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Original Article

Comparison of Effects of Dexmedetomidine and Thymoquinone on Kidney at Hind Limb Ischemia - Reperfusion Generated Rats

Alt Ekstremitede İskemi-Reperfüzyon Oluşturulan Ratlarda Deksmedetomidin ve Thymoquinone'in Böbrek Üzerine Etkilerinin Karşılaştırılması

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Abstract:

Background: In this study it is aimed to compare the effects of Dexmedetomidine (Dex) and Thymoquinone (TQ) on kidney at hind limb ischemia/reperfusion injury generated rats

Materials and Methods: 50 Wistar albino rats were included to the study. Rats were divided into 5 groups (n=10) as Sham, Control, TQ, Dex, and Dex-TQ. After anesthesia was given to the rats, ischemia was performed to left hind limb for 4 hours and then 2 hours reperfusion applied. TQ and Dex were administered intraperitoneally after the end of 4 hours ischemia and 5 minutes before start of reperfusion. At the end of study all rats were sacrificed. Blood and kidney samples were taken to evaluate Total Antioxidant Status (TAS), Total Oxidant Status (TOS) Oxidative Stress Index (OSI) values and histopathological examination.

Results: TAS value was measured that the lowest value in Control Group (0.07±0.01). TAS values of TQ, Dex, Dex-TQ groups were significantly higher than those of Control Group ($p<0.05$). There was no significant difference between TQ, Dex, Dex-TQ groups regarding to TAS values ($p>0.05$). TOS values were measured and they were the highest in the Control Group and the lowest in the Sham Group ($p<0.05$ for all). TOS values of TQ, Dex, Dex-TQ groups significantly lower than those of the Control Group ($p<0.05$) and significantly higher than those of the Sham Group ($p<0.05$). There was no significant difference between TQ, Dex, Dex-TQ groups regarding to TOS values ($p>0.05$). OSI values of TQ, Dex, Dex-TQ groups significantly lower than those of the Control Group ($p<0.05$) and higher than those of the Sham Group ($p<0.05$ for all). There was no significant difference between TQ, Dex, Dex-TQ groups regarding to OSI values ($p>0.05$ for all). The histopathological damage score was the lowest in the Sham group and the highest in the Control group. While there was no significant difference between Sham, TQ, Dex, Dex-TQ groups ($p>0.05$); It was found to be significantly lower when compared to the control group ($p<0.05$).

Conclusion: Histopathological changes were observed at kidney in hind limb ischemia/reperfusion due to oxidative stress. TQ and Dex had protective effects on renal tissues at ischemia/reperfusion injury.

Key Words: Ischemia, Reperfusion, Oxidative Stress, Dexmedetomidine, Thymoquinone

Öz

Amaç: Bu çalışmada alt ekstremite iskemi reperfüzyon hasarı oluşturulan ratlarda Deksmedetomidin (Dex) ve Thymoquinone'in (TQ) böbrek üzerine etkilerini karşılaştırılması amaçlandı.

Materyal ve Metod: Çalışmaya 50 adet Wistar albino rat dahil edildi. Sıçanlar Sham, Control, TQ, Dex ve Dex-TQ, olmak üzere 5 gruba (n=10) ayrıldı. Ratlara anestezi verildikten sonra sol alt ekstremiteye 4 saat iskemi ve 2 saat reperfüzyon uygulandı TQ ve Dex iskemi ardından reperfüzyondan 5 dakika önce intraperitoneal olarak uygulandı. Çalışma bitiminde bütün ratlar sakrifiye edildi ve ratlardan kan ve böbrek numuneleri alınarak histopatolojik değerlendirme yapıldı; Total Antioksidan Seviye (TAS), Total Oksidatif Stres (TOS) ve Oksidatif Stres İndeksi (OSİ) değerleri incelendi.

Bulgular: TAS en düşük kontrol grubunda (0.07±0.01) saptandı. TQ, Dex, Dex-TQ gruplarının TAS değerleri kontrol grubundan yüksek bulundu ($p<0.05$). TQ, Dex, Dex-TQ grupları arasında TAS açısından anlamlı fark saptanmadı ($p>0.05$).

TAS en düşük kontrol grubunda (0.07±0.01, P değeri) saptandı. TQ, Dex, Dex+TQ gruplarının TAS değerleri kontrol grubundan yüksek bulundu ($p<0.05$). TQ, Dex, Dex-TQ grupları arasında TAS açısından anlamlı fark saptanmadı ($p>0.05$). TOS en düşük Sham grubunda en yüksek Kontrol grubunda saptandı ($p<0.05$). TQ, Dex, Dex-TQ gruplarının TOS değerleri Kontrol grubundan anlamlı düşük ($p<0.05$), Sham grubundan ise anlamlı şekilde yüksek bulundu ($p<0.05$). TQ, Dex, Dex-TQ Grupları arasında TOS açısından anlamlı fark saptanmadı ($p>0.05$). TQ, Dex, Dex-TQ gruplarının OSİ değerleri Kontrol grubundan anlamlı düşük ($p<0.05$), Sham grubundan ise anlamlı şekilde yüksek bulundu ($p<0.05$). TQ, Dex, Dex-TQ Grupları arasında OSİ açısından anlamlı fark saptanmadı ($p>0.05$). Histopatolojik hasar skoru en düşük Sham grubunda en yüksek ise Kontrol grubunda görüldü. Sham, TQ, Dex, Dex-TQ grupları arasında anlamlı fark saptanmazken ($p>0.05$); Kontrol grubuyla karşılaştırıldığında anlamlı olarak düşük tespit edildi ($p<0.05$).

Sonuç: Alt ekstremite iskemi-reperfüzyonunda oksidatif stres nedeniyle uzak organlarda belirgin histopatolojik değişiklikler ortaya çıkar. Thymoquinone ve Deksmetedomidin, böbrekler üzerinde iskemi-reperfüzyon hasarının önlenmesinde koruyucu etkiye sahiptirler.

Anahtar Kelimeler: İskemi, Reperfüzyon, Oksidatif Stres, Deksmedetomidin, Thymoquinone

Introduction

Metabolites formed as a result of anaerobic metabolism in ischemia/reperfusion injury (IRI) are oxidized together with reperfusion and mixed into the circulation and cause distant organ damage (1,2). The body's defense system is activated with antioxidant enzymes against free oxygen radicals (FOR) formed after Ischemia/Reperfusion (IR) (3).

The tourniquet method, which is used in many surgeries, especially orthopedic surgery, is an IR model (4). Kidney damage may occur as a systemic complication of IRI. Anesthetic agents to be used in patient groups with risky kidney functions, in major surgeries that may increase damage to the kidney, and in surgical interventions where kidney functions need to be preserved, such as transplantation, should be chosen carefully considering their effects on the kidney (5,6).

Different agents have been tried for the treatment of IRI, and studies have generally focused on agents with antioxidant properties. The histological effects of agents on distant organs were investigated in various IR models (7,8).

In this study, it was aimed to compare the histopathological and biochemical effects of Dexmedetomidine, which is used for sedation in anesthesia and intensive care practice, and Thymoquinone, which has been shown to have antioxidant properties in various studies, on the kidney in hind limb IRI in rats.

Materials and Methods

Local Ethics Committee approval (approval decision of Harran University Animal Experiments Local Ethics Committee dated 30.04.2012 and numbered B.30.2.HRU.0.05.07.00/270) was obtained before the study. Fifty Wistar-albino female rats (average weight between 180-240 gr) were randomly divided into 5 equal groups (n = 10). Rats were kept at room temperature and 12 hours of light and 12 hours of darkness before the study. All rats were fed with tap water and standard rat chow under standard conditions. Feeding of all rats was stopped 8 hours before the intervention.

Ketamine 87 mg/kg was administered intraperitoneally (Ketalar; Parke Davis, Eczacibasi, Istanbul, Turkey) and Xylazine 13 mg/kg (Rompun; Bayer AG, Leverkusen, Germany) to all rats used in the experiment after 8 hours of fasting Additional doses were planned, if necessary, once during the experiment. Yassin et al. IR model was taken as an example (9). Left hind limbs of the rats were wrapped with an elastic bandage, and saturation loss and discoloration were achieved. At the end of the procedure, after the histological tissue sample and sufficient blood samples were taken, the rats were decapitated under anesthesia. Total working time was kept equal in all groups. At the end of the ischemia and reperfusion procedures, laparotomy was performed with a midline incision after the abdomen of the rats was disinfected. Blood samples were taken from the inferior vena cava and sent for biochemical analysis to measure Total Antioxidant Status (TAS) and Total Oxidant Status (TOS) to investigate the relationship between ischemia-reperfusion and oxidative stress. Kidney samples were taken, and histopathological examination was performed.

Preparation of Thymoquinone

Thymoquinone was dissolved using dimethyl sulfoxide (DMSO) and prepared for intraperitoneal injection.

Experimental Groups and Protocol

Rats were divided into 5 groups **Group 1 (Sham, n=10):** No procedure other than anesthesia was performed throughout the study. Tissue and blood samples were taken at the end of the reperfusion period. **Group 2 (Control, I/R, n=10):** 4 hours ischemia and 2 hours reperfusion were applied to the left hind limb with tourniquet after anesthesia, no drug was given. **Group 3 (I/R, Thymoquinone, TQ n=10):** 4 hours ischemia and 2 hours reperfusion were applied to the left hind limb with tourniquet after anesthesia, 20 mg/kg Thymoquinone was administered intraperitoneally (i.p.) 5 minutes before the tourniquet was opened. **Group 4 (I/R, Dexmedetomidine, Dex n=10):** 4 hours ischemia and 2 hours reperfusion were applied to the left hind limb with tourniquet after anesthesia. 5 minutes before the tourniquet was opened, 25mcg/kg dexmedetomidine, i.p. given **Group 5 (I/R, Dexmedetomidine + Thymoquinone, Dex-TQ n=10):** 4 hours ischemia with tourniquet and 2 hours reperfusion was applied to the left hind limb after anesthesia, 5 minutes before the tourniquet was opened 25mcg/kg dexmedetomidine and 20 mg/kg Thymoquinone i.p. given. Tissue and blood samples were taken from all rats in the groups at the end of the reperfusion period.

Histopathological Examination of Kidney Tissues: For histopathological examination, kidney tissues were individually fixed in 10% neutral buffered formaldehyde solution. Samples were embedded in paraffin blocks. Sections of 5-micron meters were taken. Stained with hematoxylin-eosin stain. A 20-lens magnification was used.

Histopathological Scoring: the severity of kidney damage was scored with the scoring system used by Solez et al. (10). In preparations for scoring, Tubular necrosis, interstitial edema, loss of brush border, and cast formation of the tubular epithelium from the basement membrane were evaluated as histological parameters. As a scoring score, it was accepted as None: 0 present:1 significant:2. The histological score was determined by summing all parameter scores for each sample.

TAS Measurement: The TAS level of the samples was measured using Rel Assay brand commercial kits. The measurement method is based on the fact that all antioxidant molecules in the sample reduce the colored ABTS cationic radical, and the colored radical decolorizes in proportion to the total concentrations of the antioxidant molecules. Trolox, a water-soluble analogue of vitamin E, is used as the calibrator. Results are expressed as mmol Trolox Equivalent/L (11). TAS results in tissues were expressed as Trolox Equivalent/gram protein.

TOS Measurement: The TOS level of the samples was measured using Rel Assay brand commercial kits. As stated in the working principle of the measurement test, the colorimetric method is used, which is based on the cumulative oxidation of the oxidant molecules contained in the samples to ferrous ion to ferric ion. Results are expressed as μmol H_2O_2 Equivalent/L (11). TOS results in tissues were expressed as μmol H_2O_2 Equivalent/gram protein.

Calculation of Oxidative Stress Index (OSI): When calculating the OSI of the samples, the TAS values are multiplied by 10 to equalize the TOS and the units. The ratio of TOS levels contained in the samples and TAS contained in the samples was stated as OSI (12). Results are expressed as Arbutrary Units (AU).

Statistical Analysis: SPSS package program was used for statistical evaluation. Kruskal Wallis and post hoc Bonferroni tests were used to evaluate the quantitative data between groups. For the Kruskal Wallis test, $p<0.05$ values were considered statistically significant.

Results

A total of 50 rats were included in this study and were divided into 5 groups with 10 in each group. The study protocol was applied to all rats, and at the end of the study, blood and tissue samples were taken from the rats and the rats were sacrificed. TAS, TOS and OSI parameters were measured in blood samples taken from rats and statistically compared between groups (Table 1).

The scores obtained as a result of the histopathological evaluations made by the specialist pathologist were statistically compared. EM samples of all groups are presented in Figure 1. The histopathological scoring of the groups is shown in Table 1.

Comparison of TAS Values of the Groups

When the mean TAS values were calculated in the blood samples taken, the lowest value was found in the control group (0.07±0.01 mmolTrolox Eqv./L), and the highest value was found in the Sham group (0.33±0.07 mmolTrolox Eqv./L) (Table 1).

When TAS was compared between the groups;

1- TAS values of Sham, TQ, Dex, Dex-TQ groups were found to be statistically significantly higher than the control group ($p<0.05$).

2- TAS value in the Sham group was found to be statistically significantly higher than the other groups. ($p<0.05$).

3- TAS values of TQ, DEX, DEX-TQ groups were compared, no statistically significant difference was found ($p>0.05$)

Comparison of TOS Values of the Groups

When the mean TOS values in the blood samples were calculated, the lowest value was found in the Sham group (18.68±3.41 µmolH2O2Eqv./L) and the highest value was found in the Control group (36.97±6.26 µmolH2O2Eqv./L) (Table 1).

1- TOS values of Sham, TQ, Dex, Dex-TQ groups were found to be statistically significantly lower than the control group ($p<0.05$).

2- The TOS value of the Sham group was found to be statistically significantly lower than the other groups. ($p<0.05$).

3- When the TOS values of the TQ, Dex, Dex-TQ groups were compared between the groups, no statistically significant difference was found ($p>0.05$)

Comparison of OSI Values of the Groups

When the mean OSI values in the blood samples were calculated, the lowest value was found in the Sham group (5.92±1.89 AU), and the highest value was found in the Control group (54.84±20.67 AU) (Table 1).

When compared between OSI groups;

1- OSI values of Sham, TQ, Dex, Dex-TQ groups were found to be statistically significantly lower than the control group ($p<0.05$).

2- The OSI value of the Sham group was found to be statistically significantly lower than the other groups. ($p<0.05$).

3- When the OSI values of the TQ, Dex, Dex-TQ groups were compared between the groups, no statistically significant difference was found ($p>0.05$)

Comparison of Histopathological Damage Scores of the Groups

Histopathological damage scoring was performed on the kidney sample of each rat by a specialist pathologist, and the mean scores of the groups were compared. The lowest value was found in the Sham group (2.60±0.69) and the highest value was found in the control group (4.60±0.69) (Table 1).

When the Histopathological Damage Score was compared between the groups;

1- Sham, TQ, Dex, Dex-TQ Groups Histopathological damage score was found to be statistically significantly lower than the control group ($p<0.05$) (Figure 1).

2- There was no statistically significant difference between Sham, TQ, Dex, Dex-TQ Groups. ($p>0.05$).

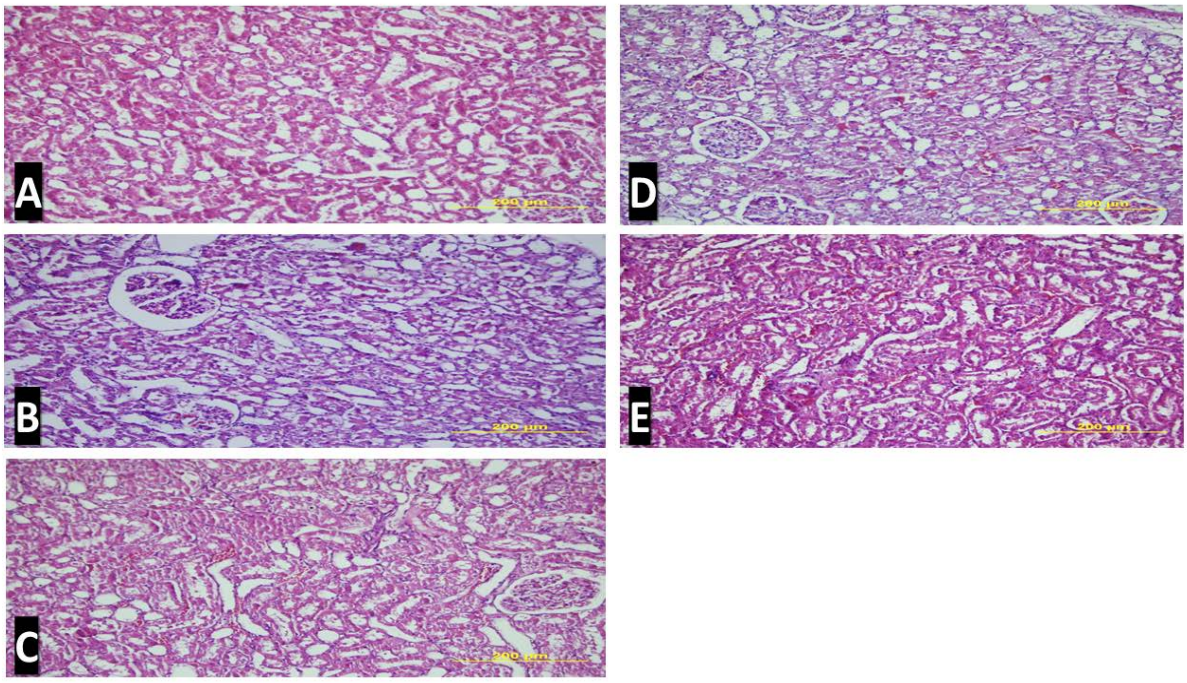

Figure 1. Histopathological examination of kidney samples of the groups (HEx20)

A. Sham Group Kidney; *Mild interstitial edema, loss of brush border and tubular cast formation were observed in focal areas.* ***B. Control Group Kidney;*** *The findings seen in diffuse tubular damage include tubular dilatation, interstitial edema, tubule epithelial necrosis, and shedding of tubular epithelium into the lumen.* ***C: Dexmedetomidine Group Kidney;*** *However, tubular necrosis, which can be distinguished in a few focal areas, was accompanied by mild interstitial edema, brush border loss and focal mild tubular cast formation in focal areas.* ***D: Dexmedetomidine + Thymoquinone Group Kidney****; However, tubular necrosis, which can be distinguished in a few focal areas, was accompanied by mild interstitial edema, brush border loss and focal mild tubular cast formation in focal areas.* ***E: Thymoquinone Group Kidney;*** *However, tubular necrosis, which can be distinguished in a few focal areas, was accompanied by mild interstitial edema, brush border loss and focal mild tubular cast formation in focal areas.*

Table 1. Comparison of TAS, TOS, OSI and Histopathological Damage Scores Between Groups

	Sham	Control	Dex	TQ	Dex-TQ	p
TAS	0.33±0.07^{+}	0.07±0.01*	0.13±0.03*$^{+}$	0.14±0.03$^{+ǂ}$	0.13±0.01$^{+ǂ}$	<0.05
TOS	18.68±3.41^{+}	36.97±6.26*	27.46±5.90*$^{+}$	27.51±3.73*$^{+}$	26.41±5.84*$^{+}$	<0.05
OSI	5.92±1.89^{+}	54.84±20.67*	21.29±7.11^{+}*	20.11±6.90$^{+ǂ}$	20.82±6.23$^{+ǂ}$	<0.05
HDS	2.60±0.69^{+}	4.60±0.69	3.10±0.87^{+}	2.80±0.91^{+}	3.10±1.44^{+}	<0.05

** Significant value according to sham group p<0.05 + Significant value compared to the control group p<0.05*

Dex: Dexmedetomidine; TQ; Thymoquinone; HDS: Histological damage scoring TAS: Total Antioxidant Status; TOS: Total Oxidant Status; OSI: Oxidative Stress Index

Discussion

Our aim in this study is to investigate the effects of Thymoquinone and Dexmedetomidine on the kidneys in IRI caused by IR in the hind limb with tourniquet in rats. As a result, histopathological damage and TAS, TOS, OSI values in TQ, DEX and DEX-TQ groups were found to be significantly more positive in terms of oxidative stress compared to the control group.

IRI occurs after the use of tourniquets in the lower extremities in various surgical operations, especially in orthopedic surgery. IRH has local and systemic effects, and kidney involvement from distant organs affects morbidity and mortality (13,14). Since the tourniquet is widely used in daily surgical practice, the experimental hind limb IR model was taken as an example to see its effects. In studies on this subject, the response of the kidneys of rats was very well determined, and rats were preferred in most of the studies (15). We also used Wistar albino rats in our study.

Many studies have been conducted on antioxidant treatments, since FOR caused by IRH causes undesirable results in many tissues and organs. Since oxidative damage plays a role in the pathogenesis of many pathologic situations such as diabetic nephropathy (16), atrial fibrillation (17), studies have been conducted using antioxidants in the treatment. Antioxidant vitamin E has been shown to reduce the damage in diabetic nephropathy in humans and alpha lipoic acid in rats (18).

Various models were used to generate hind limb IRI in rats. Femoral artery clamping or bandaging methods are used (8,19,20). In our study, Ischemia was provided to the left lower extremities of the rats with an elastic bandage, modeling the method used by Yassin et al. (9). In our study, considering previous studies, a 2-hour reperfusion was performed after 4 hours of ischemia.

The effects of various new agents such as thymoquinone and curcumin are also being investigated for the prevention of cellular damage (21,22). Many chemicals and drugs have been used in experimental models to reduce IRI, but they have not been used in daily practice due to serious side effects or unsuitable use during surgery. Therefore, the effects of sedatives and hypnotics used during anesthesia on IRH have been important (23). In our study, we preferred Dexmedetomidine, an alpha-2 agonist used for sedation in anesthesia and intensive care units, because of its protective effects against IRH (24,25).

In studies investigating the effects of dexmedetomidine on the kidney in IR models, histopathological evaluations were made. Parameters such as necrosis in the tubular epithelium, apoptosis, neutrophil infiltration, loss of brush border due to IRH in the kidneys were examined and evaluated with various damage scores. In the study of Koçoğlu et al., the protective effect of dexmedetomidine on the kidneys against IRH was demonstrated histopathologically (19). It has also been shown to be protective in the lung (26) and contralateral kidney (27) in a renal IR model. When the kidney samples taken in the IR model created by mesenteric artery occlusion were examined, histopathologically less damage was observed in the Dexmedetomidine group compared to the control group (24).

In our study, TAS, TOS, and OSI levels were measured. Although there was no significant difference between Dex, TQ and Dex-TQ groups, TAS in these 3 groups was higher than the control group, lower than the Sham group, and TOS and OSI were lower than the control group and higher than the Sham group. (Table 1) ($p<0.05$).

Thymoquinone is the active ingredient derived from N. Sativa and has become popular among medicinal plants due to its proven therapeutic properties. It has anti-inflammatory, anti-neoplastic, gastroprotective, anti-epileptic, anti-histaminic properties. Its most important feature is its antioxidant effect. It acts as an anion scavenger and neutralizes oxygen radicals. Since FOR occurring in IRI plays a role in the pathogenesis of many diseases, Thymoquinone and N. Sativa products have been used in many experimental and clinical studies due to their antioxidant properties (28).

The effects of Thymoquinone have been investigated in different IR models. As a result, thymoquinone appears to be a promising agent with its neuroprotective effect in neurodegenerative conditions such as cerebral ischemia, providing protection against oxidative stress (29,30).

In a study in which another renal IR model was applied, N.Sativa was found to be effective in reducing urea, creatinine, and tubular necrosis score when the group given N.Sativa was compared with the control group. In addition, N.Sativa's TAS was found to be higher and TOS and OSI lower than the control in both blood and kidney samples (31).

In a study investigating the effects of thymoquinone in a hind limb IR model, IR was provided by femoral artery ligation. Again, unlike our study, 2 hours of ischemia and 1 hour of reperfusion were applied. Thymoquinone at different doses (20, 40, 80mg/kg) 1 hour before reperfusion was divided into 3 groups (n:8) and administered i.p. and control and sham groups were formed to compare the results. It was concluded that thymoquinone showed antioxidant properties in the hind limb IR model and prevented the damage caused by oxidative stress on the striated muscle. Based on the EMG results, it was determined that Thymoquinone was protective in both ischemia and reperfusion phases, and the conductivity in neurons that were disrupted in ischemia was also preserved by Thymoquinone (21). In a recent study, it was reported that Thymoquinone and Dexmedetomidine together had a protective effect against erythrocyte deformity in rats treated with hind limb IRH (32).

In the hind limb IR model, we created with a tourniquet, we obtained data similar to this study. TAS in the thymoquinone group was higher than in the control; we found lower TOS and OSI. As demonstrated by the various IR models mentioned above, we also think that Thymoquinone has antioxidant properties. Thymoquinone's antioxidant property has been associated with various mechanisms.

1- The 'quinone' in its structure shows strong redox properties. It can easily pass-through barriers, easily reach the intracellular compartments, and thus scavenge oxygen radicals. Quinone reductase reduces the 2 electrons and prevents the participation of electrons in the cycle, which leads to the formation of FOR, and thus reduces oxidative stress (33).

2- Thymoquinone inhibited iron-dependent microsomal lipid peroxidation in vitro (28).

3- In case of inflammation, oxidants, eicosanoids, cytokines and lytic enzymes are released from inflammatory cells such as macrophages and neutrophils. Thymoquinone inhibits the LO and COX pathways that play a role in inflammation and suppresses oxidative stress with its anti-inflammatory effect (34).

In our study, we aimed to compare the effects of these two antioxidant agents in separate groups and in one group by giving Dexmedetomidine and Thymoquinone together, to compare their superiority over each other. As a result of the data we obtained, we could not find a statistical difference in terms of TAS, TOS, OSI and histopathologically.

Conclusion

As a result, When the data obtained from our study with rats with hind limb IR were evaluated; Thymoquinone and Dexmedetomidine significantly reduce kidney damage due to ischemia-reperfusion. These two agents have no superiority over each other in terms of oxidative stress. In surgical operations where tourniquets are used in the clinic, the kidneys are affected due to oxidative stress. These effects of Dexmedetomidine should be considered in anesthesia management and intensive care follow-ups in patient groups with poor renal functions such as ARF and CRF or in patients whose renal functions need to be preserved such as transplantation. Thymoquinone has been shown to have antioxidant properties in experimental studies. Further clinical studies are needed to benefit from these features in the clinic.

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Ethical Approval: *Ethical Approval was obtained before the study from Harran University Animal Experiments Local Ethics Committee (approval decision: dated 30.04.2012, numbered B.30.2.HRU.0.05.07.00/270).*

Author Contributions: *Concept: H.A., Ş.Y. Literature Review: E.B., H.A., Ş.Y., M.A.K. Design : H.A., Ş.Y.*

Data acquisition: E.B., M.A.K., H.H.Y., A.K. Analysis and interpretation: H.A., N.A., A.T., S.K. Writing manuscript: E.B., H.A., M.A.K. Critical revision of manuscript: E.B., H.A., M.A., Ş.Y.

Conflict of Interest: *The authors have no conflicts of interest to declare.*

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