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RESEARCH ARTICLE

The Effects of Tadalafil on the Liver After Intraperitoneal Injury in Rats

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ABSTRACT

Objective: Liver is one of the most affected tissues after abdominopelvic surgery. Many substances were employed to prevent liver damage during surgery. In this study, we aimed to investigate effects of tadalafil, phosphodiesterase-5 (PDE-5) inhibitor, on the liver after intraperitoneal abrasion.

Materials and Methods: Thirty rats were induced ileal and cecal abrasion model. Subsequently, group 1: received saline (control), group 2: tadalafil 1 mg/kg, group 3: tadalafil 10 mg/kg, group 4: tadalafil 1 mg/kg for 7 days, group 5: tadalafil 10 mg/kg for 7 days. After treatments, serum tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), intercellular adhesion molecule-1 (ICAM-1) and platelet-derived growth factor (PDGF) were analyzed by ELISA. Liver tissue samples were analyzed for tissue total oxidant/antioxidant status (TOS, TAS), thiol, TTL (total thiol level), NTL (native thiol level) using colorimetric appropriate methods.

Results: We found that serum ICAM-1 in group 5 was higher than other groups, ICAM-1 in group 4 was higher than group 2 (g1 vs. g5 p<0.001, g2 vs. g4 p=0.016, g2 vs. g5 p<0.001, g3 vs. g5 p=0.004, g4 vs. g5 p=0.03). PDGF was higher in group 5 than group 1 (p=0.025). Tissue TTL and NTL were higher in group 5 than in group 1 (p=0.035, p=0.002). TOS was higher in group 5 than groups 1 and 4 (p=0.028, p=0.028). TAS was higher in group 5 than group 3 (p=0.018).

Conclusion: High-dose and long-term administration of tadalafil increased oxidative and inflammatory responses in liver tissue.

Keywords: Liver injury, inflammation, oxidative stress, phosphodiesterase 5 inhibitors, tadalafil

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INTRODUCTION

Adhesions that occur after abdominopelvic surgery are one of the leading problems of surgeons today due to intestinal obstructions, infertility and pelvic pain.[1] Despite many studies, various surgical techniques have not been sufficient to prevent surgery-induced adhesions.[2]

Liver is primarily affected by intra-abdominal adhesions as it is anatomically close to them. In 2017, liver tissue, affected by the damage on peritoneum and cecum, was treated with recombinant technology.[3] Similarly, many techniques and substances have been tried to prevent the liver damage that develops during operations. Although useful agents have been found, complete success has not been achieved yet.

Tadalafil is a potent and selective phosphodiesterase type-5 (PDE5) inhibitor that was initially studied as a potential antianginal drug but has since grown in popularity in the treatment of erectile dysfunction and pulmonary arterial hypertension. Previous studies showed the protective effect of tadalafil against thioacetamide-induced liver fibrosis. Tadalafil pretreatment protected against thioacetamide-induced liver fibrosis in a dose-dependent manner, as evidenced by the reduction of inflammatory and fibrotic indices.[4] High doses of tadalafil (10 mg/kg) were found protective effect against ischemia reperfusion-induced liver tissue damage.[5]

Tadalafil has important effects on intracellular signaling mechanisms. It inhibits PDE-5 in smooth muscle of vasculature where PDE-5 is responsible for the degradation of cyclic

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guanosine monophosphate (cGMP).[6,7] Increased cGMP concentration results in vascular dilatation. Injury to peritoneum also leads to a release of histamine and vasoactive kinins, resulting in capillary permeability and serous accumulation. Peritoneal injury also causes the release of thromboplastin, which results in fibrin and coagulation, which may provide a matrix for adhesion formation.[8]

Herein, we analyzed the effects of short- and long-term 1 mg/kg and 10 mg/kg doses of tadalafil on the liver, after forming abrasion of the anterior surface of ileum and cecum in rats. We tried to evaluate our data with serum and tissue pro-inflammatory markers and oxidative parameters to support quantitatively after drug application.

MATERIALS and METHODS

Animals

A total number of thirty Wistar rats (200–300 g weight) were housed in stainless steel cages with free access to food and drinking water, maintained at temperature of 22°C and humidity of 60±5% with a 12-hour light/dark cycle. One week of acclimatization was allowed before starting study. Experiments were performed in accordance with the National Health Guidelines for the Care and Use of Laboratory Animals, and approved by the Kahramanmaraş Sütçü İmam University Faculty of Medicine Animal Experiments Local Ethics Committee (No: 2020/02/03, Date: 27.02.2020).

Drugs

Tadalafil (Departon®) was obtained from Abdi İbrahim Pharmaceutical Company (Istanbul, Türkiye), administered to rats by orogastric gavage after dissolving in drinking water. The doses of tadalafil 1 mg/kg and 10 mg/kg were based on our previous studies in rat models of ischemia-reperfusion, pain, and ovarian ischemia.[9–11] Ketamine (80 mg/kg i.p.) and xylacin (10 mg/kg i.p.) were used for anesthesia at the end of the experiments.

Design of Experiments and Intraperitoneal Abrasion Model

Thirty Wistar rats were randomly divided into 5 groups. Intraperitoneal abrasion was inducted in all groups, as previously described.[12] Briefly, peritoneal cavity was entered with a 3 cm vertical midline incision. Ileum and cecum were carefully removed from the abdomen. The intestine to be abraded was placed on the surgeon's left hand, its anterior surface facing up, and was stripped with sterile dry gauze. Then the abraded ileum and cecum were placed back into the intraperitoneal space, and peritoneal abrasion was inducted using dry gauze in the 2×2 cm area of parietal and visceral periton. The incision was closed with 3/0 propylene by continuous suture technique. Afterwards, the administration of tadalafil to the randomly allocated groups was carried out:

Group 1: saline per oral (p.o),

Group 2: tadalafil 1 mg/kg (p.o) single dose,

Group 3: tadalafil 10 mg/kg (p.o) single dose,

Group 4: tadalafil 1 mg/kg (p.o) for 7 days,

Group 5: tadalafil 10 mg/kg (p.o) for 7 days.

Rats were sacrificed on the 7th day when the drug dosing period ended.

Biochemical Analysis of Serum

Blood samples were centrifuged at 4000 rpm for 10 min. After the samples were centrifuged, they were prepared for use without storage. Tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), intercellular adhesion molecule-1 (ICAM-1) and platelet-derived growth factor (PDGF) were analyzed by rat enzyme immunosorbent assay, according to the manufacturer's instructions (TNF-α: Bioassay Technology Laboratory, catalog no: E0764Ra, sensitivity: 2.51 ng/L, detection range: 5–1000 ng/L. PDGF: Bioassay Technology Laboratory, catalog no: E069Ra, sensitivity: 0.023 ng/mL, range: 0.05–15 ng/mL. IL-6: Bioassay Technology Laboratory, catalog no: E0135Ra, sensitivity: 0.052 ng/L, measuring range: 0.1–40 ng/L. ICAM-1: Bioassay Technology Laboratory, catalog no: E0418Ra, sensitivity: 0.026 ng/mL, detection range: 0.05–20 ng/mL). The optical level was measured at 450 nm. Concentrations were calculated according to standard curves.

Preparation of Tissue Homogenates and Biochemical Analysis of Liver Tissue

Biochemical changes in the liver as a result of intraperitoneal damage in rats were analyzed in 5 groups. Liver tissue samples from all rats were fixed in formol. Analysis of liver tissues was conducted via total oxidant/antioxidant capacity and thiol levels using appropriate methods.[13] Briefly, liver tissue samples were quickly taken and homogenized with 0.15 Molar KCl (10%, w/v). Homogenates were centrifuged at 600×g for 10 min. Supernatants were then centrifuged at 10,000×g for 20 min. Total Antioxidant Level (TAS), Total Oxidant Level (TOS), Total Thiol Level (TTL), and Native Thiol Level (NTL) were measured colorimetrically in accordance with kit procedures (Rel Assay Diagnostic, Türkiye). Oxidative Stress Index (OSI) was obtained as a percentage of ratio of TOS to TAS. Amount of dynamic disulfide bonds was expressed by finding half the difference between total thiol and natural thiol groups. Disulfide/total thiol percentage and native thiol/total thiol percentage ratios were calculated.

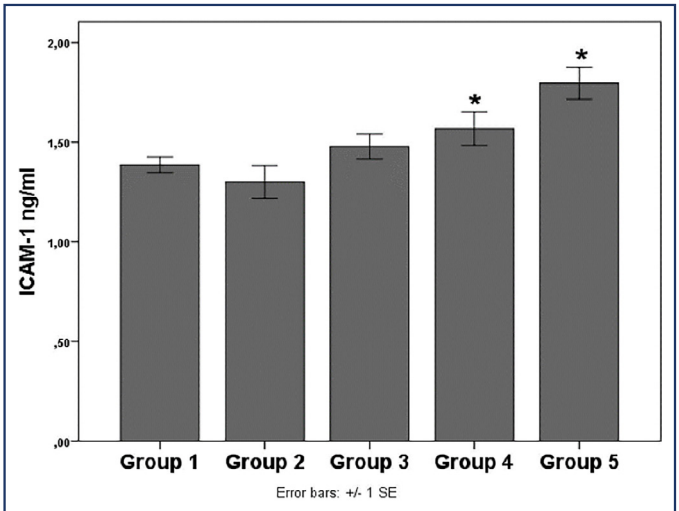

Figure 1. In serum ICAM-1 levels, group 5 was significantly higher than all other groups, and group 4 was significantly higher than group 2

*(*g5 vs. g1 p<0.001, g5 vs. g2 p<0.001, g5 vs. g3 p=0.004, g5 vs. g4 p=0.03, g4 vs. g2 p=0.016). p<0.05 were considered significant ICAM-1: Intercellular adhesion molecule-1*

Statistical Analysis

Data with normal distribution were defined as arithmetic mean and standard deviation, data without normal distribution were defined as median and range. For parametric tests, firstly, Kolmogrov-Smirnov test was used to determine whether the samples had normal distribution and variances were homogeneous. Difference between multiple groups was evaluated with one-way analysis of variance or Kruskal Wallis method. Least Significant difference test or Mann Whitney U test (with Bonferroni correction) was applied in post hoc analysis. p<0.05 was considered significant. Data were evaluated at 95% confidence interval. IBM SPSS Statistics for Windows, version 17.0 (IBM Corp., Armonk, NY, USA) SPSS 17.0 program was used for statistical analysis.

RESULTS

Serum TNF-α, IL-6, ICAM-1 and PDGF

All conditions of the rats, such as the baseline health status, their diet, or environmental conditions, were standardized before the study to avoid any confounding factors that could affect the status of the study.

Analyzing ICAM-1 in the serum samples, we found that group 5 was significantly higher than other groups, and group 4 was significantly higher than group 2 (g1 vs. g5 p<0.001, g2 vs. g4 p=0.016, g2 vs. g5 p<0.001, g3 vs. g5 p=0.004, g4 vs. g5 p=0.03) (Fig. 1, Table 1). In PDGF, we found that group 5 was significantly higher than group 1 (g1 vs. g5 p=0.025) (Fig. 2, Table 1).

Although TNF-α and IL-6 tended to increase in high doses of tadalafil, no significant difference was found between groups (Table 1).

Table 1. The effect of tadalafil on proinflammatory markers in rat serum and oxidant/antioxidant parameters in liver tissue

Variable	Group 1	Group 2	Group 3	Group 4	Group 5
ICAM-1 (ng/mL)	1.39±0.10	1.30±0.19	1.49±0.15	1.58±0.20[b]	1.80±0.20[a]
TNF-α (ng/L)	84.75 (22.62)	92.98 (4.87)	102.68 (48.77)	92.77 (15.35)	104.60 (42.56)
PDGF (ng/mL)	0.54 (0.30)	0.48 (0.03)	0.67 (0.23)	0.62 (0.64)	0.89 (0.35)[c]
IL-6 (ng/L)	2.76 (1.37)	2.57 (070)	3.28 (1.21)	3.18 (3.33)	3.42 (1.45)
TTL (µmol/L)	233.82 (92.04)	229.80 (45.84)	256.08 (75.12)	237.42 (124.68)	327.84 (121.08)[d]
NTL (µmol/L)	180.10 (42.70)	194.35 (65.10)	198.05 (29.40)	215.60 (109.30)	261.85 (78.80)[e]
Disulfide (µmol/L)	22.90 (54.57)	17.73 (9.63)	22.82 (32.63)	23.96 (24.18)	27.64 (67.56)
Red. thiol ratio	80.50 (36.02)	83.99 (11.57)	82.18 (23.05)	81.31 (18.03)	82.65 (34.49)
Oxi. thiol ratio	9.75 (18.02)	8.01 (5.79)	8.91 (11.52)	9.35 (9.01)	8.68 (17.25)
TOS (µmol/L)	5.78 (2.73)	5.94 (0.96)	6.11 (1.93)	5.86 (1.57)	7.47 (1.69)[f]
TAS (µmol/L)	1.42 (0.26)	1.42 (0.19)	1.28 (0.39)	1.53 (0.43)	1.66 (0.30)[g]
OSI	0.41 (0.15)	0.42 (0.01)	0.47 (0.28)	0.38 (0.12)	0.47 (0.11)

ICAM-1; group 5 was significantly higher than all other groups ([a]g5 vs. g1 p<0.001, g5 vs. g2 p<0.001, g5 vs. g3 p=0.004, g5 vs. g4 p=0.03), and group 4 was significantly higher than group 2 ([b]g4 vs. g2 p=0.016). PDGF; group 5 was significantly higher than group 1 ([c]g5 vs. g1 p=0.025). TTL; group 5 was significantly higher than group 1 and group 2 ([d]g5 vs. g1 p=0.035, g5 vs. g2=0.029). NTL; group 5 was significantly higher than group 1 ([e]g5 vs. g1 p=0.002). TOS; group 5 was significantly higher than group 1 and group 4 ([f]g5 vs. g1 p=0.028, g5 vs. g4 p=0.028). TAS; group 5 was significantly higher than group 3 ([g]g5 vs. g3 p=0.018). p<0.05 were considered significant. ICAM-1: Intercellular adhesion molecule-1; TNF-α: Tumor necrosis factor-α; PDGF: Platelet-derived growth factor; TTL: Total thiol level; NTL: Native thiol level; TOS: Total oxidant level; TAS: Total antioxidant level; OSI: Oxidative stress index

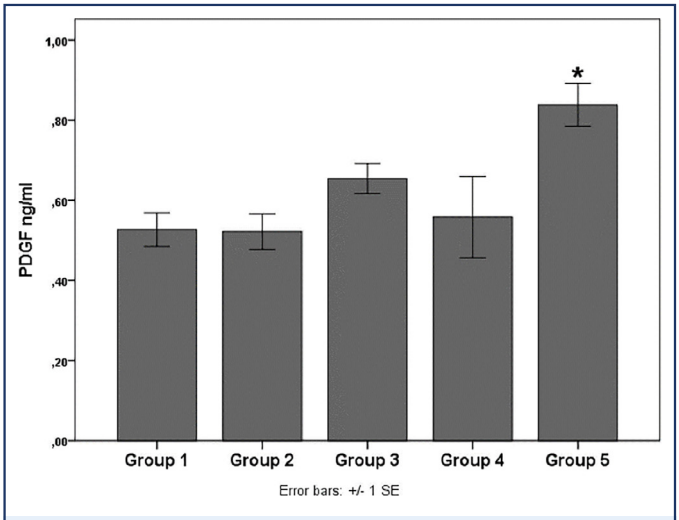

Figure 2. In serum PDGF levels, group 5 were significantly higher than group 1

*(*g5 vs. g1 p=0.025). p<0.05 were considered significant. PDGF: Platelet-derived growth factor*

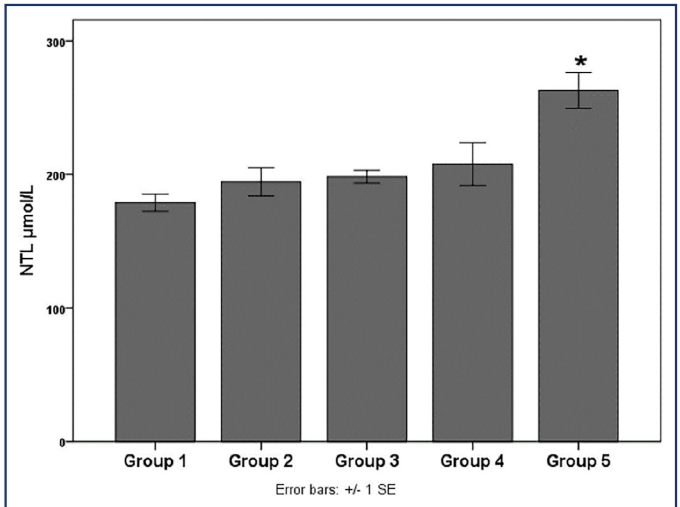

Figure 4. Liver NTL levels were significantly higher in group 5 than group 1

*(*g5 vs. g1 p=0.002). p<0.05 were considered significant. NTL: Native thiol level*

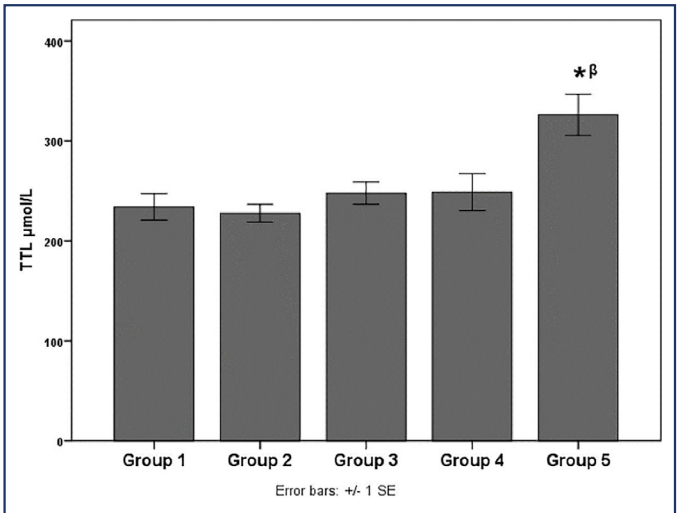

Figure 3. Liver TTL levels were significantly higher in group 5 than group 1 and group 2

*(*β g5 vs. g1 p=0.035, g5 vs. g2=0.029). p<0.05 were considered significant. TTL: Total thiol level*

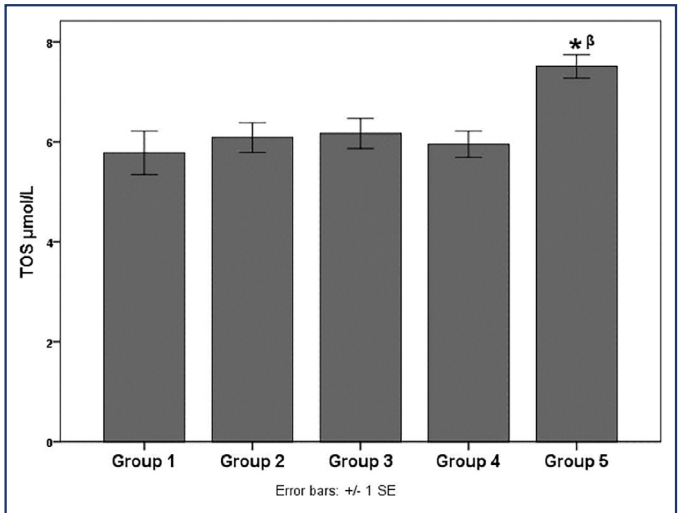

Figure 5. Liver TOS levels were significantly higher in group 5, than group 1 and group 4

*(*β g5 vs. g1 p=0.028, β g5 vs. g4 p=0.028). p<0.05 were considered significant. TOS: Total oxidant level*

Liver Tissue TAS, TOS, TTL and NTL

In the liver tissue samples, we found that TTL levels in group 5 were significantly higher than in group 1 and group 2 (g5 vs. g1 p=0.035, g5 vs. g2=0.029) (Fig. 3). We found that NTL was significantly higher in group 5 than in group 1 (g5 vs. g1 p=0.002) (Fig. 4). Group 5 had significantly higher TOS than group 1 and group 4 (g5 vs. g1 p=0.028, g5 vs. g4 p=0.028) (Fig. 5). TAS was significantly higher in group 5 than group 3 (g5 vs. g3 p=0.018) (Fig. 6).

Although the OSI, amount of dynamic disulfide bonds, disulfide/total thiol percentage (oxidized thiol) and native thiol/total thiol percentage ratios (reduced thiol) tended to increase in high doses of tadalafil, no significant difference was found between groups (Table 1).

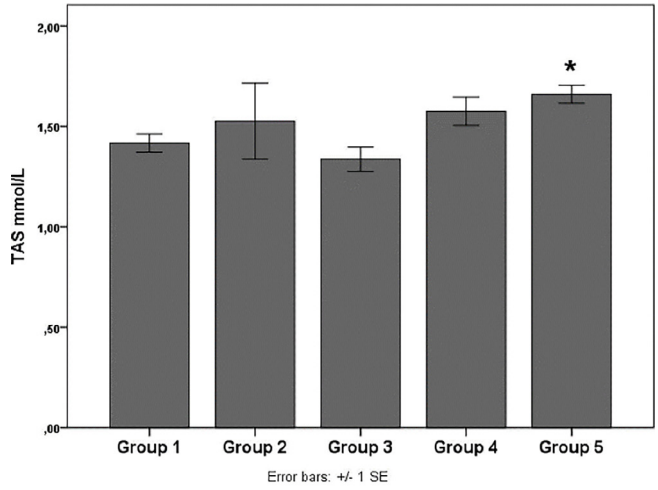

Figure 6. Liver TAS levels were significantly higher in group 5, than group 3

*(*g5 vs. g3 p=0.018). p<0.05 were considered significant. TAS: Total antioxidant level*

DISCUSSION

Many substances were employed to prevent liver damage during surgery. In this study, we evaluated the effects of tadalafil on liver after intraperitoneal injury in rats.

The most cranially located organ in the abdominal cavity of the rat is liver. The liver is primarily affected by intra-abdominal adhesions, since it is anatomically close to abdominal impacts. For this reason, we wanted to explore intraperitoneal abrasion on the liver. Although the liver is covered with peritoneum, the hilus region and the area in contact with the diaphragm are non-peritoneal. This area is in the form of a strong connective tissue.[14] The peritoneum runs over the liver from the diaphragmatic and visceral surfaces. Damage to the liver parenchyma can lead to serious changes in blood parameters. Hepatocyte death and a systemic inflammatory response are the outcomes of a complex chain of events mediated by numerous inflammatory cells and chemical mediators. Since it is not possible to evaluate liver damage with a single laboratory data, we verified the oxidation/antioxidation parameters of liver tissues and serum proinflammatory cytokines and angiogenic factors in our study.

Liver injuries occur in blunt or penetrating injuries. Acute hemorrhages and operative complications may increase mortality and morbidity.[15] Various models (including abrasion, local peritoneal excision, ischemic damage, foreign body insertion, thermal damage and bacterial contamination) were developed to experimentally induce intraperitoneal injury.[16] We preferred the abrasion model in this study, because the abrasion model mimics the mechanical trauma that occurs in laparotomy.[17]

ICAM-1, which we used in our study, is a transmembrane protein that plays a role in cell-cell interactions in endothelium and in the infiltration of leukocytes into the tissue. ICAM-1 expression is an early indicator of immune system activation and immune response. Another parameter we employed was IL-6, an interleukin that causes potent immunoglobulin and acute phase protein synthesis. TNF-α, which we used in our study, is a cell signal protein involved in systemic inflammation and acute phase reaction. The other parameter in our study, PDGF, stimulates cell growth, survival and motility. It is involved in the control of tissue homeostasis in embryonic development. Excess activity of PDGF is associated with malignant and non-malignant cell proliferation. According to our results, ICAM-1 in group 5 was significantly higher than all groups, and PDGF was significantly higher than control. High-dose/long-term administration of tadalafil increased the inflammatory response in liver tissue.

Thiol contains sulfhydryl (-SH) group, which prevents oxidative stress by turning into reversible disulfide bond (-S-S-) structures. This transformation is the earliest manifestation of radical-mediated protein oxidation. Hence, balance of thiol and disulfide is essential in immune response, apoptosis and intracellular signaling mechanisms. In our study, abnormal thiol/disulfide balance was considered as a risk factor for liver tissue damage. It exhibits a major effect on liver damage. In our study, group 5 had significantly higher TTL and NTL compared to control. TOS-TAS were also higher in group 5 compared to low dose and short duration. High-dose and long-term administration of tadalafil increased the oxidative response in liver tissue.

PDE5 inhibitors have been shown to have a potentially promising role in the treatment of inflammatory processes as well as anti-fibrotic effects.[18,19] Activation of cGMP-dependent protein kinases causes vasodilation, anti-inflammatory, and anti-proliferative effects, as well as a decrease in collagen synthesis. Tadalafil's activation of cGMP-dependent protein kinases causes vasodilation, anti-inflammatory, and anti-proliferative effects, as well as a decrease in collagen formation.[20] PDE5 inhibitors have been found to have anti-fibrotic properties as well as a potentially promising function in the treatment of inflammatory diseases.[21]

Experimental studies showed that agents that increase local tissue perfusion, such as nitric oxide (NO), and those enhancing its biological activity decrease adhesion formation. NO, produced constitutively by endothelial cells and plays an important role in the maintenance of local perfusion owing to its inhibiting effect on platelet adhesion, mast cell

degranulation and free oxygen radical production by leukocytes, plays multiple roles in the initiation, maintenance and modification of inflammatory response.[22]

In the current investigation, we demonstrated a significant increase in oxidation parameters in the group taking tadalafil in high doses for a long time compared to the other groups. High-dose and long-term administration of tadalafil increased the oxidative response in liver tissue. Abrasion in our study was not a vascular condition, but a traumatizing inflammatory condition in the tissue. Therefore, on behalf of a well-known effect of tadalafil on the NO release, tadalafil may also cause a significant increase in oxidation parameters at hepatic tissue level.

We have some limitations in this study. Since this is an experimental animal study, the number of animals in each group is smaller than the groups created in clinical studies. On the other hand, it is a positive situation that no animals died during the study. Herein, we could not evidence NO release that may affect amelioration of tissue damage and necrotic changes in the hepatocytes of tadalafil group. Another limitation is that treatment duration was relatively short. In future studies, we may plan to extend the period to three weeks with chronic applications.

CONCLUSION

In conclusion, our results initiated that the high-dose and long-term administration of tadalafil increased oxidative and inflammatory responses in liver tissue.

Disclosures

Ethics Committee Approval: The study was approved by the Kahramanmaraş Sütçü İmam University Faculty of Medicine Animal Experiments Local Ethics Committee (No: 2020/02/03, Date: 27/02/2020).

Authorship Contributions: Concept: D.A.U., D.A.A.; Design: D.A.U., D.A.A.; Supervision: D.A.U., A.U.; Funding: D.A.U.; Materials: D.A.U., D.A.A., M.S.; Data Collection or Processing: D.A.U., D.A.A., M.S.; Analysis or Interpretation: D.A.A.; Literature Search: D.A.U., D.A.A., M.S.; Writing: D.A.U.; Critical review: D.A.U., A.U.

Conflict of Interest: No conflict of interest was declared by the authors.

Informed Consent: Written informed consent was obtained from all patients.

Use of AI for Writing Assistance: Not declared.

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