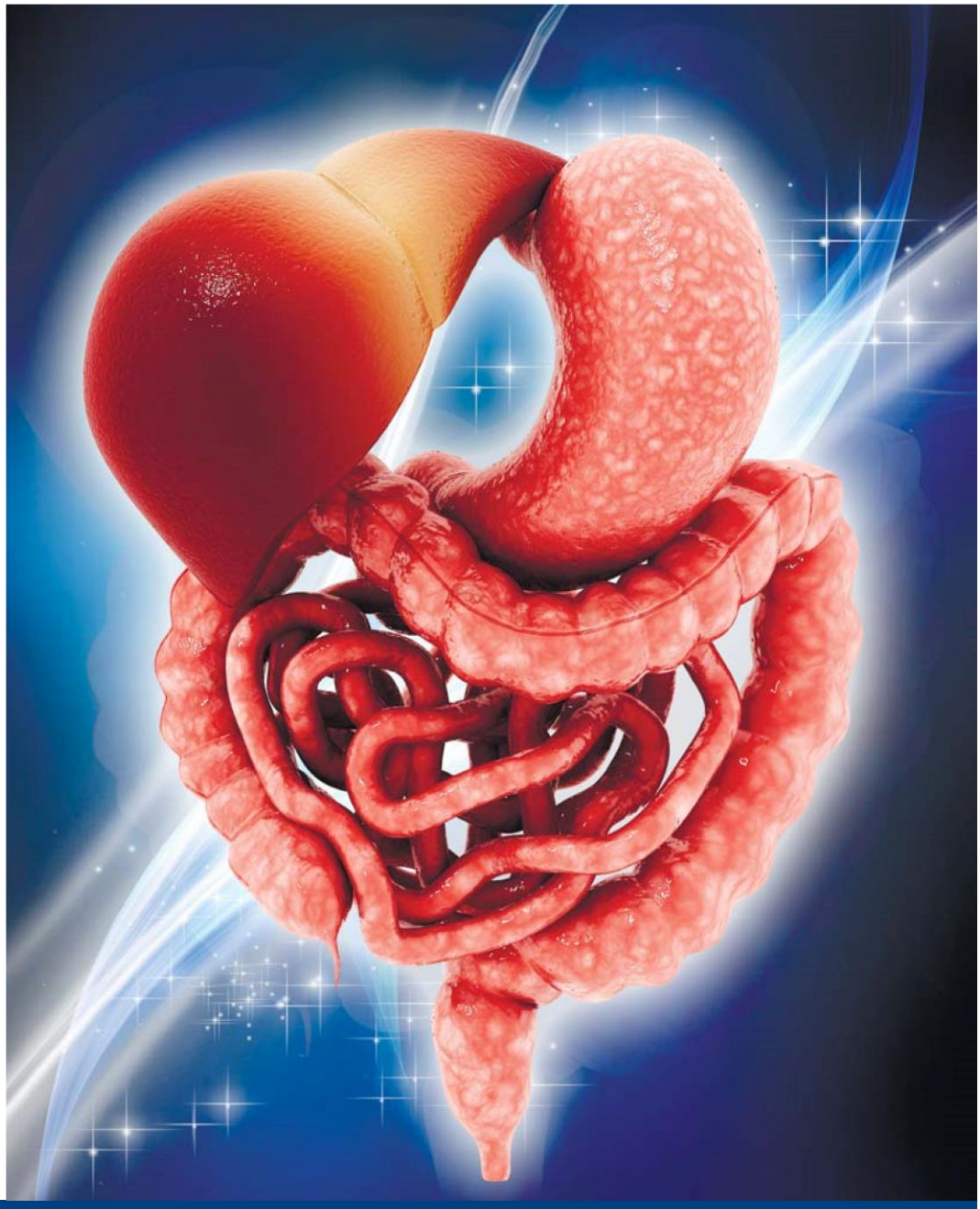

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Evolution in eradication therapy of HP -associated diseases: beyond the standards?

Evolution in eradication therapy of HP -associated diseases: beyond the standards?

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ABSTRACT

Recently special attention is paid to basically new solutions for optimization of H. pylori eradication therapy.

Objective: *to study the effectiveness and safety of Helinorm therapy in patients with HP -associated duodenal ulcers (DU).*

Material and methods. *The study included 60 patients (mean age - 36 years), divided into 3 groups (n= 20 each). Group 1 (active control) received omeprazole 20mg 2 times a day for 10 days; clarithromycin 500 mg bd; amoxicillin 1000 mg bd; De-nol 240 mg bd. Group 2 (active control) received all these drugs for 10 days, except De-nol. Group 3 (study group) additionally received Helinorm 1 capsule bd with food within 28 days. The examination was conducted at the end of therapy after 2 months after start of observation.*

Results. *Significant reduction of incidence of abdominal pain was revealed in all 3 groups: p= 0.004, 0.008 and <0.001 for groups 1, 2 and 3, respectively. Significant improvement in quality of life was observed in group 2 (GH, VT and MH scales) and group 3 (GH, BP, VT and MH scales). Histological examination after treatment just in 1 patient in group 3, in 3 and 6 patients - in groups 1 and 2, respectively.*

Conclusion. *Combination of Helinorm with standard eradication therapy improves efficiency of H. pylori eradication by 10%; contributes to relief of abdominal pain in patients with DU, has good tolerability and safety profiles, improves quality of life.*

Key words: *H. pylori, eradication therapy, duodenal ulcer, Helinorm, abdominal pain, quality of life*

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ABSTRACT
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Introduction

One of the most "popular" microorganisms in gastroenterology is *Helicobacter pylori*. It is found that the *H. pylori* infects approximately 30-35% of the population in the childhood and 50-85% in the adult population [1-5]. At the same time, it should be noted that *H. pylori*-associated diseases were developed in no more than 10-20% cases [6].

This observation is explained by the fact that the population of *H. pylori* has extremely high genetic heterogeneity, and the strains differ significantly in virulence, therefore not all of them can cause the clinical manifestations of diseases [7]. It should be noted that even infection by cytopathogenic strains does not mean the fatal inevitability of the disease. Thus the implementation of other pathogenic factors belongs to the essential characteristics of the microorganism.

Yet it is surely proved that the organism increases the risk of peptic ulcer (ulcer) and gastritis, it is a carcinogen of first order, and may contribute to the formation of gastric tumors (MALT-lymphoma, adenocarcinoma). And, despite the fact that the germ theory of gastroduodenal lesions field is unique and does not follow the classical doctrine of the development of the disease (for *H. pylori* are not fulfilled Koch's postulates, such as 100% infection cases might result in disease, i.e. the lack of development of the disease also when demonstrated in microbial culture experiment), judgments about the protective role of bacteria also remain unproven. It is a reasonable statement of one of the world's leading *Helicobacter* investigators D. Graham: "Good Helicobacter - dead Helicobacter" (of course, within the framework of the application of this maxim in patients and in high-risk groups of individuals rather than of the whole human population as a whole). Thus, clinical and research components dictate the need for eradication therapy.

There are accepted subdivisions of indications for eradication therapy in absolute and relative (Table. 1). Traditionally, in clinical practice, standard schemes of *Helicobacter* therapy (AHBT) include proton pump inhibitors (PPIs) and antibiotics. As it is known that *H. pylori* infection eradication of more than 80% is considered to be

Table 1. Indications for eradication therapy [8]

Absolute indications	Relative indications	Indications for exclusion of all other causes of diseases
Peptic ulcer disease MALT-lymphoma gastratrophia Condition after gastrectomy for gastric cancer The first line of kinship with patients with gastric cancer The desire of the patient (after full consultation of the doctor)	Functional dyspepsia Gastroesophageal reflux disease NSAID-gastropathy	Iron-deficiency anemia Idiopathic thrombocytopenic purpura B12-deficiency anemia

Table 2. Scheme recommended for eradication of *H. pylori* [8]

H. pylori therapy	Regions with a low *H. pylori* resistance to clarithromycin	Regions with a high *H. pylori* resistance to clarithromycin
Treatment 1st line	Schemes based on clarithromycin, alternatively - bismuth-based scheme (quadruple)	conduction on the basis of bismuth (quadruple) or quadruple without bismuth
Therapy 2nd line	Bismuth-based scheme (quadruple) if not used in the therapy 1st line, or a scheme based on levofloxacin	The scheme based on levofloxacin
Therapy 3rd line	Individual selection of drugs after determining the resistance of microorganisms to antibiotics	Individual selection of drugs after determining the resistance of microorganisms to antibiotics

Table 3. Results of studies to assess the resistance of *H. pylori* in Russia [13, 14]

City	Adults	Children	Year	Method	Authors
Moscow	19.3%	n / a	2005	microbiol.analysis	Kudryavtseva LV et al.
	15.8% (primary – 5.3%, secondary – 10.5%)	n / a	2011	PCR	Lazebnyk LB et al.
St. Petersburg	n/a	28%	2007	PCR	Kornienko EA Parolova NI
	n/a	39%	2008		
	40%	n / a	2009	PCR	Uspensky et al.
	7.8%	n / a	2011	microbiol.analysis	Sablin OA et al.
	36.7%	n / a	2012	micorbiol.analysis	Zhebrun AB, AV Svarval
	25%	n / a	2014	micobiol.analysis	Simanenkov VI et al.
Kazan	10–11.4%	n / a	2011	PCR	Abdulhakov RA, Abuzarova ER, SR Abdulhakov et al.
Ufa	n/a	18.47%	2010	PCR	Nizhevich AA
Smolensk	7.6% (Erythromycin)	n / a	2010	Microbiol.analysis	Dehnich NN Kostyakov EA, AA Puning
Novosibirsk	6%	n / a	2012	PCR	Osipenko MF et al.

successful. Often, this positive and effective results can not be achieved by practitioners after the first, and sometimes not even after the second course AHBT. There are still a number of problems resulting in reduced efficiency AHBT.

The main reasons contributing to the decrease in the percentage of successful eradication, are:

1. Increase of *H. pylori* resistance to antibiotics
2. Side effects of proton pump inhibitors and antibacterial drugs
3. Low level of compliance and the patient's unwillingness to take antibiotics.

It is noted that the increasing *H. pylori* resistance to antibiotics leads to a catastrophic decrease in efficiency of eradication - from 80-90% to 30-60% [9]. One of the main factors that have a negative impact on the success AHBT is characteristic for many countries, the upward trend of microorganism resistance to clarithromycin – an important component of standard 1st line triple eradication schemes. Maastricht III Consensus Guidelines prescribe the use of clarithromycin in the 1st line eradication therapy schemes if *H. pylori* resistance to this antibiotic in the area does not exceed 15-20% [10]. Summing up the results of 20 European studies that evaluated the results of a standard 1st line triple therapy including PPI, amoxicillin and clarithromycin in 2751 patients, we can conclude that in the case of sensitivity of the strains eradication is achieved in average 87.8%, and for the stability of clarithromycin - only 18.3% of patients [11] and according to some authors, in terms of resistance to clarithromycin eradication percentage decreases even to 14.3% [12]. The recommendations of the Maastricht IV consensus determined that the different regimens as 1 st and 2 nd line are recommended for regions with high and low resistance of *H. pylori* to clarithromycin (Table. 2).

H. pylori resistance to antibiotics in Russia is also actively studied. In the majority of domestic research a trend to the growth of resistant microorganisms to clarithromycin is demonstrated, which is consistent with the known global data (Table. 3).

In connection with increasing *H. pylori* resistance to clarithromycin and other antibiotics, as well as with the presence of the risk of developing resistance to new antibiotics, used to treat *Helicobacter* infections, search and development of new treatment regimens are very relevant.

One of the most promising areas for improving the schemes of eradication therapy is the additional use of probiotics in its structure, the application of which is listed in the standard *H. pylori* infection treatment: IV Maastricht Treaty, the Russian Gastroenterological Association recommendations for diagnosis and treatment of *H. pylori* in adults (2013), the V Moscow Agreement - Standards for the diagnosis and treatment of acid and *Helicobacter pylori*-associated diseases (2013) [8, 15-17].

Additional to the standard eradication therapy the combination with probiotics improves compliance, reduces the frequency and severity of side effects (intestinal dysbiosis, antibiotic-associated diarrhea), increases the effectiveness of the eradication of the bacteria by direct antagonistic effect on *H. pylori* and enhance the immune response of the human body [18-21].

Recently, special importance was given to search for fundamentally new solutions for the optimization of eradication therapy. A group of German researchers developed a substance based on inactivated cells of the probiotic bacterium *Lactobacillus reuteri* DSMZ 17648 (Pylopass ™), selected and processed by biotechnology. It is important to emphasize that *Lactobacillus reuteri* DSMZ 17648 is a specially selected lactobacillus strain possessing the unique ability to bind specifically to *H. pylori* and forming coaggregates without affecting other bacteria and the normal intestinal flora. This specific aggregation reduces the mobility of the pathogen *Helicobacter*, which no longer binds to gastrointestinal mucosa and "washed" out from the stomach, resulting in reduction of colonization by *H. pylori* in the gastric mucosa, thereby reducing the risk of gastritis and ulcer [21, 22]. Studies have shown the effectiveness of the bioactive, there has been a decrease in *H. pylori* after 2-week course of treatment according to the urease breath test. As a criterion for assessing the effectiveness of the elimination of *H. pylori* the urea breath test (UBT) was used: *H. pylori* load after 2 weeks application of Pylopass ™. It is found that in patients receiving placebo the observed change in UBT was 3% compared to the baseline, and when using Pylopass - 16% from baseline [21, 23].

In Russia, this product is registered under the trade name Helinorm, is an innovative means of *H. pylori* with a fundamentally new mechanism of action [21].

Purpose of the study: examine the efficiency with and without the use of the Helinorm product, appointed for the purpose of treatment of patients with HP-associated duodenal ulcer (DU).

Research objectives: Identify the impact of Helinorm product in combination with the eradication therapy on:

- The clinical picture of the disease;
- Endoscopic picture;
- Colonization of HP-infection;
- The quality of life of patients taking Helinorm;
- To justify the employment of Helinorm as a part of complex therapy.

Material and Methods

Study Type - prospective cohort open comparative randomized. For the distribution of patients bloc fixed randomization with variable block size has been used by groups (Randomly Mixed Permuted Blocks*).* The choice of the method of randomisation was driven by the need to ensure comparable groups of the same size - 1: 1: 1 (in the process of randomization procedure a simple random number generator was used).

The study included patients with duodenal ulcer associated with an infection of *H. pylori*. According to the inclusion criteria, shown below, the patients had a duodenal ulcer, recurrence in phase ulceration, or scar deformation of bulb DPK, against erosive bulbita or other

endoscopic manifestations of the inflammatory process in the mucosa.

Inclusion criteria were:

- The signing of informed consent;
- The lack of mental health and intelligencecially amnestic disorders;
- The presence of duodenal ulcer associated with an infection of *H. pylori*, in the acute phase at the time of enrollment;
- The absence of other acute diseases

Exclusion criteria:

- The presence of heavy organic diseases, morphologic changes or complications, such as BU (signs of bleeding from the gastrointestinal tract, perforation, penetration, stenosis piloroduodenalnoy zone, malignancy), organic intestinal lesions (tumors, diverticulosis), OCI, inflammatory bowel disease (Crohn's disease, ulcerative colitis etc.) at the time of enrollment
-The presence of severe comorbidity: no-sufficiency of blood circulation, COPD manifestations of respiratory failure, chronic renal failure, chronic hepatitis of different etiology, chronic liver failure;
- Celiac disease;
- Systemic disease of the connective tissue;
- Acceptance of steroids;
- Presence of allergic reactions or intolerable bridge components of the drug;
- Alcohol abuse;
- Pregnancy or breast-feeding;
- The inability or unwillingness to give informed consent to participate in the study or to perform research requirements;
- Mental illness, incl previously deferred, in the opinion of the investigator, make inappropriate patient participating in the study;
- Drug abuse within 1 year prior to inclusion in the investigation;
- Severe disorders history;
- Patients who are prone to give up research and The signing of informed consent;
- don´t follow doctor's instructions
- The patients participating in other clinical trials.

In the study 60 patients (mean age 36 years) were included, who were divided into 3 groups of 20 people of similar age and gender composition.

Patients of group 1 (group of active control) received the following treatment for 10 days:

- Omeprazole 20 mg 2 times/ day
- Clarithromycin 500 mg, 2 doses / day
- Amoxicillin 1000 mg 2 doses/ day
- De-nol 240 mg 2 doses/ day

Dosing regimen throughout the treatment period was unchanged.

Patients in Group 2 (Group active control) received eradication therapy for 10 days:

- Omeprazole 20 mg 2 times/ day
- Clarithromycin 500 mg 2 dose / day.
- Amoxicillin 1000 mg 2 dose / day.

Dosage regimen throughout the treatment period was also unchanged.

Patients in group 3 (the main group) received eradication therapy for 10 days:

- Omeprazole 20 mg 2 times / day.
- Clarithromycin 500 mg 2 dose / day.
- Amoxicillin 1000 mg 2 dose / day.
-. Helinorm product 1 capsule 2 times / day during 28 days (from the beginning of the study accompanying the basic starting therapy with the standard eradication regimen and continuing for 18 days after the end of the basic therapy course).

During the period of treatment a dynamic monitoring of patients was carried out. In the course of therapy and upon completion clinical examination of all patients were conducted using a standardized survey for assessment of quality of life. After 2 months from the beginning of the observation the patients underwent endoscopic examination of the upper gastrointestinal tract with a specific histological material and urease test. The study design is presented in Table 4.

Study endpoints were the following: the frequency of complaints of patients, the frequency of positive tests for *H. pylori*, the frequency of endoscopic and histological changes according to the EGD, the values of indicators on the quality of life scales of the SF-36 questionnaire.

Analysis of the resulting data of research was conducted using statistical software package SPSS 17.0 (SPSS Inc., USA) by means of methods of parametric and nonparametric statistics [24-26]. The determination of the type of data distribution was carried out using the criteria Shapiro-Wilk and Kolmogorov-Smirnov. Since the actual data distribution was different from normal, for the statistical description of the average trend of variation the median was used. For comparison of quantitative traits in dynamics paired Wilcoxon test was used (depending on the type of data distribution). The comparison of the study groups was performed using non-parametric analysis of variance (Kruskal criterion - Wallis). For the comparison of the dynamics of the qualitative features Mak-Nimar criterion was used and for comparing the frequency of outcomes in study groups the Pearson criterion $\chi 2$ and its variations (Yates correction for continuity and Fisher's exact test) were applied.

The level of statistical significance of $p < 0,05$ was considered sufficient to reject the null hypothesis and the statistical output of the statistical significance of differences in the data obtained in the study. When conducting multiple comparison, the correction to the critical level of statistical significance was performed by usding the Bonferroni correction.

Table 4. Study Design (patients 3 groups)

Визит	1	2	3	4	5
Day	-2-3	0	10	28	56
Interval (days)	0	0	±2	±3	±3
Standarized interview	X		X	X	X
Objective examination	X				X
EGD (gastrointestinal endoscopy)	X				X
Histological examination of the biopsy specimens from the HP	X				X
Urease test to determine HP	X				X
Quality of life	X				X
Pregnancy test	X		X		
Assessment of adverse events			X	X	X
Assessment of patient diaries			X		X
Evaluation of compliance			X		
eradication therapy		X			

Table 5. Dynamic frequency of gastrointestinal complaints in patients in Groups 1, 2 and 3 during the course of therapy

Complaints	surveillance moment (Beginning / end of a course of therapy)	The number of patients abs. (%)		
		Group 1 n=20	Group 2 n=20	Group 3 n=20
Abdominal pain	Start	18 (90)	15 (75)	19 (95)
	Ending	9 (45)	7 (35)	0 (0)
Heartburn	Start	0 (0)	0 (0)	0 (0)
	Ending	0 (0)	0 (0)	0 (0)
belching	Start	8 (40)	7 (35)	7 (35)
	Ending	0 (0)	0 (0)	0 (0)
Nausea	Start	6 (30)	4 (20)	7 (35)
	Ending	4 (20)	0 (0)	0 (0)
vomiting	Start	1 (5)	2 (10)	0 (0)
	Ending	0 (0)	0 (0)	0 (0)
sense of bitterness in the mouth	Start	6 (30)	7 (35)	10 (50)
	Ending	4 (20)	0 (0)	0 (0)
Borborygmus	Start	7 (35)	7 (35)	4 (20)
	Ending	0 (0)	0 (0)	0 (0)
Bloating	Start	9 (45)	10 (50)	4 (20)
	Ending	0 (0)	0 (0)	0 (0)
Diarrhea	Start	0 (0)	0 (0)	0 (0)
	Ending	1 (5)	0 (0)	0 (0)
Constipation	Start	0 (0)	0 (0)	2 (10)
	Ending	0 (0)	2 (10)	0 (0)

Table 6. Dynamics of values on the scales of SF-36 in the observation group

Scale	surveillance moment (Beginning / end of a course of therapy)	Values, scores					
		Group 1, n=20		Group 2, n=20		Group 3, n=20	
		Median	p	Median	p	Median	p
General health (GH)	Start	67	0,068	57	0,006	66,5	0,009
	ending	67		87		87	
Physical functioning (PF)	начало	87,5	0,729	87,5	0,082	85	0,074
	ending	92,5		92,5		87,5	
Role-based physical functioning (RP)	начало	75	0,842	75	0,059	87,5	0,487
	ending	75		75		75	
Role-emotional functioning (RE)	начало	83,5	0,538	83,5	0,436	67	0,322
	ending	100		100		100	
Social functioning (SF)	начало	50	1,000	50	0,541	50	0,052
	ending	50		50		63	
pain intensity (BP)	начало	78	0,360	74	0,428	58	0,031
	ending	62		84		84	
vital Activity (VT)	начало	72,5	0,360	55	<0,001	50	0,034
	ending	72,5		75		65	
Menatal health (MH)	начало	68	0,111	56	0,004	52	0,040
	ending	72		86		60	

Results of the study

All patients completed the study according to protocol.

Assessment of patient complaints

We enrolled patients at the start of monitoring most of them showing common complaints such as abdominal pain, belching, nausea, feeling of bitterness in the mouth, rumbling in the stomach and bloating. The dynamics of the frequency of gastrointestinal complaints after the treatment is shown in Table 5.

Among the most interesting of complaints pain presented the most significant effect on patients' quality of life. When comparing the end and the beginning of the observation therapy all 3 groups showed a statistically significant decrease in the incidence of pain in the stomach: the level of statistical significance was 0.004, 0.008 and <0.001 for groups 1, 2 and 3 respectively.

When pairwise comparison between groups with respect to a decrease in the incidence of pain, statistically significant differences were found between groups 3 and 1 ($\chi 2 = 12.554$, $p < 0.001$) and between 3 and 2 groups ($\chi 2 = 11.165$, $p = 0.001$), while between groups 1 and 2 showed no statistical difference was ($\chi 2 = 0.036$, $p = 0.849$).

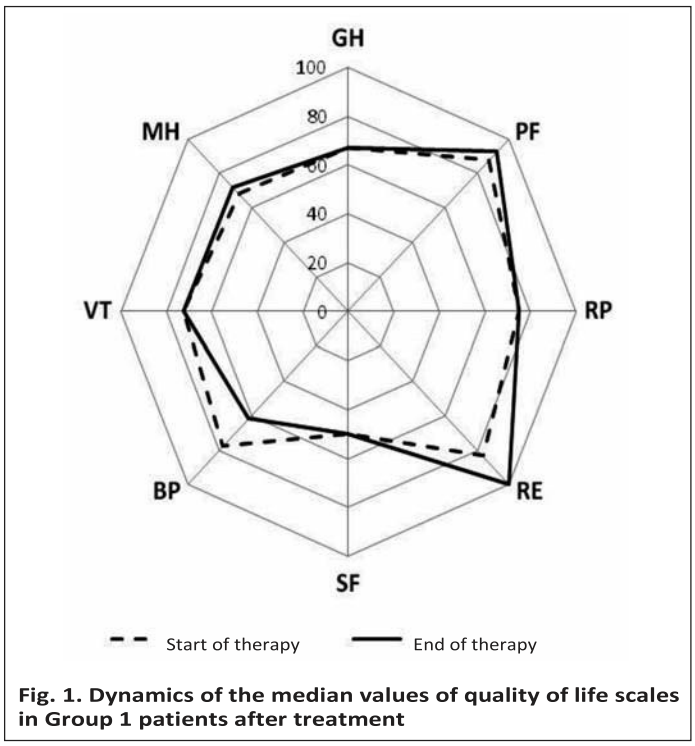

Fig. 1. Dynamics of the median values of quality of life scales in Group 1 patients after treatment

Evaluation of the quality of life of patients

After treatment a statistically significant improvement in quality of life was observed for the GH, VT and MH scales in group 2 patients, and in the group 3 patients on GH, BP, VT and MH scales, while for the patients of group 1 a statistically significant change in the quality of life was observed for any of the scales. Dynamics of quality of life of the patients is presented in Table 6 and Figures 1-3. Comparison of the dynamics of indicators of quality of life scales showed statistically significant differences between groups only in relation to "pain intensity" (BP) scale ($\chi 2$ = 2.920, p = 0.012). Close to were statistically significant differences between the groups with regard to the scale of vitality VT ($\chi 2$ = 5.942, p = 0.051). Pairwise comparisons between groups "pain intensity" index values of quality of life on the scale showed a statistically significant difference between groups 1 and 3 (U = 111.5, p = 0.015) and between groups 3 and 2 (U = 106.0, p = 0.010), while groups 1 and 2 did not differ statistically (U = 179.5, p = 0.583).

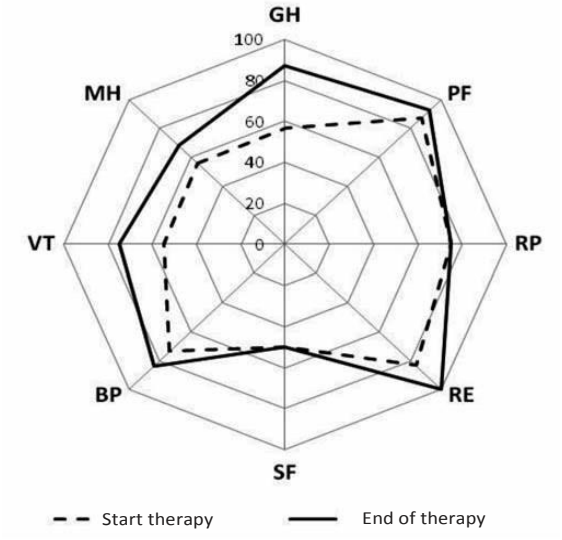

Fig.2: Dynamics of the median values of quality scales in Group 2 patients after therapy

Evaluation EGD data

According to EGD in all patients included in the study had been diagnosed with chronic *H. pylori*-associated gastritis.

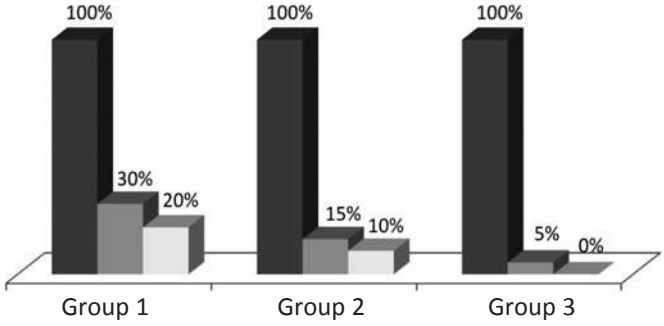

Fig. 4. Dynamics of the detection rate of *H. pylori* in the controlled groups after URSA therapy

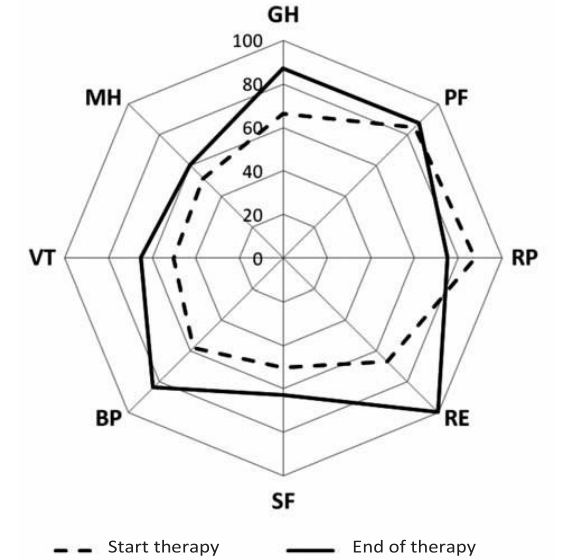

Fig.3: Dynamics of the median values of quality scales in Group 3 patients after therapy

7 (12%) patients had scar bulbs KDP deformity, 13 (22%) patients had erosions in duodenal bulb, all patients had swelling and redness of the mucous DPK.

22 (37%) patients had an ulcer duodenum, in 14 (23%) patients erosive bulbit was found, the remaining 24 (40%) patients had catarrhal duodenitis.

Against the background of the therapy all groups of patients showed an improvement in endoscopic picture - ulcerative defect healed until follow-up in all patients who had duodenal ulcers at the start, patients with erosive duodenitis and epitelizirovalis erosion restored on the available therapy. Thus hyperemia and edema of the mucous membrane of the stomach and duodenum were maintained in 5 (25%) patients in group 1 and 2 (10%) patients in group 2 and 2 (10%) of 3 patients.

Table 7. Dynamics of the results of histological examination and urease test for detection of *Helicobacter pylori* infection in the study groups

Observation unit	The number of patients with positive diagnostic result *H. pylori*, abs. (%)		The significance of differences "Before - after», p	The significance of differences between groups, p
	Start of therapy	End oft he therapy		
Microscopic examination				
group 1, n=20	20 (100)	6 (30)	<0,001	0,102
group 2, n=20	20 (100)	3 (15)	<0,001	
group 3, n=20	20 (100)	1 (5)	<0,001	
Urease test				
group 1, n=20	20 (100)	4 (20)	<0,001	0,108
group 2, n=20	20 (100)	2 (10)	<0,001	
group 3, n=20	20 (100)	0 (0)	<0,001	

Evaluation of the histological method and urease test for diagnosing H. pylori

At baseline, all patients included in the study had the diagnosis of *H. pylori* positive detected by histological examination and urease test (according to the inclusion criteria for the study).

After the treatment in all 3 groups the frequency of detection of a positive outcome of *H. pylori* diagnostics on the results of a histological (microscopic) examination and urease test was statistically significant reduced (**tab. 7, Fig. 4**). Nevertheless, in the group treated with Helinorm, after the end of therapy, only in 1 patient the histological examination revealed the presence of *H. pylori*, in contrary to the 6 and 3 patients in the control groups with the addition of De Nol and simply eradication therapy, respectively.

As seen from the data obtained from the patients enrolled in the study of detecting *H. pylori* both using the histological method and the urease test no significant differences were detected.

The discussion of the results

According to the analysis of study data after eradication therapy clinical positive dynamics were observed in all 3 groups of patients, but the pain was eliminated significantly better in the group 3 patients treated with Helinorm in addition to the standard eradication therapy. Also drew the attention of the lack of adverse events in the group receiving the Helinorm investigational product that allows you to make a favorable opinion in respect of its safety profile.

After using the product Helinorm in combination with eradication therapy an obvious improvement of quality of life was noticed compared with conventional eradication schemes of *H. pylori*, especially improving the quality of life of patients was associated with a decrease in severity of pain. The elimination of *H. pylori* demonstrated by both tests (histological and urease) was more effective in patients treated Helinorm (95 and 100%, respectively), while the endoscopic pattern was similar in all 3 groups of the observation study.

These results suggest that the inclusion of the product Helinorm in standard eradication regimen can improve the therapy of *Helicobacter* pylori-associated diseases. With regard to effectiveness this combination is comparable with the group treated with eradication therapy + De-Nol, and futhermore the good tolerability and safety profile of Helinorm qualifies the product to use it in combination with drugs to combat *H. pylori*.

Conclusion

Product Admission Helinorm with standard eradication therapy:

- improves the efficiency of eradication of H. pylori by 10%;
- has a positive effect on the clinical picture of diseases like *Helicobacter pylori*-associated duodenal ulcer and in particular it contributes to relief of abdominal pain;
- It has a good tolerability and safety;
- It improves the quality of life indicating the health and economic benefits of this treatment approach.

Thus, Helinorm can be recommended for use in patients with *Helicobacter* pylori-associated diseases..

The recommended regimen of Helinorm product is: 1 capsule 2 times per day for 28 days, in combination with eradication therapy.

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* Среди реализуемых в России БАД, подавляющих Helicobacter pylori.

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