



## Protective Effect of Oxytocin on Ovarian Histopathology at Septic Rat Model

### ABSTRACT

**Objectives:** Sepsis is the body's response to infections, and it is associated with high morbidity and mortality rates. This study aimed to examine the histopathological changes in rats with an intra-abdominal abscess model after oxytocin administration and to investigate oxytocin's potential protective effects.

**Methods:** A total of 21 Wistar Albino rats were randomly divided into three groups, with seven in each group. The sepsis group was created after cecal-ligation-perforation. The first group consisted of normal healthy rats, the second group of septic rats, and the third group of septic rats administered oxytocin. The ovaries of the rats were then surgically removed and examined histopathologically.

**Results:** The study evaluated normal ovarian tissue (Group 1), ovarian tissue with sepsis (Group 2), and ovarian tissue treated with oxytocin (Group 3) for endothelial damage (wall thickening, fibrin deposition, and swelling), vacuolization, cellular debris, proteinous material deposition, and neutrophil infiltration. Statistically significant differences were observed in endothelial damage ( $p=0.001$ ), vacuolization ( $p=0.005$ ), cellular debris ( $p=0.030$ ), proteinous material deposition ( $p=0.030$ ), neutrophil infiltration ( $p=0.001$ ), and the total score ( $p=0.001$ ). Comparing Group 2 and Group 3, no statistically significant differences were found in endothelial damage ( $p=0.063$ ), vacuolization ( $p=0.059$ ), cellular debris ( $p=0.102$ ), and proteinous material deposition ( $p=0.102$ ). However, significant differences were noted in neutrophil infiltration ( $p=0.020$ ) and the total score ( $p=0.028$ ).

**Conclusion:** The study observed that in oxytocin-administered sepsis models, the cellular changes caused by the septic condition improved in the histopathological examination of the ovarian tissue, favoring the oxytocin group.

**Keywords:** Ovary, oxytocin, rats, sepsis

Sepsis is the systemic response to infections, characterized by biochemical, molecular, and hormonal dysfunctions of the body. This condition can result in organ damage and even mortality. Sepsis cases were observed more frequently, and mortality rates were higher during periods when antibiotic treatment was less prevalent. For example, an estimated 164,000 cases of sepsis occurred each year in the United States (USA) in the late 1970s (1). In a 12-year study conducted with 101,064 patients who had sepsis and septic shock in 171 Intensive Care Units (ICUs) in Australia and New Zealand, there was a 50 percent risk reduction in in-hospital mortality (from 35% to 18%) between 2000 and 2012 (2). An underlying injury or non-communicable disease is detected in almost half of all sepsis-related mortalities. The contribution of various infectious organisms to the sepsis burden has varied over time (3,4).

Sepsis covers a spectrum that ranges from infection and bacteremia to sepsis and septic shock, which can cause Multiple Organ Dysfunction Syndrome (MODS) and mortality. Systemic Inflammatory Response Syndrome (SIRS) is no longer included in this definition because it is not always caused by infection. Septic shock is a presentation in which the inflammatory response due to infection is accompanied by vasodilation, and the circulation is impaired, but septic shock is more mortal (5). The cardinal signs of sepsis are hypotension, tachycardia, fever, and leukocytosis. As the severity deteriorates, signs of shock (e.g., cold skin and cyanosis) and organ dysfunction (e.g., oliguria, acute kidney injury, altered mental status) add to the manifestation. Rapid initiation of appropriate antibiotic treatment in the early period and aggressive treatment of tissue perfusion increase the success

Belma Gözde Özdemir<sup>1</sup>

Metin Özsoy<sup>2</sup>

Halis Özdemir<sup>3</sup>

Songül Yerlikaya Kavak<sup>4</sup>

Salih Salar<sup>5</sup>

<sup>1</sup>Malatya Training and Research Hospital, Department of Obstetrics and Gynecology, Malatya, Türkiye

<sup>2</sup>Ankara Training and Research Hospital, Department of Infection, Ankara, Türkiye

<sup>3</sup>Inonu University Faculty of Medicine, Department of Perinatology, Malatya, Türkiye

<sup>4</sup>Malatya Training and Research Hospital, Department of Pathology, Malatya, Türkiye

<sup>5</sup>Ankara Technical Universal Verification Center, Veterinarian, Ankara, Türkiye

**Corresponding author:**

Belma Gözde Özdemir

gzdgrn35@gmail.com

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of treatment (6).

One of the most important causes of sepsis is Tuboovarian Abscess (TOA). Antimicrobial treatment and surgical drainage are included in TOA treatment (7). After treatment, long-term complications are especially important for women of reproductive age. A pelvic infection can cause many consequences, especially infertility in the reproductive age. Chronic inguinal pain, extrauterine pregnancy, and subfertility/infertility are some of these sequelae (8). The inflammatory response that is secondary to infection and tissue destruction caused by oxidative stress constitute the main etiopathogenesis of these complications. In a previous study of a cohort of 100,000 women aged 20-24 years who experienced pelvic inflammatory disease, 18,600 were followed up with chronic pelvic pain, 16,800 of them had infertility, and 8,550 cases were reported to have ectopic pregnancy (9).

Oxytocin (OT) is a drug known for its effects in gynecology and obstetrics. It has also been investigated in recent years for its antioxidant effects. Oxytocin is synthesized in the supraoptic and paraventricular nuclei of the hypothalamus and is a neurohypophyseal nonapeptide hormone that performs its various actions via the OT receptor, which is a G-protein-coupled receptor (10). It was shown that oxytocin increases the survival of ischemic skin flaps in rats through the activation of growth factors or anti-inflammatory mechanisms (11). It was also shown that OT has an anti-inflammatory effect on neutrophil deposition and hyperalgesia in the hind paw of carrageenan (carrageenans or carrageenins are a family of natural linear sulfated polysaccharides extracted from red edible seaweed) (12). Previous studies have shown that it also protects neural cells against hypoxia-ischemia by reducing chromatin proteins (13).

In the study, the purpose was to examine the pathological changes following oxytocin administration in rats with an intra-abdominal abscess model and to determine whether it can be used in addition to therapeutic modalities with its known antioxidant effect.

## METHODS

### Animals

Experiments were conducted on 21 male Wistar-Albino rats (8 weeks old, weighing 200–225 g). The Animal Ethics Committee of Saki Yenilli Experimental Animals Production Laboratory (Ankara, Türkiye) approved the study. Rats were housed in separate cages with free access to food and water, in an environment controlled for temperature and a full light-dark cycle. All rats were cared for according to the “Principles for the Care of Laboratory Animals” recommended by the National Society for Medical Research and the “Guidelines for the Care and Use of Laboratory Animals” prepared by the Institute for Laboratory Animal Resources and published by the National Institutes of Health (NIH publication 8523, revised 1985). Ethical number: 17/08/2021 – 05 – 04-21.

The study was conducted in accordance with the Declaration of Helsinki, and animal experimentation procedures were carried out under fully ethical conditions.

### Experimental Procedures

A total of 21 Wistar Albino rats were randomly divided into three groups, with seven rats in each group.

Group 1: Control Group (no treatment group)

Group 2: Sepsis-Induced Group

Group 3: The group in which sepsis was induced and oxytocin was administered simultaneously

To create the sepsis model, all rats were anesthetized by administering 60mg/kg Ketamine Hydrochloride and 10mg/kg Xylazine intraperitoneally after 12 hours of fasting.

After ensuring appropriate anesthesia, abdominal shaving, and disinfection, a 2 cm midline incision was made for laparotomy. During the laparotomy, the cecum was isolated, the ascending colon was rubbed, and then the cecum was filled with stool, tied with 2/0 silk under the ileocecal valve, and the anterior surface of the cecum was punctured several times with a #22 intra-ketal needle. Oxytocin was administered to the third group 24 hours after the surgery. Synpitan Forte (Deva Holding Inc.) ampoule with 5-unit oxytocin was administered intramuscularly to the related group at doses of 0.1 mg/kg.

The rats were sacrificed at the end of the 48<sup>th</sup> hour, and their ovaries were removed under appropriate anesthesia, then fixed with 10% formaldehyde for histopathological examination.

### Histopathological Examination and Histopathological Scoring

The ovarian tissue samples dissected from the rats were fixed in 10% formaldehyde for 24 hours. A macroscopic evaluation was performed, and each ovarian tissue was sampled in one cassette. After routine tissue processing from biopsy samples, 4-micron-thick sections were taken from paraffin blocks. Deparaffinized tissue preparations were stained with Hematoxylin & Eosin and examined under a light microscope at 40x magnification. Normal ovarian tissue, ovarian tissue with sepsis, and oxytocin-treated ovarian tissue were evaluated separately.

In the microscopic evaluation, the most intense area observed at 40x magnification was graded for ovarian histopathological findings using a semi-quantitative scoring method. Pathological findings such as endothelial damage (wall thickening, fibrin deposition, and swelling), vacuolization, cellular debris, proteinous material deposition, and neutrophil infiltration were graded as 0 (normal), 1 (mild), 2 (moderate), 3 (severe), and 4 (very severe) (14).

### Statistical Analysis

Before the study commenced, a power analysis was performed according to the t-test. The alpha risk was set at 0.05, and the power of the study at 80%. The calculations were performed using the Minitab 16 statistical package program. According to the findings, it was calculated that there should be seven subjects in each group.

The data were analyzed using IBM SPSS Statistics 17.0 (IBM Corporation, Armonk, NY, USA). The distribution of continuous numerical variables was examined using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Descriptive statistics: For continuous numerical variables, mean  $\pm$  standard deviation values were used for data with normal distribution, and median and minimum-maximum values were used for data with abnormal distribution.

The significance of the difference in terms of continuous numerical variables between the groups was examined using the Wilcoxon Test when the number of independent groups was two and using the Friedman test when the number of independent groups was more than two. Unless otherwise specified, a p-value of <0.05 was considered statistically significant.

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### RESULTS

A total of 21 rats were used in this study, with 7 rats in each group. Normal ovarian tissue (Group 1), ovarian tissue with sepsis (Group 2), and ovarian tissue treated with oxytocin (Group 3) were evaluated for endothelial damage (wall thickening, fibrin deposition, and swelling), vacuolization, cellular debris, proteinous material deposition, and neutrophil infiltration. The total score of these five parameters was assessed as the total histopathological sepsis score. The groups were then compared for each parameter and in terms of total score values. Ovarian tissue with normal morphology was found in Group 1 (the Control Group). Endothelial damage, vacuolization, cellular debris, proteinous material deposition, and neutrophil infiltration were observed in the ovarian tissues of Group 2 and Group 3. Figure 1 shows the examination of normal ovarian tissue at 40x magnification as a result of treatment with hematoxylin and eosin. A microscopic examination of the tissues taken from rats that did not undergo any treatment is given here. Observation of normal tissue is instructive in terms of changes in sepsis and after oxytocin administration. Figure 2 presents an examination of inflammatory cell infiltration, thick-

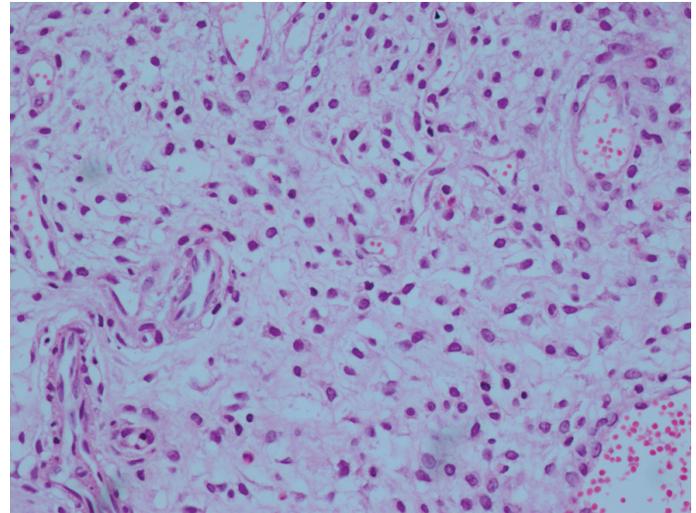


Figure 1. Normal ovarian morphology H&E 40x.

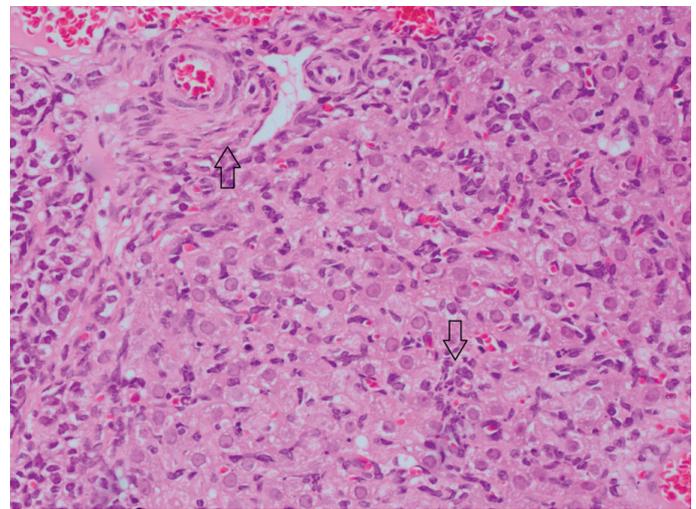


Figure 2. Inflammatory cell infiltration, vessel wall thickening, congestion, and stromal edema in sepsis. H&E 40x.

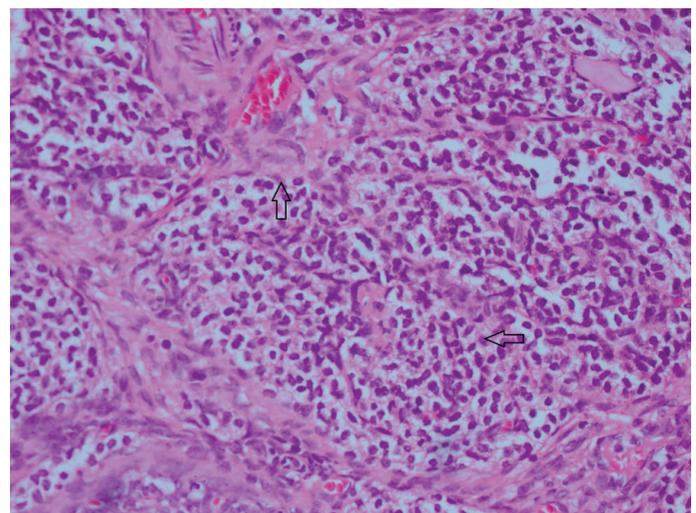


Figure 3. Reduction in inflammatory cell infiltration, vascular congestion, and stromal edema in oxytocin-treated septic ovarian tissue. H&E 40x.

**Table 1. Median and Minimum-Maximum Scores of Histopathological Findings in All Three Groups**

Histopathological Findings	Group 1: Control Group (Median, Min-Max)	Group 2: Sepsis Group (Median, Min-Max)	Group 3: Sepsis and Oxytocin Administered Group (Median, Min-Max)
Endothelial Damage	0 (0-0)	3.0 (1-3)	1.0 (1-3)
Vacuolization	0 (0-0)	2.0 (0-2)	1.0 (0-1)
Cellular Debris	0 (0-0)	1.0 (0-2)	0.0 (0-1)
Proteinous Material Deposition	0 (0-0)	1.0 (0-2)	0.0 (0-1)
Neutrophil Infiltration	0 (0-0)	2.0 (1-3)	1.0 (1-2)
Total	0 (0-0)	9.0 (3-12)	3.0 (2-8)

This table summarizes the median and range (minimum-maximum) scores for each histopathological finding across the three groups: Control Group, Sepsis Group, and Sepsis with Oxytocin Administered Group.

**Table 2. Mean Scores of Histopathological Findings in All Three Groups and Statistical Comparison**

Histopathological Findings	Group 1: Control (Mean, ±SD)	Group 2: Sepsis Group (Mean, ±SD)	Group 3: Sepsis and Oxytocin Administered Group (Mean, ±SD)	Pb
Endothelial Damage	0±0	2.28±0.95	1.42±0.78	0.001
p <sup>a</sup>		0.063		
Vacuolization	0±0	1.42±0.78	0.71±0.48	0.005
p <sup>a</sup>		0.059		
Cellular Debris	0±0	1±1.0	0.42±0.53	0.030
p <sup>a</sup>		0.102		
Proteinous Material Deposition	0±0	1±1.0	0.42±0.53	0.030
p <sup>a</sup>		0.102		
Neutrophil Infiltration	0±0	2.14±0.69	1.14±0.37	0.001
p <sup>a</sup>		0.020		
Total	0±0	7.85±4.09	4.14±2.26	0.001
p <sup>a</sup>		0.028		

<sup>a</sup>Wilcoxon Signed Ranks Test, <sup>b</sup>Friedman Test. p-value of <0.05 was considered statistically significant. This table presents the mean and standard deviation (SD) scores for each histopathological finding across the three groups: Control Group, Sepsis Group, and Sepsis with Oxytocin Administered Group. The table also includes the p-values for the statistical comparison of the groups, with significant differences indicated by a p-value of <0.05.

ening of the vessel wall, congestion, and stromal edema in the ovaries taken from the rats in which a sepsis model was prepared. It contains areas that meet the criteria for sepsis pathologically. Figure 3 shows the examination of ovarian tissue administered with oxytocin as an anti-inflammatory and antioxidant in rats with sepsis. A decrease in inflammatory cell infiltration, vascular congestion, and stromal edema is observed.

The descriptive data of the groups are presented in Tables 1 and 2 for pathological evaluation. Statistically significant differences were found in terms of endothelial damage (p=0.001), vacuolization (p=0.005), cellular debris (p=0.030), proteinous material deposition (p=0.030), neutrophil infiltration (p=0.001), and the total score (p=0.001) (Table 2). When Group 2 and Group 3 were compared, no statistically significant difference was observed for endothelial damage (p=0.063), vacuolization (p=0.059), cellular debris (p=.102), and proteinous material deposition (p=0.102). However, a statistically significant difference was found for neutrophil infiltration (p=0.020) and the total score (p=0.028) (Table 2).

## DISCUSSION

This experimental animal study evaluated the protective effects of oxytocin on tissue through its anti-inflammatory and antioxidant properties by administering oxytocin to a group of rats with a sepsis model. Statistically significant decreases were detected in the neutrophil infiltration and total histopathological sepsis scores of the oxytocin group (p=0.020, p=0.028, respectively).

The addition of anti-inflammatory and antioxidant agents to the known current treatment of abscesses and their curative and preventive results have been examined in recent studies. Oxytocin was used in another study conducted with obese rats. In an animal model of obesity and diabetes, chronic oxytocin treatment led to a reduction in visceral adipose tissue inflammation and in the plasma markers of systemic inflammation, which may play roles in disease progression (15). Another study demonstrated the presence of a neuroendocrine response contributing to oxytocin secretion during sepsis. Oxytocin was also shown to reduce the overall host response to infection by reducing the proinflammatory response and oxidative stress (16).

Similarly, in their study, Sever et al. (17) used a septic rat model and evaluated lung injury both radiologically and histopathologically. It was reported that the results of the radiological and histopathological lung damage evaluation were lower in the oxytocin-administered group, indicating that oxytocin had anti-inflammatory, antioxidant, and protective effects. Similarly, histopathological response was improved in our study. Unlike our study, no statistically significant difference was found for endothelial damage, vacuolization, cellular debris, proteinous material deposition, but a statistically significant difference was detected in neutrophil infiltration and total histopathological sepsis score. We believe that this is due to the protocol difference. Oxytocin was initiated 24 hours after surgery in our protocol, but in the study of Sever et al. (17), oxytocin was started one hour after the procedure. The faster response in neutrophil infiltration may reflect this difference.

In their study, Ragy et al. investigated the effectiveness of oxytocin in rat models with renal Ischemia/Reperfusion (IR), and evaluated laboratory values. They reported that oxytocin reduced IR-induced elevations in serum urea, creatinine, liver transaminases, and TNF- $\alpha$  levels significantly, and Nitric Oxide (NO) and Bcl-2 levels increased significantly compared to the IR Group. The authors also reported that oxytocin significantly compensated for the decrease in Total Antioxidant Capacities (TAC) observed with renal IR in renal and hepatic tissues and decreased high Malondialdehyde (MDA) levels (18). In their study conducted on rats, Alizadeh et al. (18) reported that oxytocin protected cardiomyocytes from apoptosis caused by Ischemia-Reperfusion. The importance of these two studies is that, in addition to the neuroprotective effects of oxytocin, its protective effect was also present in other organs. In the present study, however, this effect was similar to the literature data in the ovaries of rats. It was observed in the histopathological examination of the ovarian tissue in a septic rat model administered oxytocin that the septic findings reduced the changes at the cellular level.

There are some important limitations in the present study. Oxytocin activity can vary significantly depending on the concentration. Therefore, studies are required to determine the optimal dose and protocol. Here, an animal experimental model was created to investigate oxytocin efficacy; however, these results do not reflect efficacy in humans. Human studies designed for this purpose are needed in this respect.

## CONCLUSION

In this study, the antioxidant and anti-inflammatory effects of oxytocin were utilized in the ovarian tissue of rats in a septic condition, and histopathological improvement was observed in the septic ovarian tissue. In this context, the addition of oxytocin to the known treatment for pelvic inflammatory disease is significant in minimizing related damage, especially in the reproductive age. Further studies and clinical trials are necessary to explore this potential.

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**Ethics Committee Approval:** The Animal Ethics Committee of Saki Yenilli Experimental Animals Production Laboratory (Ankara, Türkiye) approved the study. Ethical number: 17/08/2021–05–04–21.

**Informed Consent:** Informed consent was obtained from all patients.

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Concept – M.Ö.; Design – H.Ö.; Supervision – B.G.Ö.; Resources – B.G.Ö.; Materials – S.S.; Data Collection and/or Processing – M.Ö.; Analysis and/or Interpretation – S.Y.K.; Literature Search – B.G.Ö.; Writing – B.G.Ö.; Critical Review – B.G.Ö.

**Declaration of Interests:** The authors have no conflict of interest to declare.

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