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ORIGINAL ARTICLE

The Effect of Dexmedetomidine on Oxidative Balance in Lung, Liver and Heart: Rat Sepsis Model

Deksmedetomidinin Akciğer, Karaciğer ve Kalpteki Oksidatif Dengeye Etkisi: Sıçan Sepsis Modeli

[1]Rahim Kocabas, [2]Sinan Oguzhan Ulukaya, [3]Eyüp Fatih Cihan, [4]Alper Yosunkaya

[1] Karamanoğlu Mehmetbey University, Faculty of Medicine, Department of Biochemistry, Karaman, Türkiye.
[2] S.B. Eskişehir City Hospital, Anesthesia and Reanimation Clinic, Eskişehir, Türkiye.
[3] S.B. Kulu Public Hospital, Anesthesia and Reanimation Clinic, Kulu/Konya, Türkiye.
[4] Necmettin Erbakan University, Faculty of Medicine, Department of Anesthesia and Reanimation, Konya, Türkiye.

Correspondence

Rahim Kocabas, Karamanoğlu Mehmetbey University, Faculty of Medicine, Department of Biochemistry, 70100 Karaman, Türkiye.

E-Mail: drrahim42@gmail.com

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ABSTRACT

Aim: Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection. Early intervention in sepsis is vital and research on the subject continues. Having sedative, analgesic, and anxiolytic properties, Dexmedetomidine (DEX) is a potent lipophilic α2-adrenoceptor agonist with imidazole structure. In recent years, there has been an increasing number of studies on the organ protective effects of DEX. In this study, it was aimed to investigate the effect of DEX administered in different periods of sepsis on the oxidative stress index in the lungs, liver and heart.
Material and methods: The study was approved by the Necmettin Erbakan University Experimental Animals Ethics Committee (2020 – 017). In the study, 50 female wistar albino rats were used as experimental animals. Animals were divided into five groups: 1st group: SHAM (n:10), 2nd group: SEPSIS (n:10), 3rd group: DEX (PreDEX, n:10) administered 30 minutes before cecal ligation puncture (CLP) procedure, group 4: DEX administered 12 hours after CLP (Post12DEX, n:10), group 5: DEX administered 24 hours after CLP (Post24DEX, n:10).
Results: In liver and heart tissues, the decrease in total antioxidant status (TAS) levels in the SEPSIS group was statistically significant compared to the Post12DEX ($p < 0.001$ and $p < 0.001$) and Post24DEX ($p = 0.007$ and $p < 0.05$) groups. In lung, liver and heart tissues, the increase in the oxidative stress index (OSI) levels in the SEPSIS group, compared to the PreDEX ($p = 0.007$, $p = 0.003$, $p < 0.001$) group, was statistically significan<t.
Conclusion: Within the limits of our study, it can be said that DEX administered until the 24th hour after CLP reduces the OSI index in the liver tissue, and DEX administered until the 12th hour in the heart tissue, thus protecting these organs against sepsis. DEX, administrated only before CLP for lung tissue, reducing the OSI index.

Keywords: Dexmedetomidine, Sepsis, Oxidative stress index, Lung, Liver, Heart.

ÖZ

Amaç: Sepsis, enfeksiyona karşı düzensiz konak yanıtının neden olduğu yaşamı tehdit eden, organ disfonksiyonudur. Sepsise erken müdahale hayati önem arz etmekte ve konuyla ilgili araştırmalar devam etmektedir. Deksmedetomidin (DEX), sedatif, analjezik, anksiyolitik özelliklere sahip imidazol yapıya sahip olan güçlü bir lipofilik α2 - adrenoseptör agonistidir. Son yıllarda DEX'in organ koruyucu etkileri ile ilgili artan sayıda çalışma mevcuttur. Bu proje önerisinde; diğer çalışmalardan farklı olarak sepsisin farklı dönemlerinde uygulanan DEX'in; akciğer, karaciğer ve kalpte oluşan oksidatif stres indeksine etkisini araştırmak amaçlanmıştır.
Materyal ve metod: Çalışma için Necmettin Erbakan Üniversitesi Deney Hayvanları Etik Kurulundan (2020 – 017) onay alındı. Çalışmada deney hayvanı olarak 50 adet dişi wistar albino sıçan kullanıldı. Hayvanlar beş gruba ayrıldı: 1. grup: SHAM (n:10), 2. grup: SEPSİS (n:10), 3. grup: Çekal ligasyon puncture (CLP) işleminden 30 dakika önce DEX (PreDEX, n:10) uygulanan, 4. grup: CLP'den 12. saat sonra DEX uygulanan (Post12DEX, n:10), 5. grup: CLP'den 24. saat sonra DEX uygulanan grup (Post24DEX, n:10) olarak tasarlandı.
Bulgular: Karaciğer ve Kalp dokularında; Post12DEX ($p < 0.001$ ve $p < 0.001$) ve Post24DEX ($p = 0.007$ ve $p < 0.05$) gruplarına göre SEPSİS grubunda total antioksidan seviyelerindeki (TAS) azalma istatiksel değerlendirme açıdan anlamlı bulundu. Akciğer, Karaciğer ve Kalp dokularında; PreDEX ($p = 0.007$, $p = 0.003$, $p < 0.001$) grubuna göre SEPSİS grubundaki oksidatif stres indeksi OSI seviyelerindeki artma istatiksel değerlendirme açıdan anlamlıydı.
Sonuç: Çalışmamız kendi sınırları içerisinde, CLP sonrası 24. saatte kadar uygulanan DEX'in karaciğer dokusunda, 12. saatte kadar uygulanan DEX'in kalp dokusunda OSI indeksini azalttığı, dolayısı ile bu organları sepsise karşı koruduğu söylenebilir. Fakat akciğer dokusunda sadece CLP öncesi uygulanan DEX OSI indeksini azaltmaktadır.

Anahtar Kelimeler: Deksmedetomidin, Sepsis, Oksidatif stres indeks, Akciğer, Karaciğer, Kalp.

Introduction

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection. It affects millions of people around the world each year, killing 16-30% of those affected. In addition, even if sepsis heals, it is an important health problem that can cause irreversible damage to some organs. Early diagnosis and treatment of sepsis increases success in sepsis. Therefore, early intervention in sepsis is of vital importance (1).

Normally, the organism has a complex antioxidant defense system that fights against free radicals and the oxidative stress/load that develops due to endogenous and exogenous causes, under physiological conditions. Free radicals are formed in the body in normal and/or pathological conditions. Free radicals and their by-products, namely the entire oxidant load, can be determined by measuring the total oxidant status

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Complaints: geneltip@selcuk.edu.tr

(TOS). Substances that fight oxidant load are called antioxidant molecules. The total potency of all these antioxidant molecules in the body can be measured by TAS analysis. TOS level increases due to free radicals and their by-products formed in intense inflammatory processes. The TOS / TAS ratio, that is, the OSI, shifts in favor of TOS. Since all these harmful products cannot be detoxified and OSI gradually increases, they cause damage, and many pathological conditions can be seen in the ongoing process, from tissue damage to death.

It can be said that sepsis causes immunosuppression that develops concurrently with hyper-inflammation, decreased endogenous antioxidant capacity, and organ dysfunction (2,3). That is, in sepsis, the increase in TOS and additionally the decrease in TAS cause the oxidant/antioxidant balance to shift towards the oxidant direction and, consequently, the OSI to increase further. Rapidly increasing oxidative stress affects the molecular mechanisms that control inflammation (3). It leads to loss of homeostasis (immune paralysis) between the pro-inflammatory and anti-inflammatory reaction. Endotoxemia re-induces the production of various inflammatory cytokines as well as reactive oxygen species (ROS). These mediators, alone or through their interactions, lead to neutrophil accumulation, local inflammation, and ultimately the secretion of secondary proinflammatory cytokines and chemokines that trigger the systemic inflammatory response syndrome and multiple organ dysfunction syndrome (MODS) (4). Oxidative stress plays a major role in the underlying pathogenesis of MODS (5). The lung is one of the first organs involved in MODS and causes acute respiratory distress, and the second most frequently affected organ is the heart, although other systems are affected after the lung. In the prolongation of sepsis, after the brain, the liver is also affected by sepsis (4). For all these reasons, it is necessary to apply effective treatments for sepsis as early as possible in order to prevent the progression of organ damage.

With its sedative, analgesic, anxiolytic properties, Dexmedetomidine (DEX) is a potent lipophilic a2-adrenoceptor agonist with an imidazole structure. In recent years, there has been an increasing number of studies on the organ protective effects of DEX. Recent studies in septic animal models have demonstrated that DEX reduces lung injury (3). In etiologies such as ischemia/reperfusion (I/R) injury of DEX, open cardiac surgery, it has been shown that it may be protective against tissue damage with its antioxidant, anti-apoptotic and anti-inflammatory properties (5–7). Again, Li et al. revealed in their study in 2019 that DEX suppressed oxidative stress in hepatocytes, thus attenuating liver damage due to sepsis (8).

Unfortunately, there is no diagnostic test to make a definitive diagnosis of sepsis. For this reason, it is always very difficult to detect sepsis when it first starts. Sepsis presents itself with different clinical pictures at different times in the clinic. Therefore, treatment approaches vary in different periods of sepsis. Intervention in these periods can contribute positively to the treatment. In studies in the literature, DEX was administered at the onset of sepsis, or additional DEX was administered in the advancing process starting with the onset of sepsis (3,6,8–12). Although the observed protection of DEX at the onset of sepsis without increasing oxidant load is important, the possible protection of DEX against sepsis in the later stages of sepsis needs to be investigated. Thus, it will shed light on the approach to sepsis cases encountered in the clinic. DEX was administered in different periods of sepsis and the research is original in this regard. The aim of this study is to investigate the effect of DEX on the oxidative stress index in the lung, liver and heart in different periods of sepsis.

Material and Methods

Approval for this study was obtained from the Necmettin Erbakan University Experimental Animals Ethics Committee with the number 2020-017. Animals were obtained from KONÜDAM Experimental Medicine Application and Research Center within the same university. The shelter and care of the animals were secured in the same center in accordance with the regulations on experimental animals.

In the study, 50 12-month-old female wistar albino rats with a body weight of 265±15 g were used. The rats were fed with five rats in each cage in rooms with a 12/12 hour light-dark period, ventilated 12 times per hour, in approximately 50% relative humidity, and an average in temperature of 22 °C.

Animals were divided into five groups. 1st group: SHAM (n:10), 2nd group: SEPSIS group (n:10), 3rd group: DEX (PreDEX) administered 30 minutes before cecal ligation puncture (CLP) procedure (n:10), 4th group: 12th hour after CLP, DEX administered group (Post12DEX) n:10), 5th group: DEX-administered group (Post24DEX) 24th hour after CLP.

Surgical procedure: A polymicrobial sepsis model was formed in rats with the CLP procedure under anesthesia (3,9–11,13). The rats were fasted three hours before the first operation. The anterior abdominal wall was cleaned with 10% povidone-iodine and shaved. The abdominal cavity was opened under sterile conditions with a 3 cm incision on the abdominal wall. The cecum was dissected without any damage to the vascularization. Then, the cecum was tied with 3/0 silk suture from the antimesenteric part of proximal ileocecal and pierced twice from the lower part of the cecal valve with an 18-gauge needle. After observing the feces output, the cecum was placed in the abdomen again. After these procedures were completed, the anterior abdominal wall was sutured with 3/0 silk sutures (14). This is how CLP processes were administered to the SEPSIS, PreDEX, Post12DEX, and Post24DEX groups. In the SHAM group, other surgical procedures were performed, except for the ligation of the cecum and piercing. 0.9% isotonic NaCl solution was used as fluid resuscitation. Intravenous cannula fluid resuscitation was administered at an amount of 10 ml/kg in the first hour and 5 ml/kg/hour in the following hours. In addition, animals were

allowed access to water and feed in their cages. All interventional procedures were performed under isofurane anesthesia while maintaining spontaneous respiration of the animals.

DEX administration: DEX was administered with a dosage of 40µg/kg in about 10 minutes intravenously to the PreDEX group 30 minutes before CLP, to the Post12DEX group 12 hours after CLP, and to the Post24DEX group 24 hours after CLP (3,5,6).

At the end of the procedure, lung, liver and heart tissue samples were taken at the 48th hour of sepsis. The procedure was terminated with cervical dislocation in accordance with euthanasia rules. The samples were transferred without delay to the freezer at -80°C until the day of analysis. TAS, TOS and OSI were evaluated in lung, liver and heart tissue from rats.

Sepsis-related animal deaths: One animal in the Post12DEX group, two animals in the Post24DEX group, and two animals in the SEPSIS group died before the 48th hour. A total of 5 animals died in the study.

Preparation of tissue homogenate: A 10% (w/v) homogenate of lung, liver and heart tissues was prepared in sodium phosphate buffer (50 mM PBS, pH 7.4) for biochemical analysis. The tissues in the ice bath (4-8°C) were homogenized for 20 seconds (Ultra-Turrax T10, Germany) and were then subjected to sonication for 30 seconds (Bandelin Sonopuls UW 2070, Germany). Homogenates were centrifuged at 10,000xg at 4°C for 15 minutes and supernatants were transferred to microtubes and stored until analysis (15).

In measurements made on tissues, TAS was measured with a TAS test kit for (Rel Assay Diagnostics, product code RL0017, Gaziantep, Türkiye), and TOS was measured with a total oxidant status test kit (Rel Assay Diagnostics, product code RL0024, Gaziantep, Türkiye) according to the manufacturer's instructions (Abbott Laboratories, Abbott Park, IL, USA) through an analyzer on the Architect C 8000 System. Results for lung, liver, and heart TAS and TOS were expressed as µmol trolox equivalent/g protein, µmol H2O2 equivalent/g protein. OSI was determined using the formula OSI=[(TOS, µmol H2O2 equivalent/L)/(TAS, µmoltrolox equivalent/L) ×100] (15).

Statistical evaluation: Statistically, SPSS 16.0 program (SPSSv16.0, Chicago, IL, USA) was used. TAS, TOS, OSI values of lung, liver and heart tissue were obtained from the data obtained by analysis of variance (one way anova). Post-Hoc evaluations are indicated in the tables. All results are given as mean±standard mean error. Values less than P<0.05 were considered statistically significant.

Results

In lung, liver and heart tissues, the decrease in TAS levels in the SEPSIS group compared to the PreDEX group was statistically significant (p =0.008, p <0.001, p <0.001). In liver and heart tissues, the decrease in TAS levels in the SEPSIS group was statistically significant compared to the Post12DEX (p <0.001 and p <0.001) and Post24DEX (p =0.007 and p <0.05) groups. In addition, in the liver tissue, the decrease in TAS levels in the Post24DEX group was found significant compared to PreDEX and Post12DEX groups (p <0.001, p <0.05), (Table 1).

In lung, liver and heart tissues, the increase in TOS levels in the SEPSIS group was statistically significant compared to the SHAM (p =0.001, p =0.006, p <0.001) and PreDEX groups (p <0.05, p =0.009, p <0.001).

In lung, liver and heart tissues, the increase in OSI levels in the SEPSIS group was statistically significant compared to the SHAM (p =0.006, p <0.05, p <0.001) and PreDEX groups (p =0.007, p =0.003, p <0.001). In addition, other significant values are given in Table 1.

Table 1: TAS, TOS and OSI values in Lung, Liver and Heart tissues.

	Groups	Lung	Liver	Heart
TAS µmol/g protein	SHAM	752 ± 36.3	251 ± 25.3 ^{b8}	790 ± 13.3 ^{b8,}
	Sepsis	766 ± 42,5	143 ± 18.3	675 ± 16.9
	$Pre^{DE}X$	1013 ± 57.7 ^{a6,b3}	377 ± 16.2 ^{a10,b10}	921 ± 24.1 $^{a2, b10}$
	$Post1^{2DE}X$	945 ± 3.60	328 ± 17.6 ^{b10}	898 ± 15.7 $^{a8, b10}$
	$Post2^{4DE}X$	904 ± 26.7	241 ± 12.5 ^{b4,c10,d1}	859 ± 43.7 ^{b1}
TOS µmol/g protein	SHAM	7.5 ± 0.81 ^{b9}	145 ± 4.44 ^{b5}	7.8 ± 0.46 ^{b10}
	Sepsis	19.3± 1.55	175 ± 6.43	14 ± 0.40
	$Pre^{DE}X$	10.9 ± 1.42 ^{b1}	146 ± 6.39 ^{b2}	7.5 ± 0.47 ^{b10}
	$Post1^{2DE}X$	16.2 ± 2.84	156 ± 4.91	13 ± 1.31 $^{b10, c1}$
	$Post2^{4DE}X$	14.0 ± 1.09	154 ± 5.06	13.6 ± 1.32 ^{a1,c1}
OSI	SHAM	1.01 ± 0.05 ^{b5}	62 ± 7.42 ^{b1}	0.97 ± 0.06 ^{b10}
	Sepsis	2.58 ± 0.27	132 ± 13.17	2.07 ± 0.04
	Pre^{DEX}	1.11 ± 0.17 ^{b4}	40 ± 3.03 ^{b7}	0.80 ± 0.04 ^{b10}
	$Post12^{DEX}$	1.67 ± 0.23	49 ± 3.55 ^{b6}	1.44 ± 0.14 ^{c1,b1}
	$Post24^{DEX}$	1.80 ± 0.29	65 ± 3.85 ^{b1}	1.57 ± 0.17 ^{c1}

Note: Between groups compared to; (SHAM: a), (Sepsis: b), (PreDEX: c), (Post12DEX: d) significant values [(1: p<0.05), (2: p=0.009), (3: p=0.008), (4: p=0.007), (5: p=0.006), (6: p=0.004), (7: p=0.003), (8: p=0.002), (9: p=0.001), (10: p <0.001)] i: According to one-way anova.

Discussion

In this experimental sepsis model study, DEX (40µg/kg) was administered at different periods of sepsis (30 minutes before CLP, 12 and 24 hours after CLP). The effect of DEX administration on the OSI index was investigated by analyzing TAS and TOS levels in lung, liver and heart tissues. Polymicrobial sepsis model was used with CLP method in the study (3,9–11,13).

Xu et al. (2019) studied the activities of super oxide dismutase (SOD), malondialdehyde (MDA), nitric oxide, and heme oxygenase -1 (HO-1) in lung tissues in their experimental sepsis model. Researchers performed DEX (40 µg/kg) application following CLP, and reported that the damage in lung tissues was caused by the increase in oxidative stress, so

MDA levels increased and this was accompanied by impaired SOD. They reported that DEX administration prevented sepsis-induced oxidative/nitrative stress by increasing HO-1 activity (3). Again, Koca et al. (2013) administered DEX at the same time as the CLP procedure and found that the histological lung damage score and the immunoreactive score in lung tissues were statistically significantly lower in the DEX group than in the SEPSIS group. However, Koca administered DEX at a dosage of 50 µg/kg in their study and ended the experiment at 6th hours, which can be considered early for sepsis after CLP (10). Wu et al. (2013) administered DEX 4 times (0th, 2nd , 4th and 6th hours) after CLP at a dosage of 5, 10, 20 µg/kg. and reported that pro-inflammatory markers such as interleukin-6 (IL-6) and tumor necrosis factor alpha (TNFa) were decreased by suppressing inflammation, and this was achieved through the activation of the Toll-like receptor 4 / Myeloid differentiation factor 88 / Nuclear kappa B pathway (11). In 2015, Zhang et al. administered DEX at the same time as CLP in a similar study design. They reported that this effect of DEX was independent of a2-adrenoreceptor and probably related to Toll-like receptor 4 / Myeloid differentiation factor 88 / Mitogen-activated protein kinase / Nuclear kappa B signaling pathway (9). In the literature, there are studies reporting that DEX has a protective effect on lung I/R reperfusion injury and acute lung injury, and even a sepsis model was created with different methods (16). In order to focus the issue on sepsis induced by the CLP method only, other studies were not mentioned.

In our study, the OSI index was found to be significantly lower in the PreDEX group compared to the SEPSIS group (Table 1). In other words, DEX showed its anti-sepsis effect with pre-CLP application. In the studies mentioned above, there are studies that analyze the pro-inflammatory cytokine level such as TNFa, anti-inflammatory enzyme such as SOD, as well as pathway analysis. However, since all of these molecules studied are in TOS/TAS balance, the results of this study are discussed in detail. The results in our study were consistent with other studies. However, when we evaluated them according to the application time of DEX, there was no significant difference in the OSI index in the groups to which DEX was administered at the 12th and 24th hours after CLP compared to the SEPSIS group. When evaluated in the light of all this information, DEX application (40 µg/kg) after the 12th hour in sepsis was insufficient to protect the lung tissue.

Unlike the CLP method, Li et al. (2019) created a sepsis model by intraperitoneal injection of lipopolysaccharide (LPS). In the study, they administered DEX at a dosage of 50 µg/kg intragastrically at the same time as the LPS injection. They reported that DEX suppressed oxidative stress and phosphorylation of hepatocytes by activating p-ERK1/2, decreased MDA and myeloperoxidase levels, thereby attenuating sepsis-induced liver injury (8). Chen et al. (2015) administered DEX at 5µg/kg/hour 30 minutes after LPS injection. In the study, markers such as TNF-a, IL-6, interleukin-1 beta and MDA were evaluated in liver tissues, and they found these values significantly lower in the DEX administered group. Researchers have reported that DEX may reduce cytokine and/or oxidative stress-mediated inflammation and ameliorate sepsis by attenuating cellular apoptosis (17).

In our study, liver TAS values significantly increased in all DEX administered groups compared to the SEPSIS group. This result can be interpreted in the way that DEX contributes positively to the antioxidant enzyme capacity of the liver. In addition, while only DEX administered early in the lung tissue (PreDEX group) contributed positively to reducing OSI, it contributed positively to reducing OSI not only in the PreDEX group, but also at the 12th and 24th hours after CLP, protecting liver tissues from oxidative damage (Table 1). When current information and findings are evaluated, DEX (40 µg/kg) administered up to 24 hours after CLP reduces the liver OSI index, thus protecting the liver from oxidant damage caused by sepsis.

Although there are limited studies on the effect of DEX application on heart tissues in sepsis, Kong et al. (2017) created a septic cardiomyopathy model with the LPS method, and determined that cardiomyopathy occurred 16 hours after sepsis with terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) and Hemotoxylin-eosin staining method. They continued their studies in this direction, and carried out DEX injection at a dosage of 10 mg/kg one hour before the LPS procedure, which is a very high rate compared to other studies. In their study, they analyzed Caspase-3, Caspase-8, B-cell lymphoma 2 (BCL-2), BCL-2 associated X, p53 mRNA and pro-inflammatory markers such as TNFa and IL-6. Researchers have reported that DEX may be protective against myocardial damage (18). Cho et al. (2016) have reported that DEX administered for 24 hours pre-operatively and post-operatively to patients undergoing cardiac surgery both reduces the length of stay in the intensive care unit and reduces undesirable hemodynamic side effects (6). In their experimental animal study, Zhang et al. (2017) reported that DEX administration (6 µg/kg/hr x 10 min + 0.7 µg/kg/h x 15 min followed by I/R before and after ischemia led to a reduction in myocardial I/R injury (12).

In our study, the TAS level increased significantly in the three groups that underwent DEX application compared to the SEPSIS group, as seen in Table 1. It can be said that DEX (40 µg/kg) application at the 12th hour after CLP contributes to the antioxidant capacity and provides protection against heart tissue damage caused by sepsis, but the protection of the DEX administration at the 24th hour is insufficient.

In support of our results, Zhang T et al. (2022) reported in their meta-analysis on the use of DEX in sepsis that the use of DEX could significantly reduce mortality compared to benzodiazepines, and reduce the inflammatory response better than other sedative

drugs. They also reported that randomized controlled trials were required to make most use of the optimal dosage of DEX (19).

The limitations of our study are that DEX was not administered at different doses and different age groups in the study. Because OSI value could be different depending on age and dose.

The originality of our study was that DEX was administered at different times of sepsis. In this respect, it has the capacity to shed light on clinical studies.

As a result, for liver tissues, DEX administered up to the 24th hour after CLP, and for heart tissues, DEX administered until the 12th hour contributes positively to reducing the OSI index in these tissues, but for lung tissues only DEX administered before CLP contributes to reducing the OSI index.

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