A comparative study of phytopreparations of Hepaklin and Silymarin in patients with metabolic syndrome and non-alcoholic fatty liver disease

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This century is characterized by an avalanche-like increase in the number of people with excessive body weight and obesity. For the past 35 years, the number of obese patients has doubled and reached 11% among men and 15% among women. The obesity has become a problem not only in developed, but also in developing countries (Arroyo-Johnson C., Mincey K.D., 2016). In 2014, there were about 1.9 billion people with overweight and 650 million were obese. Our country is no exception. According to WHO, in 2016, 61.5% of adult Ukrainians had a body mass index (BMI) greater than 25. Currently, WHO characterizes obesity as the most important cause of developing chronic disease. It even outstripped the problem of malnutrition (WHO, 2016). This is due to the fact that overweight and obesity cause an increase of cardiovascular, endocrine and oncological pathologies (Yumuk V. et al., 2015).

It is known that visceral fat is the most metabolically active. Abdominal obesity is therefore naturally accompanied by a number of changes in lipid, carbohydrate and other metabolic types as a result the risk of many diseases increases. Diagnostic criteria for the metabolic syndrome (MS) are well known. They include an increase of the waist circumference (> 80 cm in women and > 84 cm in men of the European race) and at least 2 additional criteria, such as increased BP>130/85 mm Hg; increased triglycerides (TG)>1.7 mmol / l; increased fasting plasma glucose>5.6 mmol/L; and reduced high density lipoprotein (HDL)<1 mmol/L in men and <1.3 mmol/L in women or the administration of antihypertensive, hypoglycemic and hypolipidemic drugs (Alberti KG et al., 2009; Goldenberg R. et al., 2013). In addition to the mentioned diseases, MS is often accompanied by the development of osteoarthritis, psoriasis, urolithiasis and such gastroenterological pathologies as non-alcoholic fatty liver disease (NAFLD) and biliary dyskinesia (Halmos T., Suba I., 2017).

Currently, NAFLD takes the first place among the causes of liver damage in developed countries and may become the most common cause of death from liver disease in the next decade (Younossi Z. et al., 2018). It is known that most patients with NAFLD are diagnosed with hepatic steatosis - fat accumulation in more than 5% of hepatocytes without signs of inflammation, but some patients have inflammation as a result steatohepatitis develops. Fibrosis, cirrhosis and the development of hepatocellular carcinoma in some patients will be the outcome of such process. The gold standard for diagnosis of NAFLD is a liver biopsy with morphological examination. However, the improved ultrasonic diagnostics allows to confirm the presence of hepatic steatosis quite informatively and non-invasively (Pappachan J.M. et al., 2017).

Perhaps, functional gallbladder disorder (FGD) is the most little known for practical doctors among the functional gastrointestinal disorders. In our country, this disease is better known as "biliary dyskinesia". Currently, FGD has clear diagnostic criteria, confirmed by IV Rome Consensus on functional disorders of the gastrointestinal tract. However, an evidence base, specified in the criteria for the methods of diagnosis and treatment of this pathology, is weak enough (Cotton P.B. et al., 2016). The diagnostic criteria of functional gallbladder disorder include biliary pain in patients with preserved gallbladder when cholelithiasis excluded. The reduced gallbladder contractility is observed in most of these patients. At the same time, the contractile function of the gallbladder has been shown to be normal or increased in some patients with FGD (Pihl K.D. et al., 2018). The true prevalence of biliary dyskinesia is unknown, although it is assumed that in adults, about 20% of all cholecystectomies are performed in association with this pathology (Bielefeldt K. et al., 2014).

It should be noted that the treatment issues for NAFLD and FGD are not well developed, currently (Cotton P.B. et al., 2016; Pappachan J.M. et al., 2017). In North America, patients with FGD are treated with cholecystectomy, but its efficacy is much lower than in cholelithiasis (Goussous N. et al., 2014). In case of NAFLD the primary pathology (diabetes, obesity) is treated, primarily. At the same time, only modification of the lifestyle (diet and physical exercise), as well as tocopherol and pioglitazone have proved the effectiveness and have been included in recommendations for the treatment of this pathology. Across the world, there is an active search for new drugs for NAFLD therapy (Younossi Z.M. et al., 2017).

Currently, the attention is paid to the study of both individual herbal remedies, and their complexes in the treatment of patients with metabolic syndrome and NAFLD. The effect of individual plant components on appetite, glucose tolerance, lipoprotein level and contractility of the gallbladder is noted (Yao H. et al., 2016; Valvi A.R. et al., 2016).

One of such herbal remedies is Hepaklin (Ananta Medicare Ltd.) - an Ayurvedic preparation containing 7 plant components. Each of the components of this preparation has not only a thousand-year experience of application in traditional Indian medicine, but also evidence of its effectiveness proved by modern research methods. The first

component, *Picrorhiza kurroa* rhizome extract, has anti-inflammatory (inhibits the synthesis of IL-1β, IL-6, TNF-R1, VEGF, MMP-3 and MMP-9) and antioxidant effects, as well as reduces lipid levels in the liver in NAFLD (Kumar R. et al., 2016; Shetty SN et al., 2010). The second component, *Andrographis paniculata*, has anti-inflammatory (inhibits COX-2, LPS, decreases the synthesis of IFN-γ, TNF-α, IL-1β, IL-17A and IL-6), hypoglycemic, hypolipidemic, immunomodulating, choleretic and hepatoprotective effects (Hossain MS et al., 2014; Chua LS, 2014). The next component, *Phyllanthus niruri*, has a proven anti-inflammatory, antibacterial and hepatoprotective effect, and its effectiveness in the treatment of viral hepatitis is also discussed (Sarin B. et al., 2014; Xia Y. et al., 2013). Another component is *Tephrosia purpurea*, having anti-inflammatory, antioxidant, hypoglycemic and hepatoprotective effects (Palbag S. et al., 2014). *Tinospora cordifolia* stems have anti-inflammatory, hypoglycemic, spasmolytic and choleretic effects (Hussain L. et al., 2015). *Boerhaavia diffusa* has hypoglycemic, anti-inflammatory, choleretic and hepatoprotective effects (Tacchini M. et al., 2015). *Piper longum,* which is well known to us as a spice, is the most studied component of Hepaklin. A lot of studies have shown antibacterial, anti-inflammatory, antioxidant, immunomodulating, lipid-lowering and hepatoprotective effects of long pepper (Kumar S. et al., 2011; Gutierrez R.M. et al., 2013).

Purpose of the study. Given the above, we decided to study the effect of complex phytopreparation Hepaklin on the lipid and carbohydrate metabolism, liver function and gallbladder contractility in patients with metabolic syndrome and NAFLD, and to compare Hepaklin with the well-studied plant hepatoprotector as Silymarin.

Materials and Methods

The study was open, multicenter and comparative. We observed 60 ambulatory patients with MS. The study involved 33 men (55%) and 27 women; the average age was 43.2 ± 1.5 years. The diagnosis of MS was made on the basis of generally accepted diagnostic criteria (Alberti K.G. et al., 2009). In addition to anthropometric parameters (height, waist circumference - WC, body weight and body mass index - BMI), blood pressure, glycosylated hemoglobin (HbA1c), total cholesterol, lipoprotein fractions, aminotransferases (AcAt and AlAt), bilirubin and its faction tests were carried out in all patients. When carrying out sonography of the abdominal cavity organs, the sizes of the lobes of the liver and the attenuation parameter of the ultrasound wave (Controlled Attenuation Parameter — CAP) were determined. The gallbladder contraction fraction (GCF) was also evaluated by dynamic cholecystography on the background of a standard choleretic breakfast (norm is 35 to 75%). The severity of biliary pain was assessed using a visual analog scale (VAS). Non-inclusion criteria were other causes of liver damage, such as viral hepatitis, alcohol consumption> 2 alcoholic units per day, use of hepatotoxic drugs, as well as cholelithiasis, diabetes mellitus requiring drug therapy, clinically significant hepatic, renal or cardiac failure, and hypolipidemic drugs.

The choice of CAP for assessing the severity of the degree of hepatic steatosis in patients with NAFLD was based on its high information content. It was shown that when CAP value was 206.5 to 232.5 dB/m, steatosis> S1 was diagnosed in 83% of patients; when CAP value was 232.5 to 282.5 dB/m steatosis> S2 was diagnosed in 96% and when CAP value was greater than 282.5 dB/m steatosis> S3 was diagnosed in 98% (Andrade P. et al., 2017).

Hepatic steatosis was sonographically detected in all patients involved in the study. At, Steatohepatitis was diagnosed in 22 patients on the basis of increased aminotransferases levels. In the course of cholecystography performance, biliary dyskinesia was diagnosed in 29 people. 26 of them also had reduced gallbladder contraction fraction and 3 - increased gallbladder contraction fraction.

The patients were randomized into two groups of 30 people each. In both groups there were 11 patients with stethohepatitis. Among the patients with biliary dyskinesia in the first group there were 14 with reduced and 1 with increased function of the gallbladder, and in the second group12 and 2, respectively. Characteristics of patients in both groups are presented in Table 1. As can be seen from the data presented, initially there were no significant differences in the studied parameters between patients of the two groups ($p > 0.05$). The patients of the first group were treated with Hepaklin at the dose 1 table, 3 times a day, 30 minutes before meals. In the second comparison group, Silymarin is administered at the dose 45 mg 3 times a day. The duration of treatment in both groups was 12 weeks.

Results

After 12 weeks of Hepaklin therapy in the first group of patients, we found a significant decrease in the severity of biliary pain by 67% from the baseline ($p = 0.04$) (Figure 1) and the amount of biliary sludge. There was also a trend towards the decrease of body weight (BMI decreased by 4%), the waist circumference decreased by 0.8 cm, HbA1c decreased by 0.4%, AlAt – 15%, total cholesterol – 7.5%, triglycerides – 12%, CAP – 8% and gallbladder contraction fraction increased by 45% from the baseline (Figure 2), but all these changes did not reach a significant value ($p > 0.05$). We did not find the dynamics in terms of blood pressure, AsAt, alkaline phosphatase, bilirubin and its fractions, low-density lipoproteins, C-reactive protein, and clinical blood analysis. However, in the analysis of gallbladder contractility in patients with decreased motor function, a significant improvement of gallbladder contraction fraction was observed by 85% (from 21.3 ± 5.1 to 39.5 ± 5.7, $p = 0.025$) (Fig. 2).

In the second group there was an uncertain decrease in AlAt level by 16% from the baseline. Body weight, waist circumference, levels of HbA1c, AsAt, alkaline phosphatase, bilirubin and its fractions, low density lipoproteins, C-reactive protein, clinical blood analysis remained practically at the same level, and the cholesterol and triglycerides levels even slightly increased. In this group of patients, there were also no changes in blood pressure, severity of biliary pain, gallbladder contractility and steatosis stage.

The high drug safety and no clinically significant side effects were observed in both groups. In the first and second groups, 3 and 4 patients had headaches. 4 and 2 patients had pains in the joints of the lower extremities, 3 and 1 patient had heartburn and 2 patients in each group had nausea. We have not found adverse changes in the general blood test and cholestasis and cytolysis markers.

Discussion

In the patients with metabolic syndrome, in more than a third of cases, non-alcoholic steatohepatitis was found. But others patients had the hepatic steatosis that corresponds to the data obtained in the western and eastern populations (Gaharwar R. et al., 2015; Targher G., Byrne CD, 2015). At the same time, the prevalence of biliary dyskinesia in the group of patients with MS and NAFLD is not sufficiently studied, although it is known that this pathology is more common in patients with obesity and diabetes. According to our data, 48% of such patients had NAFLD, and almost in 90% of cases its hypomotor variant was revealed.

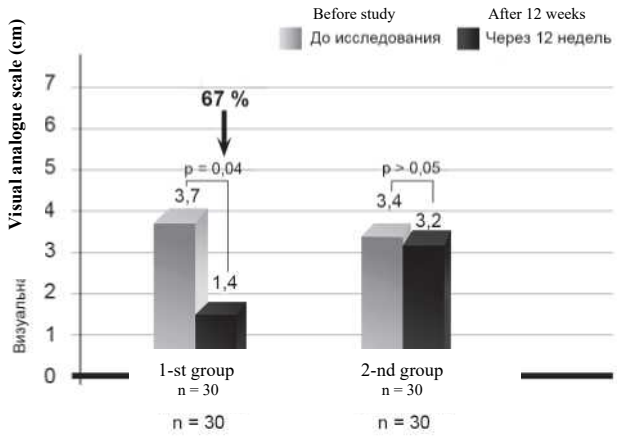

Figure 1. Change in the severity of biliary pain in the main and control groups

According to the results of our study, Hepaklin has the main therapeutic effect on the gallbladder. As a result of the 12-week application of this remedy, there were observed a significant decrease in the severity of biliary pain by 67% according to VAS, a reduction in the gallbladder contraction fraction by 85%, especially in patients with a hypomotor variant of biliary dyskinesia. Also, in patients treated with Hepaklin, there was a decrease in the amount of biliary sludge in the gallbladder. It should be noted that in the patients of the first group there was an improvement of lipid (reduction of total cholesterol and triglycerides) and carbohydrate metabolism (decreased HbA1c), as well as steatosis according to sonography was also improved, but these changes did not reach a certain level.

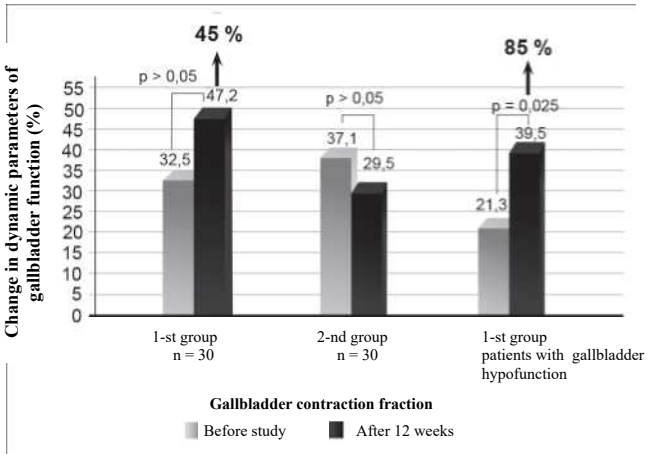

Figure 2. Change in dynamic parameters of gallbladder function

It is necessary to emphasize the high safety of the phytopreparation studied. After three months of Hepaklin administration, in isolated cases, insignificant side effects, not requiring a treatment change, were observed.

Table 1. Characteristics of groups of patients

Parameters	1st group (n = 30)	2nd group (n = 30)
Age (years)	45.8 ± 3.2	41.1 ± 3.4
Sex, male/female	17/13	16/14
BMI (kg/m^2)	29.1 ± 2.4	28.7 ± 2.7
WC , m/f (cm)	88.3 ± 3.6/85.8 ± 4.1	89.1 ± 4.0/84.5 ± 3.3
BP (mmHg)	152.3/91.4 ± 7.9/4.2	157.5/93.2 ± 8.6/5.7
Biliary Dyskinesia (%)	50	47
Biliary pain (cm)	3.7 ± 0.4	3.4 ± 0.3
CAP (dB/m)	264.7 ± 21.7	257.5 ± 23.9
Gallbladder Contraction Fraction (%)	32.5 ± 9.2	37.1 ± 10.4
HbA1c(%)	6.7 ± 1.4	6.5 ± 1.3
AlAt (u/L)	47.2 ± 2.6	49.1 ± 2.8
AsAt(u/L)	41.3 ± 2.1	40.8 ± 2.3
Total bilirubin (mmol/L)	14.54 ± 0.91	17.02 ± 0.87
Direct bilirubin (mmol/L)	2.48 ± 0.34	2.53 ± 0.42
Cholesterol (mmol/L)	6.77 ± 0.64	6.59 ± 0.61
Triglycerides (mmol/L)	2.29 ± 0.36	2.16 ± 0.34
HDL, m/f (mmol/L)	0.71/0.94 ± 0.05/0.06	0.69/0.93 ± 0.04/0.05

Table 2. Dynamics of some parameters in groups of treated patients, M ± m

Parameters	Groups			
	1st group (Hepaklin), n = 30		2nd group (Silymarin), n = 30	
	Before treatment	After treatment	Before treatment	After treatment
BMI (kg/m^2)	29.1 ± 2.4	27.9 ± 2.6	28.7 ± 2.7	27.8 ± 2.3
Biliary pain (cm)	3.7 ± 0.8	1.4 ± 0.7	3.4 ± 0.7	3.2 ± 0.6
Gallbladder Contraction Fraction (%)	32.5 ± 9.2	47.2 ± 9.8	37.1 ± 10.4	29.5 ± 9.5
CAP (dB/m)	264.7 ± 21.7	243.5 ± 26.1	257.5 ± 23.9	255.0 ± 24.4
HbAlc (%)	6.7 ± 1.4	6.3 ± 1.5	6.5 ± 1.3	6.4 ± 1.4
AlAt(u/L)	47.2 ± 2.6	40.1 ± 2.2	49.1 ± 2.8	42.3 ± 2.5
Cholesterol (mmol/L)	6.77 ± 0.64	6.26 ± 0.59	6.59 ± 0.61	6.73 ± 0.62
Triglycerides (mmol/L)	2.29 ± 0.36	2.01 ± 0.31	2.16 ± 0.34	2.27 ± 0.35

Conclusions

Thus, the natural multicomponent phytopreparation Hepaklin has a normalizing effect on the contractility of the gallbladder and reduces the severity of biliary pain in patients with metabolic syndrome and non-alcoholic fatty liver disease. Hepaklin has good tolerability and high safety.

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