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Research Article
Ameliorating Effect of Propofol on Cisplatin-Induced Liver and Kidney Damage in Rats

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Abstract

Background and Objective: Cisplatin is among the most frequently used in solid organ cancers. However, it can be dose-limiting, especially due to its side effects on the kidney and liver. This study aims to examine the protective properties of propofol from cisplatin-induced kidney and liver damage. **Materials and Methods:** A total of 24 adult female rats were included in the study and divided into 3 groups, each containing 8 rats. The 1st group was the control group. The 2nd group was administered 2.5 mg/kg/day of cisplatin 2 days a week for 4 weeks. In the 3rd group, as for that, in addition to the 2nd group, 10 mg kg^{-1} of propofol daily was injected intraperitoneally for 4 weeks. Blood-urea nitrogen (BUN), Alanine Aminotransferase (ALT), malondialdehyde (MDA), which was used for oxidative stress parameter and inflammatory cytokines (Tumor Necrosis Factor (TNF)-α and Interleukin (IL)-6) were analyzed in all three groups. In addition to these, all groups were examined histopathologically. **Results:** A significant increase was observed in BUN, IL-6, MDA and TNF-α levels after cisplatin treatment. With the addition of propofol to the treatment, on the other hand, a significant decrease was obtained in all parameters. Histopathologically, it was observed that propofol reduced the damage caused by cisplatin in liver and kidney tissue and its cytoprotective property was observed immunohistochemically through the increase in HSP-70 protein. **Conclusion:** Consequently, propofol has protective properties from cisplatin-induced nephrotoxicity and hepatotoxicity. It not only reduces oxidative stress and inflammation but also reverses damage in tissue through the increase of HSP-70.

Key words: Cisplatin, propofol, nephrotoxicity, hepatotoxicity, HSP-70, TNF-α, IL-6

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Cisplatin (cis-Diamminedichloroplatinum), an inorganic, water-soluble, alkylating agent, was first synthesized in the laboratory in 1844. This drug is used in the treatment of many different types of cancer, especially lung, testicular, bladder, head and neck cancer and shows its effect by covalently binding to DNA[1]. While cytotoxic drugs can have side effects that are quite dangerous, cisplatin is a very efficient chemotherapy treatment. When used at large dosages to treat aggressive tumours, cisplatin becomes more hazardous[2]. Diffuse cytotoxicity is the most serious adverse effect of chemotherapy drugs. Nephrotoxicity and hepatotoxicity are two of the many adverse effects that may significantly affect essential bodily processes. They are the main obstacles preventing the clinical use of cisplatin, thus[3,4]. Although medical interventions aim to lower mortality and morbidity, there appears to be a persistent issue[4]. Despite having strong anti-cancer properties, the severe side effects of cisplatin during treatment, such as ototoxicity, neurotoxicity, nephrotoxicity and myelosuppression, restrict the drug's therapeutic applicability[5-9]. Most of the research that examined the relationship between cisplatin dosage and toxic side effects discovered that there was a correlation between the total dose of cisplatin and toxic side effects. The liver and haematological system are where this is most noticeable. On the contrary hand, hepatotoxicity has been shown to happen with a single dosage or modest recurrent doses[5].

Cisplatin has found widespread use in cancer treatment and has many dose-limiting side effects. Cisplatin detoxifies largely in the liver following the kidneys during the excretion of cytotoxic metabolites. These side effects require close monitoring with a frequency of 28-36% of nephrotoxicity and less frequent hepatotoxicity[10,11]. A decrease in glomerular filtration rate is observed after treatment in approximately 1 in 3 patients[12]. Although the underlying mechanism of cisplatin-induced nephrotoxicity (CIN) is not fully understood. Oxidative stress plays an important role. Due to the abundance of mitochondria in hepatocytes, some researchers have claimed that the destruction of these organelles represents the first stage of cisplatin hepatotoxicity[13]. The primary site of oxidative stress caused by cisplatin is the mitochondrion, which is affected by decreased levels of mitochondrial protein-SH, calcium uptake inhibition and mitochondrial membrane potential and function[14]. Once cisplatin enters the cell, it damages mitochondrial and nuclear DNA and thus leads to the formation of reactive oxygen products (ROS). Lipid peroxidation, inflammation and hypoxia develop due to increased free oxygen and hydroxyl radicals[15,16]. This leads to kidney damage, an increase in creatinine and blood urea nitrogen (BUN) and a decrease in glomerular filtration[17]. Hepatotoxicity, which is often seen with low-dose repeated cisplatin therapy, may result from higher doses of cisplatin, which may be required for effective tumour suppression during intensive chemotherapy regimens[18,19]. While cisplatin-induced hepatotoxicity is less common, the underlying mechanism is oxidative damage and mitochondrial dysfunction. Histological analysis of liver parenchyma exposed to high-dose cisplatin reveals cytoplasmic changes, hepatocellular vacuolization and sinusoidal dilatation, especially in cells around the central vein[20]. An increase in Alanine Aminotransferase (ALT) and aspartate aminotransferase (AST) occurs due to liver damage[21].

Cis therapy causes lipid peroxidation, inflammation and hypoxia because it damages cell membranes, disrupts the proximal and distal tubules and elevates reactive oxygen species (ROS)[22,23]. Cis additionally leads to renal apoptosis and damage to the tubules which is ROS mediated[24]. Blood urea nitrogen (BUN) concentrations may increase as a result of renal tubular injury and serum creatinine levels may also be elevated[22]. On the contrary perspective, regulator cells following nephrotoxicity stimulated several inflammatory mediators and molecules[25,26]. Interleukin 1 beta, nuclear factor kappa beta and tumour necrosis factor-alpha all have crucial roles in the inflammatory processes driven on via Cis[25]. When proximal tubular cells are damaged by cisplatin, Heat Shock Protein 70 (HSP70) is produced, which triggers an immunological response which is TNF-α dependent[27]. Because of this, inflammatory mediators and their signalling molecules are crucial targets for the treatment of nephrotoxicity.

As of yet, nephrotoxicity has no specific therapeutic method. When taken with other chemical medications, however, therapy for Cis-induced nephrotoxicity may worsen kidney damage[28]. Short-term and/or low-volume hydration, magnesium replacement and forced diuresis with mannitol are currently used before and after treatment to prevent CIN. However, the development of dehydration after the increase in excessive diuresis is an undesirable side effect[29]. Therefore, more reliable and effective treatments are needed to prevent CIN and hepatotoxicity.

Propofol, an anaesthetic drug that has been used since 1977, is widely used both in the induction and maintenance of anaesthesia because it causes less nausea, vomiting and postoperative drowsiness compared to barbiturates[30,31]. It has also been shown to significantly reduce postoperative mortality in oncologic surgery compared to inhaled anesthetics[32]. This agent is also frequently used during chemotherapy and has been shown to cause an increase in

endothelial adhesion molecules and a decrease in toxic oxidative stress[33,34]. In severely ill patients, the systemic powerful sedative pharmaceutical propofol (2,6-diisopropyl phenol) is often used for the initiation and management of anaesthesia and sedation[35]. Propofol's biochemical composition, which includes a phenolic hydroxyl group, is similar to the composition of the natural antioxidant a-tocopherol (vitamin E). Investigations both *in vivo* and *in vitro* have shown that this phenolic chemical composition plays a role in propofol's antioxidant effect[36]. In numerous articles where free radicals are formed, such as liver/brain microsomes and rat liver mitochondria, propofol has been discovered to have the capacity to prevent the generation of lipid peroxides[37-39]. Additionally, it has been shown that rats' *in vivo* red cell antioxidant capacity is increased by propofol[40]. The preventive effect of propofol against CIS-induced nephrotoxicity and hepatotoxicity has not, however, been studied in depth. Therefore, in this investigation, the therapeutic effects of propofol were evaluated against rat liver and kidney damage brought on by CIS.

MATERIALS AND METHODS

Study area: The study was carried out at the Experimental Animals Application and Research Center, Demiroglu Bilim University, Istanbul, Turkey from March, 2021 to May, 2022.

Animals: A total of 24 adult female Wistar albino rats weighing an average of 200 g were utilized in this investigation. The caged animals were kept on a 12-hrs light/dark cycle at a mean temperature of 22±2°C. Throughout the experiment, they were fed and given water as needed. The National Institutes of Health's Guide for the Care and Use of Laboratory Animals was followed for all studies (USA). The Animal Research Ethics Committee approved this (Ethical Number: 10211005). Except where otherwise noted, all medications used in the research were purchased from Sigma-Aldrich Inc.

Experimental protocol: For the investigation, a total of twenty-four female rats were used. There were three equal subgroups formed from them. The control group was Group 1 (n = 8) and no therapy was given to them. A total of 20 mg kg^{-1} of cisplatin was administered intraperitoneally (ip) twice a week for 4 weeks to Group 2's eight individuals, along with 1 mL/kg/day of 0.9 NaCl (saline)[41]. Group 3 (n = 8) was subjected to the same concentration of cisplatin and administered with propofol (Propofol, Abbott, 10 mg mL^{-1}) daily at a dose of 10 mg kg^{-1} ip for 4 weeks, as previously reported by Tan *et al.*[42]. During the research, two rats in group 2 died. In rats administered cisplatin with propofol, there were no mortalities.

All animals were given a high-dose anaesthetic for euthanasia after the experiment, which included Ketamine (100 mg kg^{-1}, Ketasol, Richter Pharma) and xylazine (50 mg kg^{-1}, Rompun, Bayer). Then, cervical dislocation was used to kill the animals. Through cardiac puncture, blood samples were taken and utilized for biochemical investigations. Organ tissue samples from the liver and kidneys were collected for histopathology and biochemical analysis.

Measurement of BUN: An automated analyzer device was used to conduct spectrophotometric blood urea nitrogen (BUN) measurements. Results for BUN were given in mg dL^{-1}.

Measurement of plasma TNF-α, IL-6 and ALT levels: Utilizing commercialized Enzyme-Linked Immunosorbent Assay (ELISA) kits (SunRed-China, Shandong, China), the concentrations of TNF-α, IL-6 and ALT in plasma were evaluated.

Determination of lipid peroxidation (MDA): As previously mentioned by Wichterman *et al.*[43], the Thiobarbituric acid reactive substances (TBARS) were employed to identify lipid oxidation by monitoring MDA plasma levels. The TBARS reagent, trichloroacetic acid and plasma sample were combined and the combination was then incubated at 100°C for 1 hr. The materials were then centrifuged at 3000 rpm for 20 min after cooling on ice. The absorbance of the supernatant was measured at 535 nm after centrifugation. Tetra ethoxy propane was used for calibration and MDA concentrations were represented as nmol g^{-1} protein.

Liver and kidney biochemical analysis: The liver and kidney were quickly examined for biochemical examination after decapitation. The frozen tissue specimens were homogenized in five volumes of phosphate-buffered saline (PBS) utilizing a glass homogenizer (pH 7.4). Using this technique, the amount of tissue level was multiplied by five. The supernatant was obtained after 15 min of centrifugation at 5000 rpm. Bradford's technique was used to calculate the total protein. Standard bovine serum albumin was utilized in this procedure. A rat HSP-70-specific ELISA kit (SunRed-China, Shandong, China) that is readily available was used to assess the amounts of HSP-70 in the liver and kidney tissue supernatants.

Histopathological examination of liver and kidney: Ketamine (100 mg kg^{-1}, Alfamine®, Alfasan International B.V., Holland) and xylazine (10 mg kg^{-1}, Alfazyme®, Alfasan International B.V., Holland) were used to anaesthetize all animals. Four percent formaldehyde was then perfused into 0.1 M phosphate buffer saline (PBS) for histological and immunohistochemical examination. The tissues were formalin-fixed, sections were cut at a thickness of 4 µm and dyed with hematoxylin and eosin. Using an Olympus C-5050 digital camera and an Olympus BX51 microscope (Olympus, Tokyo, Japan), each tissue segment was photographed and subsequently inspected.

The blind observer used a computerized image analysis system (Image-Pro Express 1.4.5, Media Cybernetics, Inc., USA) to evaluate morphology in 10 microscopic fields for each segment at ×20 magnification. All the rats used in the research underwent semi-quantitative kidney histopathological scoring analysis for each of the following criteria from kidney sections: Tubular epithelial necrosis, luminal necrotic debris, tubular dilatation and interstitial inflammation[44]. The following 5-point scale was used to assess these parameters: 0-5% = score 0, 6-20% = score 1, 21-40% = score 2, 41-60% = score 3, 61-80% = score 4 and 81-100% = score 5.

To determine the degree of congestion, necrosis and cytoplasmic vacuolization as well as sinusoidal and central vasodilation, liver sections underwent a semi-quantitative investigation of liver damage. Histological photomicrographs, 5 sections and 10 fields in each section at ×20 magnification were examined for each rat following the liver histopathological scoring method[45]. Data were graded as follows: 0-5% = 0, 6-20% = 1, 21-40% = 2, 41-60% = 3, 61-80% = 4 and 81-100% = 5.

Statistical analysis: The SPSS Statistics for Windows, Version 15.0 (IBM Corp. Armonk, NY) program was used for all statistical analyses. One-way Analysis of Variance (ANOVA) was used for evaluating parametric variables and *post hoc* Bonferroni correction was done for subgroup evaluation. Also, a comparison of the groups of nonparametric variables was determined by the Mann-Whitney U Test. Whether the Shapiro-Wilk Test determined the normal or non-normal distribution of variables. Variables were presented as Mean Values±Standard Error of the Mean (SEM) and $p<0.05$ was considered statistically significant.

RESULTS

Effect of propofol on cisplatin-induced kidney and liver dysfunction: Kidney function tests are significantly more common as a result of cisplatin-induced renal damage. The BUN level in the cisplatin-only group significantly increased as compared to the healthy control group ($p<0.01$). Plasma ALT levels were significantly higher in the cisplatin group than they were in the control group ($p<0.01$). BUN levels were considerably lower in the group receiving 10 mg/kg/day of propofol than it was in the treated group with only cisplatin ($p<0.001$) when compared to the cisplatin-only group, plasma ALT concentrations in the propofol treatment group significantly decreased ($p<0.01$). All results were presented in Table 1.

Effect of propofol on plasma MDA, TNF-α and IL-6 levels: When cisplatin was administered, plasma levels of MDA, a marker of oxidative stress and TNF-α and IL-6, markers of inflammation, both increased significantly when compared to the control group ($p<0.01$ for TNF-α, $p<0.001$ for MDA and IL-6). The increases in these three variables caused by cisplatin were reduced by propofol administration (Table 1).

Effect of propofol on the histopathological alterations in kidney and liver tissue induced by cisplatin: Histopathological examination of kidney and liver tissue sections revealed cellular damage with cisplatin

Table 1: Effect of propofol on biochemical analysis results related to cisplatin-induced kidney and liver dysfunction

Parameters	Normal control	Cisplatin+saline	Cisplatin+10 mg kg^{-1} propofol
MDA (nM)	53.2±4.1	163.5±21.5**	77.2±9.3#
TNF-alfa (pg mL^{-1})	19.3±2.5	85.4±4.6*	39.2±2.7#
IL-6 (pg mL^{-1})	11.2±0.3	713.3±28.1**	243.9±22.3##
ALT (IU L^{-1})	42.1±5.7	64.9±7.2*	56.3±3.5#
BUN (mg dL^{-1})	45.3±5.8	102.7±11.9*	42.7±5.1##
Liver HSP-70 (mcg mg^{-1} protein)	18.4±1.6	27.5±1.8*	41.1±4.7##
Kidney HSP-70 (mcg mg^{-1} protein)	9.5±2.2	13.4±2.7*	28.4±1.9#

Results were presented as Mean±SEM. Statistical analyses were performed by one-way ANOVA Test. *$p<0.01$, ** $p<0.001$ (different from control group), #$p<0.01$ and ##$p<0.001$ (different from cisplatin and saline group)

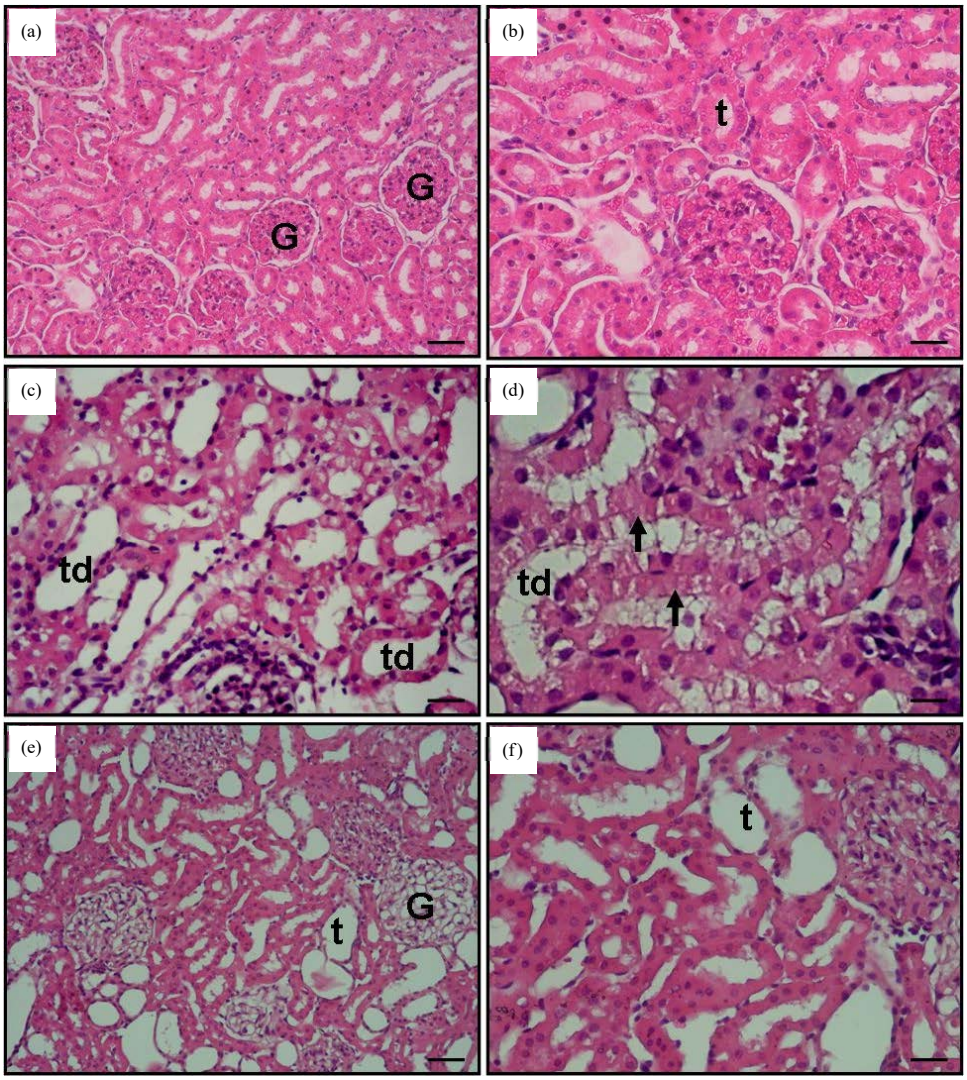

Fig. 1(a-f): Kidney histopathology H&E (×10 and ×40 Magnification), (a-b) Normal kidney tissue (control group), glomeruli (G) and tubules (t), (c-d) Cisplatin+saline group, kidney sections have tubular cell necrosis (arrow) and tubular dilatation (td) and (e-f) Cisplatin+propofol group, tubular dilatation and tubular cell necrosis were decreased

administration (Fig. 1-2). In the cisplatin-treated group, the histopathological score of tubular epithelial necrosis, luminal necrotic debris, tubular dilatation and interstitial inflammation increased significantly (Fig. 3). With propofol treatment, there is a significant decrease in kidney tissue damage (Fig. 1). The liver histopathological scoring system was used to evaluate sinusoidal and central vein dilatation, congestion, necrosis and cytoplasmic vacuolization and it was discovered that cisplatin treatment led to a significant increase in all scores compared to the control group (Fig. 4). In the propofol group, the liver parenchyma was seen to be partly intact and the overall liver histopathological score was much lower than in the cisplatin group (Fig. 2).

Effect of propofol on levels of Hsp-70 in kidney and liver tissue: The Hsp-70, a protein that works to preserve the cell's protein homeostasis against external stresses, was statistically higher in the liver tissue and the kidney tissue in the cisplatin-treated group compared to the control group ($p<0.01$) (Table 1). It was also significantly higher in the propofol-treated group compared to the cisplatin-treated group (kidney HSP-70, $p<0.01$ and Liver HSP-70, $p<0.001$) (Table 1).

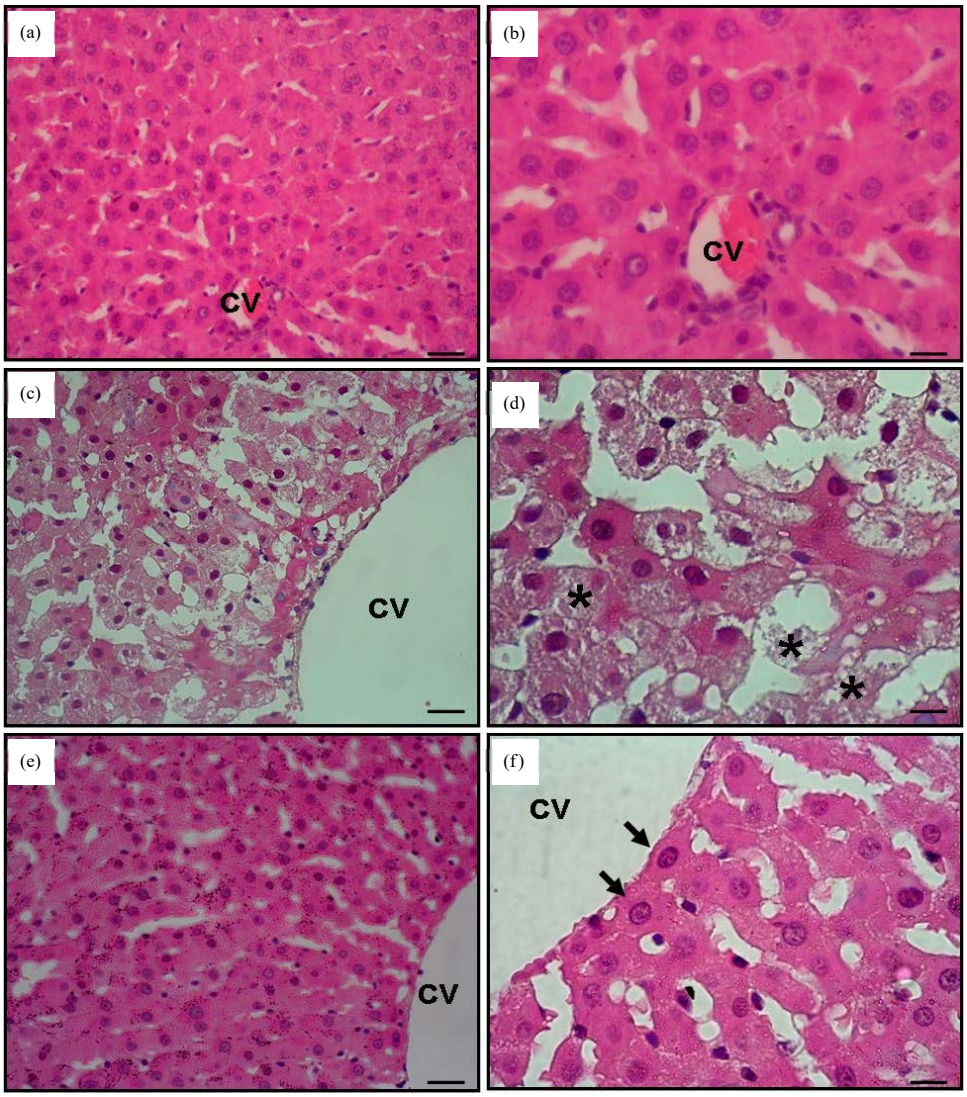

Fig. 2(a-f): Liver histopathology H&E (×10 and ×40 Magnification), (a-b) Normal liver tissue (control group), (c-d) Cisplatin+saline group, liver sections have vacuolar changes of pericentral hepatocytes, central venous (cv) dilatation and hepatocyte necrosis (asterisk) and (e-f) Cisplatin+propofol group, central venous dilatation and hepatocyte necrosis were decreased (arrow)

DISCUSSION

Despite several encouraging research, cisplatin-induced nephrotoxicity and hepatotoxicity still occur frequently. There have been several attempts to prevent or repair the oxidative damage that cisplatin causes to tissues and organs. While being an anaesthetic, propofol has been studied for this treatment because of its anti-inflammatory and antioxidant characteristics. In this investigation, we sought to demonstrate, for the first time in the literature, the protective role of propofol against cisplatin-induced nephrotoxicity and hepatotoxicity, particularly via the elevation of Hsp-70 and the decrease of MDA, IL-6 and TNF-α, by evaluating with microscopic and biochemical measurements.

Cisplatin is a significant chemotherapeutic molecule that has been employed for many years in the chemotherapy of cancer. The use of this chemical is restricted due to some of its negative effects, particularly those on the liver and kidneys. Plasma levels of BUN and creatinine are elevated as a result of kidney damage induced by cisplatin and the glomerular filtration rate decreases[46]. The elevation in plasma AST, ALT and ALP levels is essential in determining hepatotoxicity

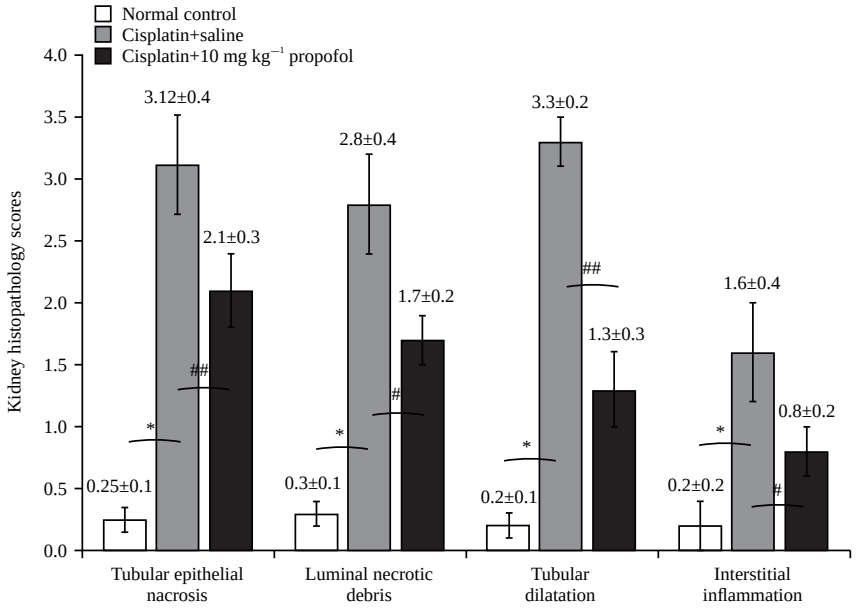

Fig. 3: Comparison of groups according to kidney histopathological scoring system

Results were presented as Mean±SEM, statistical analyses were performed by one-way ANOVA test, *p<0.0001 (different from control group), #p<0.05, ##p<0.001 (different from cisplatin+saline group), Y-axis: Kidney histopathology scores and X-axis: Kidney histopathology criteria

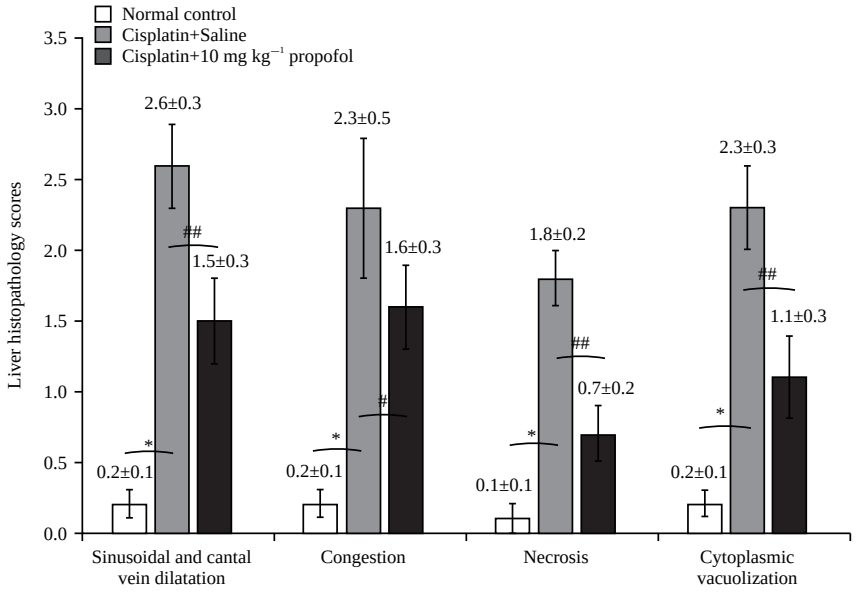

Fig. 4: Comparison of groups according to the liver histopathological scoring system

Results were presented as Mean±SEM. Statistical analyses were performed by one-way ANOVA test, *p<0.0001 (different from control group), #p<0.01, ##p<0.0001 (different from cisplatin+saline group), y-axis: Liver histopathology scores and X-axis: Liver histopathology criteria

in terms of liver damage[47]. In line with the literature, cisplatin-treated rats in our investigation exhibited nephrotoxicity and hepatotoxicity and BUN and ALT levels significantly increased in comparison to the control group. The administration of propofol to the treatment resulted in a significant drop in both variables. This mechanism may be associated with propofol's antioxidant characteristics. Propofol has been found to inhibit cisplatin-induced cytotoxicity by a different mechanism in separate research[48]. The mechanism in that research relies on propofol's ability to suppress the intercellular communication of gap junction that is created in different connexins. In a different investigation, pretreatment with propofol had a protective effect against orthotopic liver autotransplantation (OLAT) for the kidneys. Increased

expression of nuclear Nrf2 was one possible mechanism for this outcome[49]. According to another study, propofol prevents the liver from I/R damage by maintaining mitochondrial activity, which may be related to the regulation of MPTP and GSK-3b[50]. Propofol's antioxidant ability, which was supported by different research, was unable to reduce liver damage and enhance liver regeneration in rats following acetaminophen-induced liver damage[51]. Another study's findings show that, in a model of lipopolysaccharides (LPS) induced neonatal acute lung injury, propofol reduces LPO levels due to its antioxidant properties, whereas, exposure to LPS significantly increases LPO formation by producing free radicals[52]. In addition, Shokrzadeh *et al*.[53] hypothesized that propofol reduced the oxidative stress and mitochondrial dysfunction brought on by Methamphetamine (METH), which in turn reduced METH's potential to cause neurotoxicity[53]. In that respect, this investigation was the first to demonstrate propofol's protective ability against both cisplatin-induced nephrotoxicity and hepatotoxicity.

It is unclear yet what causes cisplatin to induce nephrotoxicity and hepatotoxicity. However, two significant underlying components are oxidative stress and the inflammatory process. In research by Sahu *et al*.[54], decreased nitric oxide levels in kidney tissue following cisplatin therapy led to afferent arteriole vasoconstriction and decreased glomerular capillary ultrafiltration. Furthermore, it has been shown in investigations by Aydogan *et al*.[55] and Somani *et al*.[56] that the cisplatin-induced elevation in reactive oxygen products causes a decline in ultrafiltration. By promoting lipid peroxidation, active oxygen products including superoxide anion and hydroxyl radicals harm renal tissue[57,58]. In our investigation, rats administered cisplatin had significant increases in MDA, an indication of lipid peroxidation, which thereafter reached levels in the healthy control group following propofol administration. These results agreed with earlier studies utilizing different antioxidant uptakes[59-61]. Recent *in vitro* research has shown that propofol effectively inhibited apoptotic signalling and prevented the apoptotic death of cardiac cells when they were exposed to lethal stimuli[62-64]. In studies on cardiac tissues, propofol reversed the shift of mitochondrial permeability and reduced the damage caused by ischemia-reperfusion[65-68]. These findings provide credence to the claim that propofol may stop the progression of oxidative damage. Due to its molecular structure like that of the naturally occurring antioxidant α-tocopherol (vitamin E), propofol's antioxidant mode of action may be associated. Following cisplatin therapy, an elevation in the inflammatory markers TNF-α and IL-6 also leads to liver and kidney damage[69]. Propofol has been shown to inhibit the elevation of IL-6, IL-8 and TNF-α in research where cardiopulmonary bypass was linked to a systemic inflammatory response, however, this protective effect was not found to be significant[70]. The ability of propofol to inhibit the production of lipid peroxides[71], induce the expression of the antioxidant enzyme heme oxygenase-1[6], inhibit the expression of Nitric Oxide Synthase (NOS) and stabilize the mitochondrial membrane may also contribute to its antioxidant activities[72]. Circulating immune cells generate and release TNF-α and IL-1β, which act as early immune system response controllers for the development of inflammatory cascades[73,74]. The TNF-α and IL-1β are thought to have a role in the early stages of the inflammation that results from the cisplatin-induced liver and kidney damage. The anti-inflammatory cytokine IL-4, however, may be increased by propofol[75] in the livers of rats with sepsis. Accordingly, increasing liver levels of pro-inflammatory TNF-α and IL-1β and anti-inflammatory IL-4 is one of the potential pathways behind propofol's inhibitory effects on hepatic inflammation in septic rats. It has been shown that propofol lowers TNF-α and IL-1β levels in the ischemic rat brain[76]. Propofol was shown to have inhibitory effects on TNF-α expression in lipopolysaccharide (LPS)-activated macrophages in prior research[77]. Another research team recently found that propofol had inhibitory effects on the production of hepatic and systemic IL-6 in rats with sepsis[78]. In our investigation, the cisplatin-induced inflammation that was accompanied by an increase in TNF-α, IL-6 and MDA was significantly suppressed in the propofol-treated group.

Endothelial cells produce adhesion molecules and leukocyte-endothelial adhesion increases as a result of vascular endothelial damage brought on by cisplatin[79]. Serious degeneration of both glomeruli and tubules is caused by the reduced release of NO, a chemokine crucial for maintaining vascular homeostasis, from injured endothelium tissue. Another study examining the impact of propofol pretreatment on orthotopic liver autotransplantation (OLAT)-induced remote kidney injury found that the OLAT group experienced significant histopathological kidney damage, including the formation of luminal debris, flattening of tubular cells, cellular vacuolization and loss of brush border. The renal morphological damage brought on by OLAT was significantly reduced by pretreatment with a high dosage of propofol, which also caused a small expansion of the tubules and flattened the cells that line the tubular epithelium[49]. In this

investigation, when kidney tissue was examined under a microscope, rats administered cisplatin had much more tubular epithelial necrosis, luminal necrotic debris, tubular dilatation and interstitial inflammation than the control group. All four variables showed a significant decline after propofol administration. Our study's findings demonstrate that cisplatin also causes significant liver damage. Intracellular enzymes AST and ALT move from damaged hepatic cells or alterations in their permeability brought on by cisplatin therapy, which raises their levels in plasma[80]. In research evaluating the impact of propofol on a halothane-induced liver injury model, the morphological analysis revealed total loss of architecture and severe parenchymal necrosis in the halothane group, while rats receiving halothane+propofol exhibited only moderate histological abnormalities[81]. In line with previous research in the literature[82], we found that hydropic degeneration and associated damage occur in hepatocytes when liver tissue was examined histopathologically after cisplatin treatment. With the administration of propofol, it was shown that the signs of necrosis, cytoplasmic vacuolization and sinusoidal and central venous dilatation significantly decreased. The current research was the first to demonstrate histopathologically that propofol repaired kidney and liver damage induced by cisplatin.

In stressed cells, Heat Shock Proteins (HSPs) are essential for preserving protein homeostasis. The most crucial member of this group, Hsp-70, guards the cell against protein misfolding, aggregation, or disruption brought on by proteotoxic damage. Numerous cytoprotective mechanisms for cell survival may be activated by renal tubular cells in response to oxidative stress and inflammation[83]. One of the cellular defence systems against cellular stress is the heat shock protein response. The HSP70 proteins seem to guard against the denaturation of essential proteins under stress conditions brought on by chemical toxins[83]. In an experimental kidney damage model, the HSP response has been documented[84]. Additionally, HSPs were shown to be crucial in the development of cisplatin-induced nephrotoxicity[85]. HSP was first thought to be an intracellular chaperone, although anti-inflammatory properties have also been identified[86]. In this investigation, we demonstrated that similarly to other studies, Cis-induced nephrotoxicity and hepatotoxicity increased HSP70 levels. Additionally, it was shown that under inflammatory conditions, there were positive associations between TNF-α, IL-1β and HSP70 levels[87].

Studies published in the literature have shown that the Hsp family functions as a molecular chaperone and has cytoprotective characteristics[88,89]. Under physiological circumstances, this protein is at baseline levels, but it elevates in response to heat stress, oxidative stress, or cytotoxic therapies[90]. In our investigation, the cisplatin-treated group showed a significant increase in Hsp-70 in both liver and kidney tissue. With the administration of propofol, Hsp-70 in the liver and kidney tissues increased to a level that was around three times the baseline level. This increase in Hsp-70 might be the cause of the liver and kidney tissue's summed histopathological scores considerably decreasing. According to research published in the literature, an increase in HSP-70 protein after valproic acid therapy has a protective effect against blood-brain barrier degradation and brain injury caused by subarachnoid hemorrhage[91]. Another research showed that propofol had a protective effect against blood-brain barrier damage brought on by hypoxia. In that study, propofol did not, however, enhance Hsp-70 levels. The elevated expression of Hsp-27 and Hsp-32 in astrocytes and microglial cells following propofol treatment was thought to be the reason for the aforementioned study[92]. Thiopentalin, a drug used to treat cerebral hypertension, has been found to provide cytoprotection by boosting Hsp-70 expression in T-lymphocytes[93]. By reducing NO production and boosting expression of Hsp70 by inducing the synthesis of Hsp70 at both the transcriptional and translational levels, propofol pretreatment may prevent anoxia-reoxygenation damage to neurons, according to Huang *et al.*[94]. It may be concluded based on these findings from the literature that Hsp increase may have protective effects against various stress inducers in different tissues. As a result, our investigation was the first to demonstrate that the liver and kidney tissue damage caused by cisplatin could be prevented by enhancing Hsp-70 protein via propofol treatment.

CONCLUSION

Through the antioxidant and anti-inflammatory characteristics of propofol, we were able to demonstrate in this investigation its protective effect against cisplatin-induced nephrotoxicity and hepatotoxicity. More crucially, our research showed that propofol treatment can increase Hsp-70 and decreases MDA, IL-6 and TNF-α levels and may repair the histopathologically shown damage to the liver and kidney tissue caused by cisplatin through this mechanism. These findings support the use of propofol to treat cisplatin-induced liver and kidney damage. Nevertheless, future research should focus on the underlying molecular and cellular pathways of propofol's established preventive effect.

SIGNIFICANCE STATEMENT

Cancer is the first cause of death worldwide. Cisplatin is the first chemotherapeutic agent used in cancer treatment and hepatotoxicity and nephrotoxicity are the dose-limiting side effects of cisplatin. Studies showed that propofol has an anti-oxidative effect via inhibiting lipid peroxidation. With experimental animal studies, the newest molecules and approaches can be investigated to determine effectiveness in the treatment of many diseases. Cisplatin intraperitoneal injection procedure was used to obtain cisplatin-induced hepatotoxicity and nephrotoxicity in this experimental study. The potential protective effect of propofol in reducing oxidative stress and preventing hepatotoxicity and by nephrotoxicity investigating liver and kidney histopathology and serum biomarkers was evaluated. This study aimed to investigate the tissue damage in the kidney and liver due to cisplatin and the ameliorating effects of propofol on nephrotoxicity and hepatotoxicity through the levels of Hsp-70, MDA, IL-6 and TNF-α. This work can lead to further investigation and eventually clinical trials involving human participants.

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