ORIGINAL ARTICLE

Effect of livergol on the improvement of fatty liver in patients with cancer undergoing irinotecan- and oxaliplatin-based chemotherapy regimen

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Background: The aim of this study was to determine the effect of Livergol on the improvement of fatty liver in patients with cancer undergoing irinotecan- and oxaliplatin-based chemotherapy regimen. **Materials and Methods:** This was an add-on nonrandomized clinical trial study on thirty selected eligible cancer patients undergoing irinotecan (8 patients) and oxaliplatin (22 patients) with diagnosed fatty liver disease-based liver ultrasonography, as well as alanine aminotransferase (ALT) and aspartate aminotransferase (AST). Patients in each group received Livergol at a dose of 140 mg daily for 1 month. ALT and AST levels as well as grade of fatty liver were evaluated before and after intervention. **Results:** In the oxaliplatin/Livergol group, 40% and 44.4% of patients who were in Grade 2 and 3 before intervention were altered to Grades 1 and 2, respectively ($P = 0.005$), and in irinotecan/Livergol group, the mentioned percentages were 80% and 66.7% ($P = 0.014$). The mean levels of ALT and AST enzymes were decreased in both groups after tacking Livergol; however, the observed decreases were not significantly different between groups. **Conclusion:** It was concluded that the adding of Livergol to oxaliplatin and irinotecan regimens significantly improved the fatty liver of patients and none of them was superior.

Key words: Alanine aminotransferase, aspartate aminotransferase, chemotherapy, fatty liver, livergol

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INTRODUCTION

Along with the increase in the incidence of obesity and diabetes throughout the world, nonalcoholic fatty liver disease (NAFLD) is increasingly recognized as one of the main causes of chronic liver disease.[1-3]

Noninvasive ways to diagnose this disease include elevated liver enzymes of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) in the blood. One of the studies published in this area in the United States (II NHANCS) showed that the level of ALT >30 was 7.4% among white adolescents, 11.5% among Mexican American adolescents, and 6% among black adolescents. In the same study, it was observed that the increase in ALT levels was 12.4% in males, compared with 3.5% in females.[4]

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Nonalcoholic fatty liver disease represents a range of clinical and pathological conditions which, in the absence of alcohol use, progress from a simple steatosis to nonalcoholic steatohepatitis (NASH), fibrosis, and cirrhosis and ultimately can lead to hepatocellular carcinoma.[5] Due to complications of NAFLD, treatment of this disease is necessary.[6]

Many patients need several medications to treat chronic diseases and disorders. Prescribing multiple prescriptions with several medications poses a higher risk because of drug interactions and higher complications. The liver is of paramount importance, as it acts as an intermediate metabolizer, and exposed to Zincobiotics and contaminants in the environment, as well as agents used in chemotherapy. This is due to liver function that plays a major role in detoxification and elimination of toxic substances.[7] Liver damage is

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associated with altered metabolic function (mutated) and is still a serious problem in health and treatment because of common medications used to treat liver disease which have serious side effects.[8] The mechanisms of oxaliplatin is not clear, but it may increase the proliferation rate of reactive oxygen species and glutathione sedimentation from sine endothelial cells and also may increase cells apoptosis. Furthermore, it causes liver injury such as sinusoidal obstruction syndrome or venous obstruction, acute hepatitis and cirrhosis of the liver, and even liver failure.

Studies have shown that treatment with irinotecan significantly increases the AST, ALT, and total bilirubin (TBIL) levels by two to ten times the threshold; so their levels do not return to their initial state until the end of treatment. The level of PT and ALB decreases significantly which is consistent with changes in AST, ALT, and TBIL levels suggesting that the liver is affected.

This liver injury in patients with cancer being treated with irinotecan and oxaliplatin based on chemotherapy and hepatic excretion can lead to discontinuation or reduction of the dose of the chemotherapy medications, if the patient's fatty liver leads to an increase in liver enzymes. This issue has been proven based on *in vivo* and *in vitro* studies; hence, in chronic liver disease caused by oxidative stress factors, such as fatty liver, the antioxidant agents such as silymarin can have a beneficial effect.[9]

Silymarin is made from *Silybum marianum*. The dry extract of *S. marianum* contains several components include Silibin, Silicristin, and Silidianin; the collection of which is called silymarin. Characteristics of the above include antioxidant activity, protein synthesis stimulation, antiduodenal effects against alpha-amanitin, effects on the metabolism of membrane phospholipids, and protective effects on liver cells. Silymarin prevents the binding of toxins to the liver cell receptors. Silymarin also maintains the level of glutathione in a constant level, which makes it antioxidant. Silymarin stimulates the synthesis of ribosomal protein by stimulating the nucleoplomerase A, which results in an increase in the ability to renovate liver cells.[10]

As one of the compounds of *S. marianum*, Sibilin has been examined and shown to be able to directly reduce cytotoxic effects, reduce the toxicity of agents used in cancer treatment, and increase the efficacy of factors used in chemotherapy. In a placebo-controlled trial in patients with nonalcoholic fatty liver, silymarin significantly improved the biochemical markers of patients.[11]

In other studies, it has been proven that the effect of silymarin compound can have a beneficial effect on the formation of a shorewall cell balance and apoptosis by intermediate cytokines of the tumor cells and an inhibitory effect on the spread of metastasis.[12] If the medication is proven to have an effect on the fatty liver with cancer, it can neutralize the effects of oxidative fatty acids with antioxidant effects and prevent the removal of chemotherapy medication due to impairment of liver enzymes and can probably prevent the spread of metastasis and act as an auxiliary treatment in these patients.

According to the authors' best knowledge, there is no report on the direct effect of silymarin on nonalcoholic fatty liver in cancer patients treated with irinotecan and oxaliplatin chemotherapy medications. For this reason, this study aimed to determine the effect of Livergol on the improvement of fatty liver in patients with cancer undergoing irinotecan and oxaliplatin based on chemotherapy regimen.

METHODS

Study design and participants

This was a nonrandomized single-blind clinical trial intervention study. Thirty patients including 3 men and 33 women with mean age of 49 years were consequently selected from cancer patients among those who referred to Seyed Al-Shohada Hospital, affiliated to Isfahan University of Medical Sciences, Isfahan, Iran. Inclusion criteria were as diagnosed nonalcoholic fatty liver in ultrasonography and liver enzymes and treating with chemotherapy with an irinotecan (8 patients) and oxaliplatin (22 patients) regimens. The patients with hepatobiliary cancers and drug-related complicatioor those who refused to continue the treatment for any reason were excluded from the study. Written informed consent was obtained from all participants before starting the study. Study protocol was approved by Bioethics Committee of Isfahan University of Medical Sciences.

Procedures and study protocol

Before receiving Livergol, the patients underwent liver ultrasonography by an expert radiologist using an ultrasonography system (Medison H60). All sonographic grading of fatty liver was diagnosed by an expert radiologist before and after treatment with same device and condition. The participants were divided into two groups: oxaliplatin (22 patients) and irinotecan (8 patients). In the oxaliplatin group, 3 participants (13.6%) were male and 19 participants (86.4%) were female. Eight participants of irinotecan group were female. The radiologist was blind about patients' information before and after prescribing the medication. Patients with fatty liver (reported by the liver ultrasonography) were prescribed Livergol as tablets of 140 mg daily for 1 month. At the end of a month, a liver ultrasonography (according to system protocols) was performed on studied patients by the same radiologist with

the same device for the effectiveness role of the mentioned medication. A sample of ultrasonography image of patients before and after taking the medications was shown in Figure 1. Ultrasonography data were collected before and after treatment.

Statistical analyses

Continuous and categorical data were presented as mean ± standard deviation and frequency (percentage), respectively. Normality of quantitative data was evaluated using Smirnov–Kolmogorov test and QQ plot. Nonnormal data were subjected to logarithmic transformation. Within-group analysis was conducted paired samples *t*-test for normality distributed data and Wilcoxon signed-rank test for ordinal data. Between-group comparisons for continuous normally distributed data were conducted based on mean differences (after-before intervention) using independent samples *t*-test and for ordinal data using Mann–Whitney U-test. All statistical analyses were performed using SPSS software version 16.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Table 1 shows the distribution of fatty liver grades in patients, before and after the taking Livergol, in both study groups oxaliplatin and irinotecan regimens. There is no significant difference between groups in terms of fatty liver grades before intervention ($P > 0.05$); however, in both regimens, the fatty liver grades were significantly improved in which the percentages of patients who were in Grade 2 and Grade 3 fatty liver before intervention significantly altered to Grade 1. After intervention, no significant difference was seen indicating that both regimens are individually effective but their effects are not significantly different. In the oxaliplatin/group, among who were in Grade 2 and 3 before intervention, 40% and 44.4% were altered to Grades 1 and 2, respectively ($P = 0.005$), and in irinotecan, the mentioned percentage changes were 80% and 66.7% ($P = 0.014$) [Table 1].

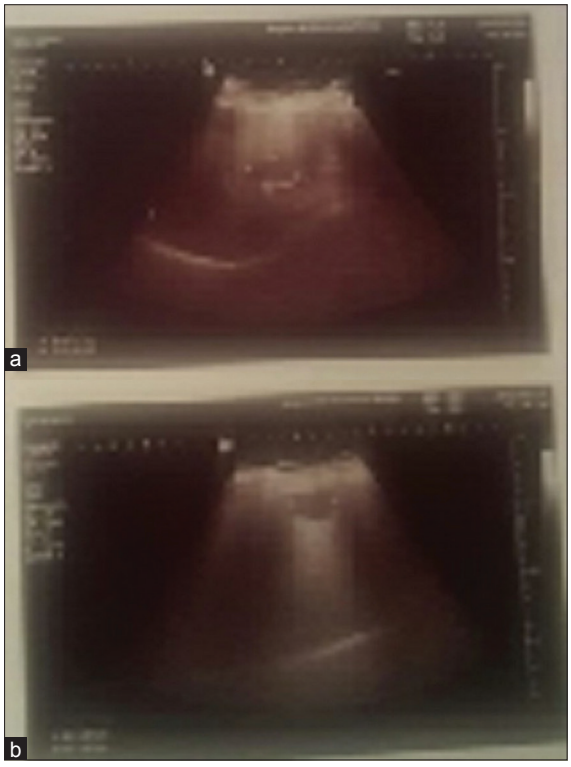

Figure 1: Sonography images of a patient (a) before and (b) after taking the medication

Table 2 shows the effect of two competitors' regimens on liver enzymes. As can be seen oxaliplatin/Livergol reduced significantly both ALT and AST, however, after tacking irinotecan/Livergol, the levels of AST significantly reduced; however, its effect on ALT was decreasing but not statistically significant. Although both interventions had decreasing effects on both ALT and AST, their impacts were not significantly different.

DISCUSSION

Nonalcoholic fatty liver disease is currently the most common cause of chronic liver disease. The accumulation

Table 1: Comparison of fatty liver grades in patients before and after intervention

Group	Grade	Frequency (%)		P^a	P^b
		Grade of fatty liver before medication	Grade of fatty liver after medication		
Oxaliplatin/ livergol	1 00	2 (9.1)	6 (27.3)	0.005	0.532
	2 00	11 (50.0)	10 (45.5)		
	3 00	9 (40.9)	6 (27.2)		
	Total	22 (100.0)	22 (100.0)		
Irinotecan/ livergol	1 00	0	4 (50.0)	0.014	
	2 00	5 (62.5)	3 (37.5)		
	3 00	3 (37.5)	1 (12.5)		
	Total	8 (100.0)	8 (100.0)		

[a]Resulted from Wilcoxon signed rank test, [b]Resulted from Mann–Whitney U-test

Table 2: Comparison of the mean levels of liver enzymes before and after taking medication

Group	Enzyme type	time	Mean±SD	*P*	Mean (SE) difference	*P*
Oxaliplatin	ALT	Before	27.59±14.87	0.001	−6.91 (1.76)	0.312
		After	20.68±8.76			
Irinotecan		Before	23.41±6.13	0.12	−2.73 (0.51)	
		After	20.68±5.02			
Oxaliplatin	AST	Before	23.41±6.13	<0.001	−3.62 (2.08)	0.329
		After	20.68±5.02			
Irinotecan		Before	23.63±4.14	0.007	−3.75 (0.99)	
		After	19.88±4.12			

SD=Standard deviation; SE=Standard error; ALT=Alanine aminotransferase; AST=Aspartate aminotransferase

of fat in the liver causes inflammation of the liver, which is called NASH. Many people have fat accumulation in the liver (nonalcoholic fatty liver), but they have no complications or problems. However, in some people, fat causes inflammation of the liver and NASH. NASH can become worse, such as liver scarring, leading to cirrhosis. In cirrhosis, liver cells are replaced by scar tissue and the liver cannot function and may be lead to liver failure, liver cancer, and death.[13] Therefore, controlling the changes in the status of liver fat and sometimes its reducing will be one of the most important keys to treat the patients.

Since fatty liver patients with increases of enzymes do not treat with chemotherapy, for this reason, the patients were chosen by the use of ultrasonography grading of fatty liver. The value of grading fatty liver could not increase the liver enzymes. However, in many cases, the expansion of grading fatty liver can cause to increase liver enzymes. This is reason why in this study the ultrasonography was used for the diagnosis of grading fatty liver.

Results of the present study showed that using of Livergol made from herbal extract of *S. marianum* can increase the hepatic cell renewal capacity by stimulating the ribosomal protein synthesis. Therefore, a regimen containing oxaliplatin and irinotecan could be an auxiliary treatment which is completely effective in preventing the progression of fatty liver grade in the patients.

As indicated in tables, in the oxaliplatin group, 40% and 44.4% of patients who were in Grade 2 and 3 before intervention, were altered to Grades 1 and 2, respectively ($P = 0.005$), and in irinotecan group, the mentioned percentages were 80% and 66.7% ($P = 0.014$).

It was proved in some studies such as the study conducted by Saller *et al*., in 2001. The results of a meta-analysis study, 84 papers and 452 patients entitled "Silybummarianum and liver disease," showed that silymarin, as an antioxidant, improves the fatty liver disease and reduces its grade by reducing the production of free radicals and preventing the binding of toxins to the liver receptors.[14] In 2004, Sko ová *et al*. also designed a study to compare the use of medications on the fatty liver. According to the findings of this study, the use of silymarin has a positive effect on the fatty liver grades in patients with fatty liver.[15]

In 2005, a review study on *S. marianum* as a treatment for alcoholic liver disease and emphasized that *S. marianum* and its derivatives have been shown to positively affect the fatty liver grade in patients with fatty liver.[16]

Over the past 10 years, it has been shown that NAFLD is the most common cause of increased liver enzymes found in the United States population. With obesity epidemic in the United States, it is estimated that 20% of the population may have abnormal liver enzymes (NAFLD). In steatosis, liver enzymes (AST and ALT) increase by 50%. However, in steatohepatitis, elevations of liver enzymes show an increase of 80%. In nonalcoholic fatty liver, the level of ALT is higher than AST.[17] So far, no definitive treatment has been found for this disease, but Ziaee *et al*. have tested the effect of silymarin tablets on patients with fatty liver.[9] In this study, in which 50 patients were divided into case and control groups, all patients had elevated liver enzymes and elevated liver echogenicity. During a 2-month follow-up and regular daily treatment of the case group with a silymarin tablet, it was found that the level of liver enzymes decreased significantly after the end of the treatment period in the case group compared to the control group.[10] In another study by Loguercio *et al*., the effect of silibin (main component of silymarin) combined with Vitamin E was examined on 85 patients already divided into two groups. The results of the study showed that the use of the new medication has been effective in reducing the level of liver enzymes and preventing the progression of liver fibrosis.[17] In this regard, another result of the present study was that the use of Livergol reduced the level of AST enzyme significantly in patients with regimens containing oxaliplatin and irinotecan. It also reduced significantly the level of ALT only in patients with a regimen containing oxaliplatin.

Kidd and Head[18] reported that *S. marianum* can be reduce the AST enzyme levels in patients with fatty liver and also conducted that there are limited treatment options such as lifestyle changes, weight loss, Vitamin E, and thioglitazones.

Abenavoli *et al*., in 2011, conducted a study on the effectiveness of silymarin in the reduction of transactivity of nonalcoholic fatty acids. In their study, the protective effect of silymarin on liver has been confirmed, and it has been reported that it reduces fatty liver grade and dangerous enzymes.[19]

In 2012, McBrid *et al*. showed that *S. marianum* can have a positive effect on the fatty liver and also reduce AST levels in patients with fatty liver.[20] Their results are not in agreement with findings of the present study, due to the use of different medication and protocol.

Due to time limitation, patients' follow up was done 1 month after intervention. Further study including 5–6 months following up patient's time and using more samples is recommended.

CONCLUSIONS

Findings of this study showed that the mean levels of ALT and AST enzymes were decreased in both groups after tacking Livergol; however, the observed decreases were not significantly different between groups. Overall, it was concluded that the adding of Livergol to oxaliplatin and irinotecan regimens significantly improved the fatty liver of patients and none of them was superior.

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Conflicts of interest
There are no conflicts of interest.

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