DOI: 10.37990/medr.1253117 Med Records 2023;5(2):372-9

MEDICAL RECORDS-International Medical Journal

Research Article

Is Dexmedetomidine Toxic on Kidney Cells (Hek-293)? Effects on Cytotoxicity, Reactive Oxygen Species (ROS) and Apoptosis

Basak Pehlivan[1], Erdogan Duran[1], Veli Fahri Pehlivan[1], Ismail Koyuncu[2]

[1]Harran University, Faculty of Medicine, Department of Anesthesia and Reanimation, Şanlıurfa, Türkiye
[2]Harran University, Faculty of Medicine, Department of Biochemistry, Şanlıurfa, Türkiye

Abstract

Aim: Dexmedetomidine; it is widely used in anesthesia and intensive care. We aimed to examine and compare the cytotoxic, reactive oxygen species (ROS) and apoptotic effects of dexmedetomidine on kidney cells (Hek-293) in vitro at two different high and cumulative doses.

Material and Methods: The half-maximum inhibitory concentration (IC50) dose of dexmedetomidine on Hek-293 cells was determined using the 3-[4,5-dimethylthiazol-2yl]-2,5-diphenyltetrazolium bromide (MTT) method. Then at two different doses of the drug; apoptotic effects were determined by Annexin-V Method, morphological examinations were determined by Acridine Orange Ethidium Bromide Method and intracellular ROS levels were determined by flow cytometry.

Results: The IC50 value of dexmedetomidine for Hek-293 cells was determined as 64.6559 µg/mL. Compared with the control group, doses of 50 and 100 µg/mL of dexmedetomidine tended to show cytotoxicity ($p<0.05$). dexmedetomidine was found to have a lower cytotoxic effect at a dose of 50 µg / mL than at a dose of 100 µg / mL ($p<0.05$).

Conclusion: In the study, it was determined that dexmedetomidine increased intracellular ROS more than clinical doses at two different concentrations on Hek-293 cells, cytotoxic doses caused an increase in ROS in cells and induced apoptosis. We think that the toxic effects of dexmedetomidine can be prevented with the data obtained from this study and further studies.

Keywords: Anesthesia, apoptosis, cytotoxicity, dexmedetomidine, human kidney cells (Hek-293), reactive oxygen species (ROS)

INTRODUCTION

Dexmedetomidine; it is frequently used in anesthesia practice and especially in intensive care. It is an effective and highly specific agonist of α-2 adrenoceptors. It has been described as a unique sedative with analgesic, sympatholytic and pulmonary functions protective properties (1,2). Dexmedetomidine may exert hypnotic effects depending on the application. If high enough dose is administered, it can produce deep sedation and even general anesthesia like ptopofol etc. This indicates that dexmedetomidine has the potential to be a general anesthetic such as propofol or thiopental (2).

It has been approved by the US Food and Drug Administration (FED) for use in intensive care units for sedation for less than 24 hours in patients with or without the need for mechanical ventilation (2). Dexmedetomidine is widely used in the intensive care unit and operating room (3) for the above indications. However, with the emergence of many positive physiological effects, clinical application methods have increased greatly in recent years (4). Dexmedetomidine is a selective α2-adrenoceptor agonist with properties such as hemodynamic stabilization, anti-inflammation, diuresis and inhibition of central sympathetic outflow. And it has been shown in many studies to have an organ-protective effect on the heart, brain, kidneys, and lungs (5–7). Dexmedetomidine has both somatic and visceral pain-reducing effects when applied as an adjuvant in central and peripheral blocks (8). A meta-analysis (reviewing 16 randomized controlled trials) showed that administration of dexmedetomidine significantly reduced postoperative pain and need for

CITATION
Pehlivan B, Duran E, Pehlivan VF, Koyuncu I. Is Dexmedetomidine Toxic on Kidney Cells (Hek-293)? Effects on Cytotoxicity, Reactive Oxygen Species (ROS) and Apoptosis. Med Records. 2023;5(2):372-9. DOI:1037990/medr.1253117

Received: 21.02.2023 **Accepted:** 29.03.2023 **Published:** 05.04.2023
Corresponding Author: Basak Pehlivan, Harran University, Faculty of Medicine, Department of Anesthesia and Reanimation, Şanlıurfa, Türkiye **E-mail**: bpehlivan@harran.edu.tr

analgesic medication but increased the risk of bradycardia (8).

The effects of dexmedetomidine on renal function are complex. It may exert a diuretic effect by inhibiting the antidiuretic effect of vasopressin (AVP) in the collecting duct (9). There are studies expressing that this effect may be independent of AVP, by increasing osmolality and protecting the renal cortical membrane (2,9). It reduces the blood flow of the kidney by decreasing the release of norepinephrine from the renal cortex (10). There is also evidence from animal studies that it reduces ischemia-reperfusion injury (10). In a recent study, it was reported that perioperative infusion reduced the frequency and severity of acute kidney injury in the postoperative period in patients undergoing heart valve surgery (11).

Despite their widespread use, the specific mechanism of action of anesthetic drugs remains unclear (12), and in some cases, these drugs lead to undesirable side effects and cause various complications. Since there is no alternative to these drugs, they continue to be used frequently despite possible complications (13). Today, studies are carried out to elucidate the mechanism of action of such complications.

The mechanism by which the kidney metabolizes and excretes various drugs and toxins significantly influences drug nephrotoxicity. High renal blood flow, equivalent to approximately 25% of cardiac output, and high drug and toxin delivery expose the kidney to significant drug concentrations (14). In addition to hepatic metabolism, some drugs are biotransformed by the renal enzyme systems, including CYP450 and flavin-containing monooxygenases (15,16). This may result in the potential generation of nephrotoxic metabolites and reactive oxygen species (17). These byproducts of biotransformation can tip the balance in favor of oxidative stress, which outpaces natural antioxidants and increases kidney damage. DNA strand breaks, nucleic acid alkylation or oxidation, lipid peroxidation, and protein damage may develop (14). The development of drug-induced nephrotoxicity is best understood by examining the factors contributing to nephrotoxicity (14).

The kidneys are the main junction in the excretion of drugs. And it is also involved in the metabolism of drugs to some extent (18). Clinical, in vivo and in vitro studies are carried out on the kidneys. Human kidney epithelial (Hek-293) cells are a good choice for an in vitro model as they allow researchers to study the physiological functions of kidney cells (19). Therefore, we used Hek-293 cells to examine the clinical and high-dose effects of Dexmedetomidine.

Although there is no toxic effect at clinical doses, it has been determined that in long-term use, if clinical doses are exceeded or repeated doses of these drugs are used for sedation, a cumulative effect may occur and have a cytotoxic effect on many cells. Apoptosis is involved in the emergence and development of various renal pathological injuries. When an organism receives a strong stimulus, it encourages excessive reactive oxygen species (ROS) production (20). Excessive ROS may activate oxidative stress by disrupting the balance between oxidative and antioxidant systems (20).

There are studies claiming that dexmedetomidine can prevent isoflurane-induced apoptosis in the brain and some other organs, or vice versa (12,21–24). The cardiac side effects of dexmedetomidine may limit its use, especially in some patients (25). In the SPICE III study in which dexmedetomidine was compared with alternative sedatives, it was associated with an increased risk of mortality in the group of patients aged 65 years and younger (25). It has also been stated that toxicity may develop in cases where single doses of drugs or continuous infusions such as anesthetic drugs are used (14,23,24,26–29). Dexmedetomidine is thought to have unknown effects at present.

Lavon et al. (30) found that moderate and high doses of dexmedetomidine increased tumor cell involvement and growth of secondary tumors in animal models. There are studies showing that dexmedetomidine may increase neuronal apoptosis at high and cumulative doses (24,28). The specific mechanism of action of dexmedetomidine is not fully known. However, it has been reported that it exerts its effect through α-2 adrenergic receptors (30). These negative findings from laboratory experiments do not necessarily corroborate similar results in human studies. Therefore, further laboratory and clinical studies are required to understand the mechanism of action of dexmedetomidine and to improve its clinical use. As a result of all these, kidney damage may develop due to drugs.

Dexmedetomidine is a useful and attractive drug that has great potential in many clinical situations. However, some extended applications of dexmedetomidine require further evaluation. In order to ensure the safe use of dexmedetomidine, it is necessary to choose the patient carefully and to determine the appropriate dose (31). There are studies showing that dexmedetomidine may have protective or toxic effects on cells. However, the mechanisms of action still remain unclear.

The most distinctive feature of this study is the in-vitro comparison of the effects of dexmedetomidine, whose clinical effects have been investigated many times, in HEK-293 cell lines for the first time, at two different high doses. Our aim is to compare the possible mechanisms of action of this drug by examining the effects of dexmedetomidine on cytotoxicity, apoptosis, and intracellular free oxygen radical (ROS) levels on Hek-293 cells in-vitro at two different high doses.

MATERIAL AND METHOD

Cells and Culture Conditions

In the study, we obtained and stocked from the American Type Culture Collection (ATCC); Hek-293 cells (Human kidney epithelial cell) (19,32) were used Cell lines were

grown in Dulbecco's Modified Eagle Medium:F12(DMEM) medium containing 1% P/S, 10% FBS and 1% glutamine. All cells were incubated at 37°C in an atmosphere of 5% CO. Cells were removed with a mixture of 0.25% trypsin, 0.03% Ethylenediamine tetraacetic acid (EDTA) and passaged at a ratio of 1:2 or 1:3 as recommended by ATCC. Unused cells were stored in a cell freezing solution prepared with 95% medium and 5% dimethylsulfoxide (DMSO) in a deep freezer at -80°C for a short or long term in liquid nitrogen.

Administration of Drugs to Cells

Cytotoxicity Analysis with MTT

The medium was refreshed 24 hours after Hek-293 cells were seeded in 96 sterile plates as 104 cells per well. Seven doses (0-2,5-5-10-25-50-100- µg/ml) were determined for the drug concentration to be applied to the cells. Dexmedetomidine was administered in 7 doses with 3 repetitions. No drug was administered to the control group. The cell lines were incubated in the incubator for 24 hours after the drug was applied. After drug administration, the cell medium was removed from the medium. The cytotoxic effect of dexmedetomidine was evaluated using the MTT [3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyltetrazolium Bromide method. Measurements were read at absorbance at 570-690 nm using a plate reader (Thermo Multiskan Go, USA). Graphics have been created. The IC50 dose was then calculated. Other tests were examined at doses of 50 and 100 µg/ml, which are one lower and one upper dose of the IC50 value found in cytotoxicity tests.

Cell Morphology and AO/EB Analysis

Cell morphology images were taken with an inverted microscope (Olympus CKX). According to cell nucleus morphology, apoptosis fluorescence in cells was examined by Acridin orange / ethidium bromide staining method. The medium was removed 24 hours after the administration of the drugs, 50 µL of AO/EB dye (Sigma Aldrich) was added and images were taken with a fluorescent microscope (Olympus CKX 51, DP73).

Determination of Apoptosis by Annexin V/PI Method

This analysis was performed using the commercially available FITC Annexin-V Apoptosis Detection Kit I (Cat No./ID:556.547, BD, New Jersey, USA) method. According to the kit protocol, shortly after administration of drugs, cells were harvested and stained immediately according to the kit protocol. The stained cells were analyzed by flow cytometry (FACS VIA, BD). Annexin V is displayed in green and PI in red. Viable cells [(FITC-)/(PI-)] were differentiated as early and moderately apoptotic [(FITC+) /(PI-)], late apoptotic and necrotic cells [(FITC+) /(PI+)].

Intracellular ROS Determination

Intracellular free radical exchange was carried out according to the protocol of the commercially available kit (MHC100111, Millipore-Merck). The Muse® Oxidative Stress Kit provides quantitative (cell count and percentage) measurements of Reactive Oxygen Species (ROS), ie superoxide radicals, in cells exposed to oxidative stress. After administration of drugs, cells were harvested using trypsin enzymes and washed with cold phosphate buffered saline (PBS). After adding 100 µl of ROS working solution, cells were incubated at 37°C for 30 minutes. After incubation the cells were analyzed by flow cytometry (FACS VIA, BD).

Statistical Analysis

The data in the study were analyzed using the SPSS Version 25.0 package program. Data were presented as mean±standard deviation (SD). After the data were checked for normality tests, pairwise comparisons were made with Student-t test. P-values less than 0.05 were considered statistically significant.

RESULTS

Cytotoxic effect of Dexmedetomidine on Hek-293

As a result of the analysis, it was determined that the cytotoxic effects of drug increased depending on the dose increase (Figure 1). The IC50 value of dexmedetomidine for Hek-293 cells was detected as 64.6559 µg/mL. Compared to the control group, dexmedetomidine tended to show cytotoxicity at doses of 50 µg/mL and 100 µg/mL (*p<0.001).

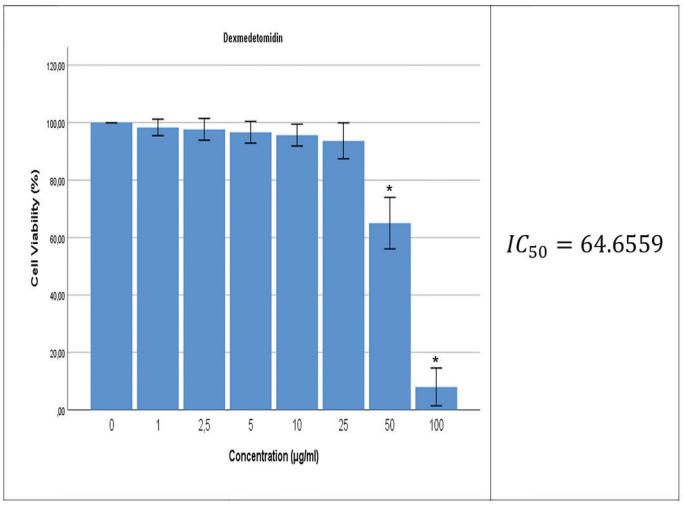

Figure 1. % Changes in viability of Hek-293 cells treated with different concentrations of dexmedetomidin for 24 hours. The data obtained are shown as mean ± standard deviation. (*p <0.001 vs control group for Dexmedetomidin. *#p<0.001 vs 50 and 100 µg/ml dose group.)

Effects of Dexmedetomidine on Hek-293 Cell Morphology and Apoptosis

The effects of 50 and 100 µg/ml doses of Dexmedetomidine on Hek-293 cell morphology were examined (Figure 2a). When the effects on cell morphology were compared with the control group, it was observed that the number of cells decreased and the number of apoptotic cells increased depending on the dose increase (Figure 2a).

The apoptotic effect of drugs on Hek-293 cells was examined using the AO/ET fluorescent staining method (Figure 2b). In the picture obtained, viable cells are seen in green, apoptotic cells in orange, and necrotic cells in

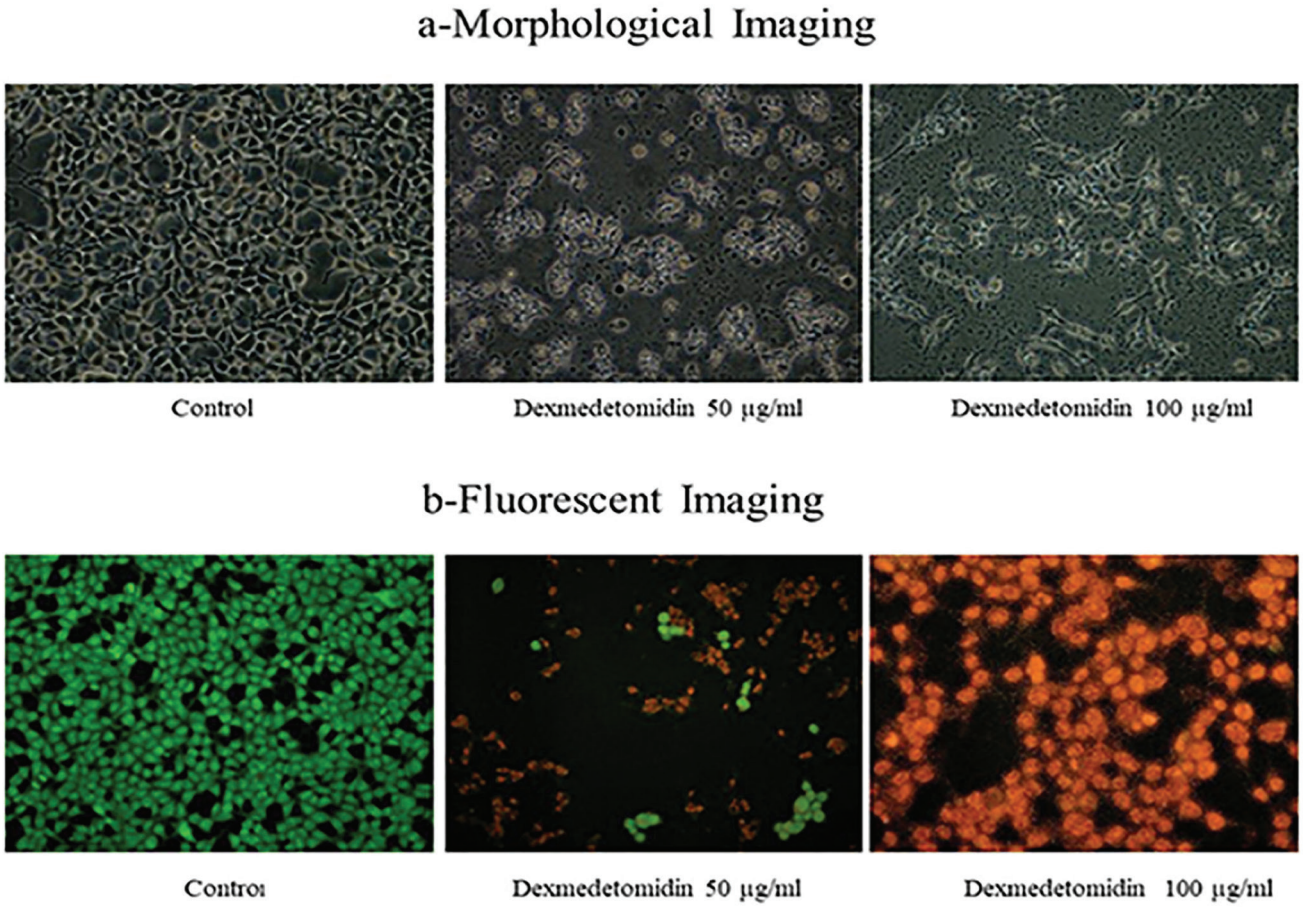

Figure 2. The image of the morphological and apoptotic effects of dexmedetomidine on Hek-293 cells

red. When the apoptotic effects of the drug are compared among themselves according to the doses; It was observed that 50 µg/ml > 100 µg/ml, while the apoptotic and cytotoxic effect was higher at 100 µg/ml dose.

Flow Cytometric Annexin-V Analysis of Hek-293 Cell Apoptotic Effect of Drugs

While 31.50% and 31.30% of dexmedetomidine-treated Hek-293 cells were viable at 50 and 100 µg/ml doses, 57.73% and 65.16% of them were observed to have necrosis (Table 1, Figure 3). These results were found to be significant compared to the control group ($p<0.000$).

When the two doses were compared, there was a statistically significant difference in viability, late apoptosis, and necrosis at a dose of 100 µg/ml ($p<0.05$).

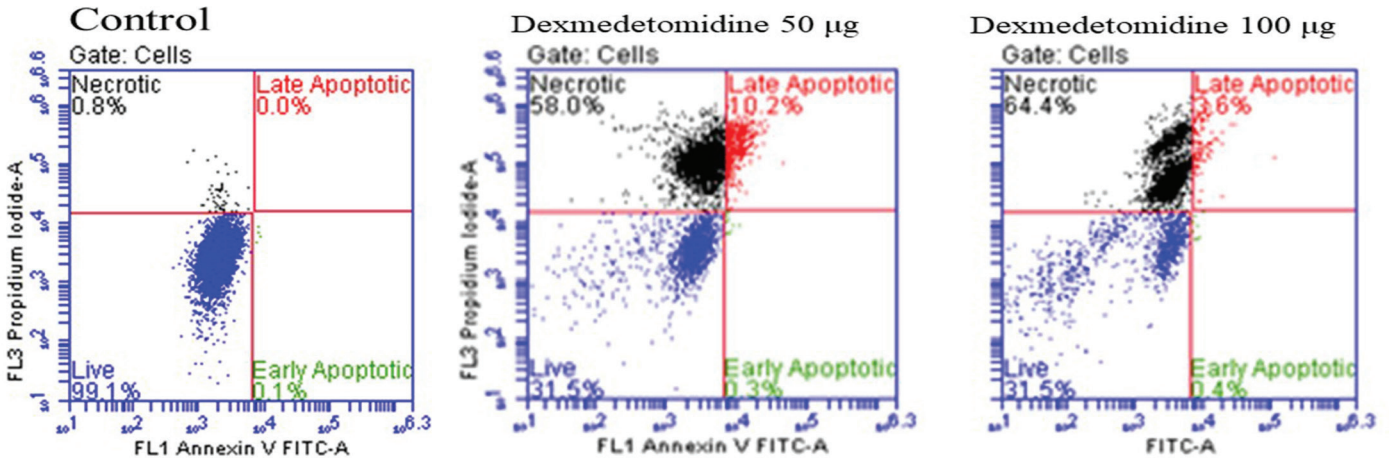

Figure 3. Flow cytometric annexin-V analysis of the Hek-293 cell apoptotic effect of Dexmedetomidine

Table 1. Flow cytometric annexin-V analysis of Hek-293 cell apoptotic effect of dexmedetomidine

Viability	Control	Doses (µg/ml)	Dexmedetomidine	*p*-value
Live	98.26±0.90	50 µg/ml	31.50±1.60	*p*=0.920 *
		100 µg/ml	31.30±2.80	*p*=0.920 *
Early Apoptotic	0.23±0.15	50 µg/ml	0.33±0.05	*p*=0.643 #
		100 µg/ml	0.30±0.10	*p*=0.643 #
Late Apoptotic	0.13±0.15	50 µg/ml	10.43±0.97	*p*=0.000 ¥
		100 µg/ml	3.20±0.36	*p*=0.000 ¥
Necrotic	1.36±0.73	50 µg/ml	57.73±2.51	*p*=0.031 α
		100 µg/ml	65.16±3.02	*p*=0.031 α

Values are given as mean±standard deviation.
p=0.920 indicates comparison of dexmedetomidine for 50 and 100 µg/ml dose groups.
*,#,¥,α indicates p values <0.05 lower for comparison of Dexmedetomidine and Control groups for all doses

Flow Cytometric Investigation of the Effects of Dexmedetomidine on the Formation of Intracellular Free Radicals (ROS) in Hek-293 Cells

It was determined that the amount of intracellular free radicals increased depending on the dose (Table 2, Figure 4). The drugs we use include intracellular free radical levels at doses of 50 and 100 µg/ml; It was determined as 57.36% and 78.30%. Significant change was observed compared to the control group (p=0.001).

Table 2. ROS effect of different doses of drugs on Hek-293 cells

	Doses	Control	Dexmedetomidin	*p*-value
ROS (-)	50 µg/ml	98.30±1.25	42.90±1.83	*p*=0.000 *
	100 µg/ml	98.30±1.25	21.26±2.63	*p*=0.000 *
ROS (+)	50 µg/ml	1.60±1.41	57.36±2.05	*p*=0.000 #
	100 µg/ml	4.03±1.89	78.30±2.40	*p*=0.000 #

Values are given as mean±standard deviation.
p=0.000 indicates comparison of dexmedetomidine for 50 and 100 µg/ml dose groups.
*,# indicate p-values less than <0.05 for comparison of groups, Dexmedetomidin and Control for all doses.

In conclusion; it was determined that with the increase in dose of dexmedetomidine, the viability decreased and accordingly the ROS formation increased. A statistically significant difference was found between the control group and the doses used in the comparisons (p<0.001).

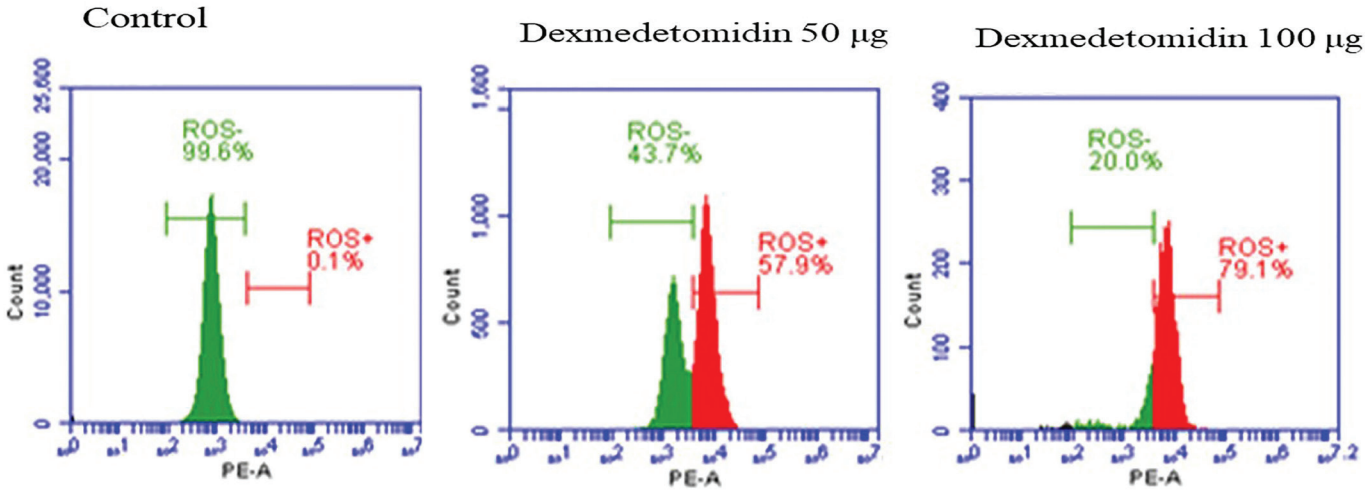

Figure 4. Flow cytometric examination of the effects of dexmedetomidine on Hek-293 cell intracellular free radical (ROS) formation

DISCUSSION

When we compared the effects of Dexmedetomidine on Hek-293 cells at two different high doses; We found that it undergoes apoptosis due to increased intracellular ROS. Dexmedetomidine IC50 dose on Hek-293 cells; We found it to be 64.65 µgr/ml. We found that it showed more toxicity at two different high doses cumulative than clinical doses. However, it did not show any cytotoxic effect at clinical doses.

Dexmedetomidine-induced cell death has been reported (24,26–28). It does not have any toxic effects at clinical doses. Dexmedetomidine has been used intraperitoneally at a dose of 25-100 µg /kg in previous studies (12,24,28,29). In our study, we found the IC50 dose in Hek-293 cells as 64.67 µg/ml and we used two different doses as 50 and 100 µg/ml according to this dose. We found that the doses we applied had a more severe cytotoxic effect compared to the control group (p<0.001).

The protective roles of dexmedetomidine during acute stress-induced kidney injury are unknown. Dexmedetomidine may be an effective drug to prevent kidney damage caused by acute stress. Dexmedetomidine also has antioxidative stress effects (33–36). Clinical and laboratory studies have reported that dexmedetomidine has a protective effect on many organs. It exerts this effect by reducing the oxidant response in organs and

inactivating apoptosis signaling pathways that protect cells from damage. Çanakçı E. et al. (2) reported that dexmedetomidine had a protective effect on the kidney in colistin-induced kidney damage, and therefore it was a very valuable sedation agent for clinicians in intensive care units. Dexmedetomidine; In long-term use, a cumulative and toxic effect may occur if clinical doses are exceeded or repeated doses of these drugs are used for sedation (14,24,27,28). Wang Z at al. (29) showed that dexmedetomidine at 10-30-50 μM doses inhibited LPS-induced ROS production and apoptosis in tubular epithelial cells of mice, but reversed the protective effects of dexmedetomidine in sepsis-associated AKI at 50 μM. They showed that the corrective effects of sepsis-associated acute kidney injury observed after treatment with dexmedetomidine are due to attenuation of oxidative stress (29). In our study, which we used above clinical doses, we found that 50 and 100 μg/ml dexmedetomidine caused cytosolic ROS formation and apoptosis, consistent with Wang Z et al's study ($p<0.05$, Table 1,2).

Hanci V et al. (37) found that 100 μmol/L dexmedetomidine increased nitric oxide synthase (NOS) and nitric expression and had a toxic effect with an increase in inflammatory cytokines. Lai et al. (38) reported that the protective effect of dexmedetomidine was related to its concentration. In in vitro experiments, they treated the increased inflammatory cytokine release by LPS with different concentrations of dexmedetomidine. In their study, they found that 0.01 μmol/L dexmedetomidine had no effect, the addition of 1 μmol/L dexmedetomidine was effectively protective, 100 μmol/L dexmedetomidine stimulated nitric oxide synthase and nitric expression and had a toxic effect. Consistent with these studies, in our study, we found that cytosolic ROS production, apoptosis and necrosis increased statistically significantly at high doses in Hek-293 cells compared to the control group ($p<0.05$, Table 1,2).

Recently, it is thought that dexmedetomidine exerts a protective effect on many vital organs, which is thought to be associated with anti-inflammation, anti-oxidative damage and inhibition of apoptosis (39). However, long-term infusions and cumulative doses are also thought to cause toxic effects. The antioxidant effect of dexmedetomidine is provided by different mechanisms in pathological conditions. However, most of the available dexmedetomidine studies are based on preclinical studies and the mechanism remains unclear. More research and clinical studies are needed. In addition, although dexmedetomidine is thought to have an organ protective effect, there are conflicting results in the literature about whether α2AR agonism is protective or toxic. However, while evaluating the positive effects of dexmedetomidine, the use of this substance at different times, effective doses and drug profile should be investigated (31). To confirm the potential of using dexmedetomidine to preserve organs in the future, it needs to be supported by realistic, important clinical observations and studies.

Although dexmedetomidine is widely used in anesthesia practice, its specific mechanism of action remains unclear (12,31). In vitro studies are frequently used to determine the effects of drugs on organisms. In these studies, researchers often select the type of cell in which drugs are metabolized or in which they show activity. The kidney is the major junction in the excretion and to some extent metabolism (18) of most drugs, especially anesthetic drugs Therefore, Hek-293 cells are a good choice for an in vitro model as they allow researchers to examine the physiological functions of kidney cells (19,32). In our study, we used Hek-293 cells to examine the clinical and high-dose effects of dexmedetomidine.

Considering the increase in anesthesia methods applied, it is of great importance that anesthesia be given safely. Patients who will be given anesthesia may be exposed to oxidant or antioxidant stress before, during and after surgery (40). Anesthesiologists are in a position to improve the postoperative outcome by taking measures against oxidative stress. Therefore, there is a need for a better understanding of the effect of anesthetic agents on oxidative stress and clinical outcomes and more studies on this subject to improve the treatment of patients.

Our study has some limitations. We tested the toxicity of dexmedetomidine using cultured cells. We primarily used established cell lines derived from primary cultured cells, not from various tissue origins. Although we performed our tests using 10% FBS, the free fraction of the drug could not be determined. It can be done in an in vivo study using experimental animals to confirm our findings. One of the limitations of our study; results from a cell model cannot simply be translated/transported into a clinical setting.

CONCLUSION

In conclusion, dexmedetomidine on Hek-293 cells in our study; It has been found to cause toxic effects by increasing intracellular ROS at two different concentrations higher than clinical doses. It was observed that this toxic effect was due to the increase in intracellular ROS that triggered apoptosis. With the examination of the data obtained as a result of this study and the new studies to be done; We believe that the benefits and complications associated with the use of this drug can be clarified and avoided.

Financial disclosures: *This research was supported by Harran University Scientific Research Projects Unit (HUBAK: 31/12/2019 date and project number: 19342).*

Conflict of Interest: *The authors declare that they have no competing interest.*

Ethical approval: *This article is an experimental study. Ethics committee approval is not required as it is performed on cultured cells.*

Authors' contributions: *Study concepts: B.P., V.F.P., E.D. Study design: B.P., V.F.P., E.D. Literature search: B.P., V.F.P., İ.K. Experimental studies: B.P., V.F.P., E.D., İ.K. Data analysis: B.P., V.F.P., I.K. Statistical analysis: V.F.P. Article preparation: B.P., V.F.P. All authors contributed to the final manuscript.*

Acknowledgement: *The authors would like to express their sincere thanks to the staff of Harran University Faculty of Medicine, Department of Biochemistry Laboratory and Hamza Erdoğdu for their support.*

REFERENCES

1. Carollo DS, Nossaman BD, Ramadhyani U.Dexmedetomidine: a review of clinical applications.Curr Opin Anaesthesiol. 2008;21:457–61.
2. Canakcı E, Karatas A, Coskun I, et al. Investigationof the nephroprotective effect of dexmedetomidineon colistin-induced nephrotoxicity in rats. BratislavaMed J. 2022;123:579–84.
3. Wunsch H, Kahn JM, Kramer AA, et al.Dexmedetomidine in the Care of Critically IllPatients from 2001 to 2007. Anesthesiology.2010;113:386–94.
4. Bae HB. Dexmedetomidine: an attractive adjunct toanesthesia. Korean J Anesthesiol. 2017;70:375.
5. Liu X, Li T, Cao L, et al. Dexmedetomidineattenuates H2O2-induced neonatal ratcardiomyocytes apoptosis through mitochondria- and ER-medicated oxidative stress pathways. MolMed Rep. 2018.
6. Yu X, Chi X, Wu S, et al. DexmedetomidinePretreatment Attenuates Kidney Injury andOxidative Stress during Orthotopic AutologousLiver Transplantation in Rats. Oxid Med CellLongev. 2016;2016:1–10.
7. Tang C, Hu Y, Gao J, et al. Dexmedetomidinepretreatment attenuates myocardial ischemiareperfusion induced acute kidney injury andendoplasmic reticulum stress in human and rat. LifeSci. 2020;257:118004.
8. Wu HH, Wang HT, Jin JJ, et al. DoesDexmedetomidine as a Neuraxial AdjuvantFacilitate Better Anesthesia and Analgesia? ASystematic Review and Meta-Analysis. PLoS One. 2014;9:e93114.
9. Yuen VM, Irwin MG, Hui TW, et al. A Double-Blind, Crossover Assessment of the Sedative andAnalgesic Effects of Intranasal Dexmedetomidine.Anesth Analg. 2007;105:374–80.
10. Billings FT, Chen SWC, Kim M, et al. α 2 -Adrenergic agonists protect against radiocontrast-induced nephropathy in mice. Am J Physiol Physiol.2008;295:741–8.
11. Cho JS, Shim JK, Soh S, et al. Perioperativedexmedetomidine reduces the incidence and severityof acute kidney injury following valvular heartsurgery. Kidney Int. 2016;89:693–700.
12. Koca U, Olguner ÇG, Ergür BU, et al. The Effects ofDexmedetomidine on Secondary Acute Lung andKidney Injuries in the Rat Model of Intra-AbdominalSepsis. Sci World J. 2013;2013:1–11.
13. Armstrong R, Riaz S, Hasan S, et al. Mechanisms ofAnesthetic Action and Neurotoxicity: Lessons fromMolluscs. Front Physiol. 2017.01138.
14. Perazella MA. Pharmacology behind Common DrugNephrotoxicities. Clin J Am Soc Nephrol. 2018;13:1897–908.
15. Aleksa K, Matsell D, Krausz K, et al. CytochromeP450 3A and 2B6 in the developing kidney:implications for ifosfamide nephrotoxicity. PediatrNephrol. 2005;20:872–85.
16. Fanos V, Cataldi L. Renal Transport of Antibioticsand Nephrotoxicity: a Review. J Chemother. 2001;13:461–72.
17. Jang KJ, Mehr AP, Hamilton GA, et al. Humankidney proximal tubule-on-a-chip for drug transportand nephrotoxicity assessment. Integr Biol. 2013;5:1119–29.
18. Mukai M, Tanaka S, Yamamoto K, et al. In vitroglucuronidation of propofol in microsomal fractionsfrom human liver, intestine and kidney: tissuedistribution and physiological role of UGT1A9. Pharmazie. 2014;69:829–32.
19. Abarikwu SO, Simple G, Onuoha SC, et al.Evaluation of the protective effects of quercetin andgallic acid against oxidative toxicity in rat's kidneyand HEK-293 cells. Toxicol Reports. 2020;7:955–62.
20. Wang H, Li D, Hu Z, et al. Protective Effects ofGreen Tea Polyphenol Against Renal Injury ThroughROS-Mediated JNK-MAPK Pathway in LeadExposed Rats. Mol Cells. 2016;39:508–13.
21. Pontén E, Viberg H, Gordh T, et al. Clonidineabolishes the adverse effects on apoptosis andbehaviour after neonatal ketamine exposure in mice.Acta Anaesthesiol Scand. 2012;56:1058–65.
22. Hwang L, Cho IY, Kim SE, et al. Dexmedetomidine ameliorates intracerebral hemorrhage-induced memory impairment by inhibiting apoptosis and enhancing brain-derived neurotrophic factor expression in the rat hippocampus. Int J Mol Med. 2013;31:1047–56.
23. Tang C, Huang X, Kang F, et al. Intranasal Dexmedetomidine on Stress Hormones, Inflammatory Markers, and Postoperative Analgesia after Functional Endoscopic Sinus Surgery. Mediators Inflamm. 2015;2015:1–9.
24. Wei Q, Chen J, Xiao F, et al. High-Dose Dexmedetomidine Promotes Apoptosis in Fetal Rat Hippocampal Neurons. Drug Des Devel Ther. 2021;15:2433–44.
25. Shehabi Y, Serpa Neto A, Howe BD, et al. Early sedation with dexmedetomidine in ventilated critically ill patients and heterogeneity of treatment effect in the SPICE III randomised controlled trial. Intensive Care Med. 2021;47:455–66.
26. Pérez-Lara JL, Santana Y, Hernández-Torres J, Díaz-Fuentes G. Acute Colonic Pseudo-Obstruction Caused by Dexmedetomidine: A Case Report and Literature Review. Am J Case Rep. 2019;20:278–84.
27. Nath S, Singh S, Pawar S. Dexmedetomidine overdosage: An unusual presentation. Indian J Anaesth. 2013;57:289.
28. Liu JR, Yuki K, Baek C, et al. Dexmedetomidine-Induced Neuroapoptosis Is Dependent on Its Cumulative Dose. Anesth Analg. 2016;123:1008–17.
29. Wang Z, Wu J, Hu Z, et al. Dexmedetomidine Alleviates Lipopolysaccharide-Induced Acute Kidney Injury by Inhibiting p75NTR-Mediated Oxidative Stress and Apoptosis. Oxid Med Cell Longev. 2020;2020:1–13.
30. Lavon H, Matzner P, Benbenishty A, et al. Dexmedetomidine promotes metastasis in rodent models of breast, lung, and colon cancers. Br J Anaesth. 2018;120:188–96.
31. Bao N, Tang B. Organ-Protective Effects and the Underlying

Mechanism of Dexmedetomidine. Mediators Inflamm. 2020;2020:1–11.

32. Song L, Shi S, Jiang W, et al. Protective role of propofol on the kidney during early unilateral ureteral obstruction through inhibition of epithelial-mesenchymal transition. Am J Transl Res. 2016;8:460–72.

33. Ning Q, Liu Z, Wang X, et al. Neurodegenerative changes and neuroapoptosis induced by systemic lipopolysaccharide administration are reversed by dexmedetomidine treatment in mice. Neurol Res. 2017;39:357–66.

34. Weng X, Zhang X, Lu X, et al. Reduced mitochondrial response sensitivity is involved in the anti apoptotic effect of dexmedetomidine pretreatment in cardiomyocytes. Int J Mol Med. 2018.

35. Park JH, Ko IG, Kim SE, et al. Dexmedetomidine Oral Mucosa Patch for Sedation Suppresses Apoptosis in Hippocampus of Normal Rats. Int Neurourol J. 2017;21:S39-47.

36. Chen Y, Feng X, Hu X, et al. Dexmedetomidine Ameliorates Acute Stress-Induced Kidney Injury by Attenuating Oxidative Stress and Apoptosis through Inhibition of the ROS/JNK Signaling Pathway. Oxid Med Cell Longev. 2018;2018:1–12.

37. Hancı V, Yurdakan G, Yurtlu S, et al. Protective effect of dexmedetomidine in a rat model of α-naphthylthiourea–induced acute lung injury. J Surg Res. 2012;178:424–30.

38. Lai YC, Tsai PS, Huang CJ. Effects of Dexmedetomidine on Regulating Endotoxin-Induced Up-Regulation of Inflammatory Molecules in Murine Macrophages. J Surg Res. 2009;154:212–9.

39. Zhu S, Lu Y. Dexmedetomidine Suppressed the Biological Behavior of HK-2 Cells Treated with LPS by Down-Regulating ALKBH5. Inflammation. 2020;43:2256–63.

40. Senoner T, Velik-Salchner C, Luckner G, Tauber H. Anesthesia-Induced Oxidative Stress: Are There Differences between Intravenous and Inhaled Anesthetics? Oxid Med Cell Longev. 2021;2021:1–11.