EXPERIMENTAL STUDY

The determination of the protective role of sildenafil administration in rats with sepsis-induced liver injury

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ABSTRACT

BACKGROUND: Sepsis is a complex syndrome which comes out after infection, characterized by activation of inflammation and infection and has a high morbidity and mortality. Sildenafil (SLD) is a selective phosphodiesterase Type 5 enzyme inhibitor and is used in the treatment of erectile dysfunction effectively all over the world. In this study, we investigated whether SLD had protective effect or not by studying the effect of SLD on reactive oxygen species and antioxidants in cecal ligation and puncture (CLP) polymicrobial sepsis model in rat liver histopathologically and biochemically.

METHODS: Rats were divided into four groups: (1) 10 mg/kg SLD given CLP group; (2) 20 mg/kg SLD given CLP group; (3) CLP group; and (4) SHAM operated group. CLP polymicrobial sepsis model was applied to the rats. All rats in our study were sacrificed by overdose general anesthetic after 16 h (thiopental sodium, 50 mg/kg). Specimens of rat liver were analyzed histopathologically and biochemically. In the study, superoxide dismutase (SOD) and glutathione (GSH) parameters were measured to indicate the antioxidant activity in liver during sepsis. To evaluate the oxidant activity, myeloperoxidase (MPO) and lipid peroxidation (LPO) parameters were measured in liver tissue.

RESULTS: SOD and MPO activities and GSH and LPO levels were high in CLP polymicrobial sepsis model when compared to SHAM group ($p<0.05$). In all SLD groups, GSH levels were high when compared to CLP group. In 20 mg/kg SLD given sepsis group, high GSH levels were observed according to SHAM group. In addition, while all SLD dose groups had a significant decrease versus CLP group in LPO levels ($p<0.05$), they had a significant increase in MPO activities. In 20 mg/kg SLD administrated rats, an improvement observed in biochemical parameters. In this study, SOD and MPO activities which were low in SHAM group increased in CLP polymicrobial sepsis model. When SLD administrated, MPO activity increased in both SHAM and CLP groups. In this study, GSH and LPO levels also increase in septic liver tissue. When SLD administrated to SHAM group, it increased VI protective GSH level and decreased detrimental LPO level. In histopathological examination, it was observed that 10 mg/kg SLD administration had a curative effect in liver tissue partly.

CONCLUSION: It was shown that acute SLD administration decreased liver damage in septic rats dose-dependently in this study. In addition, it was observed that it corrected the broken oxidant-antioxidant balance. This might mediate the protective effect of SLD in liver. However, we believe that new experimental and clinical studies should be in the future to understand the protective effect of SLD in liver.

Keywords: Liver injury; rat; sepsis; sildenafil.

INTRODUCTION

Sepsis is a complex post-infection syndrome characterized by coactivation of inflammation and coagulation. These events are manifested with systemic inflammatory response syndrome or sepsis symptoms through pro-inflammatory cytokines, procoagulants, and adhesion molecules released

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from immune system or damaged endothelial cells.[1] In the prognosis of sepsis, cytokines, coagulation system activation, and consequent organ failures are observed. The role of oxidative stress was also reported in sepsis induced organ damage.[2] Free oxygen radical formation due to sepsis and endotoxemia is very significant in the release of pro-inflammatory cytokines, which are important in acute inflammatory response associated with sepsis.[3–6] Liver plays a key role in sepsis pathology. Sepsis-induced liver dysfunction may cause multiple organ failure or ameliorate multiple organ failure.[7] Thus, prevention of sepsis-induced liver failure is important in treatment. Sildenafil (SLD) is a selective phosphodiesterase Type 5 (PDE-5) inhibitor agent in pulmonary hypertension. Its beneficial effects on pulmonary hypertension suggested that this medicine may also contribute to hepatic perfusion, and it was demonstrated that SLD had significant positive effects on hepatic hemodynamic parameters in a study.[8] In animal studies, it was also shown that SLD protected alveolar growth and angiogenesis and reduced inflammation.[9,10] It was demonstrated in biochemical and histopathological studies that SLD had a protective effect on both lung and kidney tissues by reducing oxidative stress and supporting the antioxidant system.[11] However, we could not find a study on sepsis-induced liver injury. Therefore, we can say that this information is valid.

The present study aimed to analyze the effect of SLD CLP-induced liver tissue damage in rats with cecum ligation and perforation (CLP)-induced polymicrobial sepsis on free oxygen radicals and antioxidants using histopathological and biochemical methods.

MATERIALS AND METHODS

Twenty-four 220–250 g male Wistar rats were used in the study. The rats were procured from Atatürk University Animal Laboratory and Research Center. For this study, the decision of "75" of the session numbered "10" dated October 26, 2011 was approved by the " Atatürk University Faculty of Medicine Animal Experiments Local Ethics Committee."

Research Design

Rats were distributed into four groups. Each group included six rats.

- Group 1. 10 mg/kg SLD administered cecum ligation perforation (CLP) group
- Group 2. 20 mg/kg SLD administered CLP group
- Group 3. CLP group
- Group 4. SHAM operation group.

Cecum ligation perforation (CLP) polymicrobial sepsis model was applied to the rats. In the present study, rats in all groups were terminated with general anesthesia overdose after 16 h (thiopental sodium, 50 mg/kg). The rat liver specimens were incised and placed in iced saline solution. Half of the liver was stored at −80°C in the biochemistry laboratory and the other half was stored in 10% formalin solution for histopathological tests. At the end of the study, the obtained rat livers were rapidly examined macroscopically and then the tissues were stored at −20°C for biochemical assays. Tissue enzyme activities were analyzed within 3 days the latest. Superoxide dismutase (SOD) and myeloperoxidase (MPO) activities and glutathione (GSH) and lipid peroxidase (LPO) levels were measured in the supernatants obtained from liver tissue homogenates with adequate methods reported in the literature. All measurements were conducted at ambient temperatures. SOD activity was determined based on the method described by Sun et al. (1988). MPO activity was determined based on the method described by Bradley (1982). The SHAM group shown as Group 4 is the control group. (This control group was also divided into the group given SLD and the group not given. The SHAM group shown at the bottom of the table is the group not given SLD). Changes in MPO, SOD enzyme activity, and LPO and GSH levels in liver tissue were examined before SLD was administered in the SHAM group. Changes after SLD administration were then evaluated Therefore, they are presented in the table as two separate groups as SHAM and SHAM +SLD.

Statistical Analysis

The mean and standard deviation values for the group numerical data were calculated and presented in tables. Statistical analyzes were conducted with SPSS 12.0 for Windows software. The intergroup comparison was conducted with one-way analysis of variance and Duncan's multiple range test. Data with $p<0.05$ were considered significant.

RESULTS

In the present study, SOD and GSH levels were measured to demonstrate antioxidant activity in liver tissue during sepsis. Oxidative activity was analyzed with the measurement of MPO and LPO levels in liver tissues. SOD and MPO activities and GSH and LPO levels were studied in all liver tissues and presented in Table 1. It was determined that SOD and MPO activities, GSH and LPO levels were higher in CLP polymicrobial sepsis group when compared to the SHAM group ($p<0.05$). In all SLD administered groups, high GSH levels were observed when compared to the CLP administered groups. In 20 mg/kg SLD administered rats, high GSH levels were observed when compared to the SHAM group. However, all SLD doses led to significant decreased in LPO levels when compared to the CLP group. In 20 mg/kg SLD administered rats, improvements were observed in biochemical parameters. In the present study, SOD and MPO activities, which were low in the sham group, significantly increased in CLP induced polymicrobial sepsis model. MPO, which was low in the sham group, increased with CLP induction. With SLD administration, the MPO level increased

Table 1. MPO, SOD enzyme activity and LPO and GSH level variations in liver tissues after sildenafil treatment

Treatments (Liver tissue)	N	SOD activity (mmol/min/mg tissue)	MPO activity (µmol/min/mg tissue)	LPO level (nmol/g tissue)	GSH level (nmol/mg tissue)
CLP+SLD (10 mg/kg)	6	143.3±0.1[d]	50.8±0.1[d]	54.1±0.3[d]	3.7±0.1[c]
CLP+SLD (20 mg/kg)	6	133.4±1.2[c]	61.4±0.1[e]	34.3±1.0[c]	4.1±0.1[d]
SHAM+SLD (20 mg/kg)	6	123.3±0.4[a]	31.1±0.2[b]	8.7±0.5[a]	3.7±0.1[c]
CLP	6	149.4±0.5[e]	41.0±0.5[c]	68.1±0.4[e]	3.2±0.04[b]
SHAM	6	127.2±0.6[b]	15.2±0.2[a]	25.0±0.1[b]	3.0±0.04[a]

There are no significant differences between the data in the same column based on Duncan (<=0.05) test. N: Number of rats. SOD: Superoxide dismutase; MPO: Myeloperoxidase; LPO: Lipid peroxidase; GSH: Glutathione; CLP: Cecum ligation perforation; SLD: Sildenafil; [a]:SHAM+SLD (20 mg/kg); [b]:SHAM; [c]: CLP+SLD (20 mg/kg); [d]: CLP+SLD (10 mg/kg); [e]:CLP.

in both the sham group and the CLP group. GSH and LPO levels in septic liver tissues also increased in the present study. SLD administration in the sham group also increased the protective GSH content and reduced the damaging LPO content.

Histopathological Findings

Sham Group Findings

Examination of the control group liver sections demonstrated that the contours of the vena central located at the center of hepatic lobules were regular, the hepatocytes emerging therefrom were arranged radially to form the Remark cords, and the sinusoids that were paved with endothelia between the hepatocytes allowed the passage of 1 or erythrocytes (Fig. 1a). In the periphery of the hepatic lobule, the portal area included the hepatic arteriole and the branch of the bile duct and inflammatory cells were observed between them. Periportal hepatocytes that emerged from the portal area formed cords with regular contours and surrounded the endothelia-surrounded sinusoids (Fig. 1b).

CLP Group Findings

Examination of CLP group liver sections (Fig. 2a) demonstrated that the eosinophilic staining was more visible in hepatocytes cytoplasms when compared to the control, the cell membrane contours became more irregular (Fig. 2b), the sinusoids narrowed and inflammatory cells such as neutrophils, lymphocytes were present in the sinusoids, and hyperchromatosis and degeneration were observed in the nuclei of the endothelial cells that paved the sinusoids and in hepatic arterioles and central vein. Furthermore, mild congestion and occasional apoptotic hepatocytes were noted (Fig. 2c and d).

CLP+10 mg/kg SLD Administered Group Findings

Examination of the central vein and sinusoids demonstrated mild congestion and intra-sinusoidal lymphocytes in both. However, both congestive and intra-sinusoidal inflammation were significantly reduced when compared to the CLP group. Hepatocytes in this region had eosinophilic cytoplasm (Fig. 3a). Examination of the portal area also demonstrated mild inflammation with mild congestion (Fig. 3b). Thus, it can be argued that the administration of 10 mg SLD expressed certain healing effects on the liver.

CLP+20 mg/kg SLD Administered Group Findings

Examination of the central vein and its vicinity demonstrated

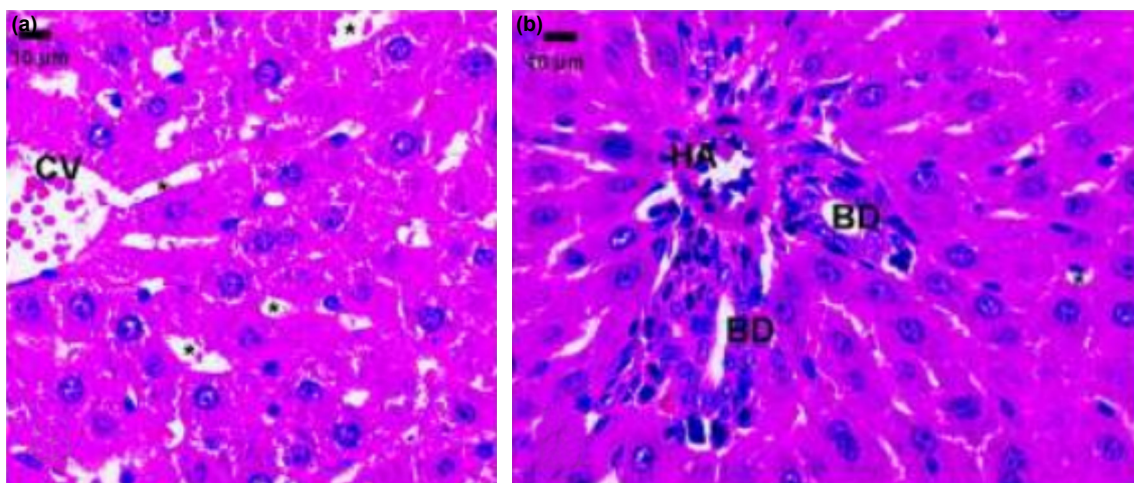

Figure 1. Control group liver sections. **(a)** Central area, **(b)** Portal area. CV: V. Centralis; *: Sinusoid; HA: Hepatic arteriole; BD: Bile duct branch. Stain H&E. Section thickness 5 µm.

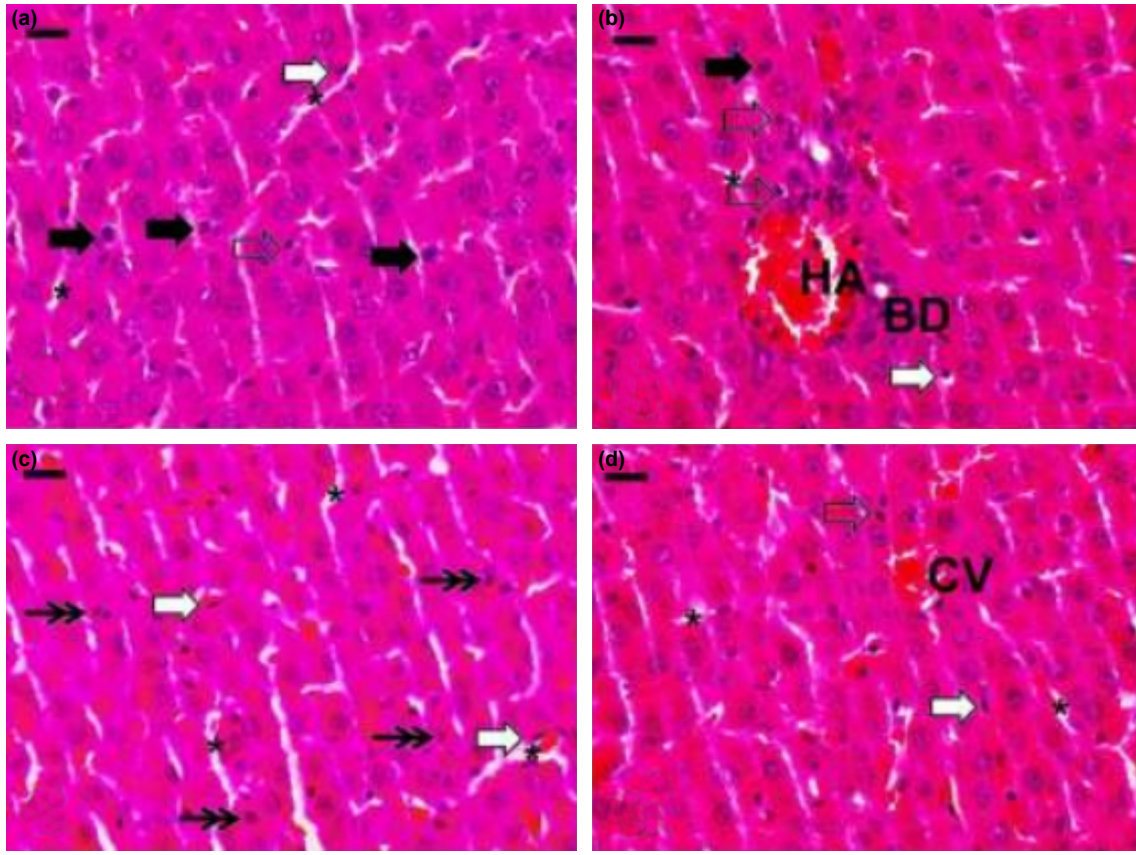

Figure 2. CLP Group liver sections. CV: V. Centralis; *: Sinusoid; HA: Hepatic arteriole; BD: Bile duct branch. White arrow: endothelium, black arrow: neutrophil infiltration, transparent arrow: lymphocyte infiltration, double arrow: apoptotic hepatocytes and particles. Bars: 15 µm, stain: H&E, section thickness: 5 µm

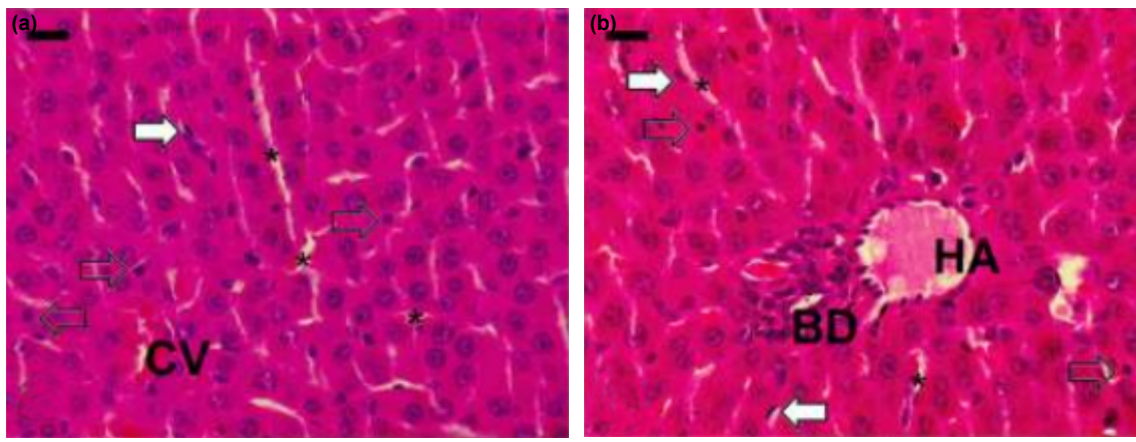

Figure 3. CLP+ 10 mg sildenafil administered group liver sections. CV: V. Centralis; *: Sinusoid; HA: Hepatic arteriole; BD: Bile duct branch. White arrow: endothelium, transparent arrow: lymphocyte infiltration. Bars: 15 µm, stain: H&E, section thickness: 5 µm.

higher basophilic staining and although endothelial sinusoids were visible similar to the control group, these did not contain inflammatory cells. Central vein and sinusoids were regular and the examination of the portal area demonstrated no inflammation. Hepatocytes were more basophilic and closer to control when compared to those in the CLP treated and 10 mg SLD administered group (Fig. 4a and b).

DISCUSSION

In experimental studies, it was demonstrated that sepsis and endotoxemia led to the production of free oxygen radicals.[4,12] In a study by Blackwel et al.,[5] free oxygen radicals were demonstrated to cause the release of pro-inflammatory cytokines and mediators, which play a significant role in sep-

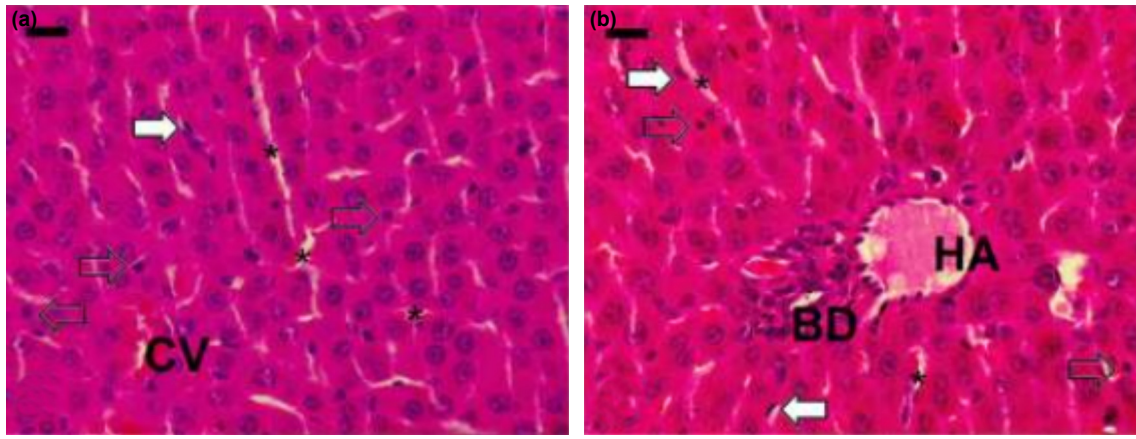

Figure 4. CLP+ 20 mg sildenafil administered group liver sections. CV: V. Centralis; *: Sinusoid; HA: Hepatic arteriole; BD: Bile duct branch. White arrow: endothelium. Bars: 15 µm, stain: H&E, section thickness: 5 µm.

sis pathophysiology, and to produce acute inflammatory response in sepsis. It was also suggested that endotoxemia and sepsis reduce the endogenous antioxidant and deteriorate oxidant antioxidant balance.[6] Among the pro-inflammatory effects of free oxygen radicals are endothelial damage, formation of chemotactic factors, cytokine release, and mitochondrial damage, which is due to the increase in free oxygen radicals and the resulting imbalance between free oxygen radicals and oxidant-antioxidant capacity.[13–15] In a study that investigated the role of the oxidative system in sepsis, Koksal et al.[16] studied the correlation between plasma and tissue malonaldehyde (MDA) and GSH levels and oxidative stress and antioxidative response in late-stage sepsis. As a result, they found that there was a positive correlation between plasma MDA and GSH concentrations and tissue MDA and GSH levels in the intra-abdominal sepsis model. Based on their findings, it was suggested that free oxygen radicals play an important role in sepsis pathophysiology in CML sepsis model. In a study by Sakaguchi et al.,[17] cell membrane damage and lipid peroxide formation in liver were examined after salmonella endotoxin administration in rats. In the study, it was demonstrated that liver lipid peroxide levels increased after endotoxin administration when compared to the control group, and liver lipid peroxide levels returned to normal levels 2 days later. In the same study, it was shown that SOD level dropped 18–48 h after endotoxin administration and then started to rise. GSH reductase and GSH peroxidase activities were shown to decrease 18 h after endotoxin administration. In the study, lower lipid peroxide formation was observed in the liver of the endotoxin administered group when compared to the control group. As a result, it was shown that lipid peroxide formation that occurred with liver cellular damage induced by endotoxemia was caused by free oxygen radicals. In the present study, it was found that SOD and MPO activities, GSH and LPO levels were higher in the CLP polymicrobial sepsis group when compared to the SHAM group. Furthermore, GSH and LPO levels were also high in septic liver tissues. In a study that investigated the effect of SLD on the oxidant-antioxidant system in the liver, it was shown to reduce tissue MDA levels, MPO activities, and serum proinflammatory cytokines and maintain GSH levels.[18] Decrease in the tissue LPO levels can be interpreted as a beneficial effect of SLD through the oxidant antioxidant balance.[18] In a study by Karakoyun et al.,[19] the impact of SLD on tissue integrity, oxidant antioxidant balance and cellular apoptosis was demonstrated through experimental colitis in rats. The beneficial effects of SLD were demonstrated on oxidant-antioxidant balance, superoxide production to cell apoptosis, and cytokine release through a nitric oxide dependent mechanism. In a study conducted by Cadirci et al.,[11] different doses of SLD were administered to different groups. The study results demonstrated that SLD administration decreased oxidant-antioxidant balance and lowered TNF-±level. This was reported be related to its preventive effect against tissue damage in lung and kidney tissues. In this study, similar to the present study, the protective effect of SLD against septic liver by correcting the impaired oxidant-antioxidant balance was reported.

Conclusion

The present study demonstrated that SLD treatment decreased the hepatic damage based on the dose and regulated the impaired oxidant-antioxidant balance in septic rats. This might be through the mediating protective effect of SLD on the liver. This study is one of the rare studies that investigated the effects of SLD on sepsis-induced liver damage, thus exhibiting the significance of the present study. However, we believe that the future experimental studies and clinical trials should be conducted to better understand the protective effects of SLD on liver.

Ethics Committee Approval: This study was approved by the Atatürk University Faculty of Medicine Animal Experiment Ethics Committee (Date: 26.10.2011, Decision No: 10/75).

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Supervision: N.O.; Resource: S.C.; Materials: E.Ç.; Data: S.C.; Analysis: O.D.; Literature search: O.D.; Writing: O.D., S.C.; Critical revision: N.O.;

Conflict of Interest: None declared.

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DENEYSEL ÇALIŞMA - *ÖZ*

Sıçanlarda sepsisle oluşturulan karaciğer hasarı üzerine sildenafil uygulamasının koruyucu rolünün belirlenmesi

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AMAÇ: Sepsis enfeksiyon sonrasında gelişen, enflamasyon ve koagülasyonun birlikte aktive olmasıyla karekterize, morbiditesi ve mortalitesi yüksek, kompleks bir sendromdur. Sildenafil selektif bir fosfodiesteraz Tip 5 (PDE–5) inhibitörü olup, tüm dünyada erektil disfonksiyon tedavisinde etkin olarak kullanılan bir ilaçtır. Biz bu çalışmayla, çekum ligasyonu ve perforasyonu (ÇLP) uygulayarak polimikrobiyal sepsis oluşturduğumuz sıçanlarda, sildenafilin ÇLP'nin indüklediği karaciğer doku hasarında, histopatolojik ve biyokimyasal olarak serbest oksijen radikalleri ve antioksidanlara olan etkisine bakarak, koruyucu etkisi olup olmadığını araştırdık.

GEREÇ VE YÖNTEM: Sıçanlar dört gruba ayrıldı. 1) 10 mg/kg sildenafil (SLD) verilmiş çekal ligasyon perforasyon (ÇLP) grubu; 2) 20 mg/kg SLD verilmiş ÇLP grubu; 3) ÇLP grubu; 4) SHAM operasyon grubu. Çekal ligasyon perforasyon (ÇLP), polimikrobiyal sepsis modeli sıçanlara uygulandı. Çalışmamızda bütün gruplardaki sıçanlar 16 saat sonra yüksek doz genel anestezi ile öldürüldü (thiopental sodyum, 50 mg/kg). Sıçanların karaciğer spesmenleri alınarak histopatolojik ve biyokimyasal olarak analiz edildi. Çalışmamızda sepsis sürecinde karaciğer dokusunda oluşan antioksidan aktiviteyi göstermek için süperoksit dismutaz (SOD) ve glutatyon (GSH) parametreleri ölçüldü. Oksidan aktivite ise miyeloperoksidaz (MPO) ve lipit peroksidasyonu (LPO) parametreleri karaciğer dokularında ölçülerek değerlendirildi.

BULGULAR: ÇLP polimikrobiyal sepsis grubunda, SHAM grubuna göre SOD ve MPO aktiviteleri, GSH ve LPO seviyeleri yüksek olarak bulundu ($p<0.05$) Sildenafil uygulanmış bütün gruplarda, ÇLP uygulanmış gruplara göre, yüksek GSH seviyeleri bulundu. 20 mg/kg sildenafil dozu uygulanmış sıçanlarda, SHAM grubuna göre yüksek GSH seviyeleri gözlendi. Bununla birlikte sildenafilin bütün dozları, ÇLP grubuna göre, LPO seviyelerinde anlamlı düşüş ($p<0.05$), MPO aktivitesinde anlamlı artış gösterdi. 20 mg/kg sildenafil uygulanmış sıçanlarda, biyokimyasal parametrelerde iyileşmeler gözlendi. Çalışmamızda SHAM grubunda düşük olan SOD ve MPO IV aktiviteleri ÇLP ile uygulanan polimikrobiyal sepsis modelinde artmıştır. SLD uygulandığında da MPO aktivitesi hem SHAM grubunda, hem ÇLP grubunda artmıştır. Çalışmamızda septik karaciğer dokularında GSH ve LPO seviyeleri de artmıştır. SLD SHAM grubuna uygulandığında da koruyucu GSH miktarını artırmış ve hasar verici LPO miktarını azaltmıştır. Yapılan histopatolojik incelemede 10 mg/kg sildenafil uygulamasının kısmen karaciğer üzerine iyileştirici etkileri olduğu gözlendi.

TARTIŞMA: Sonuç olarak, bu çalışmada akut sildenafil uygulamasının, septik sıçanlarda oluşan karaciğer hasarını doza bağımlı olarak azalttığı gösterilmiştir. Ayrıca septik sıçanlarda bozulmuş olan oksidan-antioksidan dengesini de düzelttiği gözlenmiştir. Bu da sildenafilin karaciğerdeki koruyucu etkisine aracılık ediyor olabilir. Ancak sildenafilin karaciğer üzerindeki koruyucu etkilerinin daha iyi anlaşılabilmesi için gelecekte yeni deneysel ve klinik çalışmaların yapılması gerektiği inancındayız.

Anahtar sözcükler: Karaciğer hasarı; sepsis; sıçan; sildenafil.

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