RESEARCH ARTICLE / *Araştırma Makalesi*

Does Urapidil Alleviate Lung and Renal Injuries Induced by Cecal Ligation and Puncture?

Urapidil Çekal Ligasyon ve Delme ile İndüklenen Akciğer ve Böbrek Hasarını Hafifletir mi?

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Abstract

Objective	Here, possible protective effects of Urapidil were investigated against lung and renal injuries induced by cecal ligation and puncture (CLP).
Materials and Methods	32 Sprague Dawley male rats were assigned to 4 groups as follows; sham, CLP, DMSO and Urapidil (URA) 0.5 mg/kg. Several oxidant, inflammatory and antioxidant parameters were determined in lung and renal tissues.
Results	Oxidant and inflammatory biomarkers increased while antioxidant biomarkers decreased in CLP and DMSO groups compared to sham group. Antioxidant parameters increased while oxidant and inflammatory biomarkers declined in treatment group compared to CLP and DMSO groups.
Conclusion	Present results have demonstrated that URA administration is effective against lung and renal injuries caused by CLP-related polymicrobial sepsis model.
Keywords	Urapidil; cecal ligation and puncture; lung; renal; rat.

Öz

Amaç	*Burada, çekal ligasyon ve ponksiyonun (CLP) neden olduğu akciğer ve böbrek yaralanmalarına karşı Urapidil'in olası koruyucu etkileri araştırıldı.*
Gereç ve Yöntemler	*32 Sprague Dawley erkek sıçan sham, CLP, Dimetil sülfoksit (DMSO) ve Urapidil (URA) 0.5 mg/kg şeklinde 4 gruba ayrıldı. Akciğer ve böbrek dokularında çeşitli oksidan, inflamatuvar ve antioksidan parametreler belirlendi.*
Bulgular	*CLP ve DMSO gruplarında sham grubuna göre oksidan ve inflamatuvar biyobelirteçler artarken antioksidan biyobelirteçler azalmıştır. Tedavi grubunda CLP ve DMSO gruplarına göre antioksidan parametreler artarken oksidan ve inflamatuvar biyobelirteçler azaldı.*
Sonuç	*Mevcut sonuçlar, URA uygulamasının CLP ile ilişkili polimikrobiyal sepsis modelinin neden olduğu akciğer ve böbrek hasarlarına karşı etkili olduğunu göstermiştir.*
Anahtar Kelimeler	*Urapidil; çekal ligasyon ve ponksiyon; akciğer; böbrek; sıçan.*

INTRODUCTION

Sepsis is a serious condition caused by bacterial infections. The inflammatory response of the organism intensifies over time due to sepsis causing multiple organ failure which often results in death.[1] According to a recent study, the incidence of sepsis ranged from 18% to 40%.[2] Intensive care unit patients face with death due to sepsis with a 30-70 % mortality rate.[3] The reason for this high mortality rate is that sepsis can cause impairment of vital organs such as lung, kidney, and liver. Traumatic injury or infection of these tissues activates the humoral system which causes the release of various cytokines and inflammation. Inflammatory response leads to hemostatic changes and organ dysfunction.[4] Sepsis is responsible on the formation of acute lung injury (ALI) and acute kidney injury (AKI) through oxidative stress.[5,6] Sepsis is a common and complex condition that generates excess free oxygen radicals that cause oxidative stress and multi-organ failure.[7] AKI is one of the primary complications observed during sepsis and it leads to death.[8] Oxidative stress occurs during sepsis and aggravates the harmful effects of oxidants.[9] High levels of reactive oxygen species (ROS) play role in sepsis formation through damage in lipid, carbohydrate and nucleic acid structures which may result in organ dysfunction in kidneys and lungs.[10,11] Malondialdehyde (MDA) is a lipid peroxidation metabolite and reflects severe tissue injury.[12] Total oxidant status (TOS) and total antioxidant status (TAS) values are used in the assessment of oxidative stress.[13,14] Proinflammatory cytokines including interleukin-1beta (IL-1β) and tumor necrosis factor-alpha (TNF-α) are considered as pivotal mediators for sepsis-induced lung injury.[15,16] Cecal ligation and puncture (CLP) is used to compose a polymicrobial infection scene similar with human infections.[17-19] Drainage of primary focus of infection, antimicrobial therapy and symptomatic support underlie sepsis treatment.[20]

Several herbal and pharmacological agents have been examined to restrain oxidant damage.[19,21,22] Urapidil (URA) dilates arterioles and decreases the total peripheral resistance.[23] Here, the potential protective effects of URA against lung and renal injuries induced by CLP was investigated.

Ura is an antihypertensive and vasodilator agent.[24] The literature review revealed that it has not been investigated in terms of its effects on oxidative stress and inflammation in an experimental sepsis model. Therefore, the purpose of this study is to investigate the antioxidant and anti-inflammatory effects of URA in rats in a cecal ligation and puncture sepsis model.

MATERIALS and METHODS

Current study was carried out as an experimental animal research.

Animals, Drugs and Ethical Approval

During the study, animal rights were protected in accordance with Guide for the Care and Use of Laboratory Animals (www.nap.edu/catalog/5140.html) principles. Atatürk University Experimental Animal Ethics Committee admitted the study (date: 30.03.2018 protocol no:57). The animals were acquired from Experimental Animals Research and Application Center of Atatürk University and the experimental steps were carried out at the same center. The animals were caged in laboratory conditions such as appropriate humidity, temperature and light/darkness. Standard rat feed and tap water were provided to the animals.

Experimental Design, Drugs and Animals

This paper was based on our experimental study. Before the surgical steps, all rats were applied anesthesia, they were shaved, disinfected via %10 povidone-iodine and fixed in supine position. Thiopental sodium (Ulagay, İstanbul, Turkey) was preferred for anesthesia. URA and its solvent, Dimethyl Sulfoxide (DMSO), were purchased by Sigma-Aldrich Co.

32 Sprague Dawley male rats, weighing 240-270 g were used. They were randomized to 4 groups as: Group I (Sham

group, n=8): Abdominal area was incised to approach to the peritoneum and repaired with a 3.0 silk suture without any intervention. Group II (CLP group, n=8): All steps were performed as in group I.Then, cecum is tightly ligated to 2 cm distal and pierced via an 18-gauge needle (4 holes). [19] Afterwards, it is replaced to abdominal cavity and incisional space was sutured. Group III (CLP+DMSO group, n=8): 0.3 ml DMSO was administered intraperitoneally (i.p.) 30 minutes before the CLP model. Group IV (CLP+URA 0.5 mg/kg group, n=8): URA was given i.p. 30 minutes before the CLP model. The rats were fasted following surgical process, but water was allowed ad libitum for 18 hours until they were sacrificed.

Biochemical Analysis

Tissue samples were adjusted as each specimen weighing about 100 mg. They were homogenized via 2 mL of phosphate buffer solution (PBS). Centrifuge process was performed to obtain supernatant and kept in -80°C. MDA measurement is carried out through determination of the product level which occurs in case of MDA and thiobarbituric acid formation.[25] TAS and TOS parameters were evaluated by ELISA kits (Rel Assay Diagnostics). Oxidative stress index (OSI) demonstrates the ratio of TOS to TAS. Oxidation of MPO with 0-dianisidine composes a colored complex that is used for MPO measurement.[2]6 Formazan dye is the used to gauge superoxide dismutase (SOD) level.[27] TNF-α and IL-1β parameters were gauged with appropriate kits (Elabscience, Wuhan, China).

Statistical Analyses

One-way ANOVA test was chosen for biochemical data and then Tukey HSD test was used for multiple comparisons. The results were presented as Mean±Standard Deviation (SD). Statistical significance level was considered when p value below 0.05.

RESULTS

Lung Tissue Oxidative Stress Results

Table 1 shows the effects of URA on CLP-induced lung injury. While TAS and SOD levels declined in CLP and DMSO groups, they increased in URA treatment group. MDA, TOS and MPO levels elevated in CLP and DMSO groups but URA administration decreased those parameters.

Oxidative Stress Results of Kidney Tissue

Table 2 shows the effects of URA on CLP-induced kidney injury. A reduction in TAS and SOD values was observed in CLP and DMSO groups compared to sham group. Ura administration increased the current values. On the contrary, TOS, MDA and MPO levels were found to be higher in CLP and DMSO groups compared to sham group. Levels of these oxidant molecules decreased in the group treated with URA.

Proinflammatory Cytokine Results

Figure 1 and 2 show TNF-α and IL-1β values in CLP-induced lung and renal injuries, respectively. When CLP and

Table 1 Effects of URA treatment in CLP-induced lung injury.

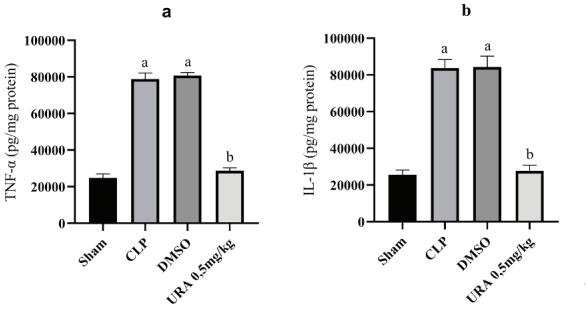
Groups/Parameters (n=8)	Sham	CLP	DMSO	URA 0.5 mg/kg
TAS (mmol/L)	2,26±0,26	0,84±0,13[a]	0,83±0,09[a]	2,24±032[b]
TOS (µmol/L)	13,10±0,80	18,05±1,33[a]	18,96±0,95[a]	14,24±0,46[b]
OSI (arbitrary unit)	0,58±0,08	2,17±0,28[a]	2,24±0,30[a]	0,64±0,11[b]
SOD (U/mg protein)	399,01±24,59	226,95±20,49[a]	229,54±27,12[a]	393,32±11,77[b]
MPO (U/g protein)	309835,14±13303,41	480946,64±24113,50[a]	501102,50±17025,31[a]	319354,89±30266,51[b]
MDA (µmol/g tissue)	78,86±6,89	128,12±7,97[a]	132,15±9,15[a]	83,30±5,14[b]

TAS; Total antioxidant status, TOS; Total oxidant status, OSI; Oxidative stress index, SOD; Superoxide dismutase, MPO; Myeloperoxidase, MDA; Malondialdehyde.
[a]p<0.001 compared to sham group. [b]p<0.001 compared to CLP group and DMSO group.

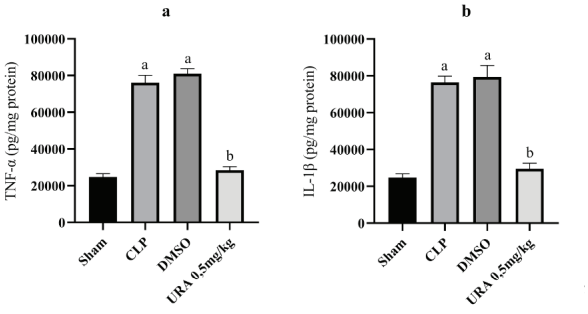
Table 2 Effects of URA treatment in CLP-induced kidney injury.				
Groups/Parameters (n=8)	Sham	CLP	DMSO	URA 0.5 mg/kg
TAS (mmol/L)	3,42±0,14	2,40±0,14[a]	2,31±0,25[a]	3,34±0,16[b]
TOS (μmol/L)	7,40±0,44	10,99±0,68[a]	11,35±0,75[a]	8,01±0,51[b]
OSI (arbitrary unit)	0,21±0,01	0,45±0,03[a]	0,49±0,07[a]	0,24±0,02[b]
SOD (U/mg protein)	350,59±51,99	202,33±13,71[a]	200,52±13,08[a]	358,78±67,75[b]
MPO (U/g protein)	16095,06±1586,52	35171,72±4819,18[a]	41903,66±2494,74[a]	16954,95±1484,18[b]
MDA (μmol/g tissue)	94,59±5,41	134,26±12,46[a]	142,75±10,35[a]	100,48±7,02[b]

TAS; Total antioxidant status, TOS; Total oxidant status, OSI; Oxidative stress index, SOD; Superoxide dismutase, MPO; Myeloperoxidase, MDA; Malondialdehyde.
[a]p<0.001 compared to sham group. [b]p<0.001 compared to CLP group and DMSO group.

DMSO groups were compared to sham group, TNF-α and IL-1β values elevated statistically in both tissues. In treatment group, TNF-α and IL-1β values diminished significantly when compared to CLP and DMSO groups.



compared with groups in rat lung tissues. [a]p<0.001 compared to sham group. [b]p<0.001 compared to CLP group.



compared with groups in rat renal tissues
[a]p<0.001 compared to sham group. [b]p<0.001 compared to CLP group.

DISCUSSION

Sepsis is a critical clinical condition with high mortality rates. Inflammation and weak immune response resulting from infections accompany to sepsis.[28] Sepsis leads to organ dysfunction and primarily affects the lungs.[29,30]. Sepsis induces acute lung injury (ALI) and acute respiratory distress syndrome (ARDS).[31] It also causes acute kidney injury (AKI) which has a high mortality rate.[32] SOD scavenges reactive oxygen species (ROS) and thus eliminates superoxide radicals.[33] TAS and TOS are preferred to evaluate the oxidative stress.[13,14]

In severe sepsis cases, it is typically to observe increased inflammatory response to infection and imbalance between oxidants and antioxidants.[34,35] In CLP model, intestinal perforation is created to obtain abdominal sepsis.[36] Increased neutrophil activation enhances the production of ROS and proinflammatory cytokines.[37] Infections may result in inflammatory response including proinflammatory cytokine activation which may lead to multiple organ dysfunction.[38] During inflammatory response, TNF-α level increases and it induces cytokine release.[39] Excessive ROS level causes lipid peroxidation and increase MDA concentration. MDA is a toxic product produced during lipid peroxidation and indicates oxidative damage indirectly.[40-42] Oxidized lipids and proteins are associated with septic mortality.[43]

Here, MDA level increased in CLP and DMSO groups for

both tissues and treatment group decreased the MDA level. MPO activity elevates in case of intense infection as increased in CLP group of the current study.[44] URA treatment declined MPO activity. Oxidative stress demonstrates the supremacy of oxidant activity against antioxidant capacity. OSI represents the oxidative stress degree.[13,45] In current study, OSI levels diminished in treatment group compared to CLP and DMSO groups.

Although antibiotic treatment is effective to reduce mortality, resistance to these drugs is an inevitable result and thus new agents would be necessary.[46] URA binds the α1-adrenoceptor in the peripheral vascular system and the serotonin (1A) receptors of 5-hydroxytryptamine (5-HT1A) receptor in the central nervous system.[47,48] Thereby, URA reduces vascular tone which results in arterial and venous vasodilatation in the systemic and the pulmonary circulations.[49]

We assessed the renal and lung tissues for oxidative stress to find out the protective effect of URA against CLP-induced renal and lung injuries. It was observed that oxidative stress diminished with URA. Inflammation, oxidative stress pathways were inhibited by URA and this may a new agent in the treatment of CLP.

CONCLUSION

URA has protective effects against CLP-induced lung and renal injuries.

Ethical Committee and Protocol no

Atatürk University Experimental Animal Ethics Committee admitted the study (date: 30.03.2018 protocol no:57).

Conflict of interest

None

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