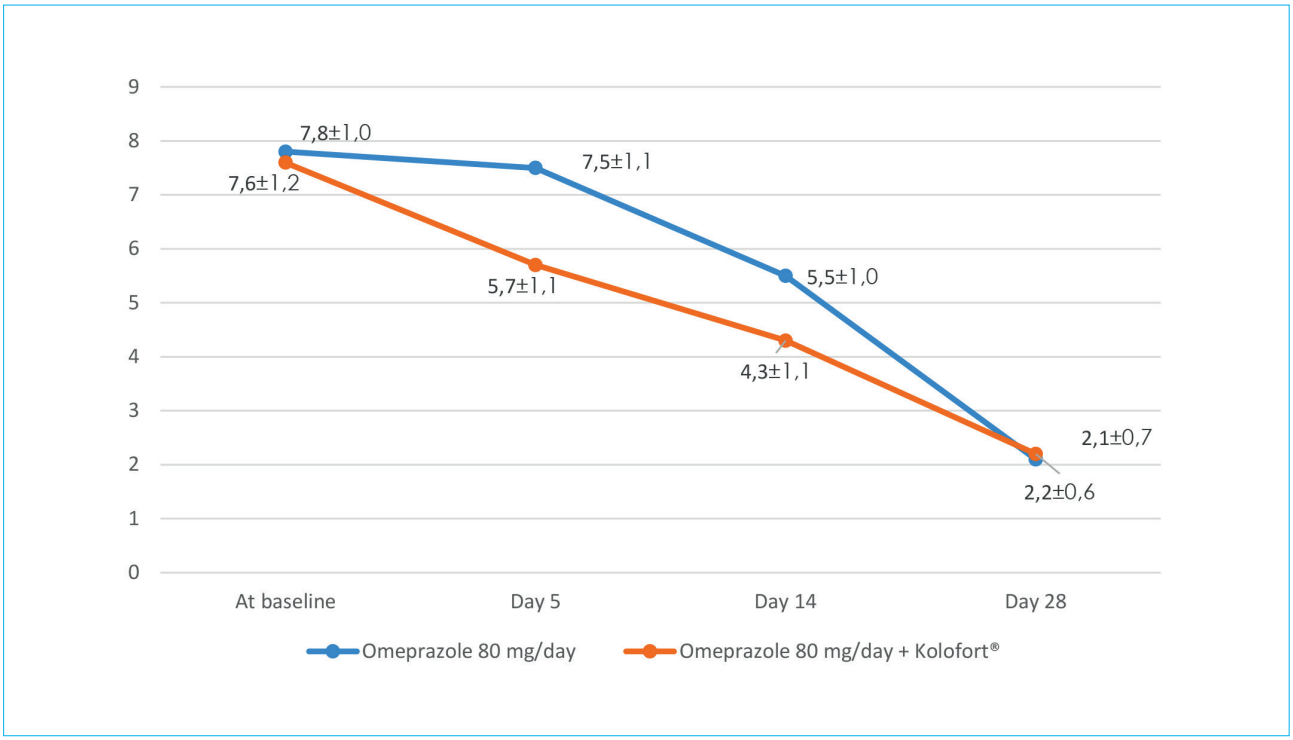

Fig. 2. Changes in other dyspeptic complaints (feeling of heaviness in the epigastric area, feeling of early satiety, nausea) according to the VAS in patients with FD after coronavirus infection

inhibitors and prokinetics are the most justified agents for the treatment of such patients [13, 14]. However, none of these products significantly affects visceral hypersensitivity, which in some cases leads to lack of effect of the therapy [5, 14, 15]. The study results obtained for Kolofort® (technologically processed antibodies to S100 protein, tumor necrosis factor alpha, and histamine) are quite promising. The product reduces the level of depression and anxiety, inflammation in the mucous membrane and the level of visceral hypersensitivity, significantly improving the management of patients with FD, including those after COVID-19 infection [4].

Table 2. Changes in the quality of life in post-COVID-19 patients as per the SF-36

Scale	Group 1		Group 2	
	Baseline	Treatment day 28	Baseline	Treatment day 28
GH (General Health)	37,0 ± 5,4	55,0 ± 5,5*	38,0 ± 5,1	70,0 ± 6,2*/**
PF (Physical Functioning)	70,0 ± 5,1	74,0 ± 5,5	72,0 ± 4,9	75,0 ± 5,2
RP (Role-Physical)	33,0 ± 11,2	57,0 ± 12,1*	36,0 ± 11,0	71,0 ± 11,5*/**
BP (Bodily Pain)	35,0 ± 6,1	51,0 ± 6,7*	37,0 ± 5,7	62,0 ± 6,0*/**
VT (Vitality)	37,0 ± 5,4	51,0 ± 5,5*	35,0 ± 5,7	59,0 ± 5,5*
RE (Role-Emotional)	32,0 ± 9,8	52,0 ± 10,1*	34,0 ± 10,0	61,0 ± 10,8*/**
SE (Social Functioning)	46,0 ± 4,3	57,0 ± 5,6*	44,0 ± 5,0	61,0 ± 5,1*
MH (Mental Health)	42,0 ± 5,6	51,0 ± 5,3*	40,0 ± 5,0	62,0 ± 5,2*/**

Note. Significant difference $p < 0.05$ * — before and after treatment; ** — between the two groups

Conclusion

The study demonstrated the efficacy of Kolofort® as add-on therapy for functional dyspepsia in patients after coronavirus infection. The product contributed to faster and more stable pain relief, faster disappearance of other dyspeptic complaints, and a significant improvement in the quality of life of patients.

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