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ORIGINAL RESEARCH
ОРИГИНАЛЬНОЕ ИССЛЕДОВАНИЕ

Hoficin and remaxol effects on metabolic intoxication and lipid peroxidation in patients with chronic non-calculous cholecystitis on the background of diffuse liver diseases

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Abstract. *Relevance*. The effect of the combined use of hoficin and remaxol on the indicators of metabolic intoxication and lipid peroxidation was studied in patients with chronic non-calculous cholecystitis on the background of diffuse liver diseases. *Materials and Methods.* The effect of the combined use of hoficin and remaxol was studied in 63 patients diagnosed with chronic non-calculous cholecystitison the background of acute chronic diffuse liver disease (CDLD), aged 20 to 53 years. Patients, by random distribution by age, gender, and severity of the clinical course of chronic non-calculous cholecystitis against the background of chronic diffuse liver damage, were divided into two equivalent groups–the analyzed group, according to which the combined use of hoficin and remaxol and the control group using conventional treatment, after which the results were compared. In patients in the analyzed group, the level of middle molecules (MM) and the concentration of lipid peroxidation (POL) products, final malonic dialdehyde (MDA) and intermediate diene conjugates (DC) in the blood serum were studied. The screening method of V.V. Nikolaichyk was used in the modification of Gabrilovich. To study the level of medium molecules, blood serum was obtained by centrifugation at 4000g for 15 minutes. The method is based on plasma purification from high-molecular peptides and proteins using trichloroacetic acid, a 10% solution, and then the level of medium-molecular peptides in terms of absorption in a monochromatic light stream was determined using direct spectrophotometry (at a wavelength of 254 nm) of the liquid. *Results and Discussion.* The content of MDA in blood plasma was estimated by M. Ushiama et al. in reaction with thiobarbituric acid. The studies were carried out in dynamics–before and after treatment. In patients with chronic non-calculous cholecystitis, an increase in serum MM levels and an increase in the concentration of POL products is observed.

The use of the herbal preparation hoficin in combination with remaxol contributes to the normalization of clinical and laboratory signs of the disease, normalization of POL products. Under the influence of hoficin in combination with remaxol, the metabolic intoxication syndrome is eliminated, which is manifested by a significant decrease in the level of medium-weight molecules to the upper limit of the norm, that is, this indicator is completely normalized, and the positive effect of treatment is observed in the first group of patients, unlike patients of the second group, in addition, the relative metabolic constancy of the internal environment of the body is restored. *Conclusion.* Patients with chronic non-calculous cholecystitis against the background of diffuse liver diseases exhibit endogenous metabolic intoxication syndrome. Increased concentration of LPO products-MDA and DC indicates activation of biomembrane lipid peroxidation. Including the herbal preparation Hoffitsin in combination with Remaxol in the general treatment course of these patients contributes to normalization of clinical and laboratory disease indicators, medium molecule levels decrease to normal, and LPO products-MDA and DC normalize. Under the influence of Hoffitsin in combination with Remaxol, metabolic intoxication syndrome is eliminated and relative metabolic constancy of the body's internal environment is restored.

Keywords: Chronic non-calculous cholecystitis, chronic diffuse liver diseases, medium molecules, lipid peroxidation, hoficin, remaxol

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Ethics approval. The study was approved by the RUDN University Ethics Commission (Protocol No. 2, dated 05.11.2020).

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Consent for publication. All patients provided voluntary informed consent to participate in the study in accordance with the Helsinki Declaration of the World Medical Association (WMA Declaration of Helsinki — Ethical Principles for Medical Research Involving Human Subjects, 2013) and the processing of personal data.

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Introduction

It has been demonstrated that combined pathology of the hepatobiliary system occur quite frequently and are accompanied by serious metabolic disorders of varying severity [1, 2]. These manifest through the accumulation of intermediate and final metabolic products in biological fluids [3–5].

Medium-mass molecules are among the metabolites with toxic effects, causing various pathological changes [6, 7]. Medium-molecular peptides negatively affect all systems and organs, adversely impacting their functions and metabolism [8].

Furthermore, in chronic non-calculous cholecystitis (CNC) against the background of chronic diffuse liver diseases (CDLD), lipid peroxidation (LPO) activation processes occur, indicating metabolic homeostasis disruption [9–12].

Among medications used for various liver pathologies, those with hepatotropic effects can be distinguished, where this action is primary [13, 14].

These drugs increase resistance and immunity of hepatocytes to damaging effects of various agents, restore liver cell functions, and regulate their regeneration [15–17]. The main pathogenetic link in various liver injuries is the development of hypoxia, which occurs due to oxidative phosphorylation disruption and adenosine triphosphate deficiency, leading to the formation of large quantities of free radicals. Both tissue and circulatory hypoxia occur in liver injuries [18–21].

Remaxola drug combining properties of a balanced polyionic solution containing succinic acid, methionine, inosine, and nicotinamide, acting as both an antihypoxant and hepatotropic agent [22–24]. This drug improves hepatocyte mitochondrial function through succinic acid, which provides antihypoxic effects [25–27].

Nicotinamide activates NAD-dependent enzyme systems. This leads to both activation of synthetic processes in hepatocytes and maintenance of their energy supply [28–30].

Methionine is converted to S-adenosylmethionine under the influence of methionine adenosyltransferase, subsequently actively participating in the synthesis of choline, lecithin, and other phospholipids [31–34].

Inosine achieves increased purine nucleotide content, necessary not only for adenosine triphosphate (ATP) and guanosine triphosphate (GTP) resynthesis but also for cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP), as well as nucleic acids. The infusion solution provides detoxifying effects, important in various liver pathologies accompanied by endotoxemia development. Due to its impact on key pathogenic mechanisms of liver damage, Remaxol can be considered a drug with universal hepatotropic action for treating various liver diseases. The tolerability, clinical efficacy, and safety of this drug have been evaluated in numerous experimental and clinical studies [35–37].

The use of Remaxol, possessing hepatoprotective, antihypoxic, and indirect antioxidant effects, significantly reduces clinical manifestations and severity of cytolytic and cholestatic syndromes in patients with liver pathology, metabolic disorders, and drug-induced hepatotoxicity [38–41].

In our comprehensive treatment of patients with CNC against CDLD background, we used the herbal preparation Hoffitsin® Evalar in combination with Remaxol. The use of herbal preparations has significant advantages over synthetic medications. These include high efficiency, low toxicity, gentle action, and accessibility to a wide population [42–44].

Hoffitsin® Evalar (Hofficin Evalar) is an artichoke leaf extract preparation manufactured by EVALAR, JSC, Russia. It is a phytopreparation with choleretic, hepatoprotective, and diuretic effects.

Artichoke leaf dry extract is obtained from fresh artichoke leaves-Cynara scolymus L., Asteraceae family; the ratio of used raw material to obtained extract is 15–35:1, with purified water as the extractant.

Pharmacological action-herbal remedy, provides choleretic and hepatoprotective effects. It increases the excretion of urea, toxins and heavy metal salts. It helps reduce blood cholesterol levels. Normalization of metabolic processes.

Hoffitsin® Evalar-used as an adjunctive treatment for cholecystitis, chronic hepatitis.

Remaxol is a metabolic drug with hepatoprotective action. POLYSAN NTFF (Russia).

A medication for treating liver and biliary tract diseases, lipotropic agent.

By pharmacological action, it is a balanced infusion solution with hepatoprotective effects.

Remaxol reduces cytolysis, manifesting in decreased levels of indicator enzymes ALT and AST.

Remaxol helps reduce bilirubin content and its fractions. It reduces activity Alkaline phosphatase (ALP) and Gamma-glutamyltransferase (GGT).

Based on preclinical safety data, Remaxol infusion solution is a practically non-toxic drug, belonging to class 5 of practically non-toxic medicinal substances.

Pharmacokinetics-with intravenous drip administration, the natural components are quickly distributed in body tissues, being utilized almost instantly.

Metabolic products are excreted in urine and do not accumulate in the body.

Study objective: to investigate the effects of Hoffitsin in combination with Remaxol on metabolic intoxication indicators and LPO in patients with CNC combined with CDLD.

Materials and methods

The combined effect of Hoffitsin and Remaxol was studied in 63 patients diagnosed with CNC against CDLD background, in the acute phase, aged 20 to 53 years. All patients provided voluntary informed consent to participate in the study in accordance with the Helsinki Declaration of the World Medical Association (WMA Declaration of Helsinki — Ethical Principles for Medical Research Involving Human Subjects, 2013) and the processing of personal data.

Patients were randomly distributed by age, gender, and clinical severity into two groups-the main group, which evaluated the comprehensive use of Hoffitsin and Remaxol on metabolic intoxication indicators and LPO, and a control group receiving conventional treatment.

The main group received conventional treatment-Diet therapy, M-anticholinergics for pain relief: Platyphylline hydrotartrate — 1 ml — 0.1% solution, myotropic antispasmodics for moderate pain intensity, probiotics, enzymes.

Additionally-Hoffitsin 200 mg, 2 tablets 3 times daily before meals for 2 weeks, Remaxol-400 ml intravenously by drip, once daily for 10 days.

MM levels, LPO products, MDA and DC in blood serum were measured using V.V. Nikolaychik's method modified by Gabrilovich. Blood plasma MDA content was determined according to M. Ushiama et al. (1978) in reaction with thiobarbituric acid, studied before and after treatment [45].

Statistical data processing was performed using Statistica 10.0, Microsoft Excel 2010. Continuous variables were presented using mean, and interquartile range values. All analyses with P values < 0.05 were considered statistically significant.

Results and discussion

Serum MM concentration before treatment, was elevated 6.2-fold — 3.22 ± 0.12g/l in the main group and 3.19 ± 0.12g/l in the control group, with normal being 0.52 ± 0.03g/l, (P < 0.05), indicating the presence of metabolic intoxication syndrome in patients with CNC against CDLD background. Also, in both groups of examined patients before treatment characterized by increased blood LPO products-MDA and DC. Thus, these biochemical parameter changes indicate metabolic disorders (Table 1).

Table 1

Level middle molecules and acidification lipid in the blood of patients before the start of treatment

Biochemical indicator	Standard	Patient examination groups		P
		Basicn=32	Comparisons n=31	
Middle molecules, g/l	0,52 ± 0,03	3,22 ± 0,12*	3,19 ± 0,12*	<0,05
Malondialdehyde, mmol/l	3,2 ± 0,2	8,9 ± 0,3	8,6 ± 0,25*	<0,05
Diene Conjugates, mmol/l	6,2 ± 0,15	18,4 ± 0,3	17,9 ± 0,25*	<0,05

Note: statistically significant differences relative to the norm p* -at p<0.05. In a separate column, the p value is the difference between the indicators of the main group and the control group.

Upon repeated examination of biochemical parameters after treatment completion, it was established that MM levels and LPO indicators-MDA and DC in the main group receiving the herbal preparation Hoffitsin showed reduction to the upper normal limit-MM level decreased to 0.54 ± 0.03g/l ($p < 0.05$), MDA-3.5±0.2μmol/l, DC-6.4 ± 0.2μmol/l (Fig. 1, 2).

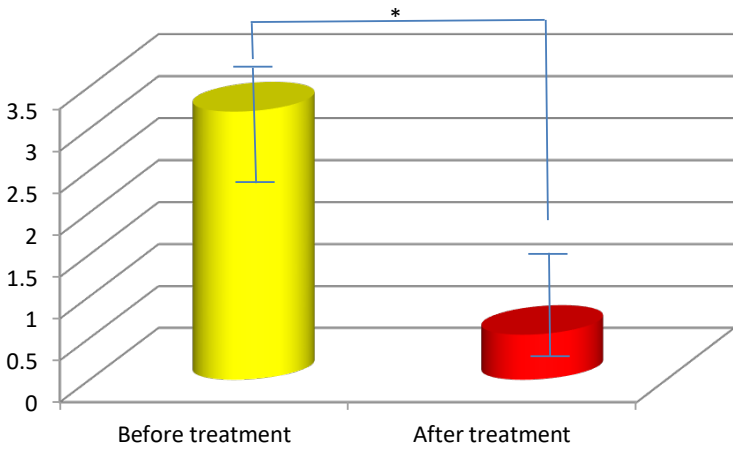

Fig. 1. Levels of medium molecules in patient blood serum;
* – p< 0.05

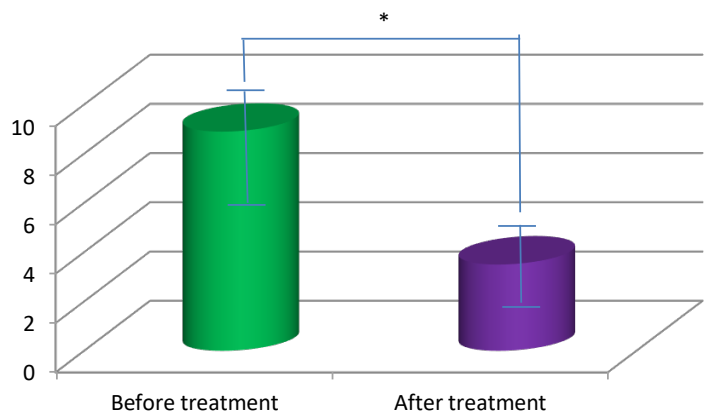

Fig. 2. Levels of terminal malondialdehyde in patient blood serum;
* – p < 0.05

In the comparison group receiving only conventional treatment, parameter reduction also occurred but less pronounced than in the main group patients and did not reach the upper normal limit-MM level decreased to 1.06±0.06g/l ($p < 0.05$), which is 2.0 times above normal, MDA-5.1 ± 0.2μmol/l, which is 1.59 times above normal. DC-10.1 ± 0.4μmol/l which is 1.62 times above normal. (Tabl. 2, Fig. 3).

Table 2

Level Middle molecules and acidification lipid in the blood of patients after treatment

Biochemical indicator	Standard	Patient examination groups		P
		Basic n=32	Comparisons n=31	
Middle molecules, g/l	0,52 ± 0,03	0,54 ± 0,03*	1,06 ± 0,06*	< 0,05
Malondialdehyde, mmol/l	3,2 ± 0,2	3,5 ± 0,2	5,1 ± 0,2*	< 0,05
Diene Conjugates, mmol/l	6,2 ± 0,15	6,4 ± 0,2	10,1 ± 0,4	< 0,05

Note: statistically significant differences relative to the norm p* — at p < 0.05. In a separate column, the p value is the difference between the indicators of the main group and the control group.

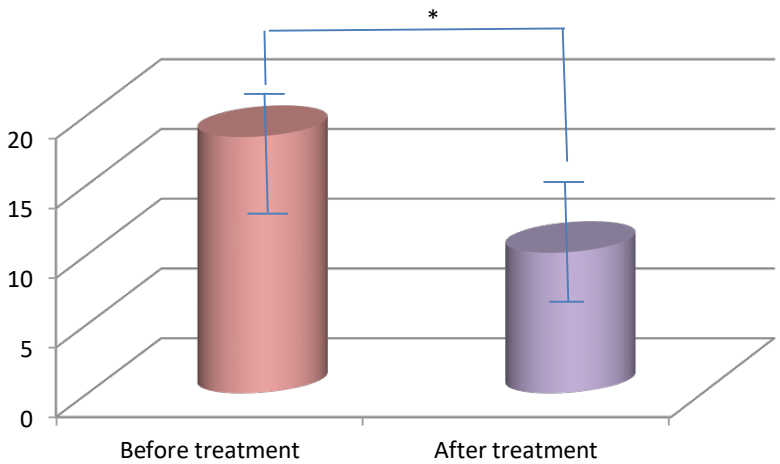

Fig. 3. Levels of diene conjugates in patient blood serum;
* — p < 0.05

Thus, the obtained data demonstrate the effectiveness of the herbal preparation Hoffitsin in combination with Remaxol in the complex treatment of CDLD patients with CNC, as these drugs help reduce MM levels, LPO indicators-MDA and DC, indicating elimination of metabolic intoxication syndrome and restoration of metabolic homeostasis.

Conclusion

1. Patients with chronic non-calculous cholecystitis against the background of diffuse liver diseases exhibit endogenous metabolic intoxication syndrome. Increased concentration of LPO products-MDA and DC indicates activation of biomembrane lipid peroxidation.

2. Including the herbal preparation Hoffitsin in combination with Remaxol in the general treatment course of these patients contributes to normalization of clinical and laboratory disease indicators, medium molecule levels decrease to normal, and LPO products-MDA and DC normalize.

3. Under the influence of Hoffitsin in combination with Remaxol, metabolic intoxication syndrome is eliminated and relative metabolic constancy of the body's internal environment is restored.

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Влияние хофицина и ремаксола на показатели метаболической интоксикации и перекисного окисления липидов у пациентов с хроническим некалькулезным холециститом на фоне диффузных заболеваний печени

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Аннотация. *Актуальность*. Исследовалось влияние комплексного применения хофицина и ремаксола на показатели метаболической интоксикации и перекисного окисления липидов у пациентов с хроническим некалькулезным холециститом (ХНХ) на фоне диффузных заболеваний печени (ХДЗП). Материалы и методы. Влияние совместного применения хофицина и ремаксола изучалось у 63 пациентов, с диагнозом ХНХ на фоне ХДЗП в стадии обострения, в возрасте от 20 до 53 лет. Пациенты, путем случайного распределения по возрасту, полу, тяжести клинического течения ХНХ на фоне ХДПП, были поделены на две равнозначные группы — анализируемую, по которой оценивалось комплексное применение хофицина и ремаксола на показатели метаболической интоксикации и ПОЛ, и контрольную группу с применением общепринятого лечения, после чего проводилось сравнение полученных результатов. У больных, находившихся в анализируемой группе, изучали уровень средних молекул (СМ) и концентрацию продуктов ПОЛ, конечного малонового диальдегида (МДА) и промежуточных-диеновых конъюгат (ДК) в сыворотке крови, использовался скрининговый метод В.В. Николайчика в модификации Габриловича. Для исследования уровня средних молекул сыворотку крови получали центрифугированием при 4000g в течение 15 мин. Метод основан на освобождении плазмы от высокомолекулярных пептидов и белков с использованием трихлоруксусной кислоты — 10% раствора, затем определялся при помощи прямой спектрофотометрии (при длине волны 254 нм) жидкости уровень среднемолекулярных пептидов по поглощению в монохроматическом световом потоке. *Результаты и обсуждение*. Содержание МДА в плазме крови оценивали по M. Ushiama и соавт. в реакции с тиобарбитуровой кислотой. Исследования проводили в динамике — перед началом лечения и после его окончания. У пациентов с хроническим некалькулезным холециститом наблюдается повышение уровня СМ в сыворотке крови и повышение концентрации продуктов ПОЛ. Применение препарата растительного происхождения хофицин в сочетании с ремаксолом способствует нормализации клинико-лабораторных признаков заболевания, нормализации продуктов ПОЛ. Под влиянием хофицина в комплексе с ремаксолом ликвидируется синдром метаболической интоксикации, что проявляется значительным снижением уровня молекул средней массы до верхней границы нормы, то есть данный показатель полностью нормализуется, и положительный эффект лечения наблюдается именно в первой группе больных, в отличие от пациентов второй группы, кроме того, восстанавливается относительное метаболическое постоянство внутренней среды организма. *Выводы*. У пациентов с хроническим некалькулезным холециститом на фоне диффузных заболеваний печени наблюдается повышение уровня средних молекул в сыворотке крови, что свидетельствует о наличии синдрома эндогенной метаболической интоксикации. Повышение концентрации продуктов ПОЛ — МДА и ДК свидетельствуют об активации пероксидации липидов биомембран. Включение препарата

растительного происхождения хофицин в сочетании с ремаксолом в комплексе лечебных мероприятий способствует нормализации клинико-лабораторных признаков заболевания, уровень средних молекул снижается до нормы и нормализации продуктов ПОЛ — МДА и ДК. Под влиянием хофицина в комплексе с ремаксолом ликвидируется синдром метаболической интоксикации и сохраняется метаболический гомеостаз.

Ключевые слова: Хронический некалькулезный холецистит, хронические диффузные заболевания печени, средние молекулы, перекисное окисление липидов, хофицин, ремаксол

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