Original Article

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Evaluating Protective Effects of Silymarin on Liver and Cardiac Side Effects of Chemotherapy Drugs in Childhood Acute Lymphoblastic Leukemia

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Abstract

Background: The protective effects of silymarin on liver and heart have been investigated and identified by many researchers. This study evaluates the protective effects of this substance on hepatotoxicity and cardiotoxcity of chemotherapy drugs in leukemic children.

Materials and Methods: In this study, 71 children, aging 2-14 years old, going through the maintenance phase of acute lymphoblastic leukemia (ALL) treatment at Children's Cancer Center of Isfahan University of Medical Sciences (Iran) in 2015 were studied. Two patients died and the remaining patients were divided into intervention and control groups. Intervention group received Mercaptopurin and Methotrexate plus Silymarin 140mg/day and control group were taking only Mercaptopurin and Methotrexate. Liver enzymes, Coagulation tests, Creatine kinase- Muscle and Brain (CK-MB), Ejection fraction and Systolic function (SF) were measured at the first, and 3 and 6 months' intervals from the commencement of study. The Data was analyzed by using SPSS and $P \leq 0.05$ was considered as statistically significant. Associations between variables were analyzed using independent t-test, chi square, and repeated measures ANOVA test.

Results: Mean levels of Alanine aminotransferase in both groups increased significantly at 6 months interval (P=0.01, 0.01, for control and intervention groups respectively). Although increment was more among controls, there were no significant differences between the two groups (P= 0.85). Furthermore, Aspartate aminotransferase and Alkaline phosphatase increased in both groups and the increment was significant in the controls (P=0.001, 0.05, for control and intervention groups respectively). Coagulation tests prolonged in the first 3 months in both groups and the prolongation was more in control group. Changes in CK-MB were not significant in intervention and controls (P=0.07, 0.10, respectively) but ejection fraction and SF decreased in both groups, especially among controls.

Conclusion: It seems that Silymarin can be useful in prevention of hepatotoxicity and cardiotoxcity of chemotherapy drugs for ALL children.

Keywords: Acute lymphoblastic leukemia, Cardiotoxity, Hepatotoxicity, Silymarin

Introduction

Although chemotherapy drugs, especially anthracyclines, have numerous benefits in the treatment of childhood acute lymphoblastic leukemia (ALL), the cardiac side effects have still limited their clinical use. Cardiac dysfunctions and disorders can range from asymptomatic diseases to severe heart failure (1-2) and include: systolic or diastolic dysfunction, cardiomyopathy, arrhythmia, and pericardial effusion (1, 3-6) . These complications are mostly created by cumulative dose of drugs, but can be presented by administration of the first dose or during the treatment without considering drug dosage or even as late as 20 years from the initial exposure (7). Duration of drug use, total amount of the drug used during treatment procedure and simultaneous prescription of the drug with another medication can increase cardiac toxicity (8). Correlations have been reported in some studies between these

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drugs and decreased cardiac function that may last many years (9,10) .Trans-thoracic echocardiography is an important safe diagnostic way for evaluating the effects of these drugs on systolic and diastolic heart function (5, 11) .

The mechanisms of anthracyclines cardiotoxicity are multi-factorial. These drugs "induce multiple forms of cellular injuries by free radical production, alter nucleic acid biology by intercalation into DNA, and modulate intracellular signaling that lead to cell death and disruption of homeostatic process, such as sarcomere maintenance" (7). So substances, such as silymarin and its isolated components, can be protective for cardiomyocytes because of their antioxidant effects and cell membrane stabilizing as well as radical scavenging potency (12, 13).

One of the other complications that most commonly are observed in the treatment of childhood ALL is hepatic side effects. Serum aminotransferases elevation associated with a combination of methotrexate and 6MP used in maintenance phase of the therapy has been commonly used (14). Five-fold elevation of these enzymes causes drug interruption (15) that can increase the risk of relapse in childhood ALL (16). Moderate rise in bilirubin or reduced levels of coagulation factors may be seen, however, there is a low risk of permanent liver damage and within few weeks after discontinuing of drug administration, the enzymes usually are normalized (17). Mercaptopurine metabolism, influenced by age and genotype and drug response, is related to red blood cell (RBC) metabolite concentrations. In patients, aged 6 years or less, steady-state is lower than the older patients and these children require higher doses to achieve clinical improvement. Hepatotoxicity, induced by 6-MP, is strongly related to concentration of 6-methylmercaptopurine nucleotide (6-MMPN) in red blood cells. A 6-MMPN threshold of 5000 pmol/8 × 108 RBC has been reported with hepatotoxicity (18).

MTX was reported to be more hepatotoxic than 6-MP and it was witnessed that its chronic low-dose may lead to hepatic cirrhosis and fibrosis in the maintenance phase of ALL treatment. MTX is usually the first drug to be adjusted or discontinued when a hepatotoxicity occurs and the enzymes abnormalities can resolve within one month after the cessation of therapy (14, 18).

Therefore, the use of hepato and cardioprotective substances, such as Silymarin, which is an herbal extract of silybum marianum plant with known hepatoprotective and cardioprotective effects may be effective for these patients (13). This substance has been used for years for its protective effects against liver and biliary diseases, toxin and drug-induced hepatitis, and cirrhosis. It can reduce the duration of therapy in acute hepatitis and can improve the liver enzyme profile in chronic hepatitis (12, 19, 20).The protective effect of silymarin on liver and heart has been more related to anti-oxidant effects which eliminate free radicals. On the other hand, it acts as a potent antioxidant by scavenging free radicals of the body. In addition, this substance can increase RNA polymerase activity in the nucleus of hepatocytes and can initiate ribosomal protein synthesis which improves hepatic cell re-generation and can inhibit lipid peroxidation, reduce glutathione oxidation, and enhance liver detoxification (13). Cardioprotective activities of Silymarin were primarily shown in sodium fluoride and Cisplatin-induced cardiotoxicity in rat models (21, 22) and then, during ischemia-reperfusion injuries and inflammations due to coronary artery bypass grafting surgeries in rats and humans (23, 24). These effects are due to replenishing endogenous antioxidant enzymes, suppressing neutrophil infiltration and reducing serum malondialdehyde as end product of myocardial lipid peroxides (13).

Based on the above information, the present study evaluated the protective

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effects of Silymarin on livers and hearts of a small group of Iranian leukemic children undergoing chemotherapy using Livergol tablet containing 70 or 140 mg Silymarinmade in Iran.

Materials and Methods

This study was conducted in a 12-month In this clinical trial (IRCT2017071935175N1), 71 children, aged 2-14 years old, in the maintenance phase of the treatment of ALL were studies. They had received antracycline 25mg/m2 /week/4 times in induction phase and 3 times in reinduction phase (totally 175mg/m2). All of the patients were selected from Children's Cancer Center (at Seyed-Al-Shohada Hospital) of Isfahan University of Medical Sciences, located in the central area of Iran in 2015. The Research Council and Ethics Committee of School of Medicine approved this study (Code: 394213, IR.MUI.REC.1394.3.213 respectively) and written informed consents were obtained from the parents who agreed with participation of their children in this study.

The inclusion criteria were diagnosis of childhood ALL based on bone marrow morphology and immunophenotype, age range of 2-14 years old, and therapy in the maintenance phase of childhood ALL (at least 6 months). Previous history of liver and heart diseases and being under any other kind of medication except chemotherapy drugs included the exclusion criteria of the study. To calculate the sample size, the standard formula suggested for clinical trials was used by considering a= 0.05 and the power of the test equal to 80%. Finally, a total of 20 cases in each group were estimated and they increased to 49 samples control group to cover 20% anticipated dropout. n=((z_1+ z_2)^2 (〖2s〗 ^2))/d^2 , z_1=1.96 ,z_2 = 0.84, d= two-tailed t-test of the difference between means for ALT and AST parameters (0.8*s).

Of all the patients included in this study (n=71) two patient died. The remainder of the patients (n=69) were divided into two intervention (n=20) and control (n=49) groups. In intervention group, the patients were taking MTX: 20mg/m2/week/po [EBEWE Pharma Ges.m.b.h. Austria] and 6MP: 75mg/m2/day/po [KOREA United Pharma Inc] at least 6 months (25) plus Silymarin: 140mg / day (26) in 2 divided doses by using Livergol herbal tablet containing 70 mg Silymarin [Goldaru Pharma Com, Iran]. Patients in control group were taking only 6MP and MTX with a similar dose in interventions.

Data collection

At the beginning phase, and within 3 and 6 months' intervals from the commencement of the study, patients' blood was tested for liver enzymes: Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Alkaline phosphatase (ALP), coagulation tests: ProthrombinTime (PT), activated Partial Thrombin Time (aPTT), International Normal Ratio (INR(and CK-MB (as a marker of heart injury). Liver enzymes were measured by biochemical methods (Elitech kit, Man Company under license of France, Iran), coagulation studies were done using Fisher kit, Netherlands, and CK-MB were also measured by biochemical methods (Parsazmoon kit, Karaj, Iran).

Ejection Fraction (EF) and SF were measured in all patients by echocardiography at the first and at intervals of 3 and 6 months from the commencement of the study. All data was recorded in specific checklists.

Statistical Analyses

Data analyses were performed using SPSS software (version 22). Continuous variables were reported as the mean ± SD, and P value ≤ 0.05 was considered as statistically significant. Changes in ALT, AST, ALP, CK- MB, PT, aPTT, INR, EF, and SF were compared in two groups at first, at two different time intervals, the first 3 and the first 6 months of study. The association between variables was investigated using independent t-test, chi-square test, and repeated measures

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ANOVA test. A two-sided α level of 0.05 was used to assess the statistical significance.

Results

71 patients participated in this study two of whom (2.8%) died and the remainder were divided as intervention and control groups. It needs to be noted that distribution of age and sex in groups did not show any significant differences (Table I). Measurement of ALT in the two groups showed that the mean levels of ALT in case and control groups increased significantly during 6 months (P-value= 0.01, 0.01, respectively), and that the ALT increment was more in control than case group, however, comparisons between the two groups revealed that there were no significant differences after 3 and 6 months of the study (Table II).

Furthermore, changes in the mean levels of AST are shown in Table II. The results showed that unlike ALT, AST increment was only significant in controls after 3 and 6 months, and there were no significant differences in comparison of ALT between two groups, after 3 and 6 months.

Alkaline phosphatase changes in the control group had similar AST changes during 6 months (P-value=0.04,) but changes in the case group and comparison s between the two groups were not significant (Table II).

According to the ANOVA test results, PT, aPTT, and INR increased in the first 3 months in both groups, but the increment was only significant in control group (P-value= 0.01, 0.03, and 0.04, respectively).

Despite the increase in CK-MB at the first 3 months in both groups, changes in CK-MB at the end of study in cases and controls were not significant (P-value= 0.07, 0.10, respectively).

Echocardiography results indicated both EF and SF decrease in the second 3 months in case and control groups (Table II). Although these changes were not significant during 6 months, according to the ANOVA test, the decline was higher in control group. In this study, two-fold ALT increase was more in cases than controls, but five-fold or more ALT increase based on age which led to discontinuation of treatment was more among controls [Table III].

Table I. Demographic variables in intervention and control groups

Variable		Control	Intervention
Gender	Boy	29(65.5%)	12(60%)
	Girl	20(34.5%)	8(40%)
	Total	49(100%)	20(100%)
Age	Mean age ±SD	6.4±3.1	6.7±3.1

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Table II. ALT, AST, ALP, PT, aPTT, INR, EF, and SF in interventions and controls at the beginning, 3, and 6 months intervals of the study

Variable	Time	Control Group	Intervention Group	P- value
ALT	At the beginning	33.8±3.7	32.8±6.2	**0.88**
	After 3 months	122.9±32.4	44.3±9.9	**0.1**
	After 6 months	52.6±7.9	50±11.4	**0.85**
	P- value	0.007	0.009	
AST	At the beginning	35.3±2.2	35.4±3.7	**0.91**
	After 3 months	87.7±14.9	37.7±4.7	**0.28**
	After 6 months	50.9±5.3	49.5±9.5	**0.88**
	P- value	0.001	0.11	
ALP	At the beginning	400.7±20	357.8±46.1	**0.33**
	After 3 months	450±26.8	400.1±48.5	**0.35**
	After 6 months	446.1±23.5	400.8±43.7	**0.33**
	P- value	0.046	0.45	
PT	At the beginning	12.9±0.27	15.8±2.4	**0.26**
	After 3 months	15.9±0.55	16.8±2.5	**0.72**
	After 6 months	13.8±0.44	16±2.5	**0.42**
	P- value	0.009	0.139	
aPTT	At the beginning	33.3±1.3	32.4±3	**0.79**
	After 3 months	43±3	46±9	**0.74**
	After 6 months	35±1.7	37.4±3.3	**0.67**
	P- value	0.031	0.27	
INR	At the beginning	1.1±0.05	1.27±0.18	**0.41**
	After 3 months	1.4±0.07	1.24±0.07	**0.17**
	After 6 months	1.2±0.06	1.18±0.05	**0.62**
	P- value	0.045	0.28	
EF	At the beginning	68±7.14	70±6.21	**0.46**
	After 3 months	69.2±6.43	72.5±4.6	**0.15**
	After 6 months	65.6±9.3	71.9±5.9	**0.04**
	P- value	0.147	0.304	
SF	At the beginning	38.2±5.4	38.7±4.5	**0.77**
	After 3 months	37.3±5	40.7±3.96	**0.07**
	After 6 months	36.1 ±5.6	39.9±4.6	**0.08**
	P- value	0.406	0.25	

Table III. Increasing two and five-fold of ALT and AST in case & control groups

Variable	Control Group		Intervention Group	
	Multiplied by 5	Multiplied by 2	Multiplied by 5	**Multiplied by 2**
ALT	10(20.4%)	15(30.6%)	2(10%)	**3(15%)**
AST	5(10.2%)	16(32.6%)	0	**2(10%)**

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Discussion

As mentioned earlier, side effects and toxicity of cytotoxic drugs is a problem in the treatment of malignancies. Toxicity of these drugs is due to their inability to differentiate between normal and malignant cells. Thus, cytoprotective compounds play a very important role in ameliorating the toxicity associated with these drugs. Compounds as dexrazoxane, glutathione, mesna, etc. have been extensively investigated in the past (27). Herbal ingredients with known cytoprotective effects, however, may also be effective in ameliorating side effects of chemotherapy drugs.

This study evaluated the effects of Silymarin as an herbal cytoprotective (13, 28-31) on livers and hearts of leukemic children during the 6 months of maintenance therapy. The findings revealed that although there were no significant differences in comparing the two groups after 3 and 6 months of study, increased liver enzymes levels were less in patients who received Silymarin than the control group. Studies that assessed the effects of herbal medicine showed the efficacy of this substance in decreasing liver enzymes and mortality of liver disease (32, 33). Saller et al., evaluated 106 liver disease patients who were treated with Silymarin and placebo and showed more reduction and normalization of liver enzymes in patients treated with Silymarin than the placebo (34). Although most of studies suggested that Silymarin is effective in reducing liver enzymes, Vargas-Mendusa et al., showed that the levels of liver enzymes are not different in patients treated with Silymarin (35). These differences in results of studies may have occurred due to the dosage of drug, stage of liver disease, and different planning in studies unraveling the need to review articles. In the present study, lack of significant difference in the amount of liver enzymes in comparison between the two groups after 6 months may be due to length of the study or dosage of drug and longer studies with more doses of Silymarin recommended.

In addition to decrease in liver enzymes, protective effects of Silymarin in the fall of clotting factors was reported in intoxicated dogs (36). Vargas-Mendusa et al., which evaluated the hepatoprothective effects of Silymarin, showed that using this substance can improve Prothrombin Time. In present study also patients received Silymarin had fewer changes in coagulation tests especially for Prothrombin Time.

Another problem in the treatment of malignancies is cardiotoxicity secondary to anthracyclines. Echocardiographic evidence of left ventricular contractile abnormalities was seen in up to 65% of patients with a history of a childhood malignancy treated with doxorubicin (37). In a study on 14,358 five-year survivors of childhood malignancies, patients that used <250 mg/m2 anthracyclinehad 2.4-fold higher risk of developing congestive heart failure compared to those patients who did not receive (38). Free radical formation caused by doxorubicin metabolism and formation of doxorubicin-iron complexes that catalyze conversion of hydrogen peroxide to hydroxyl radical and result in the generation of reactive oxygen species are the responsive of cardiotoxicity. In animal models probucol and carvedilol due to antioxidant properties have been shown protective effects against doxorubicin-induced left ventricular dysfunction. In human in vitro experiments and some clinical studies have also shown beneficial effects of antioxidant therapy on cardiac function (39).

Because of the interaction of doxorubicin with non-heme iron in the body iron chelating agents may be effective in prevention of antracyclines cardiotoxicity. Protective effects of Dexrazoxane as an iron chelator in reducing the incidence of congestive heart failure have been shown from a long time ago (40) therefore Silymarin as an iron chelating agent (41)

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may be effective on cardiotoxicity of these drugs.

In this study, EF was decreased in the second quarter in both groups and although these decreases were not significant, the amount of decline was more in controls than the interventions. Animal studies showed the protective effects of silymarin against antracyclines cardiotoxicity (42, 43) but there is lack of sufficient data in human therefore, the need for these studies is clear.

Conclusion

In conclusion, it seems that using Silymarin in leukemic children has protective effects on their liver and heart and can decrease the side effects of chemotherapy drugs.

The limitations of this study were small sample size and short duration of study. Therefore longer studies with larger sample size are recommended in the future.

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Conflict of interest

All authors declare that they have no conflict of interest.

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