ENTEROSGEL RESEARCH

Innovative entrosorption method
EnteroMed Limited

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Enterosgel
Introduction

The term “enterosorption” has been proposed to define a method of sorption therapy based on daily oral administration of “enterosorbents”. Enterosorbents were known in the past because the tradition of eating natural clays in case of poisoning, for improvement of well-being, jugulation of diarrhea, and, possibly, for treatment of deficiency in microelements, goes back to bygone times, and as a phenomenon known as geophagia it was observed particularly in primates [6, 7]. However, Enterosgel, comparing to other sorbents has unique hydrophobic and selective sorption properties, which made it effective and safe in wide range of medical applications. Enterosgel has proven it’s safety and efficacy during 35 years of clinical studies and use in major hospitals of the Soviet Union, it is recommended in the official guidance of Ministry of Health for treatment of various diseases. Since 2008 Enterosgel is certified as a medical device class IIa and available as an OTC treatment in Europe.

Enterosgel is an innovative hydrophobic intestinal adsorbent (enterosorbent), developed for safe, simple and effective cleansing of the gut from toxins, harmful substances, allergens and pathogens. It doesn’t remove water or vitamins and doesn’t stay in the body. It is completely excreted unchanged within 12-24 hours. Main clinical effects of Enterosgel are:

- **Helps to reduce or prevent toxic & allergic reactions.**
- **Helps to stop diarrhoea or shortens the duration of diarrhoea.**
- **Relieves the symptoms of indigestion.**
- **Accelerates the elimination of alcohol from the body.**
- **Helps to restore beneficial intestinal microflora.**
- **Protects the intestinal wall and promotes its healing.**
- **Reduces the toxic load on the liver and kidneys.**

There are more than 400 human clinical studies with Enterosgel , which have proven the efficacy of Enterosgel in different treatments. It can be recommended for effective relief from:

- Diarrhoea
- Indigestion
- Food poisoning
- Upset stomach
- Travellers’ tummy
- Food Allergies
- IBS-D

Enterosgel is suitable for Babies 0+, Children & Adults. It is Non-allergenic. Enterosgel can be taken during pregnancy and breast-feeding.

Enterosgel is recommended by leading gastroenterologists, dermatologists, nutritionists and other healthcare professionals. World Health Organization specialists recommend to use Enterosgel in case of food poisoning. Enterosgel can be recommended for use by healthy people to help detoxify the body, which can increase body resistance and promote general health improvement.

Living in the “gut era” with throusands of studies about gut published on PubMed, we certainly can see the importance of detoxifcation for improvement of health conditions. Enterosorption method for complex detoxofocation of the body has been developed in 1980-s and hundreds of good quality studies were published since then. This booklet provides an insight into Enterosgel enterosorption method and an update on research carried out up to date.

Ingredients of Enterosgel:

70% Polymethylsiloxane polyhydrate, 30% Purified water.

FREE FROM:

Preservatives, colouring, gluten, fat, sugar, lactose, flavours and sweeteners.

Contraindication: intestinal atony.

Possible side effect: constipation can occur in very rare instances.

Enterosgel is easy to take and has no taste: dilute in 100 ml of water or other liquid and drink 1-2 hours before or after a meal.

Acute diarrhoea	Bacterial, viral (including norovirus), gastroenteritis, IBS, travellers' diarrhoea
Chronic diarrhoea	Chronic inflammatory bowel disease, malabsorption syndrome
Indigestion	Nausea, heartburn, reflux, abdominal pain, discomfort
Intestinal microflora disturbances	Caused by taking antibiotics
Gastro-intestinal disorders	Helicobacter pylory, ulcerative colitis, duodenal ulceration, chronic hepatic conditions, chronic pancreatitis, inflammatory bowel disease
Poisoning	Food, alcohol, medicines, contaminated water
Nephrology	Chronic kidney disease
Allergy and Dermatology	Food allergy, atopic eczema, urticaria
Prophylaxis	Atherosclerosis and coronary heart disease, chronic intoxication

Age	Dosage	How often
Children under 1	1/3 of teaspoon or 1.7g up to 10g	up to 6 times a day per day
Children 1-5	1-2 teaspoons or 5-10g up to 15-30g	3 times a day per day
Children 5+	2-3 teaspoons or 10-15g up to 30-45g	3 times a day per day
Adults	1 tablespoon or 15g up to 45g	3 times a day per day

Pre-clinical data on Enterosgel

1. Structure and adsorption properties of Enterosgel

Enterosgel® is a polymethylsiloxane based hydrogel produced by polycondensation of methylsilicic acid with the loss of water and formation of siloxane bonds (=Si-0-Si=). Upon organosilica gel drying, a solid mesoporous adsorbent (xerogel) with specific surface area of up to 300 m2g_l is formed. The xerogel content in the medicinal preparation Enterosgel is about 7%. The sorption process by Enterosgel follows two mechanisms - molecular adsorption and co sedimentation in the gel. Compared with activated carbons most commonly used as oral sorbents (enterosorbents), Enterosgel possesses lower capacity towards compounds with molecular weight below 1,500 Da, but it is a much more potent adsorbent than activated carbons in its binding ability towards high molecular weight compounds such as proteins and bacterial endotoxins. In many experimental and clinical studies which evaluated oral use of Enterosgel for treatment of wound infection, abdominal sepsis, ischemic hypoxia, acute intestinal infections, viral hepatitis, complications of chemo- and radiotherapy of cancer, it has been demonstrated that enterosorption led to normalization of intestinal microflora, suppression of lipid peroxidation and oxidative modification of plasma proteins, restoration of detoxifying and synthetic liver functions, improvement of renal functions, as well as decreased manifestations of systemic toxicity. These useful sorptive properties along with positive clinical results allow the consideration of Enterosgel as an effective enterosorbent and open a wide potential for its use in combined treatment of diseases requiring long-term oral chemotherapy, such as tuberculosis, AIDS, rheumatoid arthritis and viral hepatitis C.

This hydrogel has structure of a globular porous substance that may be described in terms of traditional structure-sorption parameters such as size of a globule, specific surface area, size and volume of pores, and pore size distribution.

Stable hydrogen bonds of the type = Si-0" *H0-Si = play an important role in formation of the hydrogel structure. The preparation of a methylsilicic acid hydrogel is an intermediate stage of polymethylsiloxane synthesis, the final solid product of which is a xerogel of methylsilicic acid obtained from hydrogel by its desolvatation (dehydration) at 120°C according to Eq. (21.1):

(C H , S i O l 5 • n H 20) m (C H . S i O , s) m + n m H 20

This xerogel has well developed porosity mainly in the mesopore range, which is partially regulated during synthesis, with specific surface area up to 300 m2g_l and total pore volume up to 1 cm3g_l. However, the hydrogel rather than xerogel has attracted most interest as an enterosorbent (Fig1).

In terms of surface chemistry methylsilicic acid hydrogel, or polymethylsiloxane is a polyfunctional adsorbent which contains both hydrophobic CH3-groups and hydrophilic OH-groups. It is considered that the porous structure of the hydrogel is created by adjoining nano-granules with the size of approximately 50 nm, and with the interstitial space filled with water. These granules form larger agglomerates, which are organoleptically felt; that is why during production Enterosgel undergoes careful cavitation treatment to shift particle size distribution towards a range of 10-20 and to improve the taste of the preparation. Polymethylsiloxane hydrogel contains nearly 6-7% of the solid matrix, the rest being water. This hydrogel has unusual sorption properties different from those of the xerogel.

Enterosgel and the dispersed xerogel have near the similar adsorption capacity for methylene blue, but a completely different picture is observed in the case of adsorp tion of human serum albumin, a large molecular weight solute. The adsorption capacity ratio of Enterosgel to xerogel for HSA is 28.5:1 (Table 1).

This result indicates existence of two mechanisms of adsorption by Enterosgel, (1) physical adsorption of low and medium molecular weight solutes, and (2) co-precipitation in the gel of compounds of high molecular weight, such as blood plasma proteins, enzymes, and bacterial toxins.

As follows from Table 2, sorption capacity of a conventional carbon enterosor bent for adsorbed compounds, including medicinal preparations with molecular weight <1.5 kDa, is significantly higher than that of Enterosgel both in absolute values (mg/g) and adjusted to an average daily dose. For high molecular weight solutes the ratio Aesg/Acar bo is higher than unity. The higher binding capacity of Enterosgel could be possibly explained by co-precipitation of these compounds with the gel. Meanwhile, low capacity of enterosorbent for solutes with molecular weight <1,500 Da is very important in practice, because molecular weight of the majority of medicinal prepara tions administered orally, are low molecular substances with molecular weight in this range. In principle, this fact allows the use of Enterosgel alongside the main drug therapy without the risk of depleting the prescribed drug by adsorption with the gel.

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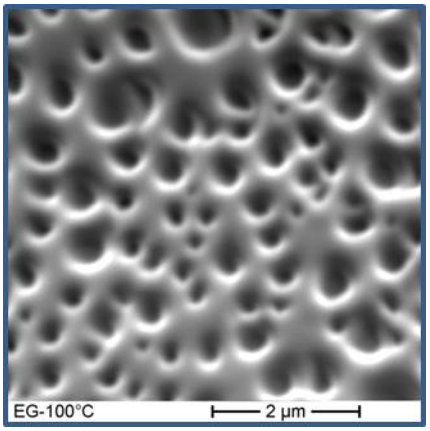
FIGURE 1

Scanning electron microscopy image of PMSPH



For evaluation of efficiency of medical sorbents, the issue of their deliganding properties, i.e. an ability to withdraw toxic protein bound compounds (ligands) is of great importance. If a sorbent possesses strong deliganding capability as, for example, some types of modem carbon hemosorbents do [11, 12], then after contact with such an adsorbent, the ratio of molar concentrations of ligand - protein carrier (ML/Mp) decreases, i.e. the transport protein transforms into a more purified state than it was initially (Table 3).

Contrary to carbon enterosorbents, Enterosgel does not possess an ability for selective removal of albumin-bound ligands regardless of their affinity with the protein carrier - weak (L-tryptophane), medium (sodium caprylate, deoxycholic acid), or strong (indole-3-carboxylic acid and unconjugated bilirubin). It means that if protein-bound toxins are removed by Enterosgel, this occurs simultaneously with adsorption of the carrier protein.

In contact with donor blood plasma at 1:5 w/w ratio, Enterosgel reduces concentration of total protein on average by 18%, albumin by 15%, a,-, a-2, P- and y-globulins by 34, 16, 25 and 12%, respectively. In parallel, total cholesterol decreases by 48%, approximately by an equal degree for high and low density cholesterols; concentration of phospholipids falls by 53% and triglycerides by 29%. This data is important for assessing the potential effect of Enterosgel as an extracting agent in extracorporeal detoxification. Enterosgel mixed with bovine bile, reduces the total cholesterol by 12%, triglycerides by 19%, phospholipids by 10%, and total bile acids by 18%, indicating a moderate decholesterolisation effect of Enterosgel.

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TABLE 1

Adsorption of low and high molecular weight solutes, in mgg~' of sili con matrix, on dispersed xerogel and on native Enterosgel

	Methylene blue, 373.9 Da	Human serum albumin, 67,000 Da
Xerogel	11.4	25
Enterosgel	17	714

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TABLE 2

Ratio of adsorptive capacity (A, m g g '1) of enterosorbents Enterosgel (ESG)/ Carboline (CARBO) adjusted to their daily doses

Solute	Molecular weight, Da	A Ent /A carbo
Paracetamol	251	0.0025
Uric acid	168	0.0056
Methyl Orange	327	0.0095
Methylene blue	374	0.0465
Rifampicin	823	0.0565
Salicylic acid	138	0.061
Vitamin B	1,355	0.263
Veronal	184	0.538
Serum Albumin	67,000	25.0
Lipopolysaccharide, LPS	From 10,000 to 500,000	1.79
Trypsin	23,300	50
IgG	150,000	100

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TABLE 3

Comparative efficacy (ML/Mp) of organosilicon and carbon enterosorbents for removal of protein bound ligands (Experimental conditions: 3% human serum albumin, phosphate buffer solution, pH 7.2, containing ligands with different degrees of affinity to the protein)

Ligand ML/M p	L-Tryptophan , 104 Da	Sodium L-caprylate , 166 Da	Deoxycholic acid , 392 Da	Indole-3-carboxylic acid, 161 Da	Unconjugated bilirubin, 584 Da
Initial	82.9	13.3	9.36	1.0	10.0
After contact with Enterosgel	81.5	13.6	8.8	1.0	10.8
After contact with Carboline	54.8	2.9	3.33	0.68	2.34

Pre-clinical data on Enterosgel

2. Toxicology of Enterosgel

In experiments assessing acute toxicity of Enterosgel carried out on rats (5 dose levels, from 50 to 10,000 mg kg-1 per day), mice and guinea pigs (500 and 5,000 mg kg-1 per day) it has been shown that Enterosgel paste is a low-toxic preparation (class IV toxicity). It has also been shown that the preparation expresses neither topical- induced irritation nor general sensitizing action towards mucosa and skin.

The study of sub-chronic toxicity of Enterosgel has been performed on male rats that for 3 months received daily doses of the preparation at 200, 400, 650, and 1,300 mg kg-1. No significant differences between animals in control and experimental groups were found by comparing their general behavior, orexia, body weight and weight of separate organs, morphological and biochemical blood composition, parameters of pro-oxidant and antioxidant homeostasis, with exception of total cholesterol level in animals that received the doses of 400 and 650 mg kg-1 body weight (2.12±0.05 and 2.02±0.07 mmolL'1vs 2.55±0.1 mmolL"1in control group).

Morphological studies performed by light and electron microscopy did not reveal any signs of toxicity of Enterosgel administered to animals at sub-chronic regimen.
In detailed studies of pregnant rats and their fetuses, no signs of embryotoxicity or teratogenic action of Enterosgel have been found, and this fact is very important due to traditional use of enterosorption for treatment of gestosis of first and second half of pregnancy. It is interesting to note that analysis of fetuses of experimental animals that received Enterosgel, for anomaly of bone system by Dawson's method showed a decrease in the number of cases with delayed ossification of cranium and breast bone compared to the control.
Safety of Enterosgel preparation in terms of mutagenic action has been shown in the tests for induction of chromosome aberrations in bone marrow cells, in cultured human peripheral blood lymphocytes, and in the Ames test for induction of reversible gene mutations in Salmonella typhimurium.

In experiments on BALB/c mice Enterosgel administered at the dose of 116 mg per animal for 2 weeks have not demonstrated immunotoxic properties according to key indices of humoral and cellular immunity. At the same time its positive influence on activity of peritoneal macrophages of experimental animals has been registered.
In experiments on rats with 2-week administration of Enterosgel at the dose of 1,500 mg kg-1 body weight, the possibility of silicon accumulation in the tissues of spleen, kidneys, lungs, stomach, small and large intestines, and cardiac muscle, was examined. No aberrations in silicon content were found in tissues and organs of experimental animals compared to control group that did not receive the preparation. No accumulation of silicon was found in organs and tissues of animals with injuries of gastro-intestinal tract mucosa caused by experimental induction of peptic gastric ulcer and ulcerative colitis, except for some elevation of silicon concentration in the gastric wall. There was no accumulation of silicon in spleen, lungs, kidneys, liver, and muscles of rats after 2-week and 4-week application of Enterosgel- containing preparation over the large facial skin wound.

The conclusion derived from the data described above is that Enterosgel does not possess any noticeable toxicity, and its use in experiments on rats has not led to silicon deposition in internal organs and tissues.

3. Enterosgel for treatment of diseases of gastrointestinal tract in adults and children from birth.

LG Nikolaeva used enterosorbents Enterosgel, activated carbon KAU and lignin sorbent Polyphepan for treatment of patients with Flexner dysentery and salmonel losis [13]. Oral adsorbent therapy accelerated the regression of symptoms of acute intestinal infection, decreased the expression of endogenous intoxication, and reduced by 2-3 days the period of contamination by enteric pathogens in the patients. In Table 21.4, the data characterizing the effect of Enterosgel administra tion (1-1.5 gkg-1 body weight per day) on treatment of rotaviral infection (intesti nal influenza) in 50 newborns, are presented [14].
This result is of special importance if one takes into account the wide spread rotaviral infection of newborns in third world countries.
L.A. Valenskaya et al showed that in children suffering from dysentery, Enterosgel administration improves digestion of maltose, studied by the method of carbohydrate load test [15].

O.A. Putilina et al. reported positive experience of Enterosgel use for treatment of dysentery and salmonellosis in adults and children, also noting a significant reduction of the period of intestinal malfunction [16].

According to Yu.A. Sukhov et al, administration of Enterosgel to patients with acute intestinal infections led to significant decrease of the plasma concentration of pro-inflammatory cytokines TNF-a and IL-2 [17].
In the work of M.A. Andreichin et al, Enterosgel was administered to patients with acute intestinal infection (All) caused by opportunistic flora and shigella Sonne [18]. It was shown that enterosorp tion promoted regression of pathogenic symptoms, decrease of integral indices of endogenous intoxication as well as normalization of such indices of intestinal mucosa injury as the level of I-FABP protein in blood plasma, and content of lyzozyme in faeces. Furthermore, a number of positive consequences of using Enterosgel were observed in reconvalescent patients during the study of their intes tinal microbiocenosis. In general, it has been shown that enterosorption signifi cantly increases the number of reconvalescents with minimal grade I dysbiosis along with simultaneous decrease of the number of cases of grades III and IV dys biosis. The same researchers found that 10-day administration of Enterosgel to 20 clinically healthy individuals resulted in positive alterations of intestinal microflora via increase of titers of bifidobacteria and lactobacilli, and decrease of present opportunistic microorganisms.

A similar result was obtained during the study of Enterosgel in rats: 90-day administration of the enterosorbent led to improvement of the state of microflora of experimental animals with disappearance of bacteria non-characteristic of intestinal ecotopes, and predominance of lactobacilli in the small intestine [10]. These experimental and clinical results undoubtedly open prospects for use of Enterosgel in prophylaxis of dysbiosis and treatment of its widespread sub-clinical forms. Introduction of Enterosgel in the conventional therapy of intestinal dysbacteriosis leads to marked positive alterations in microbio- cenosis indices in 98% patients [19]. Positive influence of Enterosgel on enteric microflora has also been observed upon administration of this preparation to patients with viral hepatitis [19], and children with severe burns [20].

Of significant interest is an attempt to use Enterosgel for therapy of chronic hard-to-treat diseases of gastro-intestinal tract such as malabsorption syndrome, gluten enteropathy, exacerbation of chronic enteritis, post-resection syndrome and the syndrome of irritated large bowel.
As follows from Table 3, administration of Enterosgel significantly acceler ates remission of patients compared with the control group.

Prophylactic and therapeutic administration of Enterosgel to rats with experimental peptic ulcer and ulcerative colitis, significantly decreased the number and surface area of lesions on gastro-intestinal tract (GIT) mucosa and reduced the severity of the syndrome of endogenous intoxication that accompanied these injuries [21, 22]. The first evidence of clinical use of Enterosgel in combined therapy of peptic gastric ulcer and duodenum was reported by S.M. Tkach, who had noted that enterosorp tion significantly reduced the number of side effects of treatment, and the rate of Helicobacter eradication increased from 83.3 to 93.3% [23].

Data concerning Enterosgel use in the treatment of nonspecific ulcerative colitis in clinic have also been published. Local disbalance of the immune system of the gastro-intestinal tract plays a significant role in pathogenesis of this autoimmune disease, and there is a potential for therapeutic treatment of ulcerative colitis by enterosorption. This statement is supported in particular by results reported by O.I. Osadchaya et al, who studied the influence of Enterosgel on humoral immunity, indices of lipid peroxidation, and level of endogenous intoxication [24]. Positive influence of Enterosgel administration was detected in such indices as content of diene conjugates, Schiff bases, circulating immune complexes (CIC), percentage of patients with positive test to serum cryoglobulins, plasma concentration of cryo globulins and plasma concentration of IL-10. These changes were moderate and did not lead to significant normalization of the altered indices. A tendency for improve ment compared to the control group was revealed in many other parameters, such as content of C-reactive protein and ceruloplasmin, degree of oxidative damage of blood plasma proteins, concentration of sodium nitrite, binding ability of blood plasma proteins, ethanol test, ratio of content of immunoglobulins of different classes, concentration of serum albumin, content of compounds with medium molecular weight (“medium molecules”), and pro-inflammatory cytokines TNF-a, IL-ip and IL-6. Being moderate in absolute value, all these shifts nevertheless are of unidirectional character and could be interpreted as a result of positive alteration of nonspecific ulcerative colitis, due to the use of Enterosgel.

TABLE 4

Dynamics, in days, of the main clinical manifestations in patients with chronic diseases of digestive system organs.

Index	Control group	Enterosgel group
Normalization of number of stools	20.5 ±1.5	6.0+ 1.4
Formation of fecal masses	21.4 ±2.5	15.4 ± 2.5
Disappearance of pain syndrome	19.4 ± 1.6	10.6 ± 1.9
Disappearance of pain meteorism	18.5± 1.0	10.5± 1.8

Pre-clinical data on Enterosgel

4. Enterosgel in treatment of hepatic and renal failure

In the study of N.A. Gorchakova et al, Enterosgel was used for the treatment of fulminant hepatitis in rats caused by administration of tetrachloromethane [25]. It was noted that enterosorption hampered lipid peroxidation in liver tissue of experimental animals, elevated activity of enzymes of the antioxidant pool and decreased activity of serum transaminases, which indicates better preservation of hepatocyte membranes.

O.R. Grek et al, used multiple administrations of CC14 in combination with drinking of 5% ethanol for modeling of chronic hepatitis in rats. They demonstrated a stable positive effect of Enterosgel administration on activity of serum transaminases and alkaline phosphatase, as well as the rate of hepatic metabolism of xenobiotics [26].

A number of authors reported positive influence of Enterosgel on the course of acute viral hepatitis A and in children and adults [27-33]. Patients who received enterosorbents had faster relief of cholemic syndrome and hyperenzymemia, attenuation of skin itching, and improvement of biochemical indices compared to patients from control group. M.A. Andreichin et al, administered Enterosgel to patients with chronic hepatitis C, who also received interferon inducers as basic therapy. It was shown that along with positive subjective effects, enterosorption leads to a decrease in the activity of serum alanine-aminotransferase (ALAT) and decrease in concentration of serum thrombomodulin that serves as an indicator of the degree of endothelial malfunction occurring as a consequence of viral depen dent injury of vascular endothelium [18].

V.V. Gebesh and I.G. Semenchenko compared the results of surgical treatment of patients with mechanical jaundice in groups that received or did not receive Enterosgel, and concluded that enterosorption led to significant improvement in the state of patients prepared for surgery and during post-surgical period [32]. Such an improvement was seen not only in indices of cholemia and enzymemia, but also in nitrogen-excreting renal function, electrolytic balance, serum concentration of albumin, and leukocyte formula. The average reduction of patients' stay in hospital was 3.5 days, and mortality in the group treated with Enterosgel decreased from 25 to 15% compared to the control group.

In the work of I.M. Skalich and N.I. Zhigarenko (1998), Enterosgel was used as a part of combined therapy for liver pathology of alcohol etiology [34], while O.I. Osadchaya et al, showed that in patients of this category, transport function of albumin due to Enterosgel administration increased from 35 ±7 to 57 ±7 mg of an organic dye (Congo red) per 1 g of protein versus 36±4 and 39±5 mgg'1in the control group and 90± 10 mgg-1 in healthy donors [24].

Use of Enterosgel for treatment of renal pathologies is of particular interest. A 2-week administration of Enterosgel had positive influence on the indices of kidney function and survival of rats with a glycerol model of renal insufficiency [35].

The use of different enterosorbents including Enterosgel for treatment of chronic renal insufficiency of II and III stages was studied in detail by N.A. Kolesnik, who showed that an optimized dose of Enterosgel of 90 g daily administered for 3 months, was able to decrease azotemia levels in 35% of patients, and to prevent its elevation in 25-30% of patients [36]. This is in agreement with results on the use of carbon enterosorbents obtained a decade earlier [1, 37].

M.F. Valentis suggested to administer Enterosgel to patients with chronic renal insufficiency for 6 months or longer, and noticed an improvement of their state as early as 4-5 days after start of treatment, particularly decrease of azotemia grade and metabolic acidosis, which allowed patients to increase their daily protein consumption [38]. These experimental and clinical results are especially interesting, because unlike activated carbon, Enterosgel has low adsorptive capacity towards low molecular uremic metabolites such as urea, creatinine, and uric acid. It is also incapable of breaking down the protein-bound uremic toxins as opposed to synthetic activated carbon enterosorbent SCN used in the former USSR, and more

5. Enterosgel for Diabetes Mellitus and Dyslipidemia

In experiments on rats with streptozotocin induced diabetes, Enterosgel preparation was shown to have normalizing influence on the indices of lipid profile, parameters of pro-oxidant-antioxidant homeostasis in liver tissue, and its histological structure [41], Decrease in concentrations of glycosylated hemoglobin, total cholesterol, triglycerides, lipoproteins of low and high density, urea and lipid hydroperoxides along with simultaneous decrease in activity of reduced glutathione, catalase, superoxide dismutase, cytochrome oxidase, and succinate dehydrogenase were significant compared to the control group. Certain positive shifts in lipidogram were also observed in rats with a simple model of alimentary cholesterolosis, as well as some decrease of activity of blood plasma ALAT and alkaline phosphatase, compared with animals from the control group [42]. It is interesting to note that, as in case with renal insufficiency, the effect of Enterosgel could not be explained by direct sorption of certain metabolites, because capacity of this sorbent towards triglycerides, cholesterol, urea, etc., is evidently insufficient. However, the experi mental results were in good agreement with clinical data for Enterosgel use in patients with diabetes and dyslipidemia.

For example, M.N. Dolzhenko et al, showed that in patients with insulin-dependent diabetes complicated with ischemic heart disease, administration of Enterosgel resulted in the decrease of low density lipoproteins by 20% on average, along with simultaneous increase of high density lipoproteins by 39% In addition to significant (compared to the control group) decrease of transaminase activity, and decrease of serum concentration of C-reactive protein - the most important marker of systemic inflammatory reaction [43, 44]. In diabetic patients with clear symptoms of non-alcoholic steatohepatosis, who received Enterosgel. total cholesterol of blood plasma decreased from 8.05 ±1.15 to 6.45 ±1.18 but remained unchanged in the control group. In patients with diabetes complicated with acute coronary syndrome, administration of Enterosgel resulted in improvement of biochemical indices and had a positive effect on systolic and diastolic function of the left ventricle, and led to the decrease of ventricular extra- systolia [43, 44].

In the study of E.A. Dotsenko and T.F. Zhiznevskaya, Enterosgel was administered for 1 month in a single dose of 15 g at night or 15 g twice a day to 48 patients with hypercholesterolemia (>6.5 mmolL'1), hypertriglyceridemia (>4 mmol L~'), or with a level of high density cholesterol below 0.7 mmolL-1 [45]. The scheme with double administration of the preparation per day was found to be more effective and led to a decrease of total cholesterol by 9%, triglycerides by 47% and index of atherogenicity by 8%. In parallel, in the control group (40 patients), concentration of triglycerides increased on average by 3%.

6. Enterosgel for Treatment of Endogenous Intoxications in Surgical Clinic

Prophylactic administration of Enterosgel to rats 4 days before acute blood loss at the level of 20-25% of the circulating blood volume was found to be effective for mitigation of biochemical manifestations of oxidative stress caused by hemic hypoxia [10].

In comprehensive experimental work of A.V. Nedelyaeva, Enterosgel was studied along with other enterosorbents in experiments with a model of severe bums in rats and mice [46]. It was shown that enterosorption had a positive influ ence on protein-synthesizing liver function and concentrations of serum albumin in wounded animals. Activity of serum transaminases and the content of products of lipid peroxidation decreased, while concentration of ceruloplasmin, a protein with antioxidant properties, increased. Administration of Enterosgel led to a decrease of the level of serum peptides of medium molecular weight and total plasma toxicity, as well as preserved glycogen content in hepatocytes.

O.I. Osadchaya and A.M.Boyarskaya recently studied the effect of Enterosgel
on the plasma concentration of pro-inflammatory cytokine TNF-a. Its level is significantly increased in severely burned patients, however, in patients treated with Enterosgel, concentration of TNF-a was significantly lower by day 19-21 com pared to the control group (184.2± 14.4 versus 256.0+15.7, and 24.2±6.0 pgmL-1 in healthy individuals). In addition, simultaneous elevation of interleukin IL-4 concentration was seen in these patients to 107.0 ±9.0 versus 94.4 + 9.8 in the control group, and 32.7±7.5 pgmL-1 in healthy individuals [48].
Taking into account the fact that carbonyl groups in blood plasma proteins are generated upon interaction of oxygen with histidine, arginine, lysine, and proline, their concentration could be used as an indicator of oxidative stress. The data pre sented in Table 21.7 provide evidence of the systemic action of Enterosgel directed at mitigation of oxidative stress.

Pre-clinical data on Enterosgel

V.N. Losytska et al. found that in patients with severe bums treated with Enterosgel, total binding of congo red by blood plasma on the 19th day after trauma increased to 80± 15 versus 50± 12 pgmg-1 of protein in the control group with the healthly standard being 100 pgmg-1 [49].

B.S. Sheiman et al, reported a significant decrease in concentration of “middle molecules” by the 10th day, and diene conju gates by the 20th day after the trauma in patients with large bums was treated with Enterosgel [50, 51]. They also observed a tendency for more rapid normalization of phagocytic activity of neutrophils in these patients compared to the control group. In patients with severe bums treated with Enterosgel some deceleration of the reaction of rosette formation occurred upon the use of autologous serum or its fractions in toxemic and in septico-toxemic stages of bum disease. This observation may indicate a mitigation of autoimmune processes influenced by enterosorption [50, 51].

O.I. Osadchaya et al, revealed an increase of functional activity of B-lymphocytes in reactions of spontaneous blast-transformation induced by autologous serum in burned patients who underwent treatment with Enterosgel [52]. I.V. Naida et al, reported a favorable influence of Enterosgel on some factors of cell immunity in elderly patients with severe bum disease [47].

A.M. Boyarskaya et al, explained the positive result of Enterosgel use in therapy of intestinal dysbiosis in bum disease, not only by local action of the enterosorbent, but also with elevation of non-specific immune resistance to the organism caused by it [20].

V.A. Mastchenko also reported a positive influence of Enterosgel on enteric microbio- cenosis in children with severe and extremely severe bum trauma [53].

N.V. Pasechko and L.P. Polivanova, who treated pigs with partial-thickness and deep bums (20% of body surface) with Enterosgel, detected a significant improvement of morphofunctional state of intestines including mucosa and structure of myocytes of the intestinal wall, compared to the controls [54].

Summarizing the experience of Enterosgel use in 400 patients of the Novosibirsk Bums Center, A.A. Shmarin noted that 2-week-long use of enterosorption in the therapy of injured individuals starting on the 3rd day after the trauma, decreased the number and intensity of pyretic reactions in patients, improved appetite and decreased the number of GIT complications [47, 55]. As a rule, in these patients leukocytosis was lower, deficiency of body weight less pronounced, superficial drying and scab sequestration occurred more rapidly, and edging epithelization of bum wound began earlier. The period of treatment of superfi cial and partial-thickness bums was reduced by 3-5 days, whilst in deep bums the period of wound preparation for autografting was reduced by 2-3 days.

V.V. Nikonov et al, proposed use of massive doses of Enterosgel combined with Fortrans laxative and various eubiotics as the means for prophylaxis of endotoxemia, oxidative stress and bacterial translocation during preparation for surgery associated with the risk of massive blood loss, and in critical state patients with multi-organ insufficiency, severe bums, sepsis, and polytrauma [56]. This scheme may be used for therapy of different pathologies such as chronic hepatitis, allergy and exacerbation of bronchial asthma.

V.V. Luzin proposed to use Enterosgel slurry in nasogastric drainage of intestine in patients with acute enteric insufficiency and expressed paresis of small intestine [57].

T.I. Chemysh, who administered Enterosgel through nasogastric pathfinder in patients with diffuse peritonitis, showed that such manipulation significantly reduced the period of enteric paresis by more than 40 h [58].

A.G. Lebedev et al, performed intestinal lavage with Enterosgel slurry through a pathfinder with double opening placed during surgery, or enterostoma, and this was found to be beneficial for symptom relief of postsurgical paresis in patients with intestinal commissure and necrotic pancreatitis [59]. Some authors suggested that administration of Enterosgel proved to be useful at different localizations of purulent inflammatory process [60].

7. Enterosgel in Oncology

T.A. Ageev et al, studied efficiency of the scheme “cyclophosphane-vincristine- prednisolone” for the therapy of transplanted lymphosarcoma, and found that administration of Enterosgel to animals decreased liver cell damage and concentration of«middle molecules»in blood serum to 0.433±0.043 a.u. vs 0.704±0.037 a.u. in the control group, without interfering with chemotherapy [61].
In the opinion of some researchers, Enterosgel is a useful means of application in oncological surgery, which reduces the number of postsurgical complications and relieves the course of postsurgical period in patients with mechanical jaundice, improves indices of enteric microbiocenosis, decreases concentration of«medium molecules » and intensity of local proteolysis [62-64]. According to their data, use of Enterosgel in patients undergoing intense courses of polychemotherapy, reduced intensity of nausea and vomiting, decreased the value of hematological indexes of intoxication, and improved the structural and functional state of the erythrocyte membrane. The number of patients with expressed (<2x 109 L_l) leukopenia was reduced on average from 33% to 18%, whilst in patients undergoing chemotherapy due to tumors of the digestive system, these differences were 21.2% vs 54.6% in the control.

L.V Guta considered administration of Enterosgel during polychemo therapy of ovarian cancer of III - IV stages useful, noting better tolerability of treatment and decrease of«middle molecules» concentration in the plasma of these patients [65].

M.I. Loseva et al, used Enterosgel for therapy of patients with acute lymphoblastic and myeloid leukosis, and registered more rapid remission of the patients along with a number of positive biochemical and clinical effects [66].

8. Enterosgel in Allergy and Skin diseases in adults and children

O.Yu. Pobereznik et al, used oral administration of Enterosgel in combination with its cutaneous application for treatment of 70 patients with eczema and allergic dermatitis, while 70 patients with the same diagnosis were assigned to the control group. The authors noted that in the group of patients treated with sorption therapy of Enterosgel, cutaneous rash disappeared 4 days earlier than in the control group, and their stay in clinic was 15.7± 1.5 days versus 19.5+1.8 days for patients not treated with Enterosgel [67].

A.A. Baranov et al, reported a notable acceleration of jugulation of obstructive syndrome and usefulness of Enterosgel for liquidation of signs of endogenous intoxication and decrease of IgE plasma content in children with bronchial asthma, periodermitis, recurrent urticaria and Quincke’s edema [68].

N.V. Banadina noted milder expression of lactase insufficiency and endotoxemia in children with bronchial asthma treated with Enterosgel [69].

V.V. Batov confirmed significant acceleration of eczema syndrome regression in patients receiving Enterosgel and their robust remis sion occurred 8.0±3.5 days earlier than in control group (25.0±4.1 days) [70].

Pre-clinical data on Enterosgel

9. Enterosgel in Other Medical Applications

A.I. Pal'tsev (1999), recommended to use Enterosgel for treatment of gestosis in the first and second half of pregnancy [71], and Yu.K. Gusak et al [72], and L.N. Ilyenko et al [73, 74] successfully applied a combination of oral and intravagi- nal administration of this sorbent for treatment of nonspecific colpitis and vaginitis.

Favorable influence of Enterosgel on the course of postsurgical period upon surgery of organs of small pelvis was reported by a number of authors, who also recom mended introducing this sorbent in therapy of placental dysfunction [73-75]

Despite its low capacity towards compounds of low and middle molecular weight, Enterosgel has attracted the attention of specialists in professional pathology, who pro pose to include it into the therapy of chronic professional intoxications with aromatic hydrocarbons, benzene, cyclohexane, aldehydes, heavy metals, and organophosphate pesticides [76-79]. Such recommendations are based on the positive influence of Enterosgel on the state of pro-oxidant-antioxidant homeostasis and detoxifying func tion of liver and kidneys, as well as its ability to mitigate systemic manifestations of endogenous intoxication syndrome and to correct intestinal dysbiosis.

Summarizing their 5-year experience of Enterosgel use in a psychiatric clinic, T.N. Pushkareva and A.P. Chuprikov proposed a few schemes for use of the prepa ration in treatment of different forms of schizophrenia, and noted that enterosorp tion did not affect concentration of psychotropic drugs in urine [80].

A.M. Mosunov and A.V. Pozdnyakov used Enterosgel for acceleration of regres sion of hepato-depressive syndrome in patients with severe diffuse liver pathology, and reported shortened terms of disability of these patients from 29.4±3.8 to 18.3 ± 2.4 days [81].

A.B. Kaydulov and I.V. Vasilenko observed fast reduction of toxic and abstinent events as well as improved functional state of the liver and decreased requirement for transfusion therapy in patients with alcoholic intoxica tion and in patients with abstinence syndrome of moderate severity, treated with Enterosgel [82].

Some publications described successful use of Enterosgel for treatment of systemic osteoporosis in post-menopausal women [83], reactive arthritis associated with chlamydia or/and yersiniosis infections [84], and severe forms of acute pneumonia in children [85, 86].

-

10. Enterosgel for Treatment of Chronic Pathologies

Enterosgel has an extremely wide range of clinical applications.

The magnitude of this range has certain explanations. Firstly, Enterosgel is not a pharmacological preparation in the conventional sense. It is rather related to the same category of biomaterials as, for example, membranes for plasmapheresis that are also used for numerous indications. Secondly, there are a num ber of typical responses of the organism associated with Enterosgel use, which are repeated in the laboratory and in the clinic in the treatment of various pathological states. These responses include normalization of intestinal microbiocenosis, suppres sion of lipid peroxidation processes and activation of antioxidant defense, improved indices of lipidogram, decreased plasma concentration of "middle molecules", decreased plasma content of circulating immune complexes and pro-inflammatory cytokines, and positive immune modulation of many parameters of cellular and humoral immunity. One should also add improvement of detoxifying and synthetic functions of the liver and restoration of properties of hepatocyte membranes, improved renal functions, and elevation of regenerative-reparative potential of a number of organs and tis sues in general. Many of these phenomena are long term characteristics and poorly correspond to the properties of Enterosgel shown in vitro, and this fact once again points out the complexity and depth of mechanisms of therapeutic action of enterosorption.

By its therapeutic action, Enterosgel is a typical enterosorbent with proven therapeutic efficacy. Among the most important patterns of Enterosgel use linked to the spectrum of its adsorptive properties, is a possibility to prescribe it in parallel with administration of practically any oral pharmacological preparation. This pattern is based on a low (compared with activated carbon sorbents) sorption ability of Enterosgel towards compounds with molecular weight below 1,500 Da, to which the large majority of medicinal compounds administered orally belong.

In Table 4 comparative data on sorption of some antituberculosis and antiretroviral preparations by Enterosgel and a modern activated carbon enterosorbent Carboline, are presented.
As it follows from Table 4, Enterosgel has low capacity towards medicinal preparations studied as opposed to activated carbon. It does not mean that carbon sorbents should not be used for elimination of toxic effects of prolonged drug therapy - for this purpose one could separate drug administration from sorbent administration by 1-2 hours, and introduce meal consumption between them, how ever, in such cases Enterosgel is surely more suitable.
The results described above suggest a large potential for use of Enterosgel in mini mization of iatrogenic intoxications and other side effects of prolonged pharmaco therapy in combined treatment of such diseases as tuberculosis, HIV-infection and AIDS, rheumatoid arthritis, unspecific ulcerative colitis, Crohn's disease, some forms of syphilis and leprosy, and upon complications of decholesterolisation therapy. In all mentioned cases, the other important element of Enterosgel use is its ability to inter fere with pathogenesis of these diseases based on the listed useful effects.
These properties of Enterosgel are of great interest for treatment of HIV-infected patients. As follows from the study on HIV patients, Enterosgel accelerates the reduction of clinical symptoms in HIV-infected patients with diarrheic syndrome. At present diarrheic syndrome in HIV-infected patients is considered to be linked with development of malabsorption syndrome and general nutrition malfunction, and with decreased effi cacy of antiretroviral preparations towards HIV, persistent immunocompetent cells in the intestine, which make an important impact on disease progression [88, 89].
Apart from mitigation of various types of toxicity that are characteristic of anti retroviral preparations, and jugulation of diarrheic syndrome, Enterosgel may be useful for treatment of HIV-infected patients as a means of supportive treatment of concomitant diseases such as tuberculosis, viral hepatitis, acute pneumonia, and malignant neoplasm.

TABLE 5

Adsorptive capacity of Enterosgel and carbon enterosorbent Carboline towards some antituberculosis and antiretroviral preparations

Preparation	Molecular weight, Da	Enterosgel, mgg 1	Carboline, mgg-1
Isoniazide	137.1	0.02 ±0.01	9.11 ±0.41 2
Pyrazinamide	123.1	0.15 ±0.02	9.94±0.48
Rifampicine	823.0	1.50 + 0.18	19.77±0.7
Stavudine	224.2	0.00 ±0.00	25.14 ± 0 .0 1
Lamivudine	229.3	0.96±0.01	140.78 ±0.00

11. Conclusions

Enterosgel is an organosilicon material possessing unusual sorptive properties. It has low capacity towards compounds with molecular weight below 1,500 Da, but it is a much more potent adsorbent than activated carbons in its binding ability towards high molecular weight compounds such as proteins and bacterial endotoxins.

Numerous experimental and clinical studies have shown a wide range for its medical applications. Enterosgel administration as an oral sorbent led to normalization of intestinal microflora, suppression of lipid peroxidation and oxidative modification of plasma proteins, restoration of detoxifying and synthetic liver functions, improvement of renal functions, as well as decreased manifestations of systemic toxicity.

Due to an unusual relationship between its sorptive properties and the molecular weight of substances adsorbed, Enterosgel practically does not bind medicinal compounds administered orally, because in the majority of cases they have molecular weight below 1,500 Da. This characteristic of Enterosgel opens many prospective avenues for its use in combined treatment of chronic diseases associated with prolonged use of toxic pharmacologic preparations.

ENTEROSGEL HUMAN CLINICAL TRIALS

Dzyublik I, Shunko Em, Barbova A.

Use of Enterosgel in treatment of rotovirus infections in newborns

Objective

To study the effect of Enterosgel in treatment of rotoviral infections in newborns.

Methods

This was randomized study on 50 newborns diagnosed with intestinal influenza. Patients were randomly assigned to receive Enterosgel 1-1.5 g per kg of body weight per day. The study assessed 13 clinical and laboratory indexes (Table 1).

Results

The two groups were compared with no difference seen in baseline characteristicsa, all with symptoms of gastroenteritis. Treatment success was significantly higher in the Enterosgel group (already on the 2nd day of the treatment) compared with control group (Diagramme 1). No adverse reactions in treatment with Enterosgel were reported. Enterosgel was tolerated well by all children in the group.

Conclusions

This study provides evidence that Enterosgel can help to improve results and duration of treatment of the newborns with rotoviral infection. The use of Enterosgel in treatment allows to significantly decrease the number of days of intoxication, respiratory disturbances, hyperbilirubinemia, disturbed thermoregulation, tympanitis, posseting of milk, diarrhoea, dysbiocenosis, stay in the hospital, excretion of rotaviruses with stool. Enterosgel also helps to decrease the rate of complications (necrotic colitis and toxicosis with exicosis)

1

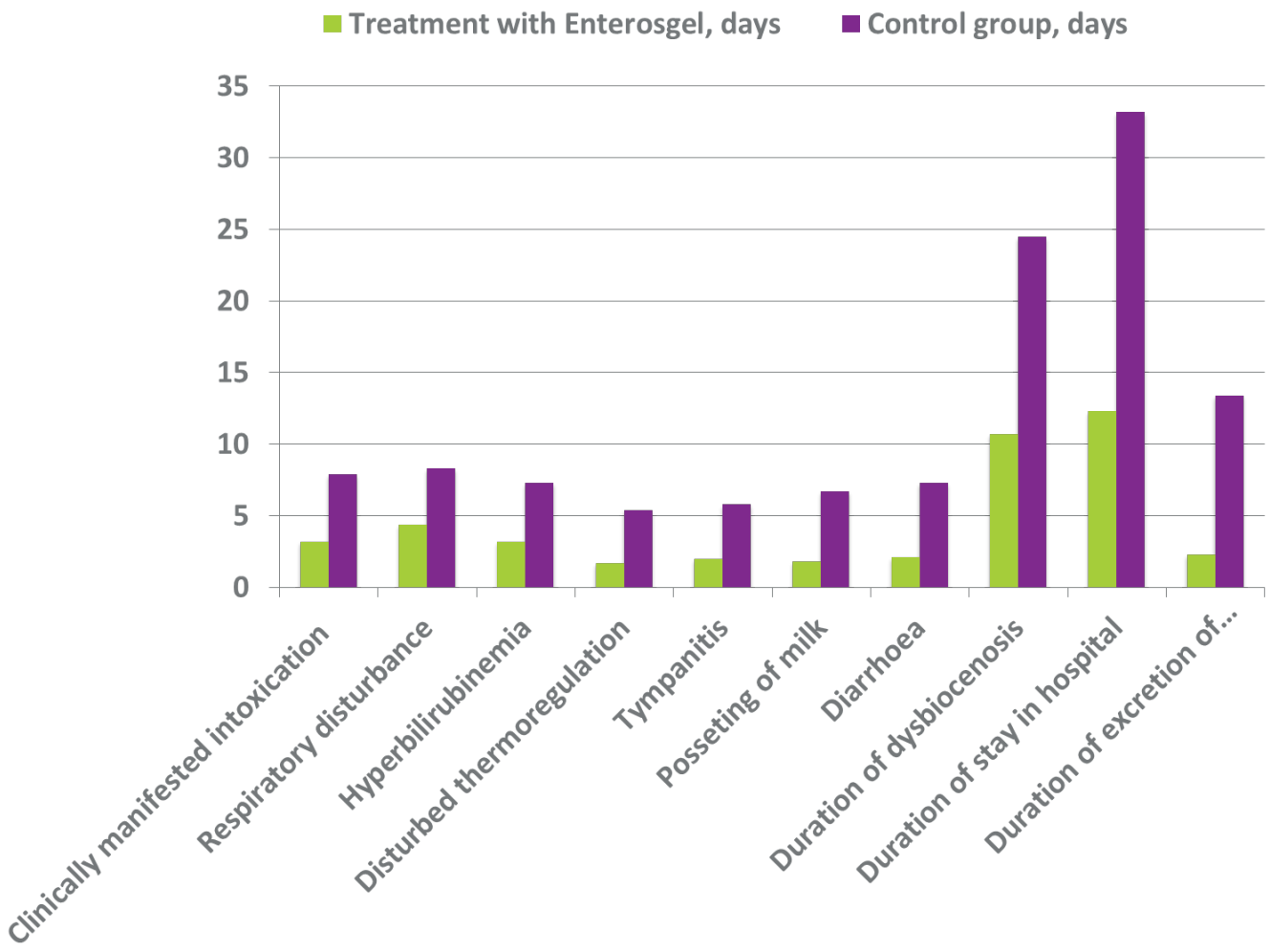
TABLE 1
Clinical and laboratory indexes of efficacy of Enterosgel in treatment of rotoviral infections in newborns

2

DIAGRAMME 1
Clinical and laboratory indexes of efficacy of Enterosgel in treatment of rotoviral infections in newborns

1997

1



2

Clinical or laboratory index	Treatment with Enterosgel, days	Control group, days
Clinically manifested intoxication	3.2	7.9
Respiratory disturbance	4.4	8.3
Hyperbilirubinemia	3.2	7.3
Disturbed thermoregulation	1.7	5.4
Tympanitis	2	5.8
Posseting of milk	1.8	6.7
Diarrhoea	2.1	7.3
Duration of dysbiocenosis	10.7	24.5
Duration of stay in hospital	12.3	33.2
Duration of excretion of rotoviruses with stool	2.3	13.4
Rate of complications %	12.3	42.5
Necrotic colitis	11.2	28.3
Toxicosis with exicosis	7.3	18.7
Rate of development of nosocomical infections	16.8	52.7

Gorodetsky, Tebechevsky F.

Use of Enterosgel in treatment of patients with hepatitis A

Objective

To study the effect of Enterosgel in complex treatment of hepatitis A in adults.

Methods

This was randomized study in 120 patients aged between 18 to 40 years diagnosed with. Alongside with Enterosgel, the subjects received standard basic pathogenic therapy: glucose 5%, vitamins, corticosteroids (only to 8 patients with severe symptoms).
The daily dose was 45-90g given 3 times a day for 7-14 days. Control group had 100 patients under basic pathogenic therapy: glucose 5%, vitamins, corticosteroids (in severe stage).

Results

In comparison with the control group, the Enterosgel group experienced disappearance of dyspeptic symptoms and cholemic crisis two days earlier. Positive influence of Enterosgel on viral hepatitis A is manifested through bilirubin and ALT dynamics in comparison with the control group Table 2. No adverse reactions were observed.

Conclusions

This study provides evidence that Enterosgel can help patients with Hepatitis A in disappearance of dyspeptic symptoms, while pigment cholemic crisis can be two days earlier than without Enterosgel. The average treatment duration in patients taking Enterosgel reduced by 3.1 days in comparison with the control group.
Tolerability of Enterosgel has been good in all the patients

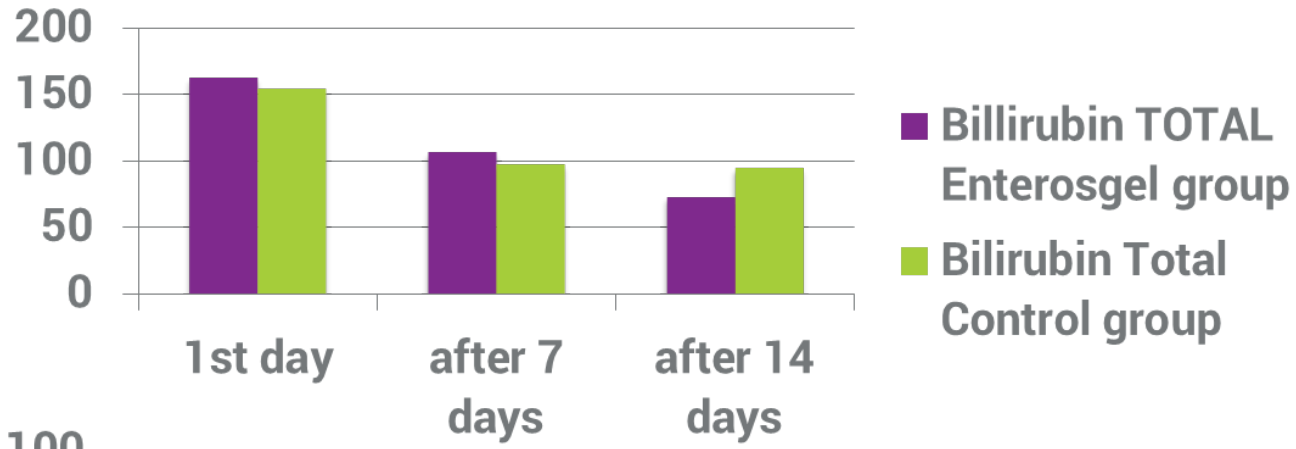
3

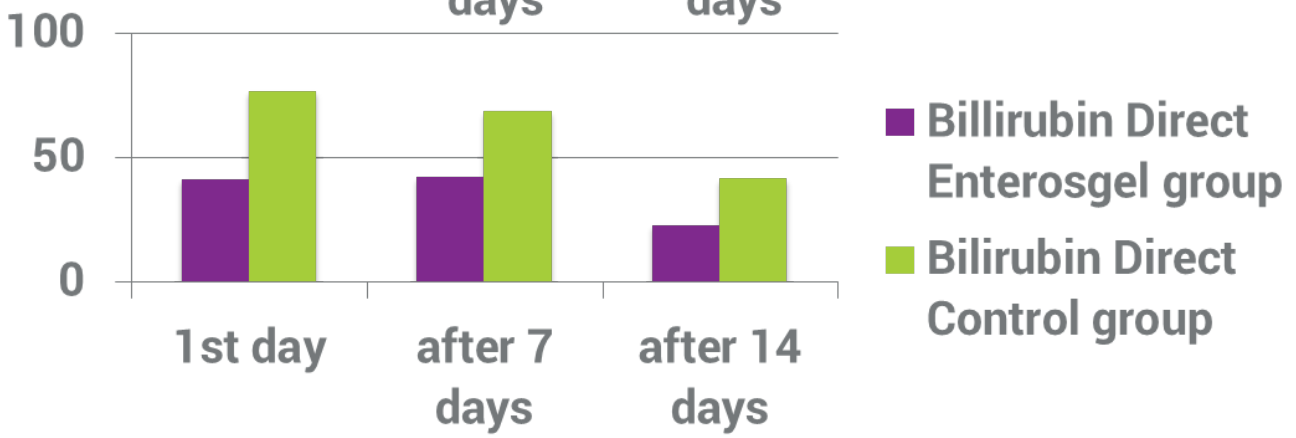
TABLE 1
Positive influence of Enterosgel on viral hepatitis A is manifested through bilirubin and ALT dynamics in comparison with the control group

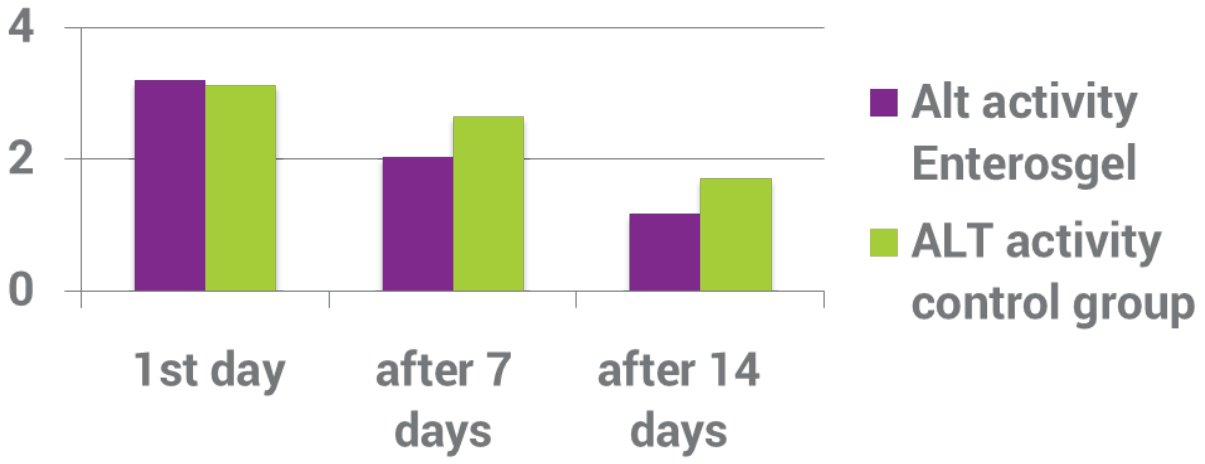
1989

3

	Bilirubin						ALT activity		
Groups	On admission		After 7 days		After 14 days		On admission	After 7 days	After 14 days
	total	direct	total	direct	total	direct			
Enterosgel	162.0	106.0	72.5	41.2	41.9	22.8	3.19	2.02	1.16
Control	153.7	97.2	94.3	76.7	68.6	41.3	3.12	2.64	1.71







Tkachenko E., Avalueva E.

The Clinical Efficacy and safety of Enterosgel in the treatment of diarrhoea-dominant irritable bowel syndrome.

Objective

To assess the dynamics of clinical symptoms, laboratory parameters, data of electrogastroenterography, psychoemotional indicators and quality of life in IBS patients during treatment with Enterosgel®.

Methods

This was a single-center, prospective, open, controlled study on 30 patients diagnosed with IBS-D. Patients were randomly assigned to receive Enterosgel 45 g per day. The control group received tridicitrate bismuthate.

Results

Evaluation of stool frequency in patients with D-IBS has allowed to reveal the beneficial effects of the course of treatment with Enterosgel®: reduction in stool frequency (full normalization of stool frequency has been observed in almost 50% of patients). According to the coprogram, after a course of treatment with Enterosgel® normalization of stool consistency, of vegetable fiber digestion and food protein components has been observed.

After a course of treatment with Enterosgel® there has been a significant and substantial reduction in IBS symptoms according to the results of the subjective assessment of the patient (standardized complaint questionnaire and GSRS questionnaire data as well as pain intensity on VAS) and objective disease manifestations (stool frequency and stool form on Bristol scale). The most clinically significant changes observed in patients of Enterosgel group were: normalization of stool frequency (up to 7 times a week), normalization of stool form (stool type 4 on the Bristol scale) and a decrease in pain severity.

After the treatment with Enterosgel® clinically significant increase in the number of bifidobacteria and clinically significant reduction of enterotoxigenic Escherichia coli has been found (before therapy its amount increased in 80% of the patients, after a course of treatment - only in 50%).

Conclusions

Enterosgel® has a positive effect, reducing abdominal pain severity and normalizing stool frequency in D-IBS patients, thus contributing to the harmonization of quality of life.

Administration of Enterosgel® in D-IBS patients was shown to decrease of GIT dysbiosis, improving the quantitative and qualitative microflora of the colon.Enterosgel® is well-tolerated, safe and can be recommended for use in D-IBS patients.

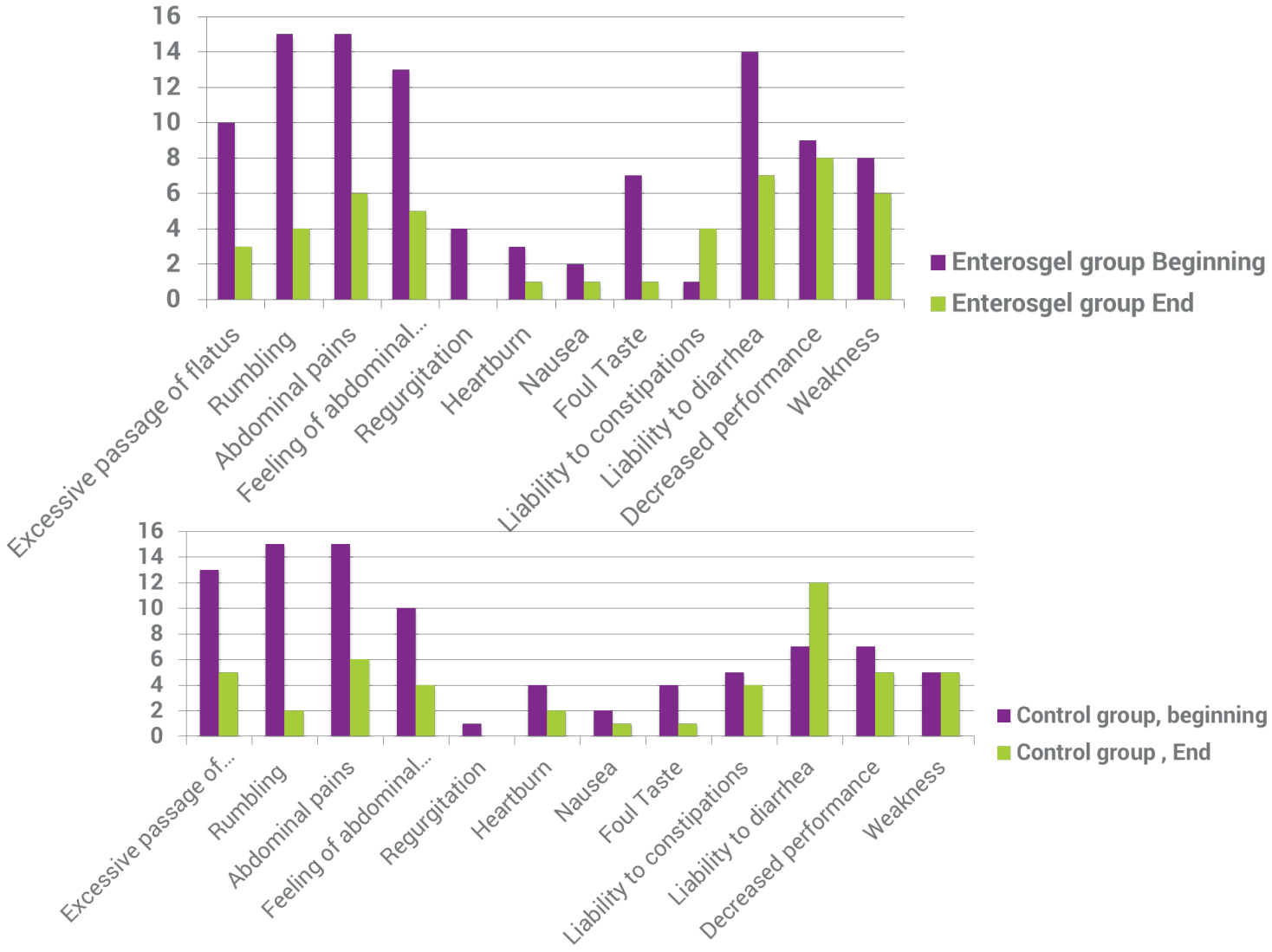
4

TABLE 3 AND DIAGRAMMES 6,7
Dinamics of gastrointestinal complaints in the Enterosgel group and control group

2014

4

Complaints	Enterosgel group Beginning	Enterosgel group End	Control group, beginning	Control group , End
Excessive passage of flatus	10	3	13	5
Rumbling	15	4	15	2
Abdominal pains	15	6	15	6
Feeling of abdominal heaviness	13	5	10	4
Regurgitation	4	0	1	0
Heartburn	3	1	4	2
Nausea	2	1	2	1
Foul Taste	7	1	4	1
Liability to constipations	1	4	5	4
Liability to diarrhea	14	7	7	12
Decreased performance	9	8	7	5
Weakness	8	6	5	5



Tkachenko E., Avalueva E.

The Clinical Efficacy and safety of Enterosgel in the treatment of Helicobacter Pylori – associated chronic gastroduodentis

Objective

To assess the dynamics of clinical symptoms, laboratory parameters, data of electrogastroenterography, psychoemotional indicators and quality of life in IBS patients during treatment with Enterosgel®.

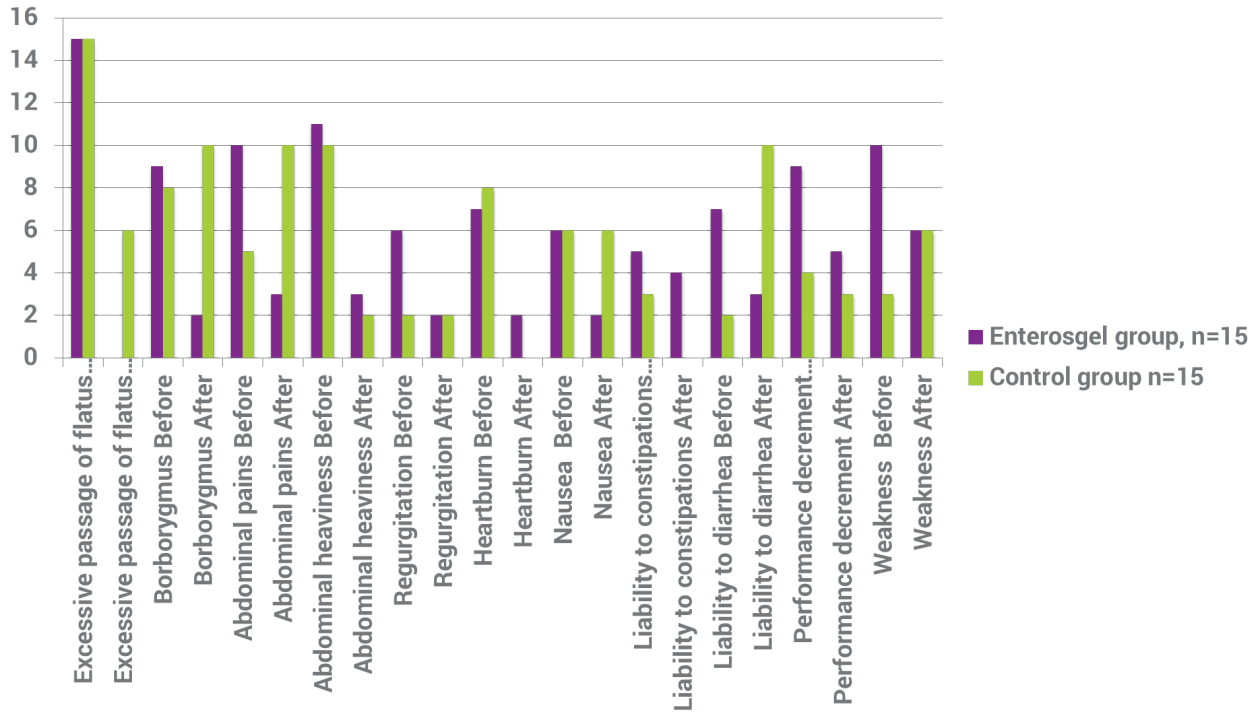
Methods

This was a single-center, prospective, open, controlled study on 30 patients (14 men and 16 women aged 18 to 60 years) diagnosed with Helicobacter Pylori – associated diseases of the upper gastrointestinal tract. Patients were randomly assigned to receive Enterosgel 70 g per day during 3 weeks. The control group received eradication therapy (omeprazole, amixicillin, clarithromycin)

During the study there was no adverse reaction in Enterosgel Group, whereas adverse events in the Control group were recorded in 47% patients using the standard eradication therapy and were associated with the development of mild diarrheal disorder.

5

DIAGRAMME 8
Dynamics of gastrointestinal complaints in patients of Enterosgel group and Control group
Before and After treatment



Results
The study showed the efficacy of Enterosgel:

Significant positive clinical dynamics was revealed in relation to gastric and intestinal dyspepsia (especially reduction of such symptoms as heartburn, regurgitation and excessive passage of flatus). While the patients receiving standard eradication therapy experienced increase in the detection rate of intestinal dyspepsia symptoms (diarrhea, abdominal pain and borborygmus), in the patients receiving Enterosgel frequency of these complaints decreased. GSRS questionnaire data showed that after a course of standard eradication therapy in patients more frequently suffered from stool loosening, while in patients treated with enterosorbent Enterosgel, severity of diarrheal syndrome decreased.

Data of fibrogastroduodenoscopy showed in patients of both groups improvement in the endoscopic picture of the upper GIT; in patients treated with standard eradication therapy, the positive trend was more pronounced and statistically significant.

Comprehensive assessment of histological mucosal changes after a therapy course with Enterosgel demonstrated significant reduction in the severity of pathological processes in the mucosa of the upper GIT (inflammation, atrophy, dysplasia etc.). During individual assessment of inflammatory changes alone, statistically significant reduction was detected in infiltration of the mucous membrane with macrophages and neutrophils in the antrum, duodenum and esophagus.

The decline in the number of patients with significant infection with Helicobacter pylori from 86% before treatment to 47%, after a course of therapy with Enterosgel.

In the analysis of psychological status of the patients it was revealed that in patients treated with Enterosgel performance on a scale of state anxiety and asthenia has significantly reduced, while in patients after eradication therapy only state anxiety has significantly decreased.

CONCLUSIONS

•This study provides evidence that Enterosgel has a positive effect on the clinical performance of the disease and is effective in reducing the symptoms of intestinal dyspepsia and diarrhea in patients with Helicobacter pylori-associated gastroduodenitis.

•After a 21-day course of Enterosgel, severity of inflammatory changes in the mucosa of the upper GIT and stomach contamination with Helicobacter pylori significantly reduced in patients with Helicobacter pylori-associated gastroduodenitis, indicating its anti-inflammatory and anti-helicobacter action.

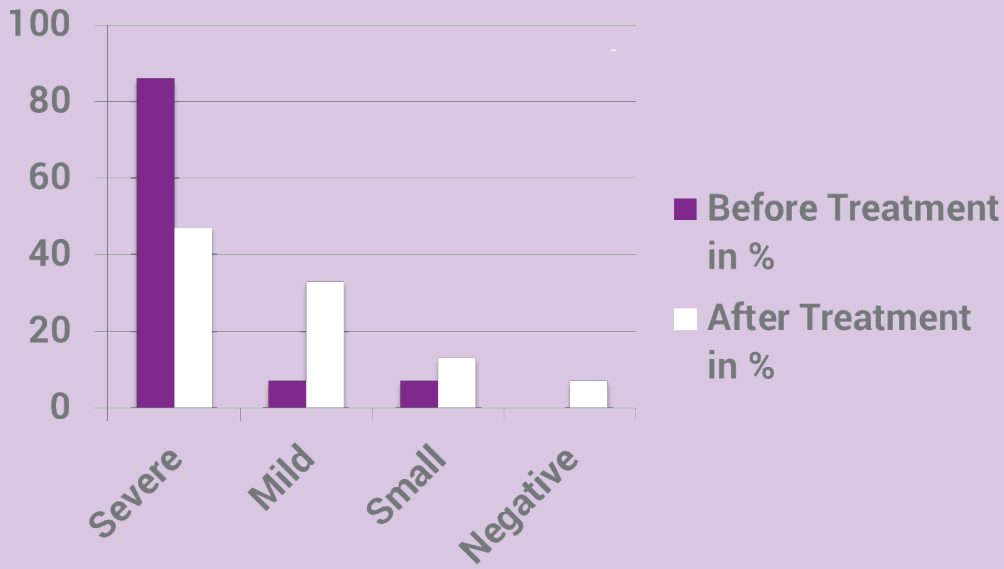
•When using Enterosgel in patients with Helicobacter pylori-associated gastroduodenitis, quality of life and psycho-emotional state has improved.
•Enterosgel drug was well-tolerated and safe when administered.

•Enterosgel drug can be recommended for use in patients with Helicobacter pylori-associated gastroduodenitis and, its positive properties in eradication of Helicobacter pylori being proven in this study, it may also be used in the treatment of other Helicobacter pylori-associated diseases of the upper GIT.

•Enterosgel may be the treatment of choice for patients with Helicobacter pylori-associated diseases of the upper GIT, in which there are significant signs of intestinal dyspepsia and diarrhea, as it is highly effective in relieving these symptoms.

6

DIAGRAMME 9
Dynamics of Helicobacter pylori infection in patients after treatment with Enterosgel®.



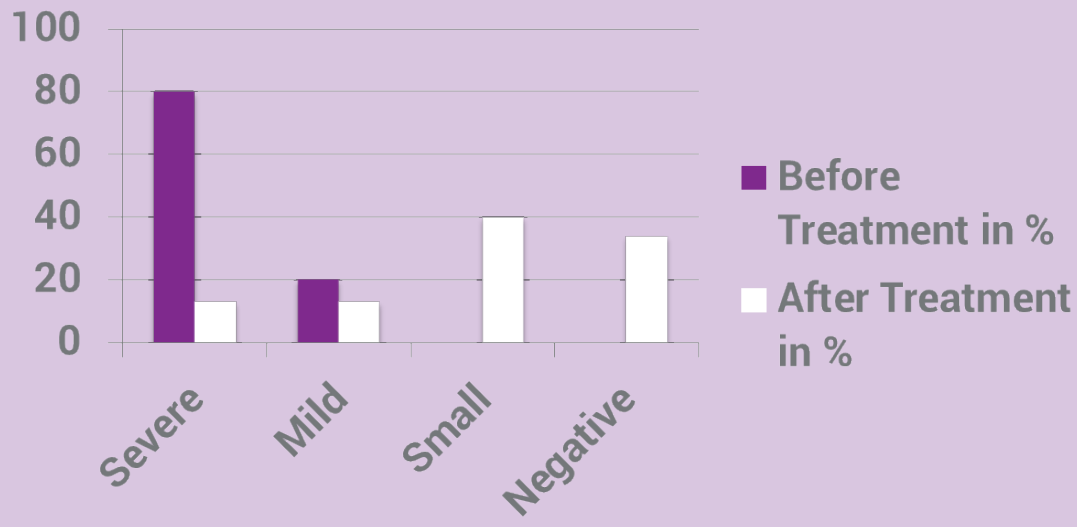
Complaints	Time of observation (beginning / end of treatment)	Number of patients, absolute. (%)		Significance of differences between the groups, p
		Group 1, n=15	Group 2, n=15	
Excessive passage of flatus	beginning	15 (100)	15 (100)	0,006
	end	0 (0)	6 (40)	
Borborygmus	beginning	9 (60)	8 (53)	0,019*
	end	2 (13)	10 (67)	
Abdominal pains	beginning	10 (67)	5 (33)	0,007**
	end	3 (20)	10 (67)	
Feeling of abdominal heaviness	beginning	11 (73)	10 (67)	0,696
	end	3 (20)	2 (13)	
Regurgitation	beginning	6 (40)	2 (13)	0,682
	end	2 (13)	2 (13)	
Heartburn	beginning	7 (47)	8 (53)	0,131
	end	2 (13)	0 (0)	
Nausea	beginning	6 (40)	6 (40)	0,280
	end	2 (13)	6 (40)	
Vomiting	beginning	0 (0)	0 (0)	-
	end	0 (0)	0 (0)	
Foul taste	beginning	0 (0)	2 (13)	-
	end	0 (0)	0 (0)	
Liability to constipations	beginning	5 (33)	3 (20)	0,091
	end	4 (27)	0 (0)	
Liability to diarrhea	beginning	7 (47)	2 (13)	0,001**
	end	3 (20)	10 (67)	
Performance decrement	beginning	9 (60)	4 (27)	0,833
	end	5 (33)	3 (20)	
Weakness	beginning	10 (67)	3 (20)	0,252
	end	6 (40)	6 (40)	

7

DIAGRAMME 10 AND TABLE 4

10 | Dynamics of Helicobacter pylori infection in patients after eradication treatment with antibiotics

04 | Dynamics of gastrointestinal complaints in patients of Enterosgel group and Control group Before and After treatment



Astahov V., Gusev V.

The Clinical Efficacy and safety of Enterosgel in complex prevention of fetoplacental dysfunction in pregnant women with earlier syphilis

Objective

To reduce the incidence of perinatal complications in women after syphilis infection with use of Enterosgel.

Methods

This was a randomized controlled study on 60 pregnant women. 30 of them, diagnosed with syphilitic infection. The control group received the conventional therapynwith drugs, which improve uterus-placental-fetal circulation, drugs normalizing metabolism and protein metabolism. The study group received Enterosgel in addition to the standard therapy at a therapeutic dose - 1 tablespoon (15g) three times a day on weeks 10-12 and 18-19 of pregnancy.

Results

In the Enterosgel group of pregnant women within preventive therapy, the gestation course was more favorable, with less complications of gestational period than in the control group. Polyhydramniosis in Enterosgel group was 3.6 times rarer, frequency of the threat of pregnancy termination being 1.3 times lower; hypochromic anemia was 1.4 times less frequent, with preeclampsia being 1.5 times less frequent.
Enterosgel application contributed to reduction in the incidence of perinatal injury: frequency of intrauterine hypoxia in the group II decreased by 3 times, 2.9 times less often was IURS syndrome. In Enterosgel group frequency of cesarean operation was 1.5 times lower, 2.4 times lower was a necessity of emergency operative delivery. Labor complications were more rarely observed in women receiving Enterosgel: pathological delivery – 1.8 times, frequency of prenatal amniorrhea – 2.5 times, bleeding in the placental and early postpartum period- 3.4 times, labor abnormality- 1.3 times less frequent.

Favorable pregnancy course and outcome affected the health and adaptation abilities of the neonates. Apgar score at minute 1 and 5 was significantly higher ($p < 0.05$) in women treated with Enterosgel ((6.89 ± 0.08/7.67 ± 0.12) vs. group I (6.5 ± 0.24/7.07 ± 0.19. An increase in weight and growth in the neonates of group II versus group I -3378.52 ± 5 g / 52.41 ± 0.48 cm vs 3316 ± 39.8 g/50.23 ± 0.52 cm. After a course of preventive therapy in pregnant women taking Enterosgel, level of peripheral vascular resistance in utero-placental and fetal-placental blood flow was lower than that of women not treated with this enterosorbent.

The course of preventive therapy including Enterosgel stimulated decrease in peripheral vascular resistance in microvasculature of the fetal part of placenta and the uterine arteries in pregnant patients of group II ($p < 0,01$), while the parameters named were lower than the corresponding values in patients of group I ($p < 0.05$).
Thus, Enterosgel use improves circulation in the mother-placenta-fetus system.

Conclusions

Enterosgel administration in pregnant patient of placental insufficiency risk group with earlier syphilitic infection allows normalizing adaptation processes in the mother-placenta-fetus system and promotes birth of more viable children.

Usenko D., Gorelov A.

The Clinical Efficacy of Enterosgel, in treatment of intestinal infections in chidren with atopic dermatitis.

Objective

To assess clinical and laboratory efficiency of modern enterosorbent Enterosgel in children suffering from atopic dermatitis

Methods

This was a randomized controlled study on 361 children aged from 3 month to 14 years. Children were diagnosed with atopic dermatitis with acute intestinal infection. 72 patients were chosen for study with enterosorbents, 155 for probiotics study and 134 children for anti-hystomine AH therapy.

Results

• This study showed that Enterosgel in treatment of children with atopic dermatitis significantly reduced duration of intoxication symptoms, fever and leukocyte intoxication index (LII) (from 2.7± 0.1 to 0.6 ± 0.1 U- in Enterosgel group ($p < 0.05$).

• Duration of gastrointestinal disorders (diarrhea syndrome and bloating) in Enterosgel group was significantly lower than in the control group.

• Reduction of most of the symptoms by day 5 of the treatment in Enterosgel group was 79.3%, against 57.9% in the control group).

• After 5-7 days of treatment, complete clinical recovery was achieved in 76.1% of patients taking Enterosgel.

• Duration of exsicosis symptoms significantly decreased in the Enterosgel group.

• Analysis of the results of occasional bacterioexcretion / viral shedding after the treatment showed that efficiency towards bacterial and viral pathogens of Enterosgel was 73.4% for bacterial AII pathogens and 80.6% - for viral pathogens. Efficiency of standard therapy did not exceed 57.2% and 40%, respectively.

• The treatment in Enterosgel group was effective in 88.7 - 89.7% of patients, and 60.8-67.9% showed complete clinical efficacy, which was characterized by reduction of the majority of pathological symptoms by the end of day 3 of hospital treatment. Treatment efficiency of patients in the control ğroup did not exceed 81%, complete efficiency was in 57.6% patients of the control group.

• No adverse reactions were reported.

Conclusions

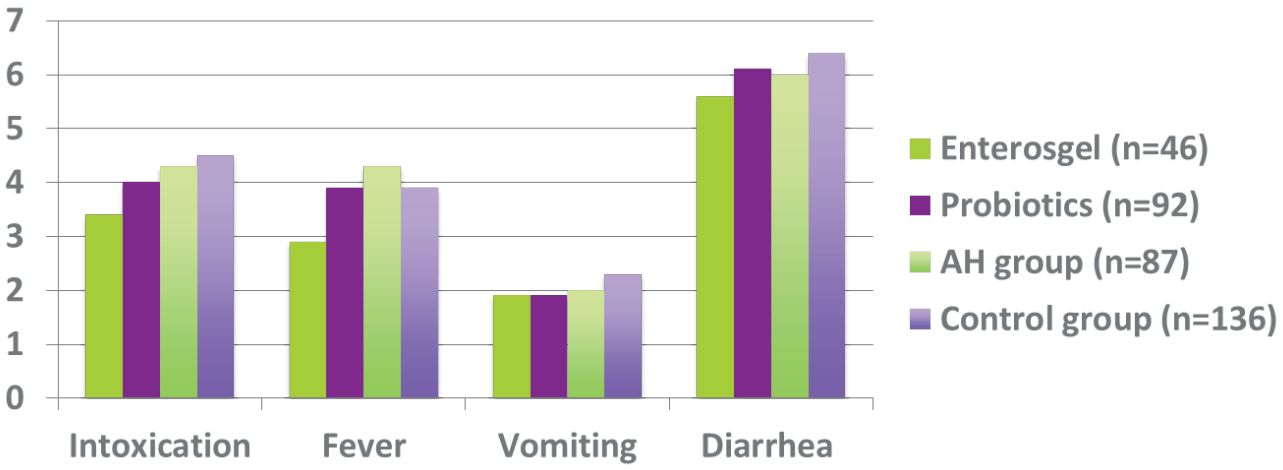
The study provides evidence that the use of Enterosgel in treatment of atopic dermatitis patients with intestinal infection lead to statistically significant reduction (58-63%) in the frequency of Atopic Dermatitis exacerbation. Enterosgel can significantly help in decreasing the duration of intoxication, vomiting, diarrhoea and fever.

8

TABLE 5 AND DIAGRAMME 11

Mean duration (in days) of clinical manifestation in Enterosgel group, Probiotic group, AH group and Control group

2013



Symptoms	Entero sgel (n=46)	Probiotics (n=92)	AH anti-hystomine n=87	Control group (n=136)
Intoxication	3.4±0,3	4.0±0,3	4.3±0,1	4.5±0,4
Fever	2.9±0,4	3.9±0,4	4.3±0,1	3.9±0,2
Vomiting	1.9±0,2	1.9±0,2	2.0±0,7	2.3±0,1
Diarrhea (Total Days)	5.6±0,5	6.1±0,3	6.0±0,1	6.4±0,5

Radchenko V., Seliverstov P.

The Clinical Efficacy and safety of Enterosgel in treatment of predialysis Cronic Renal Falure (CRF) patients.

Objective

To study the effect and safety of Enterosgel in treatment of CRF in predialysis patients.

Methods

This was a single-center, open, prospective study on 30 predialysis patients with CRF, age of the patients was 36 ± 3.7 years, 13 men and 17 women. The study group received 15g of Enterosgel 3 times a day during 4 weeks. Control group received standard CRF therapy.

Results

• The two groups were comparable with no difference in baseline characteristics.

• The main complaints in patients of all groups were weakness, fatigue, abdominal and lumbar pain, headaches, nausea, periodic vomiting and dysuria. The improvement was statistically greater in the Enterosgel group (Table 6 and Diagramme 12).

• Normalization of renal filtration function was shown in Enterosgel group, mainly by reducing the level of total protein, urea, creatinine and increase in glomerular filtration rate (Table 7).

• The remaining values (ALT, AST, glucose, cholesterol, bilirubin, K, Mg, Na, Ca, Fe, P), including vitamins A, E and D were within the reference ranges both before and after treatment. No changes of biochemical blood values characterizing liver function show that the administration of Enterosgel for four consecutive weeks is safe.

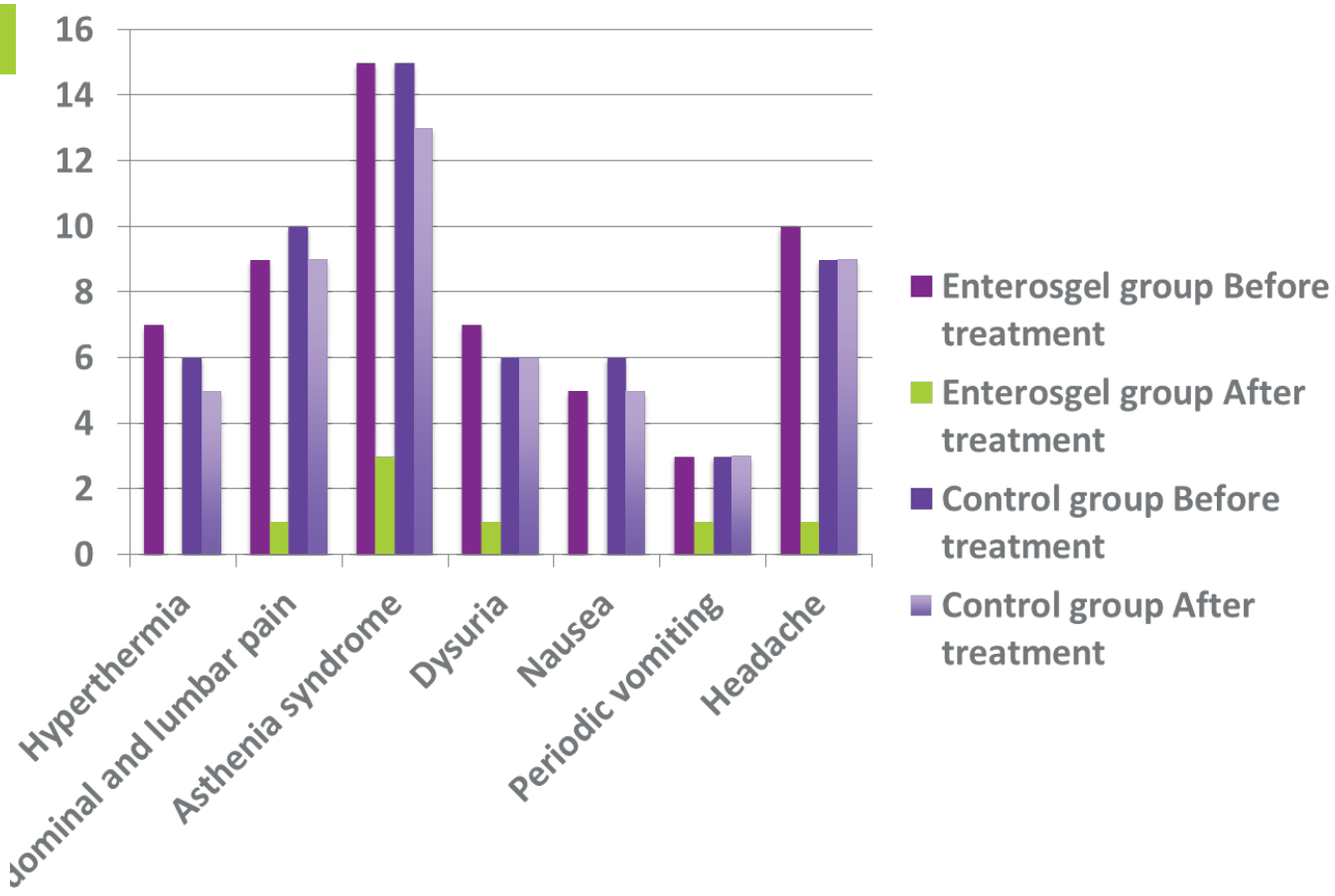
• The study of urinalysis in the patients of all groups showed decrease of urine specific gravity and, on the contrary, the increase of bye-indicators, such as: white blood cells, bacteria, protein. Table 8 shows positive changes In Enterosgel group on all indicators, which may be a confirmation of improvement of renal function and, as a result, of urinalysis values.

• Assessing the quality of life using SF-36 questionnaire 100% of Enterosgel group patients confirmed significant ($p < 0.05$) improvement of the physical health components: physical functioning improvement (PF), reduction of the bodily pain (BP), vitality (VT), social functioning (SF) and mental health (MH); due to their change, improvement of role functioning due to the physical condition (RP) was observed, thus the overall health state was improved (GH). (Figure 1).

9

TABLE 6 AND DIAGRAMME 12
Mean duration (in days) of clinical manifestation in Enterosgel group, Probiotic group, AH group and Control group

2014



Symptoms	Group 1, n=15		Group 2, n=15	
	Before treatment	After treatment	Before treatment	After treatment
Hyperthermia	7 (46,7)	0 (0)	6 (40,0)	5 (33,3)
Abdominal and lumbar pain	9 (60,0)	1 (6,7)	10 (66,7)	9 (60,0)
Asthenia syndrome	15 (100,0)	3 (20,0)	15 (100,0)	13 (86,7)
Dysuria	7 (46,7)	1 (6,7)	6 (40,0)	6 (40,0)
Nausea	5 (33,3)	0 (0)	6 (40,0)	5 (33,3)
Periodic vomiting	3 (20,0)	(1) 0	3 (20,0)	3 (20,0)
Headache	10 (66,7)	1 (6,7)	9 (60,0)	9 (60,0)

Conclusions

• The study results indicate the efficiency of Enterosgel in predialysis patients with chronic renal failure, as it promoted positive clinical effect on all the patients in the Enterosgel group. All patients experienced reduction in the abdominal and luumbar pain, in the majority of patients, asthenia, endointoxication and dysuria manifestations disappeared. Improvement of mental and emotional state was also achieved as well as tendency to improvement of quality of life.

• Enterosgel taken for 4 consecutive weeks is safe for patients, which was confirmed by subjective, physical and laboratory studies. Enterosgel used for 4 weeks did not cause any undesirable effects.

• The study provides evidence that Enterosgel has a positive effect on the clinical performance in predialysis patients with chronic renal failure;

• Enterosgel has a sorption effect, which can help to reduce endogenic intoxication and improve kidney function.

• The study shows that Enterosgel in predialysis patients with chronic renal failure, can help to improve the quality of life and psycho-emotional state;

• Enterosgel has a good tolerance, is safe and improves renal function; it can be recommended for use in predialysis patients with chronic renal failure;

• Recommended treatment with Enterosgel in the renal pathology is 15 g 3 times a day 60 minutes before meals for 4 weeks.

10

TABLE 7
Dynamics of blood biochemical parameters before and after treatment in Enterosgel group and control group

11

TABLE 8
Dynamics of urinalysis parameters, (M ± s) before and after treatment in Enterosgel group and control group

12

FIGURE 1
Dynamics of values of quality of life (SF-36) in Enterosgel group

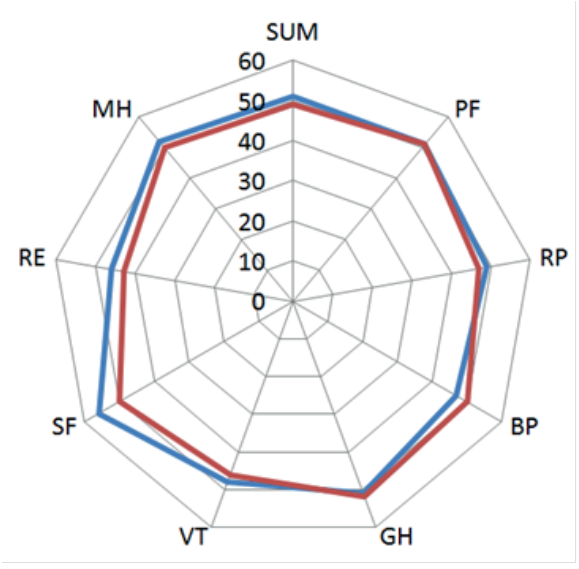
10

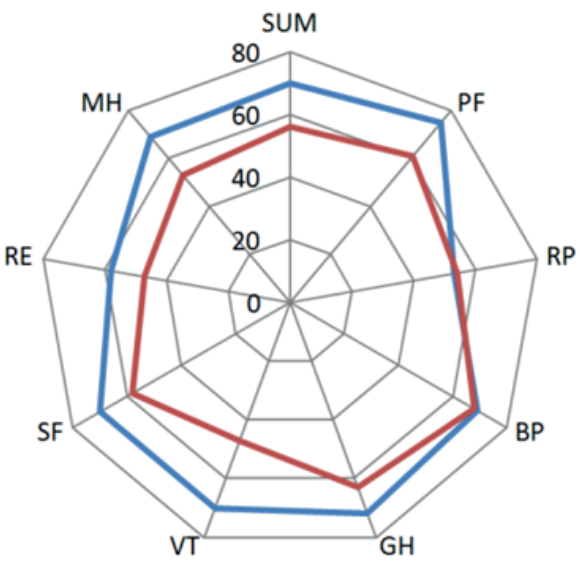
Values	Reference values	Group 1, n=15,		Group 2, n=15,		Difference significance between the groups (p)*
		Before treatment	After treatment	Before treatment	After treatment	
Total protein, g/l	65-85	91,8±3,3	70,5±3,2	69,2±3,4	72,4±4,5	p< 0.05*
Urea, mmol/l	1,3-8,3	16,4±2,9	13,4±3,5	15,2±6,1	14,5±5,9	p<0,05*
Creatinin, µmol/l	M 62-132 W 44-106	155,4±9,2	120,1±7,3	157,8±8,6	153,1±6,2	p<0,05*
GFR, ml/min	M 97-137 Ж 88-128	73,2±6,3	92,5±4,2	75,6±4,6	79,3±5,1	p<0,05*

11

Value	Reference values	Group 1, n=15,		Group 2, n=15,		Difference significance between the groups (p)*
		Before treatment	After treatment	Before treatment	After treatment	
Specific gravity, U	1,010-1,025	1,005±0,002	1,012±0,001	1,005±0,003	1,006±0,003	p<0,05*
Leukocytes, per HPF	0-5	**55,6±6,5**	**36,4±3,3**	56,0±4,1	54,3±7,5	p>0,05
Bacteria, per HPF	0	**168000,2±24,1**	**91,3±6,7**	171000,3±8,7	168000,0±19,1	p<0,05*
Protein, g/l	0	12,1±6,2	12,5±5,1	11,5±5,3	11,3±4,3	p>0,05

12





Nakhashova V.

The Clinical Efficacy of Enterosgel in treatment of patients with Chronic Pancreatitis

Objective

To study the role of imbalance of antiendotoxin systemic and mucous immunity in pathogenesis of chronic pancreatitis (CP) and the efficacy of Enterosgel and probiotics in a combined treatment.

Methods

This was a randomized controlled study on 122 patients with an exacerbation of CP aged from 27 to 76 years (60 women and 62 men). The patients were devided into 4 groups. Group 1 was taking Enterosgel, group 2 – probiotics Linex, Group 3 Enterosgel+Linex and the control group without enterosorbent or probiotics.

Results

A high level of antiendotoxic antibodies of a class A in all patients was evaluated as a compensate reaction, that is directed on strengthening of intestinal barrier by forming of adequate concentration of secretory Ig A. Patients with mild or severe CP have impaired local mechanism for neutralizing endotoxin with decreased levels of secretory Ig A anti-endotoxin antibody. Treatment of CP patients with probiotic bacteria (Linex) and enterosorbent (Enterosgel) can improve the local specific immune responses by increasing the levels of secretory Ig A anti-endotoxic antibody.
was improved (GH). (Figure 1).

Conclusions

• Clinical efficiency of probiotic Linex and enterosorbent Enterosgel in the complex CP treatment is manifested in 93,8% patients without a relapse within 3 months after the treatment. In the control group the absence of exacerbations for the entire period of observation has been registered only in 75% of patients.

• The use of probiotic Linex and enterosorbent Enterosgel stimulates improvement in conditions of mucosal antiendotoxin immunity through normalization of levels of secretory Ig A in the saliva within up to 3 months after the course of treatment conducted.

• Prophylactic treatment with Enterosgel and probiotics is recommended to the patients with unfavorable CP 3 - 4 times a year.

2008

Karlyichuk A., Kulachek F.

The Clinical Efficacy of Enterosgel in complex treatment and prophylaxis of post-operative intraperitoneal in complication of acute cholecystitis

Objective

To define efficiency of use of Enterosgel in enterosorption and colonic sanation in complex treatment and prophylaxis of intraperitoneal complications in patients with acute cholecystitis in the post-operative period.

Methods

This was a randomized controlled study on 106 patients operated due to acute cholecystitis.
Patients of the Enterosgel group (n=34) in the post-operative period took Enterosgel in complex therapy on day 1, 3, 7 and 10 after the operation. Enterosgel was administered at a dose of 15 g diluted in 150 g water 3 times a day. The second study group comprised 55 patients with a destructive form of acute cholecystitis, in which single colonic sanation had been done in the process of preoperative preparation as a prophylaxis of intraperitoneal complications and up to 6 Colonic sanations after operation. In the control group (17 patients), a standard complex treatment was conducted both in preoperative and postoperative periods.

Results

The large part of the patients was operated within 2 days from their admission. 14 (25.6%) of the patients operated due to destructive forms of acute cholecystitis experienced obstructive jaundice caused by gallstones in the common bile duct.

• A postoperative clinical examination showed that in the patients of Enterosgel and Colonic sanation groups, the temperature was normalized already by day 3 in 80.2%; 61.2 % - in the control group;

• A postoperative intestinal paralysis was mostly stopped in the first group in the same ratio – 74.4%, 79.3%, in the control group – 52.3;

• On days 7 and 8 number of leukocytes in the Enterosgel and Colonic sanation groups was (7,66±0,23)x109 and -(7,78±0,26)x109, respectively (on admission - (9,12±0,12) x 109 and (11 ± 0,54) x 109), in control group - (8,9 ± 0,68) x 109, on admission - (9,1±0,72) x 109). Before the hospital discharge, the following values were found (see Table 9).

• Postoperative complications in the patients of both study groups were observed in 5 patients (pneumonia – 2, cardiovascular and pulmonary insufficiency – 2, wound abscess – 1).

• In the patients of the control group, postoperative complications were observed in 8 patients (postoperative pancreatitis – 1, purulent cholangitis – 1, abdominal abscess – 1, wound abscess – 2, pneumonia – 2, cardiovascular insufficiency – 1).

• The study gives the evidence of positive influence of Enterosgel and colonic sanation on the biocenosis of the intestinal microflora, which is especially important in the presence of functional insufficiency and reduction of passage of toxic substances from the intestine in the portal circulation and back, reduction of the liver burden, considering the fact that Enterosgel adsorbs mostly substances with molecular weight ranging from 70 to 1000 (urea, bilirubin etc.) almost without absorption of the substances with molecular weight 1000 and more (general proteins, immunoglobulins).

Conclusions

• Enterosorption provides minimally invasive detoxification effect from various endo- and exogenous substances, with the involvement of natural detoxification functions in the process.

• Use of enterosorbent Enterosgel can improve general health status of the patients, stimulates subsiding of the general process, induces faster normalization of liver function and reduces the number of postoperative complications.

13

Group	General bilirubin, µmol/l	Creatinine, µmol/l	Urea, mmol/l	General protein, g/l	Albumin, %	Globulin, %		
						α1, α2	β	γ
Enterosgel	15.4 ± 0.48 (p<0.05)	84.3 ± 11.2 (p<0.01)	7.8 ± 0.19 (p<0.05)	81.5 ± 5.14 (p<0.5)	71.82 ± 3.01 (p<0.05)	9.8 ± 0/12 (p<0.5)	9.1 ± 0.04 (p<0.05)	18.2 ± 0.10 (p<0.05)
Colonic sanation	14.7 ± 0.53 (p<0.05)	85.72 ± 14.8 (p<0.01)	7.63 ± 0.51 (p<0.05)	84.17 ± 8.94 (p<0.5)	59.14 ± 2.11 (p<0.05)	9.31 ± 0.37 (p<0.5)	9.2 ± 0.05 (p<0.05)	18.7 ± 0.37 (p<0.05)
Control	18.2 ± 0.76	112.1 ± 18.3	8.31 ± 0.25	79.78 ± 6.32	56.71 ± 1.93	10.27 ± 0.14	9.9 ± 0.14	19.3 ± 0.04

13

TABLE 9
Laboratory values after the treatment in all groups

2014

Moroz L., Paliy M.

Use of enterosorbent Enterosgel in complex therapy of acute viral hepatitis B with concomitant intestinal dysbiosis

Objective

To study efficacy of Enterosgel in correction of dysbiotic disorders in patients with different types of viral hepatitis and its influence on the immunological values.

Methods

This was a randomized controlled study on 144 patients aged from 19 till 57 years with acute viral hepatitis B of mild severity. Diagnosis of viral hepatitis B was confirmed by determining HBsAg and AbHBcIgM in the blood serum by IFA (ELISA) and by liver puncture biopsy (LPB) in 20 (13,8%) patients.
Study participants were randomized in three groups:
Control group 1 – 24 patients without intestinal microbiocenosis disorders;
Control group 2 – 120 patients with viral hepatitis B and concomitant intestinal dysbiosis, of them 59 patients received only background therapy;
Enterosgel group – 61 patients receiving Enterosgel, with standard therapy. The groups were matched in age, gender and severity of the disease. Enterosgel was administered 15 g three times a day during 15 days.

Clinical efficiency of Enterosgel was determined according to the following values:
• subjective data (weakness, fatigue, loss of appetite, nausea, flatulence, stool disorders, heaviness in the right hypochondrium, itching);
• data of objective study (colour of skin and the mucosa, stomach percussion and palpation, change of urine color);
• laboratory values (complete blood count and urinalysis, total protein, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, prothrombine index, microbiological feces study);
• immunological values– determination of level of T-lymphocytes by method of combined rosette assay.
Dynamics of clinical and laboratory values in the groups was assessed on days 5-, 10 and 20 from initiation of the treatment. Influence of Enterosgel on immunological values was estimated by immune-stimulating activity rate (ISR) and immune-modulating activity rate (IMR). ISR was estimated according to the formula:

ISR= (Tl2/Tl1) (Tlb2/Tlb1),

Where Tl – level of T-lymphocytes in patients receiving Enterosgel before (1) and after (2) treatment; Tlb – level of T-lymphocytes in patients receiving background therapy before (1) and after (2) treatment. In case ISR>1, the sorbent possesses immune-stimulating activity.

IMR was estimated according to the formula:

IMR = Tl2-Tl1, TN = TlN-Tlb1,

Where Tl1 – percentage of T-lymphocytes before treatment, Tl2 - percentage of T-lymphocytes after treatment, TlN – mean percentage of T-lymphocytes in healthy patients

Results

• The use of Enterosgel stimulated quicker regress of symptoms in the jaundice period of hepatitis (see Table 10). In Enterosgel group flatulence persisted until day 5 of the treatment in 42% patients, until day 10– in 21% patients, until 20– in 5% patients; stool disorders persisted in 37%, 21% and 10% patients, respectively. In patients of Control group duration of these disorders was higher: flatulence persisted until day 5 in 57% patients, until day 10– in 33% patients, until day 20– in 14% patients; stool disorders persisted in 43%, 28% and 14% patients, respectively. That is, dyspeptic disorders persisted until day 20 in 1/3 of the patients of the control group and only in 1/5 of the patients of Enterosgel group. Absence of any complaints on day 20 was determined in 1/2 patients of the Enterosgel group and 1/4 patients of the control group.

• The study showed faster normalization of total bilirubin dynamics in the blood serum in patients of Enterosgel group. For example, by day 5 of the treatment, total bilirubin was equal to 255±14.35, by day 10 – 162.3±13.01, by day 20 – 49.5±3.85. In the patients of the Control group this value was 258.0±12.66, 193.5±12.4 and 80.9±3.71, respectively.

• After Enterosgel therapy, most of the patients (51; 83.6%) experienced normalization of intestinal microbiocenosis, unlike patients in the control group, in which positive changes were determined only in 25 (42.3%) patients (significant difference).

• Analysis of Enterosgel influence on immune values (except T-cell element of the immunity) showed improvement (though not a significant one) of immune homeostasis in the patients studied (Table 11). For example, in patients of group 3, ISR was 1.00, in group 2 – 0.89. Moreover, the study has determined essential positive dynamics in the level of circulating immune complexes (CIC): reduction to 136±23 in the group 3, to 245±20 in the group 2 ($p<0.05$). Regarding immune-modulating activity, although this value improved after use of

• Enterosgel, the difference with Control group was also insignificant: IMR in the group 3 was 0.58, in the group 2– 0.50. It is possible that other data on Enterosgel ifluence on immunological values in treatment of this patient category can be also used in an additional study of the status of other immunity elements.

• The study showed the evidence that the use of Enterosgel enterosorbent in patients with acute viral hepatitis B with moderate to heavy course and concomitant intestinal dysbiosis can improve elimination of dyspeptic and intoxication syndromes, accelerates positive dynamics of biochemical values and intestinal microbiosis

Conclusions

• Acute viral hepatitis B with concomitant intestinal dysbiosis is characterized by increase in endogenous intoxication and a longer duration of dyspeptic disorders, which requires additional detoxification methods.

The study suggests that the inclusion of Enterosgel in the complex therapy of patients with viral hepatitis B and dysbiosis disorders not only helps to eliminate toxicosis, but also helps faster regression of the main clinical symptoms of the disease and normalization of the intestinal microbiocenosis.

Enterosgel actively stimulates improvement of various immunological values in patients with viral hepatitis B and intestinal dysbiosis, but the most expressed effect from use of Enterosgel is a significant reduction in circulating immune complexes.

Treatment with Enterosgel is safe for the patients due to its high tolerability and absence of side effects.

Study results show necessity of inclusion of Enterosgel in the complex therapy of patients with viral hepatitis B with concomitant disbiotic disorders. It allows to improve the results of the treatment and to reduce treatment duration.

14

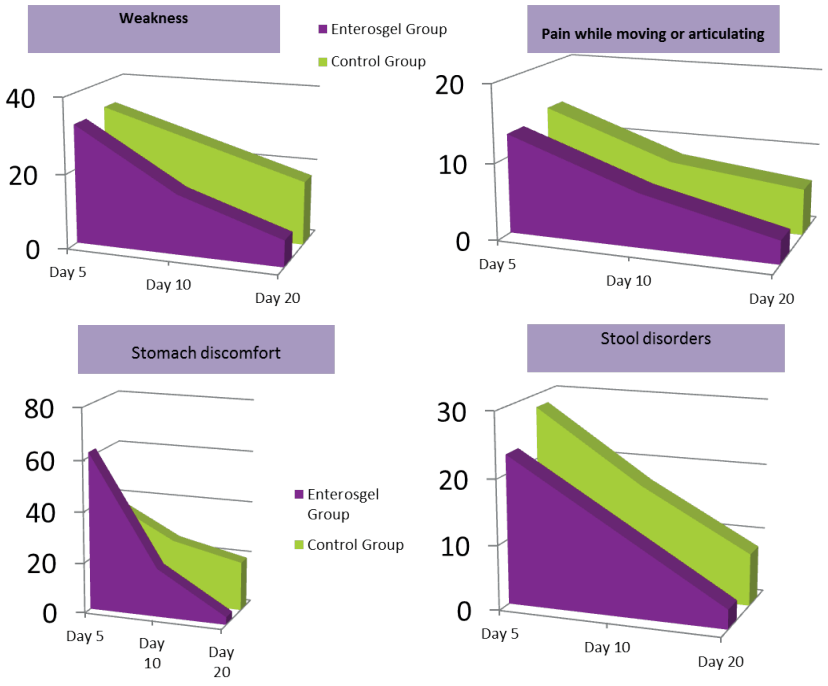
TABLE 10
Persistence duration of symptoms in the jaundice period in patients with viral hepatitis B

15

TABLE 11
Cell immunity values in patients with viral hepatitis B (M±m)

14

Clinical symptoms	Patient group 2 (n=59)						Patient group 3 (n=61)					
	Day 5		Day 10		Day 20		Day 5		Day 10		Day 20	
	Abs.	%	Abs.	%	Abs.	%	Abs.	%	Abs.	%	Abs.	%
Weakness	33	57	25	43	17	29	32	53	16	26	7	11
Pain while moving or articulating	14	24	8	14	6	10	13	21	7	11	3	5
Itching	11	19	8	14	6	10	10	16	7	11	3	5
Stomach discomfort	39	67	25	43	19	33	62	53	19	32	3	10
Stool disorders	28	48	17	29	8	14	23	37	13	21	3	10
Heaviness in the right hypochondrium	39	67	30	52	17	29	35	58	29	47	3	26
Nausea	33	57	17	29	11	19	26	42	13	21	3	5
Faltulence	30	52	19	33	8	14	26	42	13	21	3	5
Loss of appetite	30	52	11	19	6	10	29	47	10	16	3	5



15

Group of patients	Lymphocyte population, %			
	T	T-active	T-tr	T-ch
Control group				
Before treatment	**54,70±2,52**	**36,89±1,79**	**44,80±4,00**	**8,10±1,90**
After treatment	**55,46±2,58**	**41,30±1,00**	**45,50±2,27**	**8,30±1,33**
Enterosgel group				
Before treatment	**53,62±3,19**	**38,76±3,16**	**45,61±3,45**	**7,94±1,51**
After treatment	**54,53±3,21**	**40,83±3,57**	**46,17±3,70**	**8,50±1,33**

Sokolov E., Majev I.

Clinical efficacy of Enterosgel in patients with digestive system-relative pathology.

Objective

To study efficacy of Enterosgel in complex treatment of patients with diseases accompanied by diarrhea syndrome and impairment of the colonic microflora composition (chronic enterocolitises, post-resection syndrome).

Methods

This was a randomized controlled clinical trial on 38 patients with chronic diarrhoea (chronic enterocolitis, post-resection syndrome). In addition to the standard therapy 20 patients received Enterosgel in a daily dose of 45 g (per 15 g 3 times a day) for 14 days. The control group consisted of 18 patients comparable by primary diagnosis, gender and age. Therapeutic efficiency was evaluated according to the clinical data, coprological studies, dynamics of colonic microflora, endoscopic and histological analyses, immune status-related study and the complex biochemical research.

Results

• The results of clinical studies have shown high efficiency of treatment with Enterosgel. Yet on the first day, 16 patients of the Enterosgel group (80%) noted a subjective improvement. By the 3rd day, in 17 patients (85%), the number of stools decreased, on average 2 times (from 7-8 times to 3-4 times a day), a tendency to shaped feces has appeared. By 12-16 days, all patients of the Enterosgel group (100%) noted a significant reduction or disappearance of meteorism, abdominal pain, and shaped feces.

• In the Enterosgel group of patients, the normalization of bowel movements was observed during the first week (on the 5th treatment day), while in the control group only on the third week (on the 20th – 22nd days), and in some cases (3 patients) the conventional therapy had unsatisfactory results (a persistence of pain syndrome, diarrhea).

Table 12 shows significant difference in Enterosgel group: the normalization of basic clinical symptoms occurred much earlier than in the control group.

All patients of the Enterosgel group showed positive shifts in coprogram, mainly in the disappearance or the decrease in leukocytes, red blood cells and mucus, and reduction of iodophilic microflora, intracellular starch, undigested cellulose; the decrease in steatorrheaand creatorrhea symptoms. In patients of the control group, the dynamics of coprological indicators was less, and the stool analysis remained unchanged in 3 patients (Table 13 an Diagramme 13).

• The study showed positive dynamics of colonic microflora (Table 13 and Diagramme 13) in 94.1% of Enterosgel group: either reduction or complete disappearance of microorganisms such as Proteus (in 3 patients), hemolytic E. coli (in 8 patients), fungi of the Candida genus (in 5 patients).

• The study showed an increase of total coliform contents up to the normal (300 - 400 million/g) in 12 patients with initially decreased level of this indicator in 15 patients, the remaining 2 patients had a tendency to an increased count of E. Coli.

• On the control colonoscopy, positive dynamic changes were reported in 95% of the patients of the Enterosgel group; with decreased events of edema, mucosal hyperemia, disappeared petechial hemorrhages and erosions.

• On the histological examination, in 6 out of 7 cases the reduction of edema and leukocytic-plasmacytic infiltration was reported.

• The positive dynamics in decreasing symptoms of inflammation was registered in only 50% of the control group.

The study provides evidence of the immunomodulatory effect of Enterosgel. The absolute and relative count of basic lymphocyte subpopulations and serum immunoglobulin levels were used to assess the immune system status. A trend towards normalization of immunological parameters was registered in 7 patients of the Enterosgel group. The decrease of initially increased Ig A serum level in 72%, and the increase in 18% with initially reduced level of this immunoglobulin, which may testify about the immunomodulatory effect of Enterosgel. In the control group, the tendency of Ig A level to the normalization was reported in 2 patients only.

($p < 0.05$) improvement of the physical health components: physical functioning improvement (PF), reduction of the bodily pain (BP), vitality (VT), social functioning (SF) and mental health (MH); due to their change, improvement of role functioning due to the physical condition (RP) was observed, thus the overall health state was improved (GH). (Figure 1).

Conclusions

• This study showed a high clinical efficiency of Enterosgel and its positive effect on the intestinal mucosa condition, digestion and absorption processes, the composition of small and large intestine-related microflora.

• The immunomodulative effect has been shown through normalization of eubiosis and the decreased inflammation activity in the intestinal mucosa.

• No side events and cases of intolerance of Enterosgel enterosorbent were reported.

• Enterosgel can be recommended for a wide use in the treatment of chronic digestive diseases that are accompanied by diarrhoea syndrome and eubiosis impairment of small and large intestine.

Enterosgel can be taken for a long term to get the persistent therapeutic effect.

16 **TABLE 12**
Dynamics of major clinical disease manifestations under the influence of therapy in patients with chronic diarrhea (in days) (M ± m)

17 **TABLE 13**
Coprogram indicators dynamics in patients with chronic diarrhea (in absolute units) (n)

18 **DIAGRAMME 13**
Coprogram indicators dynamics in patients with chronic diarrhea (in absolute units) (n)

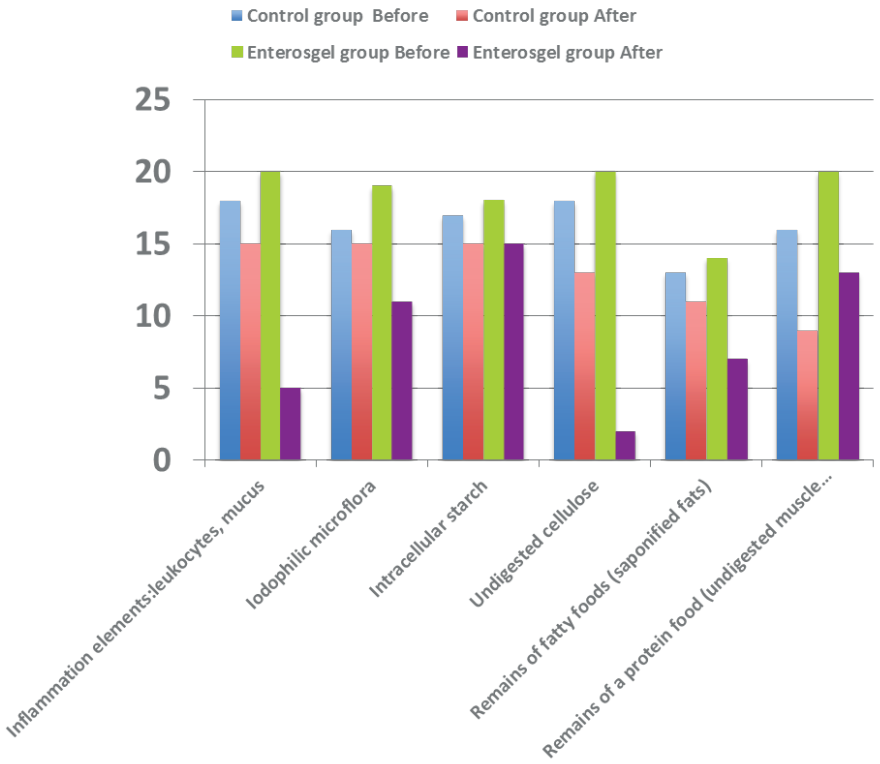
16

Indicators	Control group (n=18)	Main group (n=20)
Stools number normalization time	21.5 ± 1.2	5.0 ± 1.1*
Stool masses shaping time	22.4 ± 3.7	14.2 + 2.2*
Pain syndrome disappearance time	18.9 ± 1.3	12.5 ± 2.3*
Meteorism disappearance time	19.3 ± 2.0	12.3 ± 1.7*

17

Coprological indicators	Control group (n=18)		Enterosgel group (n=20)	
	Registration frequency (n)			
	Prior to treatment	After treatment	Prior to treatment	After treatment
Inflammation elements: leukocytes, mucus	18	15	20	5
Iodophilic microflora	16	15	19	11
Intracellular starch	17	15	18	15
Undigested cellulose	18	13	20	2
Remains of fatty foods (saponified fats)	13	11	14	7
Remains of a protein food (undigested muscle fibers)	16	9	20	13

18



Paliy I., Tchernobroviy V

Clinical efficacy of Enterosgel in complex treatment of intestinal dysbiosis

Objective

To study the clinical efficacy of Enterosgel in complex treatment of intestinal dysbiosis.

Methods

• This was a clinical trial on 51 patients with intestinal dysbiosis aged from 15 to 77 years (28 female and 23 male) with the duration of clinical manifestations of disturbed microbiocenosis from 3 months to 2 years.
• In 35 patients intestinal dysbiosis was accompanied by a manifestation of the primary or associated diseases : chronic pancreatitis 7 patients (20.0%), chronic holecystopancreatitis 6 persons (17.1%), chronic cholecystitis 5 persons (14.3%), chronic enterocolitis 6 patients (17.1%), duodenal ulcer 3 patients (8.57%), iron deficiency anemia 2 patients (5.7%), cirrhosis, diabetes mellitus, chronic proctosigmoiditis, biliary dyskinesia in 1 patient (2.8%). One patient was convalescent from viral hepatitis (HbsAg positive), one - after gemicolectomia for the caecum carcinoma.
• 33 patients had the 1st and 18 patients - the 2nd grade of intestinal dysbiosis.
• Biological coprocultural examinations were done to identify the presence and quantity of the following microflora: the pathogenic microflora of intestinal microbial family, total coliform bactery count, the E. coli with weak enzymatic properties, the hemolyzing Escherichia coli, opportunistic bacteria, enterococci, staphylococci, Proteus genus-related bacteries, Candida genus fungi, lactobacilli and bifidobacteria.

Results

• In the results of stools microbiological analysis, the elevated hemolizing E.coli levels were reported in 18 patients (39%), the coccal flora elevated levels in 14 patients (28%), the imbalance between the representatives of normal intestinal microflora was reported in 10 patients (20%), Klebsiella pneumoniae was harvested in 4 patients (8%), S.aureus 3 patients (6%), P.vulgaris 1 patient (2%) (Fig. 2).
• Clinical manifestations of dysbiosis occurred in all monitored patients (item 6) being expressed by flatulence 48 patients (94.1%), alternating diarrhea and constipation 29 patients (56.8%), constipation 12 patients (23.5%), diarrhea in 11 patients (21.6%), polifecalia 9 patients (17,6%), recurrent abdominal pain as aggravated by palpation 18 patients (35.3%)
• Patients were treated by traditional methods (diet, vitamins, eubiotic preparations) with Enterosgel perorally 3 times daily between meals and medications (1.5-2 hours before and not less than 2 hours after the meal).
• The study showed Enterosgel clinical efficacy: 98% of patients with 1st -2nd grade of intestinal dysbiosis testified on their subjective improvement of general well-being already by 4th-5th days of Enterosgel administration. A positive dynamics of bowel dysbacteriosis manifestations was reported such as the disappearance of meteorism, the pronounced tendency to normalization of bowel movements (Table 14).
• On the 5th-7th days of treatment with Enterosgel out of 50 patients (98%) pain disappeared in 43 (84.3%) and significantly decresed in 7 (13.7%) patients.
• The results of microbiological examination of intestinal dysbiosis showed that 100% of patients had normalization of bowel microbiocenosis (Table 15).
• No adverse effects in the form of vomiting, the occurrence or aggravation of preexisting allergic reactions have been reported.

Conclusions

The obtained data provides evidence of a positive influence of Enterosgel on clinical manifestations of intestinal dysbiosis. Enterosgel can be recommended for treatment of bowel dysbiosis as a symptomatic agent.
For the treatment of 1st 2nd severity grade of bowel dysbiosis, it is sufficient to take Enterosgel in dose of 15 g 3 times a day for 10-14 days. In case of 3rd grade dysbiosis or in presence of a concomitant GIT disease, the treatment cycle duration and the dose of Enterosgel must be individualized.

2000

19 **TABLE 14**
Assessment of efficiency of Enterosgel in the complex treatment of 1st-2nd intestinal dysbiosis

20 **TABLE 15**
Dynamics of coprocultural bacteriologic indicators in complex treatment with Enterosgel (n = 51)

19

Clinical symptoms	Number of patients	
	abs. number	%
Normalization of stool frequency	47	92.2
Normalization of polifekalia	9	17.6
Reduction of pathological admixtures in stool	38	74.5
Reduction of GIT-related hypermotor and dyskinetic symptoms :		
flatulency	46	90,1
abdominal pain	50	98
Absence of side effects (intolerance, allergic reactions etc.)	51	100

20

Microflora	Prior to treatment	After treatment	P_{1-2}
Pathogenic microflora of bowel bacterial family	10^2-10^6	0	**
Total count of E.coli bacteria	10^2-10^6	10^8-10^9	**
E.coli with a slightly expressed enzymatic properties	0-10^6	10^2-10^3	**
Hemolyzing E.coli	20-60%	0	**
Conditionally pathogenic bacteries	10^3-10^5	0-10^3	*
Enterococci	0	10^5-10^6	**
Staphylococci	10^3-10^5	0-10^3	*
Proteus genus-related microbes	10^5-10^6	0-10^3	**
Candida genus-relaged fungi	10^3-10^5	0-10^3	*
Lactobacteria	10^5-10^7	10^7-10^9	*
Bifidum-bacteria	10^5-10^6	10^6-10^8	*

*– significant difference grade
** – highly significant difference grade

Yurchenko A., Nikolaev V.

Clinical efficacy of Enterosgel in treatment of intoxication and diarrhoea in patients with AIDS during antiretroviral therapy.

Objective

To determine the effectiveness of Enterosgel in the treatment and prevention of (relapse) intoxication and diarrhea syndromes in AIDS patients with HAART therapy.

Methods

• This was a randomized controlled clinical trial on 69 patients at the age 34 ± 7 years diagnosed with HIV infection who had started receiving HAART drugs. The main (Enterosgel) group included 46 patients (19 women and 27 men), control group – 23 patients (7 women and 16 man). One patient in the main group and three patients in the control group had the 2nd clinical stage of HIV infection (according to WHO classification, 2002), 22 patients in the main group and 17 patients in the control group had the 3rd clinical stage of HIV infection, the 4th clinical stage of HIV was observed in 23 patients in the main and in 3 patients in the control group. Level of CD4 lymphocytes in the main group was 111 ± 137 cells / μl, control group - 138 ± 104 cells / μl.

• In the main group, a traditional therapy of diarrheal and intoxication syndromes was conducted as well as two 2-week courses of Enterosgel: the first course - along with start of HAART therapy (within the first two weeks of HAART); the second - 1.5 months after the start of HAART (HAART lasting 7 and 8 weeks), if no adverse reactions (AR) occurred. With the development of AR (diarrhea, nausea, vomiting, rash, intoxication syndrome) the second course of Enterosgel was assigned from the onset of AR. Enterosgel was administered at a dose of one tablespoon 3 times a day 2 hours after meal.

• Patients in the control group were only under HAART and traditional therapy. Patients in both groups were monitored for 2 months.

• Rate evaluation in both groups was conducted 4 times: at the beginning of HAART, on day 14 of HAART, 1,5 months after beginning of HAART, 2 months after beginning of HAART – in case no AR was observed, and in 2 weeks - in case AR was observed.

Results

• The results are shown in Tables 16.

• During HAART, adverse reactions occurred in 13 (28%) patients of the main group and in 6 (26%) patients in the control group. Nausea, vomiting, diarrhea was observed in the patients as well as general intoxication manifestations (deterioration of the general sense of well-being, weakness, laxity, headache), anemia, compromised liver function (increased transaminase level), neuropathy, rash.

• The study has shown that diarrheal syndrome disappeared more quickly in the patients of the Enterosgel group. A tendency for reduction of average values of LII, HII, the number of rod nuclear cells, eosinophils, ALT and AST was also observed. NAII levels in patients of Enterosgel group practically did not change throughout the observation period, while in the control group YAII significantly increased by the third examination.

• Unlike the main group, patients in the control group experienced an increase in the number of rod nuclear cells and eosinophils by the third examination. Levels of erythrocytes and leukocytes did not change significantly.

Side effects of Enterosgel has not been found during the study in HIV-infected patients.

Conclusions

The study provides evidence that use of Enterosgel enterosorbent in the patients with AIDS in the development of adverse reactions to antiretroviral therapy promotes more rapid reduction of diarrhea and intoxication syndrome (disappearance of subjective complaints, reduction of mean values of intoxication indexes, rod nuclear cells and eosinophils, positive dynamics to reduction of transaminase average level).

21 **TABLE 16**
Results of the 1st, 2nd, 3rd and 4th examination of the patients in both groups

2009

Examination №	LII	NII	HII	Leukocytes, 10^6/ l	% eosinophiles	% band neutrophiles	Erythrocytes, 10^{12}/ l	Hb, g/l	ALT, U/l	AST, U/l	General bilirubin, µmol/l	Direct bilirubin, µmol/l
Enterosgel group Examination # 1	2,67 ±1,47	0,21 ±0,1	3,84 ±4,37	5113 ±3392	0,025 ±0,026	0,051 ±0,028	3,54± 0,99	109,14 ±27,08	51,6± 30,2	59,2± 42,5	9,5±3,12	2,34± 1,94
Enterosgel group Examination # 2	2,16 ±1,02	0,2 ±0,14	2,91 ±1,66	4945 ±1763	0,022 ±0,024	0,033 ±0,022	3,68± 0,82	112,45 ±21,37	52,6± 43,3	55,1± 45,6	12,4± 11,7	3,7±5,9
Enterosgel group Examination # 3	2,23 ±0,99	0,19 ±0,08	2,78 ±1,57	5016 ±1673	0,02± 0,02	0,036 ±0,023	3,76± 0,76	116,37 ±21	72,9± 65,1	70,1± 52,3	14,1± 9,6	3,5±7,3
Enterosgel group Examination # 4	1,93 ±0,95	0,2 ±0,096	2,04 ±1,04	4968 ±1420	0,014 ±0,012	0,027 ±0,022	3,91± 0,85	121,03 ±22,4	57,1± 49,7	54,3± 47,1	14,2± 10,6	3,72± 8,37
Control group Examination # 1	2,29 ±0,95	0,23 ±0,10	2,51 ±1,78	4876 ±1887	0,032 ±0,023	0,046 ±0,035	4,28± 0,57	130,04 ±15,61	50±51,7	53,9± 93,5	13,3± 4,34	2,76± 2,58
Control group Examination # 2	2,39 ±0,91	0,22 ±0,12	2,86 ±1,35	5106 ±1670	0,039 ±0,027	0,048 ±0,028	4,14± 0,44	128,54 ±17,42	51±48	50,8± 36,2	11,5± 3,4	2,9±1,7
Control group Examination # 3	2,3 ±1,1	0,31 ±0,16	2,84 ±1,92	4491 ±1396	0,043 ±0,032	0,06± 0,033	4,12± 0,55	128,82 ±16,51	62±48	61±47	11,8± 3,7	2,4±1,4
Control group Examination # 4	2,1 ±0,99	0,3 ±0,12	2,32 ±1,2	4229 ±967	0,029 ±0,022	0,054 ±0,028	3,75± 0,55	127,82 ±19,59	53±40	50±29,2	12,9± 3,87	3,16± 1,57

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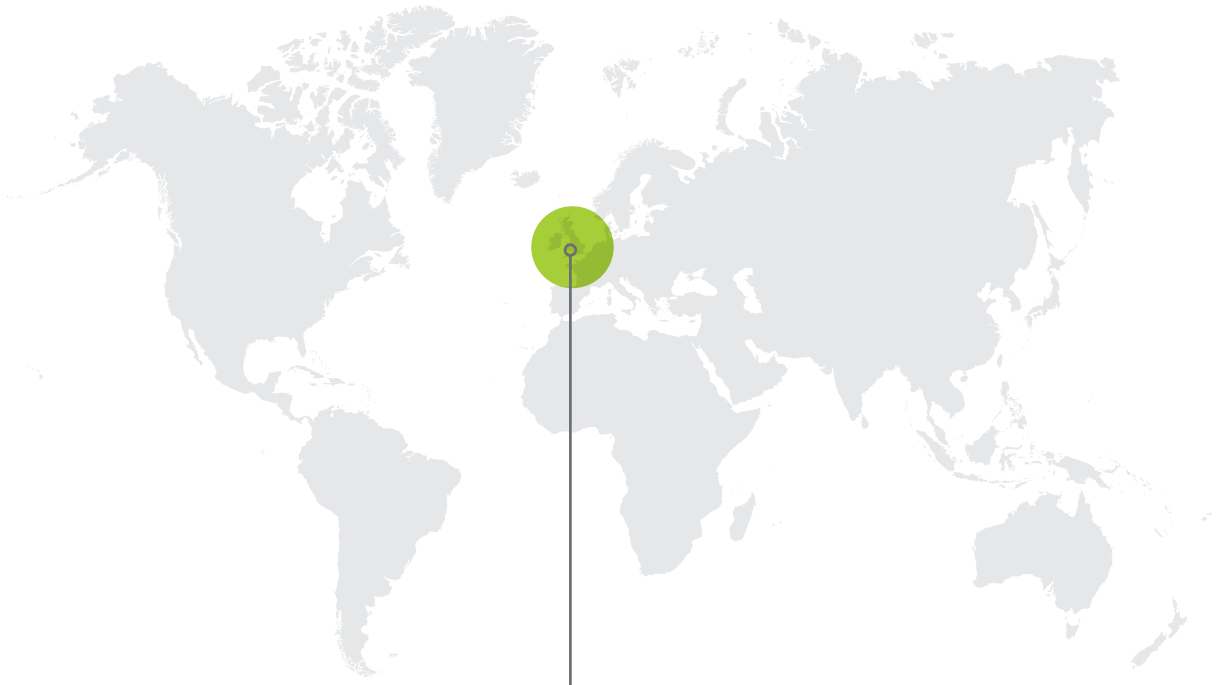
Notes:

ENTEROSGEL



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