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ORIGINAL ARTICLE

Effect of Levo-carnosine co-administration on Cisplatin induced histomorphological changes in the liver of BALB/c mice

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ABSTRACT

Objective: To study Cisplatin-induced histomorphological changes in the liver of mice and to evaluate the effects of Levo-carnosine co-administration on Cisplatin induced hepatotoxicity.

Methods: This laboratory-based experimental study was conducted at Anatomy Department, Army Medical College, Rawalpindi, Pakistan, from November 2020 to April 2022. Ninety BALB/c mice were divided into three groups (n=30 each) and maintained on a standard chow diet. group-I served as the control and received no treatment. group-II was administered intraperitoneal Cisplatin (8 mg/kg body weight) once weekly for four weeks. group-III received the same Cisplatin regimen plus daily oral Levo-carnosine (300 mg/kg body weight) via oral lavage. After four weeks, mice were euthanized, and livers were dissected, processed, and stained with Hematoxylin and Eosin to assess hepatic architecture, lobule perimeter and central vein diameter.

Results: Disrupted lobular architecture was observed in 4 (13.7%) animals in group-I, 25 (83.3%) in group-II, and 14 (46.7%) in group-III ($p<0.001$). Central vein diameter measured 6.89±1.01 μm in group-I, 18.84±2.24 μm in group II, and 9.42±1.22 μm in group-III ($p<0.001$). Post-hoc analysis revealed a significantly increased central vein diameter in group-II compared to the other two groups ($p<0.001$). Hepatic lobule perimeter was 144.86±7.9 μm in group-I, 121.59±6.89 μm in group-II, and 137.01±7.84 μm in group-III ($p<0.001$). Post-hoc analysis showed a significantly decreased hepatic lobule perimeter in group-II compared to the other groups ($p<0.001$).

Conclusion: Cisplatin administration induced histomorphological liver changes in BALB/c mice, while Levo-carnosine co-administration attenuated these effects, preserving hepatic architecture and mitigating pathological alterations, suggesting its hepatoprotective potential.

Keywords: Carnosine (MeSH); Cisplatin (MeSH); DNA Damage (MeSH); Histology (MeSH); Hepatotoxicity (Non-MeSH); Reactive Oxygen Species (MeSH); Oxidative Stress (MeSH).

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INTRODUCTION

Human liver makes up approximately 2% (1500 grams) of the total body weight and mostly occupies the right upper quadrant of the abdomen. Being the major site for metabolism and detoxification, many substances tend to accumulate in liver, especially the lipophilic drugs, making it highly susceptible to the drug induced liver injury.[1] With the advancement of chemotherapy, the quality of cancer patient lives have been improved. But it comes with a cost of bearing the adverse effects of these drugs. Liver being involved in the biotransformation of drugs bears the major grunt.[2] The hepatotoxic effect of anticancer drugs varies from hepatitis to acute liver failure but the mechanism mostly involves formation of a toxic metabolite eliciting an immune response or affecting the cellular factory, either by releasing reactive oxygen species (ROS), depleting antioxidant defense and binding with DNA, structural proteins or vital lipids.[3]

Ever since its discovery in 1960s,[4] Cisplatin is being used for treatment of vast variety of cancers including, breast, lung, colorectal, multiple myeloma, and head and neck cancers.[5] Cisplatin exerts its cytotoxic effect by inducing apoptosis in the cells through formation of DNA adducts.[6] Once within the cell, the drug actively targets DNA and the tumor cell being rapidly dividing and actively synthesizing DNA, are particularly sensitive. Although Cisplatin is one of the most effective anti-cancer drug but its toxic effect on normal cells of the body is one of the major factor impeding its use.[7] Cisplatin tends to accumulate in hepatocytes, making it vulnerable to the effects of drug. Generation of ROS is one of the prime mechanisms of hepatotoxicity reinforced by altered antioxidant defense mechanism, both enzymatic and non-enzymatic.[8] Mitochondrial generation of ROS is the most established fact involving Cisplatin hepatotoxicity as shown by increased mitochondrial lipid peroxidation following Cisplatin treatment.[9]

Levo-carnosine is a naturally occurring dipeptide made up of L-histidine and β-alanine. Levo-carnosine and its related compounds (anserine and ophidine) are found predominantly in the excitable mammalian tissue, like skeletal muscles, cardiac and nervous tissue, though in humans only carnosine is present.[10] The substance either synthesized endogenously in the body or derived from dietary sources including meat, fish and dairy products. Due to its strong capability to scavenge ROS and inactivate reactive aldehydes, Levo-carnosine acts as potent antioxidant within the body. The high water solubility of the substance enables it to provide strong antioxidant defense

system in the cytosolic environment containing high concentrations of oxidation mediators.[11] Levo-carnosine by forming adducts with reactive aldehydes, spare the glutathione which helps in restoring its levels.

Due to its efficacy, cost effect and easy availability, Cisplatin is one of the widely used chemotherapeutic agent which merits conduct of further studies on the drug in order to minimize its adverse effects to normal tissue. Considering above, current study was designed to ascertain the effect of Levo-carnosine co-administration on histomorphological change in the liver tissue of laboratory animals treated with Cisplatin chemotherapeutic regimen. It is anticipated that the results of current study will serve as a valuable resource for the medical practitioners, facilitating evidence-based decision making in order to reduce drug induced hepatotoxicity when selecting the Cisplatin as chemotherapeutic agent.

METHODS

This laboratory based experimental study was conducted at Department of Anatomy, Army Medical College, Rawalpindi Pakistan from Nov 2020 to Apr 2022. Formal permission was obtained from the Ethical Review Committee of the institute (ERC/ID/11 dated February 17, 2020).

The study was conducted on ninety adult BALB/c mice, procured from National Institute of Health (NIH), Islamabad. Inclusion criteria was healthy adult BALB/c mice (both male and female) with weight ranging between 25-30 grams and age range extending between 8-10 weeks. Exclusion criteria was mice suffering from liver disease (confirmed by serum alanine aminotransferase levels at the start of the study by rat tail vein blood sampling) or having visible injury.

Mice were kept in separate cages (7-8 mice / cage) having wooden shaving as bedding where temperature was regulated at (22±3 °C) with daily exposure of 12 hours light and dark cycle. Animal housing and procedures were performed in accordance with the standard regulations of experimental animal care[11] and as approved by the Ethical Review Committee of the institute. Mice were randomly divided into three groups with thirty mice each (n=30). i.e group-I (control), group-II (Cisplatin) and group-III (Levo-carnosine+Cisplatin). During experimental period all mice were allowed to have free access to standard chow feed and water ad libitum. Mice in group-I did not receive any treatment. Mice in group-II received intraperitoneal injection of Cisplatin 8 mg/kg body weight once a week for 4 weeks (day 7, 14, 21 & 28).[12] Whereas mice in group-III received Levo-carnosine 300 mg/kg body weight[13] (dissolved in distilled water) daily by oral lavage for 4 weeks along with intraperitoneal injection of Cisplatin 8 mg/kg body weight once a week for 4 weeks (day 7, 14, 21 & 28).[12]

After completion of experimental period, mice were euthanized by over-dose of diethyl ether anesthesia. Each animal was placed on dissection board at their back and midline incision was made in the abdomen cutting through the skin and muscles. Dissection was performed by skilled veterinarian, National Institute of Health (NIH), Islamabad. The flaps were pinned and abdominal viscera were exposed. Liver was identified on the right side under the diaphragm. Its peritoneal connections were served, inferior vena cava and hepatic veins were divided and liver was dissected out. The organ was washed with normal saline and put in labeled plastic containers having 10% formalin solution enough to submerge the tissue completely.

Samples were kept as such for 24 hours to allow fixation and then processed and sectioned into 5μm thick sections using rotary microtome. The sections were then mounted on glass slides after floating them on warm water bath at 45°C and then stained with Hematoxylin and Eosin (H&E) stain to study histological features (general architecture, hepatic lobule perimeter (size of lobule) and central vein diameter). The hepatic cords were observed to be either regular in structure as hepatocytes radiating from central vein to periphery or disrupted in structure.

Data was analyzed using IBM (International Business Machine) SPSS (Statistical Package for the Social Sciences) version 25. To describe the quantitative variables, descriptive statistics i.e. mean±standard deviation (SD) was used whereas qualitative variables are expressed as frequency and percentage. To compare the difference in quantitative variables, One-way analysis of variance (ANOVA) was applied followed by Post-hoc Tukey's test whereas qualitative data was analyzed by Chi-square test. p-value of ≤0.05 was considered significant.

RESULTS

The mean age of the mice at the beginning of study was 8.6±0.68 weeks, 8.77±0.73 weeks and 8.73±0.79 weeks in group-I, group-II and group-III respectively (p=0.647). Weight of animals was recorded at the start of study and at the time of sacrifice of animals. No statistically significant (p=0.361) difference of weight was observed between the groups at the beginning of study (Table I). The mean weight of animals at the end of study was 30.03±1.13 g, 25.73±0.83 g and 29.2±1.35 g in group-I, group-II and group-III respectively (p<0.001). Post-hoc analysis revealed mean weight at the end of study was significantly low (p<0.001) in group II as compared to the group-I and group-III. The mean weight of group-III was also significantly low (p=0.014) as compared to group-I (Table I).

On histological examination, H&E stained sections of liver tissue were examined under the light microscope. A normal lobular architecture of liver was observed in 26 (86.7%) of mice in group-I. The sections comprised of branching and anastomosing plates of hepatocytes arranged radially around the central vein, with sinusoids in between. Each hepatic lobule was hexagonal in structure with single central vein in the center and six portal areas at the angles. The hepatocytes showed uniformly stained acidophilic cytoplasm with basal round nuclei (Figure 1).

In experimental group-II, disrupted lobular architecture was observed in 25 (83.3%) of the specimen. There was moderate to moderately severe portal

Table I: Comparison of age, weight, central vein diameter and hepatic lobule perimeter in control (group I) and experimental (groups II and III)

Parameters	Group I (Control)	Group II (Cisplatin)	Group III (Carnosine +Cisplatin)	p-value
Age (weeks)	8.6±0.68	8.77±0.73	8.73±0.79	0.647
Weight at the start of study (g)	26.7±0.75	27.0±0.87	26.9±0.85	361
Weight at the end of study (g)	30.03±.13	25.73±0.83	29.2±1.35	< 0.001
Central vein diameter (μm)	6.89±1.01	18.84±2.24	9.42±1.22	< 0.001
Hepatic lobule perimeter (μm)	144.86±7.9	121.59±6.89	137.01±7.84	< 0.001
Post-hoc Tukey test results for intergroup comparisons				
Parameters	**Group I v/s Group II**	**Group II v/s Group III**	**Group I v/s Group III**	
Weight at the end of study	< 0.001	< 0.001	0.014	
Central vein diameter	< 0.001	< 0.001	< 0.001	
Hepatic lobule perimeter	< 0.001	< 0.001	< 0.001	

Values are expressed as mean ±SD; n=30 mice in each group

Table II: Comparison of hepatic architecture among control, Cisplatin-treated, and Cisplatin+Levo-carnosine-treated groups

Parameter	Findings	Group I (Control)	Group II (Cisplatin)	Group III (Carnosine +Cisplatin)	p-value
Liver Architecture	Normal	26 (86.7%)	4 (13.3 %)	11 (36.7 %)	< 0.001
	Dissolute	5 (16.7)	26 (83.3 %)	19 (63.3 %)	
Intergroup comparison of general architecture – p-value (Fisher's exact test)					
Parameter	**Group I v/s Group II**	**Group II v/s Group III**		**Group I v/s Group III**	
Liver Architecture	< 0.001	< 0.001		< 0.001	

p-value significant (≤ 0.05) n=30 mice in each group

inflammation with lymphocytic infiltration into the lobules extending from zone 3 (centrilobular) to zone 1 (periportal). The hepatocytes were irregular in shape with damaged radial arrangement. There were necrotic hepatocytes, with darkly stained small pyknotic irregular nuclei with cytoplasmic vacuolations. Whereas in experimental group-III, disrupted architecture was observed in 14 (46.7%) of specimen (Figure 1). However, the portal inflammation and necrosis of hepatocytes were less severe in group-III as compared to the group-II. Statistical analysis yielded significant (p<0.001) difference of result between the groups (Table II).

The mean central vein diameter (Figure 2) in group-I was 6.89±1.01 μm, in group-II 18.84±2.24 μm whereas in group-III it was 9.42±1.22 μm (p<0.001). Intergroup comparison by Post-hoc Tukey's test showed the mean central vein diameter in group-II was significantly increased (p<0.001) as compared to group-I and group-III. The mean central vein diameter in group-III was also significantly higher (p<0.001) than the group-I (Table I). The mean hepatic lobule perimeter was 144.86±7.9 μm, 121.59±6.89 μm and 137.01±7.84 μm in group-I, group-II and group-III respectively (p<0.001). Post-hoc intergroup comparison revealed the mean hepatic lobule perimeter in group-II was significantly decreased (p< 0.001) as compared to group-I and group-III. The mean size of hepatic lobule in group-III was also significantly lower (p<0.001) than the group-I (Table I).

DISCUSSION

In the current study we have observed significant histomorphological changes in the liver of mice following Cisplatin administration. These changes were mitigated by Levo-carnosine co-administration along with Cisplatin. According to global cancer observatory GLOBOCAN estimation, a total 117,286 people died of cancer in 2018 in Pakistan alone.[14] Cisplatin is one of the most widely used anti-cancer drug with a good response rate, when used alone or as neo-adjuvant therapy with other anticancer drugs. However, the factor hindering its clinical use is its adverse effects on normal tissues.[15]

In current study, significant weight gain was observed in group I and it was physiological gain according to the duration of study. Whereas, there was weight loss observed in group II animals which received Cisplatin treatment. A previous study conducted in Tunisia by Sioud F et al., evaluated the effect of Methanolic extract of Ephedra alata on Cisplatin-induced nephrotoxicity and hepatotoxicity. They administered Cisplatin as a single dose of 20mg/kg body weight. The study reported 10.9% decrease in body weight of animal who received only Cisplatin which is comparable to the results of this study.[16] In group III of the current study the weight change in animals was represented as weight gain but it was significantly less as compared to the control group. Levo-carnosine co-administration significantly increased the weight of animals by neutralizing deleterious effect of Cisplatin on body tissues.

Histomorphological study of liver in Cisplatin group of our study showed

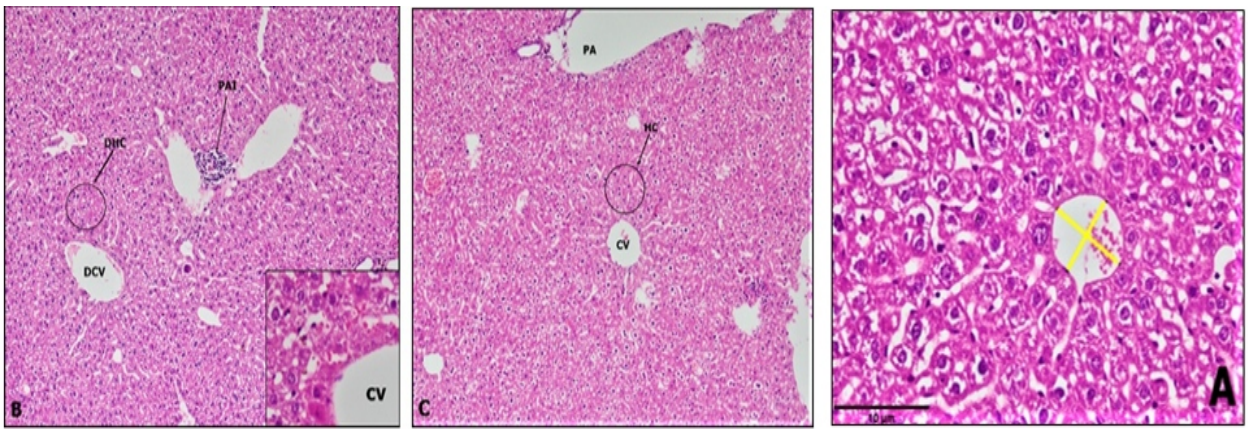

Figure 1: Photomicrographs (10X) showing comparison of general architecture in liver section of treatment groups. **A:** group I showing hepatocytes (H) arranged in radiating cords around the central vein (CV) with sinusoids (S) present between them. Also, a portal area can be seen having portal vein (PV), hepatic artery (HA) and bile duct (BD). Inset show hepatocytes 40X. **B:** group II showing disturbed hepatic cords (DHC) around a dilated central vein (DCV). Portal area inflammation (PAI) is also visible. Inset show hepatocytes with necrotic changes in cytoplasm and nucleus 40X. **C:** group III showing hepatic cord (HC) arrangement, central vein (CV) and portal area (PA) being restored.

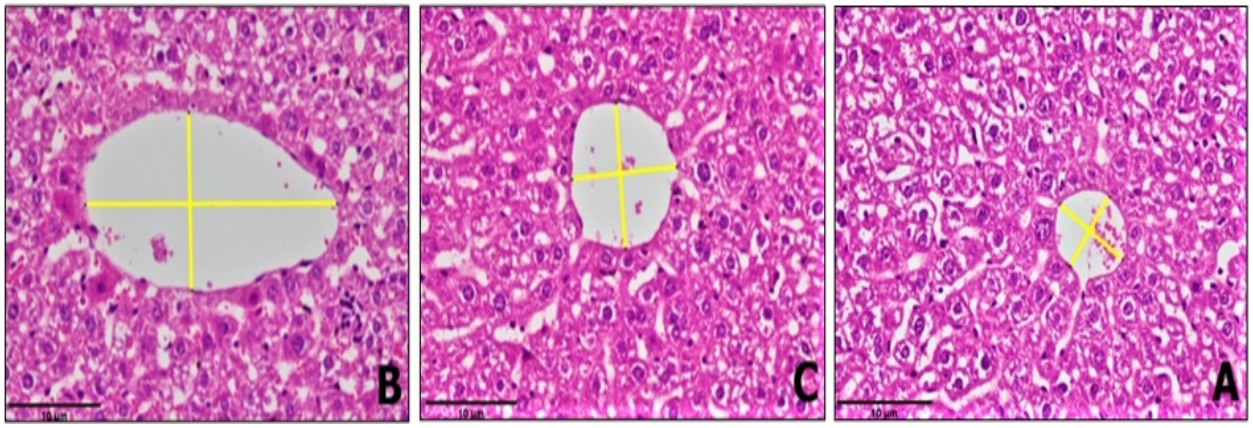

Figure 2: Photomicrograph (40X) showing comparison of central vein diameter in liver sections of treatment groups (I, II & III). **A:** group I showing normal diameter (yellow lines). **B:** group II showing increased diameter (yellow lines). **C:** group III showing restored diameter (yellow lines).

disruption of normal architecture, with irregularly shaped hepatocytes and deranged radial arrangement. There were necrotic hepatocytes, with darkly stained small pyknotic irregular nuclei and cytoplasmic vacuolation. Cisplatin induced disrupted architecture of the liver comparable to our study is also reported in Egypt by Abdel-Daim MM et al., to evaluate the role of garlic oil on Cisplatin-induced histopathological alterations in rats.[17] Cisplatin causes disruption of architecture by inducing apoptosis in hepatocytes with activation of caspase-3, the initiator of apoptotic cascade and reducing BCL-2, an anti-apoptotic protein.[18] In our carnosine treated group these histological changes were alleviated due to its properties to prevent apoptosis in hepatocytes as shown in a previous study conducted in Iran by Ghanbarinejad V et al.[19]

There was increase in the diameter of central vein in our Cisplatin treated group as compared to the other two groups. Our results are comparable to the finding of study conducted in Yemen by Almansory AH et al., who assessed the effects of Cisplatin on rat liver.[20] The increased central vein diameter is also reported in a study conducted in Egypt in which authors were experimenting to reduce the Cisplatin mediated side effects by loading it on chitosan nanoparticles.[21] This histological change was a by-product of inflammatory response induced by Cisplatin. Carnosine mitigates the proinflammatory effects of Cisplatin by reducing the TNF-α along with other inflammatory biomarkers like IL-6, C-reactive protein, and immunoglobulin G.[22] This anti-inflammatory effect of carnosine might be involved in reversal of central vein dilatation as seen in our carnosine treated group.

In current study, Cisplatin group showed significant reduction in hepatic lobule perimeter (size of lobule) that is attributed to the development of fibrotic changes in liver parenchyma. Cisplatin activates the Toll-like receptor-4 (TRL4) fibrogenic signaling pathway. TRL4 has both proinflammatory and profibrotic properties. The later change occurs due to participation in activation signals for hepatic stellate cell (HSCs).[23] The liver

injury induced by Cisplatin leads to increased production of ROS which results in an inflammatory response that leads to the activation of HSCs into fibrogenic myofibroblasts. Whereas carnosine tends to protect liver from fibrosis and hence restoring the size of hepatic lobules as shown in our carnosine treated group. Role of carnosine in preventing the hepatic fibrosis has been supported by a previous study conducted in Australia by Menon K et al.[24] Carnosine also plays a role in reduced deposition of collagen by preventing HSC activation.

In current study, we demonstrated that the Cisplatin at chemotherapeutic dose causes damage to the normal architecture of liver by shifting the redox state of the body towards oxidative stress. Levo-carnosine co-administration along with Cisplatin has notably provided ameliorative effect on liver histomorphologic changes plausibly by decreased production of ROS. Our findings imply that Levo-carnosine may be used as an adjuvant medication to treat cancer, providing protection against hepatotoxicity induced by Cisplatin. The current study had limitations as we could not measure the exact type and concentration of raised reactive oxygen species causing the oxidative stress.

CONCLUSION

This study demonstrates that Cisplatin administration induces significant histomorphological changes in the liver, including disrupted lobular architecture, increased central vein diameter, and reduced hepatic lobule perimeter. Co-administration of Levo-carnosine with Cisplatin markedly attenuated these hepatotoxic effects, as evidenced by improved hepatic architecture and reduced pathological alterations in group-III (Cisplatin) compared to group-II (Levo-carnosine+Cisplatin). These findings suggest that Levo-carnosine has a protective role against Cisplatin-induced hepatotoxicity in mice. Further research is warranted to explore the mechanisms underlying this protective effect and to evaluate the potential clinical applications of Levo-carnosine in mitigating drug-induced liver injury.

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AUTHORS' CONTRIBUTION

Following authors have made substantial contributions to the manuscript as under:

SB: Study design, acquisition, analysis and interpretation of data, drafting the manuscript, approval of the final version to be published

KQ: Conception and study design, analysis and interpretation of data, critical review, approval of the final version to be published

RK & AF: Acquisition of data, drafting the manuscript, approval of the final version to be published

MA & TF: Analysis and interpretation of data, critical review, approval of the final version to be published

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

CONFLICT OF INTEREST

Authors declared no conflict of interest, whether financial or otherwise, that could influence the integrity, objectivity, or validity of their research work.

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DATA SHARING STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request