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Original Article

Cardioprotective Effects of Octreotide against Sepsis-Induced Cardiotoxicity in Mice

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Abstract

Sepsis is a systemic inflammatory consequence resulting from microbial infection, assessed as a worldwide healthcare issue. Sepsis can result in multiorgan dysfunction, including cardiac, renal, hepatic, and cerebral dysfunction. Cardiotoxicity can occur in humans and rodents during sepsis, leading to increased mortality. The current study aims to explore the possible cardioprotective effects of octreotide during sepsis-induced cardiotoxicity. This study was done with a total of forty male albino Swiss mice, aged 8-12 weeks and weighing 25-30 gm. These animals had free access to food and water. After two weeks of adaptation, mice were divided into four groups (n=10): 1) Normal group: healthy mice; 2) CLP group: mice underwent CLP operation; 3) Vehicle group: mice received DMSO. 4) Octreotide group: mice received octreotide (10 mg/kg) subcutaneously in 2 divided doses for 5 consecutive days. All groups underwent CLP operation on the 4th day, then sacrificed on the 5th day then blood, and tissue sampling was done. The Octreotide group demonstrated a significant (P<0.05) decrease in the myocardial levels of cardiac troponin-I as compared to the CLP group. Furthermore, the octreotide group demonstrated a significant (P<0.05) decrease in the serum level of inflammatory cytokines (TNF-α, IL-6, & IL-1β) as compared to the CLP group. Additionally, the octreotide group showed a significant (P<0.05) elevation in the myocardial activity of SOD and a reduction in MDA level compared to the CLP group. Histologically, all mice in the CLP group showed a significant (P<0.05) cardiac tissue injury, while the octreotide groups showed a significant (P<0.05) reduced level of cardiac tissue injury. The results of the present study revealed that octreotide attenuates sepsis-induced cardiotoxicity through different protective effects; they include the anti-inflammatory effect through their ability to decrease serum levels of inflammatory cytokines (TNF-α, IL-1β, and IL-6). Also, the anti-oxidant effect through their ability to decrease myocardial levels of MDA and increase the myocardial activity of SOD. Additionally, the direct cardiac protective effect through the lower level of cardiac troponin- I and the reduction of histopathological changes during sepsis-induced cardiotoxicity.

Keywords: CLP, Polymicrobial sepsis, Cardiotoxicity, Cardiac troponin, Oxidative stress

1. Introduction

Sepsis can be defined as a systemic inflammatory consequence resulting from bacterial infection (1, 2). Sepsis is assessed as a worldwide healthcare issue, and the main reason for death follows an infection. Therefore, early recognition and diagnosis of sepsis can lead to the prevention of septic shock, which has a high mortality rate of about 40% and even more (3). As a systemic immune response, sepsis can result in multiorgan dysfunction, including cardiac, renal, hepatic, and cerebral dysfunction (2, 4, 5). Cardiac dysfunction, as an important organ attack, can occur in both humans and rodents during sepsis (6, 7). The pathophysiology of cardiomyopathy during sepsis

includes complicated systemic factors and molecular, metabolic, and even structural changes in the myocardial cells (8). Cardiac dysfunction is a common consequence of sepsis with increased mortality and has been linked to elevated inflammation, suppression of both glucose oxidation and fatty acid, ATP depletion, and compromising of cardiac adrenergic that aggravates heart functions furtherly (1). Following bacterial infection, the body's inflammatory reaction can progress to severe sepsis and even septic shock, characterized by ischemia, hypotension, multiorgan failure, and death (2). As a severe health consequence, sepsis can potentially raise patient death and healthcare costs (2, 5).

Because of its complexity, there is no full explanation or assumption that can give the exact mechanisms of sepsis-induced cardiotoxicity. Furthermore, pro-inflammatory cytokines have a crucial role in myocardium depression; other mechanisms that may explain sepsis-induced- cardiotoxicity may include oxidative stress pathway, calcium transport deterioration, energetic dysregulation, autonomic dysregulation, and apoptosis pathway (9, 10). Additionally, hypotension, hypovolemia, acidosis, and hypoxia may contribute to the pathophysiology of sepsis-induced- cardiotoxicity (10). On the other hand, cardiac troponin release into circulation during sepsis is due to the increased membrane permeability of cardiomyocytes (11). A more obvious explanation regarding the pathophysiology of sepsis-induced cardiotoxicity is an interaction between different mechanisms, such as inflammation, oxidative stress, metabolism, and neuroimmunomodulation pathways (9).

Octreotide, as a synthetic analogue of somatostatin, was discovered by Roger Guillemin and Andrew Schally in 1973 when they got the noble prize as they provided a new discipline for the investigation of clinical conditions associated with endocrine disorders such as Gastroenteropancreatic neuroendocrine tumours (GEP-NETs) and acromegaly (12-14).

Octreotide is an inhibitory hormone found in the central nervous system and peripheral tissues. It has an essential regulatory function in the neurotransmission and secretion of many other hormones. For instance, octreotide inhibits the release of growth hormone, thyroid-stimulating hormone, gastrointestinal hormones, pancreatic enzymes, and other neuropeptides. Additionally, gastric emptying rate, contraction of GIT smooth muscles, and intestinal blood flow are highly modulated by somatostatin (13, 14). As far as we know, there is little information on the involvement of octreotide in attenuating cardiotoxicity. Therefore, this study aimed to explore the possible protective effects of octreotide during sepsis-induced cardiotoxicity.

2. Materials and Methods

2.1. Drugs and Chemical

Celostatin®50 (octreotide 50 µg/ml) injection was obtained from Celon Lab, Telangana, India. Celostatin was given subcutaneously in a 10 mg/kg/day dose in 2 divided doses (15).

2.2. Animals of Study

The current study was done with a total of forty male albino Swiss mice, aged 8-12 weeks and weighing 25-30 gm. These animals were housed in the animal house within their cages under 12:12 light: dark cycles with 25 ℃ room temperature, 60-65% humidity, and free access to food and water.

2.3. Study Design

The forty mice were left two weeks for adaptation, and then after, mice were divided into the following four groups (n=10):

1. Normal group: Healthy mice.
2. CLP group: Mice in this group underwent CLP operation.
3. DMSO group: Mice in this group received an equivalent volume of DMSO
4. Octreotide group: Mice in this group received Oct 10 mg/kg SC in 2 divided doses for 5 consecutive days, then CLP operated on the 4th day (15).

2.4. The Experimental Model of Induced Sepsis (CLP)

In the present study, mice were selected to induce sepsis. Based on previous studies, the induction of sepsis was done via the needle using the cecal ligation and puncture model (CLP) (2, 16). An 18-G needle was used in the double puncture procedure to induce organ (cardiac) dysfunction during the early phase of polymicrobial sepsis (first 24 hours). Anaesthesia was done with 1.5 ml/kg of a xylazine (20 mg/ml)/ketamine (100 mg/ml) solution in a 1:2 ratio (17). The cecum was exposed when the abdomen was opened with a 1.5 cm midline incision. The cecum was then ligated, punctured immediately below the ileocecal valve, and returned to its anatomical location. A small amount of stool was extracted to ensure the patency of the puncture sites. Then after that, the abdomen was sutured. All animals received a subcutaneous resuscitative dose of normal saline (20 mL/kg body weight).

2.5. Sample Collection

On day five, animals were sacrificed with anaesthesia, and then both blood and tissue samples were obtained as follows:

2.6. Blood Samples

After the scarification process, blood was withdrawn using the direct cardiac puncture technique. For serum collection, withdrawn blood was left aside in a gel tube for about 20 minutes until the clotting process had occurred, then after, centrifuged at 10000 rpm for about 10 minutes, then the supernatant was preserved at -20 °C until further analysis was done.

2.7. Myocardial Tissue Samples

After blood sample collection, a thoracic operation was done to obtain myocardial tissue. The heart was cut into two parts; one was kept at -20 °C until tissue homogenate analysis was done, while the other was fixed with formalin until histopathological analysis.

2.8. Myocardial Tissue Homogenization

Tissue homogenization was done according to the previous study (18). Briefly, a razor blade was used to cut tissue pieces, and then 0.1 gm was weighed from each sample, meanwhile placed the sample was on the ice to keep it from getting warm, followed by chopping the tissue using a single-edge razor; all these procedures were done on ice. After that, 3 ml of phosphate buffer (pH=7.2) was added, then ice homogenization by grinding using a pestle until no more chunks were noticeable. The resulting sample was transferred into the Eppendorf tube and centrifuged at 10000 rpm for 10 minutes then the supernatant was collected carefully.

2.9. Outcome Measurement

2.9.1. Inflammatory Markers (TNF-α, IL-1 β, and IL-6)

According to the manufacturer's instructions, the serum level of TNF-α, IL-1 β, and IL-6 was measured using an Enzyme-Linked Immunosorbent Assay (ELISA). The plate of ELISA kits had been pre-coated with Mouse TNF-α, IL-1 β, and IL-6 antibodies, respectively. TNF-α, IL-1 β, and IL-6 presented in the samples were added and bound to antibodies coated on the wells. And then, biotinylated Mouse TNF-α, IL-1 β, and IL-6 antibodies were added and bound to TNF-α, IL-1 β, and IL-6 in the samples. Then Streptavidin-HRP was added and bound to the Biotinylated TNF-α, IL-1 β, and IL-6 antibodies. During a washing step after incubation, unbound Streptavidin-HRP has washed away. After that, the substrate solution was added, and the colour developed in accordance with the amount of Mouse TNF-α, IL-1 β, and IL-6. The reaction was terminated by adding an acidic stop solution, and absorbance was measured at 450 nm.

2.9.2. Cardiac Troponin I (cTn-I)

The myocardial level of cardiac troponin I (cTn-I) was measured using an Enzyme-Linked Immunosorbent Assay (ELISA) based on the manufacturer's instructions. The plate of the ELISA kit had been pre-coated with Mouse cTn-I antibody. The cTn-I in the sample was added, and the wells were coated with antibodies linked to cTn-I. The sample was

then incubated with biotinylated Mouse cTn-I Antibody bound to cTn-I. The biotinylated cTn-I antibody was then coupled with Streptavidin-HRP. During a washing step after incubation, unbound Streptavidin-HRP has washed away. After that, the substrate solution was added, and the colour developed in accordance with the quantity of Mouse cTn-I present. The process was stopped by adding an acidic stop solution and measuring the absorbance at 450 nm.

2.9.3. Oxidative Stress Markers

2.9.3.1. Myocardial Superoxide Dismutase (SOD)

Superoxide dismutase activity was measured using a colourimetric method by UV-VIS spectrophotometer (19). The approach is based on the generation of pyrogallol-quinone via a reactive intermediate, the semiquinone radical, and SOD's capacity to suppress this reaction via radical dismutation. Pyrogallol-quinone is a brown substance that absorbs light at 420 nm.

2.9.3.2. Myocardial Malondialdehyde (MDA)

On a spectrophotometer, malondialdehyde (MDA) was measured using the Buege & Aust Thiobarbituric acid (TBA) detection method (20). This method quantifies lipid peroxides by measuring aldehyde breakdown products of lipid peroxidation. The basic principle of the method is the reaction of one molecule of malondialdehyde and two molecules of thiobarbituric acid to form a red MDA-TBA complex which can be measured at 535 nm.

2.9.3.3. Histopathological Analysis

As mentioned previously, the myocardial tissue was fixed in 10% formalin for 24 hours (21). In summary, 5 µm thick sections were paraffin-embedded according to the usual method. After that, hematoxylin and eosin (H&E) were used to stain the samples. Under an optical microscope, each heart slice (n=3 per heart) was assessed for cardiac damage and images were taken. Histological slices from all samples were analyzed and graded according to Zingarelli, Salzman (22) ' s technique to semi-quantify the change in heart damage, as shown in table 1.

Table 1. Myocardial damage scoring system, according to Zingarelli, Salzman (22) system

Score	Tissue findings
Score 0	no damage, normal architecture
Score 1 (mild)	interstitial oedema and focal necrosis
Score 2 (moderate)	diffuse myocardial cell swelling
Score 3 (severe)	the presence of contraction bands and neutrophil infiltrate
Score 4 (highly severe)	the presence of contraction bands, leukocyte infiltrate, and haemorrhage

2.10. Statistical Analysis

Statistical analysis was performed using SPSS 26. Analysis of variance (ANOVA) with LSD post-hoc test was used to investigate differences between groups, and histological differences were confirmed using Kruskal-Wallis with Mann-Whitney U-test. Pearson correlation coefficient (r) was used to find the relationship between study parameters. Statistically, the present data significance was defined as $P \leq 0.05$.

3. Results

3.1. Octreotidediminished Cardiac Troponin

ELISA outcomes demonstrated that the myocardial level of cTn-I was significantly higher ($P<0.05$) in CLP and vehicles groups compared with healthy groups. Whileoctreotidetreated groups showed a significantly lower level ($P<0.05$) of cTn-I as compared with the untreated CLP group (Figure 1).

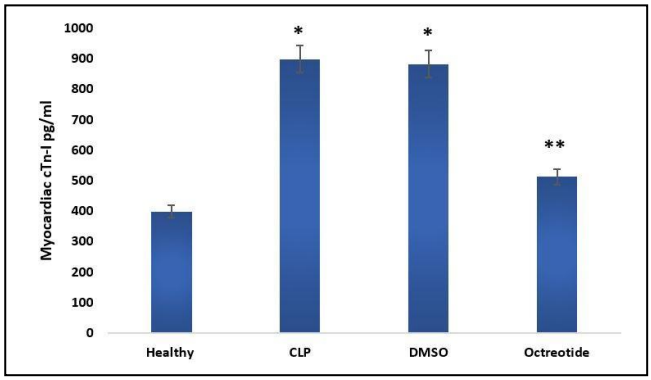

Figure 1. Mean myocardial level of cTn-I (pg/L): Data are expressed as mean±SD; *$P<0.05$ versus the healthy group; **$P<0.05$ versus the CLP group

3.2. Octreotide Attenuates Inflammatory Response

To determine the impact of octreotide on the inflammatory response that occurs during CLP-induced polymicrobial sepsis, the serum levels of inflammatory cytokines, including (TNF-α, IL-6, and IL-1β) were measured using the ELISA technique 24 after CLP-induced polymicrobial sepsis. The current study demonstrated that the serum level of inflammatory cytokines (TNF-α, IL-6, and IL-1β) was significantly higher (P<0.05) in the CLP group as compared with the healthy group. While the octreotide group showed significantly lower (P<0.05) levels of inflammatory cytokines (TNF-α, IL-6, and IL-1β) if compared with the CLP group (Figure 2).

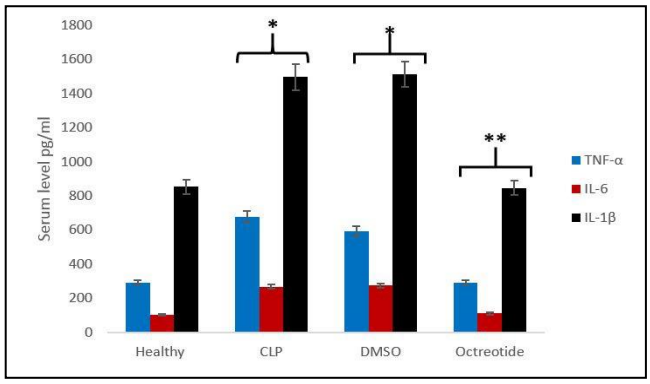

Figure 2. Mean serum level of inflammatory cytokines (TNF-α, IL-6, and IL-1β): Data are expressed as mean±SD; *P<0.05 versus the healthy group; **P<0.05 versus the CLP group

3.3. Octreotidealleviated Oxidative Stress Injury

Additionally, in the current study, the oxidative biomarkers, including malondialdehyde (MDA) level and superoxide dismutase (SOD) activity in myocardial tissue, were measured spectrophotometrically. The current study outcomes showed that the degree of myocardial SOD activity was significantly lower (P<0.05) in CLP and vehicles groups compared with healthy. While the octreotide group showed a significantly higher degree (P<0.05) of SOD activity as compared with the untreated CLP group. Furthermore, the myocardial level of MDA was significantly higher (P<0.05) in the CLP-treated group compared to the healthy group. While the octreotide group demonstrated a significantly (P<0.05) lower level of MDA as compared with the CLP group (Figures 3 and 4).

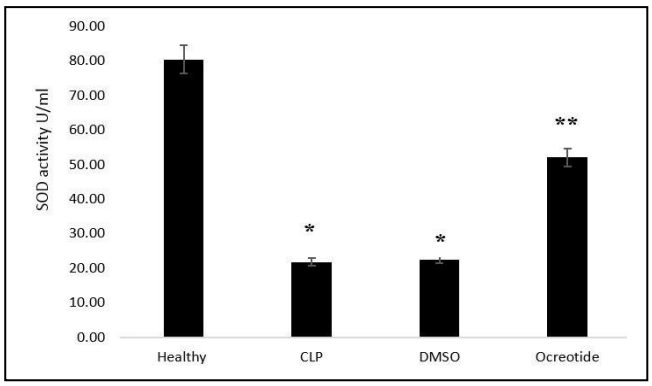

Figure 3. Mean myocardial activity of SOD (U/ml): Data are expressed as mean ± SD; *P<0.05 versus the healthy group; **P<0.05 versus the CLP group

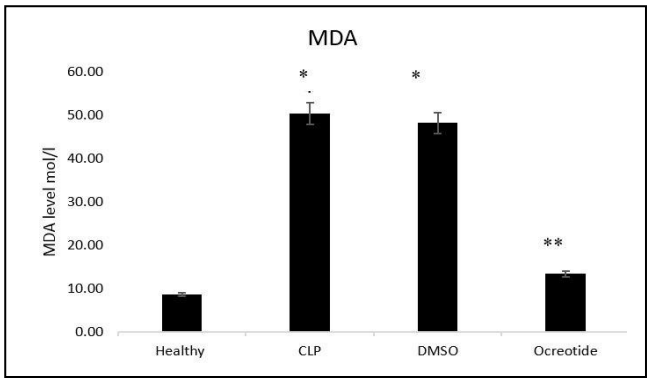

Figure 4. Mean myocardial level of MDA (mol/ml): Data are expressed as mean±SD; *P<0.05 versus the healthy group;**P<0.05 versus the CLP group

3.4. The Effects of Octreotide Sepsis-Induced Histopathological Changes

A histological investigation of myocardial tissue was conducted to provide more information on the effects of octreotide heart damage. In this histopathological analysis, serial sections of cardiac tissue were obtained after 24 hours of CLP-induced polymicrobial sepsis and subjected to Hematoxylin and Eosin staining (H&E). CLP myocardial tissue demonstrated a substantial significant (P<0.05) myocardial damage as compared to the healthy group (Figure 5**)**, with the development of contraction bands and polymorphonuclear leukocytes (PMN) infiltration, as well as necrosis, interstitial oedema and localized red

blood cell extravasation. CLP group had a highly severe histological grading from normal cardiac tissue (Figure 6). While the octreotide group showed a more significant (P<0.05) reduction in myocardial injury than the CLP group (Figure 7). The histological changes were mild with a different number of mice.

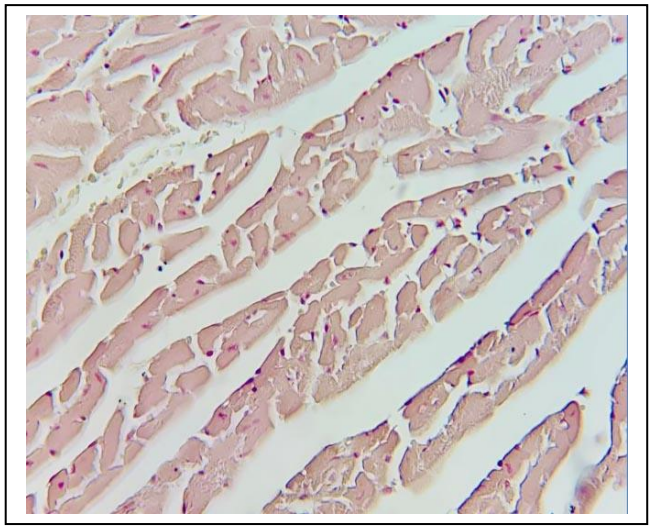

Figure 5. Myocardial tissue sections of mice in the healthy group: showed normal myocytes histology with clear cell borders and structures. H&E 10×40

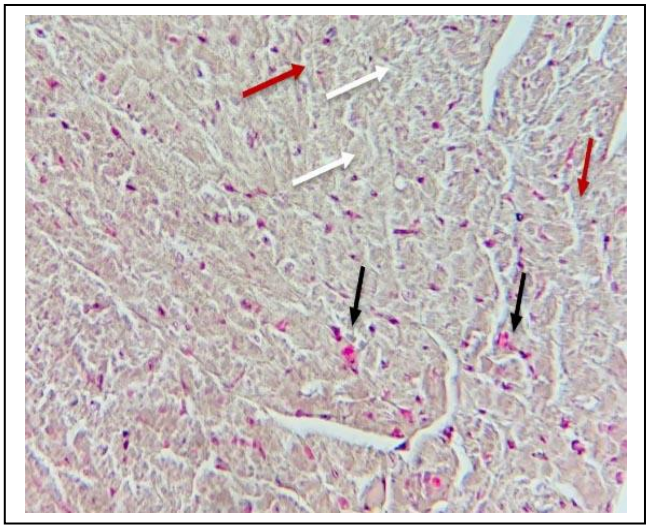

Figure 6. Myocardial tissue sections of mice in the CLP group: showed inflammation (black arrow), contraction bands (red arrow), & necrotic karyolysis (white arrow), H&E 10×40

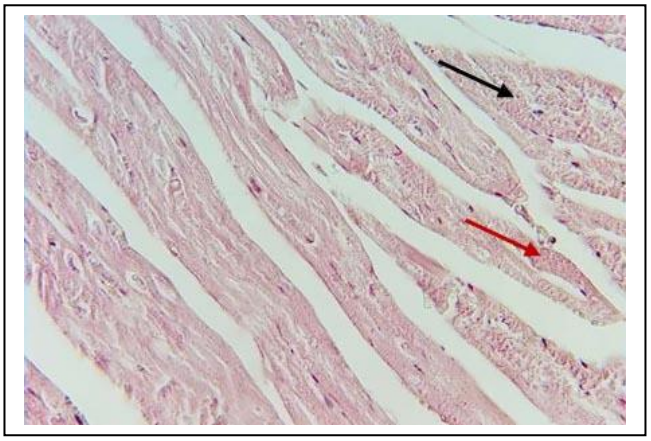

Figure 7. Myocardial tissue sections of mice in the octreotide group: showed a mild degree of inflammation & increased cytoplasmic eosinophilia (red arrow), H&E 10×40

4. Discussion

Current work demonstrated the ability of octreotide to decrease the myocardial level of troponin-IThe elevation in the levels of cardiac troponin in the CLP group can be either related to the cardiomyocytes membrane leakage or be a cytokine-dependent fashion during the inflammatory phase of induced polymicrobial sepsis (23). The level of cTn-I was significantly lower in the octreotide group compared to the CLP group. Up to current knowledge, no study has been done to evaluate the impact of octreotide on the cardiac troponin-I level after CLP-induced polymicrobial sepsis. Instead, a previous study demonstrated the protective effect of octreotide against heart injury post-severe acute pancreatitis (SAP) in a

rat model (24). Like findings can be attributed to the anti-inflammatory effect of octreotide in addition to its ability to decrease the expression level of p-selectin, as a cell adhesion mediator, that induces such pathological effects on the myocardial tissues (24, 25).

Additionally, the octreotide group demonstrated significantly lower levels of inflammatory cytokines if compared with the CLP group; these results are in accord with a previous study (15), which showed a significant reverse in the level of inflammatory cytokines in CLP rats treated with octreotide. The significant effect of octreotide in lowering the level of the inflammatory cytokine can be supported by two explanations first one by its action as an anti-inflammatory and NF-kB suppressor, which leads decrease in the translocation of the active form of NF-kB into the nucleus and limits the production of inflammatory cytokines (26), second explanation by its effect as an anti-oxidant which results in decreasing the level of oxidant molecules that act as a stimulator to inflammatory mediators (27, 28).

On the other hand, the octreotide group showed a significantly higher degree of SOD activity as compared with the untreated CLP group. These findings may occur since SOD, an anti-oxidant enzyme, is thought to become one of the body's fundamental defences against oxidative stress. The balance between free radical scavenging and generation by cellular anti-oxidant mechanisms has been demonstrated to be impaired in septic circumstances (29). Furthermore, the myocardial MDA level was significantly lower in the octreotide group compared to the CLP. M. Gul and their colleagues showed that octreotide had lowered the MDA level within the lung tissue as compared with CLP rats (30). In addition to the Nrf-2-mediated anti-oxidant activity of octreotide that was mentioned previously that surely decreases the level of MDA within the myocardium (28). The decreased level of MDA in the octreotide group reveals the anti-oxidant activity of octreotide that may be related to the ability of octreotide to decrease the degree of leukocyte infiltration, mainly neutrophils type, which consider the primary source of oxygen free radical production, thereby decreasing the level of lipid peroxidation and subsequently diminished MDA level (15).

During sepsis-induced cardiotoxicity, different histopathological changes have been seen, such as inflammatory cells within the myocardium, extravasation of blood cells, contraction bands within the myofibrils, cellular swelling, necrosis, pyknosis, karyorrhexis, and karyolysis. These histopathological changes within the myocardium during polymicrobial sepsis can be explained by the overexpression of inflammatory cytokines and increased level of oxidant molecules (31, 32). These mediators will result in cardiac tissue destruction, contraction bands, pycnosis, karyorrhexis, and karyolysis as a unique feature of myocardial necrosis (33, 34). Octreotide significantly reduced cardiac tissue injury compared to the CLP and vehicle groups. The histopathological damage scores for the octreotide group are usually nearly normal to mild.

Octreotide ameliorated sepsis-induced cardiotoxicity in mice via exhibiting potent anti-oxidant (elevated SOD and decreased MDA), anti-inflammatory (suppressed TNF-a, IL-1β, and IL-6) and cardioprotective (decreased cTn-I), and improved heart histopathological changes. Octreotide could be a good candidate therapeutic agent for protection against sepsis-induced cardiotoxicity.

Authors' Contribution

Study concept and design: Q. A. Z.
Acquisition of data: A. A. A.
Analysis and interpretation of data: W. J. A.
Drafting of the manuscript: R. H. A.
Critical revision of the manuscript for important intellectual content: Q. A. Z.
Statistical analysis: A. A. A.
Administrative, technical, and material support: Q. A. Z.

Ethics

All procedures were approved by the relevant ethics committee at the Al-Mustaqbal University College, Babylon, Iraq.

Conflict of Interest

The authors declare that they have no conflict of interest.

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