Effects of Amantadine on Liver and Lung Tissue in Hepatic Ischemia Reperfusion Injury in Rats

Amantadinin Ratlarda Hepatik İskemi Reperfüzyon Hasarinda Karaciğer ve Akciğer Dokusu Üzerine Etkileri

Fatih Sahin[1], Ayca Tas Tuna[2], Yusuf Unal[3], Mustafa Arslan[3], Hayrullah Yazar[4], Saban Cem Sezen[5], Sezen Irmak Gozukara[6] Onur Palabıyık[2]

[1]Sakarya University Training and Research Hospital, Department of Anesthesiology, Sakarya, Turkey
[2]Sakarya University, Faculty of Medicine, Department of Anesthesiology, Sakarya, Turkey
[3]Gazi University, Faculty of Medicine, Department of Anesthesiology, Ankara, Turkey
[4]Sakarya University, Faculty of Medicine, Department of Biochemistry, Sakarya, Turkey
[5]Kirikkale Uni versity, Faculty of Medicine, Department of Histology and Embryology, Kirikkale, Turkey
[6]Sakarya University Training and Research Hospital, Department of Biochemistry, Sakarya, Turkey

ABSTRACT

Background: N-Methyl D-Aspartate (NMDA) receptor blockers have been shown to have protective effects against ischemia/reperfusion (I/R) injury in various tissues. The aim of this study was to investigate the effects of amantadine on liver and lung tissue in hepatic I/R injury.
Materials and Methods: Twenty-four rats divided into 4 groups: the Sham Group (S), the Amantadine Group (A), the I/R Group (I/R) and the I/R + Amantadine Group (I/R-A). In Group A and Group I/R-A, 45 mg/kg of amantadine was administered before surgery. In Group I/R and Group I/R-A, an atraumatic vascular clamp was applied to the structures in the left portal triad for 45 minutes and reperfusion period was 2 hours after declampage. Malondialdehyde (MDA), superoxide dismutase (SOD) and catalase (CAT) enzyme levels were were studied in liver and lung tissues. Additionally tissues were examined histopathologically.
Results: No significant difference was observed in tissue MDA, SOD, and CAT levels among four groups ($p > 0.05$). Polymorphonuclear cell infiltration and the scores of hepatocyte degeneration, sinusoidal dilatation, pycnotic core, and necrosis cell were significantly higher in Group I/R than other groups ($p<0.05$). Regarding to the lung tissue, the neutrophil/lymphocyte infiltration score was significantly lower in Group S and A than in Group I/R (respectively; $p= 0.007$, 0.011), and it was significantly higher in Group I/R-A than in Group S ($p = 0.014$). The alveolar wall thickening score was significantly higher in Group I/R than the other groups ($p <0.0001$).
Conclusion: Amantadine may have a protective effect against I/R damage, as it reduces histopathological changes caused by I/R damage.

Keywords: Amantadine, Hepatic Ischemia-Reperfusion, Liver, Lung, Liver Surgery

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ÖZET

Amaç:N-Metil D-Aspartat (NMDA) reseptör blokerlerinin çeşitli dokularda iskemi/reperfüzyon (I/R) hasarına karşı koruyucu etkileri olduğu gösterilmiştir. Bu çalışmanın amacı hepatik I/R hasarında amantadinin karaciğer ve akciğer dokusu üzerindeki etkilerini araştırmaktı.
Yöntem: Yirmi dört sıçan 4 gruba ayrıldı: Grup Sham (S), Grup Amantadin (A), Grup İ/R (I/R) ve I/R + Amantadin Grubu (I/R-A). Grup A ve Grup I/R-A'ya ameliyat öncesi 45 mg/kg amantadin verildi. Grup I/R ve Grup I/R-A'da sol portal triaddaki yapılara 45 dakika boyunca atravmatik vasküler klemp uygulandı ve klemp kaldırılması sonrası 2 saat reperfüzyon uygulandı. Karaciğer ve akciğer dokularında malondialdehit (MDA), süperoksit dismutaz (SOD) ve katalaz (CAT) enzim düzeyleri çalışıldı. Ayrıca karaciğer ve akciğer dokuları histopatolojik olarak incelendi.
Bulgular: Doku MDA, SOD ve CAT düzeylerinde dört grup arasında anlamlı bir fark gözlenmedi ($p >0.05$). Polimorfonükleer hücre infiltrasyonu ve hepatosit dejenerasyonu, sinüzoidal dilatasyon, piknotik çekirdek ve nekrotik hücre skorları Grup I/R'de diğer gruplara göre anlamlı derecede yüksekti ($p<0.05$). Akciğer dokusunda nötrofil/lenfosit infiltrasyon skoru Grup S ve A'da Grup I/R'ye göre anlamlı olarak daha düşüktü (sırasıyla; $p= 0.007$, 0.011) ve Grup I/RA'da Grup S'ye göre anlamlı olarak daha yüksekti. ($p = 0.014$). Alveolar duvar kalınlaşma skoru Grup I/R'de diğer gruplara göre anlamlı derecede yüksekti ($p <0.0001$).
Sonuç: Amantadin, I/R hasarının neden olduğu histopatolojik değişiklikleri azalttığı için I/R hasarına karşı koruyucu bir etkiye sahip olabilir.

Anahtar Sözcükler: Amantadin, Hepatik İskemi- Reperfüzyon, Karaciğer, Akciğer, Karaciğer Cerrahisi

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ORCID IDs: F.S.0000-0002-8501-0675,A.T.T.0000-0001-6764-2647,Y.U.0000-0001-6260-5177,M.A.0000-0003-4882-5063,H.Y.0000-0001-9447-6322,S.C.S.0000-0003-3996-7692,S.I.G.0000-0002-4825-4611,O.P.0000-0003-3876-4279

Address for Correspondence / Yazışma Adresi: Fatih Sahin, M.D., Sakarya University Training and Research Hospital, Department of Anesthesiology, Saglik Street, No.152, *Sakarya*, Turkey E-mail: tyflfatih16@hotmail.com

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INTRODUCTION

Hepatic ischemia/reperfusion (I/R) injury is a prevalent condition with high mortality; it can occur due to trauma, transplantation and liver surgery, and hypovolemic shock (1). Ischemia is the lack of blood supply to organs and tissues due to decreased or complere cessation of arterial or venous blood flow resulting in insufficient oxygen delivery. Reperfusion of ischemic tissue causes more serious damage to the tissue (2). Many mechanisms, especially free oxygen radicals (ORs), which are formed by the introduction of molecular oxygen into the cell, play a role in the damage observed during the reperfusion period (3). Superoxide anion, hydrogen peroxide, and hydroxyl radicals are the best-known types of ORs (4).

Hepatic I/R injury causes a systemic inflammatory response. Due to the intensity of the inflammatory reaction in the post ischemic tissue, organs away from the injury that respond to reperfusion are also affected. These distant effects of I/R are most often observed in the lung, and they can lead to the development of acute lung injury or respiratory distress syndrome. Lung damage is an important cause of mortality in critically ill patients (5). Amantadine is a N-Methyl D-Aspartate (NMDA) type glutamate receptor antagonist drug that was approved for use in the United States in 1968; it is used to treat both influenza and Parkinson's disease. While it shows its antiviral effect by preventing the release of viral RNA, its inhibitory effect in the brain results in increasing dopamine release, blocking dopamine reuptake, and causing microglial activation and neuroinflammation. Amantadine has been reported to be effective intraumatic brain injury, and its use in different doses has been shown to have a neurorestorative effect in brain cortical ischemia (6).

Many drugs with NMDA receptor antagonists (ketamine, barbiturate, volatile anesthetics, morphine) have been shown to have protective effects against I/R injury in different tissues such as kidney, myocardium, skeletal muscle (7-9). However, no studies in the literature have investigated the effect of amantadine on I/R injury. Therefore, we aimed to investigate the effects of amantadine, an NMDA receptor antagonist whose neuroprotective effect has been proven in traumatic brain tissue, in lung and liver tissues in hepatic I/R injury.

MATERIALS and METHODS

Twenty-four adult male Wistar rats, each weighing 250-330 g, were kept on a 12-hour day/night cycle. The rats were placed on an electric heating pad, and their temperatures were constantly monitored using a rectal thermometer to ensure that it was kept at 37°C. All the rats were anesthetized with 100 mg/kg of ketamine (Ketalar 1 mL = 50 mg, Pfizer, Istanbul, Turkey) and 15 mg/kg of xylazine (Xylazinbio 2%, Bioveta, Czech Republic). Unresponsiveness to painful stimulation was accepted as an adequate anesthesia criterion. The tail vein was cannulated with a 26-G IV cannula. The abdominal areas were shaved. In the maintenance of anesthesia, the rats were administered ketamine intraperitoneally (i.p.) at regular intervals.

Amantadine hydrochloride (Sigma A1260-5G) was purchased from Sigma-Aldrich (St. Louis, MO, USA) and prepared by dissolving in sterile isotonic liquid.

The rats were randomly categorized into 4 groups: the Sham Group (S, n = 6), the Amantadine Group (A, n = 6), the Ischemia/Reperfusion Group (I/R, n = 6), and the Ischemia/Reperfusion + Amantadine Group (I/R-A, n = 6). After anesthesia, the rats in Group S and Group I/R waited for 15 minutes before the surgical procedure was performed. In Group A and Group I/R-A, 45 mg/kg of amantadine hydrochloride i.p was given simultaneously with the anesthesia; then, 15 minutes later the surgical procedure was performed. In Group S and Group A, a midline abdominal incision was performed in rats, but no intervention was made in the liver. In Group I/R and Group I/R-A, the liver was exposed by performing a midline abdominal incision to the rats. Firstly the liver and ligamentous of the median and left lateral lobes were examined and freed.

Portal circulation of these lobes was interrupted and hepatic artery blocked with a vascular clamp (Figure 1). Intestinal venous congestion was prevented by retaining portal and arterial inflow with venous outflow in caudate and right lateral lobes. This procedure provided tissue ischemia in approximately 65%–70% of the liver (10). After 45 min of ischemia, the clamp was removed. The rats in Group I/R and I/R-A were reperfused for 2 hours. All rats were sacrificed after a total of 180 minutes and lung and liver tissues were taken.

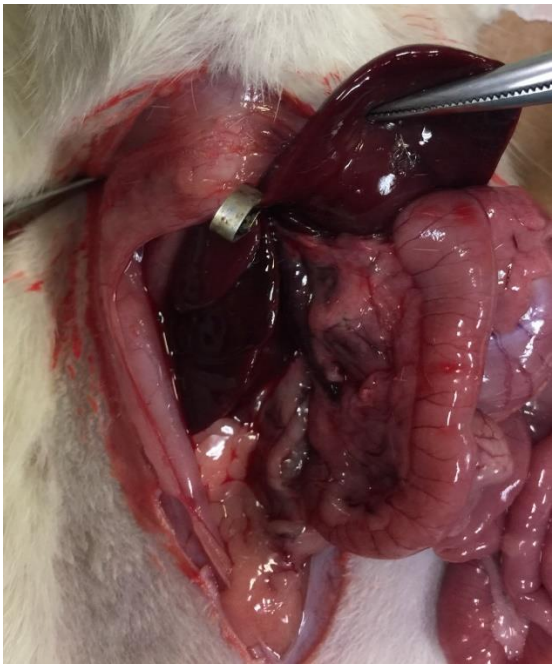


Figure 1. Liver dissection and clamping

The tissue samples were keeped at –80 ° C for biochemical examination. Lung samples and liver samples fixed with 10% formalin and embedded in paraffin for histopathological examination. Lung and liver samples were separated into small pieces by removing fat and connective tissues on ice for tissue homogenization. The samples were weighed and placed in glass tubes containing cold phosphate buffer (pH 7.4, 50 mmol / L) with a final concentration of 100 mg tissue / mL. Mechanical homogenizer (Isolab, Laborgerate GmbH, Germany) was used in the homogenization process. The homogenate obtained was centrifuged at 10,000 g at 4 ° C for 10 minutes and separated from debris and other particles. All parameters were studied from supernatants obtained after centrifugation. Tissue malondialdehyde (MDA) parameter was used to determine the level of lipid peroxidation. For the antioxidant enzyme level, superoxide dismutase (SOD) and catalase (CAT) enzyme levels were studied. MDA, SOD and CAT levels were measured by ELISA (Elabscience Biotechnology Co. Ltd, Wuhan, China) method. The intra-measurement variation coefficient of the kits was <10%. Measurements were performed on the automatic ELISA analyzer (Triturus, Grifols, Spain), following the manufacturer's protocols. The results were calculated by multiplying the obtained results by the dilution factor.

Histopathological evaluation of liver tissue was done using the "semi-qualitative evaluation" method defined by Abdal-Wahhab.[11] Tissue damage was evaluated by; hepatocyte degeneration, sinusoidal dilation, pycnotic nucleus, necrosis cell, polymorphonuclear (PMN) cell infiltration scoring in the parenchyma [negative (-) score no structural changes; a positive (+) score, a slight structural change; two (++) positive points, moderate structural change; three positive (+++) points, serious structural change]. Histopathological evaluation of the lung was performed using a four-point scoring system for neutrophil / lymphocyte infiltration and alveolar wall thickening [Grade 0 (no signs of damage), Grade 1 (mild damage), Grade 2 (moderate damage), Grade 3 (severe damage)].

Statistical Analysis

Data were transferred to IBM SPSS Statistics 23 program. The study data were given as mean ± standard deviation (mean ± SD) for numerical variables. Comparisons among multiple groups were performed using the Kruskal-Wallis test. When a difference was detected, specific differences were identified using the Bonferroni corrected Mann-Whitney U test. $p < 0.05$ was considered significant.

Ethics approval and consent to participate

All the experimental protocols were approved by the Animal Research Committee at Ankara Gazi University (G.U.ET. 17.021, 2017).

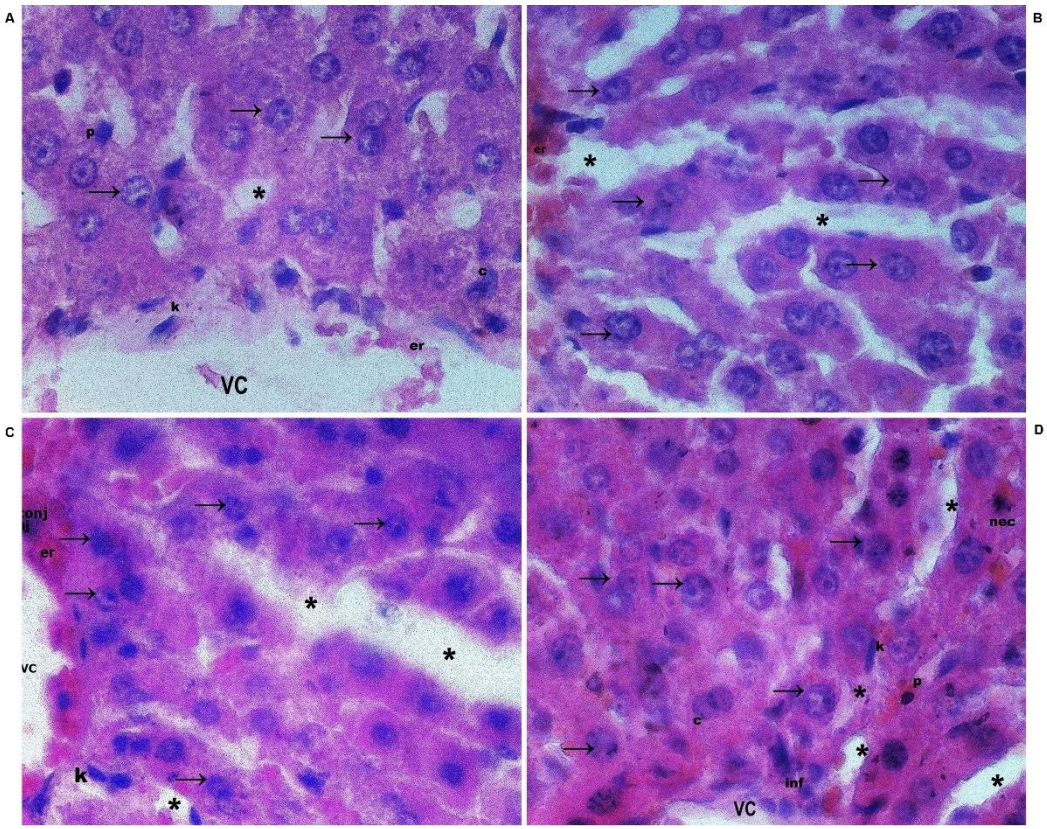
RESULTS

In histopathological examination of liver tissue, hepatocyte degeneration score, sinusoidal dilatation score, pycnotic core score, necrosis cell score, and PMN cell infiltration were statistically significantly higher in Group I/R than in Group S, Group A and Group I/R-A (respectively; p<0.001, p=0.003, p=0.002, p<0.001, p=0.035) (Table 1) (Figure 2).

Table 1: Histopathological findings of rat liver tissue (*mean ± SD*)

	Group S (n=6)	Group A (n=6)	Group I/R (n=6)	Group I/R-A (n=6)	p
Hepatocyte degeneration	0.33±0.21*	0.67±0.21*	2.17±0.31	1.00±0.26*	<0.001
Sinusoidal dilation	0.33±0.21*	0.67±0.213*	2.17±0.40	0.83±0.31*	0.003
Pycnotic nucleus	0.17±0.17*	0.50±0.22*	1.67±0.33	0.67±0.21*	0.002
Necrosis cell	0.17±0.17*	0.17±0.17*	1.67±0.33	0.17±0.17*	<0.001
PMN cell infiltration	0.50±0.22*	0.83±0.31*	1.67±0.21	0.83±0.17*	0.035

**: p<0.05 versus Group I / R*



[VC, vena centralis; ← →,hepatocytes; c, dicaryotic hepatocytes; k, kupper cell; *, sinusoid dilatation ; cong, capillary congestion; er, erythrocyte; inf, inflammation]

Figure 2. Histopathological examination of liver tissue. A; Normal liver tissue, B; Mild sinusoidal dilation after administration of amantadine, C; Increased inflammation, conjugation and sinusoidal dilation with ischemia reperfusion, D; Inflammation, conjugation, decrease in sinusoidal dilatation with amantadine administration after ischemia reperfusion. Stained with hematoxylin and eozin, X400.

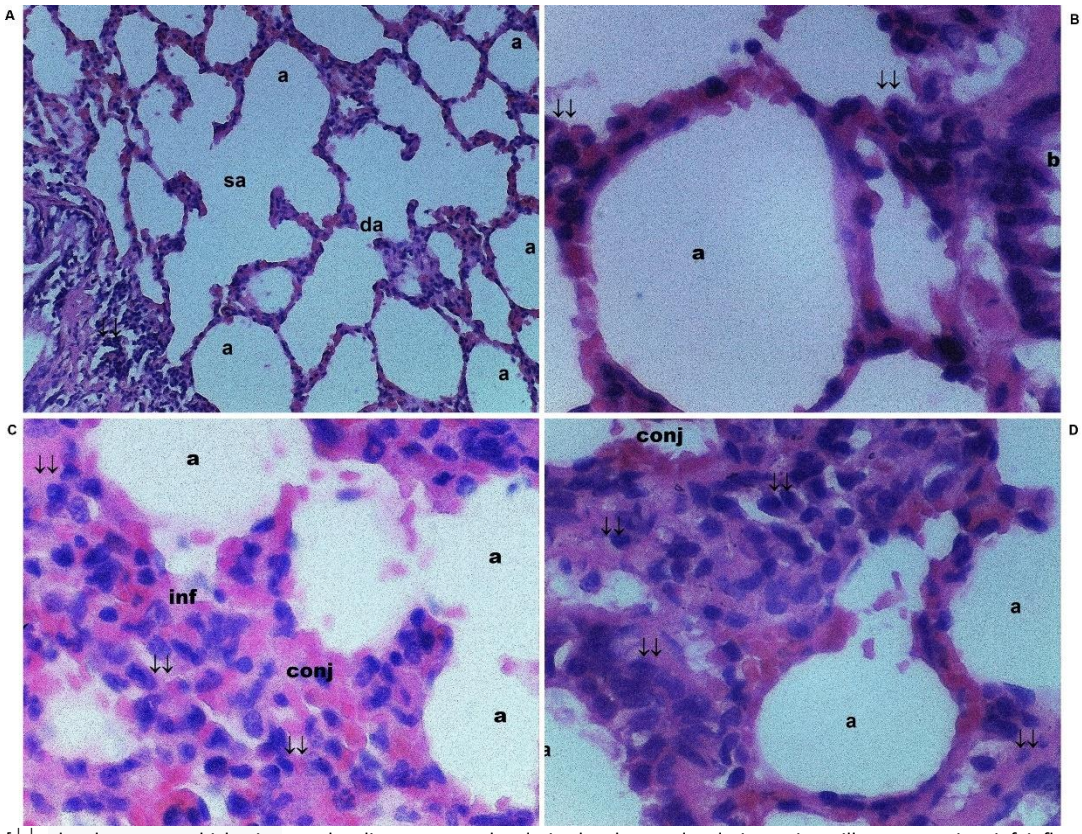
In histopathological examination of the lung tissue, the neutrophil / lymphocyte infiltration score was statistically significantly lower in Group S and Group A compared to Group I/R (respectively; p=0.007, p=0.011). It was found statistically significantly higher in Group I/R-A than Group S (p=0.014).

When the groups were compared in terms of alveolar wall thickening score, a statistically significant difference was found. The alveolar wall thickening score in Group I/R was statistically significantly higher than Group S, Group A and Group I/R-A (p<0.001) (Table 2) (Figure 3).

Table 2: Histopathological findings of rat lung tissue (*mean ± SD*)

	Group S (n=6)	Group A (n=6)	Group I/R (n=6)	Group I/R-A (n=6)	p
Neutrophil/lymphocyte infiltration	0.33±0.21*	0.50±0.22*	1.83±0.31	1.33±0.21&	0.001
Alveolar wall thickening	0.33±0.21*	0.50±0.22*	2.17±0.31	0.83±0.31*	<0.001

**: p<0.05 versus Group I / R*
&: p<0.05 versus Group S



[↓↓, alveolar septum thickening; a, alveoli; sa, saccus alveolaris; da, ductus alveolaris; conj, capillary congestion; inf, inflamation]
Figure 3. Histopathological examination of lung tissue. A; Normal lung tissue, B; Mild alveolar septum thickening with amantadine application, C; Inflammation, conjugation and thickening of the alveolar septum after ischemia reperfusion, D; Inflammation, conjugation and decrease in alveolar wall thickening with amantadine administration after ischemia reperfusion. Stained with hematoxylin and eozin, X400.

Liver tissue MDA, SOD and CAT enzyme levels were shown in Table 3. Liver tissue MDA levels were found to be decreased in Group I/R-A compared to Group S, Group A and Group I/R. However, MDA levels were not statistically significant between the groups (p=0.166). It was observed that liver tissue SOD levels decreased in Group I/R compared to Group S, Group A and Group I/R-A. In Group I/R-A, Group S was found to be lower than Group A and higher than Group I/R. However, SOD levels were not statistically significant between the groups (p = 0.476). Liver tissue CAT levels were the lowest in Group I/R and the highest in Group I/R-A. However, there was no statistically significant difference between the groups (p=0.790).

Table 3: Oxidant status parameters of rat liver tissue (*mean ± SD*)

	Group S (n=6)	Group A (n=6)	Group I/R (n=6)	Group I/R-A (n=6)	p
MDA (ng/mg)	3.14±0.29	3.36±0.17	2.95±0.75	2.65±0.28	0.166
SOD (pg/mg)	3.75±0.42	3.96±0.30	3.13±0.54	3.55±0.14	0.476
CAT (pg/mg)	4.54±0.51	4.69±0.11	4.37±0.51	4.90±0.45	0.790

(ng:nanogram, mg:miligram, pg:picogram, MDA:malondealdehyde, SOD:superoxide dismutase, CAT:catalase)

Lung tissue MDA, SOD and CAT enzyme levels are shown in Table 4. Lung tissue MDA levels were found to be increased in Group I/R compared to Group S and Group A. MDA level was the highest in Group I/R-A. However MDA levels between groups were not statistically significant (p=0.198).
Lung tissue SOD levels were found to be higher in Group I/R-A than Group S, Group A and Group I/R.. However, SOD levels between groups were not statistically significant (p=0.082). While CAT levels increased in Group I/R-A compared to Group S, Group A, Group I/R, CAT level was the lowest in Group I/R and CAT levels were similar between groups (p=0.641).

Table 4: Oxidant status parameters of rat lung tissue (*mean ± SD*)

	Group S (n=6)	Group A (n=6)	Group I/R (n=6)	Group I/R-A (n=6)	p
MDA (ng/mg)	0.56±0.04	0.48±0.06	0.58±0.07	0.68±0.04	0.138
SOD (pg/mg)	0.25±0.07	0.25±0.03	0.43±0.15	0.69±0.12	0.082
CAT (pg/mg)	11.71±0.24	11.43±0.25	11.21±0.40	11.78±0.29	0.641

(ng:nanogram, mg:miligram, pg:picogram, MDA:malondealdehyde, SOD:superoxide dismutase, CAT:catalase)

DISCUSSION

In this study, where we investigated the effects of amantadine on liver and lung tissue in the rat hepatic I/R, we found that histopathological changes occurring in the liver and lung tissue after I/R injury may be limited byamantadine treatment applied prior to the injury. In one study, systemic injection of an NMDA receptor antagonist MK-801, in the sciatic nerve I/R model, inhibits activation of tumor necrosis factor-α (TNF-α), reduces cell infiltration and demyelination, decreases inducible nitric oxide synthase and nitric oxide activity and thus it has been shown to protect against I/R injury (12). In another study, it was reported that serum AST, LDH, TNF-α, MDA, and P-selectin levels increased, angiotensin III level and total antioxidant capacity in serum decreased, and serious damage of intestinal mucosa in intestinal I/R injury significantly improved by ketamine application (13).

In the literature, we did not find any study about the effects of amantadine on I/R injury. Recent studies reported how amantadine has been used widely in their clinical practice of patients with severe brain injury. In another study on rats with traumatic brain injury, authors reported that amantadine had a potential value in antidepression treatment by using a dose of 45 or 135 mg/kg/day (14). According to this study, we choose 45 mg/kg dose of amantadine to determine if it had a protective effect against I/R injury.

After I/R injury, damage can occur both locally in the ischemic area and distant organs outside the ischemic area. Damaged tissue releases devastating proinflammatory cytokines and ORs and causes more damage to distant organs (15). It is known that hepatic I/R injury has harmful effects on distant organs such as kidney, heart, and lung (16-18).

Malondialdehyde is the end product of lipid peroxidation. The increase in MDA is an indicator of free radical formation in postischemic tissue (19). Increased free radicals cause overproduction of MDA. Elevation of MDA has been seen with liver I/R injury and is widely used to determine damage (20). In studies on hepatic I/R injury, it was reported that MDA increased after I/R injury and MDA level decreased after application of antioxidant agents (21-22). In astudy, the authors reported thatMDA level increased in lung tissue after hepatic I/R injury in diabetic rats(23). In our study; after hepatic I/R injury, MDA levels were found lower in liver tissue than the control group and higher in lung tissue. When we gave amantadine after hepatic I/R injury, we found a decrease in liver tissue MDA level and an increase in lung tissue. We think that this contradiction is related to the fact that MDA is examined in serum in all of the hepatic I/R studies in the literature, and in our study it is related to the level of MDA in tissue.

Superoxide dismutase enzyme plays an important role as an antioxidant enzyme in cleaning ORs. In the literature, there are two different opinions about SOD level in I/R injury (24,25). In the first of these; In I/R injury, it is thought that SOD activity levels in tissue and serum samples have decreased compared to the control groups and this decrease is due to the predominance of oxidant mechanisms (24). In the other opinion; SOD activity levels in I/R injury have been shown to be increased and it has been argued that this increase is an answer to suppress stress in oxidative stress (25). In our study; we observed that lung tissue SOD levels partially fit the second opinion. In other words, an increase in SOD activity after I/R in lung tissue, yet the fact that amantadine increasing SOD activity even more instead of decreasing it, made us think that amantadine does not have an antioxidant effect on lung tissue. However, when we look at the liver tissue SOD levels; we observed that the first view was similar, that is, SOD activity decreased after I/R and SOD activity increased with amantadine administration. This made us think that amantadine may have a protective effect on oxidant mechanisms on liver tissue.

Oxidoreductases, another antioxidant enzyme group, are important free radical scavenging systems and plays a cell-protective role. CAT is also one of these antioxidant enzymes. CAT catalyzes the destruction of hydrogen peroxide and high levels of CAT show antioxidant activity. In I/R studies in different tissues, it has been shown that the level of CAT decreases after I/R injury (26-28). In the literature, we did not find a study investigating distant organ CAT levels in I/R models. In our study, similar to these studies, we observed that CAT enzyme activity decreased in both liver and lung tissue after I/R injury in liver tissue and increased with amantadine administration. We think that this change in CAT enzyme activity was not statistically significant and was related to the low number of subjects.

Histopathologically in the hepatic I/R injury; it has been shown to be disrupted in the hepatic cords, bleeding, PMN cell infiltration, hepatocyte necrosis, venous thrombosis, hyperplasia of Kupffer cells, portal vein dilatation (21). In our study, we observed that hepatocyte degeneration, sinusoidal dilatation, pycnotic nucleus, PMN cell infiltration increased number of cells leading to necrosis, and decreased when amantadine was given with I/R.

Lung damage is A serious complication seen after hepatic I/R. Palladini et al. reported that acute hepatic I/R injury caused histological damage not only in the ischemic liver region but also in the lung and kidney (29). Similarly, it has been reported that necrosis, inflammatory cell, bleeding, and microsteatosis were increased significantly in the lung after hepatic I/R injury (30). After hepatic I/R injury, edema in the lung tissue, intraalveolar bleeding and endothelial activation can often be observed (31). Sahin et al. reported that the damage to lung tissue after hepatic I/R injury decreased with the administration of dexmedetomidine, an NMDA antagonist agent (32). In line with other studies, we also found that neutrophil / lymphocyte infiltration and alveolar wall thickening increased significantly in lung tissue after I/R, and when we applied amantadine, all these changes decreased.

CONCLUSION

The fact that the histopathological damage could be reversed with amantadine suggested that amantadine may have a protective effect on both liver and lung tissue, as with other NMDA antagonist agents.

Conflict of interest

No conflict of interest was declared by the authors.

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