EFFECT OF FLAXSEED OIL ON LIPOFUNDIN-INDUCED HEPATOTOXICITY IN ADULT MALE ALBINO RATS

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ABSTRACT

Objective: To find out the preventive effect of flaxseed oil on the hepatic damage produced by the Lipofundin, a soya-bean based lipid emulsion used in parenteral therapies.
Study Design: Experimental study.
Place and Duration of Study: The study was carried out at the University of Health Sciences, Lahore for a period of one year, from Jan 2015 to Dec 2015.
Material and Methods: Experimental study has been performed to study the effect of flaxseed oil on the lipofundin induced hepatotoxicity. Thirty-two male adult albino rats were obtained from animal house of University of Health Sciences, Lahore and divided into four equal groups. Group A (control group) was given flaxseed oil 3ml/kg intraperitonially daily for 10 days and sacrificed on day 11. Group B was given Lipofundin 2ml/kg intravenously daily for 10 days and sacrificed on day 11. Group C was given Lipofundin 2ml/kg intravenously daily for 10 days and sacrificed on day 21. Group D was given Lipofundin 2ml/kg intravenously for 10 days followed by Flaxseed oil 3ml/kg intraperitonially for 10 days and sacrificed on day 21.
Results: Flaxseed oil was observed to restore the hepatic tissue damage caused by the lipofundin administration.
Conclusion: Flaxseed oil has an ameliorative effect on the hepatic tissue damage caused by the Lipofundin.
Hence its use may help prevent hepatic tissue damage caused by lipofundin used in parenteral therapies.

Keywords: Flaxseed oil, Hepatotoxicity, Lipofundin.

INTRODUCTION

Parentral nutrition is given to the patients who are unable to take orally, or those suffering from poor nutrition, beacause inadequate intake of required nutrients, both micronutrients as well as macronutrients are asssoiciated with vulnerability to various and nutrituinal associated diseases and increased morality[1].

Parentral nutrition must include fluid, electrolytes, vitamins, carbohydrates, fats and proteins along with adequate amount of trace elements that are capable of fulfilling the daily requirement of the body according to the height and weight of the patient[2]. Lipids and fats are the major sources of energy in therapies that are given parentrally thus performing a vital role in preventing energy deficits[3]. These lipids are given usually in wide spread infections, injuries associated with multiple trauma and in patients suffering from severe burns[4]. Fats are included in the form of emulsions made up of long-chain triglycerides (LCT) and medium chain triglycerides (MCT) including essential fatty acids. One of such emulsions is Lipofundin 20% that is frequently used worldwide. It is a soya-bean based fat emulsion that contain both LCT and MCT[5].

Lipofundin 20% was found to be responsible for the oxidative stress and resultant hyperlipidemia and atherosclerotic lesions which was demonstrated in the experiments done on rabbits[6]. Hyperlipidemia caused by the Lipofundin 20% may be due to the high level of triglycerides in the soya bean based emulsions[7]. Total parenteral nutrition including Lipofundin was also found to cause hepatic steatosis[8].

Flax plant (Linum ustitissimum) is cultivated throughout the world for its seeds[9]. Flaxseed oil is obtained from the flaxseeds that is commonly used as a nutritional supplement throughout

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the world. It is known for its cardioprotective properties if taken daily in routine diet[10]. The hypocholesterolemic effects of flaxseed oil is well established[11]. Flaxseed intake increases the high density lipoproteins while it decreases the low density lipoproteins that helps to play an important role in preventing the cardiovascular diseases if added in daily diet[12].

Flaxseed oil supplementation also showed improvement in anti-oxidant status of liver in obese rats showing a protective role played by the flaxseed against the oxidative stress caused by the fat rich diet[13]. Flax plant is grown in western Canada and has blue colour flowers[14]. Seeds obtained from this plant are dark brown in color and oval in shape[15]. Flaxseeds are obtained from a harvest, and are popular for their nutritional benefits. The seeds are rich in omega-3 and omega-6 fatty acids, and also contain phytoesterogenic lignans, especially secoisolariciresinol diglucoside[16]. Flaxseed oil is usually extracted from the seeds by using a cold pressure procedure[14].

In the present study preventive effect of the flaxseed oil was observed on the hepatic tissue damage caused by Lipofundin administration.

MATERIAL AND METHODS

The experimental study was conducted at University of Health Sciences, Lahore over a period of one year lasting from 1st January 2015 to 31st December 2015. Thirty-two male albino rats bred in the animal house of University of Health Sciences, Lahore, were selected randomly for the experiment (simple random sampling technique). Rats were divided into four equal groups of eight animals each. Healthy rats were inclusion criteria. Ailing rats were excluded. Group A, which was our control group, was given flaxseed oil intraperitonially 3ml/kg daily for 10 days and sacrificed on day 11. Group B was given lipofundin 20% intravenously 2ml/kg daily for 10 days and sacrificed on day 11. Group C

Table-I: Showing comparison of mean weight of animal among different groups.

Parameter	Group A Mean ± SD	Group B Mean ± SD	Group C Mean ± SD	Group D Mean ± SD	*p*-value
Initial Weight of Animals (gms)	185.25 ± 11.37	186.00 ± 12.96	179.00 ± 4.79	186.93 ± 12.65	0.472
Final Weight of Animal (gms)	226.12 ± 10.83	178.75 ± 16.52	187.37 ± 5.64	207.87 ± 10.39	<0.001*

*$p<0.05$ was considered statistically significant

Table-II: Tukey HSD test showing multiple comparisons of final weight of animals among groups A, B, C and D.

(I) Groups	(J) Groups	Mean Difference(I-J)	Std. Error	*p*-value
	B	47.37500	5.75786	<0.001*
A	C	38.75000	5.75786	< 0.001*
	D	18.25000	5.75786	0.018*
	A	-47.37500	5.75786	< 0.001*
B	C	-8.62500	5.75786	0.452
	D	-29.12500	5.75786	< 0.001*
	A	-38,76000	5.75786	< 0.001*
C	B	8.62500	5.75786	0.452
	D	-20.50000	5.75786	0.007*
	A	-18.25000	5.75786	0.018*
D	B	29.12500	5.75786	< 0.001*
	C	20.50000	5.75786	0.007*

*$p<0.05$ was considered statistically significant

was given lipofundin 20% intravenously 2ml/kg daily for 10 days followed by treatment free period of 10 days and sacrificed on day 21. Group D was given lipofundin 20% intravenously 2ml/kg daily for 10 days followed by flaxseed oil intraperitonially 3ml/kg daily for the next 10 days and sacrificed on day 21.

Flaxseed oil Extraction

Fresh dried and macerated flaxseeds were used to get flaxseed oil. Flaxseeds were soaked in petroleum ether for seven days. Then filtrated, followed by collection of flaxseed oil by air drying the filtrate[17].

Lipofundin 20%

Lipofundin 20% emulsion available commercially, was used. (Braun, Melsungen AG, Melsungen, Germany)[5].

Procedure

Thirty two albino rats were divided into four groups, A, B, C and D. The groups were properly marked and placed in four cages labelled with the group's title and name of the researcher. Weight of the animals was recorded on the first and last day of treatment according to the plan. Afterwards the rats were anaesthetized by placing in an air tight jar, having a cotton swab soaked in chloroform (Trichloro-methane) for few minutes. The anaesthetized rats were placed on the dissection slab in supine position. Abdomen was opened and liver was identified, exposed and removed by separating it from diaphragm. The liver was then washed with normal saline to remove blood and then weighed with the help of digital balance (Sartorius, model TE-214-S). Liver was then placed in the 10% formaline solution in

Table-III: Chi-Square test showing comparison of frequencies and percentages of the histological parameters among different groups.

Histological Parameters		Group A n (%)	Group B n (%)	Group C n (%)	Group D n (%)	Total
Central	Absent	6.00(75%)	0.00(0%)	0.00(0%)	6.00(75%)	12.00(37.5%)
Vein	Present	2.00(25%)	8.00(100%)	8.00(100%)	2.00(25%)	20.00(62.5%)
Congestion	Total	8.00(100%)	8.00(100%)	8.00(100%)	8.00(100%)	32.00(100%)
	Chi-Square	Test	=19.200		*p*-value	=0.001*
Hepatic	Irregular	0.00(0%)	6.00(75%)	5.00(62.5%)	1.00(12.5%)	12.00(37.5%)
Lobular	Regular	8.00(100%)	2.00(25%)	3.00(37.5%)	7.00(87.5%)	20.00(62.5%)
Pattern	Total	8.00(100%)	8.00(100%)	8.00(100%)	8.00(100%)	32.00(100%)
	Chi-Square	Test	=13.583		*p*-value	=0.003*
Periportal	Absent	5.00(62.5%)	0.00(0%)	0.00(0%)	1.00(12.5%)	6.00(18.8%)
Inflammation	Mild	3.00(37.5%)	0.00(0%)	0.00(0%)	7.00(87.5%)	10.00(31.2%)
	Moderate	0.00(0%)	1.00(12.5%)	3.00(37.5%)	0.00(0%)	4.00(12.5%)
	Severe	0.00(0%)	7.00(87.5%)	5.00(62.5%)	0.00(0%)	12.00(37.5%)
	Total	8.00(100%)	8.00(100%)	8.00(100%)	8.00(100%)	32.00(100%)
	Chi-Square	Test	=28.486		*p*-value	= 0.001*
Hepatocyte	Absent	6.00(75%)	0.00(0%)	0.00(0%)	3.00(37.5%)	9.00(28.1%)
Vacuolation	Mild	2.00(25%)	0.00(0%)	0.00(0%)	4.00(50%)	6.00(18.8%)
	Moderate	0.00(0%)	0.00(0%)	0.00(0%)	1.00(12.5%)	1.00(3.1%)
	Severe	0.00(0%)	4.00(50%)	6.00(75%)	0.00(0%)	10.00(31.2%)
	Very Severe	0.00(0%)	4.00(50%)	2.00(25%)	0.00(0%)	6.00(18.8%)
	Total	8.00(100%)	8.00(100%)	8.00(100%)	8.00(100%)	32.00(100%)
	Chi-Square	Test	=39.467		*p*-value	= 0.001*

*p-value <0.05 was considered statistically significant.

properly labelled containers for 24 hours. Three to 5 millimetter pieces of tissue were cut from the median lobe of liver and placed in 10% formaline solution for 2 days for fixation. Liver tissue was then placed in an automatic tissue processor (Histotech III-USA) for processing. Processed tissue cassettes were then shifted to embedding station (Model SM C1-044-SO) and tissue blocks were made. After trimming tissue blocks to size, these were affixed in the flip of rotary microtome (Leica, RM 2125). Tissue slices of 5µm thickness were made that were then collected on the glass slides that were allowed to dry at room temperature. Slides were then hydrated and stained with haematoxylin and eosin for light microscopy. Hepatocytes were examined for their regular arrangement and vaculation while central vein was observed for the presence of congestion. Periportal polymorph nuclear infiltration was observed for grading of periportal inflammation as absent, mild, moderate and severe. Basement membrane continuity was observed in the basement membrane surrounding central vein under light microscope using PAS stain.

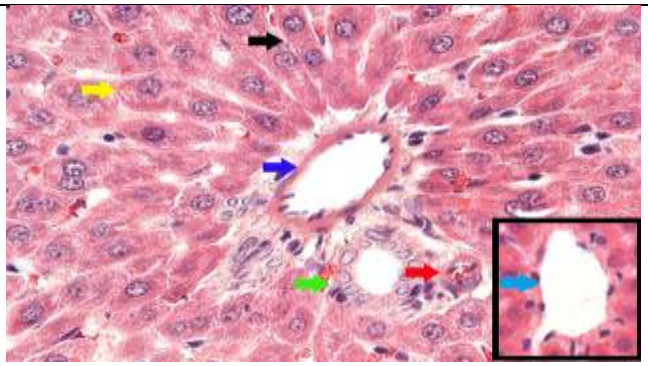

Figure-1: Showing photomicrograph of histological section of liver of group A illustrating portal area. Hepatocytes are normal with central nuclei (yellow arrow). Portal vein (dark blue arrow), hepatic artery (red arrow) and bile duct (green arrow) are normal. Parenchyma shows regularly arranged radiating cords of hepatocytes (black arrow). Inset photomicrograph shows hepatic tissue section of group A. Light blue arrow points towards the normal central vein. H&E stain. X400.

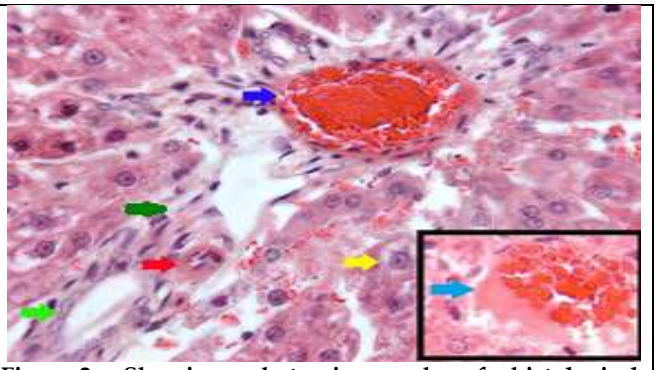

Figure-2: Showing photomicrograph of histological section of portal area of liver of group B. Hepatocytes shows vacuolation (yellow arrow). Portal vein is markedly congested (dark blue arrow). Hepatic artery (red arrow) and bile duct (light green arrow) are normal. Inflammatory cells are infiltrating in the parenchyma (dark green arrow). Inset photomicro-graph shows hepatic tissue section of group B. Light blue arrow points towards the congested central vein. H&E stain. X400.

Statistical Aanalysis

After the completion of the experimental work statistical analysis was done to analyse the data obtained. SPSS 20.0 (Statistical Package for Social Sciences version 20.0) was used for this purpose.

Data was recorded and mean ± SD was calculated for quantitative parameter in a tabulated form. One way ANOVA was applied for the comparison of parameters among different groups. Post hoc Tukey Test was used for the multiple comparison of parameters among various groups.

Light microscopic examination was done. Two slides from each animal was studied at X400 magnification. Data was recorded and percentages were calculated for qualitative histological variables that include hepatic lobular pattern, central vein congestion, periportal inflammation, vacuolation and basement membrane continuity. Then, Chi-SquareTest was applied to look for statistical significance of parameters among groups. *A p*-value <0.05 was taken from statistically significant.

RESULTS

Gross Examination

Animal Weight

Initial weight of all the thirty two animals was in the range of 175-225 grams. No statistically significant variation in initial weight

of animals was found among various groups. Final weight was recorded at the end of experiment. It was observed that mean ± SD of animal weight of groups A, B, C and D was 226.12 ± 10.83, 178.75 ± 16.52, 187.37 ± 5.64 and 207.87 ± 10.39 gms respectively at the time of sacrifice. One way ANOVA showed statistically significant variation in the mean of final weight of rats among different groups (table-I). Post hoc Tukey test showed statistically significant decrease in the average final weight of group B, C and D as compared to group A (table-II). Group B showed significant decrease in mean body weight as compared to all other groups at the end of experiment.

showed congestion of central vein in only two out of eight animals (fig-4).

Hepatic Lobular Pattern

Hepatic lobules were observed histologically for the arrangement of cords of hepatocytes radiating away from the central vein in a parallel manner. Chi-Square Test showed statistically significant change in hepatic lobular pattern (table-III). It was observed that after treatment with the lipofundin hepatic lobular pattern got distorted (fig-2). Flaxseed oil administration after the lipofundin treatment helped in the recovery of the hepatic lobular pattern towards normal (fig-4).

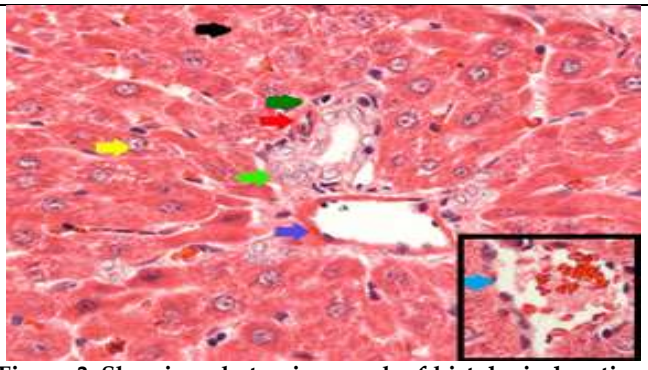

Figure-3: Showing photomicrograph of histological section of liver of group C illustrating portal area. Hepatocytes are vacuolated (yellow arrow). Hepatic lobular pattern is distorted (black arrow). Periportal inflammatory cells are seen in the periportal area (dark green arrow). Portal vein (dark blue arrow), hepatic artery (red arrow) and bile duct (light green arrow) are normal. Inset photomicrograph shows hepatic tissue section of group C. Congested central vein (light blue arrow) is shown. H&E stain. X400.

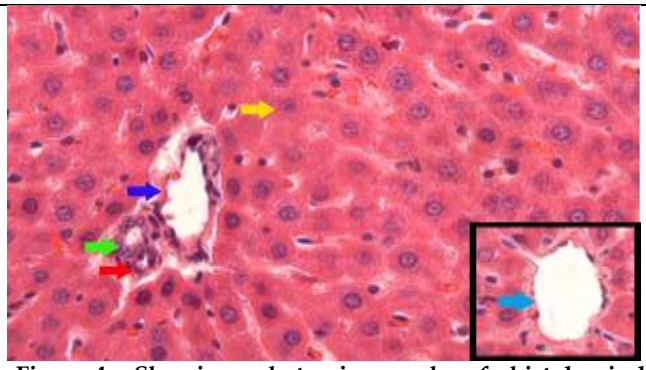

Figure-4: Showing photomicrograph of histolo-gical section of liver of group D illustrating structures in portal area. Hepatocytes shows normal histological pattern (yellow arrow). Portal vein is empty (dark blue arrow). Hepatic artery (red arrow) and bile duct (green arrow) are normal. Inset photomicrograph shows normal central vein of group D (light blue arrow). H&E stain. X400.

Histological Examination

Central Vein Congestion

Light microscopic examination of the central vein was done for the presence or absence of congestion. Data was recorded followed by the calculation of percentages of each group. Chi-Square Test showed statistically significant results (table-III). Group A showed normal histological appearance of central vein (fig-1) whereas, all the animals of lipofundin treated groups B showed congestion (fig-2). Animals of group C also showed congestion (fig-3). Group D

Periportal Inflammation

Polymorph nuclear inflammatory infiltration was observed in periportal area on histological examination of liver tissue. Periportal inflammation was found to range from moderate to severe infiltration of polymorph nuclear cells in groups treated with lipofundin (fig-2). The group that was treated with flaxseed oil after lipofundin administration, minimal periportal inflammatory infiltration was observed (fig-4). Chi-Square test was applied after calculation of percentages that showed statistically significant increase in periportal inflammation in lipofundin treated

group B and C whereas inflammatory cells were markedly decreased in group D showing that flaxseed oil played an important role in recovering the inflammatory reaction caused by lipofundin.

Vacuolation in Hepatocytes

Vacuoles present in the cytoplasm of the hepatocytes were observed. Presence or abscence of vacuolated hepatocytes were recorded and percentages calculated. Chi-square test was applied that showed that the difference in hepatocyte vacuolation among difference groups was statistically significant (table-III). Intensive hepatocyte vacuolation was observed in animals of lipofundin treated groups B and C, whereas mild vacuolation was observed in group D (fig-4).

DISCUSSION

Present study was carried out to evaluate the effect of flaxseed oil on the hepatic injury caused by the intravenous injections of lipofundin in adult male albino rats.

Animal weight was found to be decreased in group B. Group C and D showed increase in weight but there is relative less weight gain as compared to group A. Increase in weight of rats was observed in a previous study showing that dietary flaxseed oil causes a significant gain in body weight as compared to control group because of the presence of high lipid content[10]. In another study it was observed that flaxseed oil treated group showed increase in body weight as compared to the control group because of the type of lipid content present in it. Polyunsaturated fatty acids present in the flaxseed diet was found to be responsible for the change in weight of the animal[12].

Histological examination of hepatic tissue was performed to evaluate the effects of flaxseed oil and lipofundin. It was observed that there was a significant change in hepatic lobular pattern among different groups. Lobular pattern was found to be normal in flaxseed oil treated group that served as control. Intravenous infusion of lipofundin caused distortion in lobular pattern. Lipofundin causes oxidative stress in the hepatocytes that leads to distorted lobular pattern and central venous congetion. This distortion was recovered when treated with flaxseed oil after lipofundin treatment in group D (table-I). Flaxseed oil recovered it because of its anti-inflammatory and antioxidant effect. Central vein showed marked congestion after treatment with lipofundin administration. This congestion was significantly increased as compared to that found in flaxseed oil treated control group. Congestion was markedly decreased when the animals were given flaxseed oil after lipofundin treatment. Periportal inflammatory cells were increased in concentration in lipofundin treated group which was found to be recovered after flaxseed oil administration. Which showed that flaxseed oil played an anti-inflammatory effect on the injury caused by the lipofundin. Lipofundin administration was previously studied for its inflammatory effects due to the presence of polyunsaturated fatty acids and arachidonic acid metabolites that increase the production of thromboxanes along with leukotrienes resulting in inflammation[3]. Liver biopsy specimen from individuals suffering from intestinal failure showed periportal inflammatory infiltration due to the lipofundin administration as part of parentral nutrition therapy[18]. This is in agreement with the observations of the present study which showed that soya bean based oil emulsions are responsible for hepatic tissue injury. Flaxseed oil is also rich in omega-3 oils and showed the similar anti-inflammatory effect in the present study. Flaxseed contains essential fatty acids and lignans having anti-inflammatory properties.

Hepatic vacuolation due to fat accumulation was also found in lipofundin treated group which recovered after lipofundin flaxseed oil administration. It showed that flaxseed oil caused a decrease in lipid accumulation in hepatocytes (table-I). Basement membrane was found to be disrupted in lipofundin treated group which recovered after flaxseed oil treatment showing that lipofundin caused hepatic injury that recovered after flaxseed oil administration. In a

previous human based study it was observed that lipofundin administration caused periportal inflammation along with steatosis in the liver biopsy specimen. Liver biopsy of the patients given fish oil instead of soya bean based oil showed no inflammation and steatosis, indicating that oils rich in omega-3 are good for hepatocytes as compared to the soya oils[19]. In the present study we use flaxseed oil which is also rich in omega-3 fatty acids that helped in amelioration.

The present study showed that the flaxseed oil has played an important role in the protection of hepatic tissue affected by the lipofundin. Lipofundin caused damage to the hepatic tissue that was recoverd by the flaxseed oil administration. Flaxseed oil is rich in polyunsaturated fatty acids and phytoestrogenic lignans that are responsible for its anti-inflammatory and anti-oxidant properties. These properties helped a lot in the recovery of hepatic tissue damage caused by lipofundin administration.

CONCLUSION

Flaxseed oil has an ameliorative effect on the hepatic tissue damage caused by the Lipofundin. Hence its use may help prevent hepatic tissue damage caused by lipofundin used in parenteral therapies.

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CONFLICT OF INTEREST

This study has no conflict of interest to declare by any author.

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