ORİJİNAL ARAŞTIRMA ORIGINAL RESEARCH

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Protective Effects of Dexmedetomidine on Ischemia-Reperfusion Injury in Rat Ovary

Rat Overinde Oluşturulan İskemi-Reperfüzyon Hasarı Üzerine Deksmedetomidin'in Koruyucu Etkileri

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ABSTRACT Objective: Aim of this study is to evaluate the protective effect of dexmedetomidine on the histopathology and biochemical parameters in reducing damage in ischemia/reperfusion injury in rats ovary and to compare the effect of two different doses of dexmedetomidine. **Material and Methods:** Forty-two adult female Wistar Albino rats were used. Rats were separated into six groups: Sham, Torsion, Torsion+Detorsion, Torsion+Detorsion+Salin, Torsion+Detorsion+ Dexmedetomidine 10 μg/kg, and Torsion+Detorsion+Dexmedetomidine 20 μg/kg. Exception of the Sham group, ovarian torsion procedure was performed to all groups for 2 hours. Detorsion procedure was implemented to all groups for 2 hours, exception of Torsion group. Medications were given intraperitoneally half an hour before the detorsion procedure in Salin, Dexmedetomidine 10 μg and 20 μg groups. Then 2 mL of blood samples were drawn for markers of oxidative stress. The right ovaries were separated from all rats. **Results:** The oxidative stress levels and histologic scores values of ovarian tissues were higher in Torsion+Detorsion group than in Sham group ($p<0.001$). By the uses of dexmedetomidine 10 and 20 μg, a significant decrease was established in the mean levels of oxidant markers and histopathologic scores. **Conclusion:** Administration of dexmedetomidine 10 μg and 20 μg are effective in preventing tissue damage by ischemia\reperfusion injury in ovarian torsion. However, there was no difference between the dexmedetomidine 10 μg and 20 μg treatments with regards to protective activity.

Keywords: Ovary; dexmedetomidine; reperfusion injury

ÖZET Amaç: Bu çalışmanın amacı rat overlerinde deneysel olarak oluşturulan iskemi\reperfüzyon hasarına karşı deksmedetomidin tedavisinin koruyucu etkinliğini değerlendirmek ve iki farklı deksmedetomidin dozlarını karşılaştırmaktır. **Gereç ve Yöntemler:** Bu çalışmada 42 tane dişi Wistar Albino rat kullanıldı. Ratlar her biri yedişer rat olmak üzere 6 gruba ayrıldı: Sham opere, Torsiyon, Torsiyon-Detorsiyon, Torsiyon+Detorsiyon+ İzotonik sodyum klorür, Torsiyon-Detorsiyon+ Deksmedetomidin 10 μg ve Torsiyon-Detorsiyon+ Deksmedetomidin 20 μg. Sham opere grubu hariç diğer tüm gruplara iki saat boyunca ovaryan torsiyon işlemi uygulandı. Torsiyon grubu dışındaki diğer tüm gruplara 2 saat detorsiyon prosedürü uygulandı. Salin, Deksmedetomidin 10 μg ve Deksmedetomidin 20 μg gruplarında yer alan ratlara detorsiyon işleminden yarım saat önce intraperitoneal yoldan 2 ml serum fizyolojik, 10 μg/kg Deksmedetomidin ve 20 μg/kg Deksmedetomidin uygulandı. Ardından tüm ratlardan 2 ml kan alındı ve torsiyone edilen sağ ovaryum çıkarıldı. **Bulgular:** Histopatolojik hasar skorlaması ve oksidatif stres düzeyleri Torsiyon-Detorsiyon grubunda Sham opere grubuna göre daha yüksek idi ($p<0.001$). Deksmedetomidin 10 μg ve 20 μg tedavilerinin histopatolojik doku hasarını ve oksidant markerların seviyesini azaltmada etkili olduğu saptanmıştır. **Sonuç:** Deksmedetomidin uygulamalarının ovaryum torsiyonuna bağlı doku hasarını önlemede etkili olduğu; ancak 10 ve 20 μg dozda ilaç uygulamaları arasında etkinlik açısından önemli bir farkın olmadığı belirlendi.

Anahtar Kelimeler: Over; deksmedetomidin; reperfüzyon hasarı

Adnexal torsion is the fifth leading cause of emergency gynecological surgery in spite of being seen rare. It is often seen in women with reproductive age, although it can be seen in prepubertal and postmenopausal period.[1] Early diagnosis and treatment plays an important role in maintain the fertilization. Laparoscopy is a precise diagnosis and treat-

ment method of ovarian torsion.[2] Once diagnosed, the twist can be surgically detorsed to restore the normal blood flow and thus prevent necrosis. In detorsion prosedure, re-oxygenation of ischemic tissues produce the reactive oxygen species. Paradoxically reperfusion injury gives more damage than from ischemic damage to tissues.[3] Therefore, a number of anti-inflammatory and antioxidant agents, such as amlodipine, aprotinin, trapidil, cafeic acid, erythropoietin, atorvastatin and curcumin, were used to prevent ischemia/reperfusion injury.[3-9]

Dexmedetomidine (-4-5- [1-(2, 3-dimethylphenyl) methyl] -1H-imidazole) has a wide pharmacological spectrum of properties is a novel lipophilic α-methylol derivative, strong and highly selective α2-adrenoceptor agonist.[10] Dexmedetomidine has been shown to be useful in intestinal, testicular, kidney, lung and cardiac I/R injury in experimental work.[11-15]

The aim of this study is to evaluate whether dexmedetomidine administration can protect rat ovaries from I/R injury. Histologic and biochemical examinations of the ovaries were evaluated to analyze the dose dependent protective effects of dexmedetomidine administration.

MATERIALS AND METHODS

The study was conducted prospectively in the Department of Obstetrics and Gynecology Clinic of Harran University Medical Faculty, and Veterinary Faculty, between June 2014 -June 2015. Fourty-two adult female Wistar Albino rats, weighing 180-240 g, were used in the study. The study protocol was approved by the Harran University and Dollvet Ethics Committee for animal research (DOLLVET -HADYEK, date and number: 30.05. 2014/30). All animal studies were performed in accordance with the ARRIVE (Animal Research: Reporting of In Vivo Experiments) guidelines. The rats were kept for at least 7 days under appropriate conditions of temperature (25 °C) / humidity (55-60%) and a 12 h light cycle while being given sufficient water and feed stuff.

Each rat was weighed and anesthetized with intramuscular ketamine hydrochloride (50 mg/kg Ketalar; Eczacibasi, Istanbul, Turkey) and xylazine hydrochloride (10 mg/kg Rompun; Bayer AG, Germany).

The rats were randomly separated into 6 equal groups, with 7 rats in each. The groups included Sham (I), Torsion (II), Torsion+Detorsion (III), Torsion+Detorsion+Salin (IV), Torsion+ Detorsion+ Dexmedetomidine 10 μg/kg (V) and Torsion+Detorsion+ Dexmedetomidine 20 μg/kg (VI). The procedure and doses of dexmedetomidine administration were based on the previous studies that had been proven successful in I\R.[7] Until the end of the study, the investigators carrying out the biochemical and histological analyses were uninformed about the randomization.

After the preoperative sterilization, a longitudinal incision (2 cm) was performed in the midline area of the lower abdomen (Figure 1). In the Sham group, the uterine horns and both adnexa were observed and then the abdominal wall was closed with 3-0 silk sutures (Sham operation). After a 2 h period, relaparotomy was performed and right ovary was surgically removed. 2 mL blood sample was drawn from ven cava inferior to evaluate oxidative stress markers. In the adnexal Torsion model, under the right tube and right ovarian tissues were clamped and after a 2 h period of ischemia, right ovary was surgically removed through relaparotomy. Also blood sample was received as Sham group. In the Torsion-Detorsion group, right adnexal torsion (2 h of ischemia) and then adnexal detorsion (2 h of reperfusion) were performed. Following the total 4 h period, the right ovary was surgically removed through relaparotomy and blood sample was received as Sham group. In the Torsion-Detorsion-Salin group, right adnexal torsion (one and a half hours) and adnexal detorsion (2 h of reperfusion) were performed. The salin (2 mL) was intraperitoneally administered 30 min before the Sham operation. Following the total 4 h period, the right ovary was surgically removed through relaparotomy and blood sample was received as Sham group. In the Torsion-Detorsion-Dex 10 μg group, right adnexal torsion (one and a half hours) and then dexmedetomidine 10 μg/kg was administered intraperitoneally, after 30

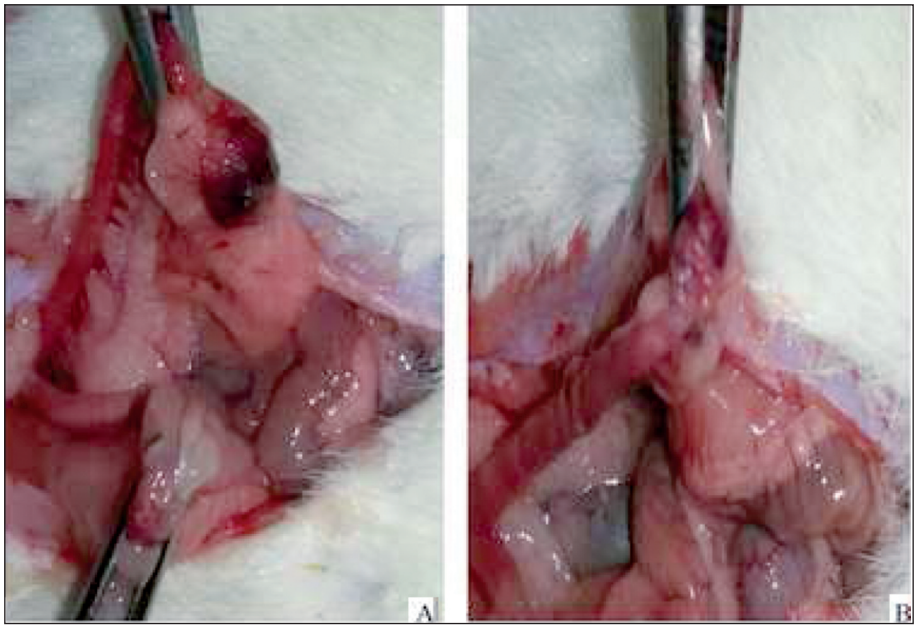

FIGURE 1: A) Above (right ovary) is ischemia generated and below (left) is normal rat ovary, **B)** Appearence of the right ovary after reperfusion.

min, adnexal detorsion (2 h of reperfusion) was performed by relaparatomy. Following the total 4 h period, the right ovary was surgically removed through relaparotomy and blood sample was received as Sham group. In the Torsion-Detorsion-Dex 20 µg group, right adnexal torsion (one and a half hours) and then dexmedetomidine 20 µg /kg was administered intraperitoneally, after 30 min, adnexal detorsion (2 h of reperfusion) was performed by relaparatomy. Following the total 4 h period, the right ovary was surgically removed through relaparotomy and blood sample was received as Sham group. When all these surgeries were achieved, the rats were sacrificed. All the samples were labeled with consecutive numbers and then transferred to the laboratory.

HISTOLOGICAL EVALUATION

Once the ovaries were fixed in 10% neutral buffered formalin for 48 h, then each ovarian tissue sample was embedded in paraffin. The samples were cut by using a 4 mm thick microtome (Leica RM2125RTS) and then stained with hematoxylin and eosin (H&E). All the sections were analyzed and photographed by a light photomicroscope (Olympus® Inc. Tokyo, Japan). At least five microscopic fields were examined to score the specimens semiquantitatively. The criteria for ovarian injury included interstitial edema, follicular cell degeneration, vascular congestion, hemorrhage, and leukocyte infiltration (Figure 2). Each specimen was scored on a scale ranging from 0 to 4 (0: none; 1: < 25%; 2: 25-50%; 3: 50-75%; 4: > 75%). The scoring system was used based from a previous study, Kara et al. were described in 2012.[16] The analysis on the ovarian sections was conducted in a blinded fashion by the same pathologist.

BIOCHEMICAL ANALYSIS

All serum samples were stored at -40°C for biochemical analysis, these are total antioxidant level (TAS), total oxidant level (TOS), oxidative stress index (OSI), interleukin 1 (IL 1), interleukin 6 (IL 6), interleukin 10 (IL 10) and tumor necrosis factor-alpha (TNF-alpha).

STATISTICAL ANALYSIS

Data analyses were achieved with SPSS for Windows 18.0 software (Statistical Package for Social Sciences; SPSS Inc., Chicago, IL). Means and standard deviations (SD) were used to describe the numerical variables. A Kolmogorov-Smirnov test was used to evaluate the distribution pattern of the data. For the comparisons among groups, the

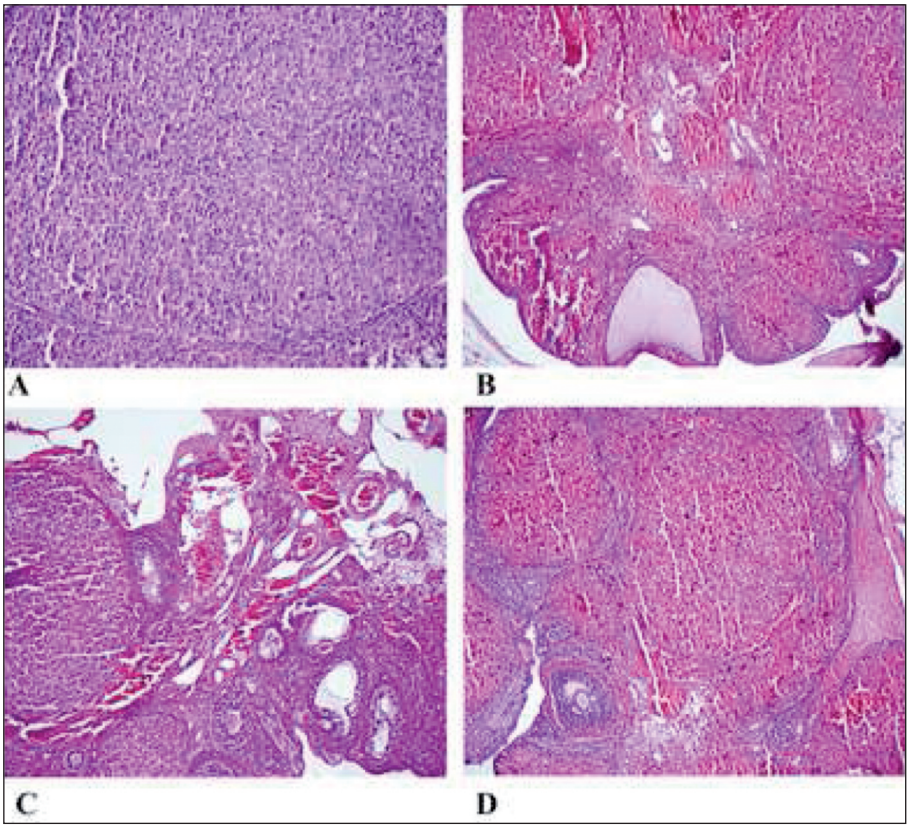

FIGURE 2: A) Normal ovarian tissue structure in the Sham group (H&E, x100); **B)** ovarian sections containing a diffuse amount of vascular congestion, hemorrhage, follicular degeneration and edema in the Torsion-Detorsion group (H&E, x100); **C)** ovarian sections containing a focal vascular congestion and hemorrhage with mild interstitial edema in the Torsion-Detorsion -Dexmedetomidine 10 mcg/kg (H&E, x100); **D)** ovarian tissue with a focal vascular congestion and hemorrhage as well as moderate interstitial edema in the Torsion-Detorsion-Dexmedetomidine 20 mcg/kg (H&E, x100).

Oneway ANOVA and Bonferroni test were used for independent groups and Wilcoxon for the dependent ones. The correlation coefficient was assessed by the Pearson's correlation test. The P value less than 0.05 was accepted as significant.

RESULTS

The levels of oxidative stress markers and the histological scores for all 6 groups are compared in Tables 1 and 2.

The highest level of TAS was observed in Dexmedetomidine groups (dexmedetomidine 10 μg and dexmedetomidine 20 μg) and the lowest level was observed in Torsion-Detorsion group. The evaluation of 10 μg and 20 μg dexmedetomidine carried out between groups were found to be equally effective in increasing the levels of TAS (for both p = 0.988, Table 1).

The highest values of TOS and OSI were observed in Torsion-Detorsion group, while the lowest levels were seen in the Sham group. Evaluation of between the Torsion-Detorsion group and the groups of 10 μg\20 μg Dexmedetomidine, both drugs significantly reduced the level of TOS (p= 0.002, p= 0.003, respectively) and OSI (p= 0.018, p= 0.039, respectively) (Table 1). There were no significant difference between the Dexmedetomidine 10 μg and 20 μg groups regarding the TOS and OSI levels (p= 0.994 for both, Table 1).

The mean levels of TNF-α, IL-1, IL- 6 and IL-10 for each group are presented in Table 1.

GROUPS ARE EVALUATED AS HISTOPATHOLOGICAL DAMAGE

Congestion, hemorrhage, leukocyte infiltration, follicle degeneration, interstitial edema obtained histologically from the rat ovaries and total score results, are presented in Table 2.

TABLE 1: The oxidative stress markers in all groups (Mean values ± SD).

	I	II	III	IV	V	VI	p
TAS	0.9±90,10	0.94±0.17	0.83±0.20	0.86±0.13	1.08±0.15	1.17±0.17	0.003
TOS	19.67±4.21	74.55±14.24	92.18±9.54	83.77±7.73	70.00±13.33	65.76±17.78	<0.001
OSI	5.56±0.96	6.70±1.15	8.71±0.39	7.29±2.98	6.59±1.86	6.28±1.68	0.034
IL 1	46.10±3.77	63.51±17.92	76.29±19.31	75.08±19.71	55.24±10.92	49.58±2.02	0.001
IL 6	11.03±3.47	22.25±2.44	25.91±1.11	25.36±1.09	12.83±2.37	11.85±1.63	<0.001
IL 10	70.99±7.47	48.00±15.58	36.73±8.92	37.89±9.48	70.72±17.11	67.64±19.12	<0.001
TNF α	44.01±6.15	73.87±12.64	118.19±15.50	117.26±16.17	51.03±8.30	49.22±6.64	<0.001

Abbrevations: SD: Standart Deviation, **TAS:** Total Antioxidant level, **TOS:** Total oxidant level, **OSI:** Oxidative Stress Index, **IL:** Interleukin **TNF- α:** Tumor necrosis factor-alpha. Groups: I) Sham, II) Torsion, III) Torsion+Detorsion, IV) Torsion+Detorsion+Salin, V) Torsion+Detorsion+Dexmedetomidine 10 µg/kg, and VI) Torsion+Detorsion+ Dexmedetomidine 20 µg/kg.

TABLE 2: Histopathologic evaluation scores of the rat ovarian tissues in all groups (Mean values ± SD).

	I	II	III	IV	V	VI	p
Vascular congestion	0.28±0.48	1.85±0.37	2.85±0.37	2.57±0.53	2.14±0.69	2.42±0.53	< 0.001
Hemorrhage	0.28±0.48	2.14±0.37	3.00±0.00	2.85±0.37	1.71±0.95	2.00±1.15	< 0.001
Leukocyte infiltration	0.28±0.48	0.42±0.53	1.57±0.53	1.42±0.78	0.28±0.75	0.14±0.37	< 0.001
Follicular degeneration	0.00±0.00	0.28±0.48	0.85±0.37	0.71±0.75	0.42±0.78	0.42±0.53	0.087
Interstitial edema	0.14±0.37	2.00±0.57	2.71±0.48	2.14±0.37	1.28±0.48	1.28±0.75	< 0.001
Total score	1.00±0.81	6.71±1.38	11.00±1.15	9.71±1.25	5.85±1.86	6.28±1.79	< 0.001

Abbrevations: SD: Standart Deviation, Groups: I) Sham, II) Torsion, III) Torsion+Detorsion, IV) Torsion+Detorsion+Salin, V) Torsion+Detorsion+Dexmedetomidine 10 µg/kg, and VI) Torsion+Detorsion+ Dexmedetomidine 20 µg/kg.

A significant difference was found among groups as congestion, hemorrhage, edema and leukocyte infiltration in terms of histopathological damage parameters ($p < 0.001$). Statistically, no significant difference was found among groups in terms of follicular degeneration in the histopathological evaluation ($p = 0.087$) (Table 2).

In evaluation of between the Torsion-Detorsion group and Dexmedetomidine groups (10 µg \ 20 µg); the reduced histopathological damage was found in the drug used groups. We found both 10 µg and 20 µg Dexmedetomidine groups equally effective in the evaluation of reducing the histopathological damage (Table 2).

The lowest level of total score was seen in the Sham group and the highest damage score was observed in the Torsion-Detorsion group. Assessment between the Torsion-Detorsion group and Dexmedetomidine groups(10 µg \ 20 µg), in the drug used groups total damage score were found decreased as statistically significant (both $p < 0.001$, Table 2). We found both 10 µg and 20 µg Dexmedetomidine groups equally effective in reducing the total damage score (both $p = 0.997$, Table 2).

The histologic morphologies of the ovaries from the treated and untreated groups are illustrated in Figure 2.

DISCUSSION

Ovarian vascular pedicle with the reduction of arterial blood flow to torsion on its axis, also results in obstruction of the venous and lymphatic drainage.[17] The reduction of blood flow due to ovarian torsion, tissue causes an increase in lipid peroxide levels lactic acid and hypoxanthine.[5,18] Even with necrotic appearance ovarian tissue, detorsion procedure should be applied in patients

whose desired fertility preservation.[19] However the ovarian tissue after detorsion procedure there is increase in production occurs neutrophil infiltration / activation, nitric oxide, cytokines such as TNF- α, and free oxygen radicals. In these cases ischemic damage lead to the formation of more tissue damage.[16,18,20] Therefore, in order to avoid I/R damage the use of antioxidant pharmacological agents may be useful during or before reperfusion.[20]

In studies Dexmedetomidine has been shown to be useful in intestinal, testicular, kidney, lung and cardiac I/R injury.[11-15] There is no study that showing the protective effect of dexmedetomidine on the I/R related tissue damage in rat ovary. We purposed to evaluate whether dexmedetomidine administration can protect rat ovaries from I/R injury, and this protection may be dose dependent.

Kip et al. investigated developing lung injury related with I/R injury applying dexmedetomidine 100 μg /kg after ischemia in diabetic rats and control group. They found that the lung injury was reduced in dexmedetomidine group.[21] Luo et al. demonstrated that dexmedetomidine prevents apoptosis in rat I/R injury renal tubular structure located in decreased apoptosis of NRK-52E cells by affecting the function of gap junctions between cells.[22] Freeman et al. have been showed dexmedetomidine significantly reduces apoptosis by preserving the structure of the neuronal structure in cell cultures compared to control group rats after aortic surgery and thus reduces the risk of paraplegia.[23] Again, Zhang et al. demonstrated in their work, I/R injury in rats after intraperitoneal injecting dexmedetomidine prevents apoptosis of epithelial prevent inflammatory reaction in the intestinal cells.[11] Kucuk et al. have done 45 minutes reperfusion after 45 minutes clemping portal vein in 24 albino rats in a study. 100 mcg/kg dexmedetomidine was given to medicated group and they took the blood levels of PON 1, glutathione S transferase, SOD and catalase. All parameters found significantly higher in treated with dexmedetomidine group, except for Glutathion S transferase.[24] Our study showed statistically significant decreased total damage score in the drug treated groups. Evaluation of dexmedetomidine 10 μg and 20 μg carried out between groups were found to be equally effective in reducing the total damage score.

Tuglu et al. revealed relationship among TAS, TOS and OSI levels in rats given dexmedetomidine dose increases 50 μg/kg to 100 μg/kg in testicular torsion and detorsion study. Dexmedetomidine dose increasement significantly elevates TAS level but reduces the OSI level. Level of TOS does not significantly change when dexmedetomidine 50 μg/kg treated group compared with other group. However, when the dexmedetomidine effect is evaluated histopathologically, there is no significant evidence.[12] We found highest TAS level in both Dexmedetomidine group (10 μg and 20 μg), and lowest TAS level in Torsion-Detorsion group. However, the assessment of between the dexmedetomidine groups (10 μg and 20 μg) were observed equally effective in improving the TAS levels. Also both drug doses significantly reduced the oxidative and inflammatory markers TOS, OSI, TNF-α, IL 1 and IL 6 levels, and significantly increased IL 10 level which is an antiinflammatory marker. However, there was no significant difference in reducing blood oxidative stress parameters between the dexmedetomidine 10 μg and 20 μg groups. All results of this study are consistent with the literature. Also, the present study revealed a statistically significant decrease in terms of all histopathologic parameters in the drug used groups. But the evaluation of dexmedetomidine 10 μg and 20 μg groups showed that both drug doses were equally effective in reducing of the histopathological damage.

CONCLUSION

We concluded dexmedetomidine (10 μg/20 μg), antioxidant and antiinflammatory pharmacological agent, may be useful in preventing tissue damage in patients with ovarian torsion. Further studies are required to make strong our conclusion.

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Conflict of Interest

Authors declared no conflict of interest or financial support.

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