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Mitigating Cisplatin-Induced Nephrotoxicity in Rats: A Comparative Study of Ambroxol and Coenzyme Q10 Effects

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Abstract

BACKGROUND/AIMS: Cisplatin (Cis), used in the treatment of various types of cancer, causes serious kidney damage. In this study, the protective effects of ambroxol (Amb) and coenzyme Q10 (CoQ10) were examined to reduce the toxic effect of Cis on the kidneys.

MATERIALS AND METHODS: Adult female rats were divided into 6 groups; control, Cis, Amb, CoQ10, Cis + Amb and Cis + CoQ10. The rats were sacrificed at the end of the 7-day experimental period. Blood and tissue samples were taken for biochemical and histomorphological examinations. Biochemically, urea and creatinine were analyzed from serum, and TNF-α and malondialdehyde (MDA) analyses were performed from serum and tissues. Histologically, H&E and immunohistochemical caspase-3 staining analyses were performed.

RESULTS: Serum urea, creatinine, TNF-α, and MDA (both serum and tissue values) were quite high in the Cis group, and there was a significant difference between them and all other groups ($p<0.05$). As a result of biochemical analyses, no significant difference was detected between Cis + Amb and Cis + CoQ10 ($p>0.05$). Under light microscopy, the Cis group showed the most damage. It was observed that Cis + Amb and Cis + CoQ10 groups reduced kidney damage. There was a significant difference between the Cis-only group and the Cis + Amb group in terms of glomerular and tubular damage ($p<0.05$). In the Cis group, caspase-3 expression was significantly increased compared to the other groups, and a statistical difference in caspase-3 expression was found between the Cis + Amb and Cis + CoQ10 groups ($p<0.05$).

CONCLUSION: Ambroxol and coenzyme Q10 were found to be effective in reducing kidney damage caused by cisplatin.

Keywords: Cisplatin, kidney, urea, TNF-α, caspase-3

INTRODUCTION

Cisplatin (Cis), an anticancer agent, is a platinum-based metal-binding agent. It is used therapeutically in most types of cancer, such as lung, testicular, ovarian, and breast cancer.[1] The major factors limiting the use of Cis include nausea, vomiting, nephrotoxicity, hepatotoxicity, neurotoxicity, and ototoxicity.[2] Acute kidney injury due to nephrotoxicity is seen in 20-30% of patients.[3] These toxic effects caused by Cis may occur due to inflammation, oxidative stress, and apoptosis.[1,2] When Cis is taken into the cell, it becomes positively charged and it binds to DNA, RNA, and proteins. By binding to purine bases, it prevents DNA replication and transcription by causing structural defects in the form of single, intra-chain cross-links and inter-chain cross-links. The cell cycle is arrested in the G2 phase and apoptosis occurs.[4] Cell and tissue damage caused by increased reactive oxygen species (ROS) due to Cis can be reduced by substances with high antioxidant potential, such as silymarin, gallic acid, selenium, and vitamin E.[5-7] Since Cis is

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excreted through the kidneys, the structural changes in the kidneys due to the drug are evident. Studies have shown kidney damage such as tubular damage, cytoplasmic vacuole formation, cell degeneration, and mononuclear cell infiltration after Cis injection.[8,9]

Ambroxol (Amb) is an agent used in mucus-related respiratory diseases with a mucolytic effect. Surfactant facilitates mucus outflow by regulating protein production and increasing ciliary movement.[10] It has also been reported to have antioxidant and anti-inflammatory effects.[11,12] Bishr et al.[13] demonstrated the positive effect of ambroxol on the kidneys in Cis nephrotoxicity. Liu et al.[14] demonstrated that Amb alleviated kidney damage caused by cardiopulmonary bypass.

Coenzyme Q10 (CoQ10), also known as ubiquinone, is a lipid-soluble molecule that is primarily produced within the human body. It participates in the transfer of electrons and protons within the mitochondrial respiratory chain. Alongside Amb, it possesses antioxidant and anti-inflammatory qualities, shielding biomolecules interacting with reactive oxygen radicals and lipoperoxides.[15] Some studies suggest that CoQ10 may be effective in kidney damage caused by Cis.[16,17]

Although there are many studies on the effects of Cis on the kidney, there are few studies showing the protective effects of Amb and CoQ10.[13,15,16] In this study, the aim was to examine the possible protective effects of Amb and CoQ10 against the toxic effects of Cis on the kidneys, light microscopically, immunohistochemically, and biochemically.

MATERIALS AND METHODS

This study was approved by the Near East University Local Ethics Committee for Animal Experiments (approval number: 2020/11, date: 27.11.2020). Animals were kept in plastic cages at optimal temperature (22±1 °C) and in a 12-hour light, 12-hour dark environment. They were provided with water and feed ad libitum throughout the experiment.

Drugs

In the study, a cytotoxic drug containing 50 mg/100 mL Cis (Koçak-İstanbul), a mucolytic and expectorant drug containing 30 mg/5 mL Amb hydrochloric acid with the trade name Sekrol, and CoQ10 capsules containing 30 mg of active ingredient with the trade name Webber Naturals were used. We determined the doses of 50 mg/kg Amb and 10 mg/kg CoQ10 administered to the rats based on doses used in previous studies. In a study investigating Amb against Cis-induced hepatorenal toxicity, it was reported that doses of 35 and 70 mg/kg Amb reduced toxicity.[13] In another study, a protective effect of 50 mg/kg Amb was observed against acetaminophen-induced hepatotoxicity.[18]

The ameliorative effect of 10 mg/kg CoQ10 in reducing Cis-induced damage in various organs has been reported in numerous studies.[19] Taking these references into account, we used a 50 mg/kg dose of Amb and a 10 mg/kg dose of CoQ10 in our study.[20]

Animals and Experimental Design

Thirty-six female Wistar albino rats, each weighing approximately 250-300 grams, were used in the experiment. The investigation was conducted at a single center, utilizing a randomized, controlled, single-blind design (analyst remained blinded of the treatments assigned to the rats). The rats were divided into six groups; each containing six rats. Chemical agents were applied to the rats as shown in Table 1, and at the end of the 7th day, the rats were euthanized under anesthesia.

Collection of Blood and Tissue Samples

At the end of the experiment, all rats were sacrificed. Kidney tissue was taken from the subjects through an incision in their abdomen, for both biochemical and histopathological examinations. After samples were taken for biochemical analysis, erythrocytes were removed by perfusion with cold physiological saline (0.9% NaCl).[21] Subsequently, it was dried with filter paper and divided into two separate parts. Then, the specimen to be used for biochemical analyses was placed in sample containers filled with 50 mM phosphate buffer (pH 7.4).[22] Tissue pieces to be used for histological examination were fixed with 10% formaldehyde.

Measurement of TNF-α, an Inflammation Marker

TNF-α analysis, one of the pro-inflammatory cytokines, was measured with rat-specific ELISA test kits (ElabScience, Cat. No: EEL-R0019, Lot No: UQC179VSYP) using blood samples and tissue homogenates. The manufacturers' instructions were followed to perform the assay. MW-12A Microplate Washer and MR-96 Microplate Reader (Mindray, Shenzhen, China) were used during assay procedures. The results were given as pg/mL in plasma and pg/mg protein in tissues.

Determination of Lipid Peroxidation Level

Malondialdehyde (MDA), the most stable lipid peroxidation product, was measured in blood samples and tissue homogenates. Cayman brand test kit (Cat. No: 10009055, Lot No: 613569) was used for MDA analysis. The test was performed using the spectrophotometric method

Table 1. The timeline illustrates the schedule of drug administrations and the sacrifice day across all groups during the 7-day experimental period

Day	0	1	2	3	4	5	6	7
Control (C)	Saline i.p.	-	-	-	-	-	-	-
Cisplatin (Cis)	-	Cis i.p. (7 mg/kg)	-	-		-	-	-
Ambroxol (Amb)	-	Amb p.o. (50 mg/kg, BID)	Amb p.o. BID	Amb p.o. BID	Amb p.o. BID	Amb p.o. BID	Amb p.o. BID	Amb p.o. BID
Coenzyme Q10 (CoQ10)	-	CoQ10 p.o. (10 mg/kg, BID)	CoQ10 p.o. BID	CoQ10 p.o. BID	CoQ10 p.o. BID	CoQ10 p.o. BID	CoQ10 p.o. BID	CoQ10 p.o. BID
Cis + Amb	-	Cis i.p. + Amb p.o. (50 mg/kg, BID)	Amb p.o. BID	Amb p.o. BID	Amb p.o. BID	Amb p.o. BID	Amb p.o. BID	Amb p.o. BID
Cis + CoQ10	-	Cis i.p. + CoQ10 p.o. (10 mg/kg, BID)	CoQ10 p.o. BID	CoQ10 p.o. BID	CoQ10 p.o. BID	CoQ10 p.o. BID	CoQ10 p.o. BID	CoQ10 p.o. BID
Sacrifice								**Day 7**

i.p.: Intraperitoneal injection, p.o.: Oral gavage, BID: Twice daily administration

based on the reaction with thiobarbituric acid at 100 °C in an acidic environment and measuring the absorbance of the reaction mixture at 530-540 nm.[23] The results were given as nmol/mL in plasma and nmol/mg protein in tissues.

Histological Procedures

The fixed tissues were passed through a tissue tracking device (Leica TP1020, Leica Biosystems Nussloch GmbH, Germany) and embedded in paraffin (Leica EG1150 H).[5] µm thick sections were taken with a microtome device (Leica RM2255), and H&E (Bancroft and Gamble 2008) staining was performed. Histomorphological examination of the sections was performed with a light microscope (Leica DM500) coupled with the Leica Microsystem Framework integrated digital imaging analysis system (Leica Application Suite version 3.0 Series 38132019 Leica ICC50 HD). Kidney tissue sections were evaluated in terms of glomerular damage, tubular damage, and mononuclear cell infiltration criteria. For each criterion, 10 different areas were scored as none (0), mild (1), moderate (2), and severe (3).[24] A mouse and rabbit-specific HRP/DAB (ABC) Detection IHC kit (ab64264) and a primary antibody, caspase-3 (ab4051), diluted 1:100, were used for immunohistochemical staining. Caspase-3 positivity in kidney tissue was evaluated using the ImageJ program.

Statistical Analysis

SPSS (IBM SPSS statistical version 26.0) software (SPSS Inc., Chicago, IL, USA) was used for statistical analyses. Data groups were compared using Kruskal-Wallis analysis followed by Mann-Whitney U tests. A $p<0.05$ difference was considered statistically significant.

RESULTS

Biochemical Results

The values of kidney serum urea, creatinine, TNF-α, and MDA, along with kidney tissue TNF-α and MDA, are presented in Tables 2-4.

Urea and creatinine levels, which indicate kidney function, were at normal levels in the control groups. When the values in Table 2 were examined, it was evident that the urea level in the group given only Amb was lower than that of the control group ($p<0.05$). Creatinine values were similar in the control, Amb, and CoQ10 groups. The Cis group experienced the most kidney damage. Urea and creatinine values were significantly higher than those of the other groups ($p<0.05$). Urea and creatinine levels decreased in the cis + Amb group. Although no decrease comparable to that caused by Amb was observed in the Cis + CoQ10 group, urea and creatinine values were observed to decrease.

When the serum MDA levels in Table 3 are examined to evaluate the lipid peroxidation levels of the experimental groups, the control groups are observed to have the lowest MDA values. The Cis group had the highest MDA value, and a statistical difference was observed between this group and all other groups ($p<0.05$). It has been determined that the antioxidant effects of Amb and CoQ10 compound reduce the level of MDA, which is a product of oxidative damage. Serum TNF-α values, one of the inflammation markers, were observed at lower levels in the control groups than in the Cis group ($p<0.05$). The Cis group had the highest TNF-α value. TNF-α value in the Cis + Amb and Cis + CoQ10 groups was lower compared to the Cis group ($p<0.05$). Amb and CoQ10 reduced Cis-induced inflammation (Table 3). Although no significant difference was detected between the Cis + Amb and Cis + CoQ10 groups, as seen in Table 3 ($p>0.05$), Amb was descriptively more effective in reducing TNF-α serum levels than CoQ10.

In terms of TNF-α levels measured in kidney tissue, the group with the highest TNF-α value among all groups was the Cis group. Statistical

Table 2. The rat blood sample parameters that reflect kidney damages. Results are represented as mean ± SD (n=6)

Mean ± SD	Biochemistry Parameters	
	Urea (mg/dL)	Creatinine (mg/dL)
Control	47.50±7.12^{a}	0.538±0.061^{h}
Ambroxol	31.83±3.25^{b,c,d}	0.551±0.047^{i}
Coenzyme Q10	42.66±6.28^{e}	0.550±0.037^{j}
Cisplatin	586.83±135.62^{a,b,e,f,g}	6.608±1.27^{h,i,j,k,l}
Cis + Amb	71.83±49.04^{c,f}	0.850±0.513^{k}
Cis + CoQ10	100.50±81.93^{d,g}	1.001±0.689^{l}
p values	0.000***	0.002**

The letters used in the table indicate statistically significant differences between groups. Groups not sharing the same letter have a significant difference at the $p<0.05$ level. Differences among control groups are excluded from this evaluation.
SD: Standard deviation, Cis: Cisplatin, Amb: Ambroxol, CoQ10: Coenzyme Q10.

Table 3. The rat blood sample parameters that reflect kidney damages. Results are represented as mean ± SD (n=6)

Mean ± SD	Serum TNF-α and MDA parameters	
	Serum TNF-α (pg/mL)	Serum MDA (nmol/mL)
Control	1253.60±234.42^{a}	41.41±17.61^{h,i,j}
Ambroxol	1265.90±377.91^{b}	39.41±19.18^{k,l,m}
Coenzyme Q10	1038.03±222.98^{c,d,e}	50.38±22.26^{n,o,p}
Cisplatin	3124.01±441.71^{a,b,c,f,g}	240.77±22.16^{h,k,n,r,s}
Cis + Amb	1633.03±437.04^{d,f}	185±22.26^{i,l,o,r}
Cis + CoQ10	1877.41±6^{e,g}	181.79±33.67^{j,m,p,s}
p values	0.001**	0.000***

The letters used in the table indicate statistically significant differences between groups. Groups sharing the same letter have a significant difference at the $p < 0.05$ level. Differences among control groups are excluded from this evaluation.
SD: Standard deviation, Cis: Cisplatin, Amb: Ambroxol, CoQ10: Coenzyme Q10, MDA: Malondialdehyde.

Table 4. The rat tissue sample parameters that reflect kidney damages. Results are represented as mean ± SD (n=6)

Mean ± SD	TNF-α and MDA parameters	
	Kidney TNF-α (pg/mg)	Kidney MDA (nmol/mg)
Control	20.14±16.73^{a,b,c}	2.15±1.05^{i,j,k}
Ambroxol	38.97±19.47^{d,e}	4.03±2.06^{l,m,n}
Coenzyme Q10	45.23±40.09^{f}	4.52±2.86^{o,p,r}
Cis	207.95±67.33^{a,d,f,g,h}	18.45±5.00^{i,l,o,s,t}
Cis + Amb	86.33±34.40^{b,e,g}	10.08±3.80^{j,m,p,s}
Cis + CoQ10	59.20±31.98^{c,h}	11.24±4.73^{k,n,r,t}
p values	0.000***	0.002**

The letters used in the table indicate statistically significant differences between groups. Groups sharing the same letter have a significant difference at the $p<0.05$ level. Differences among control groups are excluded from this evaluation.
SD: Standard deviation, Cis: Cisplatin, Amb: Ambroxol, CoQ10: Coenzyme Q10, MDA: Malondialdehyde.

significance was observed between the Cis group and all other groups ($p<0.05$). According to the data in Table 4, no statistical difference was observed between the Cis + CoQ10 group and the cis+amb group ($p>0.05$). However, the TNF-α value decreased more in the Cis + CoQ10 group compared to Cis + Amb. The MDA value, in Table 4, which shows lipid peroxidation in kidney tissue, was again detected at the highest level in the Cis group. The MDA value statistically significantly decreased in the Amb and CoQ10 treatment group compared to the Cis group ($p<0.05$).

Histomorphological Results

Kidney tissues from all experimental groups were evaluated under light microscopy, and the histological scoring results are summarized in Table 5.

When the histomorphological scoring data in Table 5 are examined, it is evident that the renal tissues in the Cis group exhibit higher levels of tubular necrosis, glomerular damage, and mononuclear cell infiltration. A statistically significant difference was observed between the Cis group and the control group ($p<0.05$). Cis + Amb or Cis + CoQ10 reduced the extent of renal damage compared to the Cis group. According to the data in Table 5, the Cis + Amb group significantly decreased tubular necrosis, and glomerular damage relative to the Cis group ($p<0.05$).

Under light microscopy, the control groups had a normal structure (Figure 1A). Vacuolization and degeneration in tubule cells, and intertubular and interglomerular hemorrhage foci were observed in the kidney tissue of the Cis group (Figure 1B). In some regions, it was found that the glomerulus spaces in the corpusculum renis completely disappeared (Figure 1C), and mononuclear cell infiltration was observed around the corpusculum renis (Figure 1D). It was determined that hemorrhage foci continued to be present in the tissue sections of the Cis + Amb and Cis + CoQ10 groups, but their amount decreased compared to the Cis group (Figures 1E, F).

Table 5. Scores of kidney histomorphological measurements in the rat groups. Results are represented as mean ± SD (n=6)

Mean ± SD	Histomorphological scoring criteria of the kidney		
	Tubular necrosis	Glomerular damage	Mononuclear cell infiltration
Control	$0.033\pm0.051^{a,b,c}$	$0.033\pm0.051^{k,l}$	$0.167\pm0.0408^{s,t,u}$
Ambrokxol	$0.050\pm0.054^{d,e,f}$	$0.000\pm0.000^{m,n,o}$	$0.050\pm0.054^{v,w,x}$
Coenzyme Q10	$0.066\pm0.051^{g,h,ı}$	0.083 ± 0.075^{p}	$0.050\pm0.083^{y,z,a}$
Cisplatin	$0.783\pm0.440^{a,d,g,j}$	$0.633\pm0.294^{k,m,p,r}$	$0.366\pm0.242^{s,v,y}$
Cis + Amb	$0.266\pm0.136^{b,e,h,j}$	$0.200\pm0.178^{n,r}$	$0.316\pm0.213^{t,w,z}$
Cis + CoQ10	$0.500\pm0.340^{c,f,ı}$	$0.283\pm0.306^{l,o}$	$0.333\pm0.081^{u,x,a}$
p values	0.000***	0.000***	0.000***

The letters used in the table indicate statistically significant differences between groups. Groups sharing the same letter have a significant difference at the $p<0.05$ level. Differences among control groups are excluded from this evaluation.
SD: Standard deviation, Cis: Cisplatin, Amb: Ambroxol, CoQ10: Coenzyme Q10.

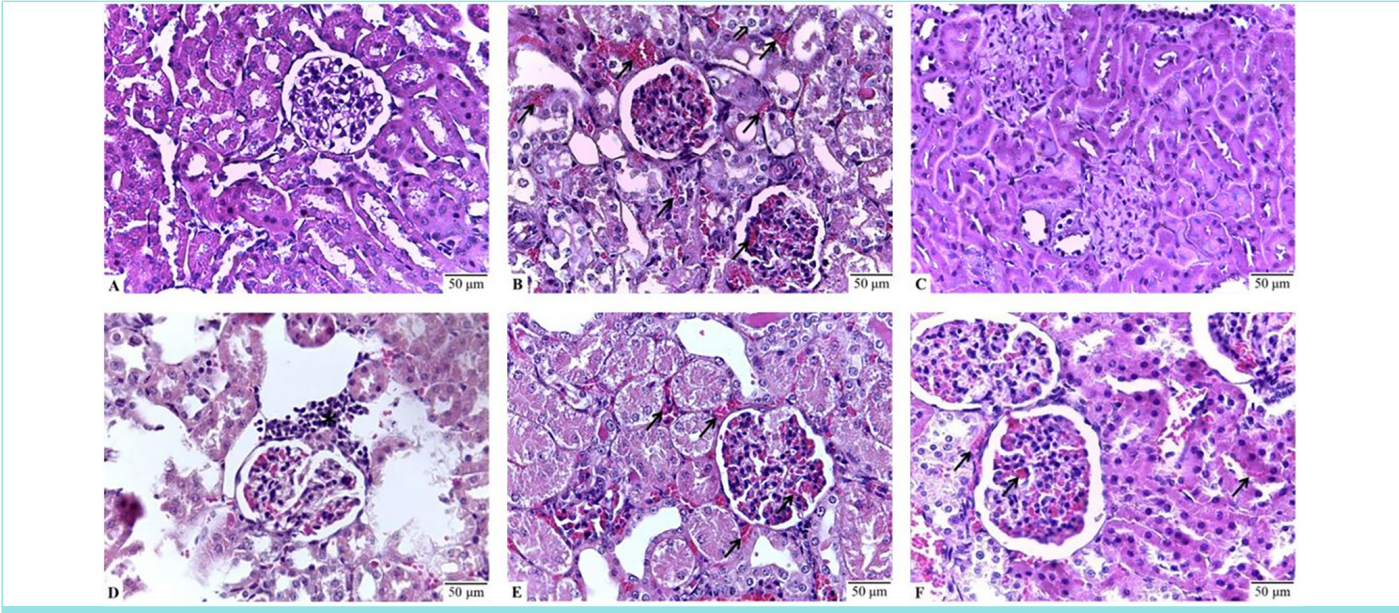

Figure 1. H&E stained light microscopic images of the experimental groups. Normal kidney tissue from the control group (Figure 1A) can be observed. In the cisplatin group, intertubular and interglomerular hemorrhage (➔), vacuolization of tubule epithelial cells (⇒) (Figure 1B), disappearance of the space between Bowman's capsule and glomeruli (Figure 1C), and mononuclear cell infiltration (*) (Figure 1D) are observed. It is observed that intertubular and interglomerular hemorrhage decreased in the Cis + Amb (Figure 1E) and Cis + CoQ10 (Figure 1F) groups.

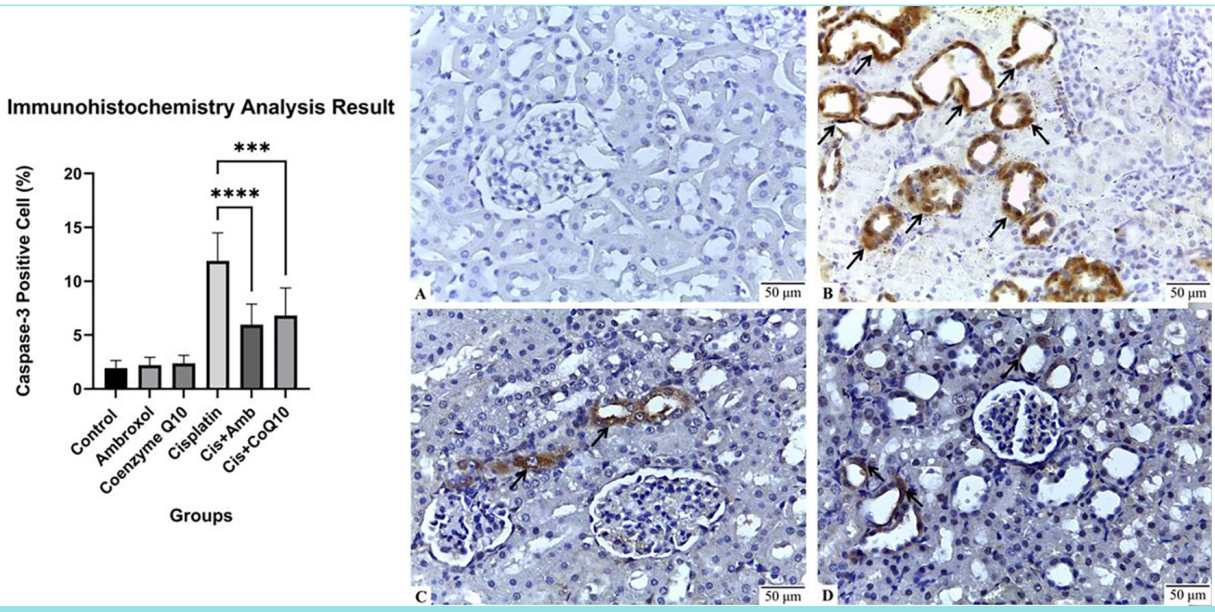

Figure 2. Evaluated by measuring stained area percentage on image J software. Light microscopic images of the experimental groups stained with caspase-3 are also shown. Cas-3 expression is not observed in the control (Figure 2A) group. It is observed that caspase-3 expression is increased in tubule epithelial cells in the cisplatin group (➔) (Figure 2B), while it is decreased in the Cis + Amb, (Figure 1C), and Cis + CoQ10 (Figure 2D) groups.

In the immunohistochemical caspase-3 staining performed for apoptotic cell evaluation, the highest expression was observed in the Cis group (Figure 2B). A statistical difference was detected between the Cis group and the other groups ($p<0.05$). Cas-3 expression was significantly reduced in the groups treated with Cis + Amb and Cis + CoQ10 compared to Cis (Figure 2C, D). There was no statistically significant difference between "Cis + Amb" and "Cis + CoQ10" in reducing the number of caspase-3 positive cells, although Amb showed a numerically greater effect than CoQ10 ($p>0.05$) (Figure 2).

DISCUSSION

Cis remains one of the most widely used anticancer drugs today, even though it has considerable side effects that endanger the patient's life.[5] The kidneys are particularly affected by Cis, resulting in inhibition of their functions and serious tissue damage. Ongoing investigations seek to prevent and mitigate Cis's toxic effects.[25,26] This study evaluated the histomorphological and biochemical protective effects of Amb and CoQ10 against Cis toxicity in kidney tissue. The protective effects were quantified and analysed. Cis administered as a single intraperitoneal dose of 7 mg/kg caused kidney damage in rats. It has been shown that kidney damage can be reduced by giving twice daily Amb at 50 mg/kg and CoQ10 at 10 mg/kg. Amb, one of the drugs we tested in the study, is an agent used as a mucolytic. In the studies, its antioxidant properties and protective effects on tissue have been shown. Recently, the presence of a protective effect on renal tissue has been suggested in both experimental and clinical studies. In a clinical study conducted in China, it was emphasized, that the administration of Amb before cardiopulmonary bypass reduced renal damage in children.[14] The protective effect of Amb in rats with renal ischaemia-reperfusion injury was suggested both biochemically and histopathologically.[27] CoQ10 is also known to have a protective effect on kidney tissue in both experimental and clinical studies.[28,29]

Cis hinders the mitochondrial respiratory complex, leading to elevated ROS. Elevated levels of ROS inhibit the antioxidant system, leading to oxidative stress, lipid peroxidation, alterations in cell fluidity and permeability, and disruptions in gene expression, consequently inducing cell death.[30,31] Cis initially increases serum urea and creatinine levels in kidney tissue.[32,33] Consistent with prior research, our study identified a marked elevation in urea and creatinine concentrations in the Cis-treated group, indicative of impaired kidney function. Amb and CoQ10 were effective in reducing increased urea and creatinine values. Bishr et al.[13] administered Amb intraperitoneally to rats at two different doses (35 and 75 mg/kg), Fouad et al.[16] administered CoQ10 to mice intraperitoneally at a dose of 10 mg/kg. In this study, Amb was administered at a dose of 50 mg/kg and CoQ10 at a dose of 10 mg/kg, via oral gavage.

Cellular damage caused by Cis is associated with an increase in inflammation due to the secretion of TNF-α.[34] TNF-α, a pro-inflammatory cytokine, ensures the mobilization and activation of further leukocytes.[35] In our study, inflammation caused by Cis was evidenced by measuring TNF-α from both serum and tissue. Amb and CoQ10, administered to counteract the effects of Cis on inflammation, mitigated acute kidney injury by reducing TNF-α levels. Dupre et al.[36] and Deng et al.[37] demonstrated the positive effects of anti-inflammatory agents against the kidney toxicity of Cis. Gültekin et al.[27] showed that Amb was effective in reducing the TNF-α level in the ischemia reperfusion model created in kidney tissue. Mirmalek et al.[38] reported that CoQ10 reduced inflammation in experimental acute pancreatitis.

MDA is an indicator of lipid peroxidation, disrupts membrane permeability in the cell, causes protein denaturation, and leads to the destruction of important antioxidant enzymes such as catalase. Cis increases MDA levels by causing lipid peroxidation in cells.[39] In this study in which Cis toxicity was established, it was observed that the MDA level in serum and kidney tissue increased significantly, and that Amb

and CoQ10 were effective in reducing lipid peroxidation in the groups treated with Amb and CoQ10. In a study in which hepatic ischemia and reperfusion were performed, it was reported that Amb reduced MDA levels.[40] In another study, Hossain et al.[41] reported that CoQ10 reduced the MDA increase caused by carbofuran.

Cis activates TNF-α in the kidneys, increasing inflammation and attracting leukocytes to the area. In the light microscopic examination results of our study, it was observed that Cis increased the number of inflammatory cells and that Bowman spaces narrowed. Intertubular congestion increased, and there was degeneration and epithelial shedding in tubule cells in some places. Amb and CoQ10 reduced mononuclear cell infiltration, although they did not completely prevent tubular and glomerular damage. Several studies corroborate our findings.[16,27,37]

Apoptosis is observed in tubule cells as a result of the toxic effect of Cis on the kidney.36 Cis binds to apoptotic protease activating factor-1 after cytochrome C passes into the cytosol in cells. This resulting complex activates procaspase-9. Caspase-9 also activates other caspases (3, 6, 7).[32] Caspase-3 is an enzyme that completely destroys cells by causing the proteins that form the cytoskeleton and the DNA to break down.[31] Bish et al.[13] biochemically demonstrated that Amb reduced the caspase-3 increase caused by Cis. In this study, the effect of Cis on the increase in caspase-3 expression was demonstrated by immunohistochemical staining. It was observed that Cis increased apoptosis, especially in kidney tubule epithelial cells, and CoQ10 decreased it. In a study on CoQ10 against the acute liver toxicity of acetaminophen, CoQ10 was found to be effective in reducing the amount of caspase-3.19 The reducing effect of CoQ10 on caspase-3 has been reported in acute nephrotoxicity caused by Cis in mice.[16]

Study Limitations

In this study, some markers of inflammation could not be examined immunohistochemically. In addition, the gene expression of these molecules could not be examined and compared.

CONCLUSION

The present study aimed to investigate the potential of Amb and CoQ10 to mitigate experimentally induced Cis nephrotoxicity. Results showed elevated levels of urea and creatinine, indicative of impaired renal function, as well as heightened values of TNF-α and MDA, markers of inflammation and lipid peroxidation, in Cis-administered rats. In addition, light microscopy revealed tubular degeneration, congestion-hemorrhage, and increased apoptotic cell death. Cis toxicity was reduced in groups treated with Amb and CoQ10, but was not entirely prevented. Biochemical and histomorphological analysis indicates that Amb is more effective at reducing damage than CoQ10. Further investigation into the effects of various doses and durations of Amb and CoQ10 on Cis toxicity at the molecular level will yield more detailed information.

MAIN POINTS

- Cisplatin (Cis) treatment causes significant kidney damage, leading to increased inflammation and oxidative stress markers (TNF-α, malondialdehyde) in serum and tissue.
- Ambroxol (Amb) and coenzyme Q10 (CoQ10) significantly reduce Cis-induced kidney injury both biochemically and histologically.
- Caspase-3 expression, an indicator of apoptotic cell death, is decreased in groups treated with Amb and CoQ10, contributing to kidney tissue protection.

ETHICS

Ethics Committee Approval: This study was approved by the Near East University Local Ethics Committee for Animal Experiments (approval number: 2020/11, date: 27.11.2020).

Informed Consent: Since the study was conducted on animals, informed consent is not required.

Footnotes

Authorship Contributions

Surgical and Medical Practices: H.Ş., N.G., S.S., A.Ö.Ş., A.K., Concept: H.Ş., N.G., S.S., A.Ö.Ş., A.K., Design: H.Ş., N.G., S.S., A.Ö.Ş., A.K., Data Collection and/or Processing: H.Ş., N.G., S.S., A.Ö.Ş., A.K., Analysis and/or Interpretation: H.Ş., N.G., S.S., A.Ö.Ş., A.K., Literature Search: H.Ş., Writing: H.Ş.

DISCLOSURES

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

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