Medical Journal of Bakırköy

Med J Bakirkoy 2023;19:180-185
DOI: 10.4274/BMJ.galenos.2023.2022.4-20

Research

# Effects of Dexmetatomidine and Midazolam on Immunity in Sepsis-induced Rats

## Deksmedetomidin ve Midazolam'ın Sepsis Oluşturulmuş Sıçanlarda Bağışıklık Üzerine Etkileri

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## ABSTRACT

**Objective:** Intensive care patients may need sedation for many reasons. The anti-inflammatory effects of different sedation options in sepsis were compared. Although the anti-inflammatory effects of some agents in sepsis have been investigated, there is insufficient evidence about the effects of alpha 2 agonists, especially dexmetatomidine. In this study, the anti-inflammatory effects of midazolam and dexmetatomidine in septic rats were investigated and compared.

**Methods:** Wistar Albino-type male rats with an experimental sepsis model were used in this study. Thirty-two male rats, which had no renal disease or hepatic insufficiency, were randomly divided into 4 groups. Simple laparotomy and placebo surgery were performed in the control group. After laparotomy, cecal ligation and puncture were performed in the septic group. Cecal ligation perforation (CLP) procedure was also applied to the other two groups, but 8 hours after the procedure, dexmetatomidine was given at a dose of 0.01 mg/kg to group dex rats, while midazolam was given 0.01 mg/kg to group midazolam rats. After 24 hours, blood samples were taken from all groups to measure the levels of IL-1, IL-6, and TNF-α, which were considered sepsis precursors, at the end of CLP. In addition, a histopathological examination of liver and kidney tissue was performed.

**Results:** When compared with the control group, TNF-α, IL-1, and IL-6 levels were found to be high in the sepsis group (p=0.002, p=0.027, p=0.017). Significant decreases were observed in both serum and tissue in these parameters in all groups. When these two agents were compared, it was seen that the anti-inflammatory effect was higher in the dexmedetomidine-administered group than in the midazolam administered rats.

**Conclusion:** It has been concluded that dexmedetomidine and midazolam reduce the pro-inflammatory markers that have an important role in the pathophysiology of sepsis. Also, they have immunomodulatory effects. Besides these features, it is seen that dexmetatomidine is superior to midazolam in this respect.

**Keywords:** Systemic inflammatory response syndrome, dexmedetomidine, midazolam, intensive care units, immunity, rats

## ÖZ

**Amaç:** Yoğun bakım hastaları birçok nedenden dolayı sedasyona ihtiyaç duyabilir. Sepsiste farklı sedasyon seçeneklerinin anti-enflamatuvar etkileri karşılaştırıldı. Sepsiste bazı ajanların anti-enflamatuvar etkileri araştırılmış olsada, alfa 2 agonistlerinin, özellikle deksmedetomidinin etkileri hakkında yeterli kanıt yoktur. Bu çalışmada midazolam ve deksmedetomidinin septik sıçanlarda anti-enflamatuvar etkileri araştırılmış ve birbirleriyle karşılaştırılmıştır.

**Gereç ve Yöntem:** Bu çalışmada deneysel sepsis modeline sahip Wistar Albino tipi erkek sıçanlar kullanıldı. Renal veya hepatik disfonksiyonu olmayan 32 erkek sıçan rastgele 4 gruba ayrıldı. Kontrol grubuna basit laparotomi ve plasebo ameliyatı yapıldı. Septik grupta sadece çekal ligasyon ve ponksiyon yapıldı. Çekal ligasyon perforasyonundan (CLP) 8 saat sonra deksmedetomidin grubuna 0,01 mg/kg deksmedetomidin verilirken, midazolam grubuna 0,01 mg/kg midazolam verildi. CLP'den 24 saat sonra, IL-1, IL-6 ve TNF-α düzeylerini ölçmek için tüm gruplardan kan örnekleri alındı. Ayrıca karaciğer ve böbrek dokuları histopatolojik olarak incelendi.

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**Cite as:** Özkan F, Yüksek A, Demirel A, Kantekin Ç. Effects of Dexmetatomidine and Midazolam on Immunity in Sepsis-induced Rats. Med J Bakirkoy 2023;19:180-185

**Received:** 26.04.2022
**Accepted:** 04.04.2023



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**Bulgular:** Kontrol grubu ile karşılaştırıldığında sepsis grubunda TNF-α, IL-1 ve IL-6 seviyeleri yüksek bulundu. Hem deksmedetomidin grubunda hem de midazolam grubunda bu parametreler hem serumda hem de dokuda anlamlı düşüş gösterdi. Bu iki ajan karşılaştırıldığında, deksmedetomidin uygulanan grupta anti-enflamatuvar etkinin midazolam uygulanan sıçanlara göre daha yüksek olduğu görüldü.

**Sonuç:** Deksmedetomidin ve midazolamın sepsis patofizyolojisinde önemli rolü olduğu, immünomodülatör etkileri olan proenflamatuvar belirteçleri azalttığı ve bu açıdan deksmedetomidinin midazolamdan üstün olduğu sonucuna varılmıştır (p=0,002, p=0,027, p=0,017).

**Anahtar Kelimeler:** Sistemik enflamatuvar yanıt sendromu, deksmedetomidin, midazolam, yoğun bakım ünitesi, immünite, sıçanlar

## INTRODUCTION

Sepsis; describes the systemic inflammatory response to infection and has been one of the life-threatening problems in the history of medicine. Sepsis and septic shock are clinical pictures that require urgent treatment and they still have a high level of morbidity and mortality, which has more than 40% mortality rate today (1). Despite our increasing knowledge and treatment options, sepsis is still one of the leading causes of mortality in intensive care units. One of the most important factors that can reduce mortality is a fast, appropriate, and intensive treatment approach. Mortality is related to the underlying medical conditions, infectious agents, ability to respond to infection, appropriate antimicrobial therapy, and the development process of septic shock. There is not enough information about the actual number of sepsis cases in the world, and the existing data are mostly estimated. However, it can be seen in many clinical pictures, It is thought that sepsis is greater than the number of patients diagnosed with it (2).

Septic patients are frequently treated in intensive care units, and the use of sedation in septic patients is one of the most confusing issues, as in all intensive care patients. The indications of sedative agents and their effects on mechanical ventilation durations, hospital stay, and mortality have been the subject of many studies (3). However, there are limited studies on its effects on prognosis in sepsis (4).

Midazolam is a short-acting benzodiazepine derivative containing an imidazole ring. It acts by increasing the effect of the GABA neurotransmitter, which is involved in nerve conduction in many parts of the central nervous system especially in the cortex (5-7). Dexmetatomidine is a very potent and selective α2 adrenoreceptor agonist (6). It is used as an anesthetic adjuvant that creates analgesia and sedation. It reduces the need for anesthetics and tremors after anesthesia as well as the consumption of perioperatively used rocuronium and inhalation agents, moreover, it creates hemodynamic stability dexmedetomidine (5). Dexmetatomidine suppresses the stress response to surgery (8,9).

On the other hand, excessive secretion of inflammatory cytokines such as TNF-α, IL-8, and IL-6 was observed in the pathophysiological sepsis process. Recent studies have shown that midazolam decreases the plasma IL-1β, 6, 8 and TNF-α levels in critically ill patients (10). Therefore, midazolam was shown to inhibit the proliferation of CD3 + T-cells and the T helper 1 (Th1) cellular immune response in a rat model (11). These studies suggest that midazolam may be beneficial for septic patients with uncontrolled immuno-inflammatory responses. Dexmedetomidine, which is used for similar purposes, has been shown to help improve the outcome in animal models of sepsis by enhancing macrophage phagocytosis and bacterial clearance with its α-2 agonistic feature as well as its sedative effects (12). The anti-inflammatory effect may also need to be considered as a factor in the selection of sedation agencies in septic patients. However, it is not known which agent is more effective than the other in this respect.

In this study, a sepsis model was created in rats using the cecal ligation perforation (CLP) method, and the anti-inflammatory effects of dexmetatomidine and midazolam were examined and their superiority to each other was compared.

## METHODS

All animal procedures were approved by an ethics committee (Kırıkkale University Animal Experiments Local Ethics Committee-decision no: 17/07, date: 01.03.2017) and conducted in accordance with international guidelines for the care and use of animals. For this study, 32 Wistar Albino-type male rats, which weigh 200-300 g, were used. The number of rats was determined by calculating the effect size in the power analysis and considering the number of animals in similar articles (13). The total sample size was calculated with 0.86 power and 0.5 effect size, with the least animal waste. All animals were acclimatized for 7 days before experimentation in the laboratory of the institute, where all animals were kept at 22±2 °C and 55±10% relative humidity on a constant 12-hour (h) dark/light cycle. All animals were kept in standard cages and fed the same rodent chow and water. The number of animals to be included in the study was determined by the power analysis performed with similar studies in the literature (14). Rats with mortality between the creation of the sepsis model and the collection of blood

samples were determined as the criteria for exclusion from the study.

CLP method: Surgery was initiated after 2 h of fasting. The modified cecal ligation and the puncture method was used to create sepsis in rats. Although this method is uncertain for clinical sepsis, its inflammatory markers and clinical outcomes are similar to sepsis. As it is used in many studies, it is accepted as one of the most suitable models for creating sepsis model (14). Anesthesia was completed by injecting 50 mg/kg ketamine hydrochloride (KetalarR) and 10 mg/kg xylazine hydrochloride (RometarR). The surgical area was shaved and the skin was antisepsised with betadine, and the whole process was performed under sterile conditions. The abdomen was opened with a 2-3 cm incision from the midline. The cecum was tied with 3/0 silk of the rats in this group so that the intestinal continuity was not disturbed and some of the cecum contents were removed by piercing 2-3 times with an 18 gauche needle. Then, the cecum was placed in the abdomen and sutured with 3/0 silk.

The animals were randomly divided into 4 groups of 8 animals each. The groups were, respectively, named as the "control" group, the "sepsis" group, the Dex" group (sepsis model + dexmedetomidine), and the "midazolam" group (sepsis model + midazolam).

Rats that underwent the CLP procedure were considered as the sepsis group. In addition to the sepsis model, dexmetatomidine - administered rats were determined as the "dex" group, and midazolam - administered rats were determined as the "midazolam" group. The same anesthesia and CLP procedures were applied in the "sepsis", "dex" and "midazolam" groups. In the control group, after the anesthesia procedure, the abdomen was opened and the cecum was observed to be intact and resutured.

In the dex and midazolam groups, dexmetatomidine or midazolam was administered intravenously at a dose of 0.01 mg/kg at the postoperative 8$^{th}$ h. According to the CLP procedure, we decided to administer the anesthetic drugs at the 8$^{th}$ h because the animals started to show symptoms of fever, malaise, and diarrhea between 8 and 12 h postoperatively (15). In the other two groups, normal saline was given via the tail vein at the same time and in the same volume. The chosen doses of these drugs were based on previous studies and our preliminary experiments (11,16).

At the postoperative 24$^{th}$ h, the incision line was widened to include the chest cavity by opening from the old incision line. Severe sepsis symptoms and hypothermia can be seen in rats 24 h after CLP, and there are literature studies recommending euthanasia for this reason (15). Taking into account the half-lives of the drugs given at the postoperative 24$^{th}$ h, it was predicted as the earliest time they could have an effect. Approximately 3-4 mL of blood samples were taken intracardiac and placed in biochemistry tubes. Following the blood samples, liver and kidney tissue samples were collected and placed in formaldehyde tubes. The commercially available enzyme-linked immune sorbent assay (ELISA) kits were used according to the manufacturers' recommendations: Rat TNF-alpha ELISA Kit (Elabscience, Cat: E-EL-R0019), Rat IL-1-beta ELISA Kit (Elabscience, Cat: E-EL-R0012), and Rat IL-6 ELISA Kit (Elabscience, Cat: E-EL-R0015). The collected tissues were homogenized for 5 minutes (min) at 4 °C using an electric blender. The homogenate was centrifuged at 4000 rpm at 4 °C. TNF-α, IL-1, and IL-6 analyses were performed from the obtained solution with rapid kits.

From the obtained results, inflammatory marker levels among the groups were analyzed statistically in terms of anti-inflammatory effects in both plasma and tissues.

**Statistical Analysis**

The normal distribution of the data's developmental parameters, which were obtained at the end of the study, was evaluated with the Kolmogorov-Smirnov test. Since the data did not show a normal distribution ($p<0.05$), the Kruskal-Wallis H test was used. The Mann-Whitney U test with Bonferroni correction was used for multiple comparisons. A $p<0.05$ was considered statistically significant. In the Shapiro-Wilk test for biochemical data, which were normally distributed, were expressed as mean ($\bar{X}$) ± standard deviation and the data that were not normally distributed were expressed as median (minimum-maximum). One-Way analysis of variance (ANOVA) was used for comparisons between groups for normally distributed data, and Tamhane and Tukey's HSD test was used for multiple comparisons between groups.

**Power Analysis**

t-tests - Means: Difference between two dependent means (matched pairs)
Analysis:A priori: Compute required sample size
Input: Tail(s) = One
Effect size dz = 0.5
α err prob = 0.05
Power (1-β err prob) = 0.86
Output: Noncentrality parameter δ= 2.8284271
Critical t = 1.6955188
Df = 31
Total sample size = 32
Actual power = 0.8688531

## RESULTS

In this study, 32 Wistar Albino-type male rats, which weigh 200-300 g, were used. Neither mortality nor exclusion requirement was observed in the study animals. In this study, TNF-α, IL-1, and IL-6 were used as indicators for sepsis, and there was a significant difference in these values between the control and sepsis groups. It was concluded that the sepsis model was successfully created. In all three plasma, kidney and liver samples, inflammatory markers were significantly higher in the sepsis group than in the control group ($p<0.001$). The comparison between the groups is presented in Table 1. When the IL-1β values were examined, a significant decrease was observed in the dex and midazolam groups compared to the sepsis group ($p<0.001$). In addition, in the dex group plasma IL-1β values were lower than in the midazolam group ($p=0.002$). IL-1β values in kidney and liver tissues were similar in the dex and midazolam groups but these values were significantly lower than in the septic group ($p<0.001$). TNF-α values were also significantly higher in the septic group than in the control, dex and midazolam groups ($p<0.001$). Plasma TNF values were significantly lower in the dex group ($p=0.027$), whereas TNF values in the liver ($p=0.360$) and kidney ($p=0.579$) tissues were similar in the dex and midazolam groups. IL-6 levels were significantly higher in the septic group compared to the control group, and significantly lower in the dexmetatomidine and midazolam applied groups compared to the sepsis group ($p<0.001$). IL-6 levels in both serum and tissues were similar in the dex and midazolam groups ($p=0.098$). The comparison of the groups is presented in Table 1.

## DISCUSSION

The significant difference in inflammatory markers between the sepsis and control groups in our study showed that the sepsis model was successfully established. In the dex and midazolam groups, inflammatory markers were significantly reduced compared with the sepsis group. This showed that both of these agents have anti-inflammatory effects. Similar to serum, inflammatory markers were significantly decreased in liver and kidney tissue samples. When dexmetatomidine and midazolam were compared, it was observed that serum TNF-α, IL-1, and IL-6 levels were significantly decreased in the dex group, which was compared with the midazolam group; therefore, dexmetatomidine had a greater anti-inflammatory effect than midazolam.

Midazolam and dexmetatomidine are commonly used sedation agents in intensive care units (17). Septic patients may need sedation with or without mechanical ventilation support. In these patients, hemodynamic and cognitive effects usually our first concerns in the selection of sedation agents. Decreased systemic vascular resistance and increased permeability present hypotension as an important problem in these patients. It is desired that the sedation agents applied minimally contribute to hypotension or even fix it.

In a meta-analysis, sedation agents were examined in sepsis patients and it was found that dexmetatomidine caused 51% less 28-day mortality compared to other sedative agents (18). Dexmetatomidine has anxiolytic and sedative effects but does not have a respiratory depressant effect. With this advantage, it is widely used in intensive care units and clinical anesthesia. Two hundred forty two patients were included in the aforementioned analysis, which compares dexmetatomidine with propofol, lorazepam and midazolam.

**Table 1. The p-value was given for the total comparison of the four groups, and the comparison of the 4 groups with each other was shown**

| Parameters | Control n=8 | Sepsis n=8 | Sepsis + Dex n=8 | Sepsis + Midazol n=8 | p |
|---|---|---|---|---|---|
| **IL-1β of serum (pg/mL)** | 27.19±1.75 | 140.38±17.35 | 75.62±8.75 | 96.59±5.73 | **<0.05** |
| **IL-1β of liver (pg/mg)** | 108.39±10.04 | 489.90±71.75 | 213.47±23.53 | 262.28±16.29 | **<0.05** |
| **IL-1β of kidney (pg/mg)** | 36.51±5.24 | 175.23±30.28 | 78.07±8.11 | 90.81±5.91 | **<0.05** |
| **TNF-α of serum (pg/mL)** | 43.13±4.61 | 319.84±24.21 | 160.68±16.22 | 185.45±12.57 | **<0.05** |
| **TNF-α of liver (pg/mg)** | 100.34±7.49 | 693.09±69.39 | 350.16±35.55 | 390.94±28.11 | **<0.05** |
| **TNF-α of kidney (pg/mg)** | 68.02±4.67 | 458.17±48.82 | 232.26±23.50 | 256.97±18.64 | **<0.05** |
| **IL-6 of serum (pg/mL)** | 193.57±15.88 | 1093.20±188.54 | 565.26±62.34 | 572.39±47.93 | **<0.05** |
| **IL-6 of liver (pg/mg)** | 454.24±52.90 | 2377.19±467.77 | 1235.70±144.51 | 1211.43±106.90 | **<0.05** |
| **IL-6 of kidney (pg/mg)** | 314.57±38.43 | 1163.12±69.74 | 830.02±95.44 | 810.52±69.99 | **<0.05** |

As the most important benefit in increasing survival, it was concluded that dexmetatomidine is more hemodynamically stable than other sedatives. In fact, no hypotension or bradycardia was reported in the 214 studies reviewed in this meta-analysis (19). However, when we look at the literature, it is seen that the most common side effects are hypotension and bradycardia. In the same study, after 24 h of treatment, TNF-α levels, IL-1β, and IL-6 were significantly lower in patients treated with dexmetatomidine. This led the authors to conclude that the anti-inflammatory effect of dexmetatomidine may also have affected survival in septic patients (19,20). In sepsis, the catabolic process is the precursor, and sedative drugs can be useful for treating sepsis by stopping this destruction. When we evaluated many studies in the literature, we predicted that sedative drugs may be beneficial in our study.

In our study, a significant difference was observed in plasma TNF-α, IL-1β, and IL-6 levels in rats treated with dex compared with the sepsis group. In some similar studies, it was observed that it decreased the levels of proinflammatory cytokines, and mortality decreased in rats with sepsis (21). It was noted that the effect was dose dependent. In our study group, only a single dose of dexmetatomidine and midazolam was tried to reduce the number of subjects used, and the effects of increasing doses were not analyzed. Dexmetatomidine is most commonly used for sedation in intensive care by infusion at a dose of 1 mcg/kg and maintenance doses of 0.2-0.7 mcg/kg after loading (22). According to our study, even a single dose of sedation showed an anti-inflammatory effect. Besides, new studies on more animals or subjects are needed for the effect of different doses (23).

Midazolam is one of the agents frequently used in intensive care sedation. Its anti-inflammatory effects and its effects on mortality in sepsis patients have been the subject of some studies before (24). Midazolam binds to specific receptors on macrophages, reducing the production of TNF-α, IL-1β, and IL-6. Similar to midazolam, remimidazolam also showed anti-inflammatory effects, the mechanism of which is thought to be the activation of benzodiazepine receptors and a decrease in p98 level (25). However, opposing studies have suggested that midazolam does not alter the lipopolysaccharide-stimulated cytokine response (26). Therefore, the anti-inflammatory effect of midazolam still seems controversial. In our study, TNF-α, IL-1β, and IL-6 were significantly decreased in rats using midazolam. Similarly, in a study using sedative agents, midazolam was shown to reduce inflammatory markers in peritoneal lavage fluid (27).

Infection-induced sepsis can lead to organ failure because of both cytokine responses and hemodynamic disorders. The effects of inflammatory mediators, especially in the liver, kidney, and brain, increase mortality (28). In our study, it was observed that both midazolam and dexmetatomidine had anti-inflammatory effects in the liver and kidney compared to the sepsis group. In Koca et al. (29) on 21 rats, dexmetatomidine reduced sepsis-induced lung and kidney injuries and apoptosis in septic rat models of intra-abdominal sepsis . In the study of Qui et al. (30), dexmetatomidine decreased IL-1β, IL-6 and TNF-α, NF-κB activity, and TLR4 expression, acted on the rat kidney tissues and provided a protective effect on the renal tissues.

An important point of our study is that dexmetatomidine is more effective than midazolam on serum anti-inflammatory markers, however, there is no difference between midazolam and dex in terms of TNF-α, IL-1β, and IL-6 levels in kidney and liver tissue. These two sedative agents showed similar anti-inflammatory effects in liver and kidney. This finding suggests that dexmetatomidine may be more beneficial in patients with sepsis without organ dysfunction or hemodynamic stability. We think that dexmetatomidine is more effective than midazolam because its hypotension-producing effect is less than that of other sedatives and because it affects hemodynamic stability less. Further comparison is needed for these two agents in terms of their effects on organs.

First, our study was conducted on animal models, and the results may not be certain for septic intensive care patients. When the literature is examined, it is observed that many studies have been carried out in this area in rats and the results have been adapted to humans (31). Another limitation is that both midazolam and dexmetatomidine were given in a single dose in our study. However, sedation is often used as an infusion in the intensive care unit. Different doses were not used to reduce the number of animals used. In this study, the anti-inflammatory effects of dexmetatomidine and midazolam were proven in both plasma and liver-kidney tissues, and it was concluded that more studies are required for the effects of different doses.

## CONCLUSION

Our study results show that both midazolam and dexmetatomidine have an anti-inflammatory effect by causing a decrease in TNF-α, IL-1β, and IL-6 levels in rats in the sepsis model. Dexmedetomidine provides a significant decrease in serum anti-inflammatory levels compared to midazolam, and the effects of these two sedative agents are similar in the liver and kidney.

*Our article was written by producing from the thesis study.

## ETHICS

**Ethics Committee Approval:** All animal procedures were approved by an ethics committee (Kırıkkale University Animal Experiments Local Ethics Committee-decision no: 17/07, date: 01.03.2017) and conducted in accordance with international guidelines for the care and use of animals.

**Informed Consent:** Experimental study.

### Authorship Contributions

Surgical and Medical Practices: F.Ö., A.Y., A.D., Ç.K., Concept: F.Ö., Ç.K., Design: F.Ö., Ç.K., Data Collection or Processing: F.Ö., A.Y., A.D., Analysis or Interpretation: F.Ö., A.Y., A.D., Literature Search: F.Ö., A.Y., Writing: F.Ö., A.Y., A.D.

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Financial Disclosure:** The authors declare that this study received no financial support.

## REFERENCES


1. Bauer M, Gerlach H, Vogelmann T, Preissing F, Stiefel J, Adam D. Mortality in sepsis and septic shock in Europe, North America and Australia between 2009 and 2019- results from a systematic review and meta-analysis. Crit Care 2020;24:239.
2. Bone RC, Grodzin CJ, Balk RA. Sepsis: a new hypothesis for pathogenesis of the disease process. Chest 1997;112:235-43.
3. Train SE, Dieffenbach PB, Massaro AF, Devlin JW. Sedation, Neuromuscular Blockade, and Mortality in Acute Respiratory Distress Syndrome: Important Questions Remain. Crit Care Med 2022;50:e89-90.
4. Shehabi Y, Murfin B, James A, Al-Bassam W, Bellomo R. Trials of dexmedetomidine sedation in ventilated critically ill septic patients: Challenges, limitations and opportunities. Anaesth Crit Care Pain Med 2021;40:100925.
5. Bhana N, Goa KL, McClellan KJ. Dexmedetomidine. Drugs 2000;59:263-8; discussion 269-70.
6. Gertler R, Brown HC, Mitchell DH, Silvius EN. Dexmedetomidine: a novel sedative-analgesic agent. Proc (Bayl Univ Med Cent) 2001;14:13-21.
7. Mo Y, Zimmermann AE. Role of dexmedetomidine for the prevention and treatment of delirium in intensive care unit patients. Ann Pharmacother 2013;47:869-76.
8. Bajwa S, Kulshrestha A. Dexmedetomidine: an adjuvant making large inroads into clinical practice. Ann Med Health Sci Res 2013;3:475-83.
9. Zheng L, Zhao J, Zheng L, Jing S, Wang X. Effect of Dexmedetomidine on Perioperative Stress Response and Immune Function in Patients With Tumors. Technol Cancer Res Treat 2020;19:1533033820977542.
10. Helmy SA, Al-Attiyah RJ. The immunomodulatory effects of prolonged intravenous infusion of propofol versus midazolam in critically ill surgical patients. Anaesthesia 2001;56:4-8.
11. Ohta N, Ohashi Y, Takayama C, Mashimo T, Fujino Y. Midazolam suppresses maturation of murine dendritic cells and priming of lipopolysaccharide-induced t helper 1-type immune response. Anesthesiology 2011;114:355-62.
12. Li Y, Wu B, Hu C, Hu J, Lian Q, Li J, et al. The role of the vagus nerve on dexmedetomidine promoting survival and lung protection in a sepsis model in rats. Eur J Pharmacol 2022;914:174668.
13. Uludag O. Effect of Sugammadex and Rocuronium Combination on Cranial Neurotoxicity in Rats: Experimental Study. Kafkas Univ Vet Fak Derg 2019;25:793-9.
14. Zhang J, Wang Z, Wang Y, Zhou G, Li H. The effect of dexmedetomidine on inflammatory response of septic rats. BMC Anesthesiol 2015;15:68.
15. Toscano MG, Ganea D, Gamero AM. Cecal ligation puncture procedure. J Vis Exp 2011;(51):2860.
16. Zhang J, Zhang H, Zhao L, Zhao Z, Liu Y. Effect and Mechanism of Lidocaine Pretreatment Combined with Dexmedetomidine on Oxidative Stress in Patients with Intracranial Aneurysm Clipping. J Healthc Eng 2021;2021:4293900.
17. Sandeep Sharma,Muhammad F. Hashmi,Dominic J. Valentino III , Sedation Vacation in the ICU,In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan. 2021 Sep 18. Bookshelf ID: NBK513327
18. Zamani MM, Keshavarz-Fathi M, Fakhri-Bafghi MS, Hirbod-Mobarakeh A, Rezaei N, Nader ND. Survival benefits of dexmedetomidine used for sedating septic patients in intensive care setting: A systematic review. J Crit Care 2016;32:93-100.
19. Arcangeli A, D'Alò C, Gaspari R. Dexmedetomidine use in general anaesthesia. Curr Drug Targets. 2009;10:687-95.
20. Zamani MM, Keshavarz-Fathi M, Fakhri-Bafghi MS, Hirbod-Mobarakeh A, Rezaei N, Bahrami A, et al. Survival benefits of dexmedetomidine used for sedating septic patients in intensive care setting: A systematic review. J Crit Care 2016;32:93-100.
21. Afonso J, Reis F. Dexmedetomidine: current role in anesthesia and intensive care. Rev Bras Anestesiol 2012;62:118-33.
22. Naaz S, Ozair E. Dexmedetomidine in current anaesthesia practice-a review. J Clin Diagn Res. 2014;8:GE01-4. Erratum in: J Clin Diagn Res 2022;16:ZZ01.
23. Taniguchi T, Kurita A, Kobayashi K, Yamamoto K, Inaba H. Dose- and time-related effects of dexmedetomidine on mortality and inflammatory responses to endotoxin-induced shock in rats. J Anesth 2008;22:221-8.
24. O'Donnell NG, McSharry CP, Wilkinson PC, Asbury AJ. Comparison of the inhibitory effect of propofol, thiopentone and midazolam on neutrophil polarization in vitro in the presence or absence of human serum albumin. Br J Anaesth 1992;69:70-4.
25. Fang H, Zhang Y, Wang J, Li L, An S, Huang Q, et al. Remimazolam reduces sepsis-associated acute liver injury by activation of peripheral benzodiazepine receptors and p38 inhibition of macrophages. Int Immunopharmacol 2021;101:108331.
26. Takaono M, Yogosawa T, Okawa-Takatsuji M, Aotsuka S. Effects of intravenous anesthetics on interleukin (IL)-6 and IL-10 production by lipopolysaccharide-stimulated mononuclear cells from healthy volunteers. Acta Anaesthesiol Scand 2002;46:176-9.
27. Xiao D, Zhang D, Xiang D, Liu QI, Liu Y, Lv L, et al. Effects of fentanyl, midazolam and their combination on immune function and mortality in mice with sepsis. Exp Ther Med 2015;9:1494-500.
28. Sezer A, Memiş D, Usta U, Süt N. The effect of dexmedetomidine on liver histopathology in a rat sepsis model: an experimental pilot study. Ulus Travma Acil Cerrahi Derg 2010;16:108-12.
29. Koca U, Olguner ÇG, Ergür BU, Altekin E, Taşdöğen A, Duru S, et al. The effects of dexmedetomidine on secondary acute lung and kidney injuries in the rat model of intra-abdominal sepsis. ScientificWorldJournal 2013;2013:292687.
30. Qiu R, Yao W, Ji H, Yuan D, Gao X, Sha W, et al. Dexmedetomidine restores septic renal function via promoting inflammation resolution in a rat sepsis model. Life Sci 2018;204:1-8.
31. Dardalas I, Stamoula E, Rigopoulos P, Malliou F, Tsaousi G, Aidoni Z, et al. Dexmedetomidine effects in different experimental sepsis in vivo models. Eur J Pharmacol 2019;856:172401.