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Cardioprotective effect of liraglutide alone and in combination with L-arginine against cyclophosphamide-induced cardiotoxicity

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Abstract

Background and objective: Many chemotherapeutic drugs may induce cardiotoxicity which limits their clinical use. Cyclophosphamide is an anticancer drug that is associated with dose dependent cardiotoxicity. Cardioprotective agents are being investigated as a means to prevent or treat cardiotoxicity. The aim of this study is to investigate the possible protective effects of liraglutide, alone and in combination with L-arginine, against cyclophosphamide induced cardiotoxicity in rats.

Methods: This study was conducted on 28 male Wistar albino rats, which were distributed into four groups, with each consisting of seven rats. Group C functioned as negative control while group CP acted as positive control. Group L received liraglutide and LA group was given liraglutide and L-arginine. After 21 days of treatment, the rats from group CP, L, and LA were injected with cyclophosphamide to induce cardiotoxicity. Blood samples were collected for measurement of hs-Troponin T (hs-TnT), heart-fatty acid binding protein (H-FABP), superoxide dismutase (SOD), and neutrophil gelatinase associated lipocalin (NGAL) while the hearts were taken for histopathological examination.

Results: Cyclophosphamide administration significantly increased myocardial injury markers (hs-troponin T and H-FABP), and inflammatory/renal injury marker (NGAL) while it significantly reduced antioxidant enzyme (SOD) in the serum with histopathological analysis showing signs of cardiotoxicity. Liraglutide alone and in combination with L-arginine improved the biochemical parameters and histopathological structure of the heart compared to cyclophosphamide group.

Conclusion: The findings from this prospective study suggest that liraglutide pretreatment, alone and in combination with L-arginine, provided cardioprotection against cyclophosphamide-induced cardiotoxicity.

Keywords: Cyclophosphamide; Liraglutide; L-arginine; Cardiovascular diseases; Cardioprotective agents.

Introduction

Cardiotoxicity is toxicity that occurs in the heart as a consequence of direct or indirect exposure to drugs or other chemicals.[1] Chemotherapy-induced cardiotoxicity is a well-characterized subtype of drug-induced cardiotoxicity. It represents a critical challenge in oncology, as chemotherapeutic agents that target rapidly dividing cancer cells often cause unintended damage to cardiac cells.[2]

Cyclophosphamide is an alkylating compound that has been available since 1959 and is regarded as one of the most essential medications in cancer treatment.[3] However, cyclophosphamide is associated with dose dependent-cardiotoxicity, which is mainly induced via its toxic metabolite causing oxidative stress, eventually resulting in death to cardiomyocytes. It greatly limits its clinical use with an incidence rate of cardiotoxicity being 8-20% in the elderly and 5% in pediatric populations.[4,5]

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Due to this on-growing concern, the need for cardiac care has become a part of cancer treatment and cardioprotective therapies have been examined over the past twenty years with several studies evaluating the role of cardio protectants in treating and preventing harmful cardiac effects from antineoplastic drugs.[6,7]

Liraglutide, a glucagon like peptide-1 (GLP-1) receptor agonist recognized for its beneficial properties, including antioxidant and anti-inflammatory actions, has shown promise in protecting cardiac tissues from damage.[8] While the cardioprotective effects of liraglutide have been widely investigated in various pathological and experimental settings, its potential protective effect in chemotherapy-induced cardiotoxicity remains limited, with no studies investigating its effect in cyclophosphamide-induced cardiotoxicity. Similarly, L-arginine supplementation has demonstrated cardioprotective effect by enhancing nitric oxide bioavailability and reducing oxidative stress in the vascular endothelium.[9] However, no study has evaluated the combination of liraglutide with L-arginine against cyclophosphamide-induced cardiotoxicity. Therefore, this study aims to investigate the cardioprotective effects of liraglutide, both alone and in combination with L-arginine, against cyclophosphamide-induced cardiotoxicity.

Methods

Animals

A total of 28 healthy male Wistar Albino rats (250-300g, 5-6 months old) were obtained and housed at the animal facility of Hawler Medical University, College of Pharmacy (Erbil, Iraq). The rats were put in their own cages at 18-25°C, at an air-conditioned room that met standard humidity conditions (50-60%), with a regulated cycle of 12 hours of light followed by 12 hours of darkness. Unlimited access to water and rodent pellet diets were provided. This study has been approved by ethics committee at Hawler Medical University/ Collage of Pharmacy with approval number of HMU-EC-PH 29202024-45. The research was carried out by following the ethical guidelines of the animal house and all necessary measures were taken to minimize the discomfort and suffering of the rats.

Materials

Heart fatty acid binding protein (H-FABP) and neutrophil gelatinase associated lipocalin (NGAL) ELISA rat kits were purchased from BT-Lab (Shanghai, China). Superoxide dismutase (SOD) ELISA rat kit was obtained from SUNLONGBIOTECH (Shanghai, China). For highly sensitive troponin T kits (hs-cTnT), Roche Diagnostics kits (Mannheim, Germany) were used. Liraglutide (6mg/mL) and L-arginine (700mg capsule) were obtained from a local pharmacy in Erbil city/Iraq and were manufactured by Novo Nordisk (Bagsværd, Denmark) and Pure Encapsulation (Istanbul, Turkey), respectively. Cyclophosphamide (500mg) was manufactured by Baxter (Istanbul, Turkey).

Experimental design

In this study, 28 male Wistar albino rats were randomly assigned into four groups, with seven rats in each group (n=7). Group C was designated as negative control group. The positive control was represented as group CP. Both group C and CP received sterile water for 21 days. Group L was given liraglutide (300µg/kg)[10] via subcutaneous injection for 21 days. Group LA received liraglutide (300µg/kg)[10] subcutaneously and L-arginine (200mg/kg)[11] orally through gavage for 21 days. On 22nd day of experiment, the rats of group CP, L, and LA were injected intraperitonially with (150mg/kg) of cyclophosphamide to induce cardiotoxicity.[12] On 23rd day of the study, the rats were put under anesthesia (10mg/kg xylazine and 125mg/kg ketamine administered intraperitoneally).[13] Blood was obtained through cardiac puncture and centrifuged to isolate the serum for biochemical analysis. At the end of the experiment, the hearts were excised from

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the sacrificed rats of all four groups for histopathological analysis and subsequently immersed and fixed in 10% formalin.

Biochemical assay

Serum heart-fatty acid binding protein (H-FABP), superoxide dismutase (SOD), interleukin-6 (IL-6), and neutrophil gelatinase associated lipocalin (NGAL) were evaluated using rat specific ELISA kits while serum highly sensitive Troponin T (hs-TnT) was measured using Cobas-Roche analyzer.

Histopathological study

Hearts from all four groups were excised and fixed in formalin for histopathological evaluation. The biopsy samples were embedded in wax, stained with hematoxylin and eosin (H&E), and subsequently, placed under microscope for examination. Photomicrographs of the slides were subsequently captured.

Statistical analysis

Data analysis was carried out through statistical package for the social sciences (SPSS, version 23.0), with results presented as mean ± standard error of mean (SEM). The significance of differences among all groups was determined using one-way analysis of variance (ANOVA). Group comparisons were performed using Tukey's post hoc test, and differences were regarded as statistically significant if the *P*-value was below 0.05.

Results

As presented in (Table 1), rats treated with cyclophosphamide showed a significant increase in hs-TnT level in comparison to the control group (from 0.148±0.0273 ng/L to 3.458±0.5984 ng/L) (*P* <0.001). Liraglutide pre-administration significantly lowered hs-TnT levels compared to the cardiotoxic group (from 3.458±0.5984 ng/L to 2.155±0.1289 ng/L) (*P* = 0.033). The combination therapy of liraglutide and L-arginine also led to a significant decrease in hs-TnT when compared to the disease group (from 3.458±0.5984 ng/L to 0.925±0.0469 ng/L) (*P* <0.001).

H-FABP levels were significantly elevated in the cardiotoxic cyclophosphamide group in relation to the control group (from 26.57±0.885 ng/mL to 40.55±1.558 ng/mL) (*P* <0.001). However, pretreatment with liraglutide led to a significant decline in H-FABP levels relative to the disease group (from 40.55±1.558 ng/mL to 35.65±1.046 ng/mL) (*P* = 0.012).

Additionally, the combination of liraglutide and L-arginine led to a more pronounced reduction in H-FABP levels (from 40.55±1.558 ng/mL to 33.53±0.656 ng/mL) (*P* <0.001).

Intraperitoneal injection of cyclophosphamide resulted in significant suppression of the antioxidant enzyme SOD in contrast to untreated group (from 396.323±16.608 pg/mL to 176.162±10.878 pg/mL) (*P* <0.001). While liraglutide pretherapy group was accompanied with significant rise in serum SOD levels compared to cardiotoxic group (from 176.162±10.878 pg/mL to 226.688±9.109 pg/mL) (*P* = 0.03). Pretreatment with liraglutide and L-arginine in combination also resulted in significant elevation in SOD activity compared to disease group (from 176.162±10.878 pg/mL to 301.115±8.665 pg/mL) (*P* <0.001).

NGAL levels were significantly elevated in cyclophosphamide-treated rats compared to negative control (from 8.791±0.232 ng/mL to 12.793±0.587 ng/mL) (*P* <0.001). Pre-treatment with liraglutide led to a reduction in NGAL levels compared to disease group (from 12.793±0.587 ng/mL to 11.155±0.4077 ng/mL)(*P* = 0.022). The combination of liraglutide and L-arginine resulted in a significant reduction in NGAL levels compared to untreated group (from 12.793±0.587 ng/mL to 10.695±0.1665 ng/mL) (*P* = 0.003).

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Table 1 Effects of liraglutide (300µg/kg) alone and liraglutide (300µg/kg) with L-arginine (200mg/kg) combination on myocardial injury, antioxidant, inflammatory, and renal biomarkers. Group C serves as negative control, groups represents the cardiotoxic disease group, group L is liraglutide pretreatment group, and group LA is the liraglutide and L-arginine pretreatment group

Serum biomarkers	Experimental Groups				*P*-Value
	Group C	Group CP	Group L	Group LA	(ANOVA)
Hs-TnT (ng/L)	0.148^{a} ±0.0273	3.458^{c} ±0.5984	2.155^{b} ±0.1289	0.925^{a} ±0.0469	<0.001
H-FABP (ng/mL)	26.57^{a} ±0.885	40.55^{c} ±1.558	35.65^{b} ±1.046	33.53^{b} ±0.656	<0.001
SOD (pg/mL)	396.323^{d} ±16.608	176.162^{a} ±10.878	226.688^{b} ±9.109	301.115^{c} ±8.665	<0.001
NGAL (ng/mL)	8.791^{a} ±0.232	12.793^{c} ±0.587	11.155^{b} ±0.4077	10.695^{b} ±0.1665	<0.001

Values are expressed as mean ±SEM.
Within each row, means detonated with different superscript letters (a, b, c, d) indicate statistically significant difference between groups. Same letters indicate no statistically significant difference.

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After three weeks of treatment followed by induction of cardiotoxicity, hearts from all four groups were excised for histopathological analysis. The control group (C) showed normal arrangement of myocytes. The cyclophosphamide-induced cardiotoxic control group (CP) showed signs of cardiotoxicity with scattered necrotic myocardial cells, degeneration, scattered inflammatory cells, vascular congestion, and edema. The cardiotoxic group treated with liraglutide (L) showed mild edema, vascular congestions, and fewer focal necrosis and fewer scattered inflammatory cell infiltration, and cardiotoxic group treated with liraglutide and L-arginine combination (LA) showed mild edema and fewer scattered inflammatory and necrotic cells (Figure 1).

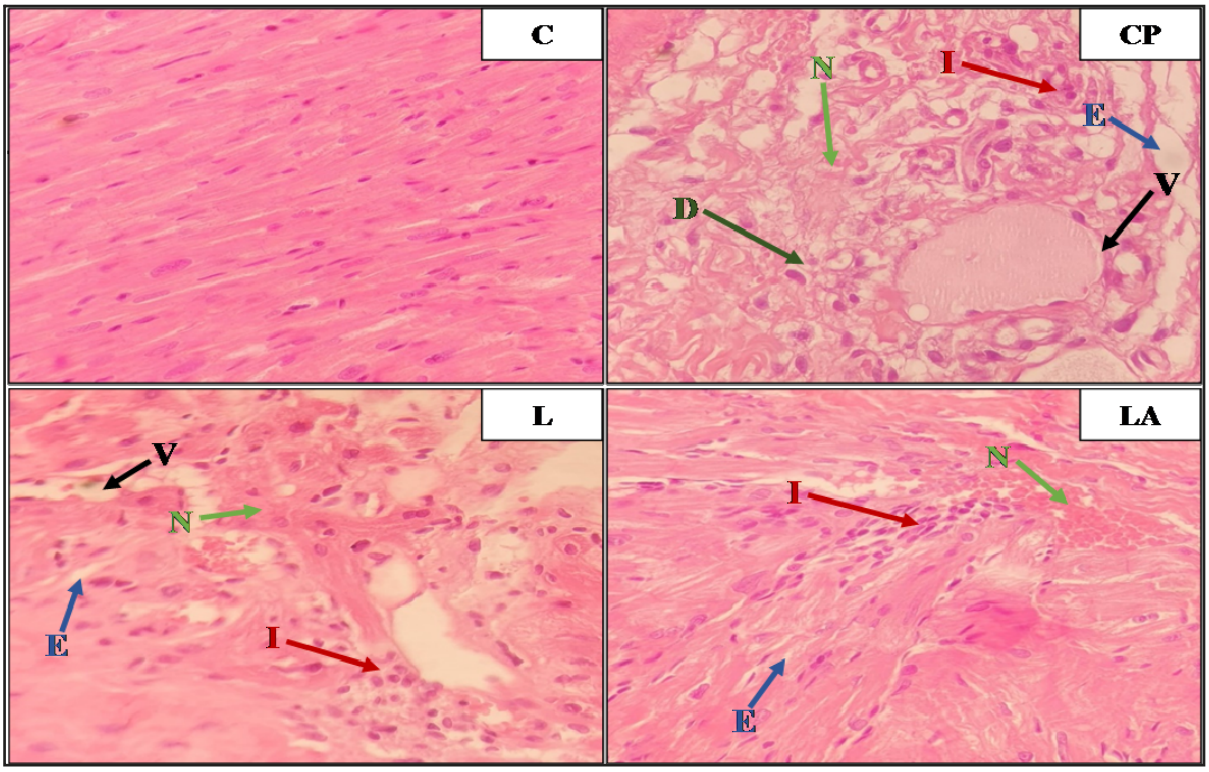

Figure 1 Images of H&E stained sections of heart tissue. The negative control (C), the cyclophosphamide-induced cardiotoxic group (CP), the cardiotoxic group treated with liraglutide (L), and cardiotoxic group treated with liraglutide and L-arginine combination (LA). (I: inflammatory cells, N: necrosis, E; edema; D: degeneration, B; V: vascular congestion) (H&E X400)

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Discussion

Cyclophosphamide is an antineoplastic drug used for management of cancer and autoimmune diseases. However, its cardiotoxic effect greatly limits its clinical use. Cyclophosphamide damages the myocardium mainly through its toxic metabolite called acrolein which causes oxidative stress, mitochondrial damage, endothelial dysfunction, myocardial inflammation, and ultimately death of the heart muscle cells. It can manifestas arrhythmias, hypertension, myocardial infarction, or even heart failure.[4,5,14] Because of this, preventive and early interventional strategies are required in order to improve the clinical application of this drug.

This study evaluated the cardioprotective efficacy of liraglutide, both alone and in combination with L-arginine, against cyclophosphamide-induced cardiomyopathy. To the best of current knowledge, this is the first study to explore this effect in this context. The results indicate that both liraglutide and its conjugation with L-arginine significantly mitigated cyclophosphamide's harmful impact on the heart, as evidenced by improvements in biochemical markers related to myocardial injury, oxidative stress, inflammation and renal function.

In the present study, there was increased levels of myocardial injury markers (hs-TnT and H-FABP) in the cyclophosphamide-treated group, which indicate significant myocardial tissue damage, primarily driven by mechanisms such as oxidative stress and free radical generation.[14] In clinical environments, both H-FABP and hsTnT have been assessed as biomarkers for myocardial injury and adverse cardiovascular events.[15]

The results from this study demonstrate that pretreatment with liraglutide alone and in combination with L-arginine significantly diminished the levels of hs-TnT and H-FABP, indicating its capacity to maintain myocardial integrity. This corresponds with prior research demonstrating the cardioprotective effects of liraglutide in diminishing myocardial injury indicators across diverse cardiotoxicity models.[16,17] The cardioprotective properties of liraglutide and its combination with L-arginine can be ascribed to their diverse mechanisms of action. Liraglutide likely exerts its advantageous effects in the heart through its antioxidant, anti-inflammatory, and anti-apoptotic actions through GLP-1 receptor.[18,19] L-arginine, on the other hand, increases nitric oxide synthesis, which enhances endothelial function, diminishes oxidative stress, and mitigates inflammation,[20] thereby safeguarding against myocardial damage.

Oxidative stress is a key contributor to cyclophosphamide-induced cardiotoxicity,[14] as evidenced by the significant decrease in SOD levels in the cyclophosphamide-treated group. Antioxidant enzymes such as SOD are the main defense system against oxidative stress.[21] In this study, liraglutide alone effectively enhanced SOD levels, highlighting its antioxidant improving potential. The combination of liraglutide and L-arginine also caused a further rise in SOD concentration, likely because both agents act on nrf2 pathway and increase transcription of SOD.[22,23] This aligns with findings from previous studies that showed liraglutide can mitigate cardiotoxicity by increasing SOD activity,[17,19] with previous research reporting that combinational therapy of L-arginine with other cardioprotective agents may causefurther enhancement in SOD concentration.[24]

The heart and kidneys exhibit a bidirectional relationship, indicating that both organs share physiological and pathological conditions.[25] The detrimental impact of cyclophosphamide on renal function is an additional factor that may lead to compromised cardiac health. NGAL is a biomarker indicative of acute renal injury and inflammation.[26]

The increase in NGAL levels in the cyclophosphamide-treated group indicates that cyclophosphamide-induced toxicity

extends beyond the heart to impact renal function as well. This is consistent with prior studies indicating that cyclophosphamide administration is linked to elevation in renal injury biomarkers.[27] The main mechanism of the renal damage caused by cyclophosphamide is oxidative stress induced by its toxic metabolites. Oxidative stress happens when there is overproduction of free radicals that disrupts the normal oxidant/antioxidant equilibrium, resulting in kidney damage.[28] Pretherapy with liraglutide alone and in combination with L-arginine markedly decreased serum NGAL, suggesting its potential to safeguard against cardio-renal injury. This finding corroborates with earlier research that reported liraglutide, alone and in combination with other protective agents, is able to reduce NGAL levels in rats via mechanisms that include GSK-3β and NR-F2/HO-1 inhibition, which results in reduction of inflammation, oxidative stress apoptosis, and overall kidney damage.[29] With regard to histopathological analysis, both treatment groups that received treatment showed less structural changes such as necrosis, inflammatory infiltrate, vascular congestion, and edema compared to cyclophosphamide group, which further support the cardioprotective effect of the studied agents.

Conclusion

Pretreatment with liraglutide, alone and in combination with L-arginine, reduced markers of myocardial injury such as hs-TnT and H-FABP, inflammatory and renal injury marker NGAL, and increased antioxidant enzyme SOD. Additionally, both pretreatments also improved structural changes in the heart. This suggests that pre-therapy with these agents provide cardioprotection against cyclophosphamide -induced cardiotoxicity.

Competing interests

The authors declare that they have no competing interests.

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